Clinical trial results:
Feasibility of Randomizing Danish Citizens Aged 65-79 Years to High-Dose Quadrivalent Influenza Vaccine vs. Standard-Dose Quadrivalent Influenza Vaccine in a Pragmatic Registry-Based Setting

Summary

EudraCT number	2021-003170-31
Trial protocol	DK
Global end of trial date	31 May 2022

Results information

Result version number	v1 (current)
This version publication date	17 June 2023
First version publication date	17 June 2023

Trial information

Trial identification

Sponsor protocol code	QHD00027

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05048589
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev and Gentofte Hospital
Sponsor organisation address	Gentofte Hospitalsvej 8, 3.th., Hellerup, Denmark, 2900
Public contact	Niklas Dyrby Johansen, Herlev and Gentofte Hospital, +45 20204794, niklas.dyrby.johansen@regionh.dk
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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	20 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2022
Global end of trial reached?	Yes
Global end of trial date	31 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Descriptive objective 1: Identifying and recruiting a large sample of Danish citizens aged 65-79 years in the coming 2021/2022 influenza season to assess feasibility, reliability, and validity of the proposed pragmatic RCT study design as assessed by operational endpoints

Protection of trial subjects:

The trial was approved by the Regional Danish Committee on Biomedical Research Ethics and the Danish Medicines Agency and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 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	Denmark: 12551
Worldwide total number of subjects	12551
EEA total number of subjects	12551

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)	2
From 65 to 84 years	12549
85 years and over	0

Subject disposition

Recruitment	
Recruitment details: -	
Pre-assignment	
Screening details: -	
Pre-assignment period milestones	
Number of subjects started	12551
Number of subjects completed	12477
Pre-assignment subject non-completion reasons	
Reason: Number of subjects	Consent withdrawn by subject: 72
Reason: Number of subjects	Protocol deviation: 2

Period 1	
Period 1 title	Overall trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	High-Dose Quadrivalent Influenza Vaccine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	High-Dose Quadrivalent Influenza Vaccine
Investigational medicinal product code	MA number: 62663, ATC: J07BB02
Other name	Efluelda®, Fluzone® High-Dose Quadrivalent
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details:	
Single dose vaccine, 60 micrograms of hemagglutinin antigen for each of the 4 influenza strains	
Arm title	Standard-Dose Quadrivalent Influenza Vaccine
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Standard-Dose Quadrivalent Influenza Vaccine
Investigational medicinal product code	ATC: J07BB02
Other name	Influvactetra, Vaxigriptetra
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details:	
Single dose vaccine, 15 micrograms of hemagglutinin antigen for each of the 4 influenza strains	

Number of subjects in period 1[1]	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine
Started	6245	6232
Completed	6245	6232

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Since we are unable to include data for participants excluded due to withdrawn consent and protocol deviations in this report, we had to technically exclude those prior to the baseline period in this system.

Baseline characteristics

Reporting groups	
Reporting group title	High-Dose Quadrivalent Influenza Vaccine
Reporting group description: -	
Reporting group title	Standard-Dose Quadrivalent Influenza Vaccine
Reporting group description: -	

Reporting group values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine	Total
Number of subjects	6245	6232	12477
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)	0	0	0
From 65-84 years	6245	6232	12477
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	71.8	71.7	
standard deviation	± 3.9	± 3.9	-
Gender categorical Units: Subjects			
Female	2956	2921	5877
Male	3289	3311	6600
Chronic cardiovascular disease Units: Subjects			
Chronic cardiovascular disease	1227	1313	2540
No chronic cardiovascular disease	5018	4919	9937
Ischemic heart disease Units: Subjects			
Ischemic heart disease	450	512	962
No ischemic heart disease	5795	5720	11515
Atrial fibrillation Units: Subjects			
Atrial fibrillation	458	420	878
No atrial fibrillation	5787	5812	11599
Cerebrovascular disease Units: Subjects			
Cerebrovascular disease	219	237	456
No cerebrovascular disease	6026	5995	12021
Hypertension			

Units: Subjects			
Hypertension	3254	3215	6469
No hypertension	2991	3017	6008
Diabetes Units: Subjects			
Diabetes	574	588	1162
No diabetes	5671	5644	11315
Chronic lung disease Units: Subjects			
Chronic lung disease	435	415	850
No chronic lung disease	5810	5817	11627
Chronic obstructive pulmonary disease Units: Subjects			
Chronic obstructive pulmonary disease	227	190	417
No chronic obstructive pulmonary disease	6018	6042	12060
Cancer Units: Subjects			
Cancer	695	668	1363
No cancer	5550	5564	11114
Immunodeficiency Units: Subjects			
Immunodeficiency	244	239	483
No immunodeficiency	6001	5993	11994

Subject analysis sets

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

Subject analysis set description:

Full analysis set

Reporting group values	Full analysis set		
Number of subjects	12477		
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	12477		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	±		

Gender categorical Units: Subjects			
Female Male			
Chronic cardiovascular disease Units: Subjects			
Chronic cardiovascular disease No chronic cardiovascular disease	2540 9937		
Ischemic heart disease Units: Subjects			
Ischemic heart disease No ischemic heart disease	962 11515		
Atrial fibrillation Units: Subjects			
Atrial fibrillation No atrial fibrillation	878 11599		
Cerebrovascular disease Units: Subjects			
Cerebrovascular disease No cerebrovascular disease	456 12021		
Hypertension Units: Subjects			
Hypertension No hypertension	6469 6008		
Diabetes Units: Subjects			
Diabetes No diabetes	1162 11315		
Chronic lung disease Units: Subjects			
Chronic lung disease No chronic lung disease	850 11627		
Chronic obstructive pulmonary disease Units: Subjects			
Chronic obstructive pulmonary disease No chronic obstructive pulmonary disease	417 12060		
Cancer Units: Subjects			
Cancer No cancer	1363 11114		
Immunodeficiency Units: Subjects			
Immunodeficiency No immunodeficiency	483 11994		

End points

End points reporting groups

Reporting group title	High-Dose Quadrivalent Influenza Vaccine
Reporting group description: -	
Reporting group title	Standard-Dose Quadrivalent Influenza Vaccine
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set	

Primary: Number of participants included and randomized

End point title	Number of participants included and randomized[1]
End point description:	
The trial was a pilot/feasibility trial. This endpoint is a feasibility endpoint describing the total number of participants included and randomized. This endpoint was assigned as the primary endpoint for technical reasons only.	
End point type	Primary
End point timeframe:	
01/10/2021 to 20/11/2021	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The trial was a pilot/feasibility trial with only descriptive endpoints/objectives.

End point values	Full analysis set			
Subject group type	Subject analysis set [2]			
Number of subjects analysed				
Units: Persons				
Feasibility	12551			

Notes:

[2] - Feasibility endpoint describing the total number of participants included and randomized.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of persons contacted by recruitment letter

End point title	Number of persons contacted by recruitment letter
End point description:	
The trial was a pilot/feasibility trial. This endpoint is a feasibility endpoint describing the total number of persons contacted by recruitment letter.	
End point type	Other pre-specified
End point timeframe:	
24/09/2021 to 01/10/2021	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	[3]			
Units: Persons				
Feasibility	34000			

Notes:

[3] - Feasibility endpoint describing the total number of persons contacted by recruitment letter.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Agreement between randomized assignment and actual received vaccine

End point title	Agreement between randomized assignment and actual received vaccine

End point description:

End point type	Other pre-specified

End point timeframe:

The trial was a pilot/feasibility trial. This endpoint is a feasibility endpoint describing the agreement between randomized assignment and actual received vaccine in each randomization group.

End point values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6245	6232		
Units: Participants receiving correct vaccine				
Feasibility	6242	6226		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Hospitalization for influenza or pneumonia

End point title	Hospitalization for influenza or pneumonia

End point description:

End point type	Other pre-specified

End point timeframe:

14 days after vaccination to 31/05/2022

End point values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6245	6232		
Units: Participants				
Vaccine effectiveness	10	28		

Statistical analyses

Statistical analysis title	rVE for hospitalization for pneumonia or influenza

Statistical analysis description:

The trial was a pilot/feasibility trial. Descriptive relative vaccine effectiveness (rVE) estimates were calculated without statistical hypothesis testing.

Comparison groups	Standard-Dose Quadrivalent Influenza Vaccine v High-Dose Quadrivalent Influenza Vaccine
Number of subjects included in analysis	12477
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Relative vaccine effectiveness
Point estimate	64.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.4
upper limit	84.6

Notes:

[4] - Descriptive estimate.

Other pre-specified: Hospitalization for respiratory disease

End point title	Hospitalization for respiratory disease

End point description:

End point type	Other pre-specified

End point timeframe:

14 days after vaccination to 31/05/2022

End point values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6245	6232		
Units: Participants				
Vaccine effectiveness	24	40		

Statistical analyses

Statistical analysis title	rVE for hospitalization for respiratory disease

Statistical analysis description:

The trial was a pilot/feasibility trial. Descriptive relative vaccine effectiveness (rVE) estimates were calculated without statistical hypothesis testing.

Comparison groups	High-Dose Quadrivalent Influenza Vaccine v Standard-Dose Quadrivalent Influenza Vaccine
Number of subjects included in analysis	12477
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Relative vaccine effectiveness
Point estimate	40.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	65.5

Notes:

[5] - Descriptive estimate.

Other pre-specified: Hospitalization for cardio-respiratory disease

End point title	Hospitalization for cardio-respiratory disease

End point description:

End point type	Other pre-specified

End point timeframe:

14 days after vaccination to 31/05/2022

End point values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6245	6232		
Units: Participants				
Vaccine effectiveness	103	117		

Statistical analyses

Statistical analysis title	rVE for cardiorespiratory hospitalization

Statistical analysis description:

The trial was a pilot/feasibility trial. Descriptive relative vaccine effectiveness (rVE) estimates were calculated without statistical hypothesis testing.

Comparison groups	High-Dose Quadrivalent Influenza Vaccine v Standard-Dose Quadrivalent Influenza Vaccine
Number of subjects included in analysis	12477
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Relative vaccine effectiveness
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.5
upper limit	33.3

Notes:

[6] - Descriptive estimate.

Other pre-specified: Hospitalization for cardiovascular disease

End point title	Hospitalization for cardiovascular disease

End point description:

End point type	Other pre-specified

End point timeframe:

14 days after vaccination to 31/05/2022

End point values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6245	6232		
Units: Participants				
Vaccine effectiveness	82	81		

Statistical analyses

Statistical analysis title	rVE for cardiovascular hospitalization

Statistical analysis description:

The trial was a pilot/feasibility trial. Descriptive relative vaccine effectiveness (rVE) estimates were calculated without statistical hypothesis testing.

Comparison groups	High-Dose Quadrivalent Influenza Vaccine v Standard-Dose Quadrivalent Influenza Vaccine
Number of subjects included in analysis	12477
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Relative vaccine effectiveness
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.1
upper limit	26.6

Notes:

[7] - Descriptive estimate.

Other pre-specified: Hospitalization for any cause

End point title	Hospitalization for any cause

End point description:

End point type	Other pre-specified

End point timeframe:

14 days after vaccination to 31/05/2022

End point values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6245	6232		
Units: Participants				
Vaccine effectiveness	513	550		

Statistical analyses

Statistical analysis title	rVE for hospitalization for any cause

Statistical analysis description:

The trial was a pilot/feasibility trial. Descriptive relative vaccine effectiveness (rVE) estimates were calculated without statistical hypothesis testing.

Comparison groups	High-Dose Quadrivalent Influenza Vaccine v Standard-Dose Quadrivalent Influenza Vaccine

Number of subjects included in analysis	12477
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Relative vaccine effectiveness
Point estimate	6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	17.6

Notes:

[8] - Descriptive estimate.

Other pre-specified: All-cause death

End point title	All-cause death

End point description:

End point type	Other pre-specified

End point timeframe:

14 days after vaccination to 31/05/2022

End point values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6245	6232		
Units: Participants				
Vaccine effectiveness	21	41		

Statistical analyses

Statistical analysis title	rVE for all-cause death

Statistical analysis description:

The trial was a pilot/feasibility trial. Descriptive relative vaccine effectiveness (rVE) estimates were calculated without statistical hypothesis testing.

Comparison groups	High-Dose Quadrivalent Influenza Vaccine v Standard-Dose Quadrivalent Influenza Vaccine
Number of subjects included in analysis	12477
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Relative vaccine effectiveness
Point estimate	48.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	11.5
upper limit	71.3

Notes:

[9] - Descriptive estimate.

Other pre-specified: Hospitalization for COVID-19

End point title	Hospitalization for COVID-19

End point description:

End point type	Other pre-specified

End point timeframe:

14 days after vaccination to 31/05/2022

End point values	High-Dose Quadrivalent Influenza Vaccine	Standard-Dose Quadrivalent Influenza Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6245	6232		
Units: Participants				
Vaccine effectiveness	15	12		

Statistical analyses

Statistical analysis title	rVE for hospitalization for COVID-19

Statistical analysis description:

The trial was a pilot/feasibility trial. Descriptive relative vaccine effectiveness (rVE) estimates were calculated without statistical hypothesis testing.

Comparison groups	High-Dose Quadrivalent Influenza Vaccine v Standard-Dose Quadrivalent Influenza Vaccine
Number of subjects included in analysis	12477
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Relative vaccine effectiveness
Point estimate	-24.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-191.9
upper limit	45.5

Notes:

[10] - Descriptive estimate.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From time of vaccination until approx. 3 months after vaccination.

Adverse event reporting additional description:

Safety surveillance was performed using a registry-based approach, and after agreement with applicable authorities, only serious adverse events (SAEs), defined in this pragmatic trial as deaths and hospitalizations, were recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD-10
Dictionary version	10

Reporting groups

Reporting group title	Standard-Dose Quadrivalent Influenza Vaccine

Reporting group description:

Participants receiving standard-dose quadrivalent influenza vaccine

Reporting group title	High-Dose Quadrivalent Influenza Vaccine

Reporting group description:

Participants receiving high-dose quadrivalent influenza vaccine

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: In agreement with applicable authorities, only serious adverse events were recorded in this pragmatic randomized trial.

Serious adverse events	Standard-Dose Quadrivalent Influenza Vaccine	High-Dose Quadrivalent Influenza Vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	405 / 6229 (6.50%)	373 / 6248 (5.97%)	
number of deaths (all causes)	13	8	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Injury	Additional description: Injury-related SAEs		
subjects affected / exposed	98 / 6229 (1.57%)	94 / 6248 (1.50%)	
occurrences causally related to treatment / all	0 / 100	0 / 101	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiovascular disorder	Additional description: Cardiovascular SAEs		
subjects affected / exposed	87 / 6229 (1.40%)	63 / 6248 (1.01%)	
occurrences causally related to treatment / all	0 / 107	0 / 71	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death	Additional description: Deaths during safety surveillance period		

subjects affected / exposed	13 / 6229 (0.21%)	8 / 6248 (0.13%)	
occurrences causally related to treatment / all	0 / 13	0 / 8	
deaths causally related to treatment / all	0 / 8	0 / 8	
Hyperthermia	Additional description: Fever, unspecified		
subjects affected / exposed	1 / 6229 (0.02%)	1 / 6248 (0.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache, unspecified		
subjects affected / exposed	3 / 6229 (0.05%)	3 / 6248 (0.05%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder	Additional description: Gastrointestinal SAEs		
subjects affected / exposed	24 / 6229 (0.39%)	23 / 6248 (0.37%)	
occurrences causally related to treatment / all	0 / 28	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder	Additional description: Respiratory SAEs		
subjects affected / exposed	26 / 6229 (0.42%)	24 / 6248 (0.38%)	
occurrences causally related to treatment / all	0 / 32	0 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	16 / 6229 (0.26%)	20 / 6248 (0.32%)	
occurrences causally related to treatment / all	0 / 19	1 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin discomfort	Additional description: Disturbances of skin sensation		
subjects affected / exposed	3 / 6229 (0.05%)	0 / 6248 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection	Additional description: Infection-related SAEs		

subjects affected / exposed	19 / 6229 (0.31%)	22 / 6248 (0.35%)	
occurrences causally related to treatment / all	0 / 25	0 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard-Dose Quadrivalent Influenza Vaccine	High-Dose Quadrivalent Influenza Vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 6229 (0.00%)	0 / 6248 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2021	Change from EHR-based to registry-based safety surveillance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported