Clinical trial results:
Effect of High-Dose Quadrivalent Influenza Vaccine (Efluelda®) versus Standard-Dose (QIV-SD), in subjects 65 years of age and older on innate immunity, including gene expression.

Summary

EudraCT number	2021-004573-32
Trial protocol	FR
Global end of trial date	14 February 2023

Results information

Result version number	v1 (current)
This version publication date	19 August 2023
First version publication date	19 August 2023
Summary attachment (see zip file)	INFLUOMICS_abstract_CSR RIPH1_V1.0_20230517 (INFLUOMICS_abstract_CSR RIPH1_V1.0_20230517.pdf)

Trial information

Trial identification

Sponsor protocol code	21-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05154383
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Hospitalier Annecy Genevois
Sponsor organisation address	1 avenue de l'hôpital, Epagny Metz-Tessy, France, 74370
Public contact	DRCI - Marion GHIDI, Centre Hospitalier Annecy Genevois, 033 450637031, mghidi@ch-annecygenevois.fr
Scientific contact	DRCI - Marion GHIDI, Centre Hospitalier Annecy Genevois, 033 450637031, mghidi@ch-annecygenevois.fr

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	17 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 July 2022
Global end of trial reached?	Yes
Global end of trial date	14 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of QIV-HD and QIV-SD vaccines in subjects 65 years of age and older on:
- the early systemic innate immune response through transcriptomic analysis i.e. innate gene signature including interferon signaling pathways,
- innate cells including antigen presenting and inflammatory cells,
- gene signature associate with adaptive immune response before and after the influenza vaccination,
- humoral immunity i.e. HI titers, at different time points.

Protection of trial subjects:

The study was performed in compliance with the requirements of the French Agency for the Safety of Health Products (Agence Nationale de la Sécurité du Médicament et des Produits de Santé - ANSM). The study gained initial full regulatory approval from the 2021/10/05, CHANGE was issued with the following EudraCT number 2021-004573-32. First protocol amendment was approved by the regulatory approval on 2022/01/24.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2021
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	France: 59
Worldwide total number of subjects	59
EEA total number of subjects	59

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)	0
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Number of patients planned: 60 evaluable subjects (volunteers).
Number of patients randomized and analyzed: 59 (one was excluded before randomization because diagnosed with an active high-grade lymphoma, which is corresponding to a non-inclusion criterion).
28 subjects received QIV-SD vaccine and 31 subjects received QIV-HD vaccine.

Pre-assignment

Screening details:

Inclusion criteria :
- Aged 65 years or older, the day of inclusion
Non-inclusion criteria :
- Any vaccine injection (including for COVID-19) in the 4 weeks preceding study inclusion
- Plan to receive any vaccine (including for COVID-19) in the 24 hours following study inclusion
- Already vaccinated against influenza for 2021-2022 season

Period 1

Period 1 title	Visit 1: 7 days before vaccination visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	QIV-HD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Efluelda
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Dose: Each 0.7mL dose contains 60 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Arm title	QIV-SD

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	InfluvacTetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use, Injection

Dosage and administration details:

Each 0.5mL dose contains 15 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Number of subjects in period 1	QIV-HD	QIV-SD
Started	31	28
Completed	31	28

Period 2	
Period 2 title	Visit 2: vaccination visit (day 0)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	QIV-HD

Arm description:

Subjects who receive the Sanofi Pasteur Quadrivalent Influenza Vaccine High-Dose Quadrivalent vaccine.

Arm type	Experimental
Investigational medicinal product name	Efluelda
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Dose: Each 0.7mL dose contains 60 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Arm title	QIV-SD

Arm description:

Subjects who received Quadrivalent Influenza Vaccine - Standard-Dose.

Arm type	Active comparator
Investigational medicinal product name	InfluvacTetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Each 0.5mL dose contains 15 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Visit 1 correspond to the inclusion visit and informed consent form signature (= Day -7). Visit 2 will take place 7 days after Visit 1, and correspond to the randomization and vaccine administration (= Day 0).

Number of subjects in period 2	QIV-HD	QIV-SD
Started	31	28
Completed	31	28

Period 3	
Period 3 title	Visit 3: 1 days after vaccination visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	QIV-HD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Efluelda
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Dose: Each 0.7mL dose contains 60 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Arm title	QIV-SD

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	InfluvacTetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Each 0.5mL dose contains 15 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Number of subjects in period 3	QIV-HD	QIV-SD
Started	31	28
Completed	31	28

Period 4	
Period 4 title	Visit 4: 21 days after vaccination visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	QIV-HD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Efluelda
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Dose: Each 0.7mL dose contains 60 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Arm title	QIV-SD

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	InfluvacTetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Each 0.5mL dose contains 15 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Number of subjects in period 4	QIV-HD	QIV-SD
Started	31	28
Completed	31	28

Period 5	
Period 5 title	Visit 5: 90 days after vaccination visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	QIV-HD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Efluelda
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Dose: Each 0.7mL dose contains 60 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Arm title	QIV-SD

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	InfluvacTetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Each 0.5mL dose contains 15 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Number of subjects in period 5	QIV-HD	QIV-SD
Started	31	28
Completed	31	28

Period 6	
Period 6 title	Visit6: 210 days after vaccination visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	QIV-HD

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Efluelda
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Dose: Each 0.7mL dose contains 60 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Arm title	QIV-SD

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	InfluvacTetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Each 0.5mL dose contains 15 µg hemagglutinin (HA) of each influenza strain. Strains were determined based on World Health Organization (WHO) and European Union (EU) recommendations for the 2021-2022 Northern Hemisphere (NH) influenza season.
Injected into the upper arm (deltoid area).

Number of subjects in period 6	QIV-HD	QIV-SD
Started	31	28
Completed	31	28

Baseline characteristics

Reporting groups	
Reporting group title	QIV-HD
Reporting group description:	
Subjects who receive the Sanofi Pasteur Quadrivalent Influenza Vaccine High-Dose Quadrivalent vaccine.	
Reporting group title	QIV-SD
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine - Standard-Dose.	

Reporting group values	QIV-HD	QIV-SD	Total
Number of subjects	31	28	59
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	70	70	
inter-quartile range (Q1-Q3)	69 to 74	67 to 72	-
Gender categorical			
Units: Subjects			
Female	14	11	25
Male	17	17	34
Body Mass Index (BMI)			
BMI = weight[kg] / height²[m²]			
Units: kg/m²			
median			
inter-quartile range (Q1-Q3)			-
Charlson Comorbidity Index (CCI)			
Age-adjusted Charlson comorbidity score			
Units: Points			
median			
inter-quartile range (Q1-Q3)			-

Subject analysis sets	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full analysis set (FAS) was comprised of the 59 trial participants who received one dose of the study vaccines and had a post-vaccination blood sample. Participants were randomized with equal probability into two subsets: QIV-SD (N = 28) and QIV-HD (N = 31) vaccine groups.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per protocol (PP) population is strictly overlapping with the FAS

Subject analysis set title	Safety Set (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety set (SS) population is strictly overlapping with the FAS

Reporting group values	Full Analysis Set (FAS)	Per Protocol (PP)	Safety Set (SS)
Number of subjects	59	59	59
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	70	70	70
inter-quartile range (Q1-Q3)	68 to 73	68 to 73	68 to 73
Gender categorical Units: Subjects			
Female	25	25	25
Male	34	34	34
Body Mass Index (BMI)			
BMI = weight[kg] / height²[m²]			
Units: kg/m²			
median	24	24	24
inter-quartile range (Q1-Q3)	23 to 27	23 to 27	23 to 27
Charlson Comorbidity Index (CCI)			
Age-adjusted Charlson comorbidity score			
Units: Points			
median	3.0	3.0	3.0
inter-quartile range (Q1-Q3)	2.0 to 4.0	2.0 to 4.0	2.0 to 4.0

End points

End points reporting groups

Reporting group title	QIV-HD
Reporting group description: -	
Reporting group title	QIV-SD
Reporting group description: -	
Reporting group title	QIV-HD
Reporting group description:	
Subjects who receive the Sanofi Pasteur Quadrivalent Influenza Vaccine High-Dose Quadrivalent vaccine.	
Reporting group title	QIV-SD
Reporting group description:	
Subjects who received Quadrivalent Influenza Vaccine - Standard-Dose.	
Reporting group title	QIV-HD
Reporting group description: -	
Reporting group title	QIV-SD
Reporting group description: -	
Reporting group title	QIV-HD
Reporting group description: -	
Reporting group title	QIV-SD
Reporting group description: -	
Reporting group title	QIV-HD
Reporting group description: -	
Reporting group title	QIV-SD
Reporting group description: -	
Reporting group title	QIV-HD
Reporting group description: -	
Reporting group title	QIV-SD
Reporting group description: -	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full analysis set (FAS) was comprised of the 59 trial participants who received one dose of the study vaccines and had a post-vaccination blood sample. Participants were randomized with equal probability into two subsets: QIV-SD (N = 28) and QIV-HD (N = 31) vaccine groups.	
Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per protocol (PP) population is strictly overlapping with the FAS	
Subject analysis set title	Safety Set (SS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety set (SS) population is strictly overlapping with the FAS	

Primary: Immunogenicity

End point title	Immunogenicity[1]
End point description:	
Parameters were presented by vaccine group, and against flu strain, with their 95% Confidence Interval (95%CI) for D21, D90, and D210: 1. Geometric Mean (GM) of titers on D0 and (D21, D90, D210) with and without log transformation 2. Distribution of titers against flu	

3. Rate of subjects with titer ≥ 1:10 on D0 and (D21, D90, D210)
4. Rate of subjects with titer ≥ 1:40 on D0 and (D21, D90, D210) - Seroprotection
5. Seroconversion or significant increase rate from D0 to (D21, D90, D210)
6. GM of titer ratio (D21, D90, D210)/D0 (immunological response):
a. Individual evolution of ratios
b. Distribution of evolution of ratios
c. Mean evolution of ratios
7. Evolution of (log) antibody titers over time

End point type	Primary

End point timeframe:

D0, D21, D90, and D210

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: Multiple influenza strains

End point values	QIV-HD	QIV-SD	QIV-HD	QIV-HD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	28	31	31
Units: titers				
geometric mean (confidence interval 95%)	38.7 (24.8 to 52.6)	38.2 (25.5 to 50.9)	222.9 (156.3 to 289.5)	372.9 (267.9 to 477.9)

End point values	QIV-SD	QIV-HD	QIV-SD	QIV-SD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	31	28	28
Units: titers				
geometric mean (confidence interval 95%)	259.2 (178.1 to 340.3)	546.5 (353.6 to 739.4)	302.1 (118.6 to 485.6)	199.1 (132.0 to 266.2)

End point values	Full Analysis Set (FAS)	Per Protocol (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	59		
Units: titers				
geometric mean (confidence interval 95%)	247.5 (183.5 to 311.4)	247.5 (183.5 to 311.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Transcriptomic

End point title	Transcriptomic

End point description:

See protocol

End point type	Secondary

End point timeframe:

D0 and D1

End point values	QIV-HD	QIV-SD	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	31	27	58	
Units: Differential Gene Expression				
number (not applicable)	293	65	358	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Occurence of ILI and other adverse events

End point type	Secondary

End point timeframe:

D0 to D210

End point values	QIV-HD	QIV-SD	Safety Set (SS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	31	28	59	
Units: Number of event	4	1	5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Immediate Post-vaccination Observation Period : participants will be kept under observation for 15 minutes after each vaccination.
Adverse events of special interest and SAEs will be collected throughout the study from Visit 1 to Visit 6.

Adverse event reporting additional description:

Information on SAEs will be collected and assessed throughout the study, from Visit 1 to Visit 6. However, before the first study product administration, only SAEs related to study procedures are to be collected in the CRF.
All SAEs will be recorded and reported to the Sponsor and under no circumstance should this exceed 24 hours.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	QIV-HD
Reporting group description: -	
Reporting group title	QIV-SD
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: 5 serious adverse events.
0 non-serious adverse event.

Serious adverse events	QIV-HD	QIV-SD	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 31 (9.68%)	1 / 28 (3.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
5 years and 1 month			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
5 days			
subjects affected / exposed	0 / 31 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
189 days			

subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
231 days			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
5 days			
subjects affected / exposed	1 / 31 (3.23%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	QIV-HD	QIV-SD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 28 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2022	- Modification of a non-inclusion criterion (reduction of the vaccination exclusion period in the study to 24 hours after administration of the influenza vaccine instead of 4 weeks, i.e. COVID vaccination possible after the last blood sample in the study, intended for transcriptomic and cytometric analyses). - Complete pharmacy circuit updated (ordering, labeling, stock management, and InfluvacTetra® vaccine chosen as comparator). - Updating of the insurance certificate to include 70 patients in order to reach the 60 evaluable patients stipulated in the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported