



Clinical trial results:

A Open-label, Randomized, Multicenter Study of the Safety, Tolerability, and Immunogenicity of GARDASIL™ Given Concomitantly with REPEVAX™ in Healthy Adolescents 11-17 Years of Age

Summary

EudraCT number	2006-000764-85
Trial protocol	FI DE DK BE
Global end of trial date	24 May 2007

Results information

Result version number	v2 (current)
This version publication date	07 October 2016
First version publication date	08 September 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	V501-024
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00337428
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, New Jersey, 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	24 May 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2007
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:

The purpose of this study was to demonstrate the following:

- 1) Antibody response to HPV types 6, 11, 16, and 18 was not impaired when a first dose of REPEVAX™ was administered concomitantly with the first dose of Quadrivalent Human Papillomavirus (qHPV) vaccine (GARDASIL™/Silgard™) compared to the administration of qHPV vaccine (GARDASIL™/Silgard™) alone.
- (2) Antibody response to diphtheria, tetanus, pertussis and poliomyelitis was not impaired when the first dose of qHPV vaccine (GARDASIL™/Silgard™) was administered concomitantly with a first dose of REPEVAX™ compared to the administration of REPEVAX™ alone.
- (3) Concomitant administration of the first dose of qHPV vaccine (GARDASIL™/Silgard™) with REPEVAX™ was generally well tolerated compared to when the first dose of qHPV vaccine (GARDASIL™/Silgard™) was given separately from REPEVAX™.

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. The following additional measure for this study were in place for the protection of trial participants:

Participants were observed for 30 minutes each vaccination for any immediate reaction or evidence of allergic phenomena.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 99
Country: Number of subjects enrolled	Denmark: 160
Country: Number of subjects enrolled	Finland: 374
Country: Number of subjects enrolled	Germany: 210
Worldwide total number of subjects	843
EEA total number of subjects	843

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)	0
Children (2-11 years)	477
Adolescents (12-17 years)	366
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:

The study enrolled healthy participants, 11-17 years old, with 0 lifetime sexual partners, vaccinated against diphtheria, tetanus, pertussis and polio but had not received the vaccine in the past 5 years or any prior human papillomavirus (HPV) vaccine. Additional inclusion and exclusion criteria applied.

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	qHPV Vaccine + REPEVAX™ (Concomitant)

Arm description:

Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) vaccine and REPEVAX™ administered on Day 1 at different injection sites.

Arm type	Active comparator
Investigational medicinal product name	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) Vaccine from Current Manufacturing Facility (CMF)
Investigational medicinal product code	
Other name	GARDASIL™/Silgard™
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

Investigational medicinal product name	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) Vaccine from Final Manufacturing Facility (FMF)
Investigational medicinal product code	
Other name	GARDASIL™/Silgard™
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

Investigational medicinal product name	REPEVAX™ (Concomitant)
Investigational medicinal product code	
Other name	dTap-IPV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Administered as a single 0.5-mL intramuscular dose at Day in a limb opposite that of qHPV injection

Arm title	qHPV Vaccine + REPEVAX™ (Non-concomitant)
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Arm description:

Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) vaccine administered on Day 1 followed by REPEVAX™ administered at Month 1.

Arm type	Active comparator
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Investigational medicinal product name	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) Vaccine from Current Manufacturing Facility (CMF)
Investigational medicinal product code	
Other name	GARDASIL™/Silgard™
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	
Investigational medicinal product name	Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) Vaccine from Final Manufacturing Facility (FMF)
Investigational medicinal product code	
Other name	GARDASIL™/Silgard™
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	
Investigational medicinal product name	REPEVAX™ (Non-Concomitant)
Investigational medicinal product code	
Other name	dTap-IPV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
Administered as a single 0.5-mL intramuscular dose at Month 1 in a limb opposite that of qHPV injection	

Number of subjects in period 1	qHPV Vaccine + REPEVAX™ (Concomitant)	qHPV Vaccine + REPEVAX™ (Non-concomitant)
Started	419	424
Completed	415	421
Not completed	4	3
Consent withdrawn by subject	1	2
Unwilling to Continue	1	-
Lack of Time	1	1
Anorexia (unrelated to vaccine)	1	-

Baseline characteristics

Reporting groups

Reporting group title	qHPV Vaccine + REPEVAX™ (Concomitant)
Reporting group description: Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) vaccine and REPEVAX™ administered on Day 1 at different injection sites.	
Reporting group title	qHPV Vaccine + REPEVAX™ (Non-concomitant)
Reporting group description: Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) vaccine administered on Day 1 followed by REPEVAX™ administered at Month 1.	

Reporting group values	qHPV Vaccine + REPEVAX™ (Concomitant)	qHPV Vaccine + REPEVAX™ (Non-concomitant)	Total
Number of subjects	419	424	843
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	229	248	477
Adolescents (12-17 years)	190	176	366
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	12.1	12.1	-
standard deviation	± 1.5	± 1.5	-
Gender Categorical Units: Subjects			
Female	295	288	583
Male	124	136	260
Race/Ethnicity Units: Subjects			
Asian	1	3	4
Black	3	3	6
Multi-racial	2	3	5
White	413	415	828

End points

End points reporting groups

Reporting group title	qHPV Vaccine + REPEVAX™ (Concomitant)
Reporting group description:	
Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) vaccine and REPEVAX™ administered on Day 1 at different injection sites.	
Reporting group title	qHPV Vaccine + REPEVAX™ (Non-concomitant)
Reporting group description:	
Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) vaccine administered on Day 1 followed by REPEVAX™ administered at Month 1.	

Primary: Geometric Mean Titers (GMTs) for HPV Types 6, 11, 16, and 18 Antibody at Month 7 (4 Weeks Postdose 3)

End point title	Geometric Mean Titers (GMTs) for HPV Types 6, 11, 16, and 18 Antibody at Month 7 (4 Weeks Postdose 3)
End point description:	
Serum antibodies to HPV Types 6, 11, 16, and 18 were measured with a Competitive Luminex Immunoassay. Titers were reported in milli Merck Units (mMU)/milliliter (mL). GMTs from participants who received qHPV vaccine and REPEVAX™ together at Day 1 (concomitant) were compared to GMTs from participants who received qHPV vaccine at Day 1 followed by REPEVAX™ 1 month later (non-concomitant). An analysis of non-inferiority compared GMTs for each HPV type using an ANOVA model with a response of log individual titers and fixed effects for treatment group, manufacturing facility, study site, and the treatment-by-site interaction. The analysis was performed in the per-protocol population that included participants with no major protocol violations, who were seronegative at baseline to the relevant HPV type, and had post-vaccination data.	
End point type	Primary
End point timeframe:	
Up to 7 Months (4 Weeks Postdose 3)	

End point values	qHPV Vaccine + REPEVAX™ (Concomitant)	qHPV Vaccine + REPEVAX™ (Non-concomitant)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	424		
Units: milli Merck Units (mMU)/milliliter (mL)				
geometric mean (confidence interval 95%)				
Anti-HPV Type 6 (n = 367, 376)	1151.3 (1007.5 to 1315.7)	1244.9 (1092.4 to 1418.6)		
Anti-HPV Type 11 (n = 367, 376)	1338.3 (1209 to 1481.4)	1460.7 (1322.4 to 1613.3)		
Anti-HPV Type 16 (n = 370, 378)	5835.7 (5195.7 to 6554.6)	6508.1 (5810.3 to 7289.6)		
Anti-HPV Type 18 (n = 372, 378)	1096 (958.8 to 1252.8)	1308.8 (1148.1 to 1491.9)		

Statistical analyses

Statistical analysis title	GMTs for Anti-HPV Type 6
Statistical analysis description: Analysis of non-inferiority of the GMTs for Anti-HPV Type 6 induced in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority of GMT was demonstrated if there was <2-fold decrease in GMT for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the GMT ratio (concomitant/non-concomitant) was >0.5.¶	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA

Statistical analysis title	GMTs for Anti-HPV Type 11
Statistical analysis description: Analysis of non-inferiority of the GMTs for Anti-HPV Type 11 induced in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority of GMT was demonstrated if there was <2-fold decrease in GMT for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the GMT ratio (concomitant/non-concomitant) was >0.5.¶	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA

Statistical analysis title	GMTs for Anti-HPV Type 16
Statistical analysis description: Analysis of non-inferiority of the GMTs for Anti-HPV Type 16 induced in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority of GMT was demonstrated if there was <2-fold decrease in GMT for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the GMT ratio (concomitant/non-concomitant) was >0.5.¶	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)

Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA

Statistical analysis title	GMTs for Anti-HPV Type 18
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Statistical analysis description:

Analysis of non-inferiority of the GMTs for Anti-HPV Type 18 induced in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority of GMT was demonstrated if there was <2-fold decrease in GMT for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the GMT ratio (concomitant/non-concomitant) was >0.5.¶

Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA

Primary: Number of Participants Who Seroconverted for HPV Types 6, 11, 16, and 18 by Month 7 (4 Weeks Postdose 3)

End point title	Number of Participants Who Seroconverted for HPV Types 6, 11, 16, and 18 by Month 7 (4 Weeks Postdose 3)
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End point description:

Seroconversion to HPV Types 6, 11, 16, and 18 was defined as changing serostatus from seronegative to seropositive as measured by GMT. Cutoff values for HPV seropositivity are ≥20 mMU/mL for Type 6 and 16, ≥16 mMU/mL for Type 11, and ≥24 mMU/mL for Type 18. Seroconversion of participants who received qHPV vaccine and REPEVAX™ together at Day 1 (concomitant) was compared to seroconversion of participants who received qHPV vaccine at Day 1 followed by REPEVAX™ 1 month later (non-concomitant). An analysis of non-inferiority compared seroconversion for each HPV type using methods developed by Miettinen and Nurminen adjusting for manufacturing facility for qHPV vaccine. The analysis was performed in the per-protocol population that included participants with no major protocol violations, who were seronegative at baseline to the relevant HPV type, and had post-vaccination data.

End point type	Primary
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End point timeframe:

Up to 7 Months (4 Weeks Postdose 3)

End point values	qHPV Vaccine + REPEVAX™ (Concomitant)	qHPV Vaccine + REPEVAX™ (Non-concomitant)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	424		
Units: Number of Participants				
Anti-HPV Type 6 (n = 367, 376)	367	375		
Anti-HPV Type 11 (n = 367, 376)	367	376		

Anti-HPV Type 16 (n = 370, 378)	370	378		
Anti-HPV Type 18 (n = 372, 378)	372	378		

Statistical analyses

Statistical analysis title	Seroconversion for Anti-HPV Type 6
Statistical analysis description:	
Analysis of non-inferiority of seroconversion for Anti-HPV Type 6 in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority for seroconversion was demonstrated if there was <5 percentage point decrease in seroconversion for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the percentage point difference (concomitant-non-concomitant) was >-5.	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Statistical analysis title	Seroconversion for Anti-HPV Type 11
Statistical analysis description:	
Analysis of non-inferiority of seroconversion for Anti-HPV Type 11 in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority for seroconversion was demonstrated if there was <5 percentage point decrease in seroconversion for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the percentage point difference (concomitant-non-concomitant) was >-5.	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Statistical analysis title	Seroconversion for Anti-HPV Type 16
Statistical analysis description:	
Analysis of non-inferiority of seroconversion for Anti-HPV Type 16 in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority for seroconversion was demonstrated if there was <5 percentage point decrease in seroconversion for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the percentage point difference (concomitant-non-concomitant) was >-5.	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)

Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Statistical analysis title	Seroconversion for Anti-HPV Type 18
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Statistical analysis description:

Analysis of non-inferiority of seroconversion for Anti-HPV Type 18 in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority for seroconversion was demonstrated if there was <5 percentage point decrease in seroconversion for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the percentage point difference (concomitant-non-concomitant) was >-5.

Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Primary: Geometric Mean Titers (GMTs) for Pertussis Toxoid (Anti-PT), Filamentous Haemagglutinin (Anti-FHA), Pertactin (Anti-PRN), and Fimbrial Agglutinogens (Anti-FIM) Antibodies One Month Post-vaccination With REPEVAX™

End point title	Geometric Mean Titers (GMTs) for Pertussis Toxoid (Anti-PT), Filamentous Haemagglutinin (Anti-FHA), Pertactin (Anti-PRN), and Fimbrial Agglutinogens (Anti-FIM) Antibodies One Month Post-vaccination With REPEVAX™
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End point description:

Serum antibodies to Pertussis Toxoid Antibody (Anti-PT), Filamentous Haemagglutinin Antibody (Anti-FHA), Pertactin (Anti-PRN), and Fimbrial Agglutinogens Antibody (Anti-FIM) were measured with an enzyme-linked immunosorbent assay (ELISA). Titers were reported in ELISA units/mL (ELU/mL) and the lower limit of quantitation for the assay is 5.0, 3.0, 5.0, and 5.0 ELU/mL for Anti-PT, Anti-FHA, Anti-PRN, and Anti-FIM, respectively. GMTs from participants who received qHPV vaccine and REPEVAX™ together at Day 1 (concomitant) were compared to GMTs from participants who received qHPV vaccine at Day 1 followed by REPEVAX™ 1 month later (non-concomitant). An analysis of non-inferiority compared GMTs using an ANOVA model with a response of log individual titers and fixed effects for treatment group, manufacturing facility, study site, and the treatment-by-site interaction.

End point type	Primary
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End point timeframe:

Up to 1 Month (1 Month Postdose1)

End point values	qHPV Vaccine + REPEVAX™ (Concomitant)	qHPV Vaccine + REPEVAX™ (Non-concomitant)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	424		
Units: ELU/mL				

geometric mean (confidence interval 95%)				
GMTs for Anti-PT (n = 381, 378)	38.1 (33.2 to 43.7)	35.7 (31.1 to 40.9)		
GMTs for Anti-FHA (n = 382, 381)	140.3 (127.5 to 154.4)	140.7 (127.9 to 154.7)		
GMTs for Anti-PRN (n = 382, 381)	504.1 (442.7 to 574)	552.8 (485.9 to 629.1)		
GMTs for Anti-FIM (n = 381, 381)	561.2 (478.9 to 657.7)	506.4 (432.5 to 592.8)		

Statistical analyses

Statistical analysis title	GMTs for Anti-PT
Statistical analysis description:	
Analysis of non-inferiority of the GMTs for Anti-PT induced in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority of GMT was demonstrated if there was <1.5-fold decrease in GMT for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the GMT ratio (concomitant/non-concomitant) was >0.67.	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA

Statistical analysis title	GMTs for Anti-FHA
Statistical analysis description:	
Analysis of non-inferiority of the GMTs for Anti-FHA induced in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority of GMT was demonstrated if there was <1.5-fold decrease in GMT for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the GMT ratio (concomitant/non-concomitant) was >0.67.	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA

Statistical analysis title	GMTs for Anti-PRN
Statistical analysis description:	
Analysis of non-inferiority of the GMTs for Anti-PRN induced in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority of GMT was demonstrated if there was <1.5-fold decrease in GMT for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the GMT ratio (concomitant/non-concomitant) was >0.67.	

Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA

Statistical analysis title	GMTs for Anti-FIM
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Statistical analysis description:

Analysis of non-inferiority of the GMTs for Anti-FIM induced in participants who received concomitant compared with non-concomitant administration of qHPV vaccine and REPEVAX. Non-inferiority of GMT was demonstrated if there was <1.5-fold decrease in GMT for concomitant compared to non-concomitant administration and the lower limit of the 95% CI for the GMT ratio (concomitant/non-concomitant) was >0.67.

Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA

Primary: Number of Participants Who Achieved Acceptable Levels of Titers to Diphtheria (Diphtheria ≥ 0.1 IU/mL) One Month Post-vaccination With REPEVAX™

End point title	Number of Participants Who Achieved Acceptable Levels of Titers to Diphtheria (Diphtheria ≥ 0.1 IU/mL) One Month Post-vaccination With REPEVAX™
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End point description:

Diphtheria antitoxin titers were measured using a neutralization assay in Vero cell culture that compares the antitoxin level in the serum of participants with the World Health Organization International Standard for Diphtheria Antitoxin. An acceptable level of response was defined as ≥0.1 International Units (IU)/milliliter (mL). Response levels of participants who received qHPV vaccine and REPEVAX™ together at Day 1 (concomitant) were compared to participants who received qHPV vaccine at Day 1 followed by REPEVAX™ 1 month later (non-concomitant). An analysis of non-inferiority compared response levels using methods developed by Miettinen and Nurminen adjusting for manufacturing facility for qHPV vaccine. The analysis was performed in the per-protocol population that included participants with no major protocol violations, who were seronegative at baseline to the relevant HPV type, and had post-vaccination data.

End point type	Primary
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End point timeframe:

Up to 1 Month (1 Month Postdose 1)

End point values	qHPV Vaccine + REPEVAX™ (Concomitant)	qHPV Vaccine + REPEVAX™ (Non-concomitant)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	380	380		
Units: Number of Participants	380	379		

Statistical analyses

Statistical analysis title	Participants With ≥ 0.1 IU/mL Antitoxin Titers
Statistical analysis description:	
Non-inferiority was demonstrated if there was <10 percentage point decrease in the percent of participants with ≥ 0.1 IU/mL for concomitant group compared to non-concomitant group and the lower limit of the 95% CI for the percentage point difference is greater than -10.	
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Primary: Number of Participants Who Achieved Acceptable Levels of Titers to Tetanus (Tetanus ≥ 0.1 IU/mL) One Month Post-vaccination With REPEVAX™

End point title	Number of Participants Who Achieved Acceptable Levels of Titers to Tetanus (Tetanus ≥ 0.1 IU/mL) One Month Post-vaccination With REPEVAX™
End point description:	
Tetanus antitoxin titers were measured using an indirect, non-competitive enzyme immunoassay (EIA) that compares the antitoxin level in the serum of participants with the World Health Organization International Standard for Tetanus Immunoglobulin. An acceptable level of response was defined as ≥ 0.1 International Units (IU)/milliliter (mL). Response levels of participants who received qHPV vaccine and REPEVAX™ together at Day 1 (concomitant) were compared to participants who received qHPV vaccine at Day 1 followed by REPEVAX™ 1 month later (non-concomitant). An analysis of non-inferiority compared response levels using methods developed by Miettinen and Nurminen adjusting for manufacturing facility for qHPV vaccine. The analysis was performed in the per-protocol population that included participants with no major protocol violations, who were seronegative at baseline to the relevant HPV type, and had post-vaccination data.	
End point type	Primary
End point timeframe:	
Up to 1 Month (1 Month Postdose 1)	

End point values	qHPV Vaccine + REPEVAX™ (Concomitant)	qHPV Vaccine + REPEVAX™ (Non-concomitant)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	380		
Units: Number of Participants	381	380		

Statistical analyses

Statistical analysis title	Participants With ≥ 0.1 IU/mL Tetanus Titers
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	761
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Primary: Number of Participants Who Achieved Acceptable Levels of Titers to Poliovirus Types 1, 2 and 3 ($\geq 1:8$ Dilution) One Month Post-vaccination With REPEVAX™

End point title	Number of Participants Who Achieved Acceptable Levels of Titers to Poliovirus Types 1, 2 and 3 ($\geq 1:8$ Dilution) One Month Post-vaccination With REPEVAX™
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End point description:

Poliovirus antibody was measured using a poliovirus neutralization assay that assesses the ability of serial dilutions of participant sera to neutralize known amounts of type-specific Sabin poliovirus strains (Types 1, 2, and 3). An acceptable level of response was defined as participants who achieve detectable serum neutralizing antibodies (Neut Abs) at a $\geq 1:8$ dilution (Dil) of sera. The response of participants who received qHPV vaccine and REPEVAX™ together at Day 1 (concomitant) was compared to participants who received qHPV vaccine at Day 1 followed by REPEVAX™ 1 month later (non-concomitant). An analysis of non-inferiority compared response levels using methods developed by Miettinen and Nurminen adjusting for manufacturing facility for qHPV vaccine. The analysis was performed in the per-protocol population that included participants with no major protocol violations, who were seronegative at baseline to the relevant HPV type, and had post-vaccination data.

End point type	Primary
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End point timeframe:

Up to 1 Month (1 Month Postdose 1)

End point values	qHPV Vaccine + REPEVAX™ (Concomitant)	qHPV Vaccine + REPEVAX™ (Non-concomitant)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	424		
Units: Number of Participants				
Poliovirus Type 1 (n = 367, 377)	367	376		
Poliovirus Type 2 (n = 369, 377)	369	376		

Poliovirus Type 3 (n = 361, 375)	360	375		
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Statistical analyses

Statistical analysis title	Participants With Type 1 Neut Abs at $\geq 1:8$ Dil
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Statistical analysis title	Participants With Type 2 Neut Abs at $\geq 1:8$ Dil
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Statistical analysis title	Participants With Type 3 Neut Abs at $\geq 1:8$ Dil
Comparison groups	qHPV Vaccine + REPEVAX™ (Concomitant) v qHPV Vaccine + REPEVAX™ (Non-concomitant)
Number of subjects included in analysis	843
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from Day 1 until Month 7.

Adverse event reporting additional description:

AEs were collected on participants who received ≥ 1 dose of study vaccine (qHPV or Repevax). Fevers and injection-site AEs were reported for Days 1-5 and all other AEs for Days 1-15. Injection-site AEs are reported separately for those associated with qHPV (AE term-qHPV) and those that are associated with Repevax (AE term-Repevax).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.1
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Reporting groups

Reporting group title	qHPV Vaccine + Repevax concomitant
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Reporting group description:

Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) vaccine and REPEVAX™ administered on Day 1 at different injection sites.

The number exposed reflects 1 participant who was randomized into the Non-Concomitant Vaccination group and received study vaccines concomitantly and appears in the qHPV vaccine + Repevax (Concomitant Column).

Reporting group title	qHPV Vaccine + Repevax non-concomitant
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Reporting group description:

Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant (qHPV) vaccine administered on Day 1 followed by REPEVAX™ administered at Month 1.

The number exposed reflects 1 participant who was randomized into the Non-Concomitant Vaccination group and received study vaccines concomitantly and appears in the qHPV vaccine + Repevax (Concomitant Column).

Serious adverse events	qHPV Vaccine + Repevax concomitant	qHPV Vaccine + Repevax non- concomitant	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 420 (0.24%)	3 / 423 (0.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			

subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ligament disorder			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (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: 0 %

Non-serious adverse events	qHPV Vaccine + Repevax concomitant	qHPV Vaccine + Repevax non- concomitant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	405 / 420 (96.43%)	406 / 423 (95.98%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 420 (0.48%)	0 / 423 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			

Hypotension subjects affected / exposed occurrences (all)	0 / 420 (0.00%) 0	1 / 423 (0.24%) 1	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	2 / 420 (0.48%) 2	2 / 423 (0.47%) 2	
Axillary pain subjects affected / exposed occurrences (all)	2 / 420 (0.48%) 2	2 / 423 (0.47%) 2	
Chills subjects affected / exposed occurrences (all)	3 / 420 (0.71%) 3	1 / 423 (0.24%) 1	
Facial pain subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	13 / 420 (3.10%) 13	8 / 423 (1.89%) 8	
Feeling cold subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Feeling of body temperature change subjects affected / exposed occurrences (all)	0 / 420 (0.00%) 0	2 / 423 (0.47%) 2	
Influenza like illness subjects affected / exposed occurrences (all)	3 / 420 (0.71%) 3	2 / 423 (0.47%) 2	
Injection site bruising-qHPV subjects affected / exposed occurrences (all)	6 / 420 (1.43%) 6	5 / 423 (1.18%) 5	
Injection site discolouration-qHPV subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	1 / 423 (0.24%) 1	
Injection site erythema-qHPV			

subjects affected / exposed	77 / 420 (18.33%)	63 / 423 (14.89%)
occurrences (all)	98	85
Injection site haematoma-qHPV		
subjects affected / exposed	5 / 420 (1.19%)	7 / 423 (1.65%)
occurrences (all)	5	8
Injection site haemorrhage-qHPV		
subjects affected / exposed	3 / 420 (0.71%)	4 / 423 (0.95%)
occurrences (all)	3	4
Injection site induration-qHPV		
subjects affected / exposed	4 / 420 (0.95%)	5 / 423 (1.18%)
occurrences (all)	4	5
Injection site irritation-qHPV		
subjects affected / exposed	1 / 420 (0.24%)	2 / 423 (0.47%)
occurrences (all)	2	2
Injection site movement impairment-qHPV		
subjects affected / exposed	1 / 420 (0.24%)	3 / 423 (0.71%)
occurrences (all)	2	5
Injection site nodule-qHPV		
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)
occurrences (all)	1	0
Injection site pain-qHPV		
subjects affected / exposed	335 / 420 (79.76%)	304 / 423 (71.87%)
occurrences (all)	641	630
Injection site pruritus-qHPV		
subjects affected / exposed	8 / 420 (1.90%)	11 / 423 (2.60%)
occurrences (all)	8	11
Injection site reaction-qHPV		
subjects affected / exposed	1 / 420 (0.24%)	1 / 423 (0.24%)
occurrences (all)	1	1
Injection site swelling-qHPV		
subjects affected / exposed	89 / 420 (21.19%)	90 / 423 (21.28%)
occurrences (all)	131	119
Injection site warmth-qHPV		
subjects affected / exposed	1 / 420 (0.24%)	2 / 423 (0.47%)
occurrences (all)	1	3

Local swelling		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Malaise		
subjects affected / exposed	5 / 420 (1.19%)	2 / 423 (0.47%)
occurrences (all)	5	2
Pyrexia		
subjects affected / exposed	50 / 420 (11.90%)	55 / 423 (13.00%)
occurrences (all)	53	60
Vessel puncture site pain		
subjects affected / exposed	1 / 420 (0.24%)	1 / 423 (0.24%)
occurrences (all)	1	1
Injection site anaesthesia-Repevax		
subjects affected / exposed	1 / 420 (0.24%)	1 / 423 (0.24%)
occurrences (all)	1	1
Injection site bruising-Repevax		
subjects affected / exposed	4 / 420 (0.95%)	2 / 423 (0.47%)
occurrences (all)	4	2
Injection site discolouration-Repevax		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Injection site erythema-Repevax		
subjects affected / exposed	77 / 420 (18.33%)	79 / 423 (18.68%)
occurrences (all)	77	80
Injection site haematoma-Repevax		
subjects affected / exposed	3 / 420 (0.71%)	4 / 423 (0.95%)
occurrences (all)	3	4
Injection site haemorrhage-Repevax		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Injection site induration-Repevax		
subjects affected / exposed	3 / 420 (0.71%)	3 / 423 (0.71%)
occurrences (all)	3	3
Injection site irritation-Repevax		
subjects affected / exposed	4 / 420 (0.95%)	5 / 423 (1.18%)
occurrences (all)	4	5

Injection site mass-Repevax subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Injection site movement impairment-Repevax subjects affected / exposed occurrences (all)	3 / 420 (0.71%) 3	3 / 423 (0.71%) 3	
Injection site nodule-Repevax subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Injection site pain-Repevax subjects affected / exposed occurrences (all)	350 / 420 (83.33%) 383	346 / 423 (81.80%) 373	
Injection site papule-Repevax subjects affected / exposed occurrences (all)	0 / 420 (0.00%) 0	1 / 423 (0.24%) 1	
Injection site pruritus-Repevax subjects affected / exposed occurrences (all)	4 / 420 (0.95%) 4	7 / 423 (1.65%) 7	
Injection site rash-Repevax subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Injection site reaction-Repevax subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Injection site swelling-Repevax subjects affected / exposed occurrences (all)	130 / 420 (30.95%) 132	131 / 423 (30.97%) 132	
Injection site warmth-Repevax subjects affected / exposed occurrences (all)	4 / 420 (0.95%) 4	2 / 423 (0.47%) 2	
Immune system disorders			
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 420 (0.00%) 0	2 / 423 (0.47%) 2	
Seasonal allergy			

subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 2	0 / 423 (0.00%) 0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	4 / 420 (0.95%)	3 / 423 (0.71%)	
occurrences (all)	4	4	
Metrorrhagia			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	14 / 420 (3.33%)	11 / 423 (2.60%)	
occurrences (all)	15	11	
Dyspnoea			
subjects affected / exposed	3 / 420 (0.71%)	0 / 423 (0.00%)	
occurrences (all)	3	0	
Epistaxis			
subjects affected / exposed	2 / 420 (0.48%)	1 / 423 (0.24%)	
occurrences (all)	2	2	
Nasal congestion			
subjects affected / exposed	2 / 420 (0.48%)	3 / 423 (0.71%)	
occurrences (all)	2	3	
Pharyngolaryngeal pain			
subjects affected / exposed	22 / 420 (5.24%)	24 / 423 (5.67%)	
occurrences (all)	23	29	
Rhinitis allergic			
subjects affected / exposed	2 / 420 (0.48%)	1 / 423 (0.24%)	
occurrences (all)	2	2	
Rhinorrhoea			
subjects affected / exposed	1 / 420 (0.24%)	2 / 423 (0.47%)	
occurrences (all)	2	2	
Throat irritation			

subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Listless			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 420 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Heart rate increased			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Arthropod sting			
subjects affected / exposed	0 / 420 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Brain contusion			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Concussion			
subjects affected / exposed	1 / 420 (0.24%)	2 / 423 (0.47%)	
occurrences (all)	1	2	
Contusion			

subjects affected / exposed	0 / 420 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Excoriation			
subjects affected / exposed	0 / 420 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Fracture			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Joint injury			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Joint sprain			
subjects affected / exposed	2 / 420 (0.48%)	1 / 423 (0.24%)	
occurrences (all)	2	1	
Muscle strain			
subjects affected / exposed	0 / 420 (0.00%)	3 / 423 (0.71%)	
occurrences (all)	0	3	
Post-traumatic pain			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	2	
Procedural dizziness			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	2 / 420 (0.48%)	2 / 423 (0.47%)	
occurrences (all)	3	4	
Thermal burn			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	2 / 420 (0.48%)	0 / 423 (0.00%)	
occurrences (all)	2	0	
Incision site haemorrhage			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	14 / 420 (3.33%)	10 / 423 (2.36%)	
occurrences (all)	15	11	
Headache			
subjects affected / exposed	132 / 420 (31.43%)	112 / 423 (26.48%)	
occurrences (all)	193	168	
Hyperaesthesia			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Loss of consciousness			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	0 / 420 (0.00%)	3 / 423 (0.71%)	
occurrences (all)	0	3	
Paraesthesia			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	2 / 420 (0.48%)	0 / 423 (0.00%)	
occurrences (all)	2	0	
Syncope			
subjects affected / exposed	2 / 420 (0.48%)	1 / 423 (0.24%)	
occurrences (all)	2	1	
Syncope vasovagal			
subjects affected / exposed	1 / 420 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Hypochromasia			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Lymphadenitis			

subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	4 / 420 (0.95%)	2 / 423 (0.47%)	
occurrences (all)	4	3	
Motion sickness			
subjects affected / exposed	2 / 420 (0.48%)	0 / 423 (0.00%)	
occurrences (all)	2	0	
Vertigo			
subjects affected / exposed	2 / 420 (0.48%)	2 / 423 (0.47%)	
occurrences (all)	2	2	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 420 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	
Conjunctivitis allergic			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	0 / 420 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Lacrimation increased			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Ocular discomfort			

subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 420 (4.76%)	12 / 423 (2.84%)	
occurrences (all)	26	16	
Abdominal pain lower			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	14 / 420 (3.33%)	16 / 423 (3.78%)	
occurrences (all)	15	18	
Aphthous stomatitis			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	9 / 420 (2.14%)	18 / 423 (4.26%)	
occurrences (all)	9	21	
Dyspepsia			
subjects affected / exposed	1 / 420 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	2	
Enteritis			
subjects affected / exposed	0 / 420 (0.00%)	2 / 423 (0.47%)	
occurrences (all)	0	2	
Gastritis			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Lip swelling			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	

Nausea			
subjects affected / exposed	21 / 420 (5.00%)	19 / 423 (4.49%)	
occurrences (all)	27	21	
Stomatitis			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	2	
Teething			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	2 / 420 (0.48%)	2 / 423 (0.47%)	
occurrences (all)	2	2	
Vomiting			
subjects affected / exposed	11 / 420 (2.62%)	11 / 423 (2.60%)	
occurrences (all)	11	13	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	2 / 420 (0.48%)	1 / 423 (0.24%)	
occurrences (all)	2	1	
Erythema			
subjects affected / exposed	3 / 420 (0.71%)	2 / 423 (0.47%)	
occurrences (all)	3	2	
Hyperhidrosis			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	3 / 420 (0.71%)	2 / 423 (0.47%)	
occurrences (all)	3	2	
Rash			
subjects affected / exposed	3 / 420 (0.71%)	2 / 423 (0.47%)	
occurrences (all)	3	2	
Rash macular			

subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	1 / 423 (0.24%) 1	
Rash pruritic subjects affected / exposed occurrences (all)	0 / 420 (0.00%) 0	1 / 423 (0.24%) 1	
Subcutaneous nodule subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Urticaria subjects affected / exposed occurrences (all)	4 / 420 (0.95%) 4	1 / 423 (0.24%) 1	
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	6 / 420 (1.43%) 6	8 / 423 (1.89%) 9	
Back pain subjects affected / exposed occurrences (all)	5 / 420 (1.19%) 5	5 / 423 (1.18%) 5	
Bone pain subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Coccydynia subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Groin pain subjects affected / exposed occurrences (all)	0 / 420 (0.00%) 0	1 / 423 (0.24%) 1	
Growing pains subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Joint swelling			

subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	2 / 420 (0.48%)	1 / 423 (0.24%)	
occurrences (all)	2	1	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 420 (0.24%)	2 / 423 (0.47%)	
occurrences (all)	1	2	
Myalgia			
subjects affected / exposed	3 / 420 (0.71%)	5 / 423 (1.18%)	
occurrences (all)	4	5	
Neck pain			
subjects affected / exposed	3 / 420 (0.71%)	3 / 423 (0.71%)	
occurrences (all)	3	3	
Pain in extremity			
subjects affected / exposed	8 / 420 (1.90%)	6 / 423 (1.42%)	
occurrences (all)	10	8	
Sensation of heaviness			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Tendonitis			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)	
occurrences (all)	1	0	
Blister infected			
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	1 / 420 (0.24%)	2 / 423 (0.47%)	
occurrences (all)	1	2	
Cystitis			
subjects affected / exposed	1 / 420 (0.24%)	1 / 423 (0.24%)	
occurrences (all)	1	1	

Ear infection		
subjects affected / exposed	0 / 420 (0.00%)	2 / 423 (0.47%)
occurrences (all)	0	2
Gastroenteritis		
subjects affected / exposed	10 / 420 (2.38%)	7 / 423 (1.65%)
occurrences (all)	11	9
Hordeolum		
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)
occurrences (all)	1	0
Infection		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	11 / 420 (2.62%)	10 / 423 (2.36%)
occurrences (all)	12	13
Laryngitis		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Lice infestation		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Localised infection		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Nasopharyngitis		
subjects affected / exposed	25 / 420 (5.95%)	28 / 423 (6.62%)
occurrences (all)	25	29
Oral herpes		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Otitis externa		
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)
occurrences (all)	1	0
Otitis media		
subjects affected / exposed	1 / 420 (0.24%)	2 / 423 (0.47%)
occurrences (all)	1	2

Pharyngitis		
subjects affected / exposed	6 / 420 (1.43%)	2 / 423 (0.47%)
occurrences (all)	6	2
Pneumonia		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Respiratory tract infection		
subjects affected / exposed	2 / 420 (0.48%)	7 / 423 (1.65%)
occurrences (all)	2	7
Rhinitis		
subjects affected / exposed	19 / 420 (4.52%)	20 / 423 (4.73%)
occurrences (all)	21	23
Sialoadenitis		
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)
occurrences (all)	1	0
Sinusitis		
subjects affected / exposed	6 / 420 (1.43%)	2 / 423 (0.47%)
occurrences (all)	6	2
Tinea versicolour		
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)
occurrences (all)	1	0
Tonsillitis		
subjects affected / exposed	0 / 420 (0.00%)	3 / 423 (0.71%)
occurrences (all)	0	3
Upper respiratory tract infection		
subjects affected / exposed	21 / 420 (5.00%)	10 / 423 (2.36%)
occurrences (all)	23	12
Urinary tract infection		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1
Viral infection		
subjects affected / exposed	1 / 420 (0.24%)	0 / 423 (0.00%)
occurrences (all)	1	0
Viral tonsillitis		
subjects affected / exposed	0 / 420 (0.00%)	1 / 423 (0.24%)
occurrences (all)	0	1

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	0 / 423 (0.00%) 0	
Metabolism and nutrition disorders			
Anorexia subjects affected / exposed occurrences (all)	1 / 420 (0.24%) 1	2 / 423 (0.47%) 2	
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 420 (0.00%) 0	1 / 423 (0.24%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported