Clinical trial results:
A randomised, double-blind, placebo-controlled, single-centre phase IIb trial as part of the EU-funded UNISEC project to assess the immunogenicity and safety of different formulations and dosing regimens of FLU-v vaccine administered subcutaneously in healthy adults aged 18-60 years.

Summary

EudraCT number	2015-001932-38
Trial protocol	NL
Global end of trial date	18 July 2017

Results information

Result version number	v1 (current)
This version publication date	12 April 2019
First version publication date	12 April 2019

Trial information

Trial identification

Sponsor protocol code	FLU-v-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02962908
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PepTcell
Sponsor organisation address	Central Point, 45 Beech Street, London, United Kingdom, EC2Y 8AD
Public contact	Gregory Stoloff, PepTcell Limited (trading as SEEK), 44 207 153 6575, gregory.stoloff@seekacure.com
Scientific contact	Dr Olga Pleguezuelos, PepTcell Limited (trading as SEEK), 44 207 153 6570, olga.pleguezuelos@seekacure.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2017
Global end of trial reached?	Yes
Global end of trial date	18 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

(1) Cellular Immunogenicity
- To evaluate the cellular immune responses based on multi-parametric FACS analysis in all subjects at 0 and 42 and 180 days following FLU-v vaccination.
- To evaluate the cellular immune responses based on IFN-γ ELISA assays in all subjects at 0 and 42 and 180 days following FLU-v vaccination.

(2) Safety
- To evaluate the solicited AEs in all subjects until 21 days after the last dosing of the study vaccine (FLU-v).
- To evaluate the unsolicited AEs and SAEs in all subjects during the whole study period.

Protection of trial subjects:

Subjects were submitted to two subcutaneous injections and three blood samplings. If subjects showed influenza symptoms a nasopharyngeal swab was taken.
There were minimal risks to these procedures who were performed by trained personnel. Doctors and nurses were always available if subjects had any concerns or suffered any discomfort. Subjects were allowed to take over the counter anti-inflammatories to alleviate any adverse events post-vaccination. Subjects remained under observation for 30min post-vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 August 2016
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	Netherlands: 175
Worldwide total number of subjects	175
EEA total number of subjects	175

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	175
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy volunteers 18-60 years old were recruited from the Zwolle city of the Netherlands during the summer of 2016. Interested subjects were screened over the phone before being invited for the screening visit on Site.

Pre-assignment

Screening details:

195 subjects were screened, 3 were lost to follow up, 9 withdrew consent and 8 failed inclusion/exclusion criteria. 175 subjects were randomised. 1 subject in 1x adjuvanted FLU-v arm received the wrong treatment and could not be included in any arm for analysis leaving the total number as 174 subjects.

Period 1

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

Blinding implementation details:

The only personnel unblinded were those formulating the vaccine ready for administration and there were not involved in other trial-related activities. The appearance of the placebo and active treatments were the same and therefore no masking of the syringes was required.
The randomisation codes remained in the pharmacy under locked key only accessible to unblinded personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	2x Non-adjuvanted FLU-v

Arm description:

FLU-v on Day 0 and Day 21
FLU-v: Subcutaneous injection in the upper arm with 500 ug of FLU-v as 0.5ml suspension in 0.01M HCl and
0.01M NaOH

Arm type	Experimental
Investigational medicinal product name	FLU-v
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

500micrograms in 0.5ml

Arm title	1x Adjuvanted FLU-v

Arm description:

adjuvanted FLU-v on Day 0, saline (0.5mL) on Day 21
adjuvanted FLU-v: Subcutaneous injection in the upper arm with 500ug of FLU-v emulsified in 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection
Saline: Subcutaneous injection in the upper arm with 0.5ml of saline

Arm type	Experimental

Investigational medicinal product name	FLU-v
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

500ug in 0.5ml

Arm title	Non-adjuvanted Placebo

Arm description:

saline solution (0.5ml) on Day 0 and Day 21
Saline: Subcutaneous injection in the upper arm with 0.5ml of saline

Arm type	Non-adjuvanted Placebo

No investigational medicinal product assigned in this arm

Arm title	Adjuvanted Placebo

Arm description:

Adjuvanted placebo on Day 0, saline (0.5mL) on Day 21
Adjuvanted placebo: Subcutaneous injection in the upper arm with an emulsion made with 0.25ml of Montanide
ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection
Saline: Subcutaneous injection in the upper arm with 0.5ml of saline

Arm type	Adjuvanted Placebo

No investigational medicinal product assigned in this arm

Number of subjects in period 1	2x Non-adjuvanted FLU-v	1x Adjuvanted FLU-v	Non-adjuvanted Placebo
Started	58	58	32
vaccination completed	58	54	32
day 42 sample collected	58	51	32
day 180 sample collected	58	50	32
Completed	58	50	32
Not completed	0	8	0
Consent withdrawn by subject	-	3	-
Physician decision	-	1	-
Lost to follow-up	-	3	-
Protocol deviation	-	1	-

Number of subjects in period 1	Adjuvanted Placebo
Started	27
vaccination completed	26
day 42 sample collected	26
day 180 sample collected	24
Completed	24
Not completed	3
Consent withdrawn by subject	2

Physician decision	-
Lost to follow-up	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	2x Non-adjuvanted FLU-v
Reporting group description:	
FLU-v on Day 0 and Day 21 FLU-v: Subcutaneous injection in the upper arm with 500 ug of FLU-v as 0.5ml suspension in 0.01M HCl and 0.01M NaOH	
Reporting group title	1x Adjuvanted FLU-v
Reporting group description:	
adjuvanted FLU-v on Day 0, saline (0.5mL) on Day 21 adjuvanted FLU-v: Subcutaneous injection in the upper arm with 500ug of FLU-v emulsified in 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection Saline: Subcutaneous injection in the upper arm with 0.5ml of saline	
Reporting group title	Non-adjuvanted Placebo
Reporting group description:	
saline solution (0.5ml) on Day 0 and Day 21 Saline: Subcutaneous injection in the upper arm with 0.5ml of saline	
Reporting group title	Adjuvanted Placebo
Reporting group description:	
Adjuvanted placebo on Day 0, saline (0.5mL) on Day 21 Adjuvanted placebo: Subcutaneous injection in the upper arm with an emulsion made with 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection Saline: Subcutaneous injection in the upper arm with 0.5ml of saline	

Reporting group values	2x Non-adjuvanted FLU-v	1x Adjuvanted FLU-v	Non-adjuvanted Placebo
Number of subjects	58	58	32
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	58	58	32
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	40.02	40.12	41.19
standard deviation	± 13.691	± 12.221	± 12.458
Gender categorical Units: Subjects			
Female	36	31	18
Male	22	27	14

Reporting group values	Adjuvanted Placebo	Total	

Number of subjects	27	175	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	27	175	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	39.07		
standard deviation	± 13.074	-	
Gender categorical Units: Subjects			
Female	13	98	
Male	14	77	

Subject analysis sets

Subject analysis set title	Full analysis data set
Subject analysis set type	Full analysis

Subject analysis set description:

The safety population includes all subjects that received at least one influenza injection

Reporting group values	Full analysis data set		
Number of subjects	167		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	167		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	40.11		
standard deviation	± 12.847		
Gender categorical Units: Subjects			
Female	95		

Male	72		

End points

End points reporting groups

Reporting group title	2x Non-adjuvanted FLU-v
Reporting group description:	
FLU-v on Day 0 and Day 21 FLU-v: Subcutaneous injection in the upper arm with 500 ug of FLU-v as 0.5ml suspension in 0.01M HCl and 0.01M NaOH	
Reporting group title	1x Adjuvanted FLU-v
Reporting group description:	
adjuvanted FLU-v on Day 0, saline (0.5mL) on Day 21 adjuvanted FLU-v: Subcutaneous injection in the upper arm with 500ug of FLU-v emulsified in 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection Saline: Subcutaneous injection in the upper arm with 0.5ml of saline	
Reporting group title	Non-adjuvanted Placebo
Reporting group description:	
saline solution (0.5ml) on Day 0 and Day 21 Saline: Subcutaneous injection in the upper arm with 0.5ml of saline	
Reporting group title	Adjuvanted Placebo
Reporting group description:	
Adjuvanted placebo on Day 0, saline (0.5mL) on Day 21 Adjuvanted placebo: Subcutaneous injection in the upper arm with an emulsion made with 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection Saline: Subcutaneous injection in the upper arm with 0.5ml of saline	

Subject analysis set title	Full analysis data set
Subject analysis set type	Full analysis
Subject analysis set description:	
The safety population includes all subjects that received at least one influenza injection	

Primary: Percentage of CD4+ TH1 Cytokine Responders

End point title	Percentage of CD4+ TH1 Cytokine Responders
End point description:	
To compare the number of subjects that showed at least a two-fold increase on day 42 and day 180 following vaccination in the number of CD4+T-cells secreting TH1 cytokines in all groups.	
End point type	Primary
End point timeframe:	
prevaccination, day 42 (21 days after last vaccination) and day 180.	

End point values	2x Non-adjuvanted FLU-v	1x Adjuvanted FLU-v	Non-adjuvanted Placebo	Adjuvanted Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	51	32	26
Units: Percentage of subjects responders				
number (not applicable)				
IFN gamma CD4+ day 42	12.96	76	3.33	8.70
TNF alpha CD4+ day 42	5.46	44	3.33	0

IL-2 CD4+ day 42	1.82	56	3.33	0
IFN gamm CD4+ day 180	14.29	63.27	6.67	4.76
TNF alpha CD4+ day 180	3.57	24.49	3.33	0
IL-2 CD4+ day 180	1.79	57.14	3.33	0

Statistical analyses

Statistical analysis title	IFNg day 42 nonadjuvanted FLUv vs nonadj placebo
Statistical analysis description:	
Comparison of IFNgamma responders on day 42. Differences considered significant if p-value <0.05.	
Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.249
Method	Chi-squared

Statistical analysis title	IFNg Adj-FLU-v vs AdjPlacebo day 42
Statistical analysis description:	
Comparison of IFNgamma responders on day 42. Differences considered significant if pvalue <0.05.	
Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared

Statistical analysis title	TNF day 42 nonadjuvanted FLUv vs non-adj placebo
Statistical analysis description:	
Comparison of TNF alpha responders on day 42. Differences considered significant if pvalue <0.05.	
Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	TNF day 42adjuvanted FLUv vs adj placebo
Statistical analysis description:	
Comparison of TNF alpha responders on day 42. Differences considered significant if pvalue	

<0.05.

Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared

Statistical analysis title	IL-2 day 42 nonadjuvanted FLUv vs nonadj placebo

Statistical analysis description:

Comparison of IL-2 responders on day 42. Differences considered significant if p-value <0.05.

Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	IL-2 day 42adjuvanted FLUv vs adj placebo

Statistical analysis description:

Comparison of IL-2 responders on day 42. Differences considered significant if p-value <0.05.

Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared

Statistical analysis title	IFNg day 180 nonadjuvanted FLUv vs nonadj placebo

Statistical analysis description:

Comparison of IFNgamma responders on day 180.Differences considered significant if pvalue <0.05.

Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.483
Method	Fisher exact
Parameter estimate	Cox proportional hazard

Statistical analysis title	IFNg day 180 adjuvanted FLUv vs adj placebo
Statistical analysis description: Comparison of IFNgamma responders on day 180.Differences considered significant if p-value <0.05.	
Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared

Statistical analysis title	TNF day 180 nonadjuvanted FLUv vs non-adj placebo
Statistical analysis description: Comparison of TNF alpha responders on day 180. Differences considered significant if p-value <0.05.	
Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	TNF day 180 adjuvanted FLUv vs adj placebo
Statistical analysis description: Comparison of TNF alpha responders on day 180. Differences considered significant if p-value <0.05.	
Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.013
Method	Fisher exact

Statistical analysis title	IL-2 day 180 nonadjuvanted FLUv vs non-adj placebo
Statistical analysis description: Comparison of IL-2 responders on day 180. Differences considered significant if p-value <0.05.	
Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Statistical analysis title	IL-2 day 180 adjuvanted FLUv vs adj placebo

Statistical analysis description:	
Comparison of IL-2 responders on day 180. Differences considered significant if p-value <0.05.	
Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared

Primary: Percentage of Responders on Day 42 and Day 180 for IFNgamma Secretion by PBMCs

End point title	Percentage of Responders on Day 42 and Day 180 for IFNgamma Secretion by PBMCs
End point description:	
Responders were defined as subjects having at least a two-fold increase in the amount of IFNg secreted on day 42 and day 180 compared the amount secreted on day 0. IFNg was measured by ELISA	
End point type	Primary
End point timeframe:	
prevaccination (day 0) to postvaccination (day 42 and day 180)	

End point values	2x Non-adjuvanted FLU-v	1x Adjuvanted FLU-v	Non-adjuvanted Placebo	Adjuvanted Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	51	32	26
Units: percentage of responder subjects				
number (not applicable)				
day 42	59.57	95.46	40.00	45.00
day 180	45.83	93.02	56.52	55.00

Statistical analyses

Statistical analysis title	day 42 non-adj FLU-v vs Non-Adj placebo
Statistical analysis description:	
Comparison of number of responders on day 42. A subject was considered a "responder" if an increase of secreted IFNgamma of at least two fold was observed from day 0 to day 42.	
Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.113
Method	Chi-squared

Statistical analysis title	day 42 adjuvanted FLUv vs adj placebo

Statistical analysis description:

Comparison of number of responders on day 42. A subject was considered a "responder" if an increase of secreted IFNgamma of at least two fold was observed from day 0 to day 42.

Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	day 180 non-adj FLU-v vs Non-Adj placebo

Statistical analysis description:

Comparison of number of responders on day 180. A subject was considered a "responder" if an increase of secreted IFNgamma of at least two fold was observed from day 0 to day 180.

Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.399
Method	Chi-squared

Statistical analysis title	day 180 adjuvanted FLUv vs adj placebo

Statistical analysis description:

Comparison of number of responders on day 180. A subject was considered a "responder" if an increase of secreted IFNgamma of at least two fold was observed from day 0 to day 180.

Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Fisher exact

Secondary: Antibody Responses to FLU-v

End point title	Antibody Responses to FLU-v

End point description:

To evaluate the humoral immune responses specific to FLU-v from baseline in all groups 42 and 180 days following FLU-v vaccination. Specific FLU-v IgG antibodies were measured by ELISA. The geometric mean for each treatment group was provided.

End point type	Secondary

End point timeframe:

prevaccination, day 42 (21 days after last vaccination) and day 180.
Analysis Population

End point values	2x Non-adjuvanted FLU-v	1x Adjuvanted FLU-v	Non-adjuvanted Placebo	Adjuvanted Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	51	32	26
Units: IgG ng/ml				
geometric mean (standard error)				
day 0	499.11 (± 103.19)	362.86 (± 82.93)	331.16 (± 59.00)	371.89 (± 67.47)
day 42	2593.02 (± 1652.34)	8740.48 (± 2432.9)	336.37 (± 58.92)	381.17 (± 61.18)
day 180	1276.34 (± 344.52)	4769.16 (± 1131.67)	344.88 (± 66.57)	387.26 (± 61.48)

Statistical analyses

Statistical analysis title	day 42 non-adj FLU-v vs Non-Adj placebo
Statistical analysis description: Comparison of geometric mean IgG titers specific to FLU-v antigens on day 42 postvaccination.	
Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	day 42 adjuvanted FLUv vs adj placebo
Statistical analysis description: Comparison of geometric mean IgG titers specific to FLU-v antigens on day 42 postvaccination.	
Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	day 180 non-adj FLU-v vs Non-Adj placebo
Statistical analysis description: Comparison of geometric mean IgG titers specific to FLU-v antigens on day 180 postvaccination.	
Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Cox proportional hazard

Statistical analysis title	day 180 adjuvanted FLUv vs adj placebo
Statistical analysis description:	
Comparison of geometric mean IgG titers specific to FLU-v antigens on day 180 postvaccination.	
Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Other pre-specified: Percentage of subjects positive for influenza infection	
End point title	Percentage of subjects positive for influenza infection
End point description:	
During the influenza season (Dec 2016 to March 2017), fully vaccinated subjects will contact the trial center immediately if they feel unwell for 24h, with a sudden onset of flu-like symptoms. The medical staff will arrange for a nasopharyngeal swab to be performed if the subject has at least one respiratory (cough, sore throat, shortness of breath, runny nose, stuffy nose, sneezing and earache) and one systemic symptom (fever, malaise, headache and myalgia (muscle and joint pain). Swabs should be taken from the reported subjects within 3 days from the trial center being contacted or within 4 days of the onset of symptoms, whatever time is shorter.	
End point type	Other pre-specified
End point timeframe:	
For up to 4 months during the influenza season	

End point values	2x Non-adjuvanted FLU-v	1x Adjuvanted FLU-v	Non-adjuvanted Placebo	Adjuvanted Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	58	51	32	26
Units: Percentage of subjects				
number (not applicable)				
positive for influenza A	5.2	7.8	6.3	19.2
positive for influenza B	0	2.0	3.1	3.8
positive for influenza H1	0	0	0	0
positive for influenza H3	5.2	7.8	6.3	19.2
positive for any influenza	5.2	9.8	9.4	23.1

End point values	Full analysis data set			
Subject group type	Subject analysis set			
Number of subjects analysed	167			
Units: Percentage of subjects				
number (not applicable)				
positive for influenza A	8.4			
positive for influenza B	1.8			
positive for influenza H1	0			
positive for influenza H3	8.4			
positive for any influenza	10.2			

Statistical analyses

Statistical analysis title	Subjects tested positive for any influenza

Statistical analysis description:

Differences in the infection rates against any of the strains tested between treatment group and corresponding placebo.

Comparison groups	2x Non-adjuvanted FLU-v v Non-adjuvanted Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.662
Method	Fisher exact

Statistical analysis title	subjects who tested positive for influenza

Statistical analysis description:

Differences in the infection rates against any of the strains tested between treatment group and corresponding placebo.

Comparison groups	1x Adjuvanted FLU-v v Adjuvanted Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.168
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From vaccination to the end of the study

Adverse event reporting additional description:

Solicited Adverse Events were collected for 21 days after each vaccination. Subjects had to fill in the AEs diary
card daily and return to the clinic on the next scheduled visit.
Unsolicited Adverse Events and Severe Adverse Events were collected at any time during the study directly to
the PI or study doctor.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	2x Non-adjuvanted FLU-v

Reporting group description:

FLU-v on Day 0 and Day 21
FLU-v: Subcutaneous injection in the upper arm with 500 ug of FLU-v as 0.5ml suspension in 0.01M HCl and
0.01M NaOH

Reporting group title	1x Adjuvanted FLU-v

Reporting group description:

adjuvanted FLU-v on Day 0, saline (0.5mL) on Day 21
adjuvanted FLU-v: Subcutaneous injection in the upper arm with 500ug of FLU-v emulsified in 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection
Saline: Subcutaneous injection in the upper arm with 0.5ml of saline

Reporting group title	Non-adjuvanted Placebo

Reporting group description:

saline solution (0.5ml) on Day 0 and Day 21
Saline: Subcutaneous injection in the upper arm with 0.5ml of saline

Reporting group title	Adjuvanted Placebo

Reporting group description:

Adjuvanted placebo on Day 0, saline (0.5mL) on Day 21
Saline: Subcutaneous injection in the upper arm with 0.5ml of saline
Adjuvanted placebo: Subcutaneous injection in the upper arm with an emulsion made with 0.25ml of Montanide
ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection

Serious adverse events	2x Non-adjuvanted FLU-v	1x Adjuvanted FLU-v	Non-adjuvanted Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 58 (3.45%)	2 / 57 (3.51%)	0 / 32 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
upper lim	Additional description: mild/ treatment unrelated, 16 day duration		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abdominal hernia repair	Additional description: mild/ treatment unrelated, 1 day duration		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction	Additional description: severe/ unlikely related to treatment		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression	Additional description: moderate/ treatment unrelated		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol abuse	Additional description: moderate/ treatment unrelated		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Adjuvanted Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
upper lim	Additional description: mild/ treatment unrelated, 16 day duration		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abdominal hernia repair	Additional description: mild/ treatment unrelated, 1 day duration		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction	Additional description: severe/ unlikely related to treatment		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression	Additional description: moderate/ treatment unrelated		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alcohol abuse	Additional description: moderate/ treatment unrelated		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	2x Non-adjuvanted FLU-v	1x Adjuvanted FLU-v	Non-adjuvanted Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 58 (84.48%)	54 / 57 (94.74%)	28 / 32 (87.50%)
Nervous system disorders			

Headache			
subjects affected / exposed	13 / 58 (22.41%)	19 / 57 (33.33%)	14 / 32 (43.75%)
occurrences (all)	20	30	18
Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 58 (3.45%)	3 / 57 (5.26%)	1 / 32 (3.13%)
occurrences (all)	2	4	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	7 / 58 (12.07%)	4 / 57 (7.02%)	3 / 32 (9.38%)
occurrences (all)	8	4	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 58 (24.14%)	17 / 57 (29.82%)	11 / 32 (34.38%)
occurrences (all)	16	25	12
Injection site haematoma			
subjects affected / exposed	5 / 58 (8.62%)	19 / 57 (33.33%)	0 / 32 (0.00%)
occurrences (all)	6	19	0
Influenza like illness			
subjects affected / exposed	11 / 58 (18.97%)	18 / 57 (31.58%)	10 / 32 (31.25%)
occurrences (all)	12	19	11
Injection site erythema			
subjects affected / exposed	13 / 58 (22.41%)	38 / 57 (66.67%)	0 / 32 (0.00%)
occurrences (all)	15	40	0
Injection site induration			
subjects affected / exposed	16 / 58 (27.59%)	49 / 57 (85.96%)	0 / 32 (0.00%)
occurrences (all)	18	49	0
Injection site pain			
subjects affected / exposed	4 / 58 (6.90%)	39 / 57 (68.42%)	4 / 32 (12.50%)
occurrences (all)	6	46	4
Injection site pruritus			
subjects affected / exposed	9 / 58 (15.52%)	22 / 57 (38.60%)	0 / 32 (0.00%)
occurrences (all)	10	23	0
Injection site swelling			
subjects affected / exposed	6 / 58 (10.34%)	38 / 57 (66.67%)	0 / 32 (0.00%)
occurrences (all)	7	39	0

Injection site warmth			
subjects affected / exposed	7 / 58 (12.07%)	29 / 57 (50.88%)	1 / 32 (3.13%)
occurrences (all)	9	30	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 58 (12.07%)	7 / 57 (12.28%)	1 / 32 (3.13%)
occurrences (all)	7	8	2
Vomiting			
subjects affected / exposed	3 / 58 (5.17%)	5 / 57 (8.77%)	2 / 32 (6.25%)
occurrences (all)	3	6	2
Diarrhoea			
subjects affected / exposed	6 / 58 (10.34%)	8 / 57 (14.04%)	4 / 32 (12.50%)
occurrences (all)	8	9	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 58 (27.59%)	17 / 57 (29.82%)	8 / 32 (25.00%)
occurrences (all)	18	20	9
Nasal congestion			
subjects affected / exposed	15 / 58 (25.86%)	11 / 57 (19.30%)	9 / 32 (28.13%)
occurrences (all)	16	12	12
Pharyngitis			
subjects affected / exposed	21 / 58 (36.21%)	15 / 57 (26.32%)	14 / 32 (43.75%)
occurrences (all)	24	19	17
Rhinorrhoea			
subjects affected / exposed	20 / 58 (34.48%)	17 / 57 (29.82%)	14 / 32 (43.75%)
occurrences (all)	25	19	20
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 58 (5.17%)	3 / 57 (5.26%)	3 / 32 (9.38%)
occurrences (all)	3	3	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 58 (8.62%)	5 / 57 (8.77%)	6 / 32 (18.75%)
occurrences (all)	5	7	7
Myalgia			

subjects affected / exposed	11 / 58 (18.97%)	9 / 57 (15.79%)	6 / 32 (18.75%)
occurrences (all)	12	12	6
Pain in extremity			
subjects affected / exposed	2 / 58 (3.45%)	6 / 57 (10.53%)	0 / 32 (0.00%)
occurrences (all)	2	6	0
Arthralgia			
subjects affected / exposed	4 / 58 (6.90%)	5 / 57 (8.77%)	1 / 32 (3.13%)
occurrences (all)	5	6	1
Infections and infestations			
Herpes simplex			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 58 (3.45%)	2 / 57 (3.51%)	3 / 32 (9.38%)
occurrences (all)	2	2	3
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 58 (24.14%)	14 / 57 (24.56%)	13 / 32 (40.63%)
occurrences (all)	15	15	14
Metabolism and nutrition disorders			
Decreased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 58 (1.72%)	11 / 57 (19.30%)	0 / 32 (0.00%)
occurrences (all)	1	12	0

Non-serious adverse events	Adjuvanted Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	13		
Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	6		
Injection site haematoma			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	5		
Influenza like illness			
subjects affected / exposed	9 / 27 (33.33%)		
occurrences (all)	12		
Injection site erythema			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	6		
Injection site induration			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	11		
Injection site pain			
subjects affected / exposed	11 / 27 (40.74%)		
occurrences (all)	12		
Injection site pruritus			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	14		
Injection site swelling			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	7		
Injection site warmth			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Vomiting			

subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	5		
Nasal congestion			
subjects affected / exposed	8 / 27 (29.63%)		
occurrences (all)	9		
Pharyngitis			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	8		
Rhinorrhoea			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Herpes simplex alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Upper respiratory tract infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1 6 / 27 (22.22%) 6		
Metabolism and nutrition disorders Decreased appetite alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Recruitment stopped early at 175 subjects instead of 222. Dropout rate was lower than anticipated (4% vs 20%). The number of participants recruited was considered to be sufficient to provide statistically significant data in the primary endpoints.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28376743