Clinical trial results:
The immune-response and safety of COVID-19 vaccination in patients with chronic kidney disease, on dialysis, or living with a kidney transplant

Summary

EudraCT number	2021-000868-30
Trial protocol	NL
Global end of trial date	23 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-IR study - primary endpoint (the_recovac_immune_response_study__the.25 (1).pdf) RECOVAC-IR study - study design (gfab186.pdf) RECOVAC-IR study - follow-up (ciac557.pdf) T-cell response (sars_cov_2_spike_specific_ifn___t_cell_response.12.pdf) B-cell response (1-s2.0-S1600613523004926-main.pdf)

Trial information

Trial identification

Sponsor protocol code	NL76215.042.20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04741386
WHO universal trial number (UTN)	-
Other trial identifiers	RECOVAC: consortium

Notes:

Sponsors

Sponsor organisation name	University Medical Center Groningen
Sponsor organisation address	Hanzeplein 1, Groningen, Netherlands, 9713 GZ
Public contact	study coordinator, RECOVAC consortium, 0031 0503616161, a.l.messchendorp@umcg.nl
Scientific contact	study coordinator, RECOVAC consortium, 0031 0503616161, a.l.messchendorp@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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of vaccination against COVID-19 in patients with CKD4/5, patients on dialysis, and kidneytransplant recipients as compared to controls.

The primary endpoint is the antibody based immune response on day 28 after the second vaccination. Participants will be classified as
responders or non-responders. The percentage of responders of each patient cohort will be compared with the percentage responders in the control group.

Protection of trial subjects:

If the subjects had not participated in this trial, they could have received the same vaccine via the national vaccination campaign with no additional safety surveillance. Furthermore, vaccination of all participants will probably be completed within 8 weeks. Therefore, interim safety analysis is deemed not necessary and not feasible. Biweekly investigator meetings will be held until 4 weeks after the last patient has received the last vaccination and less frequently thereafter to discuss, among others, the different types of AEs.

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 February 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: 843
Worldwide total number of subjects	843
EEA total number of subjects	843

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)	515
From 65 to 84 years	328
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

As of februari 2021 subjects were recruited in 4 UMCs in the Netherlands (UMCG, Erasmusmc, AUMC and Radboudumc). Patients were recruited via the out patient clinics of the centers. Controls were recruited via patients; controls were parteners, siblings or household members of patients. An equal amount of subjects was anticipated in each center.

Pre-assignment

Screening details:

A total of 1093 subjects were approached for participation in this study and 854 subjects agreed to participate. Of these 854, 11 were screeningfailures leaving 843 patients that were included in the study (200 controls, 173 CKD G4/5, 172 Dialysis, 298 kidney transplant recipients).

Pre-assignment period milestones

Number of subjects started	854[1]
Number of subjects completed	843

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screeningfailure - use of immunosuppression: 5
Reason: Number of subjects	Screeningfailure - eGFR too low or too high: 5
Reason: Number of subjects	Screeningfailure - active malignancy: 1

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: Screeningfailures were included in this pre-assignment period

Period 1

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

Arms

Arm title	COVID-19 vaccination

Arm description:

Four different cohorts were included in the study.
Cohort A, the control group, consisted of subjects without kidney disease (eGFR >45 mL/min/1.73m2), cohort B of patients with severely impaired kidney function (eGFR <30 mL/min/1.73m2 or chronic kidney disease (CKD) stages G4/5); cohort C of patients on hemodialysis or peritoneal dialysis; and cohort D of kidney transplant recipients.
The control cohort included partners, siblings, or household members of participants in cohorts B, C, and D.
The numbers of participants in each cohort were equally divided over the 4 participating centers. All participants received 2 mRNA-1273 COVID-19 vaccinations (Moderna Biotech Spain, S.L.) with an interval of 28 d according to the manufacturer’s instructions.

Arm type	Experimental
Investigational medicinal product name	COVID-19 vaccine
Investigational medicinal product code	SUB207171
Other name	mRNA-1273
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

0,5 ml solution with 100 microgram mRNA injected into the muscle for 2 times with an interval of 28 days between each injection

Number of subjects in period 1	COVID-19 vaccination
Started	843
Completed day 28 after vaccination	837
Included for analysis primary endpoint	800 [2]
Included for analysis 6 months	745 [3]
Completed	801
Not completed	42
Adverse event, serious fatal	19
Consent withdrawn by subject	9
Physician decision	1
Lost to follow-up	13

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The numbers of patients included for analysis is provided - 'per protocol analysis'

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The numbers of patients included for analysis is provided - 'per protocol analysis'

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	843	843	
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	58.3		
standard deviation	± 13.9	-	
Gender categorical Units: Subjects			
Female	374	374	
Male	469	469	

Subject analysis sets

Subject analysis set title	Cohort A - Control
Subject analysis set type	Per protocol

Subject analysis set description:

Four different cohorts were included in the study.
Cohort A, the control group, consisted of subjects without kidney disease (eGFR >45 mL/min/1.73m2).
The control cohort included partners, siblings, or household members of participants in cohorts B, C, and D.
The numbers of participants in each cohort were equally divided over the 4 participating centers.
Baseline characteristics for al control subjects that were included in the per protocol analysis of the primary outcome of the study is depicted in the attached article by Sanders et al., Transplantation 2021.

Subject analysis set title	Cohort B - CKD G4/5
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort B consists of patients with severely impaired kidney function (eGFR <30 mL/min/1.73m2 or chronic kidney disease (CKD) stages G4/5).

Baseline characteristics for all CKD G4/5 patients that were included in the per protocol analysis of the primary outcome of the study is depicted in the attached article by Sanders et al., Transplantation 2021

Subject analysis set title	Cohort C - Dialysis

Subject analysis set type	Per protocol

Subject analysis set description:

Cohort C consists of patients on hemodialysis or peritoneal dialysis.

Baseline characteristics for all dialysis patients that were included in the per protocol analysis of the primary outcome of the study is depicted in the attached article by Sanders et al., Transplantation 2021.

Subject analysis set title	Cohort D - Kidney transplant recipients
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort D consists of kidney tranplant recipients

Baseline characteristics for all kidney transplant recipients that were included in the per protocol analysis of the primary outcome of the study is depicted in the attached article by Sanders et al., Transplantation 2021.

Reporting group values	Cohort A - Control	Cohort B - CKD G4/5	Cohort C - Dialysis
Number of subjects	200	173	172
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	58.2	61.0	59.8
standard deviation	± 13.4	± 13.1	± 14.2
Gender categorical Units: Subjects			
Female	120	62	58
Male	80	111	114

Reporting group values	Cohort D - Kidney transplant recipients		
Number of subjects	298		
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	56.0		
standard deviation	± 14.1		
Gender categorical Units: Subjects			
Female	134		
Male	164		

End points

End points reporting groups

Reporting group title	COVID-19 vaccination

Reporting group description:

Four different cohorts were included in the study.
Cohort A, the control group, consisted of subjects without kidney disease (eGFR >45 mL/min/1.73m2), cohort B of patients with severely impaired kidney function (eGFR <30 mL/min/1.73m2 or chronic kidney disease (CKD) stages G4/5); cohort C of patients on hemodialysis or peritoneal dialysis; and cohort D of kidney transplant recipients.
The control cohort included partners, siblings, or household members of participants in cohorts B, C, and D.
The numbers of participants in each cohort were equally divided over the 4 participating centers. All participants received 2 mRNA-1273 COVID-19 vaccinations (Moderna Biotech Spain, S.L.) with an interval of 28 d according to the manufacturer's instructions.

Subject analysis set title	Cohort A - Control
Subject analysis set type	Per protocol

Subject analysis set description:

Four different cohorts were included in the study.
Cohort A, the control group, consisted of subjects without kidney disease (eGFR >45 mL/min/1.73m2).
The control cohort included partners, siblings, or household members of participants in cohorts B, C, and D.
The numbers of participants in each cohort were equally divided over the 4 participating centers.
Baseline characteristics for al control subjects that were included in the per protocol analysis of the primary outcome of the study is depicted in the attached article by Sanders et al., Transplantation 2021.

Subject analysis set title	Cohort B - CKD G4/5
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort B consists of patients with severely impaired kidney function (eGFR <30 mL/min/1.73m2 or chronic kidney disease (CKD) stages G4/5).

Baseline characteristics for all CKD G4/5 patients that were included in the per protocol analysis of the primary outcome of the study is depicted in the attached article by Sanders et al., Transplantation 2021

Subject analysis set title	Cohort C - Dialysis
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort C consists of patients on hemodialysis or peritoneal dialysis.

Baseline characteristics for all dialysis patients that were included in the per protocol analysis of the primary outcome of the study is depicted in the attached article by Sanders et al., Transplantation 2021.

Subject analysis set title	Cohort D - Kidney transplant recipients
Subject analysis set type	Per protocol

Subject analysis set description:

Cohort D consists of kidney tranplant recipients

Baseline characteristics for all kidney transplant recipients that were included in the per protocol analysis of the primary outcome of the study is depicted in the attached article by Sanders et al., Transplantation 2021.

Primary: SARS-CoV-2 specific seroconversion rate

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

End point description:

SARS-CoV-2 Spike S1-specific IgG antibodies were measured in serum samples by a validated fluorescent bead-based multiplex-immunoassay with a specificity and sensitivity of 99.7% and 91.6%, respectively. Concentrations were interpolated from a reference consisting of pooled sera using a 5-parameter logistic fit and NIBSC/WHO COVID-19 reference serum 20/136, and expressed as international binding antibody units per mL (BAU/mL). SARS-CoV-2 Spike S1-specific IgG antibodies were measured at baseline for exclusion of subjects who had a previous SARS-CoV-2 infection before vaccination, and at second vaccination to assess the immune-response after the first vaccination. Primary outcome was defined as seroconversion rate at 28 d after the second vaccination. Participants were classified as responder or nonresponder based on seroconversion with a threshold for seropositivity based on receiver operator curve analysis set at S1-specific IgG antibody concentration ≥10 BAU/mL.

End point type	Primary

End point timeframe:

28 days after second 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: All statistical analyses are provided via the attached articles

End point values	COVID-19 vaccination	Cohort A - Control	Cohort B - CKD G4/5	Cohort C - Dialysis
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	800[2]	191	162	159
Units: Number of subjects				
Responder	675	191	162	158
Non-responder	125	0	0	1

Notes:

[2] - See flow-chart attached article Sanders et al, Transplantation 2022

End point values	Cohort D - Kidney transplant recipients			
Subject group type	Subject analysis set			
Number of subjects analysed	288			
Units: Number of subjects				
Responder	164			
Non-responder	124			

Statistical analyses

No statistical analyses for this end point

Secondary: Durability of antibody response

End point title	Durability of antibody response

End point description:

Change in antibody response (antibody level 28 days after second vaccination / antibody level 6 months after second vaccination)

End point type	Secondary

End point timeframe:

SARS-CoV2 specific antibodies 28 days and at 6 months after second vaccination

End point values	COVID-19 vaccination	Cohort A - Control	Cohort B - CKD G4/5	Cohort C - Dialysis
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	745[3]	181	152	145
Units: fold change				
median (inter-quartile range (Q1-Q3))	6.32 (2.86 to 11.7)	7.72 (4.97 to 12.5)	7.53 (4.17 to 11.6)	9.00 (5.43 to 15.0)

Notes:

[3] - See flow chart figure 1 article Sanders et al, CID, 2023

End point values	Cohort D - Kidney transplant recipients			
Subject group type	Subject analysis set			
Number of subjects analysed	267			
Units: fold change				
median (inter-quartile range (Q1-Q3))	2.25 (0.51 to 7.31)			

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:

SARS-CoV2-specific T cells were measured using an IFN-γ ELISPOT assay. Individuals with a S-specific response of ≥50 SFCs/106 PBMCs after vaccination and a ≥2-fold increase between the 28 d postvaccination and baseline were defined as a responder.

End point type	Secondary

End point timeframe:

baseline and 28 days after second vaccination

End point values	COVID-19 vaccination	Cohort A - Control	Cohort B - CKD G4/5	Cohort C - Dialysis
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	390[4]	92	80	77
Units: Number of subjects				
Responder	228	70	56	42
Non-responder	162	12	25	33

Notes:

[4] - See flowchart figure 1 of article Imhof et al., Transpl direct, 2022

End point values	Cohort D - Kidney transplant recipients			
Subject group type	Subject analysis set			
Number of subjects analysed	141			
Units: Number of subjects				
Responder	60			
Non-responder	81			

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 specific memory B cell response

End point title	SARS-CoV-2 specific memory B cell response

End point description:

Measurement was performed by a commercially available B cell ELISpot, according to the manufacturer's instructions (U-CyTech biosciences)

End point type	Secondary

End point timeframe:

Baseline and 28 days after second vaccination

End point values	COVID-19 vaccination	Cohort A - Control	Cohort B - CKD G4/5	Cohort C - Dialysis
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	115[5]	35	29	20
Units: 10^6 PBMCs				
median (inter-quartile range (Q1-Q3))	100 (50 to 200)	158 (63 to 631)	79 (25 to 316)	100 (20 to 501)

Notes:

[5] - See Malahe et al, AJT, 2023

End point values	Cohort D - Kidney transplant recipients			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: 10^6 PBMCs				
median (inter-quartile range (Q1-Q3))	25 (5 to 50)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Sollicited AEs were collected for 7 days after each vaccination. In this study SAEs are reported until 6 months after the second vaccination.

Adverse event reporting additional description:

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to COVID-19 vaccination. In this study, solicited AEs will be reported by all participants on a daily basis for 7 days after each vaccination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Controls

Reporting group description:

Cohort A - partners, siblings or householdmembers of patients

Reporting group title	CKD G4/5

Reporting group description:

Kidney patients with a kidney function <30 ml/min/1.73m2

Reporting group title	Dialysis

Reporting group description:

Kidney patients on either hemodialysis or peritoneal dialysis

Reporting group title	Kidney Transplant Recipients

Reporting group description: -

Serious adverse events	Controls	CKD G4/5	Dialysis
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 200 (0.00%)	10 / 173 (5.78%)	18 / 172 (10.47%)
number of deaths (all causes)	0	4	6
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Any SAE	Additional description: See articles Sanders et al. CID, 2022 and Trasplantation 2022		
subjects affected / exposed	0 / 200 (0.00%)	10 / 173 (5.78%)	18 / 172 (10.47%)
occurrences causally related to treatment / all	0 / 0	2 / 10	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 6

Serious adverse events	Kidney Transplant Recipients		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 298 (8.05%)		
number of deaths (all causes)	6		
number of deaths resulting from	0		

adverse events			
Infections and infestations			
Any SAE	Additional description: See articles Sanders et al. CID, 2022 and Trasplantation 2022		
subjects affected / exposed	24 / 298 (8.05%)		
occurrences causally related to treatment / all	2 / 24		
deaths causally related to treatment / all	0 / 6		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Controls	CKD G4/5	Dialysis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 200 (92.50%)	156 / 173 (90.17%)	140 / 172 (81.40%)
Infections and infestations			
Any sollicited AE	Additional description: A full description of these sollicited AEs can be found in article Sanders et al. Transplantation 2021		
subjects affected / exposed	185 / 200 (92.50%)	156 / 173 (90.17%)	140 / 172 (81.40%)
occurrences (all)	185	156	140

Non-serious adverse events	Kidney Transplant Recipients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	280 / 298 (93.96%)		
Infections and infestations			
Any sollicited AE	Additional description: A full description of these sollicited AEs can be found in article Sanders et al. Transplantation 2021		
subjects affected / exposed	280 / 298 (93.96%)		
occurrences (all)	280		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2021	1. Definition of primary endpoint is added 2. How to deal with subjects that were tested positive for COVID-19 is added 3. Corona questionnaire has been updated 4. SAEs will be reported only untill 6 months after vaccination
23 November 2021	1. The study is shortned to 6 months after second vaccination (instead of 12 months) due to an extra vaccination that is applied by the Dutch government in these medical risk groups 2. Kidney transplant patients in this study are invited for a follow-up study 3. Patients not participating in this follow-up study and whom are invited for a third vaccination via the government will be offered antibody measurement via the current study.

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/34753894

http://www.ncbi.nlm.nih.gov/pubmed/34450647

http://www.ncbi.nlm.nih.gov/pubmed/37270109

http://www.ncbi.nlm.nih.gov/pubmed/37198189

http://www.ncbi.nlm.nih.gov/pubmed/35796536

http://www.ncbi.nlm.nih.gov/pubmed/36284929