



## Clinical trial results:

**A phase IV, uncontrolled, open-label, multi-center study in children and adolescents: Evaluation of long-term immunogenicity in subjects boosted with a new pediatric TBE vaccine (free of protein-derived stabilizer) in study V48P4E1, five years after first booster immunization**  
**Summary**

EudraCT number	2014-005105-20
Trial protocol	Outside EU/EEA
Global end of trial date	24 May 2007

### Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	14 May 2015

### Trial information

#### Trial identification

Sponsor protocol code	V48P4E3
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00452621
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics GmbH & Co. KG
Sponsor organisation address	Postfach 1630, Marburg, Germany, 35006
Public contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.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 November 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 May 2007
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To investigate the kinetics of the immune response of subjects who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up) with respect to antibody titers in terms of:

- percentage of subjects with titers  $\geq 10$
- percentage of subjects with titers  $\geq 2$
- geometric mean titer (GMT)

as measured by Neutralization Test (NT, in-house, Novartis Vaccines), from Day 0 as defined in protocol V48P4 to year 5 ( $\pm 90$  days) after the first booster immunization with the new TBE vaccine

Protection of trial subjects:

This study was performed with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, the applicable regulatory requirements(s) for the country in which the study was conducted, and applicable standard operating procedures (SOPs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 232
Worldwide total number of subjects	232
EEA total number of subjects	232

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	0

months)	
Children (2-11 years)	121
Adolescents (12-17 years)	111
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

18 centers in Germany

### Pre-assignment

Screening details:

All enrolled subjects were included in the trial

The classification of the age group (Age Classification I & II) refers to the age of the subjects in Study V48P4.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	1-2 years

Arm description:

Subjects aged 1-2 years (Age Classification II) and who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up)

Arm type	no product administered
Investigational medicinal product name	no product was administered in this extension study
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Route of administration not applicable

Dosage and administration details:

Not applicable as this study does not involve administration of product. The pharmaceutical form selected for this study is applicable only to the parent study.

<b>Arm title</b>	3-11 years
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Arm description:

Subjects aged 3-11 years (Age Classification II) and who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up)

Arm type	no product administered
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	1-5 years

Arm description:

Subjects aged 1-5 years (Age Classification I) and who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up)

Arm type	no product administered
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	6-11 years

Arm description:

Subjects aged 6-11 years (Age Classification I) and who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up)

Arm type	no product administered
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	1-2 years	3-11 years	1-5 years
Started	51	181	127
Completed	51	181	127

<b>Number of subjects in period 1</b>	6-11 years
Started	105
Completed	105

## Baseline characteristics

### Reporting groups

Reporting group title	Enrolled
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Reporting group description: -

Reporting group values	Enrolled	Total	
Number of subjects	232	232	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	121	121	
Adolescents (12-17 years)	111	111	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
PPS			
Units: years			
arithmetic mean	11.5		
standard deviation	± 2.8	-	
Gender categorical			
Units: Subjects			
Female	104	104	
Male	128	128	

## End points

### End points reporting groups

Reporting group title	1-2 years
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Reporting group description:

Subjects aged 1-2 years (Age Classification II) and who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up)

Reporting group title	3-11 years
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Reporting group description:

Subjects aged 3-11 years (Age Classification II) and who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up)

Reporting group title	1-5 years
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Reporting group description:

Subjects aged 1-5 years (Age Classification I) and who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up)

Reporting group title	6-11 years
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Reporting group description:

Subjects aged 6-11 years (Age Classification I) and who participated in studies V48P4 (primary immunization), V48P4E1 (first booster immunization) and V48P4E2 (serological follow-up)

Subject analysis set title	Enrolled population
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Subject analysis set type	Full analysis
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Subject analysis set description:

All enrolled subjects

Subject analysis set title	Full Analysis Set (FAS), Immunogenicity
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Subject analysis set type	Full analysis
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Subject analysis set description:

All enrolled subjects:

- who participated in the studies V48P4, V48P4E1 and V48P4E2

- who provided an evaluable serum sample

Subjects who received a booster vaccination after V48P4E2 were included in the FAS and assigned to a NT titer of 2 and an ELISA below detection limit, respectively

Subject analysis set title	Per Protocol Set (PPS), Immunogenicity
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Subject analysis set type	Per protocol
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Subject analysis set description:

All subjects in the PPS:

- who were part of the PPS of study V48P4E2

- had no major protocol violation as defined prior to the analysis

Subjects who received a booster vaccination after V48P4E2 were included in the PPS and assigned to a NT titer of 2 and an ELISA below detection limit, respectively

Subject analysis set title	Uninfluenced Per Protocol Population (UPPS)
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Subject analysis set type	Per protocol
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Subject analysis set description:

Uninfluenced Per Protocol Population (UPPS) which consisted of all those subjects in the Per Protocol Population, which had not received an additional (i.e. not study related) TBE booster in the study period of V48P4E2 or after.

### Primary: 1. Percentage of Subjects With Antibody Titers $\geq 2$ as Measured by Neutralization Test( NT)- PPS

End point title	1. Percentage of Subjects With Antibody Titers $\geq 2$ as Measured by Neutralization Test( NT)- PPS <sup>[1]</sup>
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End point description:

Immunogenicity was measured in terms of the Percentage of Subjects With Antibody Titers  $\geq 2$  as Measured by NT

End point type	Primary
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End point timeframe:

Day 0, Day 42, Booster Day 0, Booster Day 21, 3 Years after booster, 5 Years after booster

Notes:

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

Justification: Statistical analysis not applicable

End point values	1-2 years	3-11 years	1-5 years	6-11 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	161	110	95
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 0 (Visit 1 of V48P4)	0 (0 to 8)	0 (0 to 2)	0 (0 to 3)	0 (0 to 4)
Day 42 (Visit 4 of V48P4)	100 (92 to 100)	100 (98 to 100)	100 (97 to 100)	100 (96 to 100)
Booster Day 0 (Visit 5 V48P4E1)	100 (92 to 100)	100 (98 to 100)	100 (97 to 100)	100 (96 to 100)
Booster Day 21 (Visit 6 of V48P4E1)	100 (92 to 100)	100 (98 to 100)	100 (97 to 100)	100 (96 to 100)
Years 3 after booster (Visit 7 of V48P4E2)	100 (92 to 100)	100 (98 to 100)	100 (97 to 100)	100 (96 to 100)
Years 5 after booster (Visit 8 of V48P4E3)	100 (92 to 100)	100 (98 to 100)	100 (97 to 100)	100 (96 to 100)

## Statistical analyses

No statistical analyses for this end point

## Primary: 2. Percentage of Subjects With Antibody Titers $\geq 10$ as Measured by NT-PPS

End point title	2. Percentage of Subjects With Antibody Titers $\geq 10$ as Measured by NT- PPS <sup>[2]</sup>
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End point description:

Immunogenicity was measured in terms of the Percentage of Subjects With Antibody Titers  $\geq 10$  as Measured by NT

End point type	Primary
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End point timeframe:

Day 0, Day 42, Booster Day 0, Booster Day 21, 3 Years after booster, 5 Years after booster

Notes:

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

Justification: Statistical analysis not applicable

End point values	1-2 years	3-11 years	1-5 years	6-11 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	161	110	95
Units: Percentages of Subjects				
number (confidence interval 95%)				
Day 0 (Visit 1 of V48P4)	0 (0 to 8)	0 (0 to 2)	0 (0 to 3)	0 (0 to 4)
Day 42 (Visit 4 of V48P4)	100 (92 to 100)	97 (93 to 99)	99 (95 to 100)	96 (90 to 99)



Booster Day 0 (Visit 5 V48P4E1)	100 (92 to 100)	99 (96 to 100)	100 (97 to 100)	98 (93 to 100)
Booster Day 21 (Visit 6 of V48P4E1)	100 (92 to 100)	100 (98 to 100)	100 (97 to 100)	100 (96 to 100)
Years 3 after booster (Visit 7 of V48P4E2)	100 (92 to 100)	100 (98 to 100)	100 (97 to 100)	100 (96 to 100)
Years 5 after booster (Visit 8 of V48P4E3)	70 (55 to 83)	86 (79 to 91)	80 (71 to 87)	85 (77 to 92)

## Statistical analyses

No statistical analyses for this end point

### Primary: 3.Geometric Mean Antibody Titers (GMT)as Measured by NT- PPS

End point title	3.Geometric Mean Antibody Titers (GMT)as Measured by NT-PPS <sup>[3]</sup>
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End point description:

Immunogenicity was measured in terms of the Geometric Mean Antibody Titers (GMT)as Measured by NT

End point type	Primary
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End point timeframe:

Day 0, Day 42, Booster Day 0, Booster Day 21, 3 Years after booster, 5 Years after booster

Notes:

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

Justification: Statistical analysis not applicable

End point values	1-2 years	3-11 years	1-5 years	6-11 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	161	110	95
Units: Titers				
geometric mean (confidence interval 95%)				
Day 0 (Visit 1of V48P4)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)
Day 42 (Visit 4 of V48P4)	70 (52 to 93)	46 (40 to 53)	57 (47 to 69)	43 (36 to 51)
Booster Day 0 (Visit 5 V48P4E1)	200 (155 to 258)	104 (90 to 120)	154 (130 to 183)	89 (74 to 106)
Booster Day 21 (Visit 6 of V48P4E1)	5750 (4146 to 7976)	3807 (3201 to 4528)	4863 (3954 to 5980)	3471 (2763 to 4360)
Years 3 after booster (Visit 7 of V48P4E2)	472 (335 to 664)	426 (358 to 508)	494 (400 to 610)	377 (301 to 473)
Years 5 after booster (Visit 8 of V48P4E3)	99 (44 to 223)	268 (188 to 383)	186 (117 to 297)	259 (162 to 414)

## Statistical analyses

No statistical analyses for this end point

### Primary: 4. Ratios of Geometric Mean Antibody Titers (GMT)as Measured by NT- PPS

End point title	4. Ratios of Geometric Mean Antibody Titers (GMT)as Measured by NT- PPS <sup>[4]</sup>
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End point description:

Immunogenicity was measured in terms of the Ratios of Geometric Mean Antibody Titers (GMT) as Measured by NT

End point type	Primary
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End point timeframe:

Day 42, Booster Day 0, Booster Day 21, 3 Years after booster, 5 Years after booster

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: Statistical analysis not applicable

End point values	1-2 years	3-11 years	1-5 years	6-11 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	161	110	95
Units: Ratios				
number (confidence interval 95%)				
Year 5 (Visit 8) / Day 42 (Visit 4)	1.43 (0.6 to 3.36)	5.87 (3.99 to 8.64)	3.27 (1.95 to 5.47)	6 (3.63 to 9.92)
Year 5 (Visit 8) / Day 0 (Visit 5)	0.5 (0.2 to 1.22)	2.59 (1.79 to 3.74)	1.21 (0.72 to 2.01)	2.92 (1.8 to 4.73)
Year 5 (Visit 8) / Day 21 (Visit 6)	0.017 (0.0073 to 0.041)	0.071 (0.05 to 0.1)	0.038 (0.024 to 0.061)	0.075 (0.046 to 0.12)
Year 5 (Visit 8) / Year 3 (Visit 7)	0.21 (0.083 to 0.53)	0.63 (0.45 to 0.87)	0.38 (0.23 to 0.61)	0.69 (0.44 to 1.08)

## Statistical analyses

No statistical analyses for this end point

## Primary: 5. Percentage of Subjects With Antibody Titers $\geq 2$ as Measured by NT - UPPS

End point title	5. Percentage of Subjects With Antibody Titers $\geq 2$ as Measured by NT -UPPS <sup>[5]</sup>
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End point description:

Immunogenicity was measured in terms of the Percentage of Subjects With Antibody Titers  $\geq 2$  as Measured by NT

End point type	Primary
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End point timeframe:

Day 0, Day 42, Booster Day 0, Booster Day 21, 3 Years after booster, 5 Years after booster

Notes:

[5] - 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: Statistical analysis not applicable

End point values	1-2 years	3-11 years	1-5 years	6-11 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	138	88	81
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 0 (Visit 1 of V48P4)	0 (0 to 11)	0 (0 to 3)	0 (0 to 4)	0 (0 to 4)
Day 42 (Visit 4 of V48P4)	100 (89 to 100)	100 (97 to 100)	100 (96 to 100)	100 (96 to 100)

Booster Day 0 (Visit 5 V48P4E1)	100 (89 to 100)	100 (97 to 100)	100 (96 to 100)	100 (96 to 100)
Booster Day 21 (Visit 6 of V48P4E1)	100 (89 to 100)	100 (97 to 100)	100 (96 to 100)	100 (96 to 100)
Years 3 after booster (Visit 7 of V48P4E2)	100 (89 to 100)	100 (97 to 100)	100 (96 to 100)	100 (96 to 100)
Years 5 after booster (Visit 8 of V48P4E3)	100 (89 to 100)	100 (97 to 100)	100 (96 to 100)	100 (96 to 100)

## Statistical analyses

No statistical analyses for this end point

### Primary: 6. Percentage of Subjects With Antibody Titers $\geq 10$ as Measured by NT-UPPS

End point title	6. Percentage of Subjects With Antibody Titers $\geq 10$ as Measured by NT-UPPS <sup>[6]</sup>
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End point description:

Immunogenicity was measured in terms of the Percentage of Subjects With Antibody Titers  $\geq 10$  as Measured by NT

End point type	Primary
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End point timeframe:

Day 0, Day 42, Booster Day 0, Booster Day 21, 3 Years after booster, 5 Years after booster

Notes:

[6] - 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: Statistical analysis not applicable

End point values	1-2 years	3-11 years	1-5 years	6-11 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	138	88	81
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 0 (Visit 1 of V48P4)	0 (0 to 11)	0 (0 to 3)	0 (0 to 4)	0 (0 to 4)
Day 42 (Visit 4 of V48P4)	100 (89 to 100)	97 (93 to 99)	99 (94 to 100)	96 (90 to 99)
Booster Day 0 (Visit 5 V48P4E1)	100 (89 to 100)	99 (96 to 100)	100 (96 to 100)	99 (93 to 100)
Booster Day 21 (Visit 6 of V48P4E1)	100 (89 to 100)	100 (97 to 100)	100 (96 to 100)	100 (96 to 100)
Years 3 after booster (Visit 7 of V48P4E2)	100 (89 to 100)	100 (97 to 100)	100 (96 to 100)	100 (96 to 100)
Years 5 after booster (Visit 8 of V48P4E3)	100 (89 to 100)	100 (97 to 100)	100 (96 to 100)	100 (96 to 100)

## Statistical analyses

No statistical analyses for this end point

### Primary: 7. Geometric Mean Antibody Titers (GMT) as Measured by NT-UPPS

End point title	7. Geometric Mean Antibody Titers (GMT)as Measured by NT-UPPS <sup>[7]</sup>
End point description: Immunogenicity was measured in terms of the Geometric Mean Antibody Titers (GMT)as Measured by NT	
End point type	Primary
End point timeframe: Day 0, Day 42, Booster Day 0, Booster Day 21, 3 Years after booster, 5 Years after booster	
Notes: [7] - 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: Statistical analysis not applicable	

End point values	1-2 years	3-11 years	1-5 years	6-11 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	138	88	81
Units: Titers				
geometric mean (confidence interval 95%)				
Day 0 (Visit 1of V48P4)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)
Day 42 (Visit 4 of V48P4)	72 (50 to 105)	44 (38 to 52)	56 (45 to 69)	42 (35 to 50)
Booster Day 0 (Visit 5 V48P4E1)	169 (125 to 228)	103 (89 to 121)	142 (117 to 172)	88 (73 to 107)
Booster Day 21 (Visit 6 of V48P4E1)	5278 (3554 to 7841)	3801 (3141 to 4599)	4741 (3704 to 6011)	3389 (2648 to 4338)
Years 3 after booster (Visit 7 of V48P4E2)	369 (253 to 538)	431 (356 to 523)	466 (368 to 591)	373 (291 to 479)
Years 5 after booster (Visit 8 of V48P4E3)	511 (368 to 709)	607 (498 to 741)	578 (459 to 728)	600 (460 to 781)

## Statistical analyses

No statistical analyses for this end point

## Primary: 8. Ratios of Geometric Mean Antibody Titers (GMT)as Measured by NT-UPPS

End point title	8. Ratios of Geometric Mean Antibody Titers (GMT)as Measured by NT-UPPS <sup>[8]</sup>
End point description: Immunogenicity was measured in terms of the Ratios of Geometric Mean Antibody Titers (GMT)as Measured by NT	
End point type	Primary
End point timeframe: Day 42, Booster Day 0, Booster Day 21, 3 Years after booster, 5 Years after booster	
Notes: [8] - 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: Statistical analysis not applicable	

<b>End point values</b>	1-2 years	3-11 years	1-5 years	6-11 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	138	88	81
Units: Ratios				
number (confidence interval 95%)				
Year 5 (Visit 8) / Day 42 (Visit 4)	7.07 (4.07 to 12)	14 (11 to 17)	10 (7.47 to 14)	14 (11 to 19)
Year 5 (Visit 8) / Day 0 (Visit 5)	3.03 (2.1 to 4.36)	5.87 (4.74 to 7.27)	4.07 (3.14 to 5.28)	6.77 (5.17 to 8.88)
Year 5 (Visit 8) / Day 21 (Visit 6)	0.097 (0.072 to 0.13)	0.16 (0.14 to 0.19)	0.12 (0.1 to 0.14)	0.18 (0.14 to 0.22)
Year 5 (Visit 8) / Year 3 (Visit 7)	1.38 (1.08 to 1.78)	1.41 (1.25 to 1.59)	1.24 (1.09 to 1.41)	1.61 (1.36 to 1.9)

## Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

NA

Adverse event reporting additional description:

NA

Assessment type	Non-systematic
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### Dictionary used

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Dictionary name	NA
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Dictionary version	NA
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Frequency threshold for reporting non-serious adverse events: 0 %

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Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: NA

## 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