Clinical trial results:
A Phase III, Randomized, Observer Blind, Multicenter Study to Evaluate the Safety and Immunogenicity of Repeated Exposure to an Adjuvanted Quadrivalent Subunit Influenza Virus Vaccine (aQIV), Administered to Subjects Previously Vaccinated in Trial V118_05

Summary

EudraCT number	2014-002599-95
Trial protocol	FI
Global end of trial date	13 January 2016

Results information

Result version number	v1 (current)
This version publication date	27 September 2017
First version publication date	27 September 2017

Trial information

Trial identification

Sponsor protocol code	V118_05E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02255409
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seqirus UK Limited
Sponsor organisation address	The Point, 29 Market Street, Maidenhead, United Kingdom, SL6 8AA
Public contact	Clinical Trial Disclosure Manager, Seqirus, Seqirus.Clinicaltrials@seqirus.com
Scientific contact	Clinical Trial Disclosure Manager, Seqirus, Seqirus.Clinicaltrials@seqirus.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001715-PIP01-14
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Immunogenicity Objective: To evaluate the antibody responses to homologous (CBER criteria) influenza strains post vaccination with aQIV or a non-adjuvanted comparator influenza vaccine in children previously vaccinated in parent trial V118_05.

Primary Safety Objective: To evaluate the safety of revaccination of aQIV or nonadjuvanted comparator vaccine in children previously vaccinated in parent trial V118_05

Protection of trial subjects:

This clinical study was designed and was to be implemented and reported in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations (CFR) Title 21, and Japanese Ministry of Health, Labor, and Welfare, sponsor codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki European Council 2001, US CFR, ICH 1997).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 100
Country: Number of subjects enrolled	United States: 507
Worldwide total number of subjects	607
EEA total number of subjects	100

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)	101
Children (2-11 years)	506
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 30 sites in 2 countries

Pre-assignment

Screening details:

All enrolled subjects were included in the trial

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	aQIV

Arm description:

Subjects approximately ≥12 months to 7 years of age who had received aQIV in the parent study V118_05 received aQIV in the present study V118_05E1.

Arm type	Experimental
Investigational medicinal product name	Adjuvanted Quadrivalent Influenza Vaccine (aQIV) -surface antigen, inactivated, adjuvanted with MF59
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.5ml (0.25 mL for subjects <36 months)

Arm title	Comparator QIV

Arm description:

Subjects approximately ≥12 months to 7 years of age who had received TIV/QIV in the parent study V118_05 received QIV in the present study V118_05E1.

Arm type	Experimental
Investigational medicinal product name	Inactivated Quadrivalent Influenza Virus Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

IM/0.5ml (0.25 mL for subjects <36 months)

Number of subjects in period 1	aQIV	Comparator QIV
Started	318	289
Completed	304	258
Not completed	14	31
Consent withdrawn by subject	1	5
Lost to follow-up	10	19
Administrative reason	3	7

Baseline characteristics

Reporting groups	
Reporting group title	aQIV
Reporting group description:	
Subjects approximately ≥12 months to 7 years of age who had received aQIV in the parent study V118_05 received aQIV in the present study V118_05E1.	
Reporting group title	Comparator QIV
Reporting group description:	
Subjects approximately ≥12 months to 7 years of age who had received TIV/QIV in the parent study V118_05 received QIV in the present study V118_05E1.	

Reporting group values	aQIV	Comparator QIV	Total
Number of subjects	318	289	607
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)	51	50	101
Children (2-11 years)	267	239	506
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: months			
arithmetic mean	44.7	42	
standard deviation	± 19.04	± 17.47	-
Gender categorical			
Units: Subjects			
Female	171	155	326
Male	147	134	281

End points

End points reporting groups

Reporting group title	aQIV
Reporting group description:	
Subjects approximately ≥12 months to 7 years of age who had received aQIV in the parent study V118_05 received aQIV in the present study V118_05E1.	
Reporting group title	Comparator QIV
Reporting group description:	
Subjects approximately ≥12 months to 7 years of age who had received TIV/QIV in the parent study V118_05 received QIV in the present study V118_05E1.	
Subject analysis set title	Full Analysis Set - Homologous
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the Enrolled Set, who received a study vaccination and provided evaluable serum samples against vaccine strains for both before (baseline) and after vaccination.	
Subject analysis set title	Full Analysis Set - Heterologous
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the Enrolled Set, who received a study vaccination and provided evaluable serum samples against heterologous strains for both before (baseline) and after vaccination.	

Primary: Immunogenicity Endpoint: Percentage of subjects achieving seroconversion - Homologous Strains (Day 22)

End point title	Immunogenicity Endpoint: Percentage of subjects achieving seroconversion - Homologous Strains (Day 22)[1]
End point description:	
Antibody responses assessed in terms of percentage of subjects achieving seroconversion at 21 days after vaccination against vaccine strains. Seroconversion is defined as HI ≥1:40 for subjects negative at baseline (ie, HI titer <1:10); or a minimum 4-fold increase in HI titer for subjects positive at baseline (ie, HI titer HI ≥1:10). The immunogenicity responses of the study vaccines were evaluated following measurements established by the current CBER criteria for the pediatric population. The CBER criteria were met if the lower bound of the 2-sided 95% CI for the percent of subjects achieving SC for HI antibody met or exceeded 40%	
End point type	Primary
End point timeframe:	
21 days after vaccination	

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: The analysis of the primary endpoint was descriptive.

End point values	aQIV	Comparator QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	257		
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1	57.9 (52.2 to 63.6)	56.4 (50.1 to 62.6)		

A/H3N2	50.7 (44.9 to 56.4)	56.6 (50.3 to 62.8)		
B/Yamagata	73.5 (68.2 to 78.4)	57.2 (50.9 to 63.3)		
B/Victoria	72.2 (66.8 to 77.2)	58 (51.7 to 64.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Immunogenicity Endpoint: Percentage of subjects achieving HI titer ≥ 1:40 - Homologous Strains (Day 22)

End point title	Immunogenicity Endpoint: Percentage of subjects achieving HI titer ≥ 1:40 - Homologous Strains (Day 22)[2]

End point description:

Antibody responses assessed in terms of percentage of subjects achieving HI titer ≥1:40 at 21 days after vaccination against vaccine strains.

The immunogenicity responses of the study vaccines were evaluated following measurements established by the current CBER criteria for the pediatric population. The CBER criteria were met if the lower bound of the 2-sided 95% CI for the percent of subjects achieving an HI titer ≥1:40 met or exceeded 70%.

End point type	Primary

End point timeframe:

21 days after 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: The analysis of the primary endpoint was descriptive.

End point values	aQIV	Comparator QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	257		
Units: Percentage of subjects				
number (confidence interval 95%)				
A/H1N1	100 (98.8 to 100)	99.6 (97.9 to 100)		
A/H3N2	99.7 (98.2 to 100)	100 (98.6 to 100)		
B/Yamagata	95.7 (92.8 to 97.7)	81.3 (76 to 85.9)		
B/Victoria	98 (95.7 to 99.3)	72 (66.1 to 77.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Safety Endpoint: Subjects reporting SAEs, AEs leading to withdrawal from the study, new onset of chronic diseases (NOCD), adverse events of special interest

(AESI) and medically attended AEs

End point title	Safety Endpoint: Subjects reporting SAEs, AEs leading to withdrawal from the study, new onset of chronic diseases (NOCD), adverse events of special interest (AESI) and medically attended AEs[3]

End point description:

Safety was assessed in terms of number of subjects reporting SAEs, AEs leading to withdrawal, NOCDs, AESI and medically attended AEs.

End point type	Primary

End point timeframe:

Up to 12 months after 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: The analysis of the primary endpoint was descriptive.

End point values	aQIV	Comparator QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	288		
Units: Number of subjects				
SAEs	7	4		
At least possibly related SAEs	0	0		
NOCDs	13	7		
AESI	1	1		
Medically attended AEs	161	141		
AEs leading to withdrawal	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Endpoint: Subjects with solicited local and systemic AEs and other solicited data

End point title	Safety Endpoint: Subjects with solicited local and systemic AEs and other solicited data

End point description:

Safety was assessed in terms of percentage of subjects reporting solicited local and systemic adverse events following vaccination.

End point type	Secondary

End point timeframe:

7 days following vaccination

End point values	aQIV	Comparator QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	288		
Units: number of subjects				
Any	202	148		
Local	173	112		
Systemic	127	80		
Other	66	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: Geometric Mean Titers Ratios - Homologous Strains (Day 22)

End point title	Immunogenicity Endpoint: Geometric Mean Titers Ratios - Homologous Strains (Day 22)

End point description:

GMT Ratio: aQIV (GMT) over QIV (GMT)

End point type	Secondary

End point timeframe:

21 days after vaccination

End point values	Full Analysis Set - Homologous			
Subject group type	Subject analysis set			
Number of subjects analysed	582[4]			
Units: Titers				
geometric mean (confidence interval 95%)				
A/H1N1	1.48 (1.3 to 1.7)			
A/H3N2	1.34 (1.2 to 1.5)			
B/Yamagata	1.75 (1.5 to 2)			
B/Victoria	1.49 (1.2 to 1.8)			

Notes:

[4] - aQIV N=309, QIV N=273

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: Geometric Mean Titers Ratios - Heterologous

Strains (Day 22)

End point title	Immunogenicity Endpoint: Geometric Mean Titers Ratios - Heterologous Strains (Day 22)

End point description:

GMT Ratio: aQIV (GMT) over QIV (GMT)

Heterologous strains tested: A/H3N2 is Influenza A H3N2 Hong Kong/2014 Ab; B/Yamagata is Influenza B/Phuket/2013 Ab

End point type	Secondary

End point timeframe:

21 days after vaccination

End point values	Full Analysis Set - Heterologous			
Subject group type	Subject analysis set			
Number of subjects analysed	293[5]			
Units: Titer ratios				
geometric mean (confidence interval 95%)				
A/H3N2	1.57 (1.3 to 1.9)			
B/Yamagata	2.21 (1.8 to 2.7)			

Notes:

[5] - aQIV N=155, QIV N=138

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 through Day366	
Adverse event reporting additional description:	
Solicited local and systemic AEs were reported from day 1 through day 7 after vaccination. All unsolicited AEs were captured through day 22. SAEs, AEs leading to withdrawal, NOCDs, AESIs were captured from day 1 through day 366	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	aQIV
Reporting group description:	
Subjects approximately ≥12 months to 7 years of age who had received aQIV in the parent trial received aQIV in the present study.	
Reporting group title	Comparator QIV
Reporting group description:	
Subjects ≥12 months to 7 years of age who had received a comparator non adjuvanted TIV/QIV in the parent study V118_05 received a non adjuvanted QIV in the present study V118_05E1.	

Serious adverse events	aQIV	Comparator QIV	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 318 (2.20%)	4 / 289 (1.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Right ventricle outflow tract obstruction			
subjects affected / exposed	1 / 318 (0.31%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 318 (0.31%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 318 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 318 (0.31%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 318 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	aQIV	Comparator QIV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	253 / 318 (79.56%)	210 / 289 (72.66%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	74 / 318 (23.27%)	53 / 289 (18.34%)	
occurrences (all)	74	53	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	24 / 318 (7.55%)	30 / 289 (10.38%)	
occurrences (all)	24	30	
Injection site erythema			
subjects affected / exposed	88 / 318 (27.67%)	58 / 289 (20.07%)	
occurrences (all)	88	58	
Injection site haemorrhage			
subjects affected / exposed	30 / 318 (9.43%)	25 / 289 (8.65%)	
occurrences (all)	30	25	
Injection site induration			
subjects affected / exposed	58 / 318 (18.24%)	32 / 289 (11.07%)	
occurrences (all)	58	32	
Injection site pain			
subjects affected / exposed	147 / 318 (46.23%)	82 / 289 (28.37%)	
occurrences (all)	147	82	
Pyrexia			
subjects affected / exposed	55 / 318 (17.30%)	37 / 289 (12.80%)	
occurrences (all)	55	37	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	33 / 318 (10.38%)	20 / 289 (6.92%)	
occurrences (all)	33	20	
Vomiting			
subjects affected / exposed	19 / 318 (5.97%)	11 / 289 (3.81%)	
occurrences (all)	19	11	
Psychiatric disorders			

Eating disorder			
subjects affected / exposed	55 / 318 (17.30%)	30 / 289 (10.38%)	
occurrences (all)	55	30	
Irritability			
subjects affected / exposed	83 / 318 (26.10%)	49 / 289 (16.96%)	
occurrences (all)	83	49	
Infections and infestations			
Otitis media			
subjects affected / exposed	37 / 318 (11.64%)	34 / 289 (11.76%)	
occurrences (all)	37	34	
Pharyngitis streptococcal			
subjects affected / exposed	16 / 318 (5.03%)	6 / 289 (2.08%)	
occurrences (all)	16	6	
Upper respiratory tract infection			
subjects affected / exposed	32 / 318 (10.06%)	38 / 289 (13.15%)	
occurrences (all)	32	38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2014	- The immunogenicity endpoints were updated to include secondary immunogenicity endpoints at Day 181. The percentage of subjects achieving seroconversion and HI titer ≥1:40 at Day 181 were included as additional secondary immunogenicity endpoints. - Secondary objectives were updated to clarify that the 2 vaccine groups would be compared with regard to antibody response to homologous and heterologous influenza strains for the following endpoints: GMT, GMR (Day 22:Day 1), percentage of subjects achieving seroconversion, and percentage of subjects achieving HI titer ≥1:40.
27 October 2014	- Text was added throughout the protocol to provide clarity on what information regarding influenza high risk status should be collected and the analysis to be conducted using this data. - The Medically Attended Adverse Events section was added to provide clarity on definition of medically attended AEs, where and when they should be recorded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported