Clinical trial results:
Safety of Two Doses of Avaxim® 80U Pediatric (Inactivated Hepatitis A vaccine) Administered 6 Months Apart in Healthy Toddlers, Children and Adolescents Aged 12 Months to 15 Years in China

Summary

EudraCT number	2015-003190-14
Trial protocol	Outside EU/EEA
Global end of trial date	10 October 2014

Results information

Result version number	v1 (current)
This version publication date	17 June 2016
First version publication date	17 June 2016

Trial information

Trial identification

Sponsor protocol code	HAF87

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02011763
WHO universal trial number (UTN)	U1111-1127-7652

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon cedex 07, France, F-69367
Public contact	Responsible Medical Officer, Sanofi Pasteur SA, 33 04 37 37 7384, eric.desauziers@sanofipasteur.com
Scientific contact	Responsible Medical Officer, Sanofi Pasteur SA, 33 04 37 37 7384, eric.desauziers@sanofipasteur.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the safety of Avaxim 80U Pediatric vaccine after each dose of vaccine administered 6 months apart, in subjects aged 12 months to 15 years.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were enrolled and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	06 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 355
Worldwide total number of subjects	355
EEA total number of subjects	0

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)	270
Children (2-11 years)	51
Adolescents (12-17 years)	34
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 06 December 2013 to 11 February 2014 at 1 clinic center in China.

Pre-assignment

Screening details:

A total of 355 subjects who met all inclusion and none of the exclusion criteria were enrolled and vaccinated in this trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Avaxim® 80U Pediatric Group 1

Arm description:

Infants and toddlers (≤ 23 months) received 2 injections of Avaxim® 80U Pediatric vaccine 6 months apart.

Arm type	Experimental
Investigational medicinal product name	Avaxim® 80U Pediatric
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each on Day 0 and Day 180.

Arm title	Avaxim® 80U Pediatric Group 2

Arm description:

Children (aged 2 to 11 years) and adolescents (aged 12 to 15 years) received 2 injections of Avaxim® 80U Pediatric vaccine.

Arm type	Experimental
Investigational medicinal product name	Avaxim® 80U Pediatric
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, 1 injection each on Day 0 and Day 180.

Number of subjects in period 1	Avaxim® 80U Pediatric Group 1	Avaxim® 80U Pediatric Group 2
Started	270	85
Completed	257	75
Not completed	13	10
Consent withdrawn by subject	12	6
Lost to follow-up	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Avaxim® 80U Pediatric Group 1
Reporting group description:	
Infants and toddlers (≤ 23 months) received 2 injections of Avaxim® 80U Pediatric vaccine 6 months apart.	
Reporting group title	Avaxim® 80U Pediatric Group 2
Reporting group description:	
Children (aged 2 to 11 years) and adolescents (aged 12 to 15 years) received 2 injections of Avaxim® 80U Pediatric vaccine.	

Reporting group values	Avaxim® 80U Pediatric Group 1	Avaxim® 80U Pediatric Group 2	Total
Number of subjects	270	85	355
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	270	0	270
Children (2-11 years)	0	51	51
Adolescents (12-17 years)	0	34	34
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	1.6	9.8	
standard deviation	± 0.1	± 3.4	-
Gender categorical			
Units: Subjects			
Female	137	35	172
Male	133	50	183

End points

End points reporting groups

Reporting group title	Avaxim® 80U Pediatric Group 1
Reporting group description:	
Infants and toddlers (≤ 23 months) received 2 injections of Avaxim® 80U Pediatric vaccine 6 months apart.	
Reporting group title	Avaxim® 80U Pediatric Group 2
Reporting group description:	
Children (aged 2 to 11 years) and adolescents (aged 12 to 15 years) received 2 injections of Avaxim® 80U Pediatric vaccine.	

Primary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions After Any Vaccination with AVAXIM™ 80U-Pediatric Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions After Any Vaccination with AVAXIM™ 80U-Pediatric Vaccine[1]

End point description:

Solicited inj. site reactions: Tenderness, Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, Irritability, Headache, Malaise, and Myalgia.
Grade 3 inj. site reactions: Tenderness (≤ 23 months), Cries when injected limb is moved or the movement of the injected limb is reduced; Pain (2 to 11 years), Incapacitating, unable to perform usual activities; Pain (≥ 12 years), Significant, prevents daily activity; Erythema and Swelling (China Food and Drug Administration; CFDA), > 30 mm. Grade 3 systemic reactions (≤ 23 months): Fever (CFDA), > 39.0°C; Vomiting, ≥ 6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, > 3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥ 3 feeds or refuses most feeds; Irritability, Inconsolable. Grade 3 systemic reactions (≥ 2 years): Fever (CFDA), > 39.0°C; Headache, Malaise, and Myalgia, Significant, prevents daily activity

End point type	Primary

End point timeframe:

Day 0 up to Day 7 post-any dose

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Avaxim® 80U Pediatric Group 1	Avaxim® 80U Pediatric Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	84		
Units: Percentage of subjects				
number (not applicable)				
Any Injection site Tenderness	16.4	0		
Grade 3 Injection site Tenderness	0	0		
Any Injection site Pain	0	33.3		
Grade 3 Injection site Pain	0	0		
Any Injection site Erythema	3.4	3.6		
Grade 3 Injection site Erythema	0	0		
Any Injection site Swelling	1.9	3.6		
Grade 3 Injection site Swelling	0	1.2		
Any Fever	12.7	2.4		

Grade 3 Fever	1.5	0		
Any Vomiting	3.4	0		
Grade 3 Vomiting	0.4	0		
Any Crying abnormal	8.2	0		
Grade 3 Crying abnormal	0.4	0		
Any Drowsiness	7.1	0		
Grade 3 Drowsiness	0	0		
Any Appetite lost	8.2	0		
Grade 3 Appetite lost	0.7	0		
Any Irritability	10.1	0		
Grade 3 Irritability	0.4	0		
Any Headache	0	8.3		
Grade 3 Headache	0	0		
Any Malaise	0	15.5		
Grade 3 Malaise	0	0		
Any Myalgia	0	15.5		
Grade 3 Myalgia	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions After First Dose Vaccination with AVAXIM™ 80U-Pediatric Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions After First Dose Vaccination with AVAXIM™ 80U-Pediatric Vaccine[2]

End point description:

Solicited inj. site reactions: Tenderness, Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, Irritability, Headache, Malaise, and Myalgia.
Grade 3 inj. site reactions: Tenderness (≤ 23 months), Cries when injected limb is moved or the movement of the injected limb is reduced; Pain (2 to 11 years), Incapacitating, unable to perform usual activities; Pain (≥ 12 years), Significant, prevents daily activity; Erythema and Swelling (China Food and Drug Administration; CFDA), > 30 mm. Grade 3 systemic reactions (≤ 23 months): Fever (CFDA), > 39.0°C; Vomiting, ≥ 6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, > 3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥ 3 feeds or refuses most feeds; Irritability, Inconsolable. Grade 3 systemic reactions (≥ 2 years): Fever (CFDA), > 39.0°C; Headache, Malaise, and Myalgia, Significant, prevents daily activity

End point type	Primary

End point timeframe:

Day 0 up to Day 7 post-dose 1

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Avaxim® 80U Pediatric Group 1	Avaxim® 80U Pediatric Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	84		
Units: Percentage of subjects				
number (not applicable)				
Any Injection site Tenderness	11.2	0		
Grade 3 Injection site Tenderness	0	0		
Any Injection site Pain	0	25		
Grade 3 Injection site Pain	0	0		
Any Injection site Erythema	3.4	3.6		
Grade 3 Injection site Erythema	0	0		
Any Injection site Swelling	1.9	3.6		
Grade 3 Injection site Swelling	0	1.2		
Any Fever	11.9	2.4		
Grade 3 Fever	1.5	0		
Any Vomiting	2.6	0		
Grade 3 Vomiting	0.4	0		
Any Crying abnormal	8.2	0		
Grade 3 Crying abnormal	0.4	0		
Any Drowsiness	6.3	0		
Grade 3 Drowsiness	0	0		
Any Appetite lost	7.8	0		
Grade 3 Appetite lost	0.7	0		
Any Irritability	9.3	0		
Grade 3 Irritability	0.4	0		
Any Headache	0	6		
Grade 3 Headache	0	0		
Any Malaise	0	10.7		
Grade 3 Malaise	0	0		
Any Myalgia	0	8.3		
Grade 3 Myalgia	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions After Second Dose Vaccination with AVAXIM™ 80U-Pediatric Vaccine

End point title	Percentage of Subjects Reporting Solicited Injection-site and Systemic Reactions After Second Dose Vaccination with AVAXIM™ 80U-Pediatric Vaccine[3]

End point description:

Solicited inj. site reactions: Tenderness, Pain, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, Irritability, Headache, Malaise, and Myalgia.
Grade 3 inj. site reactions: Tenderness (≤ 23 months), Cries when injected limb is moved or the movement of the injected limb is reduced; Pain (2 to 11 years), Incapacitating, unable to perform usual activities; Pain (≥ 12 years), Significant, prevents daily activity; Erythema and Swelling (China Food and Drug Administration; CFDA), > 30 mm. Grade 3 systemic reactions (≤ 23 months): Fever (CFDA), > 39.0°C; Vomiting, ≥ 6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, > 3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refuses ≥ 3 feeds or

refuses most feeds; Irritability, Inconsolable. Grade 3 systemic reactions (≥ 2 years): Fever (CFDA), > 39.0°C; Headache, Malaise, and Myalgia, Significant, prevents daily activity

End point type	Primary

End point timeframe:

Day 0 up to Day 7 post-dose 2

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Avaxim® 80U Pediatric Group 1	Avaxim® 80U Pediatric Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	75		
Units: Percentage of subjects				
number (not applicable)				
Any Injection site Tenderness	5.9	0		
Grade 3 Injection site Tenderness	0	0		
Any Injection site Pain	0	18.7		
Grade 3 Injection site Pain	0	0		
Any Injection site Erythema	0	0		
Grade 3 Injection site Erythema	0	0		
Any Injection site Swelling	0	0		
Grade 3 Injection site Swelling	0	0		
Any Fever	1.2	0		
Grade 3 Fever	0	0		
Any Vomiting	0.8	0		
Grade 3 Vomiting	0	0		
Any Crying abnormal	0.4	0		
Grade 3 Crying abnormal	0	0		
Any Drowsiness	0.8	0		
Grade 3 Drowsiness	0	0		
Any Appetite lost	0.4	0		
Grade 3 Appetite lost	0	0		
Any Irritability	0.8	0		
Grade 3 Irritability	0	0		
Any Headache	0	2.7		
Grade 3 Headache	0	0		
Any Malaise	0	5.3		
Grade 3 Malaise	0	0		
Any Myalgia	0	8		
Grade 3 Myalgia	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse event data were collected from Day 0 up to Day 7 post-dose 2.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Infants and toddlers (≤ 23 months) who received 2 injections of Avaxim® 80U Pediatric vaccine 6 months apart.	
Reporting group title	Group 2
Reporting group description:	
Children (aged 2 to 11 years) and adolescents (aged 12 to 15 years) who received 2 injections of Avaxim® 80U Pediatric vaccine.	

Serious adverse events	Group 1	Group 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 270 (0.00%)	0 / 85 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 1	Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 270 (16.30%)	28 / 85 (32.94%)	
Nervous system disorders			
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed	19 / 270 (7.04%)	0 / 85 (0.00%)	
occurrences (all)	19	0	
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 270 (0.00%)	7 / 85 (8.24%)	
occurrences (all)	0	7	

General disorders and administration site conditions			
Injection site Tenderness			
alternative assessment type: Systematic			
subjects affected / exposed	44 / 270 (16.30%)	0 / 85 (0.00%)	
occurrences (all)	44	0	
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 270 (0.00%)	28 / 85 (32.94%)	
occurrences (all)	0	28	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	34 / 270 (12.59%)	2 / 85 (2.35%)	
occurrences (all)	34	2	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 270 (0.00%)	13 / 85 (15.29%)	
occurrences (all)	0	13	
Psychiatric disorders			
Crying abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 270 (8.15%)	0 / 85 (0.00%)	
occurrences (all)	22	0	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	27 / 270 (10.00%)	0 / 85 (0.00%)	
occurrences (all)	27	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 270 (0.00%)	13 / 85 (15.29%)	
occurrences (all)	0	13	
Metabolism and nutrition disorders			
Appetite lost			
alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	22 / 270 (8.15%) 22	0 / 85 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2014	Clarification of interim/preliminary statistical analyses and timelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A sponsor’s QC visit found 22 Diary Cards had similar handwriting. A site staff filled the cards based on discussion with the subjects. A subset analysis without the 22 subjects was done. Outcome is comparable to results of full safety analysis set.

Notes: