Clinical trial results:
Phase IIb Study of the Efficacy of FLU-v, a Broad Spectrum Influenza Vaccine in an H1N1 Influenza Healthy Human Challenge Model.

Summary

EudraCT number	2016-002134-74
Trial protocol	GB
Global end of trial date	25 May 2017

Results information

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

Trial information

Trial identification

Sponsor protocol code	FLU-v-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03180801
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PepTcell Ltd (t/a SEEK)
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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	24 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2017
Global end of trial reached?	Yes
Global end of trial date	25 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of FLU-v on reducing the incidence of Mild to Moderate Influenza Disease (MMID) defined as detectable viral shedding plus at least one symptom of influenza.

Protection of trial subjects:

Subjects were submitted to two subcutaneous injections with vaccine or placebo, blood samplings, intranasal inoculation with influenza virus and nasal swabs.
There were minimal risks to these procedures as they 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.
Subjects were closely monitored under quarantine after inoculation with influenza virus. The virus was GMP manufactured, dosage was optimised in previous clinical trials approved by the FDA sponsored by NIAID-NIH, US.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 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	United Kingdom: 153
Worldwide total number of subjects	153
EEA total number of subjects	153

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)	153
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place at two UK sites, London and Manchester, during Q3 and Q4 of 2017.

Pre-assignment

Screening details:

Only subjects with an HAI<40 for the influenza challenge strain at the time of screening were allowed to enrol the study.

Period 1

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

Blinding implementation details:

Only pharmacy staff responsible for vaccine formulation were unblinded. The randomisation codes were kept locked in the pharmacy and only unblinded staff had access to them.
The placebo and active doses were identical in appearance, thus there was no need for masking the contents of the syringe.

Arms

Are arms mutually exclusive?	Yes
Arm title	Adjuvanted Placebo

Arm description:

Received two doses of adjuvanted placebo 21 days apart and 21 days after the last vaccination were inoculated with influenza.

Arm type	Placebo
Investigational medicinal product name	Adjuvanted placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5ml of water in oil emulsion composed of 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection.

Arm title	1x adjuvanted FLU-v

Arm description:

Subjects received one dose of adjuvanted FLU-v and 21 days later a dose of adjuvanted placebo, followed by intranasal influenza inoculation 21 days after that.

Arm type	Experimental
Investigational medicinal product name	Adjuvanted placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5ml of water in oil emulsion composed of 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection.

Investigational medicinal product name	Adjuvanted FLU-v
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Emulsion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

500 micrograms of FLU-v reconstituted in 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and emulsified with 0.25ml of water for injection.

Arm title	2x Adjuvanted FLU-v

Arm description:

Subjects received two doses of adjuvanted FLU-v 21 days apart, and 21 days after the last dose were intranasally inoculated with influenza.

Arm type	Experimental
Investigational medicinal product name	Adjuvanted placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5ml of water in oil emulsion composed of 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and 0.25ml of water for injection.

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

Dosage and administration details:

500 micrograms of FLU-v reconstituted in 0.25ml of Montanide ISA-51 adjuvant (Seppic, France) and emulsified with 0.25ml of water for injection.

Number of subjects in period 1	Adjuvanted Placebo	1x adjuvanted FLU-v	2x Adjuvanted FLU-v
Started	50	52	51
Vaccinated	50	48	48
Completed	42	40	41
Not completed	8	12	10
Consent withdrawn by subject	2	2	1
Physician decision	3	3	1
Adverse event, non-fatal	1	-	2
Non-compliance	1	4	-
Lost to follow-up	-	2	3
inoculation target reached	1	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Adjuvanted Placebo
Reporting group description:	
Received two doses of adjuvanted placebo 21 days apart and 21 days after the last vaccination were inoculated with influenza.	
Reporting group title	1x adjuvanted FLU-v
Reporting group description:	
Subjects received one dose of adjuvanted FLU-v and 21 days later a dose of adjuvanted placebo, followed by intranasal influenza inoculation 21 days after that.	
Reporting group title	2x Adjuvanted FLU-v
Reporting group description:	
Subjects received two doses of adjuvanted FLU-v 21 days apart, and 21 days after the last dose were intranasally inoculated with influenza.	

Reporting group values	Adjuvanted Placebo	1x adjuvanted FLU-v	2x Adjuvanted FLU-v
Number of subjects	50	52	51
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)	50	52	51
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	28.9	30.2	27.6
standard deviation	± 7.6	± 9.3	± 8.7
Gender categorical Units: Subjects			
Female	17	19	14
Male	33	33	37

Reporting group values	Total		
Number of subjects	153		
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)	153		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	50		
Male	103		

Subject analysis sets

Subject analysis set title	Placebo Efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT includes those participants in the adjuvanted placebo group who received both vaccination and challenge with an influenza virus.

Subject analysis set title	1xFLU-v Efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Includes all subjects in the 1 dose adjuvanted FLU-v group who completed the vaccinations and were challenge with influenza.

Subject analysis set title	2xFLU-v efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Includes all subjects in the 2 dose adjuvanted FLU-v who completed all vaccinations and were challenged with influenza.

Reporting group values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis
Number of subjects	42	40	41
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)	42	40	41
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	28.8	29.9	27.4
standard deviation	± 7.5	± 8.9	± 9.2

Gender categorical Units: Subjects			
Female	13	12	11
Male	29	28	30

End points

End points reporting groups

Reporting group title	Adjuvanted Placebo

Reporting group description:

Received two doses of adjuvanted placebo 21 days apart and 21 days after the last vaccination were inoculated with influenza.

Reporting group title	1x adjuvanted FLU-v

Reporting group description:

Subjects received one dose of adjuvanted FLU-v and 21 days later a dose of adjuvanted placebo, followed by intranasal influenza inoculation 21 days after that.

Reporting group title	2x Adjuvanted FLU-v

Reporting group description:

Subjects received two doses of adjuvanted FLU-v 21 days apart, and 21 days after the last dose were intranasally inoculated with influenza.

Subject analysis set title	Placebo Efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT includes those participants in the adjuvanted placebo group who received both vaccination and challenge with an influenza virus.

Subject analysis set title	1xFLU-v Efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Includes all subjects in the 1 dose adjuvanted FLU-v group who completed the vaccinations and were challenge with influenza.

Subject analysis set title	2xFLU-v efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Includes all subjects in the 2 dose adjuvanted FLU-v who completed all vaccinations and were challenged with influenza.

Primary: Incidence of MMID

End point title	Incidence of MMID

End point description:

To determine the effect of FLU-v on reducing the incidence of Mild to Moderate Influenza Disease (MMID) defined as detectable viral shedding plus at least one symptom of influenza. This analysis was done in the ITT population which included all subjects that completed vaccination and inoculation milestones.

End point type	Primary

End point timeframe:

From 24h post-viral inoculation (Day 1) until the end of the quarantine phase on Day 7

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: Number of subjects				
Positive for MMID	23	13	15	

Negative for MMID	19	27	26	

Statistical analyses

Statistical analysis title	1xFLU-v vs Placebo: incidence MMID

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower MMID rate.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0349 [1]
Method	Fisher exact

Notes:

[1] - P-value<0.05 was considered significant, therefore the difference in the incidence of MMID in the 1xFLU-v group compared to placebo is significant.

Statistical analysis title	2xFLU-v vs Placebo: Incidence of MMID

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower MMID rate.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0745 [2]
Method	Fisher exact

Notes:

[2] - P-value<0.05 was considered significant. The p-value obtained shows that difference in incidence of MMID between the 2xFLU-v and Placebo is not quite significant.

Primary: Incidence of Treatment Emergent AEs

End point title	Incidence of Treatment Emergent AEs

End point description:

To determine the safety and tolerability of FLU-v by means of recording the incidence of TEAEs.

End point type	Primary

End point timeframe:

From the first administration of treatment to the end of the study.

End point values	Adjuvanted Placebo	1x adjuvanted FLU-v	2x Adjuvanted FLU-v	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	52	51	
Units: number of TEAEs				
arithmetic mean (standard error)				
Overall	1.86 (± 0.26)	1.38 (± 0.24)	2.35 (± 0.27)	

Pre-inoculation	1.00 (± 0.21)	0.81 (± 0.13)	1.51 (± 0.19)	
Post-inoculation	0.86 (± 0.16)	0.58 (± 0.15)	0.84 (± 0.16)	

Statistical analyses

Statistical analysis title	Comparison of TEAEs pre-inoculation

Statistical analysis description:

One sided Fisher's exact test is used to test if AE rates of vaccine group is higher than the placebo group.

Comparison groups	Adjuvanted Placebo v 1x adjuvanted FLU-v
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6474 [3]
Method	Fisher exact

Notes:

[3] - The difference in pre-inoculation TEAEs is not significant.

Statistical analysis title	Comparison of TEAEs pre-inoculation

Statistical analysis description:

One sided Fisher's exact test is used to test if AE rates of vaccine group is higher than the placebo group.

Comparison groups	Adjuvanted Placebo v 2x Adjuvanted FLU-v
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9995 [4]
Method	Fisher exact

Notes:

[4] - The difference in pre-inoculation TEAEs is not significant.

Statistical analysis title	Comparison of TEAEs post-inoculation

Statistical analysis description:

One sided Fisher's exact test is used to test if AE rates of vaccine group is higher than the placebo group.

Comparison groups	Adjuvanted Placebo v 1x adjuvanted FLU-v
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.024 [5]
Method	Fisher exact

Notes:

[5] - The lower rate of post-inoculation TEAEs in the 1xFLU-v group compared to placebo is significant.

Statistical analysis title	Comparison of TEAEs post-inoculation

Statistical analysis description:

One sided Fisher's exact test is used to test if AE rates of vaccine group is higher than the placebo group.

Comparison groups	Adjuvanted Placebo v 2x Adjuvanted FLU-v
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.186 [6]
Method	Fisher exact

Notes:

[6] - The difference in post-inoculation TEAEs in the 2xFLU-v group compared to placebo is not significant.

Primary: TEAEs relatedness and severity

End point title	TEAEs relatedness and severity[7]

End point description:

Number of subjects with one or more AE are reported by severity and relatedness to vaccine or challenge virus inoculation.

End point type	Primary

End point timeframe:

From the day the first treatment was administered until the ned of the study.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis were performed only summary numeration of the TEAEs in the different categories of relatedness and severity.

End point values	Adjuvanted Placebo	1x adjuvanted FLU-v	2x Adjuvanted FLU-v	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	52	51	
Units: Number of subjects				
Subjects with TEAEs definately related to vaccine	7	24	29	
Subjects with TEAEs probably related to vaccine	1	0	6	
Subjects with TEAEs possibly related to vaccine	3	2	3	
Subjects with TEAEs definately related to virus	1	0	0	
Subjects with TEAEs probably related to virus	3	1	1	
Subjects with TEAEs possibly related to virus	4	3	6	
Subjects with mild TEAEs	37	33	42	
Subjects with moderate TEAEs	13	4	11	
Subjects with severe TEAEs	0	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of symptomatic and asymptomatic subjects

End point title	Number of symptomatic and asymptomatic subjects

End point description:

Number of subjects experiencing no symptoms, at least one influenza symptom and at least two influenza symptoms.

End point type	Secondary

End point timeframe:

Quarantine period from day 1 to day 7

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: Number of subjects				
no symptoms	5	6	11	
at least one symptom	37	34	30	
at least two symptoms	27	16	23	

Statistical analyses

Statistical analysis title	At least one symptom

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower rate of "at least one symptom" than placebo.

Comparison groups	1xFLU-v Efficacy analysis v Placebo Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4648 [8]
Method	Fisher exact

Notes:

[8] - Differences with a P-value<0.05 were considered significant. The results of this analysis are not significant.

Statistical analysis title	At least one symptom

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower rate of "at least one symptom" than placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0736 [9]
Method	Fisher exact

Notes:

[9] - Differences with a P-value<0.05 were considered significant. The results of this analysis are not quite significant.

Statistical analysis title	At least two symptoms

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower rate of "at least two symptoms" than placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0235 [10]
Method	Fisher exact

Notes:

[10] - Differences with a P-value<0.05 were considered significant. The results of this analysis are significant.

Statistical analysis title	At least two symptoms

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower rate of "at least two symptoms" than placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2955 [11]
Method	Fisher exact

Notes:

[11] - Differences with a P-value<0.05 were considered significant. The results of this analysis are not significant.

Statistical analysis title	No symptoms

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower rate of "no symptoms" than placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05 [12]
Method	Fisher exact

Notes:

[12] - Differences were considered significant if P-value<0.05. The results show that the differences in this analysis are not significant.

Statistical analysis title	No symptoms

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower rate of "no symptoms" than placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.05 [13]
Method	Fisher exact

Notes:

[13] - Differences were considered significant if P-value<0.05. The results show that the differences in this analysis are not significant.

Secondary: Number of subjects with detectable viral shedding

End point title	Number of subjects with detectable viral shedding

End point description:

Subjects were swabbed intranasally daily in the morning and evening. Swabs were tested for the presence of virus using a Respiratory Pathogen Panel (RPP) Luminex test. If influenza virus was detected then the subject was positive for shedding.

End point type	Secondary

End point timeframe:

Quarantine period from day 1 to day 7.

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: Number of subjects	23	15	18	

Statistical analyses

Statistical analysis title	incidence of viral shedding

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower rate of shedding compared to placebo.

Comparison groups	1xFLU-v Efficacy analysis v Placebo Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0891 [14]
Method	Fisher exact

Notes:

[14] - Differences were considered significant if the p-value<0.05. In this analysis the difference is not quite significant.

Statistical analysis title	incidence of viral shedding

Statistical analysis description:

One-sided Fisher exact test is used to test if vaccine group has lower rate of shedding compared to placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2208 [15]
Method	Fisher exact

Notes:

[15] - Differences were considered significant if the p-value<0.05. In this analysis the difference is not significant.

Secondary: Shedding duration

End point title	Shedding duration

End point description:

Number of days from day 1 with a positive test for viral shedding in nasal swabs tested by Luminex RPP assay.

End point type	Secondary

End point timeframe:

Starting from evening of Day 1 post-inoculation up to Day 7.

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: days				
arithmetic mean (standard error)	1.95 (± 0.3574)	1.20 (± 0.3084)	1.90 (± 0.3917)	

Statistical analyses

Statistical analysis title	Shedding duration

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has shorter shedding duration than placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0501 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - Differences are considered significant if the p-value<0.05. This analysis indicates that the difference is almost significant.

Statistical analysis title	Shedding duration

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has shorter shedding duration than placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3139 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - Differences are considered significant if the p-value<0.05. This analysis indicates that the difference is not significant.

Secondary: Total viral shedding

End point title	Total viral shedding

End point description:

Subjects were swabbed daily (morning and evening) whilst under quarantine. The swabs were tested by RT-PCR to measure the number of copies of viral genetic material.

End point type	Secondary

End point timeframe:

Starting from evening of Day 1 post-inoculation up to Day 7.

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	40	
Units: hours*log10 copy number/ml				
arithmetic mean (standard error)	153.67 (± 33.39)	98.47 (± 27.39)	138.79 (± 31.73)	

Statistical analyses

Statistical analysis title	Total viral shedding (AUC)

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has smaller shedding AUC than the placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1018 [18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - Differences were considered significant if p-value<0.05. The difference in this analysis is not quite significant.

Statistical analysis title	Total viral shedding (AUC)

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has smaller shedding AUC than the placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4808 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - Differences were considered significant if p-value<0.05. The difference in this analysis is not significant.

Secondary: Peak viral shedding

End point title	Peak viral shedding

End point description:

The highest RT-qPCR (log10 copy number/ml) recorded for each subject under quarantine.

End point type	Secondary

End point timeframe:

Starting from evening of Day 1 post-inoculation up to Day 7.

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: log10 copy number/ml				
arithmetic mean (standard error)	2.24 (± 0.40)	1.54 (± 0.39)	2.28 (± 0.42)	

Statistical analyses

Statistical analysis title	Peak viral shedding

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has lower peak viral shedding than the placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.128 [20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - Differences are considered significant if p-value<0.05. The difference in this analysis is not quite significant.

Statistical analysis title	Peak viral shedding

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has lower peak viral shedding than the placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6007 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - Differences are considered significant if p-value<0.05. The difference in this analysis is not significant.

Secondary: Symptom duration

End point title	Symptom duration

End point description:

Number of symptomatic days as per physician's assessment.

End point type	Secondary

End point timeframe:

Starting from evening of Day 1 post-inoculation up to Day 7.

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: days				
arithmetic mean (standard error)	3.26 (± 0.37)	2.67 (± 0.35)	2.76 (± 0.37)	

Statistical analyses

Statistical analysis title	Duration of symptoms

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has shorter duration of symptoms than the placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1416 [22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - Differences are considered significant when p-value<0.05. The difference in this analysis is not quite significant.

Statistical analysis title	Duration of symptoms

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has shorter duration of symptoms than the placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1469 [23]
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - Differences are considered significant when p-value<0.05. The difference in this analysis is not quite significant.

Secondary: Average number of symptoms experienced

End point title	Average number of symptoms experienced

End point description:

Sum of symptoms experienced divided by the number of days in which symptoms were collected.

End point type	Secondary

End point timeframe:

Starting from evening of Day 1 post-inoculation up to Day 7.

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: number of symptoms				
arithmetic mean (standard error)	2.57 (± 0.33)	2.08 (± 0.32)	2.51 (± 0.41)	

Statistical analyses

Statistical analysis title	Total average symptoms experienced

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has fewer number of symptoms than placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0795 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - Differences are considered significant if p-value<0.05. The difference in this analysis is not quite significant.

Statistical analysis title	Total average symptoms experienced

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has fewer number of symptoms than placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.271 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - Differences are considered significant if p-value<0.05. The difference in this analysis is not significant.

Secondary: Peak number of symptoms

End point title	Peak number of symptoms

End point description:

The highest number of symptoms recorded in a time point as per physician's assessment.

End point type	Secondary

End point timeframe:

Starting from evening of Day 1 post-inoculation up to Day 7.

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: number of symptoms				
arithmetic mean (standard error)	2.12 (± 0.26)	1.68 (± 0.22)	1.88 (± 0.28)	

Statistical analyses

Statistical analysis title	Peak number of symptoms

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has fewer peak number of symptoms than placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0985 [26]
Method	Wilcoxon (Mann-Whitney)

Notes:

[26] - Differences are considered significant if p-value<0.05. The difference in this analysis is not quite significant.

Statistical analysis title	Peak number of symptoms

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has fewer peak number of symptoms than placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.178 [27]
Method	Wilcoxon (Mann-Whitney)

Notes:

[27] - Differences are considered significant if p-value<0.05. The difference in this analysis is not significant.

Secondary: Self-assessed symptom severity score (FLU-PRO)

End point title	Self-assessed symptom severity score (FLU-PRO)

End point description:

The mean of self-assessed daily symptom score over all study quarantine days.

End point type	Secondary

End point timeframe:

Starting from evening of Day 1 post-inoculation up to Day 7.

End point values	Placebo Efficacy analysis	1xFLU-v Efficacy analysis	2xFLU-v efficacy analysis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	41	
Units: symptom score				
arithmetic mean (standard error)	0.05 (± 0.01)	0.03 (± 0.01)	0.04 (± 0.01)	

Statistical analyses

Statistical analysis title	Total symptom score (FLU-PRO)

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has lower FluPro scores than placebo.

Comparison groups	Placebo Efficacy analysis v 1xFLU-v Efficacy analysis
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0638 [28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - Differences are considered significant if p-value<0.05. The difference in this analysis is not quite significant.

Statistical analysis title	Total symptom score (FLU-PRO)

Statistical analysis description:

One-sided Wilcoxon test is used to test if vaccine group has lower FluPro scores than placebo.

Comparison groups	Placebo Efficacy analysis v 2xFLU-v efficacy analysis
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2009 [29]
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - Differences are considered significant if p-value<0.05. The difference in this analysis is not significant.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the date of first administration of vaccine to the date of inoculation with the challenge virus.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Adjuvanted Placebo
Reporting group description: Received two doses of adjuvanted placebo 21 days apart and 21 days after the last vaccination were inoculated with influenza.	
Reporting group title	1x adjuvanted FLU-v
Reporting group description: Subjects received one dose of adjuvanted FLU-v and 21 days later a dose of adjuvanted placebo, followed by intranasal influenza inoculation 21 days after that.	
Reporting group title	2x Adjuvanted FLU-v
Reporting group description: Subjects received two doses of adjuvanted FLU-v 21 days apart, and 21 days after the last dose were intranasally inoculated with influenza.	

Serious adverse events	Adjuvanted Placebo	1x adjuvanted FLU-v	2x Adjuvanted FLU-v
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	0 / 51 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Adjuvanted Placebo	1x adjuvanted FLU-v	2x Adjuvanted FLU-v
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 50 (80.00%)	33 / 52 (63.46%)	45 / 51 (88.24%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 50 (6.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences (all)	3	0	2
Aspartate aminotransferase increased			

subjects affected / exposed	3 / 50 (6.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences (all)	3	0	2
Neutrophil count decreased			
subjects affected / exposed	2 / 50 (4.00%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 50 (8.00%)	2 / 52 (3.85%)	2 / 51 (3.92%)
occurrences (all)	4	2	2
Headache			
subjects affected / exposed	11 / 50 (22.00%)	5 / 52 (9.62%)	13 / 51 (25.49%)
occurrences (all)	11	5	13
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	9 / 50 (18.00%)	24 / 52 (46.15%)	31 / 51 (60.78%)
occurrences (all)	9	24	31
Injection site pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	0	1	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	3	1	1
Nausea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	3 / 51 (5.88%)
occurrences (all)	1	0	3
Toothache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	3 / 50 (6.00%)	2 / 52 (3.85%)	1 / 51 (1.96%)
occurrences (all)	3	2	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 52 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	6 / 50 (12.00%)	0 / 52 (0.00%)	3 / 51 (5.88%)
occurrences (all)	6	0	3
Oral herpes			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	1	1	3
Upper respiratory tract infection			
subjects affected / exposed	14 / 50 (28.00%)	9 / 52 (17.31%)	8 / 51 (15.69%)
occurrences (all)	14	9	8
Laceration			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 50 (4.00%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2016	Section 7.2; Inclusion Criteria 9: Clarification to participant asthma history prior to entry into study. Section 7.2; Inclusion Criteria 11: Clarification on the time-point for acquiring a subject's medical history from their GP. Section 18.7.1; Informed consent procedure: Amended to include Investigator or delegate to conduct participant consenting. Section 18.7.3; Information for General Practitioners: Amendment to the requirement for participant's medical history from their GP.
18 April 2017	Pages 1, 6 and 12 updated to reflect change in PI. Section 6.3.1 and throughout updated to reflect exploratory endpoints may be reported separately from CSR. Section 9.3.1 correction for consistency that subjects will be admitted to the Quarantine unit with a minimum 20 days not 21 days post second vaccination. Section 9.3.1 and throughout a clarification that serology test and result must be available within 90 days of Day 0 inoculation Section 13.1.2 inspection of the eyes removed from mandatory list in directed physical examination. Section 13.2.2 language inserted to state how missing Flu-PRO data will be handled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/17668898

http://www.ncbi.nlm.nih.gov/pubmed/2257516

http://www.ncbi.nlm.nih.gov/pubmed/25994549

http://www.ncbi.nlm.nih.gov/pubmed/26084515

http://www.ncbi.nlm.nih.gov/pubmed/25416753