Clinical trial results:
A Phase IIIb, open, randomized, controlled, multicenter study of the immunogenicity and safety of GlaxoSmithKline Biologicals' inactivated hepatitis A vaccine (Havrix) [720 El.U/0.5 mL dose] administered on a 0, 6-month schedule concomitantly with Merck and Company, Inc. measles-mumps-rubella vaccine (M-M-RII) and Merck and Company, Inc. varicella vaccine (VARIVAX) to healthy children 15 months of age.

Summary

EudraCT number	2015-001509-15
Trial protocol	Outside EU/EEA
Global end of trial date	09 June 2009

Results information

Result version number	v2 (current)
This version publication date	28 March 2023
First version publication date	31 July 2015
Version creation reason	• Correction of full data set Correction of full data set and alignment between registries.

Trial information

Trial identification

Sponsor protocol code	208109/231

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00197015
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.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	15 February 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2009
Global end of trial reached?	Yes
Global end of trial date	09 June 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of the anti-HAV immune response (with respect to both seropositivity rates and GMCs) 31 days following the second dose of Havrix when the first dose of Havrix is co-administered with M-M-RII and VARIVAX (HAV+MMR+V Group) compared to Havrix given alone (HAV Group),
To demonstrate the non-inferiority of the anti-measles, anti-mumps, anti-rubella and anti-varicella immune responses (with respect to seroconversion rates for anti-measles, anti-mumps and anti-varicella and seroresponse rate for anti-rubella) 42 days following the co-administration of M-M-RII and VARIVAX with the first dose of Havrix (HAV+MMR+V Group) compared to when M-M-RII and VARIVAX are given alone (MMR+VHAV Group).

Protection of trial subjects:

All subjects were supervised closely for at least 30 minutes following vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines. Subjects were followed-up from the time the subject consents to participate in the study until she/he is discharged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2003
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	United States: 1474
Worldwide total number of subjects	1474
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1474
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: -

Pre-assignment

Screening details:

While the total numbers of subjects enrolled in the study was 1474, the total number of subjects that entered the study was 1241. The remaining subjects received a subject number but no vaccine dose and were therefore excluded from the analysis and group assignment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	HAV Group

Arm description:

Subjects received 2 doses of Havrix (1 dose at Day 0 and 1 dose between Month 6 and Month 9)

Arm type	Active comparator
Investigational medicinal product name	Havrix
Investigational medicinal product code	
Other name	HAV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly, in the left anterolateral thigh.

Arm title	HAV+MMR+V Group

Arm description:

Subjects received 1 dose of Havrix, coadministered with M-M-R II and VARIVAX, at Day 0 and 1 dose of Havrix between Month 6 and Month 9

Arm type	Experimental
Investigational medicinal product name	Havrix
Investigational medicinal product code	
Other name	HAV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly, in the left anterolateral thigh.

Investigational medicinal product name	M-M-R II
Investigational medicinal product code	
Other name	MMR
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose administered subcutaneously, in the deltoid region.

Investigational medicinal product name	VARIVAX
Investigational medicinal product code	
Other name	Varicella

Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose administered subcutaneously, in the deltoid region.

Arm title	MMR+VHAV Group

Arm description:

Subjects received 1 dose of M-M-R II and VARIVAX at Day 0 and then 2 doses of Havrix (1 dose at Day 42 and 1 dose between Month 7.5 and Month 10.5)

Arm type	Active comparator
Investigational medicinal product name	Havrix
Investigational medicinal product code	
Other name	HAV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly, in the left anterolateral thigh.

Investigational medicinal product name	M-M-R II
Investigational medicinal product code	
Other name	MMR
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose administered subcutaneously, in the deltoid region.

Investigational medicinal product name	VARIVAX
Investigational medicinal product code	
Other name	Varicella
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 dose administered subcutaneously, in the deltoid region.

Number of subjects in period 1[1]	HAV Group	HAV+MMR+V Group	MMR+VHAV Group
Started	324	462	455
Completed	274	385	366
Not completed	50	77	89
Adverse event, serious fatal	3	1	-
Consent withdrawn by subject	17	34	37
Unspecified	2	2	3
Lost to follow-up	28	37	46
Protocol deviation	-	3	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: While the total number of subjects enrolled in the study was 1474, the total number of subjects that entered the study was 1241. The remaining subjects received a subject number but no vaccine dose and were therefore excluded from the analysis and group assignment.

Baseline characteristics

Reporting groups	
Reporting group title	HAV Group
Reporting group description:	
Subjects received 2 doses of Havrix (1 dose at Day 0 and 1 dose between Month 6 and Month 9)	
Reporting group title	HAV+MMR+V Group
Reporting group description:	
Subjects received 1 dose of Havrix, coadministered with M-M-R II and VARIVAX, at Day 0 and 1 dose of Havrix between Month 6 and Month 9	
Reporting group title	MMR+VHAV Group
Reporting group description:	
Subjects received 1 dose of M-M-R II and VARIVAX at Day 0 and then 2 doses of Havrix (1 dose at Day 42 and 1 dose between Month 7.5 and Month 10.5)	

Reporting group values	HAV Group	HAV+MMR+V Group	MMR+VHAV Group
Number of subjects	324	462	455
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: months			
arithmetic mean	15	15	15
standard deviation	± 0.27	± 0.25	± 0.22
Gender categorical Units: Subjects			
Female	154	232	208
Male	170	230	247

Reporting group values	Total		
Number of subjects	1241		
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: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	594		
Male	647		

End points

End points reporting groups

Reporting group title	HAV Group
Reporting group description:	
Subjects received 2 doses of Havrix (1 dose at Day 0 and 1 dose between Month 6 and Month 9)	
Reporting group title	HAV+MMR+V Group
Reporting group description:	
Subjects received 1 dose of Havrix, coadministered with M-M-R II and VARIVAX, at Day 0 and 1 dose of Havrix between Month 6 and Month 9	
Reporting group title	MMR+VHAV Group
Reporting group description:	
Subjects received 1 dose of M-M-R II and VARIVAX at Day 0 and then 2 doses of Havrix (1 dose at Day 42 and 1 dose between Month 7.5 and Month 10.5)	

Primary: Anti-hepatitis A virus (HAV) antibody concentrations in HAV and HAV+MMR+V groups

End point title	Anti-hepatitis A virus (HAV) antibody concentrations in HAV and HAV+MMR+V groups[1]
End point description:	
Concentrations are given as geometric mean concentrations (GMCs) expressed as milli-international units per milliliter (mIU/mL).	
End point type	Primary
End point timeframe:	
31 days following the second dose of Havrix	

Notes:

[1] - 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: This outcome measure applies to subjects from the HAV and HAV+MMR+V Groups.

End point values	HAV Group	HAV+MMR+V Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	286		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-hepatitis A virus (HAV) antibodies	1390.4 (1186.3 to 1629.6)	1895.2 (1682.7 to 2134.5)		

Statistical analyses

Statistical analysis title	Non-inferiority of HAV+MMR+V vs. HAV vaccine

Statistical analysis description:

To demonstrate non-inferiority of the anti-hepatitis A virus (HAV) immune response (with respect to geometric mean concentrations [GMCs]) 31 days following the second dose of HAV when the first dose of HAV is co-administered with MMR and Varicella (HAV+MMR+V Group) compared to HAV given alone (HAV Group). Non-inferiority was to rule out more than a 2-fold decrease in the anti-HAV GMC between the HAV+MMR+V Group and the HAV Group 31 days following the second dose of HAV.

Comparison groups	HAV+MMR+V Group v HAV Group
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted GMC ratio
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	1.74

Primary: Number of subjects with anti-hepatitis A virus (HAV) antibody concentration equal or above the cut-off value in HAV and HAV+MMR+V groups

End point title	Number of subjects with anti-hepatitis A virus (HAV) antibody concentration equal or above the cut-off value in HAV and HAV+MMR+V groups[2]

End point description:

Anti-HAV antibody cut-off value assessed include 15 milli-international units per milliliter (mIU/mL).

End point type	Primary

End point timeframe:

31 days following the second dose of Havrix

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: This outcome measure applies to subjects in the HAV and HAV+MMR+V Groups.

End point values	HAV Group	HAV+MMR+V Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	286		
Units: Subjects	204	285		

Statistical analyses

Statistical analysis title	Non-inferiority of HAV+MMR+V vs. HAV vaccine

Statistical analysis description:

To demonstrate non-inferiority of the anti-hepatitis A virus (HAV) immune response (than a 5% decrease in the anti-HAV seropositivity rate) 31 days following the second dose of HAV when the first dose of HAV is co-administered with MMR and Varicella (HAV+MMR+V Group) compared to HAV given alone (HAV Group). Non-inferiority was to rule out more than a 5% decrease in the anti-HAV seropositivity rate between the HAV+MMR+V Group and the HAV Group 31 days following the second dose of HAV.

Comparison groups	HAV+MMR+V Group v HAV Group

Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seropositivity rate
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	3.06

Primary: Number of subjects seroconverted for anti-measles, anti-mumps and anti-varicella antibodies in HAV+MMR+V and MMR+VHAV groups

End point title	Number of subjects seroconverted for anti-measles, anti-mumps and anti-varicella antibodies in HAV+MMR+V and MMR+VHAV groups[3]

End point description:

Seroconversion is defined as the appearance of antibodies with titers greater than or equal to the predefined cut-off value in the serum of subject seronegative before vaccination. Cut-off values assessed include 150 milli-international units per milliliter (mIU/mL) for anti-measles antibodies, 28 Effective Dose 50 (ED50) for anti-mumps antibodies and 1:5 for anti-varicella antibodies.

End point type	Primary

End point timeframe:

42 days following the administration of M-M-R II and VARIVAX

Notes:

[3] - 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: This outcome measure applies to subjects in the HAV+MMR+V and MMR+VHAV Groups.

End point values	HAV+MMR+V Group	MMR+VHAV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	250		
Units: Subjects				
Anti-measles (n= 250, 268)	267	247		
Anti-mumps (n= 197, 212)	207	193		
Anti-varicella (n= 171, 193)	187	168		

Statistical analyses

Statistical analysis title	Non-inferiority of HAV+MMR+V vs. MMR+VHAV

Statistical analysis description:

To demonstrate the non-inferiority of the anti-measles (with respect to seroconversion rates) 42 days following the co-administration of MMR and Varicella with the first dose of HAV (HAV+MMR+V Group) compared to when MMR and Varicella are given alone (MMR+VHAV Group). Non-inferiority was to rule out more than a 5% decrease in anti-measles seroconversion rates between the HAV+MMR+V Group and the MMR+VHAV Group 42 days following the administration of MMR and Varicella.

Comparison groups	HAV+MMR+V Group v MMR+VHAV Group

Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seroconevrsion rate
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	3.14

Statistical analysis title	Non-inferiority of HAV+MMR+V vs. MMR+VHAV

Statistical analysis description:

To demonstrate the non-inferiority of the anti-mumps (with respect to seroconversion rates) 42 days following the co-administration of MMR and Varicella with the first dose of HAV (HAV+MMR+V Group) compared to when MMR and Varicella are given alone (MMR+VHAV Group). Non-inferiority was to rule out more than a 5% decrease in anti-mumps seroconversion rates between the HAV+MMR+V Group and the MMR+VHAV Group 42 days following the administration of MMR and Varicella.

Comparison groups	HAV+MMR+V Group v MMR+VHAV Group
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seroconversion rate
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.23
upper limit	3.43

Statistical analysis title	Non-inferiority of HAV+MMR+V vs. MMR+VHAV

Statistical analysis description:

To demonstrate the non-inferiority of the anti-rubella (with respect to seroresponse rate) 42 days following the co-administration of MMR and Varicella with the first dose of HAV (HAV+MMR+V Group) compared to when MMR and Varicella are given alone (MMR+VHAV Group). Non-inferiority was to rule out more than a 5% decrease in the anti-rubella seroresponse rate between the HAV+MMR+V Group and the MMR+VHAV Group 42 days following the administration of MMR and Varicella.

Comparison groups	HAV+MMR+V Group v MMR+VHAV Group
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seroresponse rate
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	1.92

Statistical analysis title	Non-inferiority of HAV+MMR+V vs. MMR+VHAV

Statistical analysis description:

To demonstrate the non-inferiority of the anti-varicella (with respect to seroconversion rates) 42 days following the co-administration of MMR and Varicella with the first dose of HAV (HAV+MMR+V Group) compared to when MMR and Varicella are given alone (MMR+VHAV Group). Non-inferiority was to rule out more than a 10% decrease in the anti-varicella seroconversion rates between the HAV+MMR+V Group and the MMR+VHAV Group 42 days following the administration of MMR and Varicella.

Comparison groups	HAV+MMR+V Group v MMR+VHAV Group
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in seroconversion rates
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.11
upper limit	2.28

Primary: Number of subjects with vaccine response for anti-rubella antibodies in HAV+MMR+V and MMR+VHAV groups

End point title	Number of subjects with vaccine response for anti-rubella antibodies in HAV+MMR+V and MMR+VHAV groups[4][5]

End point description:

Vaccine response is defined as the appearance of antibodies with titers greater than or equal to the predefined cut-off value in the serum of subject seronegative before vaccination. Cut-off value assessed include 10 milli-international units per milliliter (mIU/mL).

End point type	Primary

End point timeframe:

42 days following administration of M-M-R II and VARIVAX

Notes:

[4] - 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: This outcome measure applies to subjects in the HAV+MMR+V and MMR+VHAV Groups.

[5] - 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: This outcome measure applies to subjects in the HAV+MMR+V and MMR+VHAV Groups.

End point values	HAV+MMR+V Group	MMR+VHAV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	247		
Units: Subjects				
Vaccine response for anti-rubella antibodies	270	246		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-measles, anti-mumps, anti-rubella and anti-varicella antibody titers in HAV+MMR+V and MMR+VHAV groups

End point title	Anti-measles, anti-mumps, anti-rubella and anti-varicella antibody titers in HAV+MMR+V and MMR+VHAV groups[6]

End point description:

Titers are given as geometric mean titers (GMTs).

End point type	Secondary

End point timeframe:

42 days following the administration of M-M-R II and VARIVAX

Notes:

[6] - 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: This outcome measure applies to subjects in the HAV+MMR+V and MMR+VHAV Groups.

End point values	HAV+MMR+V Group	MMR+VHAV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	269		
Units: titers				
geometric mean (confidence interval 95%)				
Anti-measles (n= 269, 301)	3136.3 (2922 to 3366.3)	3218.3 (2940.9 to 3521.8)		
Anti-rubella (n= 269, 304)	76 (70.7 to 81.7)	88.3 (81.9 to 95.3)		
Anti-varicella (n= 218, 260)	286.9 (252.1 to 326.5)	281.7 (246.7 to 321.8)		
Anti-mumps (n= 244, 276)	170.3 (152.2 to 190.5)	215.7 (190.9 to 243.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-hepatitis A virus (HAV) antibody concentrations in HAV and HAV+MMR+V groups

End point title	Anti-hepatitis A virus (HAV) antibody concentrations in HAV and HAV+MMR+V groups[7]

End point description:

Concentrations are given as geometric mean concentrations (GMCs).

End point type	Secondary

End point timeframe:

42 days following the first dose of Havrix®

Notes:

[7] - 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: This outcome measure applies to subjects from the HAV and HAV+MMR+V Groups.

End point values	HAV Group	HAV+MMR+V Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	306		
Units: milli-international units per milliliter				
geometric mean (confidence interval 95%)				
Anti-hepatitis A virus (HAV) antibodies	43.1 (37.9 to 49.1)	43.5 (39.3 to 48.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-hepatitis A virus (HAV) antibody concentration equal or above the cut-off value in HAV and HAV+MMR+V groups

End point title	Number of subjects with anti-hepatitis A virus (HAV) antibody concentration equal or above the cut-off value in HAV and HAV+MMR+V groups[8]

End point description:

Anti-HAV antibody cut-off value assessed include 15 milli-international units per millilitre (mIU/mL).

End point type	Secondary

End point timeframe:

42 days following the first dose of Havrix

Notes:

[8] - 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: This outcome measure applies to subjects from the HAV and HAV+MMR+V Groups.

End point values	HAV Group	HAV+MMR+V Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	306		
Units: Subjects				
Anti-hepatitis A virus (HAV) antibodies	194	276		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-hepatitis A virus (HAV) antibody concentrations in MMR+VHAV Group

End point title	Anti-hepatitis A virus (HAV) antibody concentrations in MMR+VHAV Group[9]

End point description:

Concentrations are given as geometric mean concentrations (GMCs).

End point type	Secondary

End point timeframe:

31 days following the second dose of Havrix

Notes:

[9] - 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: This outcome measure applies to subjects from the MMR+VHAV Group only.

End point values	MMR+VHAV Group			
Subject group type	Reporting group			
Number of subjects analysed	237			
Units: milli-international units per milliliter				
geometric mean (confidence interval 95%)				
Anti-hepatitis A virus (HAV) antibodies	1770.3 (1569.9 to 1996.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-hepatitis A virus (HAV) antibody concentrations above the cut-off value in MMR+VHAV Group

End point title	Number of subjects with anti-hepatitis A virus (HAV) antibody concentrations above the cut-off value in MMR+VHAV Group[10]

End point description:

Anti-HAV antibody cut-off value assessed include 15 milli-international units per millilitre (mIU/mL).

End point type	Secondary

End point timeframe:

31 days following the second dose of Havrix

Notes:

[10] - 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: This outcome measure applies to subjects from the MMR+VHAV Group only.

End point values	MMR+VHAV Group			
Subject group type	Reporting group			
Number of subjects analysed	237			
Units: Subjects				
Anti-hepatitis A virus (HAV) antibodies	237			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with vaccine response to Havrix

End point title	Number of subjects with vaccine response to Havrix

End point description:

Vaccine response was defined as: 1) a detectable anti-hepatitis A virus (HAV) antibody concentration 31 days following the second dose in subjects who were initially seronegative; and 2) a 2-fold increase in anti-HAV antibody concentrations above the pre-study concentration 31 days following the second dose in subjects who were initially seropositive.

End point type	Secondary

End point timeframe:

31 days following the second dose of Havrix

End point values	HAV Group	HAV+MMR+V Group	MMR+VHAV Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	194	259	224	
Units: Subjects				
Vaccine response to Havrix®	192	257	224	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited local symptoms

End point title	Number of subjects reporting solicited local symptoms

End point description:

Solicited local symptoms assessed include pain, rash (local), redness and swelling.

End point type	Secondary

End point timeframe:

During the 4-day period following each dose of vaccine

End point values	HAV Group	HAV+MMR+V Group	MMR+VHAV Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304	419	411	
Units: Subjects				
Pain	103	187	162	
Rash (local)	0	4	3	
Redness	97	151	149	
Swelling	45	82	70	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting solicited general symptoms

End point title	Number of subjects reporting solicited general symptoms

End point description:

Solicited general symptoms assessed include drowsiness, fever, irritability, loss of appetite and rash (general).

End point type	Secondary

End point timeframe:

During the 4-day period following each dose of vaccine

End point values	HAV Group	HAV+MMR+V Group	MMR+VHAV Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304	411	424	
Units: Subjects				
Drowsiness	95	178	179	
Fever	54	80	110	
Irritability	144	216	238	
Loss of appetite	94	154	170	
Rash (general)	5	10	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting measles, mumps, rubella and varicella specific solicited general adverse events

End point title	Number of subjects reporting measles, mumps, rubella and varicella specific solicited general adverse events[11]

End point description:

Specific adverse events assessed include papules, vesicles, crusts, parotid/salivary gland swelling and suspected signs of meningitis/febrile seizures.

End point type	Secondary

End point timeframe:

During the 43-day period following each dose of vaccine

Notes:

[11] - 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: This outcome measure applies to subjects in the HAV+MMR+V and MMR+VHAV Groups.

End point values	HAV+MMR+V Group	MMR+VHAV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	455		
Units: Subjects				
Papules	23	23		
Vesicles	17	17		
Crusts	12	12		

Parotid/salivary gland swelling	1	0		
Suspected signs of meningitidis/febrile seizures	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited adverse events (AEs)

End point title	Number of subjects reporting unsolicited adverse events (AEs)

End point description:

Unsolicited AE covers any AE reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary

End point timeframe:

During the 31-day period following each dose of vaccine

End point values	HAV Group	HAV+MMR+V Group	MMR+VHAV Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	462	455	
Units: Subjects				
AEs	186	249	286	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs)

End point title	Number of subjects reporting serious adverse events (SAEs)

End point description:

SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject.

End point type	Secondary

End point timeframe:

During the Active Phase (from Day 0 up to Day 31 after the second dose) and the Extended Safety Follow-up Phase of the study (from Day 31 after the second dose up to study end)

End point values	HAV Group	HAV+MMR+V Group	MMR+VHAV Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	462	455	
Units: subjects				
Active Phase (n= 324, 462, 455)	1	5	6	
Extended Safety Follow-up Phase (n=287,395,276)	6	11	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting new chronic illnesses

End point title	Number of subjects reporting new chronic illnesses

End point description:

New Chronic illnesses include autoimmune disorders, asthma, type I diabetes, allergies.

End point type	Secondary

End point timeframe:

During the Active Phase (from Day 0 up to Day 31 after the second dose) and the Extended Safety Follow-up Phase of the study (from Day 31 after the second dose up to study end)

End point values	HAV Group	HAV+MMR+V Group	MMR+VHAV Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	462	455	
Units: subjects				
Active Phase (n= 324, 462, 455)	0	0	0	
Extended Safety Follow-Up Phase (n=287,395,376)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting medically significant events

End point title	Number of subjects reporting medically significant events

End point description:

Medically significant events include, but are not limited to, diabetes, autoimmune disease, asthma, allergies and/or conditions prompting emergency room or physician office visits that are not related to well-child care, vaccination or common acute illnesses (e.g., upper respiratory infection, otitis media, pharyngitis, gastroenteritis, injury and visits for routine physical examination).

End point type	Secondary

End point timeframe:

During the Active Phase (from Day 0 up to Day 31 after the second dose) and the Extended Safety Follow-up Phase of the study (from Day 31 after the second dose up to study end)

End point values	HAV Group	HAV+MMR+V Group	MMR+VHAV Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	462	455	
Units: Subjects				
Active Phase (n= 324, 455, 462)	0	0	0	
Extended Safety Follow-Up Phase (n= 287, 376, 395)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: From Day 0 to 31 (active phase); Day 31 to last contact (ESFU). Solicited local and general symptoms: during the 4-day period (Days 0-3) post-vaccination. Unsolicited AEs: during the 31-day period (Days 0-30) post-vaccination

Adverse event reporting additional description:

The number of occurrences reported for solicited symptoms, adverse events, and serious adverse events were not available for posting. The number of subjects affected by each specific event was indicated as the number of occurrences.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	HAV Group

Reporting group description:

Subjects received 2 doses of Havrix (1 dose at Day 0 and 1 dose between Month 6 and Month 9)

Reporting group title	MMR+VHAV Group

Reporting group description:

Subjects received 1 dose of M-M-R II and VARIVAX at Day 0 and then 2 doses of Havrix (1 dose at Day 42 and 1 dose between Month 7.5 and Month 10.5)

Reporting group title	HAV+MMR+V Group

Reporting group description:

Subjects received 1 dose of Havrix, coadministered with M-M-R II and VARIVAX, at Day 0 and 1 dose of Havrix between Month 6 and Month 9

Serious adverse events	HAV Group	MMR+VHAV Group	HAV+MMR+V Group
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 324 (2.16%)	12 / 455 (2.64%)	16 / 462 (3.46%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 455 (0.00%)	0 / 462 (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
Injury, poisoning and procedural complications			
Burns second degree			

subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Chemical poisoning			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Humerus fracture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Accidental overdose			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Animal bite			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Mental retardation			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autism			
subjects affected / exposed	1 / 324 (0.31%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			

subjects affected / exposed	1 / 324 (0.31%)	0 / 455 (0.00%)	0 / 462 (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
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Ileus			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed[1]	0 / 287 (0.00%)	0 / 376 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Breathing-related sleep disorder			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			

subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Gastroenteritis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed[2]	1 / 287 (0.35%)	1 / 376 (0.27%)	0 / 395 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			

subjects affected / exposed	1 / 324 (0.31%)	0 / 455 (0.00%)	0 / 462 (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
Localised infection			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	0 / 324 (0.00%)	0 / 455 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Viral infection			
subjects affected / exposed	0 / 324 (0.00%)	1 / 455 (0.22%)	0 / 462 (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
Metabolism and nutrition disorders			
Dehydratation			
subjects affected / exposed	2 / 324 (0.62%)	1 / 455 (0.22%)	2 / 462 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

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

Non-serious adverse events	HAV Group	MMR+VHAV Group	HAV+MMR+V Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	251 / 324 (77.47%)	366 / 455 (80.44%)	363 / 462 (78.57%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	34 / 324 (10.49%)	68 / 455 (14.95%)	56 / 462 (12.12%)
occurrences (all)	34	68	56
Papules			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 324 (0.00%)	23 / 455 (5.05%)	23 / 462 (4.98%)
occurrences (all)	0	23	23
Drowsiness			
alternative assessment type: Systematic			
subjects affected / exposed[3]	95 / 304 (31.25%)	179 / 411 (43.55%)	178 / 424 (41.98%)
occurrences (all)	95	179	178
Fever			
alternative assessment type: Systematic			
subjects affected / exposed[4]	54 / 304 (17.76%)	110 / 411 (26.76%)	80 / 424 (18.87%)
occurrences (all)	54	110	80
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed[5]	144 / 304 (47.37%)	238 / 411 (57.91%)	216 / 424 (50.94%)
occurrences (all)	144	238	216
Loss of appetite			
alternative assessment type: Systematic			
subjects affected / exposed[6]	94 / 304 (30.92%)	170 / 411 (41.36%)	154 / 424 (36.32%)
occurrences (all)	94	170	154

Pain			
alternative assessment type: Systematic			
subjects affected / exposed[7]	103 / 304 (33.88%)	162 / 411 (39.42%)	187 / 419 (44.63%)
occurrences (all)	103	162	187
Redness			
alternative assessment type: Systematic			
subjects affected / exposed[8]	97 / 304 (31.91%)	149 / 411 (36.25%)	151 / 419 (36.04%)
occurrences (all)	97	149	151
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed[9]	45 / 304 (14.80%)	70 / 411 (17.03%)	82 / 419 (19.57%)
occurrences (all)	45	70	82
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 324 (4.94%)	39 / 455 (8.57%)	22 / 462 (4.76%)
occurrences (all)	16	39	22
Teething			
subjects affected / exposed	25 / 324 (7.72%)	24 / 455 (5.27%)	19 / 462 (4.11%)
occurrences (all)	25	24	19
Vomiting			
subjects affected / exposed	14 / 324 (4.32%)	30 / 455 (6.59%)	12 / 462 (2.60%)
occurrences (all)	14	30	12
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 324 (6.48%)	20 / 455 (4.40%)	23 / 462 (4.98%)
occurrences (all)	21	20	23
Rhinorrhoea			
subjects affected / exposed	20 / 324 (6.17%)	22 / 455 (4.84%)	17 / 462 (3.68%)
occurrences (all)	20	22	17
Infections and infestations			
Otitis media			
subjects affected / exposed	35 / 324 (10.80%)	79 / 455 (17.36%)	65 / 462 (14.07%)
occurrences (all)	35	79	65
Upper respiratory tract infection			
subjects affected / exposed	31 / 324 (9.57%)	64 / 455 (14.07%)	58 / 462 (12.55%)
occurrences (all)	31	64	58

Nasopharyngitis subjects affected / exposed occurrences (all)	19 / 324 (5.86%) 19	19 / 455 (4.18%) 19	19 / 462 (4.11%) 19

Notes:

[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: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

[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: For a given subject cohort and the analysis of a given measurement, missing or non evaluable measurements were not replaced. Therefore, an analysis excluded data points for subjects with missing or non-evaluable measurements i.e. analysis of solicited symptoms will exclude vaccinated subjects without documented Diary Cards.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2006	The primary reasons for this amendment are: • to revise the clinically acceptable non-inferiority limits for the seroconversion rates for measles, mumps (i.e., from 10% to 5%) and the seroresponse rate for rubella (i.e., from 10% to 5%), • to increase the sample size of both the HAV+MMR+V and the MMR+VHAV Groups to 554 subjects in order to meet the revised non-inferiority limits and to ensure an adequate number of subjects enrolled given the high-drop-out rate between Visits 1 and 2, •to delete the inclusion of the HAV Group in the randomization of the additional 388 subjects to be enrolled because there was sufficient data available for the administration of Havrix only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported