Clinical trial results:
Optimal Repeated Dose Strategy for SARS-CoV-2 Vaccination in Kidney Transplant patients

Summary

EudraCT number	2021-004558-44
Trial protocol	NL
Global end of trial date	12 March 2022

Results information

Result version number	v1 (current)
This version publication date	31 December 2023
First version publication date	31 December 2023
Summary attachment (see zip file)	RECOVAC Repeated Vaccination study (1-s2.0-S1473309922006508-main.pdf)

Trial information

Trial identification

Sponsor protocol code	2021-00604

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05030974
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Groningen
Sponsor organisation address	Hanzeplein 1, groningen, Netherlands, 9713 RZ
Public contact	JSF Sanders, UMCG, j.sanders@umcg.nl
Scientific contact	JSF Sanders, UMCG, j.sanders@umcg.nl

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	25 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the immunogenicity (expressed as percentage of responders) of various COVID-19 booster vaccination strategies in kidney transplant patients that failed to mount a sufficient antibody response after two primary doses of the mRNA-1273 vaccine.

Protection of trial subjects:

The vaccines that are used in this study are approved by the EMA and administered to millions of people worldwide. In addition, there is experience with using these vaccines for third dose administrations. In one of the groups (B.2) the dose of 200 µg the vaccine is twice the standard dose (100 µg), but data from a published phase I trial with two administrations of 250 µg and additional information from the manufacturer do not raise safety concerns. Furthermore, the third or fourth vaccination, and in a subset (n=80) the interruption of one of the three immunosuppressive drugs, of all participants will probably be completed within 1-2 months. It will not be acceptable to postpone a third or fourth vaccination in this population since they are already eligible for third or fourth vaccination via clinical care. Therefore, interim safety analysis is deemed not feasible.
Biweekly investigator meetings will be held until 4 weeks after the last patient has received the last vaccine administration and less frequently thereafter to discuss, among others, the different types of AEs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 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	Netherlands: 333
Worldwide total number of subjects	333
EEA total number of subjects	333

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	210
From 65 to 84 years	122
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Seronegative kidney transplant recipients were primarily recruited from previous RECOVAC studies (NCT04741386 and NCT04841785). Patients were also recruited from the participating centres when a negative seroresponse was detected with a validated in-hospital assay 14-56 days after a third mRNA vaccination.

Pre-assignment

Screening details:

A total of 1464 seronegative kidney transplant recipients were approached for inclusion in the study. Of these, 345 agreed to participate. Five withdrew before the screening visit and 7 patients were screeningfailures, leaving 233 patients for randomisation.

Pre-assignment period milestones

Number of subjects started	1464[1]
Intermediate milestone: Number of subjects	Agreed to participate: 345
Intermediate milestone: Number of subjects	Screened: 340
Number of subjects completed	333

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Was not interested: 1119
Reason: Number of subjects	Withdrew before screening: 5
Reason: Number of subjects	Screenfailure: 7

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: We included subjects that were approached and invited for a screening visit. After excluding patients that did not want to participate and screeningfailures, the numbers of enrollment are achieved

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	Alternative vaccination group - 1x mRNA-1273

Arm description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5×10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Arm type	Active comparator
Investigational medicinal product name	COVID-19 vaccine
Investigational medicinal product code	
Other name	mRNA-1273, spikevax
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Spikevax is administered as a dose of 0.5 mL. One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Arm title	Alternative vaccination group - 2x mRNA-1273

Arm description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5 × 10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Arm type	Experimental
Investigational medicinal product name	COVID-19 vaccine
Investigational medicinal product code	
Other name	mRNA-1273, spikevax
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

In this group, spikevax was administered as a dose of 2x 0.5 mL in both upper arms.

Arm title	Alternative vaccination group - Ad26.COV2-S

Arm description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5 × 10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Arm type	Experimental
Investigational medicinal product name	COVID-19 vaccine
Investigational medicinal product code	
Other name	Ad26.COV2-S, Janssen COVID-19 vaccine
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The Janssen Ad26.COV2.S vaccine is administered as a single dose of 0.5 mL (5x1010 viral particles, corresponding to not less than 8.92 log10 infectious units).

Arm title	mycophenolate mofetil +

Arm description:

In cohort two, only patients receiving triple immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate mofetil or mycophenolic acid, and steroids were included. These patients were randomly assigned to either continuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil+) or discontinuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil−) from 1 week before until 1 week after vaccination with a single 100 µg intramuscular dose of the mRNA-1273 vaccine. This cohort is referred to as the mycophenolate mofetil− mycophenolic acid discontinuation study group.

Arm type	Active comparator
Investigational medicinal product name	COVID-19 vaccine
Investigational medicinal product code	
Other name	mRNA-1273, spikevax
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Spikevax is administered as a dose of 0.5 mL. One dose (0.5 mL) contains 100 micrograms of

messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Arm title	mycophenolate mofetil -

Arm description:

In cohort two, only patients receiving triple immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate mofetil or mycophenolic acid, and steroids were included. These patients were randomly assigned to either continuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil+) or discontinuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil−) from 1 week before until 1 week after vaccination with a single 100 µg intramuscular dose of the mRNA-1273 vaccine. This cohort is referred to as the mycophenolate mofetil– mycophenolic acid discontinuation study group.

Arm type	Active comparator
Investigational medicinal product name	COVID-19 vaccine
Investigational medicinal product code	
Other name	mRNA-1273, spikevax
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Spikevax is administered as a dose of 0.5 mL. One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Number of subjects in period 1	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S
Started	75	77	78
Completed	74	75	75
Not completed	1	2	3
Consent withdrawn by subject	-	-	-
COVID-19	1	2	3
Lost to follow-up	-	-	-

Number of subjects in period 1	mycophenolate mofetil +	mycophenolate mofetil -
Started	51	52
Completed	47	48
Not completed	4	4
Consent withdrawn by subject	-	1
COVID-19	3	2
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Alternative vaccination group - 1x mRNA-1273

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5×10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	Alternative vaccination group - 2x mRNA-1273

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5×10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	Alternative vaccination group - Ad26.COV2-S

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5×10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	mycophenolate mofetil +

Reporting group description:

In cohort two, only patients receiving triple immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate mofetil or mycophenolic acid, and steroids were included. These patients were randomly assigned to either continuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil+) or discontinuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil−) from 1 week before until 1 week after vaccination with a single 100 µg intramuscular dose of the mRNA-1273 vaccine. This cohort is referred to as the mycophenolate mofetil– mycophenolic acid discontinuation study group.

Reporting group title	mycophenolate mofetil -

Reporting group description:

In cohort two, only patients receiving triple immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate mofetil or mycophenolic acid, and steroids were included. These patients were randomly assigned to either continuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil+) or discontinuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil−) from 1 week before until 1 week after vaccination with a single 100 µg intramuscular dose of the mRNA-1273 vaccine. This cohort is referred to as the mycophenolate mofetil– mycophenolic acid discontinuation study group.

Reporting group values	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S
Number of subjects	75	77	78
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			
arithmetic mean	57.4	57.7	60.6
standard deviation	± 13.4	± 12.1	± 12.3
Gender categorical			
Units: Subjects			
Female	27	30	27
Male	48	47	51

Reporting group values	mycophenolate mofetil +	mycophenolate mofetil -	Total
Number of subjects	51	52	333
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	59.1	60.5	
standard deviation	± 11.9	± 12.3	-
Gender categorical			
Units: Subjects			
Female	26	18	128
Male	25	34	205

End points

End points reporting groups

Reporting group title	Alternative vaccination group - 1x mRNA-1273

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5 × 10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	Alternative vaccination group - 2x mRNA-1273

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5 × 10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	Alternative vaccination group - Ad26.COV2-S

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5 × 10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	mycophenolate mofetil +

Reporting group description:

In cohort two, only patients receiving triple immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate mofetil or mycophenolic acid, and steroids were included. These patients were randomly assigned to either continuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil+) or discontinuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil−) from 1 week before until 1 week after vaccination with a single 100 µg intramuscular dose of the mRNA-1273 vaccine. This cohort is referred to as the mycophenolate mofetil– mycophenolic acid discontinuation study group.

Reporting group title	mycophenolate mofetil -

Reporting group description:

In cohort two, only patients receiving triple immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate mofetil or mycophenolic acid, and steroids were included. These patients were randomly assigned to either continuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil+) or discontinuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil−) from 1 week before until 1 week after vaccination with a single 100 µg intramuscular dose of the mRNA-1273 vaccine. This cohort is referred to as the mycophenolate mofetil– mycophenolic acid discontinuation study group.

Primary: SARS-CoV-2 specific seroconversion rate

End point title	SARS-CoV-2 specific seroconversion rate[1]

End point description:

The primary endpoint is the percentage of subjects with a serum anti-S1 IgG concentration ≥10 BAU/mL measured with a validated fluorescent bead-based multiplex-immunoassay at 28 days after the third or fourth vaccine administration.

End point type	Primary

End point timeframe:

28 days after repeated COVID-19 vaccination

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 statistical analysis are described in the article that is attached as a summary

End point values	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S	mycophenolate mofetil +
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	72	73	46
Units: number of patients				
Non-Responder	23	23	27	15
Responder	50	49	46	31

End point values	mycophenolate mofetil -			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: number of patients				
Non-Responder	9			
Responder	37			

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 specific antibody concentrations

End point title	SARS-CoV-2 specific antibody concentrations

End point description:

End point type	Secondary

End point timeframe:

28 dat after repeated COVID-19 vaccination

End point values	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S	mycophenolate mofetil +
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	72	73	46
Units: BAU/mL				
median (inter-quartile range (Q1-Q3))	156 (2.47 to 797)	92.2 (1.77 to 648)	74.7 (1.60 to 250)	143 (4.58 to 966)

End point values	mycophenolate mofetil -			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: BAU/mL				
median (inter-quartile range (Q1-Q3))	119 (23.0 to 1279)			

Statistical analyses

No statistical analyses for this end point

Secondary: Neultralisation titer against ancestral SARS-CoV-2

End point title	Neultralisation titer against ancestral SARS-CoV-2

End point description:

Plaque reduction neutralisation tests against the ancestral, delta, and omicron SARS-CoV-2 variants were done. For feasibility, it was a priori decided to measure neutralising antibodies only in a random sample of 25 KTRs in each study group.

End point type	Secondary

End point timeframe:

28 days after repeated vaccination

End point values	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S	mycophenolate mofetil +
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	24	25	25
Units: PRNT50				
median (inter-quartile range (Q1-Q3))	33 (10 to 464)	65 (10 to 1393)	143 (10 to 549)	58 (10 to 616)

End point values	mycophenolate mofetil -			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: PRNT50				
median (inter-quartile range (Q1-Q3))	100 (10 to 781)			

Statistical analyses

No statistical analyses for this end point

Secondary: Neutralisation titer against Delta SARS-CoV-2

End point title	Neutralisation titer against Delta SARS-CoV-2

End point description:

End point type	Secondary

End point timeframe:

28 days after repeated vaccination

End point values	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S	mycophenolate mofetil +
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	24	25	25
Units: PRNT50				
median (inter-quartile range (Q1-Q3))	10 (10 to 250)	10 (10 to 361)	52 (10 to 522)	10 (10 to 537)

End point values	mycophenolate mofetil -			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: PRNT50				
median (inter-quartile range (Q1-Q3))	90 (10 to 934)			

Statistical analyses

No statistical analyses for this end point

Secondary: Neutralisation titer against Omicron SARS-CoV-2

End point title	Neutralisation titer against Omicron SARS-CoV-2

End point description:

End point type	Secondary

End point timeframe:

28 days after repeated vaccination

End point values	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S	mycophenolate mofetil +
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	24	25	25
Units: PRNT50				
median (inter-quartile range (Q1-Q3))	10 (10 to 10)	10 (10 to 39)	10 (10 to 10)	10 (10 to 10)

End point values	mycophenolate mofetil -			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: PRNT50				
median (inter-quartile range (Q1-Q3))	10 (10 to 84)			

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 specific T cell response

End point title	SARS-CoV-2 specific T cell response

End point description:

Measuring ex vivo production of T cell related cytokines by peripheral blood mononuclear cells (PBMC) in ELISpot assays

End point type	Secondary

End point timeframe:

28 days after repeated vaccination

End point values	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S	mycophenolate mofetil +
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	22	21	25
Units: SFCs/10^6 PBMCs				
median (inter-quartile range (Q1-Q3))	55.0 (13.9 to 128)	50.0 (1.53 to 158)	26.7 (14.2 to 123)	86.6 (28.3 to 228)

End point values	mycophenolate mofetil -			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: SFCs/10^6 PBMCs				

median (inter-quartile range (Q1-Q3))	51.6 (20.0 to 214)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs - during 7 days after vaccination
SAEs - within 28 days after vaccination

Adverse event reporting additional description:

In this study, solicited AEs are reported by all participants on a daily basis for 7 days after vaccine administration and all SAEs are reported that occur within 28 days after vaccination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Alternative vaccination group - 1x mRNA-1273

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5×10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	Alternative vaccination group - 2x mRNA-1273

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5×10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	Alternative vaccination group - Ad26.COV2-S

Reporting group description:

The study was done in two different cohorts. In cohort one, KTRs receiving any combination of immunosuppressive drugs were included. These patients were randomly assigned in a 1:1:1 manner to receive either a single dose of the mRNA-1273 vaccine (100 µg, intramuscularly), two doses of mRNA-1273 simultaneously in both upper arms (2 × 100 µg, intramuscularly), or the Ad26.COV2-S vaccine (Janssen Biologics, Leiden, The Netherlands; 5×10^{1} viral particles, intramuscularly). This cohort is referred to as the alternative vaccination study group.

Reporting group title	mycophenolate mofetil +

Reporting group description:

In cohort two, only patients receiving triple immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate mofetil or mycophenolic acid, and steroids were included. These patients were randomly assigned to either continuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil+) or discontinuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil−) from 1 week before until 1 week after vaccination with a single 100 µg intramuscular dose of the mRNA-1273 vaccine. This cohort is referred to as the mycophenolate mofetil– mycophenolic acid discontinuation study group.

Reporting group title	mycophenolate mofetil -

Reporting group description:

In cohort two, only patients receiving triple immunosuppressive therapy consisting of a calcineurin inhibitor, mycophenolate mofetil or mycophenolic acid, and steroids were included. These patients were randomly assigned to either continuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil+) or discontinuation of mycophenolate mofetil or mycophenolic acid (mycophenolate mofetil−) from 1 week before until 1 week after vaccination with a single 100 µg intramuscular dose of the mRNA-1273 vaccine. This cohort is referred to as the mycophenolate mofetil– mycophenolic acid discontinuation study group.

Serious adverse events	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 75 (4.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Dehydration			
subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 78 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 78 (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
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 78 (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
COVID-19			
subjects affected / exposed	0 / 75 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	mycophenolate mofetil +	mycophenolate mofetil -	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 51 (1.96%)	1 / 51 (1.96%)	
number of deaths (all causes)	0	0	

number of deaths resulting from adverse events			
General disorders and administration site conditions			
Dehydration			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (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: 1 %

Non-serious adverse events	Alternative vaccination group - 1x mRNA-1273	Alternative vaccination group - 2x mRNA-1273	Alternative vaccination group - Ad26.COV2-S
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 75 (90.67%)	72 / 77 (93.51%)	60 / 78 (76.92%)
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 75 (33.33%)	31 / 77 (40.26%)	40 / 78 (51.28%)
occurrences (all)	25	31	40

General disorders and administration site conditions			
Nausea			
subjects affected / exposed	13 / 75 (17.33%)	16 / 77 (20.78%)	12 / 78 (15.38%)
occurrences (all)	13	16	12
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	5 / 75 (6.67%)	10 / 77 (12.99%)	3 / 78 (3.85%)
occurrences (all)	5	10	3
Induration			
subjects affected / exposed	8 / 75 (10.67%)	17 / 77 (22.08%)	5 / 78 (6.41%)
occurrences (all)	8	17	5
Pain	Additional description: Pain at injection side		
subjects affected / exposed	64 / 75 (85.33%)	67 / 77 (87.01%)	38 / 78 (48.72%)
occurrences (all)	64	67	38
Endocrine disorders			
Fatigue			
subjects affected / exposed	36 / 75 (48.00%)	44 / 77 (57.14%)	37 / 78 (47.44%)
occurrences (all)	36	44	37
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 75 (28.00%)	19 / 77 (24.68%)	24 / 78 (30.77%)
occurrences (all)	21	19	24
Myalgia			
subjects affected / exposed	32 / 75 (42.67%)	43 / 77 (55.84%)	31 / 78 (39.74%)
occurrences (all)	32	43	31
Infections and infestations			
Fever			
subjects affected / exposed	2 / 75 (2.67%)	5 / 77 (6.49%)	1 / 78 (1.28%)
occurrences (all)	2	5	1
Chills			
subjects affected / exposed	15 / 75 (20.00%)	27 / 77 (35.06%)	13 / 78 (16.67%)
occurrences (all)	15	27	13

Non-serious adverse events	mycophenolate mofetil +	mycophenolate mofetil -	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 51 (96.08%)	47 / 51 (92.16%)	

Nervous system disorders			
Headache			
subjects affected / exposed	22 / 51 (43.14%)	20 / 51 (39.22%)	
occurrences (all)	22	20	
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	10 / 51 (19.61%)	9 / 51 (17.65%)	
occurrences (all)	10	9	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	12 / 51 (23.53%)	10 / 51 (19.61%)	
occurrences (all)	12	10	
Induration			
subjects affected / exposed	15 / 51 (29.41%)	15 / 51 (29.41%)	
occurrences (all)	15	15	
Pain	Additional description: Pain at injection side		
subjects affected / exposed	47 / 51 (92.16%)	45 / 51 (88.24%)	
occurrences (all)	47	45	
Endocrine disorders			
Fatigue			
subjects affected / exposed	28 / 51 (54.90%)	23 / 51 (45.10%)	
occurrences (all)	28	23	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 51 (29.41%)	15 / 51 (29.41%)	
occurrences (all)	15	15	
Myalgia			
subjects affected / exposed	19 / 51 (37.25%)	22 / 51 (43.14%)	
occurrences (all)	19	22	
Infections and infestations			
Fever			
subjects affected / exposed	3 / 51 (5.88%)	3 / 51 (5.88%)	
occurrences (all)	3	3	
Chills			
subjects affected / exposed	18 / 51 (35.29%)	12 / 51 (23.53%)	
occurrences (all)	18	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 December 2021	1. Addition of extra exclusion criterion of vaccination with COVID-19 Janssen vaccine ; exclusion of subjects with ITP or aHus or patients with recurrent or recent (<2 years) trombotic events. 2. Adjustment of exclusion criterion that subject could not be vaccinated within a month before inclusion: adjusted to a week before start of study. 3. Inclusion of subjects who were seronegative after 3 previous mRNA vaccinations
01 March 2022	The plan was to follow subjects for 1 year after repeated vaccination. However, due to increasing SARS-CoV-2 infections, the government decided to offer a repeated vaccination sooner than anticipated after our study. Moreover, many subjects expierenced COVID-19 after the study. Therefore adequate analysis of the effect of the different vaccination strategies on the long term would be very difficult, maybe impossible. We therefore decided to end the study after the primary endpoint of 28 days after vaccination. The time point 6 months and 12 months after vaccination were removed from the original protocol.

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/36354032