Clinical trial results:
A Randomized, Parallel Group, Single-Blind, Phase 2 Study to Evaluate the immune response of two classes of SARS-Cov-2 Vaccines employed as Third Vaccination in Patients under current Rituximab Therapy and no humoral response after standard mRNA vaccination

Summary

EudraCT number	2021-002348-57
Trial protocol	AT
Global end of trial date	08 November 2021

Results information

Result version number	v1 (current)
This version publication date	23 August 2023
First version publication date	23 August 2023
Summary attachment (see zip file)	Study summary (Study summary.docx)

Trial information

Trial identification

Sponsor protocol code	2021-002348-57

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienna, Austria,
Public contact	Selma Tobudic, Medical University of Vienna, 0043 1404004440, selma.tobudic@meduniwien.ac.at
Scientific contact	Selma Tobudic, Medical University of Vienna, 0043 1404004440, selma.tobudic@meduniwien.ac.at

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	21 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 August 2021
Global end of trial reached?	Yes
Global end of trial date	08 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study aims to investigate the humoral and cellular immune responses after a second boost vaccination with either an mRNA or an vector vaccine against SARS-CoV-2 in adult patients treated with rituximab who did not develop antibodies to the first two vaccinations with an mRNA vaccine.
Primary Objective:
To assess the immunogenicity to a third vaccination mRNA-SARS-CoV-2 vaccine (Biontech/Pfizer or Moderna) compared to a vector SARS-CoV-2 (AstraZeneca) vaccination as a second boost in patients with rituximab by measuring quantitative antibody levels by enzyme-linked immunosorbent assay test (ELISA) and neutralization test (NT) or pseudo viral neutralization assay.
Null hypothesis:
There is no statistical difference in the seroconversion rate between patients receiving a third mRNA vaccination and the patients receiving a second boost with AstraZeneca.

Protection of trial subjects:

The trial was approved by the local IRB. An insurance was acquired for all participants. All included participants signed an informed consent and were given adequate time to consider their decision. All types of vaccines used were approved in the use against SARS-CoV-2. Participants received emergency contact information 24/7 in case of unexpected adverse events.

Background therapy:

All patients recvied rituximab i.v. infusions in regular intervals as part of their routine care (inclusion criteria), as well as, when deemed necessesary, additional immunosuppressive medication. All Background therapy was left unaltered during the clinical trial.

Evidence for comparator:

Both groups recivied a vaccine compound which was approved for SARS-CoV-2, thus the safety and efficacy was proven (Falsey et al NEJM 2021, Polack et al NEJM 2021, Baden et al NEJM 2021).

Actual start date of recruitment	25 May 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	32
From 65 to 84 years	27
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Adults (≥18 years) with chronic inflammatory rheumatic or neurologic diseases under current rituximab therapy and without detectable SARS-CoV-2 spike (S) were recruited at the rheumatology and neurology outpatient department of the Vienna General Hospital.

Pre-assignment

Screening details:

68 patients were screened for this trial. 8 patients did not fullfill the inclusion criteria and were thus not included.

Pre-assignment period milestones

Number of subjects started	60
Intermediate milestone: Number of subjects	Randomization: 60
Number of subjects completed	55

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 4

Period 1

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

Blinding implementation details:

Binding of vaccines was ensured by using pre-arranged dose aliquots in syringes without reference to the type used by the Central Pharmacy of the Vienna General Hospital.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vector vaccine

Arm description:

Patient being randomized to the vector vaccine ChAdOx1 nCoV-19 (Oxford–AstraZeneca) arm.

Arm type	Active comparator
Investigational medicinal product name	Vaxzevria
Investigational medicinal product code	ChAdOx1-S
Other name	Covid-19 Vaccine AstraZeneca
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0,5 mL dispersion for intramuscular use.

Arm title	mRNA vaccine

Arm description:

Patient being randomized to the mRNA vaccine (BNT162b2 or mRNA-1273, respective of their initial vaccination compound) arm.

Arm type	Active comparator

Investigational medicinal product name	COVID-19 Vaccine Moderna
Investigational medicinal product code	mRNA-1273
Other name	Spikevax
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

100 µg for intramuscular use

Investigational medicinal product name	Comirnaty
Investigational medicinal product code	BNT162B2
Other name	Biontech/Pfizer COVID Vaccine
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

30 µg dispersion for intramuscular use

Number of subjects in period 1[1]	Vector vaccine	mRNA vaccine
Started	27	28
Vaccination	27	28
Week 1 - cellular immunity	27	28
Week 4 - humoral immunity	27	28
Completed	27	28

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: Patients were revoked their consent in the pre-assignment period.

Period 2

Period 2 title	Extension period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded, open label

Arms

Arm title	mRNA vaccine

Arm description:

4th dose open label mRNA vaccination

Arm type	Experimental
Investigational medicinal product name	COVID-19 Vaccine Moderna
Investigational medicinal product code	mRNA-1273
Other name	Spikevax
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details: 100 µg for intramuscular use	
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	BNT162B2
Other name	Biontech/Pfizer COVID Vaccine
Pharmaceutical forms	Concentrate for dispersion for injection
Routes of administration	Intramuscular use
Dosage and administration details: 30 µg dispersion for intramuscular use	

Number of subjects in period 2[2]	mRNA vaccine
Started	37
4th vaccination	37
Week 1 - Cellular immunity	37
Week 4 - Humoral immunity	36
Completed	36
Not completed	1
Adverse event, non-fatal	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Patients withdrew their consent to the extension period before starting in the period.

Baseline characteristics

Reporting groups	
Reporting group title	Vector vaccine
Reporting group description:	
Patient being randomized to the vector vaccine ChAdOx1 nCoV-19 (Oxford–AstraZeneca) arm.	
Reporting group title	mRNA vaccine
Reporting group description:	
Patient being randomized to the mRNA vaccine (BNT162b2 or mRNA-1273, respective of their initial vaccination compound) arm.	

Reporting group values	Vector vaccine	mRNA vaccine	Total
Number of subjects	27	28	55
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			
arithmetic mean	60.9	58.9	
standard deviation	± 15.0	± 18.4	-
Gender categorical			
Units: Subjects			
Female	18	23	41
Male	9	5	14
Detectable peripheral B cells			
Units: Subjects			
B cell detectable	8	10	18
B cells not detectable	19	18	37

End points

End points reporting groups	
Reporting group title	Vector vaccine
Reporting group description:	
Patient being randomized to the vector vaccine ChAdOx1 nCoV-19 (Oxford–AstraZeneca) arm.	
Reporting group title	mRNA vaccine
Reporting group description:	
Patient being randomized to the mRNA vaccine (BNT162b2 or mRNA-1273, respective of their initial vaccination compound) arm.	
Reporting group title	mRNA vaccine
Reporting group description:	
4th dose open label mRNA vaccination	

Primary: Rate of seroconversion	
End point title	Rate of seroconversion
End point description:	
End point type	Primary
End point timeframe:	
4 weeks after baseline (=vaccination)	

End point values	Vector vaccine	mRNA vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Rate of seroconversion				
Seroconversion	6	9		
No Seroconversion	21	19		

Statistical analyses

Statistical analysis title	Chi-Squared
Comparison groups	Vector vaccine v mRNA vaccine
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6
Method	Chi-squared

Secondary: Detectable cellular immunity

End point title	Detectable cellular immunity

End point description:

End point type	Secondary

End point timeframe:

Cellular immunit at week 1 after baseline (=vaccination)

End point values	Vector vaccine	mRNA vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[1]	16[2]		
Units: Rate of detectable cellular immunity				
Cellular immunity	20	13		
No cellular immunity	0	3		

Notes:

[1] - Matched samples before and after the third vaccination were available from 36 patients.

[2] - Matched samples before and after the third vaccination were available from 36 patients.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Factors associated with seroconversion

End point title	Factors associated with seroconversion

End point description:

End point type	Post-hoc

End point timeframe:

At week 4 after vaccination

End point values	Vector vaccine	mRNA vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Rate of seroconversion				
Seroconversion	6	9		
No seroconversion	21	19		

Statistical analyses

Statistical analysis title	Multivariable logistic regression
Comparison groups	mRNA vaccine v Vector vaccine

Number of subjects included in analysis	55
Analysis specification	Post-hoc
Analysis type	other[3]
P-value	< 0.001 [4]
Method	Regression, Logistic

Notes:

[3] - Exploratory post-hoc univariate logistic regression models revealed that detectable peripheral B cells strongly favoured the likelihood of seroconversion (OR: 22.67, 95% CI 5.46 to 125.10), while co-medication with any conventional synthetic disease-modifying antirheumatic drug (csDMARD) favoured non-seroconversion. Compared with mRNA booster vaccination, the vector vaccine showed a lower likelihood of inducing humoral response though not statistically significant.

[4] - Detectable peripheral B cells.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
4 weeks.	
Adverse event reporting additional description:	
Paper based diary for vaccine related AEs.	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICD
Dictionary version	10

Reporting groups	
Reporting group title	Vector vaccine
Reporting group description:	
Patient being randomized to the vector vaccine ChAdOx1 nCoV-19 (Oxford–AstraZeneca) arm.	
Reporting group title	mRNA vaccine
Reporting group description:	
Patient being randomized to the mRNA vaccine (BNT162b2 or mRNA-1273, respective of their initial vaccination compound) arm.	

Serious adverse events	Vector vaccine	mRNA vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation	Additional description: Reoccurance of known Afbil before vaccination.		
subjects affected / exposed	1 / 27 (3.70%)	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: 3 %

Non-serious adverse events	Vector vaccine	mRNA vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 27 (88.89%)	22 / 28 (78.57%)	
General disorders and administration site conditions			
Fever			

subjects affected / exposed	7 / 27 (25.93%)	6 / 28 (21.43%)	
occurrences (all)	7	6	
Local reaction			
subjects affected / exposed	11 / 27 (40.74%)	12 / 28 (42.86%)	
occurrences (all)	11	12	
Fatigue			
subjects affected / exposed	21 / 27 (77.78%)	13 / 28 (46.43%)	
occurrences (all)	21	13	
Headache			
subjects affected / exposed	14 / 27 (51.85%)	14 / 28 (50.00%)	
occurrences (all)	14	14	
Arthralgia			
subjects affected / exposed	13 / 27 (48.15%)	8 / 28 (28.57%)	
occurrences (all)	13	8	
Myalgia			
subjects affected / exposed	15 / 27 (55.56%)	9 / 28 (32.14%)	
occurrences (all)	15	9	
Nausea			
subjects affected / exposed	10 / 27 (37.04%)	7 / 28 (25.00%)	
occurrences (all)	10	7	
Pruritus			
subjects affected / exposed	5 / 27 (18.52%)	3 / 28 (10.71%)	
occurrences (all)	5	3	
Local pain			
subjects affected / exposed	10 / 27 (37.04%)	16 / 28 (57.14%)	
occurrences (all)	10	16	
Worsening of underlying disease	Additional description: Subjective by participant.		
subjects affected / exposed	5 / 27 (18.52%)	2 / 28 (7.14%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

One limitation of the trial is the absence of a placebo control, which was considered unethical in this high-risk population.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35977809

http://www.ncbi.nlm.nih.gov/pubmed/35027397