Clinical trial results:
A Phase 3 randomized, double-blind, placebo-controlled study of SHB004 (10% topical azithromycin) administered locally twice daily for three consecutive days for the prevention of Borreliosis in subjects bitten by a tick.

Summary

EudraCT number	2011-000117-39
Trial protocol	DE AT
Global end of trial date	03 December 2012

Results information

Result version number	v1 (current)
This version publication date	28 August 2016
First version publication date	28 August 2016

Trial information

Trial identification

Sponsor protocol code	A2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ixodes AG
Sponsor organisation address	Geissacher 10 , Zumikon, Switzerland, 8126
Public contact	Mr. Luzi von Bidder, Ixodes AG, ixodes@bluewin.ch
Scientific contact	Dr. Gustave Huber, Ixodes AG, gustave.huber@bluewin.ch

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2012
Global end of trial reached?	Yes
Global end of trial date	03 December 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate a reduction in the rate of treatment failure within the ITT set at Day 57 by at least 50% in response to SHB004 (10% topical azithromycin) administered locally within four calendar days after the tick bite had been first noticed, twice daily for three consecutive days, as compared to placebo. Treatment failure is defined as seroconversion (IgM and/or IgG) and / or appearance of erythema migrans throughout the study in baseline-seronegative (IgM and IgG) subjects. Subjects experiencing an additional tick bite are not counted as treatment failure unless they experience an erythema migrans occurring before the additional tick bite.

Protection of trial subjects:

Patients were monitored throughout participation in the study for occurrence of adverse events after drug administration.

Background therapy:

Medications necessary for the wellbeing of a patient were permitted except for:
- Immunomodulatory drugs
- Cytostatics;
- Systemic steroids
- Any kind of systemic antibiotics or antibiotics applied topically to the site of the tick bite.

Evidence for comparator:

Placebo. No topical product for treating Borrelia infection which could have been used as active comparator in the trial was available.

Actual start date of recruitment	07 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 255
Country: Number of subjects enrolled	Germany: 1118
Worldwide total number of subjects	1373
EEA total number of subjects	1373

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1190
From 65 to 84 years	183
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients bitten by a tick (single bite) were enrolled who had such tick collected, and who were able to receive the first treatment administration at the latest on the 4th calendar day from the day the tick bite was first noticed.

Pre-assignment

Screening details:

Visit 1 was the screening and baseline visit and included informed consent, tick collection, screening assessments and first study drug administration.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The placebo has the same appearance as the IMP. Patients were assigned to a treatment group based on a randomization list.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active treatment

Arm description:

Subjects completing study drug application and Day 7 and Day 30 Visits. The IMP was applied topically twice a day (once in the morning and once in the evening, 12 hours apart; time window of ±2 hours) for 3 consecutive days.

Arm type	Experimental
Investigational medicinal product name	10% topical azithromycin
Investigational medicinal product code	SHB004
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

Application twice a day (once in the morning and once in the evening, 12 hours apart; time window of ±2 hours) for 3 consecutive days

Arm title	Placebo

Arm description:

Subjects completing study drug application and Day 7 and Day 30 Visits. Placebo was applied topically twice a day (once in the morning and once in the evening, 12 hours apart; time window of ±2 hours) for 3 consecutive days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

Placebo gel was applied topically twice a day (once in the morning and once in the evening, 12 hours... more apart; time window of ±2 hours) for 3 consecutive days.

Number of subjects in period 1	Active treatment	Placebo
Started	687	686
Completed	637	645
Not completed	50	41
prohibited medication	18	20
Consent withdrawn by subject	3	3
New disease	-	1
Skin tolerance score >=3	1	3
Lyme disease	9	6
Pregnancy	-	1
Blind broken	1	1
Not defined	3	3
Lost to follow-up	3	1
Protocol deviation	12	2

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
All patients screened.	

Reporting group values	Baseline	Total	
Number of subjects	1373	1373	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	45.5		
standard deviation	± 15.42	-	
Gender categorical Units: Subjects			
Female	681	681	
Male	692	692	

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects following the principle of ITT. Subjects were included in the analysis according to the treatment to which they were randomized. Subjects for whom another tick bite (confirmed by the investigator) was reported at any time during the study were excluded from the ITT set.	
Subject analysis set title	All subjects randomized
Subject analysis set type	Full analysis
Subject analysis set description:	
Randomized patients whether they received study medication or not.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of study medication.	
Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized subjects who:
- were compliant with the study protocol
- were bitten by a positive tick and who were seronegative at baseline.
Subject presenting any of the following were excluded from the PP set:
- failure to meet the inclusion and exclusion criteria
- major protocol violations as determined by the investigator / medical review (performed at a blind data review meeting prior to database lock).
- non-compliance for study medication. The minimum number of doses required to be considered for the PP population was 4. The number of maximum doses received to remain in the PP population was 7.

Subject analysis set title	Modified ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

As ITT but defined based on isolated IgM seroconversion or isolated IgG seroconversion.

Reporting group values	ITT	All subjects randomized	Safety set
Number of subjects	995	1371	1371
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	44	45.5	45.5
standard deviation	± 15.03	± 15.42	± 15.42
Gender categorical Units: Subjects			
Female	510	681	681
Male	485	690	690

Reporting group values	PP	Modified ITT	
Number of subjects	134	995	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous Units: years			
arithmetic mean	44.6	44	
standard deviation	± 16.76	± 15.03	
Gender categorical Units: Subjects			
Female	74	510	
Male	60	485	

End points

End points reporting groups

Reporting group title	Active treatment

Reporting group description:

Subjects completing study drug application and Day 7 and Day 30 Visits. The IMP was applied topically twice a day (once in the morning and once in the evening, 12 hours apart; time window of ±2 hours) for 3 consecutive days.

Reporting group title	Placebo

Reporting group description:

Subjects completing study drug application and Day 7 and Day 30 Visits. Placebo was applied topically twice a day (once in the morning and once in the evening, 12 hours apart; time window of ±2 hours) for 3 consecutive days.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects following the principle of ITT. Subjects were included in the analysis according to the treatment to which they were randomized. Subjects for whom another tick bite (confirmed by the investigator) was reported at any time during the study were excluded from the ITT set.

Subject analysis set title	All subjects randomized
Subject analysis set type	Full analysis

Subject analysis set description:

Randomized patients whether they received study medication or not.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of study medication.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized subjects who:
- were compliant with the study protocol
- were bitten by a positive tick and who were seronegative at baseline.
Subject presenting any of the following were excluded from the PP set:
- failure to meet the inclusion and exclusion criteria
- major protocol violations as determined by the investigator / medical review (performed at a blind data review meeting prior to database lock).
- non-compliance for study medication. The minimum number of doses required to be considered for the PP population was 4. The number of maximum doses received to remain in the PP population was 7.

Subject analysis set title	Modified ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

As ITT but defined based on isolated IgM seroconversion or isolated IgG seroconversion.

Primary: Rate of treatment failures ITT

End point title	Rate of treatment failures ITT

End point description:

Rate of treatment failure at Day 57 (with an allowed time-window of +14 days) in the ITT set.
Treatment failure is defined as seroconversion (IgM and / or IgG) and / or appearance of EM throughout the study in baseline-seronegative (IgM and / or IgG) subjects.

End point type	Primary

End point timeframe:

Determined on Day 57.

End point values	Active treatment	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	505	490	995	
Units: Number of patients	11	11	22	

Statistical analyses

Statistical analysis title	Comparison between treatment arms

Statistical analysis description:

Treatment difference in preventing an infection with Borrelia s.l as measured by treatment failure at Day 57 was determined by an analysis of the proportions (Wald type test statistic, overall 1-sided $\alpha = 0.025$, power = 80%, Pocock efficacy boundaries, futility stop in case of a 1-sided p-value ≥ 0.1587) and repeated confidence intervals for the relative risk (based on Farrington-Manning test).

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.1587
Method	t-test, 1-sided

Secondary: Rate of treatment failures modified ITT

End point title	Rate of treatment failures modified ITT

End point description:

End point type	Secondary

End point timeframe:

Rate of treatment failure at Day 57 (with an allowed time-window of +14 days) in the ITT set. Treatment failure is defined as seroconversion (IgM and/or IgG) and/or appearance of EM throughout the study in baseline-seronegative (IgM and/or IgG) subjects.

End point values	Active treatment	Placebo	Modified ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	505	490	995	
Units: Number of patients	10	8	18	

Statistical analyses

Statistical analysis title	Difference between geoups
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6595
Method	t-test, 1-sided
Parameter estimate	Risk ratio (RR)
Point estimate	1.2129
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	3.4735

Secondary: Rate of treatment failures excluding isolated IgM (ITT)	
End point title	Rate of treatment failures excluding isolated IgM (ITT)
End point description:	
End point type	Secondary
End point timeframe:	
End of study	

End point values	Active treatment	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	505	490	995	
Units: Number of patients	10	10	20	

Statistical analyses

Statistical analysis title	Difference between groups
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4728
Method	t-test, 1-sided
Parameter estimate	Risk ratio (RR)
Point estimate	0.9703
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	2.6248

Secondary: Rate of treatment failures excluding isolated IgG (ITT)	
End point title	Rate of treatment failures excluding isolated IgG (ITT)
End point description:	
End point type	Secondary
End point timeframe:	
End of study	

End point values	Active treatment	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	505	490	995	
Units: Number of patients	11	9	20	

Statistical analyses

Statistical analysis title	Difference between groups
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6494
Method	t-test, 1-sided
Parameter estimate	Risk ratio (RR)
Point estimate	1.1859
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	3.2247

Secondary: Rate of treatment failures - All treated patients Set A	
End point title	Rate of treatment failures - All treated patients Set A
End point description:	
All Treated Subjects Set A: Counting drop-outs as TF. Treatment failure defined as seroconversion (IgM and / or IgG) and/ or appearance of erythema migrans throughout the study in baseline-seronegative (IgM and/or IgG) subjects.	
End point type	Secondary
End point timeframe:	
End of study	

End point values	Active treatment	Placebo	All subjects randomized	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	685	686	1371	
Units: Number of patients	55	46	101	

Statistical analyses

Statistical analysis title	Difference between groups
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	1371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8259
Method	t-test, 1-sided
Parameter estimate	Risk ratio (RR)
Point estimate	1.1974
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	1.8725

Secondary: Rate of treatment failures - All treated patients Set B

End point title	Rate of treatment failures - All treated patients Set B

End point description:

All Treated patients but drop-outs are not counted as treatment failures.
Treatment failure defined as seroconversion (IgM and/or IgG) and/or appearance of erythema migrans throughout the study in baseline-seronegative (IgM and / or IgG) subjects.

End point type	Secondary

End point timeframe:

End of study

End point values	Active treatment	Placebo	All subjects randomized	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	685	686	1371	
Units: Number of patients	12	13	25	

Statistical analyses

Statistical analysis title	Difference between groups
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	1371
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4215
Method	t-test, 1-sided
Parameter estimate	Risk ratio (RR)
Point estimate	0.9244
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	2.2696

Secondary: Rate of treatment failures - All treated patients Set C

End point title	Rate of treatment failures - All treated patients Set C
End point description:	
All Treated Set C is identical to All Treated Subjects Set B but patients with an additional tick bite were not counted as treatment failure. Treatment failure defined as seroconversion (IgM and/or IgG) and/or appearance of erythema migrans throughout the study in baseline-seronegative (IgM and/or IgG) subjects.	
End point type	Secondary
End point timeframe:	
End of study	

End point values	Active treatment	Placebo	All subjects randomized	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	685	686	1371	
Units: Number of patients	11	11	22	

Statistical analyses

Statistical analysis title	Difference between groups
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	1371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5014
Method	t-test, 1-sided
Parameter estimate	Risk ratio (RR)
Point estimate	1.0015

Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	2.5995

Other pre-specified: Rate of treatment failures - PP

End point title	Rate of treatment failures - PP

End point description:

End point type	Other pre-specified

End point timeframe:

seroconversion (IgM and/or IgG) and/or appearance of EM throughout the study in baseline-seronegative (IgM and/or IgG) subjects

End point values	Active treatment	Placebo	PP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	62	72	134	
Units: Number of patients	3	5	8	

Statistical analyses

Statistical analysis title	Difference between groups
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304
Method	t-test, 1-sided
Parameter estimate	Risk ratio (RR)
Point estimate	0.6968
Confidence interval	
level	Other: 80 %
sides	1-sided
upper limit	3.1369

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Whole duration of study	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1
Reporting groups	
Reporting group title	Active drug (IMP)
Reporting group description: Patients receiving the IMP	
Reporting group title	Placebo
Reporting group description: Patients receiving matching placebo	

Serious adverse events	Active drug (IMP)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 685 (0.44%)	8 / 686 (1.17%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents	Additional description: Fentanyl intoxication		

subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine	Additional description: Tension headache		
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
abortion			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Active drug (IMP)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	178 / 685 (25.99%)	175 / 686 (25.51%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibrous histiocytoma			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Metastasis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Pituitary tumour benign			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Prostate cancer			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	0 / 685 (0.00%)	3 / 686 (0.44%)	
occurrences (all)	0	3	
Hypotension			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Venous insufficiency			

subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Dental care			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Dental operation			
subjects affected / exposed	2 / 685 (0.29%)	0 / 686 (0.00%)	
occurrences (all)	2	0	
Tooth extraction			
subjects affected / exposed	1 / 685 (0.15%)	2 / 686 (0.29%)	
occurrences (all)	1	2	
Wisdom teeth removal			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Administration site reaction			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Application site dryness			
subjects affected / exposed	2 / 685 (0.29%)	0 / 686 (0.00%)	
occurrences (all)	2	0	
Application site eczema			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Application site erythema			
subjects affected / exposed	2 / 685 (0.29%)	2 / 686 (0.29%)	
occurrences (all)	2	2	
Application site pruritus			
subjects affected / exposed	5 / 685 (0.73%)	3 / 686 (0.44%)	
occurrences (all)	5	3	
Fatigue			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Feeling cold			

subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
influenza like illness			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Local reaction			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Local swelling			
subjects affected / exposed	2 / 685 (0.29%)	2 / 686 (0.29%)	
occurrences (all)	2	13	
Oedema peripheral			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	4 / 685 (0.58%)	4 / 686 (0.58%)	
occurrences (all)	4	4	
Secretion discharge			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Thirst			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	2 / 685 (0.29%)	1 / 686 (0.15%)	
occurrences (all)	2	1	
allergy to arthopod sting			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Allergy to plants			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Behcet's syndrome			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	

Seasonal allergy			
subjects affected / exposed	1 / 685 (0.15%)	3 / 686 (0.44%)	
occurrences (all)	1	3	
Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Breast inflammation			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed	2 / 685 (0.29%)	2 / 686 (0.29%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Allergic respiratory disease			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	2 / 685 (0.29%)	1 / 686 (0.15%)	
occurrences (all)	2	2	
Dysphonia			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	6 / 685 (0.88%)	3 / 686 (0.44%)	
occurrences (all)	6	3	
Rhinorrhoea			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Throat irritation			

subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	2 / 685 (0.29%)	0 / 686 (0.00%)	
occurrences (all)	3	0	
Tension			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	2 / 685 (0.29%)	0 / 686 (0.00%)	
occurrences (all)	2	0	
Arthropod bite			
subjects affected / exposed	1 / 685 (0.15%)	6 / 686 (0.87%)	
occurrences (all)	1	7	
Arthropod sting			
subjects affected / exposed	3 / 685 (0.44%)	4 / 686 (0.58%)	
occurrences (all)	3	4	
Contusion			
subjects affected / exposed	0 / 685 (0.00%)	2 / 686 (0.29%)	
occurrences (all)	0	2	
Excoriation			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	2	
Foot fracture			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Joint dislocation			

subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Joint injury			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Joint sprain			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Muscle strain			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Procedural nausea			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	2 / 685 (0.29%)	1 / 686 (0.15%)	
occurrences (all)	2	1	
Sports injury			
subjects affected / exposed	2 / 685 (0.29%)	0 / 686 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Tachyarrhythmia			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	

Nervous system disorders			
Anaesthesia			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Burning sensation			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Depressed level of consciousness			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	37 / 685 (5.40%)	38 / 686 (5.54%)	
occurrences (all)	48	51	
Migraine			
subjects affected / exposed	3 / 685 (0.44%)	0 / 686 (0.00%)	
occurrences (all)	3	0	
Paraesthesia			
subjects affected / exposed	0 / 685 (0.00%)	2 / 686 (0.29%)	
occurrences (all)	0	2	
Sciatica			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	3 / 685 (0.44%)	0 / 686 (0.00%)	
occurrences (all)	3	0	
Eye disorders			

Conjunctivitis			
subjects affected / exposed	2 / 685 (0.29%)	0 / 686 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis allergic			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	3	
Eye irritation			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 685 (0.00%)	2 / 686 (0.29%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	7 / 685 (1.02%)	3 / 686 (0.44%)	
occurrences (all)	7	3	
Gastritis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 685 (0.00%)	2 / 686 (0.29%)	
occurrences (all)	0	2	
Periodontitis			
subjects affected / exposed	0 / 685 (0.00%)	2 / 686 (0.29%)	
occurrences (all)	0	2	
Stomatitis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Toothache			

subjects affected / exposed	3 / 685 (0.44%)	2 / 686 (0.29%)	
occurrences (all)	3	2	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	0 / 685 (0.00%)	2 / 686 (0.29%)	
occurrences (all)	0	2	
Eczema			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	6 / 685 (0.88%)	3 / 686 (0.44%)	
occurrences (all)	6	3	
Granuloma annulare			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Pityriasis rosea			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	14 / 685 (2.04%)	11 / 686 (1.60%)	
occurrences (all)	14	13	
Rash			

subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Skin discolouration			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Skin reaction			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	2 / 685 (0.29%)	0 / 686 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Hyperthyroidism			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Ankle deformity			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	8 / 685 (1.17%)	4 / 686 (0.58%)	
occurrences (all)	8	7	
Arthritis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Back pain			

subjects affected / exposed	2 / 685 (0.29%)	5 / 686 (0.73%)	
occurrences (all)	2	7	
Bursitis			
subjects affected / exposed	0 / 685 (0.00%)	2 / 686 (0.29%)	
occurrences (all)	0	2	
Intervertebral disc protrusion			
subjects affected / exposed	3 / 685 (0.44%)	0 / 686 (0.00%)	
occurrences (all)	3	0	
Morphoea			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	2 / 685 (0.29%)	1 / 686 (0.15%)	
occurrences (all)	2	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	2 / 685 (0.29%)	0 / 686 (0.00%)	
occurrences (all)	3	0	
Myalgia			
subjects affected / exposed	1 / 685 (0.15%)	3 / 686 (0.44%)	
occurrences (all)	1	3	
Neck pain			
subjects affected / exposed	0 / 685 (0.00%)	2 / 686 (0.29%)	
occurrences (all)	0	2	
Osteoarthritis			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	2 / 685 (0.29%)	2 / 686 (0.29%)	
occurrences (all)	2	2	
Tendonitis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Tenosynovitis			

subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Trigger finger			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Abscess jaw			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Bronchitis			
subjects affected / exposed	2 / 685 (0.29%)	3 / 686 (0.44%)	
occurrences (all)	2	3	
Bronchopneumonia			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 685 (0.15%)	4 / 686 (0.58%)	
occurrences (all)	1	4	
Diverticulitis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Erythema migrans			
subjects affected / exposed	10 / 685 (1.46%)	8 / 686 (1.17%)	
occurrences (all)	11	9	
Eye infection			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Fungal skin infection			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	

Gastroenteritis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal infection			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Genital herpes			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Genital infection fungal			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 685 (0.00%)	4 / 686 (0.58%)	
occurrences (all)	0	4	
Laryngitis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	32 / 685 (4.67%)	37 / 686 (5.39%)	
occurrences (all)	32	39	
Oral candidiasis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	1 / 685 (0.15%)	4 / 686 (0.58%)	
occurrences (all)	1	5	
Otitis externa			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Pertussis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	

Pharyngitis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 685 (0.15%)	1 / 686 (0.15%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	3 / 685 (0.44%)	3 / 686 (0.44%)	
occurrences (all)	3	4	
Skin infection			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Tinea pedis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Tinea versicolour			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	2 / 685 (0.29%)	1 / 686 (0.15%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	

Vaginal infection			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 685 (0.15%)	0 / 686 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 685 (0.00%)	1 / 686 (0.15%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2011	Details on inclusion and exclusion criteria: Only subjects with known active infectious mononucleosis were excluded, not those reporting a past infection (exclusion criterion #4). Exclusion criterion #10 was reworded to history of "one or more" tick bites (instead of "tick bites") within the last 60 days (to clarify that just one tick bite in the history was sufficient to exclude the subject). Subjects must be withdrawn if they develop Lyme Disease /Borreliosis. Furthermore, it was detailed, that patients received the necessary therapy in case they developed Lyme Disease / Borreliosis. The statistical aspects of the study were detailed to fully comply with the confirmatory character of this phase III study. A detailed description of the adaptive interim assessment was added. The sample size was re-calculated according to the three stage group sequential design (two interim analyses and one final analysis).
03 August 2011	Definition of the primary endpoint was clarified. A new secondary efficacy endpoint was introduced based on seroconversion as measured by (i) IgM or (ii) IgM and IgG or (iii) IgM and IgG and appearance of EM in baseline-seronegative subjects. Efficacy analysis is only conducted on IgM and / or IgG baseline-seronegative subjects. Secondary efficacy analysis 1 will be performed for all treated subjects, the modified ITT and PP sets on the primary efficacy endpoint (rate of treatment failures at Day 57) and will include the same analyses as for the primary efficacy Analysis. Secondary efficacy analysis 2 will check for the reduction in the rate of seroconversion as demonstrated by (i) IgM seroconversion only, (ii) IgM and IgG seroconversion and (iii) IgM and IgG seroconversion and appearance of EM in the All Treated Subjects, ITT, modified ITT and PP set, respectively. The testing procedure will be the same as for the primary efficacy endpoint. Note that (i), (ii) and (iii) are secondary alternatives for the definition of treatment failures. The previous version did not allow entry for subjects with a skin reaction at the tick bite scored at 2 or higher than 2 . However, after having enrolled approximately 300 subjects in 2011, it was recognized, that this criterion prevented several subjects from participation, as their skin reaction to the tick bite scored '2'. Missing data conventions were updated. Changes in statistical section of the study protocol.

28 November 2012	The protocol stated, that the analysis of treatment failures based on seroconversion should be according to MIQ 12 (MiQ12 (2000). Lyme-Borreliose by B. Wilske, L. Zöller, V. Brade, H. Eiffert, U. B. Göbel, G. Stanek). However, the MIQ was not correctly reflected in the previous version and this is corrected accordingly. The previous protocol failed to count IgM based seroconversion as Treatment Failure (TF) and this is corrected. In the previous version of the protocol, the IDMC was responsible to decide on doubtful cases of treatment failures (TF) and agree if the doubtful case is to be counted as TF or not. This is only detailed in this protocol to ensure, that the current MIQ (see above) is reflected. The protocol is particularly pointing the IDMC's attention to cases within which serological results switch from "negative" (deemed as 'negative' by the MIQ; Visit 1) to "borderline" (deemed as 'questionable' by the MIQ; Visit 4). A stricter futility boundary was introduced (futility stop in case of a 1-sided p-value ≥ 0.1587, compared to ≥ 0.5 in protocol version 3), and this boundary is considered as binding. The mITT set was changed. The previous protocol used the serostatus of the index tick to define the mITT set. The new mITT set introduced here is as the ITT set but TF defined on IgM only seroconversion or IgG only seroconversion (e.g. not in combination with an EM) are excluded. Changes to the PP set became necessary accordingly and the Borrelia status of the index tick is integrated within this analysis set. It has been detailed, at which point the second interim analysis analysis is to be conducted. Details on the asymptotic distribution of the test statistic have been added. Determination of sample size: A larger treatment effect is assumed in the sample size calculation (relative risk of 0.4, corresponding to treatment failures rates of 3.1% for placebo and 1.24% for SHB004).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported