



## Clinical trial results:

### A phase III randomized, placebo-controlled clinical trial to study the efficacy and safety of V260 in healthy infants in Japan

#### Summary

EudraCT number	2017-000264-15
Trial protocol	Outside EU/EEA
Global end of trial date	26 August 2009

#### Results information

Result version number	v1 (current)
This version publication date	06 May 2017
First version publication date	06 May 2017

#### Trial information

##### Trial identification

Sponsor protocol code	V260-029
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00718237
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	26 August 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 August 2009
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The purpose of the study is to evaluate whether V260 is effective and well tolerated in healthy Japanese infants.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 August 2008
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	Japan: 762
Worldwide total number of subjects	762
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)	762
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:

Healthy Japanese infants with no known history of rotavirus gastroenteritis were enrolled in the study.

### Pre-assignment

Screening details:

A total of 768 participants were screened and 762 were enrolled in the study.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	RotaTeq™

Arm description:

Three doses of RotaTeq™ (Rotavirus vaccine, live, oral, pentavalent) administered 28 to 70 days apart beginning on Day 1, with 14 days of safety follow-up after each vaccination, and follow-up for acute gastrointestinal episodes (AGEs) until a total of 30 cases are confirmed (up to approximately 25 months).

Arm type	Experimental
Investigational medicinal product name	RotaTeq™ (Rotavirus vaccine, live, oral, pentavalent)
Investigational medicinal product code	
Other name	V260
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Three 2-mL doses of oral solution administered 28 to 70 days apart

<b>Arm title</b>	Placebo
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Arm description:

Three doses of placebo administered 28 to 70 days apart beginning on Day 1, with 14 days of safety follow-up after each vaccination, and follow-up for AGEs until a total of 30 cases are confirmed (up to approximately 25 months).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Three 2-mL doses of oral solution administered 28 to 70 days apart

<b>Number of subjects in period 1</b>	RotaTeq™	Placebo
Started	381	381
Vaccinated at Visit 1	380	381
Vaccinated at Visit 2	373	374
Vaccinated at Visit 3	371	369
Completed	368	366
Not completed	13	15
Physician decision	1	-
Consent withdrawn by subject	9	10
Adverse Event	1	3
Lost to follow-up	2	2

## Baseline characteristics

### Reporting groups

Reporting group title	RotaTeq™
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Reporting group description:

Three doses of RotaTeq™ (Rotavirus vaccine, live, oral, pentavalent) administered 28 to 70 days apart beginning on Day 1, with 14 days of safety follow-up after each vaccination, and follow-up for acute gastrointestinal episodes (AGEs) until a total of 30 cases are confirmed (up to approximately 25 months).

Reporting group title	Placebo
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Reporting group description:

Three doses of placebo administered 28 to 70 days apart beginning on Day 1, with 14 days of safety follow-up after each vaccination, and follow-up for AGEs until a total of 30 cases are confirmed (up to approximately 25 months).

Reporting group values	RotaTeq™	Placebo	Total
Number of subjects	381	381	762
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	381	381	762
Age Continuous Units: weeks			
arithmetic mean	7.6	7.5	
standard deviation	± 1.7	± 1.6	-
Gender Categorical Units: Subjects			
Female	173	182	355
Male	208	199	407

## End points

### End points reporting groups

Reporting group title	RotaTeq™
Reporting group description: Three doses of RotaTeq™ (Rotavirus vaccine, live, oral, pentavalent) administered 28 to 70 days apart beginning on Day 1, with 14 days of safety follow-up after each vaccination, and follow-up for acute gastrointestinal episodes (AGEs) until a total of 30 cases are confirmed (up to approximately 25 months).	
Reporting group title	Placebo
Reporting group description: Three doses of placebo administered 28 to 70 days apart beginning on Day 1, with 14 days of safety follow-up after each vaccination, and follow-up for AGEs until a total of 30 cases are confirmed (up to approximately 25 months).	
Subject analysis set title	RotaTeq™ Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: Participants randomized to receive RotaTeq™ except those excluded with protocol deviations that may affect the results of the primary efficacy endpoint.	
Subject analysis set title	Placebo Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: Participants randomized to receive placebo except those excluded with protocol deviations that may affect the results of the primary efficacy endpoint.	

### Primary: Incidence Rate of Rotavirus Gastroenteritis of Any Severity Caused by Rotavirus Serotypes G1, G2, G3, G4 and G-serotypes Associated With P1A

End point title	Incidence Rate of Rotavirus Gastroenteritis of Any Severity Caused by Rotavirus Serotypes G1, G2, G3, G4 and G-serotypes Associated With P1A
End point description: Any severity cases of rotavirus gastroenteritis caused by G1, G2, G3, G4 or G-serotypes associated with P1A occurring at least 14 days postdose 3 in the per-protocol population using per-protocol case definition. The population analyzed was per-protocol participants except those unevaluable due to 1) detection of wild-type rotavirus in stool prior to 14 days Postdose 3, 2) incomplete clinical and/or laboratory results, or 3) stool samples collected out of day range.	
End point type	Primary
End point timeframe: From 14 days Postdose 3 onward	

End point values	RotaTeq™ Per Protocol	Placebo Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	355	356		
Units: Participants	7	27		

## Statistical analyses

<b>Statistical analysis title</b>	Vaccine Efficacy
Statistical analysis description: Efficacy = 1-RR, expressed as a percentage; the RR is the incidence in the vaccine group / the incidence in the placebo group, adjusted for the ratio of the follow-up period in each group.	
Comparison groups	RotaTeq™ Per Protocol v Placebo Per Protocol
Number of subjects included in analysis	711
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[1]</sup>
Method	Exact Conditional Test
Parameter estimate	Vaccine Efficacy
Point estimate	74.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.9
upper limit	90.6

Notes:

[1] - Hypothesis: Efficacy >0%. Based on  $p < 1/(1+k)$ ; p = proportion of participants with outcome in vaccine group relative to total number of participants with outcome; k = ratio of follow-up time; placebo/vaccine. Based on conditional binomial approach.

### **Secondary: Incidence Rate of Moderate to Severe Rotavirus Gastroenteritis Caused by Rotavirus Serotypes G1, G2, G3, G4 and G-serotypes Associated With P1A**

End point title	Incidence Rate of Moderate to Severe Rotavirus Gastroenteritis Caused by Rotavirus Serotypes G1, G2, G3, G4 and G-serotypes Associated With P1A
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End point description:

Moderate to severe cases of rotavirus gastroenteritis caused by G1, G2, G3, G4 or G-serotypes associated with P1A occurring at least 14 days postdose 3 in the per-protocol population using per-protocol case definition. Severity score was calculated based on frequency and duration of diarrhea, vomiting, elevated temperature, and behavioral changes. Score of >8 and ≤16 was considered moderate, and >16 was considered severe. The population analyzed was per-protocol participants except those unevaluable due to 1) detection of wild-type rotavirus in stool prior to 14 days Postdose 3, 2) incomplete clinical and/or laboratory results, or 3) stool samples collected out of day range.

End point type	Secondary
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End point timeframe:

From 14 days Postdose 3 onward

<b>End point values</b>	RotaTeq™ Per Protocol	Placebo Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	354	356		
Units: Participants	5	25		

### **Statistical analyses**

<b>Statistical analysis title</b>	Vaccine Efficacy
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Statistical analysis description:

Efficacy = 1-RR, expressed as a percentage; the RR is the incidence in the vaccine group / the incidence

in the placebo group, adjusted for the ratio of the follow-up period in each group.

Comparison groups	RotaTeq™ Per Protocol v Placebo Per Protocol
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Exact Conditional Test
Parameter estimate	Vaccine Efficacy
Point estimate	80.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.4
upper limit	94.1

Notes:

[2] - Hypothesis: Efficacy >0%. Based on  $p < 1/(1+k)$ ; p = proportion of participants with outcome in vaccine group relative to total number of participants with outcome; k = ratio of follow-up time; placebo/vaccine. Based on conditional binomial approach.

### Secondary: Incidence Rate of Severe Rotavirus Gastroenteritis Caused by Rotavirus Serotypes G1, G2, G3, G4 and G-serotypes Associated With P1A

End point title	Incidence Rate of Severe Rotavirus Gastroenteritis Caused by Rotavirus Serotypes G1, G2, G3, G4 and G-serotypes Associated With P1A
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End point description:

Severe cases of rotavirus gastroenteritis caused by G1, G2, G3, G4 or G-serotypes associated with P1A occurring at least 14 days postdose 3 in the per-protocol population using per-protocol case definition. Severity score was calculated based on frequency and duration of diarrhea, vomiting, elevated temperature, and behavioral changes. Score of >8 and ≤16 was considered moderate, and >16 was considered severe. The population analyzed was per-protocol participants except those unevaluable due to 1) detection of wild-type rotavirus in stool prior to 14 days Postdose 3, 2) incomplete clinical and/or laboratory results, or 3) stool samples collected out of day range.

End point type	Secondary
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End point timeframe:

From 14 days Postdose 3 onward

End point values	RotaTeq™ Per Protocol	Placebo Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	354	355		
Units: Participants	0	10		

### Statistical analyses

Statistical analysis title	Vaccine Efficacy
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Statistical analysis description:

Efficacy = 1-RR, expressed as a percentage; the RR is the incidence in the vaccine group / the incidence in the placebo group, adjusted for the ratio of the follow-up period in each group.

Comparison groups	RotaTeq™ Per Protocol v Placebo Per Protocol
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Number of subjects included in analysis	709
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 <sup>[3]</sup>
Method	Exact Conditional Test
Parameter estimate	Vaccine Efficacy
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.4
upper limit	100

Notes:

[3] - Hypothesis: Efficacy >0%. Based on  $p < 1/(1+k)$ ; p = proportion of participants with outcome in vaccine group relative to total number of participants with outcome; k = ratio of follow-up time; placebo/vaccine. Based on conditional binomial approach.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

14-day period following each vaccination. Any death, Vaccine related serious adverse events (AEs) and Intussusception were collected during the study period.

Adverse event reporting additional description:

Parents/guardians were asked to record AEs on a standardized Vaccine Report Card (VRC) up to 14 days after each vaccination. Solicited AEs included diarrhea and vomiting. Temperature was also measured daily for 7 days after each vaccination.

The number of participants exposed is the number of participants who received study treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

At least one dose of placebo administered 28 to 70 days apart, beginning on Day 1.

Reporting group title	RotaTeq™
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Reporting group description:

At least one dose of RotaTeq™ (Rotavirus vaccine, live, oral, pentavalent) administered 28 to 70 days apart, beginning on Day 1.

Serious adverse events	Placebo	RotaTeq™	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 381 (2.36%)	7 / 380 (1.84%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Congenital absence of bile ducts			
subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Infantile spasms			
subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			

subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 381 (0.26%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	0 / 381 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychomotor retardation			
subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 381 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			

subjects affected / exposed	0 / 381 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis coxsackie viral			
subjects affected / exposed	0 / 381 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 381 (0.00%)	1 / 380 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 381 (0.00%)	2 / 380 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 381 (0.26%)	0 / 380 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	RotaTeq™	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	175 / 381 (45.93%)	179 / 380 (47.11%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	31 / 381 (8.14%)	29 / 380 (7.63%)	
occurrences (all)	40	33	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 381 (0.79%)	7 / 380 (1.84%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 381 (1.84%)	11 / 380 (2.89%)	
occurrences (all)	7	11	
Diarrhoea			
subjects affected / exposed	47 / 381 (12.34%)	46 / 380 (12.11%)	
occurrences (all)	65	64	
Infantile spitting up			
subjects affected / exposed	2 / 381 (0.52%)	6 / 380 (1.58%)	
occurrences (all)	3	11	
Vomiting			
subjects affected / exposed	29 / 381 (7.61%)	31 / 380 (8.16%)	
occurrences (all)	39	53	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 381 (1.05%)	1 / 380 (0.26%)	
occurrences (all)	4	1	
Cough			
subjects affected / exposed	8 / 381 (2.10%)	1 / 380 (0.26%)	
occurrences (all)	10	1	
Rhinorrhoea			
subjects affected / exposed	6 / 381 (1.57%)	5 / 380 (1.32%)	
occurrences (all)	7	5	
Upper respiratory tract inflammation			

subjects affected / exposed occurrences (all)	16 / 381 (4.20%) 16	27 / 380 (7.11%) 32	
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	6 / 381 (1.57%)	9 / 380 (2.37%)	
occurrences (all)	7	11	
Eczema			
subjects affected / exposed	12 / 381 (3.15%)	14 / 380 (3.68%)	
occurrences (all)	12	15	
Eczema infantile			
subjects affected / exposed	10 / 381 (2.62%)	7 / 380 (1.84%)	
occurrences (all)	10	7	
Rash			
subjects affected / exposed	4 / 381 (1.05%)	2 / 380 (0.53%)	
occurrences (all)	4	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 381 (2.10%)	7 / 380 (1.84%)	
occurrences (all)	9	7	
Gastroenteritis			
subjects affected / exposed	14 / 381 (3.67%)	27 / 380 (7.11%)	
occurrences (all)	16	38	
Nasopharyngitis			
subjects affected / exposed	37 / 381 (9.71%)	37 / 380 (9.74%)	
occurrences (all)	46	43	
Respiratory syncytial virus infection			
subjects affected / exposed	2 / 381 (0.52%)	4 / 380 (1.05%)	
occurrences (all)	2	4	
Rhinitis			
subjects affected / exposed	8 / 381 (2.10%)	0 / 380 (0.00%)	
occurrences (all)	9	0	
Upper respiratory tract infection			
subjects affected / exposed	9 / 381 (2.36%)	4 / 380 (1.05%)	
occurrences (all)	10	4	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported