



## Clinical trial results:

### A Phase III, Open-Label, Clinical Trial to Study the Safety and Immunogenicity of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Particle (VLP) Vaccine in 9- to 15-Year- Old Japanese Boys

#### Summary

EudraCT number	2015-004212-37
Trial protocol	Outside EU/EEA
Global end of trial date	08 August 2018

#### Results information

Result version number	v1 (current)
This version publication date	16 March 2019
First version publication date	16 March 2019

#### Trial information

##### Trial identification

Sponsor protocol code	V501-200
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576054
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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	08 August 2018
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	08 August 2018
Was the trial ended prematurely?	No

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Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of the study is to demonstrate that administration of V501 induces high seroconversion rates for the vaccine HPV types (6, 11, 16 and 18) at 4 weeks post dose 3 in 9- to 15-year-old Japanese boys.

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 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Japan: 101
Worldwide total number of subjects	101
EEA total number of subjects	0

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Notes:

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**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)	0
Children (2-11 years)	36
Adolescents (12-17 years)	65
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Healthy Japanese male participants between the ages of 9 and 15 years (inclusive) were enrolled in the study. Additional inclusion/exclusion criteria applied.

### Period 1

Period 1 title	Vaccination Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	V501
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Arm description:

V501 administered as a 0.5 mL intramuscular injection at Day 1, Month 2 and Month 6.

Arm type	Experimental
Investigational medicinal product name	Quadrivalent HPV (Type 6, 11, 16 and 18) L1 Virus-Like Particle (VLP) vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Administered as a 0.5 mL intramuscular injection at Day 1, Month 2 and Month 6.

Number of subjects in period 1	V501
Started	101
Vaccination 1	100
Vaccination 2	100
Vaccination 3	100
Completed	100
Not completed	1
Consent withdrawn by subject	1

<b>Period 2</b>	
Period 2 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
<b>Arms</b>	
<b>Arm title</b>	V501
Arm description:	
Participants that completed Period 1 of the study.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 2</b>	V501
Started	100
Completed	100

## Baseline characteristics

### Reporting groups

Reporting group title	V501
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Reporting group description:

V501 administered as a 0.5 mL intramuscular injection at Day 1, Month 2 and Month 6.

Reporting group values	V501	Total	
Number of subjects	101	101	
Age Categorical			
Units: Subjects			
9 to 12 years of age	53	53	
13 to 16 years of age	48	48	
Age Continuous			
Units: years			
arithmetic mean	12.2		
standard deviation	± 2.0	-	
Gender Categorical			
Units: Subjects			
Male	101	101	
Race			
Units: Subjects			
Asian	101	101	
Ethnicity			
Units: Subjects			
Not Hispanic Or Latino	101	101	

## End points

### End points reporting groups

Reporting group title	V501
Reporting group description: V501 administered as a 0.5 mL intramuscular injection at Day 1, Month 2 and Month 6.	
Reporting group title	V501
Reporting group description: Participants that completed Period 1 of the study.	
Subject analysis set title	V501-Efficacy
Subject analysis set type	Per protocol
Subject analysis set description: All participants that received all 3 vaccinations within acceptable day ranges, were seronegative to the relevant HPV type at day 1, did not have protocol violations that could interfere with evaluation of the immune response, and provided Month 7 serology result within 21 to 49 days post dose 3.	
Subject analysis set title	V501-Safety
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received at least 1 study vaccination and had follow-up safety data.	
Subject analysis set title	Participants Aged 9 to 15 years (PN 200)-Efficacy
Subject analysis set type	Per protocol
Subject analysis set description: All participants aged 9 to 15 years of age that received all 3 vaccinations within acceptable day ranges, were seronegative to the relevant HPV type at day 1, did not have protocol violations that could interfere with evaluation of the immune response, and provided Month 7 serology result within 21 to 49 days post dose 3.	

### Primary: Percentage of Participants with Seroconversion for HPV Types 6, 11, 16, and 18

End point title	Percentage of Participants with Seroconversion for HPV Types 6, 11, 16, and 18 <sup>[1]</sup>
End point description: Antibodies to HPV Types 6, 11, 16, and 18 were measured using a competitive Luminex immunoassay 4 weeks after 3rd vaccination (Month 7). Antibody titers were expressed as milli Merck units/mL (mMU/mL). Seroconversion was defined as an anti-HPV 6 titer $\geq 20$ milliMerck units per milliliter (mMU/mL), an anti-HPV 11 titer $\geq 16$ mMU/mL, an anti-HPV 16 titer of $\geq 20$ mMU/mL and an anti-HPV 18 titer of $\geq 24$ mMU/mL.	
End point type	Primary
End point timeframe: Four weeks postdose 3 (Month 7)	

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: No statistical analysis was planned for this endpoint.

<b>End point values</b>	V501-Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: Percentage of Participants				
arithmetic mean (confidence interval 95%)				
Anti-HPV 6 (n=98)	94.9 (88.5 to 98.3)			

Anti-HPV 11 (n=98)	99.0 (94.4 to 100.0)			
Anti-HPV 16 (n=99)	99.0 (94.4 to 100.0)			
Anti-HPV 18 (n=98)	99.0 (94.4 to 100.0)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants with Elevated Oral Temperature ( $\geq 37.5^{\circ}\text{C}$ )

End point title	Percentage of Participants with Elevated Oral Temperature ( $\geq 37.5^{\circ}\text{C}$ ) <sup>[2]</sup>
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End point description:

The parent/guardian of the participant was to record the participant's oral temperature in the evening after each study vaccination and daily for 4 days after each study vaccination. Elevated temperature was defined as  $\geq 99.5^{\circ}\text{F}$  ( $\geq 37.5^{\circ}\text{C}$ ). The percentage of participants that had an elevated temperature was summarized.

End point type	Primary
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End point timeframe:

Up to Day 5 after any vaccination

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: No statistical analysis was planned for this endpoint.

End point values	V501-Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: Percentage of participants				
number (not applicable)				
$\geq 37.5^{\circ}\text{C}$ ( $99.5^{\circ}\text{F}$ ) and $< 38.0^{\circ}\text{C}$ ( $100.4^{\circ}\text{F}$ )	3.0			
$\geq 38.0^{\circ}\text{C}$ ( $100.4^{\circ}\text{F}$ ) and $< 38.5^{\circ}\text{C}$ ( $101.3^{\circ}\text{F}$ )	1.0			
$\geq 38.5^{\circ}\text{C}$ ( $101.3^{\circ}\text{F}$ )	2.0			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants with an Injection-site Adverse Event

End point title	Percentage of Participants with an Injection-site Adverse
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End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study drug. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug or a protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study drug or

protocol-specified procedure is also an AE. The parent/guardian of the participant was to record the presence of any vaccination report card (VRC)-prompted injection-site AEs that occurred in the 5 days after any vaccination. The percentage of participants with an injection-site AE prompted on the VRC (erythema, pain, and swelling) was summarized.

End point type	Primary
End point timeframe:	
Up to Day 5 after any vaccination	

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: No statistical analysis was planned for this endpoint.

<b>End point values</b>	V501-Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: Percentage of Participants				
number (not applicable)	64.0			

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants with a Systemic Adverse Event

End point title	Percentage of Participants with a Systemic Adverse Event <sup>[4]</sup>
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End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with study drug. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug or a protocol-specified procedure, whether or not considered related to the study drug or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the study drug or protocol-specified procedure is also an AE. The parent/guardian of the participant was to record the presence of any VRC-prompted systemic AEs that occurred in the 5 days after any vaccination. The percentage of participants with a systemic AE was summarized.

End point type	Primary
End point timeframe:	
Up to Day 15 after any vaccination	

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: No statistical analysis was planned for this endpoint.

<b>End point values</b>	V501-Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: Percentage of Participants				
number (not applicable)	21.0			

## Statistical analyses



No statistical analyses for this end point

### Primary: Percentage of Participants with a Serious Adverse Event

End point title	Percentage of Participants with a Serious Adverse Event <sup>[5]</sup>
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End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the sponsor's product, whether or not considered related to the use of the product. A serious adverse event (SAE) is an AE that results in death, is life threatening, results in a persistent or significant disability or incapacity, results in or prolongs an existing hospitalization, is a congenital anomaly or birth defect, is a cancer, is an overdose, or is another important medical event. The percentage of participants that experienced 1 or more SAEs were summarized.

End point type	Primary
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End point timeframe:

Up to Day 15 after any vaccination

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: No statistical analysis was planned for this endpoint.

End point values	V501-Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: Percentage of Participants				
number (not applicable)	0.0			

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants with a Vaccine-related Serious Adverse Event

End point title	Percentage of Participants with a Vaccine-related Serious Adverse Event <sup>[6]</sup>
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End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the sponsor's product, whether or not considered related to the use of the product. A serious adverse event (SAE) is an AE that results in death, is life threatening, results in a persistent or significant disability or incapacity, results in or prolongs an existing hospitalization, is a congenital anomaly or birth defect, is a cancer, is an overdose, or is another important medical event. The percentage of participants that experienced 1 or more SAEs that were considered at least possibly related to the study vaccine were summarized.

End point type	Primary
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End point timeframe:

Up to 30 months

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: No statistical analysis was planned for this endpoint.

<b>End point values</b>	V501-Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: Percentage of Participants				
number (not applicable)	0.0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric Mean Titers for Serum Anti-HPV Types 6, 11, 16, and 18 at Month 7

End point title	Geometric Mean Titers for Serum Anti-HPV Types 6, 11, 16, and 18 at Month 7
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End point description:

Antibodies to HPV Types 6, 11, 16, and 18 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL). GMTs obtained for each anti-HPV from this study were compared to each of the anti-HPV GMTs obtained in study V501-122 (NCT NCT01862874) in which Japanese males 16 to 26 years received V501 in the same 3 dose regimen, to test a hypothesis that would demonstrate non-inferiority. Due to limitations in EudraCT data entry system, these comparisons cannot be included in the record. The comparisons can be viewed at <https://clinicaltrials.gov/> (NCT02576054).

End point type	Secondary
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End point timeframe:

Four weeks postdose 3 (Month 7)

<b>End point values</b>	Participants Aged 9 to 15 years (PN 200)-Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: mMU/mL				
arithmetic mean (confidence interval 95%)				
Anti-HPV 6 (n=98)	482.9 (351.1 to 664.1)			
Anti-HPV 11 (n=98)	1052.8 (851.3 to 1302.0)			
Anti-HPV 16 (n=99)	3878.3 (2908.5 to 5171.6)			
Anti-HPV 18 (n=98)	1114.5 (871.6 to 1425.1)			

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Geometric Mean Titers for Serum Anti-HPV Types 6, 11, 16, and 18: Persistence at Month 18**

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End point title	Geometric Mean Titers for Serum Anti-HPV Types 6, 11, 16, and 18: Persistence at Month 18
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End point description:

Antibodies to HPV Types 6, 11, 16, and 18 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL).

End point type	Secondary
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End point timeframe:

12 months postdose 3 (Month 18)

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End point values	V501-Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: mMU/mL				
arithmetic mean (confidence interval 95%)				
Anti-HPV 6 (n=97)	222.0 (181.8 to 271.3)			
Anti-HPV 11 (n=97)	259.9 (210.7 to 320.7)			
Anti-HPV 16 (n=98)	1154.1 (937.3 to 1421.0)			
Anti-HPV 18 (n=97)	212.1 (165.6 to 271.7)			

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Geometric Mean Titers for Serum Anti-HPV Types 6, 11, 16, and 18: Persistence at Month 30**

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End point title	Geometric Mean Titers for Serum Anti-HPV Types 6, 11, 16, and 18: Persistence at Month 30
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End point description:

Antibodies to HPV Types 6, 11, 16, and 18 were measured using a competitive Luminex immunoassay. Antibody titers were expressed as milli Merck units/mL (mMU/mL).

End point type	Secondary
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End point timeframe:

24 months postdose 3 (Month 30)

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<b>End point values</b>	V501-Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: mMU/mL				
arithmetic mean (confidence interval 95%)				
Anti-HPV 6 (n=98)	177.5 (145.0 to 217.2)			
Anti-HPV 11 (n=98)	181.5 (146.3 to 225.2)			
Anti-HPV 16 (n=99)	831.3 (680.7 to 1015.1)			
Anti-HPV 18 (n=98)	144.2 (112.2 to 185.2)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with Seroconversion for HPV Types 6, 11, 16, and 18: Persistence at Month 18

End point title	Percentage of Participants with Seroconversion for HPV Types 6, 11, 16, and 18: Persistence at Month 18
End point description:	
Serum antibodies to HPV types were measured with a Competitive Luminex Immunoassay. The serostatus cutoffs (milli Merck U/mL) for HPV types were as follows: HPV Type 6: $\geq 20$ ; HPV Type 11: $\geq 16$ ; HPV Type 16: $\geq 20$ ; HPV Type 18: $\geq 24$	
End point type	Secondary
End point timeframe:	
12 months postdose 3 (Month 18)	

<b>End point values</b>	V501-Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: Percentage of Participants				
number (confidence interval 95%)				
Anti-HPV 6 (n=97)	97.9 (92.7 to 99.7)			
Anti-HPV 11 (n=97)	100.0 (96.3 to 100.0)			
Anti-HPV 16 (n=98)	99.0 (94.4 to 100.0)			
Anti HPV 18 (n=97)	94.8 (88.4 to 98.3)			

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of Participants with Seroconversion for HPV Types 6, 11, 16, and 18: Persistence at Month 30**

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End point title	Percentage of Participants with Seroconversion for HPV Types 6, 11, 16, and 18: Persistence at Month 30
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End point description:

Serum antibodies to HPV types were measured with a Competitive Luminex Immunoassay. The serostatus cutoffs (milli Merck U/mL) for HPV types were as follows: HPV Type 6:  $\geq 20$ ; HPV Type 11:  $\geq 16$ ; HPV Type 16:  $\geq 20$ ; HPV Type 18:  $\geq 24$

End point type	Secondary
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End point timeframe:

24 months postdose 3 (Month 30)

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End point values	V501-Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: Percentage of Participants				
number (confidence interval 95%)				
Anti-HPV 6 (n=98)	98.0 (92.8 to 99.8)			
Anti-HPV 11 (n=98)	98.0 (92.8 to 99.8)			
Anti-HPV 16 (n=99)	99.0 (94.5 to 100.0)			
Anti-HPV 18 (n=98)	93.9 (87.1 to 97.7)			

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 30 months

Adverse event reporting additional description:

Safety population included all participants that received at least 1 vaccination.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	V501
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Reporting group description: -

Serious adverse events	V501		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	V501		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 100 (67.00%)		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	31 / 100 (31.00%)		
occurrences (all)	57		
Injection site pain			
subjects affected / exposed	57 / 100 (57.00%)		
occurrences (all)	130		
Injection site pruritus			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	10		
Injection site swelling			

subjects affected / exposed occurrences (all)	34 / 100 (34.00%) 63		
Pyrexia subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 8		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 100 (9.00%) 11		

## 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