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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

SYNOPSIS

Name of Sponsor/Company: Baxter Innovations GmbH		*(For National Authority Use only)*
Name of Investigational Product (IP)	Multivalent recombinant OspA Lyme Borreliosis Vaccine (mv rOspA LB Vaccine)	
Name(s) of Active Ingredient(s)	Recombinant lipidated OspA antigens (rOspA 1/2, rOspA 5/3 and rOspA 6/4)	
CLINICAL CONDITION(S)/INDICATION(S)		
Prophylaxis of Lyme borreliosis		
PROTOCOL IDENTIFIER	730901 Amendment 7, EudraCT Number: 2010-023384-18	
PROTOCOL TITLE	Randomized, double-blind, Phase 1/2 clinical study to investigate the safety and immunogenicity of a multivalent recombinant OspA Lyme Borreliosis Vaccine (mv rOspA LB Vaccine) in healthy subjects aged 18 to 70 years.	
Short Title	Multivalent recombinant OspA Lyme Borreliosis Vaccine (mv rOspA LB Vaccine, Phase 1/2)	
STUDY PHASE	Ph1/2	

INVESTIGATORS AND STUDY SITE(S): Parts A – J:

(01) [redacted] MD, [redacted] MD/ [redacted] Austria

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(10) [redacted] Germany

PUBLICATION (REFERENCE):

Wressnigg N, Pöllabauer EM, Aichinger G et al. Safety and immunogenicity of a novel multivalent OspA vaccine against Lyme borreliosis in healthy adults: A double-blind, randomised, dose-escalation Phase 1/2 trial. Lancet. Infect. Dis. Published online May 10, 2013.

STUDY PERIOD	
Initiation	Initiation (first subject in Part A, cohorts 1 - 3): 2011 Mar. 01 Initiation (first subject in Part E, cohorts 4 & 5): 2011 Nov. 21
Study Completion	Completion (last subject out, Part J): 2014 Feb 28
Duration	Duration of Parts A to J: 3 years.
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
• To obtain safety and immunogenicity data of different dose levels of an mv rOspA LB Vaccine with and without adjuvant in seronegative healthy subjects aged 18 to 70 years. The outcome shall provide the basis for dose/formulation selection for Section 2 of the study. • To evaluate the safety and immunogenicity of the optimal dose(s)/formulation of the mv rOspA LB Vaccine in a larger population of seronegative and seropositive (subjects testing positive for antibodies against *B. burgdorferi* s.l. C6 peptide) healthy subjects aged 18 to 70 years.	
Primary Objective	
The two co-primary objectives (assessed sequentially) in this study are: • To evaluate the safety characteristics and immunogenicity of the mv rOspA LB Vaccine using 6 different formulations (3 dose levels with and without adjuvant) and to identify the optimal dose level(s) and/or formulation of the mv rOspA LB Vaccine in seronegative healthy subjects aged 18 to 70 years. This has been addressed in Parts A to C of the study and has provided the basis for dose/formulation selection for Section 2. • To evaluate the safety and immunogenicity of the optimal dose(s)/formulation of the mv rOspA LB Vaccine in a larger population of healthy seronegative and seropositive (subjects testing positive for antibodies against *B. burgdorferi* s.l. C6 peptide) subjects aged 18 to 70 years.	
Secondary Objective(s)	
The secondary objective was to assess antibody persistence and response to booster vaccinations with the mv rOspA LB Vaccine.	
Tertiary Objective(s)	
None specified	
STUDY DESIGN	
Study Type/ Classification/ Discipline	Safety and Immunogenicity
Control Type	Not applicable
Study Indication Type	Prevention
Intervention model	Not applicable
Blinding/Masking	Double-blind

Study Design

This is a randomized, double-blind, dose-escalation, 6-arm, Phase 1/2 clinical study. In Section 1 of the study, the safety and immunogenicity of an mv rOspA LB Vaccine using 6 different formulations (3 dose levels with and without adjuvant) was investigated in seronegative healthy subjects aged 18 to 70 years.

In Section 2 of the study the safety and immunogenicity of the optimal dose(s)/formulation of the mv rOspA LB Vaccine (as determined in Section 1) was investigated in healthy seronegative and seropositive subjects aged 18 to 70 years.

Section 3 investigated safety and antibody persistence of a booster vaccination in seronegative and seropositive subjects who received the 60 µg adjuvanted formulation for their primary vaccination series in Section 2.

Section 1:

Subjects were recruited in three sequential cohorts and assigned to one of 6 study arms:

STUDY ARM	TOTAL N	COHORT 1	COHORT 2	COHORT 3	DOSAGE (µg)	FORMULATION [$Al(OH)_3$] [a]
1	50	10	40	-	30	+
2	50	10	40	-	30	-
3	50	-	10	40	60	+
4	50	-	10	40	60	-
5	50	-	10	40	90	+
6	50	-	10	40	90	-
Total	**300**	20	120	160		

[a] aluminum hydroxide, + with $Al(OH)_3$, - without $Al(OH)_3$

A total of approximately 300 adult (18 to 49 years, approximately 2/3 of the study population) and elderly subjects (50 to 70 years, approximately 1/3) received 3 intramuscular injections of the mv rOspA LB Vaccine containing 30, 60 or 90 µg total protein in either an adjuvanted or a non-adjuvanted formulation at the following intervals:

1st Vaccination: Day 1
2nd Vaccination: Day 29
3rd Vaccination: Day 57

Subjects returned to the study site for follow-up visits 7 and 28 days after the first, second and third vaccinations as well as 6 and 9 months after the first vaccination.

Subjects were recruited in 3 cohorts for Section 1 as follows:

Cohort 1:

Cohort 1 was comprised of approximately 20 subjects randomized at a 1:1 ratio to receive the 30 µg dose of the mv rOspA LB Vaccine in either an adjuvanted or non-adjuvanted formulation.

	First, approximately 6 subjects were vaccinated on the first day. As no immediate safety concerns arose, vaccination of the remaining subjects in Cohort 1 proceeded on the next day. Data Monitoring Committee (DMC) Review 1: Based on the safety data obtained seven days after the first vaccination of all 20 subjects in Cohort 1, the DMC recommended (i) to proceed to Cohort 2 and (ii) to administer the second vaccine dose to Cohort 1. The DMC evaluate the following parameters: • AEs • Results of physical examinations • Safety laboratory results <u>Cohort 2:</u> Cohort 2 consisted of approximately 120 subjects comprising: 1) the remaining 40 subjects in study arms 1 and 2 (80 subjects in total) randomized at a 1:1 ratio to receive the 30 µg dose of the mv rOspA LB Vaccine in either an adjuvanted or non-adjuvanted formulation, and 2) the first 10 subjects in study arms 3 to 6 (40 subjects in total) randomized at a 1:1:1:1 ratio to receive the 60 µg or 90 µg dose of the mv rOspA LB Vaccine in either an adjuvanted or non-adjuvanted formulation. Initially approximately 40 subjects were randomized to study arms 1 and 2. The next 40 subjects were randomized to study arms 3 to 6. Of these, approximately 12 subjects were vaccinated on the first day. As no immediate safety concerns arose, vaccination of the remaining subjects in study arms 3 to 6 proceeded on the next day. Finally, the remaining 40 subjects in study arms 1 and 2 were enrolled. DMC Review 2: The DMC reviewed the safety data in Cohort 2 obtained seven days after the first vaccination from at least 50 subjects in study arms 1 and 2 as well as all safety data in study arms 3 to 6. This review also included all available safety data from the study at that time point, including data after the first and second vaccination for subjects in Cohort 1. Based on this safety evaluation the DMC gave a recommendation on whether (i) to administer the second vaccine dose to Cohort 2 (ii) to recruit the remaining 160 subjects into Cohort 3 and (iii) continue vaccination in Cohort 1. <u>Cohort 3:</u> Cohort 3 consisted of the remaining approximately 160 subjects in study arms 3 to 6 randomized at a 1:1:1:1 ratio to receive the 60 µg or 90 µg dose of the mv rOspA LB Vaccine in either an adjuvanted or non-adjuvanted formulation.

DMC Review 3:

Once safety data through seven days after the first vaccination in Cohort 3 were available, these were reviewed by the DMC. This DMC review also included all safety data from the study available at this time point. A recommendation was given on whether to continue vaccination.

Additional DMC safety reviews may be scheduled at any time during the study. Should safety concerns arise, study enrolment and vaccination will be suspended.

DMC Review 4:

Once a final evaluation of safety and immunogenicity data from Day 85, cohorts 1, 2 and 3 was available, the DMC was involved – together with the Sponsor – in the review of the data and the selection of the optimal dose(s)/formulation to be used in Section 2.

Section 2:

Based on the safety and immunogenicity results obtained in Section 1 (including data up to 28 days after the third vaccination), the optimal dose(s)/formulation to be used in Section 2 were selected:

A booster vaccination was administered approximately 9 to 12 months after the first vaccination to subjects in study arms 1 to 5[i] of Section 1 of the study. Subjects were given the same dose/formulation for the booster vaccination as during the primary vaccination series in Section 1. Subjects were to return to the study site 28 and 180 days after the booster vaccination.

In addition, in Section 2 of the study, approximately 350 subjects were recruited in two parallel cohorts (cohorts 4 and 5) and randomized at a 1:1 ratio to receive either the 30 µg adjuvanted or 60 µg adjuvanted formulation of the mv rOspA LB Vaccine. Section 2 was conducted in a blinded fashion.

Seronegative subjects in Cohort 4 consisted of adults aged 18 to 49 years (approximately 2/3 of the study population) and elderly subjects (50 to 70 years, approximately 1/3). Seropositve subjects in Cohort 5 consisted of adults aged 18 to 70 years.

Seronegative and seropositive subjects received 3 intramuscular injections of either the 30 µg or 60 µg adjuvanted formulations of the mv rOspA LB Vaccine at the following intervals:

1st Vaccination:	Day 1
2nd Vaccination:	Day 29
3rd Vaccination:	Day 57
Booster Vaccination:	Day 181 or Day 271-365

[i] Study arm 6 was not selected for the booster vaccination based on the reactogenicity profile observed after the first vaccination.

Subjects returned to the study site for follow-up visits 28 days after the first, second and third vaccination. At Day 181, all subjects were randomized to receive a booster vaccination either at 6 months or at 9 to 12 months after the first vaccination. All subjects were to return to the study site for a follow-up visit 28 and 180 days after the booster vaccination visit.

Study Arm	Cohort	Subjects (18-70 yrs)	Total N	Dosage (µg)	Formulation [$Al(OH)_3$] [a]	N (Booster)	Booster (month)
1	4	Seronegative	100	30	+	50	6
						50	9 - 12
	5	Seropositive	75	30	+	37	6
						37	9 - 12
3	4	Seronegative	100	60	+	50	6
						50	9 - 12
	5	Seropositive	75	60	+	37	6
						37	9 - 12
	Total		**350**				

[a] aluminum hydroxide, + with $Al(OH)_3$

Section 3:

Based on the safety and immunogenicity results obtained in Section 1 and Section 2 the 60 µg adjuvanted formulation was selected for further evaluation of the optimal booster interval and investigation of antibody persistence.

In Section 3 of the study, approximately 87 subjects who were randomized to the 9-12 month booster group continued their participation. Section 3 was conducted open-label.

Seronegative and seropositive subjects who received the 60 µg adjuvanted formulation of the mv rOspA LB Vaccine as 3-dose primary vaccination and as a booster vaccination at 9-12-months in previous study parts, continued participation in the study.

Study Arm	Group	Subjects[b] (18-70 yrs)	N	Dosage (µg)	Formulation [$Al(OH)_3$]	Antibody Persistence (Month)
3	9-12M[a]	Cohort 4	50	60	+	24, 27
		Cohort 5	37			
	Total		**87**			

[a] Subjects having received a 9-12-month booster in Section 2;
[b] details on Cohorts see Section 2;
+ with aluminum hydroxide

	Subjects in the 9-12 month booster group returned to the study site for a follow-up visit at approximately Month 24 (i.e. in November 2013) and Month 27 (i.e. in February 2014) for evaluation of antibody persistence. The study has been conducted in 10 parts: Part A was completed once all subjects in cohorts 1, 2 and 3 had received the primary vaccination series including the first, second and third vaccination and the study visit 28 days after the third vaccination (Visit 8; Day 85). Part B started with the end of Part A and was completed once all subjects in cohorts 1, 2 and 3 had attended the visit approximately 9 months after the first vaccination (Visit 10; Day 271). Part C started with the booster vaccination of subjects in selected study arms from Section 1 of the study 9 to 12 months after the first vaccination and was completed approximately 28 days after the booster vaccination (Visit 12). Part D started with the end of Part C and was completed approximately 6 months after the booster vaccination (Visit 13). Part E started once a final evaluation of safety and immunogenicity data from Part A was available and was completed once all subjects in Cohorts 4 and 5 received the primary vaccination series including the first, second and third vaccination and the study visit 28 days after the third vaccination (Day 85). Part F started with the end of Part E and was completed when all subjects in cohorts 4 and 5 randomized to receive the 6 month booster at Day 181 received this vaccination and completed the follow up visit 28 days later. For subjects randomized to receive the 9-12 months booster vaccination, Part F ended with the randomization visit. Part G, started with the end of Part F and was completed once all subjects in cohorts 4 and 5 who were randomized to receive the 9- to 12-month booster vaccination had the booster vaccination visit (Day 271-Day 365) and the follow-up visit 28 days after the booster. Part H; started with the end of Part F or Part G, as applicable, and was completed once all subjects in Cohorts 4 and 5 had completed the follow-up visit 6 months after either booster vaccination. Part I started with Visit 12 and was completed once all subjects in the 9-12-month booster group have completed the follow-up visit (Visit 12). Part J started with the end of Part I and was completed once all subjects in the 9-12 month booster group completed the final follow-up visit (Visit 13). Individual study parts are analyzed separately. Clinical study reports for the other study parts may be combined depending on data availability.

CRITERIA FOR EVALUATION

Immunogenicity:

Primary Immunogenicity Outcome: The primary immunogenicity endpoint is the antibody response determined 28 days after the third vaccination to each of the six rOspA serotypes contained in the vaccine, which is relevant only for Study Parts A and E and is not applicable for Study Parts I or J

Secondary Immunogenicity Outcome(s): The following endpoints were determined for each of the 6 rOspA serotypes contained in the vaccine:

- Antibody response 12 & 15 months after the booster vaccination;
- Fold increase in antibody titer compared to baseline determined 12 & 15 months after the booster vaccination;
- Seroconversion rate (at least 4-fold increase of each rOspA type-specific IgG titer) as compared to baseline determined 12 & 15 months after the booster vaccination.

Safety:

Primary Safety Outcome: The primary safety endpoint is the frequency and severity of injection site and systemic reactions within 7 days after each vaccination, this is applicable to Study Parts A, C, E, F and G only and is not applicable to Study Parts I & J.

Secondary Safety Outcome(s): The secondary safety endpoint is the frequency and severity of adverse events (AEs) observed during the entire study period. For Study Parts I & J, this is the period after Visit 11 (6 months after the booster) up to and including Visit 13 (15 months after the booster)

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION, AND BATCH NUMBER

Investigational Product(s)	Multivalent recombinant OspA Lyme Borreliosis Vaccine (mv rOspA LB Vaccine) containing three chimeric OspA molecules comprising the protective portions from two different OspA antigens: • rOspA 1/2 (*B. burgdorferi s.s* OspA type 1 combined with *B. afzelii* OspA type 2), • rOspA 6/4 (*B. garinii* OspA serotype 6, with *B. bavariensis* OspA serotype 4); • rOspA 5/3 (*B. garinii* OspA serotype 5 combined with OspA serotype 3). One dose of the mv rOspA LB Vaccine contains 30, 60 or 90 µg protein in either an aluminum hydroxide [$Al(OH)_3$] adjuvanted or non-adjuvanted formulation. **Dosage form**: Suspension for injection **Dosage frequency**: Three vaccinations at 4-week intervals (Day 1, 29 and 57) and a booster vaccination 6 months or 9 to 12 months after the first vaccination **Mode of Administration:** Intramuscular *(musculus deltoideus)* **Batch number(s):** [redacted]

Placebo/ Control/ Comparator	None.
Duration of treatment:	For Study Parts A to D: 19 months from first vaccination to 6 months after the booster vaccination (9–12 months). For Study Parts E to J: approximately 27 months from first vaccination to 15 months after the booster vaccination (administered at 6 or 9–12 months). Duration of entire study Parts A to J: 3 years.
SUBJECT SELECTION	
Planned	Total 650 Section 1: 300 (seronegative subjects, cohorts 1, 2 and 3) Section 2: 350 (199 seronegative subjects in cohort 4 and 151 seropositive subjects in cohort 5) Section 3: 73 (40 seronegative subjects in cohort 4 and 33 seropositive subjects in cohort 5)
Analyzed	33 seronegative and 31 seropositive who received the 9-12 month booster vaccination with the 60 µg adjuvanted mv rOspA LB Vaccine dose and attended the visit on Day 181 post booster.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	

Inclusion Criteria:

Subjects who meet **ALL** of the following criteria are eligible for this study:

- Subject is 18 to 70[ii] years old at the time of screening.
- Subject has an understanding of the study, agrees to its provisions, and gives written informed consent prior to study entry;
- Subject is generally healthy[iii], as determined by the Investigator's clinical judgment through collection of medical history and the performance of a physical examination;
- Subject is physically and mentally capable of participating in the study and willing to adhere to study procedures;
- Subject agrees to keep a daily record of symptoms for the duration of the study;
- If female of childbearing potential, presents with a negative urine pregnancy test, and agrees to employ adequate birth control measures for the duration of the study.

[ii] From the 18th birthday to the last day before the 71st birthday

[iii] Subjects are considered ***generally healthy*** if they have no active disease (acute illness, exacerbation of a chronic condition or a chronic – progressive illness) which requires treatment and/or follow-up other than controlled, Stage I hypertension, or a disease that is identified as an exclusion criterion.

Additional inclusion criterion for subjects in Cohort 5 only:

- Subject is seropositive for *Borrelia burgdorferi* sensu lato (s.l.) antibodies at study entry

Exclusion Criteria

Subjects who meet **ANY** of the following criteria are **NOT** eligible for this study:

- Subject has a physician-diagnosed chronic illness related to LB or active LB;
- Subject has been treated for LB with antibiotics within 3 months of study entry.
- Subject had a tick bite within 3 weeks prior to screening or first vaccination[iv];
- Subject has a history or active infection with *Babesia microtii* (babesiosis) or Anaplasma phagocytophilum (ehrlichiosis);
- Subject currently has or has a history of significant cardiovascular, respiratory (including asthma), metabolic, neurological, hepatic, rheumatic, autoimmune, hematological, gastrointestinal or renal disorder[v];
- Subject has clinically significant abnormal laboratory values at screening[vi];
- Subject currently has or has a history of immunodeficiency;
- Subject tests positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV)[vii];
- Subject has a disease or is currently undergoing a form of treatment or was undergoing a form of treatment within 30 days prior to study entry that could be expected to influence immune response. Such treatment includes, but is not limited to: systemic or high dose inhaled (>800 µg/day of beclomethasone dipropionate or equivalent) corticosteroids, radiation treatment, or other immunosuppressive or cytotoxic drugs;
- Subject has a history of anaphylaxis or severe allergic reactions;
- Subject has a rash, dermatologic condition or tattoos which might interfere with injection site reaction rating;
- Subject has a body mass index > 35.0;
- Subject has received any blood products or immunoglobulins within 90 days prior to vaccination in this study;
- Subject has donated blood or plasma within 30 days prior to vaccination in this study;
- Subject has received any live vaccine within 4 weeks or inactivated vaccine within 2 weeks prior to vaccination in this study[iv];

[iv] Subjects may be re-screened at a later date and vaccinated after an appropriate interval.

[v] A significant disorder is defined as a disease or medical condition associated with impaired health status, increased risk for complications, requiring medical treatment and/or follow-up.

[vi] **NOTE**: a 1.5 fold or greater increase over the upper limit of normal (ULN) for ALT and AST, and a value of > 1.5 mg/dl for creatinine is considered clinically significant.
Furthermore, any laboratory parameters included in the FDA toxicity grading scale and graded as moderate or higher are to be considered clinically significant. Clinical significance of all other laboratory parameters will be evaluated by the investigator using his/her clinical expertise and judgment**.**

[vii] For subjects in Cohort 1 for whom the original exclusion criterion "*Subject has a history of testing positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV). No confirmatory testing for previous infection with these viruses will be conducted as part of this study*" is applicable, testing will be performed at a later time point upon implementation of Amendment 2.

- Subject has functional or surgical asplenia;
- Subject has a known or suspected problem with alcohol or drug abuse;
- Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study;
- Subject is pregnant or lactating at the time of study enrollment;
- Subject is a member of the team conducting the study or in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees of the Investigator or site personnel conducting the study.

Additional exclusion criteria for subjects in Cohorts 1, 2, 3 and 4:

- Subject is seropositive for *Borrelia burgdorferi s.l.* antibodies at study entry.[viii]

Eligibility Criteria for the Booster Vaccination

Subjects who meet **ALL** of the following criteria are eligible for the **booster** vaccination:

- Subject completed Part A (for subjects in Section 1) or Part E (for subjects in Section 2) of the study per protocol;
- Subject is generally healthy[ix], as determined by the Investigator's clinical judgment through collection of medical history and the performance of a physical examination.

Subjects who meet **ANY** of the following criteria are **NOT** eligible for the **booster** vaccination:

- Subject has developed a physician-diagnosed chronic illness related to LB or active LB since the third vaccination (for subjects in Section 1 and Section 2);
- Subject has a disease or is undergoing a form of treatment or was undergoing a form of treatment within 30 days prior to the booster vaccination that can be expected to influence immune response. Such treatment includes, but is not limited to, systemic or high dose inhaled (> 800 µg/day of beclomethasone dipropionate or equivalent), corticosteroids, radiation treatment or other immunosuppressive or cytotoxic drugs;
- Subject has developed an allergic reaction to a component of the vaccine since the third vaccination (for subjects in Section 1 and Section 2);
- Subject is pregnant or lactating at the time of booster vaccination;
- Subject has received any blood products or immunoglobulins within 90 days prior to the booster vaccination;
- Subject has received any live vaccine within 4 weeks or inactivated vaccine within 2 weeks prior to the booster vaccination;
- Subject has donated blood or plasma within 30 days prior to vaccination in this study;
- Subject has undergone a splenectomy since the third vaccination (for subjects in Section 1 and Section 2).

[viii] For subjects with a borderline result the test shall be repeated. If the second test confirms a borderline result, the subject shall be excluded.

[ix] For subjects in Section 1 and 2: Subjects are considered ***generally healthy*** if they have no active disease (acute illness, exacerbation of a chronic condition or a chronic – progressive illness) which requires treatment and/or follow-up other than controlled, Stage I hypertension, or a disease that is identified as an exclusion criterion.

Delay Criteria for Vaccination

- Subject has an acute illness with or without elevated body temperature (≥38.0 °C) within 3 days prior to the scheduled vaccination. Subjects may be rescheduled for vaccination at a later date provided that the illness has resolved (body temperature < 38.0 °C).
- Subject has received antipyretics within 4 hours prior to the scheduled time of vaccination. In this case the vaccination should be performed at a later date.
- Subject had a tick bite within 3 weeks prior to the second, third or booster vaccination. Subject may be rescheduled for vaccination 3 weeks after the tick bite.

In addition, the following criteria must be met:

1) For a rescheduled **first** vaccination:
   - All other inclusion/exclusion criteria are met;
   - The rescheduled visit is within the specified time window for the first vaccination visit.

   In case not all of these criteria are met, the subject will be excluded from the study.
2) For a rescheduled **second** or **third** vaccination:
   - The rescheduled visit should be within the specified time window for the respective visit.
3) For a rescheduled **booster** vaccination:
   - All eligibility criteria are met and
   - The re-scheduled visit should be within the specified time window for the respective visit.

   For subjects in Section 1 and Section 2, if the time window for the second, third or booster vaccination cannot be met, the subject may still be vaccinated but deviation from protocol specified procedures must be properly annotated.

STATISTICAL METHODS

Section 1: Approximately 50 subjects per study group were planned to be enrolled into the study (Parts A to D). With this sample size a specific study group has a 92% chance of detecting at least one AE that has a prevalence of 1:20. When the study groups with all doses of the adjuvanted or non-adjuvanted formulations are combined, a sample size of 300 subjects has a 95% chance of detecting at least one AE that occurs with a frequency of 1:100.

Due to the lack of any previous data to assess the magnitude and the variance of the expected immune response to the vaccine the power of the immunogenicity analysis could not be evaluated.

Assuming a drop-out rate of around 10%, approximately 45 subjects per study group are available for immunogenicity evaluation. With 45 subjects the 90% C.I. of the seroconversion rates extends no more than 12.0% from the observed rates if these are approximately 90%. If an observed rate lies approximately at 80%, the 90% confidence interval extends no more than 12.3% from the observed rate.

Section 2: Assuming a drop-out rate of around 10%, approximately 135 seronegative subjects per study group are available for immunogenicity evaluation (Parts E to H). With 135 subjects, the 90% C.I. of the seroconversion rates extends no more than 5.7% from the observed rates if these are approximately 90%. If an observed rate lies approximately at 80%, the 90% confidence interval extends no more than 6.5% from the observed rate.

Assuming a drop-out rate of around 10%, approximately 67 seropositive subjects per study group are available for immunogenicity evaluation (Parts E to H). With 67 subjects, the 90% C.I. of the seroconversion rates extends no more than 8.7% from the observed rates if these are approximately 90%. If an observed rate lies approximately at 80%, the 90% confidence interval extends no more than 10.7% from the observed rate.

Planned Statistical Analysis

Point estimates and their 90% CI are assessed.

Analysis of primary immunogenicity endpoint:

The primary immunogenicity endpoint is the immune response measured 28 days after the third vaccination. This is relevant only for Study Parts A and E and is not applicable for Study Parts I & J.

Analysis of primary safety endpoint:

The primary safety endpoint is the frequency and severity of injection site and systemic reactions within 7 days after each vaccination, this is applicable to Study Parts A, C, E, F and G only and is not applicable for Study Parts I & J.

Analysis of secondary endpoints:

Immunogenicity:

For the log-transformed IgG titer response against the 6 OspA serotypes, a longitudinal analysis is performed within a repeated mixed model ANCOVA framework, accounting for the fixed effect of time, logarithmic titer at booster time point and age (years) as covariates and for the random subject effect. Least-square vaccine group means are computed and then back transformed by exponentiation into geometric means.

CIs are interpreted in a descriptive manner and no adjustment for multiplicity is made.

For all secondary immunogenicity endpoints, point estimates are calculated.

The 2-sided 90% exact CI for the proportion of subject with seroconversion are calculated for all treatment groups.

Safety:

All secondary endpoints are analyzed for each study group separately. For each secondary safety endpoint, the proportion of subjects experiencing the respective event are calculated for all treatment groups.

Symptoms of local and systemic AEs observed during the entire study period are presented in summary tables. Summary tables indicate the number and proportion of subjects who experienced local and systemic events.

In addition, tables are prepared to list each AE, the number of subjects in each treatment group who experienced an event at least once, and the proportion of subjects with AE(s). AEs are grouped by system organ class. Each event is then divided into defined severity grades (mild, moderate, severe). The tables also divide the AEs into those considered at least possibly related to vaccination and those considered not related. SAEs are listed separately.

All AEs for each subject, including the same event on several occasions are listed, giving both MedDRA preferred term and the original term used by the Investigator, for duration, severity grade, seriousness, relation to vaccination, date of onset, timing of onset in relation to vaccination. For SAEs, outcome, treatment and relevant medical history are also included.

The listings are categorized by study site and study group.

All analyses of safety data is performed on the safety dataset.

SUMMARY – CONCLUSIONS

Immunogenicity Results:

Primary Immunogenicity Outcome:

The primary immunogenicity endpoint is the antibody response determined 28 days after the third vaccination to each of the six rOspA serotypes contained in the vaccine, this is not applicable for Study Parts I & J. Results of the analysis of the primary immunogenicity endpoints for the subjects in this part of the study are provided in the CSR, for Part E, Version 2012 September 14.

Secondary Immunogenicity Outcome(s):

In Study Parts I & J seropersistence was evaluated in the period from 6 months post booster up to 15 months after the booster vaccination administered 9-12 months after the first vaccination with the mv rOspA LB Vaccine.

Antibody persistence 12 months post booster vaccination (Month 24)

At 12 months post booster vaccination GM antibody titers had decreased, but persisted at levels ranging across OspA serotypes from 1913.4 (OspA-2) to 3164.4 U/mL (OspA-5) in seronegative subjects. Antibody titers remained at levels ranging from 20.7 to 32.7 fold above baseline across serotype. Similarly, seroconversion rates over baseline ranged from 87.1% to 93.5% in seronegative subjects (total population).

Similarly in seropositive subjects, GM antibody titers persisted at levels ranging across OspA serotypes from 2212.7 (OspA-2) to 3309.1 U/mL (OspA-5). Antibody titers remained at levels ranging from 13.4 to 32.0 fold above baseline across serotype. Seroconversion rates over baseline ranged from 74.2% to 93.5% in seropositive subjects (total population).

For the combined cohorts (seronegative and seropositive subjects), at 12 months post booster vaccination GM antibody titers persisted at levels ranging across OspA serotypes from 2057.6 (OspA-2) to 3236.0 U/mL (OspA-5). Antibody titers remained at levels ranging from 16.7 to 32.4 fold above baseline across serotype and seroconversion rates over baseline ranged from 83.9% to 93.5% (total population).

Hence, 12 months post booster vaccination, antibody persisted in seronegative and seropositive subjects and, irrespective of age, a high percentage of subjects retained antibody levels consistent with seroconversion.

Antibody persistence 15 months after the booster vaccination (Month 27)

At 15 months post booster vaccination GM antibody titers had decreased further, but persisted at levels ranging across OspA serotypes from 1117.9 (OspA-6) to 1581.0 U/mL (OspA-4) in seronegative subjects. Antibody titers remained at levels ranging from 12.4 to 17.8 fold above baseline across serotype and seroconversion rates over baseline ranged from 86.2% to 96.6% in seronegative subjects (total population).

In seropositive subjects, GM antibody titers persisted at levels ranging across OspA serotypes from 1279.4 (OspA-1) to 1829.7 U/mL (OspA-4). Antibody titers remained at levels ranging from 8.7 to 15.3 fold above baseline across serotype and seroconversion rates over baseline ranged from 61.3% to 93.5% in seropositive subjects (total population).

For the combined cohorts (seronegative and seropositive subjects), at 15 months post booster vaccination GM antibody titers persisted at levels ranging across OspA serotypes from 1226.7 (OspA-1 and OspA-6) to 1705.0 U/mL (OspA-4). Antibody titers remained at levels ranging from 11.2 to 16.2 fold above baseline across serotype and seroconversion rates over baseline ranged from 76.7% to 91.7% (total population).

Hence, antibody titers decreased further 15 months post booster vaccination, however antibody persisted in seronegative and seropositive subjects and, irrespective of age, a high percentage of subjects retained antibody levels consistent with seroconversion.

Analysis of covariance (repeated mixed model ANCOVA) of data post booster vaccination showed a significant effect of time, with antibody responses (for all OspA serotypes) significantly higher at peak titer (29 days after the booster vaccination) in seronegative and seropositive subjects than 15 months post booster. Although titers decreased at each successive time point measured post booster, the decrease was gradual and there were considerable overlaps in confidence intervals between Day 181 post booster and Month 24, and between Month 24 and Month 27.

In conclusion, 12 and 15 months after the administration of a booster vaccination 9-12 months after the first vaccination, persistence of antibody against all six OspA serotypes was demonstrated in seronegative and seropositive subjects vaccinated with the 60 µg alum-adjuvanted vaccine dose. At 12 and 15 months post booster, antibody persisted at comparable levels in seronegative and seropositive subjects. Seroconversion rates greater than 76.7% against all six OspA serotypes were obtained 15 months post booster.

Safety Results:

Primary Safety Outcome

The primary safety endpoint is the frequency and severity of injection site and systemic reactions within 7 days after each vaccination, this is applicable to Study Parts A, C, E, F and G only and is not applicable for Study Parts I & J.

Secondary Safety Outcome(s)

Study Parts I & J covered the period from 6 months to 15 months after the booster vaccination administered 9-12 months after the primary vaccination series with the 60 µg adjuvanted dose formulation of the mv rOspA LB Vaccine. No investigational product was administered during the study period evaluated.
No deaths, no SAEs, no related non serious systemic or local AEs occurred during study Parts I & J. No vaccine-related arthritis or symptoms suggesting LB were reported during the study period.

Non-serious systemic AEs were reported in 9 seronegative subjects and 5 seropositive subjects, all of which were assessed as not related to vaccination by the Investigator. Most non-serious systemic AEs were mild or moderate and the majority resolved within 24 days or less.

Conclusion:

The mv rOspA LB Vaccine was safe and immunogenic in healthy seronegative and seropositive adults aged 18 to 70 years and antibody titers against all six rOspA serotypes persisted 12 and 15 months after a booster vaccination administered 9-12 months after the first vaccination with the 60 µg antigen dose in an adjuvanted formulation.

On the basis of the immunogenicity and safety data, the following conclusions can be made:

- The vaccine was well tolerated in seronegative and seropositive subjects.
- Antibody persisted in seronegative and seropositive subjects 12 and 15 months after the booster administered 9-12 months after the first vaccination.
- At 12 and 15 months post booster vaccination, GM antibody titers across the 6 OspA serotypes persisted at comparable levels in seronegative and seropositive subjects.
- Seroconversion levels close to 100% against all six OspA serotypes were obtained for seronegative and seropositive subjects 12 and 15 months after the booster vaccination (Month 24 and Month 27 respectively).
- Study 730901 has demonstrated the safety and efficacy of Baxter's mv rOspA vaccine, which has the potential to be an important tool in mitigating the growing effect of LB in Europe and the US.

Date of Report: 2014 June 23