Clinical trial results:
Pneumococcal vaccination of rheumatoid arthritis patients in immunomodulatory therapy

Summary

EudraCT number	2014-001299-79
Trial protocol	DK
Global end of trial date	19 June 2017

Results information

Result version number	v1 (current)
This version publication date	12 August 2021
First version publication date	12 August 2021
Summary attachment (see zip file)	IMVX2014 summary (IMVX summary.docx)

Trial information

Trial identification

Sponsor protocol code	IMVX2014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of infectious Diseases, Odense University Hospital
Sponsor organisation address	Sdr. Boulevard 29, Entrance 18, 2nd floor Penthouse, Odense C, Denmark, 5000
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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	15 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 June 2017
Global end of trial reached?	Yes
Global end of trial date	19 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the serological responses to prime-boost pneumococcal vaccination with PCV13 followed by PPV23 among patients with RA treated with bDMARD according to dosing and intervals between immunizations, according to individual biological drug groups, and compared to responses in patients with RA treated with csDMARD.

Protection of trial subjects:

Adverse effect/reactions were reported after vaccination with the 13-valent protein conjugated pneumococcal vaccine (PCV13) followed by the 23-valent polysaccharide pneumococcal vaccine (PPV23) 4 or 6 months later. Both vaccines are natonally and internatonally approved to prevent pneumococcal disease in our study poulation.
All participants were offered follow up after vaccination as a part of the trial. In case of the adverse effects/reactions were not resolved after 4 weeks the participants was referred to a specialist who could examine the partcipant regarding the symptoms. All serious adverse effects were reported during the trial.

Background therapy:

Only PCV13 and PPV23 were used across all groups.

Evidence for comparator:

National Danish and international guidelines recommend pneumococcal vaccination with PCV13 followed by PPV23 at least 8 weeks later to prevent penumococcal disease among risk Groups. Our risk group was immunosuppressed rheumatoid arthritis patients (RA) treated with either conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) or biological disease modifying anti-rheumatic drugs (bDMARD).
Previous studies have show that vaccination with either the 7-valent conjugated pneumococcal vaccine (PCV7) or PPV23 gave a rise i pneumococcal antibodies among RA patients.

Actual start date of recruitment	01 May 2014
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: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	58
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 2 centers starting 01 October 2014.
All participants were recruited from af survey carried out in the two centers. All aprticipants signed a informed consent.

Pre-assignment

Screening details:

192 participants were screened from a previous survey carried out in the two centers.
Screening criteria: a diagnosis of RA, age > 18 years, and ongoing immunosuppressive therapy with cDMARDs and/or bDMARDs.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

csDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (16 weeks)

Arm type	Control arm
Investigational medicinal product name	13-valent conjugate pneumooccal vaccine
Investigational medicinal product code	
Other name	Prevenar 13
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL contains polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The vaccine administered as an intramuscular injection in the deltoid or the gluteus maximus muscle.

Investigational medicinal product name	23-valent polysaccharide pneumooccal vaccine
Investigational medicinal product code	
Other name	Pneumovax
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL contains polysaccharides of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. The vaccine administered as an intramuscular injection in the deltoid or the gluteus maximus muscle.

Arm title	Arm IA

Arm description:

bDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (16 weeks)

Arm type	Active comparator
Investigational medicinal product name	13-valent conjugate pneumooccal vaccine
Investigational medicinal product code	
Other name	Prevenar 13
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL contains polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The vaccine administered as an intramuscular injection in the deltoid or the gluteus maximus muscle.

Investigational medicinal product name	13-valent conjugate pneumooccal vaccine
Investigational medicinal product code	
Other name	Prevenar 13
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL contains polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The vaccine administered as an intramuscular injection in the deltoid or the gluteus maximus muscle.

Arm title	Arm IB

Arm description:

bDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (24 weeks)

Arm type	Active comparator
Investigational medicinal product name	13-valent conjugate pneumooccal vaccine
Investigational medicinal product code	
Other name	Prevenar 13
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL contains polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The vaccine administered as an intramuscular injection in the deltoid or the gluteus maximus muscle.

Investigational medicinal product name	23-valent polysaccharide pneumooccal vaccine
Investigational medicinal product code	
Other name	Pneumovax
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL contains polysaccharides of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. The vaccine administered as an intramuscular injection in the deltoid or the gluteus maximus muscle.

Arm title	Arm II

Arm description:

bDMARD treated participants. Vaccination: Double PCV13 (0 weeks) + PPV23 (16 weeks)

Arm type	Active comparator
Investigational medicinal product name	13-valent conjugate pneumooccal vaccine
Investigational medicinal product code	
Other name	Prevenar 13
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL contains polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. The vaccine administered as an intramuscular injection in the deltoid or the gluteus maximus muscle.

Investigational medicinal product name	23-valent polysaccharide pneumooccal vaccine
Investigational medicinal product code	
Other name	Pneumovax
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL contains polysaccharides of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. The vaccine administered as an intramuscular injection in the deltoid or the gluteus maximus muscle.

Number of subjects in period 1	Control	Arm IA	Arm IB
Started	35	21	23
Completed	33	20	22
Not completed	2	1	1
Adverse event, non-fatal	2	1	1

Number of subjects in period 1	Arm II
Started	21
Completed	21
Not completed	0
Adverse event, non-fatal	-

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
csDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (16 weeks)	
Reporting group title	Arm IA
Reporting group description:	
bDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (16 weeks)	
Reporting group title	Arm IB
Reporting group description:	
bDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (24 weeks)	
Reporting group title	Arm II
Reporting group description:	
bDMARD treated participants. Vaccination: Double PCV13 (0 weeks) + PPV23 (16 weeks)	

Reporting group values	Control	Arm IA	Arm IB
Number of subjects	35	21	23
Age categorical			
The median age among the 96 participants was 62 years (range 23-82 years). The demographics were similar in the four arms			
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)	21	14	12
From 65-84 years	14	7	11
85 years and over	0	0	0
Age continuous			
The overall median age was 62 years (range 23-82 years).			
Units: years			
median	59	62	59
full range (min-max)	23 to 82	32 to 73	38 to 75
Gender categorical			
Units: Subjects			
Female	21	14	13
Male	14	7	10
RA disease duration			
Duration of RA disease. The median duration was 12 years (range 0.5-33 years)			
Units: years			
median	7	11	14
full range (min-max)	0 to 54	3 to 33	5 to 32

Reporting group values	Arm II	Total	
Number of subjects	21	100	
Age categorical			
The median age among the 96 participants was 62 years (range 23-82 years). The demographics were similar in the four arms			
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)	11	58	
From 65-84 years	10	42	
85 years and over	0	0	
Age continuous			
The overall median age was 62 years (range 23-82 years).			
Units: years			
median	64		
full range (min-max)	46 to 82	-	
Gender categorical			
Units: Subjects			
Female	14	62	
Male	7	38	
RA disease duration			
Duration of RA disease. The median duration was 12 years (range 0.5-33 years)			
Units: years			
median	15		
full range (min-max)	0.5 to 30	-	

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
csDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (16 weeks)	
Reporting group title	Arm IA
Reporting group description:	
bDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (16 weeks)	
Reporting group title	Arm IB
Reporting group description:	
bDMARD treated participants. Vaccination: Single PCV13 (0 weeks) + PPV23 (24 weeks)	
Reporting group title	Arm II
Reporting group description:	
bDMARD treated participants. Vaccination: Double PCV13 (0 weeks) + PPV23 (16 weeks)	

Primary: primary endpoint

End point title	primary endpoint
End point description:	
The participants had a blood test drawn before and 4 weeks after each vaccination. Specific antipneumoccal antibodies for 12 specific serotypes were measured (mg/L). The prmary endpoint was defined as theproportion of participants in each treatment group responsive to ≥ 6 of 12 antipneumococcal antibody serotypes at week 4 after completion of the prime-boost vaccination series. A positive serological response was defined as a 4-fold increase from baseline or achieving a level of > 0.35 mg/L.	
End point type	Primary
End point timeframe:	
The participants were vaccinated with PCV13 followed by PPV23. The primary endpoint was the seological response after completion after completion of the vaccination series.	

End point values	Control	Arm IA	Arm IB	Arm II
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	20	22	21
Units: subjects	33	20	22	21

Statistical analyses

Statistical analysis title	Statistical analysis for serological response
Statistical analysis description:	
Descriptive statistics are presented along with 95% CI for vaccine response. For variables that were not normally distributed, the median (range) was reported. For binary variables, the number (%) of participants was listed relatively to the total number of participants. Serological responses for pneumococcal antibodies were log-trans-formed and tested with Shapiro-Wilk test for normality.	
Comparison groups	Control v Arm IA v Arm IB v Arm II

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - The geometric mean concentration (GMC) and geometric mean fold rise for each serotype were calculated before and 4 weeks after both vaccinations. Differences in serological outcome between the 3 randomization arms, the 2 treatment Groups (bDMARD and csDMARD), and in subgroup analysis for the bDMARD were tested using 2-sample t-test or Fisher’s exact test as appropriate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events collected 28 November 2014 - 18 February 2016.
For each participant adverse events were collected up to six months after completion of the prime-boost vaccination.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Control group

Reporting group description:

Participants in control group suffering from adverse and serious adverse events after completion of PCV13 and PPV23 prime-boost vaccination.

Reporting group title	Arm IA

Reporting group description:

Participants in Arm IA suffering from adverse and serious adverse events after completion of PCV13 and PPV23 prime-boost vaccination.

Reporting group title	Arm IB

Reporting group description:

Participants in Arm IB suffering from adverse and serious adverse events after completion of PCV13 and PPV23 prime-boost vaccination.

Reporting group title	Arm II

Reporting group description:

Participants in Arm II suffering from adverse and serious adverse events after completion of PCV13 and PPV23 prime-boost vaccination.

Serious adverse events	Control group	Arm IA	Arm IB
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 33 (15.15%)	1 / 20 (5.00%)	5 / 22 (22.73%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain	Additional description: One participant was admitted because of cancer pain after chemotherapy treatment		
subjects affected / exposed	1 / 33 (3.03%)	0 / 20 (0.00%)	0 / 22 (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
cancer	Additional description: One participant was diagnosed with cancer mamma		
subjects affected / exposed	0 / 33 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Transient ischaemic attack	Additional description: One participant experienced a transient ischemic attack.		
subjects affected / exposed	0 / 33 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Chest pain	Additional description: One participant experienced chest pain. Acute myocardial infarction was refuted.		
subjects affected / exposed	1 / 33 (3.03%)	0 / 20 (0.00%)	0 / 22 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	Additional description: One participant experienced pulmonary embolism		
subjects affected / exposed	0 / 33 (0.00%)	1 / 20 (5.00%)	0 / 22 (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
Infections and infestations			
Pneumonia	Additional description: A total of 5 participants suffered from pneumonia. One participant suffered from pneumonia 3 times. They all resulted in admission to the hospital.		
subjects affected / exposed	1 / 33 (3.03%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis	Additional description: Two participants suffered from urosepsis. One of them was admitted 2 times during the trial.		
subjects affected / exposed	1 / 33 (3.03%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
post operative infection	Additional description: One participant experienced post operative infection. The operation was elective and not related to the vaccination		
subjects affected / exposed	0 / 33 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection	Additional description: One participant experienced a toe infection caused by Staphylococcus aureus		
subjects affected / exposed	0 / 33 (0.00%)	0 / 20 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm II		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 21 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain	Additional description: One participant was admitted because of cancer pain after chemotherapy treatment		
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
cancer	Additional description: One participant was diagnosed with cancer mamma		
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Transient ischaemic attack	Additional description: One participant experienced a transient ischemic attack.		
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Chest pain	Additional description: One participant experienced chest pain. Acute myocardial infarction was refuted.		
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	Additional description: One participant experienced pulmonary embolism		
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia	Additional description: A total of 5 participants suffered from pneumonia. One participant suffered from pneumonia 3 times. They all resulted in admission to the hospital.		
subjects affected / exposed	3 / 21 (14.29%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Urosepsis	Additional description: Two participants suffered from urosepsis. One of them was admitted 2 times during the trial.		
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
post operative infection	Additional description: One participant experienced post operative infection. The operation was elective and not related to the vaccination		
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin infection	Additional description: One participant experienced a toe infection caused by Staphylococcus aureus		
subjects affected / exposed	0 / 21 (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	Control group	Arm IA	Arm IB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 33 (87.88%)	18 / 20 (90.00%)	17 / 22 (77.27%)
Skin and subcutaneous tissue disorders			
Pain of skin, Swelling, Erythema, Itching	Additional description: Local reaction after vaccination		
subjects affected / exposed	29 / 33 (87.88%)	18 / 20 (90.00%)	17 / 22 (77.27%)
occurrences (all)	62	33	49

Non-serious adverse events	Arm II		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 21 (85.71%)		
Skin and subcutaneous tissue disorders			
Pain of skin, Swelling, Erythema, Itching	Additional description: Local reaction after vaccination		
subjects affected / exposed	18 / 21 (85.71%)		
occurrences (all)	42		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2015	Number of participants reduced from 300 to 100. Thus resukting in a new power calculation.

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/28966211