Clinical trial results:
Immunogenicity and Safety of AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™ in 12-13 Months old Healthy Hepatitis A Seronegative Turkish Children

Summary

EudraCT number	2015-005192-24
Trial protocol	Outside EU/EEA
Global end of trial date	01 October 2009

Results information

Result version number	v1 (current)
This version publication date	26 March 2016
First version publication date	26 March 2016

Trial information

Trial identification

Sponsor protocol code	HAF65

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00313950
WHO universal trial number (UTN)	-

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 4 37 37 74 62, Anvar.Rassouli@sanofipasteur.com
Scientific contact	Responsible Medical Officer, Sanofi Pasteur SA, 33 4 37 37 74 62, Anvar.Rassouli@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?	Yes
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	27 July 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 October 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To compare the immunogenicity of AVAXIM 80U-Pediatric vaccine administered in hepatitis A virus (HAV) seronegative children aged 12 to 13 months alone or in association with TRIMOVAX vaccine at 2 different sites, in terms of percentage of seroprotected subjects (titer ≥20 mIU/mL) 4 weeks after the first dose (D28).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized 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	28 September 2006
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	Turkey: 470
Worldwide total number of subjects	470
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)	470
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study subjects were enrolled from 28 September 2006 to 06 February 2009 at 2 clinic centers in Turkey.

Pre-assignment

Screening details:

A total of 470 subjects who met all of the inclusion and none of the exclusion criteria were randomized and vaccinated in this study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

This was a blind observer study. The Investigator was a blind observer of safety. To reduce bias, product preparation/administration and assessment of safety were performed by two different individuals in separate rooms. Neither the Investigator nor the subjects/parents witnessed vaccine preparation and the Investigator did not witness the vaccine administration. In an emergency (i.e., serious adverse event), the code could be broken based on code-breaking procedures.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A; AVAXIM 80U Pediatric/TRIMOVAX

Arm description:

Subjects received 1 dose of AVAXIM 80U-Pediatric on Day 0 and 1 dose of TRIMOVAX on Day 28. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.

Arm type	Experimental
Investigational medicinal product name	Inactivated Hepatitis A vaccine: 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 injection into the deltoid, 1 injection on Day 0.

Investigational medicinal product name	Live attenuated MMR vaccine: TRIMOVAX™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the deltoid, 1 injection on Day 28.

Arm title	Group B; TRIMOVAX/AVAXIM 80U Pediatric

Arm description:

Subjects received 1 dose of TRIMOVAX on Day 0 and 1 dose of AVAXIM 80U-Pediatric on Day 28. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.

Arm type	Experimental

Investigational medicinal product name	Inactivated Hepatitis A vaccine: 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 injection into the deltoid, 1 injection on Day 28.

Investigational medicinal product name	Live attenuated MMR vaccine: TRIMOVAX™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the deltoid, 1 injection on Day 0.

Arm title	Group C; AVAXIM 80U Pediatric and TRIMOVAX

Arm description:

Subjects received 1 dose each of AVAXIM 80U-Pediatric and TRIMOVAX on Day 0. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.

Arm type	Experimental
Investigational medicinal product name	Inactivated Hepatitis A vaccine: 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 injection into the deltoid, 1 injection on Day 0.

Investigational medicinal product name	Live attenuated MMR vaccine: TRIMOVAX™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular injection into the deltoid, 1 injection on Day 0.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: A double-blind design could not be used due to the different vaccine forms. The Investigator was a blind observer of safety.

Number of subjects in period 1	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX
Started	188	94	188
Completed	160	81	157
Not completed	28	13	31
Consent withdrawn by subject	2	3	3
Adverse event, non-fatal	1	1	-
Lost to follow-up	17	4	15
Protocol deviation	8	5	13

Baseline characteristics

Reporting groups	
Reporting group title	Group A; AVAXIM 80U Pediatric/TRIMOVAX
Reporting group description:	
Subjects received 1 dose of AVAXIM 80U-Pediatric on Day 0 and 1 dose of TRIMOVAX on Day 28. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	
Reporting group title	Group B; TRIMOVAX/AVAXIM 80U Pediatric
Reporting group description:	
Subjects received 1 dose of TRIMOVAX on Day 0 and 1 dose of AVAXIM 80U-Pediatric on Day 28. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	
Reporting group title	Group C; AVAXIM 80U Pediatric and TRIMOVAX
Reporting group description:	
Subjects received 1 dose each of AVAXIM 80U-Pediatric and TRIMOVAX on Day 0. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	

Reporting group values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX
Number of subjects	188	94	188
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)	188	94	188
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
arithmetic mean	12.3	12.26	12.32
standard deviation	± 0.22	± 0.18	± 0.22
Gender categorical Units: Subjects			
Female	84	45	80
Male	104	49	108

Reporting group values	Total		
Number of subjects	470		
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)	470		

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: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	209		
Male	261		

End points

End points reporting groups

Reporting group title	Group A; AVAXIM 80U Pediatric/TRIMOVAX
Reporting group description:	
Subjects received 1 dose of AVAXIM 80U-Pediatric on Day 0 and 1 dose of TRIMOVAX on Day 28. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	
Reporting group title	Group B; TRIMOVAX/AVAXIM 80U Pediatric
Reporting group description:	
Subjects received 1 dose of TRIMOVAX on Day 0 and 1 dose of AVAXIM 80U-Pediatric on Day 28. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	
Reporting group title	Group C; AVAXIM 80U Pediatric and TRIMOVAX
Reporting group description:	
Subjects received 1 dose each of AVAXIM 80U-Pediatric and TRIMOVAX on Day 0. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	

Primary: Percentage of Hepatitis A Seronegative Subjects With Seroprotection Against Inactivated Hepatitis A Antigen After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Percentage of Hepatitis A Seronegative Subjects With Seroprotection Against Inactivated Hepatitis A Antigen After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™
End point description:	
Anti-Hepatitis A virus total immunoglobulin antibodies were measured by the commercially available Axsym HAVAB 2.0 kit, a microparticle enzyme immunoassay. Seroprotection was defined as anti-Hepatitis A virus antibody titer ≥ 20 mIU/mL on Day 28.	
End point type	Primary
End point timeframe:	
Day 28 post-vaccination	

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	84	164	
Units: Percentage of subjects				
number (not applicable)				
Anti-Hepatitis A virus	93.6	1.19	92.68	

Statistical analyses

Statistical analysis title	Non-inferiority (Group C - Group A)
Statistical analysis description:	
Non-inferiority analysis of seroprotection rates between Group C (AVAXIM 80U-Pediatric and TRIMOVAX on Day 0) and Group A (AVAXIM 80U-Pediatric on Day 0 and TRIMOVAX on Day 28).	

Comparison groups	Group C; AVAXIM 80U Pediatric and TRIMOVAX v Group A; AVAXIM 80U Pediatric/TRIMOVAX
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference between Group C and Group A
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.68
upper limit	4.69

Notes:

[1] - Non-inferiority was demonstrated if the lower limit of the 95% confidence interval (CI) of the difference was greater than -5%. Group C was not inferior to Group A.

Secondary: Geometric Mean Titers (GMTs) of Hepatitis A Antibodies After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Geometric Mean Titers (GMTs) of Hepatitis A Antibodies After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point description:

Anti-Hepatitis A virus total immunoglobulin antibodies were measured by the commercially available Axsym HAVAB 2.0 kit, a microparticle enzyme immunoassay.

End point type	Secondary

End point timeframe:

Day 7 and Day 28 post-vaccination

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	187	94	187	
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Geometric mean titers; Day 7	4.93 (4.49 to 5.42)	5.12 (4.43 to 5.93)	5.51 (4.95 to 6.13)	
Geometric mean titers; Day 28	46.52 (42.29 to 51.17)	3.67 (3.28 to 4.11)	43.15 (39.45 to 47.21)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Hepatitis A Seronegative Subjects With Hepatitis Antibodies at ≥5 mIU/mL and ≥20 mIU/mL After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Percentage of Hepatitis A Seronegative Subjects With Hepatitis

	Antibodies at ≥5 mIU/mL and ≥20 mIU/mL After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point description:

Anti-Hepatitis A virus total immunoglobulin antibodies were measured by the commercially available Axsym HAVAB 2.0 kit, a microparticle enzyme immunoassay.

End point type	Secondary

End point timeframe:

Day 7 and Day 28 post-vaccination

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	187	94	187	
Units: Percentage of subjects				
number (not applicable)				
Anti-Hepatitis A virus; Day 7; ≥ 5 mIU/mL	58.3	59.6	62	
Anti-Hepatitis A virus; Day 28; ≥ 5 mIU/mL	98.3	39.3	100	
Anti-Hepatitis A virus; Day 7; ≥ 20 mIU/mL	1.1	2.1	4.8	
Anti-Hepatitis A virus; Day 28; ≥ 20 mIU/mL	93.8	1.2	92.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios (GMTR) of Hepatitis A Antibodies After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Geometric Mean Titer Ratios (GMTR) of Hepatitis A Antibodies After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™[2]

End point description:

Anti-Hepatitis A virus total immunoglobulin antibodies were measured by the commercially available Axsym HAVAB 2.0 kit, a microparticle enzyme immunoassay.

End point type	Secondary

End point timeframe:

Day 28/Day 7 post-vaccination

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group C; AVAXIM 80U Pediatric and TRIMOVAX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	187		
Units: Titer ratios (1/dil)				
geometric mean (confidence interval 95%)				
Geometric mean titer ratios; Day 28	9.43 (8.18 to 10.87)	7.99 (6.98 to 9.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Hepatitis A Antibodies After Booster Vaccination with AVAXIM™ 80U-Pediatric Following A Primary Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Geometric Mean Titers (GMTs) of Hepatitis A Antibodies After Booster Vaccination with AVAXIM™ 80U-Pediatric Following A Primary Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point description:

Anti-Hepatitis A virus total immunoglobulin antibodies were measured by the commercially available Axsym HAVAB 2.0 kit, a microparticle enzyme immunoassay.

End point type	Secondary

End point timeframe:

Day 213 and Day 243 post-vaccination

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154	80	148	
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Geometric mean titers; Day 213	217.11 (191.03 to 246.75)	97.92 (78.58 to 122.02)	144.06 (127.03 to 163.37)	
Geometric mean titers; Day 243	5078.74 (4433.11 to 5818.41)	3271 (2657.87 to 4025.56)	4314.86 (3757.76 to 4954.54)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Hepatitis A Seronegative Subjects With Hepatitis Antibodies at ≥5 mIU/mL and ≥20 mIU/mL After Booster Vaccination with AVAXIM™ 80U-Pediatric After A Primary Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIM

End point title	Percentage of Hepatitis A Seronegative Subjects With Hepatitis Antibodies at ≥5 mIU/mL and ≥20 mIU/mL After Booster Vaccination with AVAXIM™ 80U-Pediatric After A Primary Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIM

End point description:

Anti-Hepatitis A virus total immunoglobulin antibodies were measured by the commercially available Axsym HAVAB 2.0 kit, a microparticle enzyme immunoassay.

End point type	Secondary

End point timeframe:

Day 213 and Day 243 post-vaccination

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154	80	148	
Units: Percentage of subjects				
number (not applicable)				
Anti-Hepatitis A virus; Day 213; ≥ 5 mIU/mL	100	100	100	
Anti-Hepatitis A virus; Day 243; ≥ 5 mIU/mL	100	100	100	
Anti-Hepatitis A virus; Day 213; ≥ 20 mIU/mL	100	94.9	99.3	
Anti-Hepatitis A virus; Day 243; ≥ 20 mIU/mL	100	100	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios (GMTR) of Hepatitis A Antibodies After Booster Vaccination with AVAXIM™ 80U-Pediatric Following A Primary Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Geometric Mean Titer Ratios (GMTR) of Hepatitis A Antibodies After Booster Vaccination with AVAXIM™ 80U-Pediatric Following A Primary Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point description:

Anti-Hepatitis A virus total immunoglobulin antibodies were measured by the commercially available Axsym HAVAB 2.0 kit, a microparticle enzyme immunoassay.

End point type	Secondary

End point timeframe:

Day 243/Day 213 post-vaccination

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154	80	148	
Units: Titer ratios (1/dil)				
geometric mean (confidence interval 95%)				
Geometric mean titer ratios; Day 243	23.39 (20.69 to 26.44)	33.5 (28.36 to 39.58)	29.95 (26.35 to 34.05)	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of Anti-Measles, Mumps, and Rubella Responses After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Geometric Mean Titers (GMTs) of Anti-Measles, Mumps, and Rubella Responses After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point description:

Anti-Measles, Mumps, and Rubella immunoglobulin antibodies were measured by enzyme-linked immunosorbent assay (ELISA).

End point type	Secondary

End point timeframe:

Day 28 post-vaccination

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	92	186	
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
Geometric mean titers of Anti-Measles; Day 28	221.12 (1.29 to 37928.87)	2074.24 (1745.06 to 2465.52)	2103.77 (1856.55 to 2383.9)	
Geometric mean titers of Anti-Mumps; Day 28	24.91 (4.58 to 135.45)	61.3 (52.48 to 71.61)	64.92 (58.52 to 72.03)	
Geometric mean titers of Anti-Rubella; Day 28	44.4 (44.4 to 44.4)	92.85 (75.75 to 113.82)	96.42 (83.91 to 110.79)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Anti-Measles, Mumps, and Rubella Responses After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Summary of Anti-Measles, Mumps, and Rubella Responses After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point description:

Anti-Measles, Mumps, and Rubella immunoglobulin antibodies were measured by enzyme-linked immunosorbent assay (ELISA).

End point type	Secondary

End point timeframe:

Day 7 and Day 28 post-vaccination

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	92	186	
Units: Percentage of subjects				
number (not applicable)				
Anti-Measles antibody titers; Day 7; ≥ 120 mIU/mL	2.7	1.1	2.7	
Anti-Measles antibody titers; Day 28; ≥ 120 mIU/mL	1.1	96.5	96.5	
Anti-Mumps antibody titers; Day 7; ≥ 10 AU/mL	4.8	7.6	4.3	
Anti-Mumps antibody titers; Day 28; ≥ 10 AU/mL	2.2	96.5	96.5	
Anti-Rubella antibody titers; Day 7; ≥ 10 IU/mL	0.5	0	0.5	
Anti-Rubella antibody titers; Day 28; ≥ 10 IU/mL	0.6	97.6	96.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or

Concomitantly with TRIMOVAX™

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point description:

Solicited injection site reactions: Tenderness, Erythema, and Swelling (occurring after at least 1 of the 2 vaccinations for Group C). Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, Irritability.

Grade 3 solicited injection site reactions: Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥ 5 cm. Grade 3 systemic reactions: Fever, ≥ 39.6°C rectal; Vomiting, ≥ 6 episodes/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.

End point type	Secondary

End point timeframe:

Within 8 days of injections administered on Day 0

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	182	88	177	
Units: Percentage of subjects				
number (not applicable)				
Injection site Tenderness	22	22.7	27.1	
Grade 3 Injection site Tenderness	1.1	0	2.3	
Injection site Erythema	7.7	8	14.7	
Grade 3 Injection site Erythema	0	0	0	
Injection site Swelling	5.5	5.7	8.5	
Grade 3 Injection site Swelling	0	0	0	
Fever	6	9.1	12.4	
Grade 3 Fever	0	1.1	0	
Vomiting	17	21.6	23.7	
Grade 3 Vomiting	0.5	1.1	1.1	
Crying abnormal	25.8	34.1	32.8	
Grade 3 Crying abnormal	2.2	0	3.4	
Drowsiness	13.2	15.9	20.3	
Grade 3 Drowsiness	0	0	0	
Appetite lost	34.1	31.8	41.2	
Grade 3 Appetite lost	3.8	10.2	6.8	
Irritability	45.6	53.4	51.4	
Grade 3 Irritability	4.9	8	7.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Booster Vaccination with AVAXIM™ 80U-Pediatric Following A Primary Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point title	Percentage of Subjects Reporting Solicited Injection-site or Systemic Reaction After Booster Vaccination with AVAXIM™ 80U-Pediatric Following A Primary Vaccination with AVAXIM™ 80U-Pediatric Administered Alone or Concomitantly with TRIMOVAX™

End point description:

Solicited injection site reactions: Tenderness, Erythema, and Swelling. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, Irritability.

Grade 3 solicited injection site reactions: Tenderness, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥ 5 cm. Grade 3 systemic reactions: Fever, ≥ 39.6°C rectal; Vomiting, ≥ 6 episodes/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.

End point type	Secondary

End point timeframe:

Within 8 days of injections administered on Day 213

End point values	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	182	88	177	
Units: Percentage of subjects				
number (not applicable)				
Injection site Tenderness	19.8	21.6	22.6	
Grade 3 Injection site Tenderness	2.2	4.5	2.3	
Injection site Erythema	8.2	11.4	9	
Grade 3 Injection site Erythema	0	0	0	
Injection site Swelling	3.8	8	6.8	
Grade 3 Injection site Swelling	0	0	0	
Fever	6.6	5.7	8.5	
Grade 3 Fever	0.5	0	0	
Vomiting	4.4	5.7	9	
Grade 3 Vomiting	0.5	0	1.1	
Crying abnormal	17	13.6	22	
Grade 3 Crying abnormal	1.6	2.3	1.7	
Drowsiness	7.7	4.5	11.9	
Grade 3 Drowsiness	1.1	0	1.7	
Appetite lost	26.4	25	27.7	
Grade 3 Appetite lost	3.8	4.5	5.6	
Irritability	28.6	27.3	32.8	
Grade 3 Irritability	2.2	3.4	5.6	

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 8 after vaccinations on Day 213.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12

Reporting groups	
Reporting group title	Group A; AVAXIM 80U Pediatric/TRIMOVAX
Reporting group description:	
Subjects received 1 dose of AVAXIM 80U-Pediatric on Day 0 and 1 dose of TRIMOVAX on Day 28. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	
Reporting group title	Group B; TRIMOVAX/AVAXIM 80U Pediatric
Reporting group description:	
Subjects received 1 dose of TRIMOVAX on Day 0 and 1 dose of AVAXIM 80U-Pediatric on Day 28. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	
Reporting group title	Group C; AVAXIM 80U Pediatric and TRIMOVAX
Reporting group description:	
Subjects received 1 dose each of AVAXIM 80U-Pediatric and TRIMOVAX on Day 0. All subjects received a booster dose of AVAXIM 80U-Pediatric on Day 213.	

Serious adverse events	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 188 (1.06%)	1 / 94 (1.06%)	3 / 188 (1.60%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 94 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 94 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			

subjects affected / exposed	0 / 188 (0.00%)	0 / 94 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cow milk allergy			
subjects affected / exposed	0 / 188 (0.00%)	1 / 94 (1.06%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 94 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Group A; AVAXIM 80U Pediatric/TRIMOVAX	Group B; TRIMOVAX/AVAXIM 80U Pediatric	Group C; AVAXIM 80U Pediatric and TRIMOVAX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 188 (60.11%)	55 / 94 (58.51%)	125 / 188 (66.49%)
Nervous system disorders			
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[1]	24 / 182 (13.19%)	14 / 88 (15.91%)	36 / 177 (20.34%)
occurrences (all)	24	14	36
General disorders and administration site conditions			
Injection site Tenderness			
alternative assessment type: Systematic			
subjects affected / exposed[2]	40 / 182 (21.98%)	20 / 88 (22.73%)	48 / 177 (27.12%)
occurrences (all)	40	20	48
Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed[3]	15 / 182 (8.24%)	10 / 88 (11.36%)	26 / 177 (14.69%)
occurrences (all)	15	10	26
Injection site Swelling			
alternative assessment type: Systematic			

subjects affected / exposed[4]	10 / 182 (5.49%)	7 / 88 (7.95%)	15 / 177 (8.47%)
occurrences (all)	10	7	15
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[5]	12 / 182 (6.59%)	8 / 88 (9.09%)	22 / 177 (12.43%)
occurrences (all)	12	8	22
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed[6]	31 / 182 (17.03%)	19 / 88 (21.59%)	42 / 177 (23.73%)
occurrences (all)	31	19	42
Psychiatric disorders			
Crying abnormal			
alternative assessment type: Systematic			
subjects affected / exposed[7]	47 / 182 (25.82%)	30 / 88 (34.09%)	58 / 177 (32.77%)
occurrences (all)	47	30	58
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[8]	83 / 182 (45.60%)	47 / 88 (53.41%)	91 / 177 (51.41%)
occurrences (all)	83	47	91
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 188 (5.32%)	6 / 94 (6.38%)	12 / 188 (6.38%)
occurrences (all)	10	6	12
Metabolism and nutrition disorders			
Appetite lost			
alternative assessment type: Systematic			
subjects affected / exposed[9]	62 / 182 (34.07%)	28 / 88 (31.82%)	73 / 177 (41.24%)
occurrences (all)	62	28	73

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 0; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 0; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 213; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 0; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 213; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 0; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 0; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 0; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.
[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This was a solicited adverse event recorded in a diary card within 8 days of injections administered on Day 0; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2006	Mono-measles vaccination at 9 months of age was removed and replaced with the measles, mumps, and rubella vaccination at 12 months; age inclusion criteria was revised to include only 12- and 13-month infants; study design was defined as monocentric and study duration was 7 months.
28 April 2006	Blood sample analysis procedures were updated.
05 February 2007	The number of sites was updated to 2 centers; the schedule for the follow-up visits was revised, and the length of the entire study duration was updated to 8 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported