Establishing the safety, tolerability and immunogenicity of intradermal delivery of mRNA SARS-CoV-2 vaccine in healthy adults

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Primary objectives:- to describe tolerability, safety and immunogenicity in healthy adults of the intradermal delivery of one or two fractional doses of 10 µg and 20 µg mRNA-1273 LPN vaccine (Moderna).- to compare the immunogenicity in healthy…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON51021

Source
ToetsingOnline

Brief title
IDSCOVA

Condition

- Viral infectious disorders

Synonym
COVID-19

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,crowdfunding;Bontius stichting,U-Needle B.V.

Intervention

Keyword: intradermale toediening, mRNA vaccin, SARS-CoV-2, veiligheid

Outcome measures

Primary outcome

- Nature, frequency and severity of local reactions. Solicited adverse events include: pain, redness and swelling at the injection site and pain and swelling at the regional lymph nodes

- Nature, frequency and severity of systemic events. Solicited adverse events include: fever, fatigue, headache, chills, vomiting, diarrhoea, new or worsened muscle pain, and new or worsened joint pain.

- Use of antipyretics and painkillers

- SARS-CoV 2 WT neutralising antibody titres rate on Day 43

- SARS-CoV-2-spike protein-specific binding IgG level on D43

- To determine non-inferiority of the humoral immune responses elicited by intradermal by means of the U-needle or intramuscular delivery of mRNA-1273 vaccine in healthy adults after two fractional doses of 20 µg, and standard intramuscular delivery of 100 µg

- for the booster, the above will be measured on Day 29 after the booster

Secondary outcome

- Kinetics of SARS-CoV 2 WT neutralising antibody (seroconversion, GMT and GM fold rise) and of SARS-CoV-2-spike protein-specific binding IgG antibody levels and RBD- specific binding IgG antibody levels (seroconversion, GMC and GM fold

rise) over time

- Positive SARS-CoV-2 PCR (with or without clinical symptoms) of

nasopharyngeal/throat swab

- Seroconversion SARS-CoV-2 (Nucleocapsid Serology)

- Proportion of afucosylated IgG variants

- SARS-CoV-2 WT neutralising antibodies in nasal fluid

- SARS-CoV-2-spike protein-specific binding IgG and IGA antibody levels and

RBD- specific binding IgG and IGA antibody levels in nasal fluid

- Parameters quantifying germinal centre activity

- Whole blood interferon-gamma release assay to SARS-CoV-2 antigen

- To compare the diameter of the wheal after intradermal injection by standard

or U-needle

Study description

Background summary

The intradermal route is a highly effective way to administer vaccines. The vaccine is deposited right into the papillary dermis which is rich in antigen presenting cells. As a consequence, a fractional vaccine dose introduced directly into the papillary dermis (intradermal administration, ID) might be as effective as the intramuscular administration of the full standard dose to achieve a protective immune response. Especially in circumstances of limited vaccine stockpiles, vaccination with a fractional dose through the intradermal route can be applied as a dose-sparing strategy. Because the vaccine is administered much more superficially, the local side effects, such as redness and induration, are more visible at the site of injection than after intramuscular injection.

Globally the race to national mass vaccination campaigns to protect against infection with SARS-CoV-2 has started. The first registered mRNA COVID vaccines are currently in limited supply leading to a selection of those who receive the vaccine, instead of vaccinating everyone. Production limitations threaten to

delay the roll-out of the national vaccination campaigns. In preclinical studies the intradermal route has been shown to be a very effective way for mRNA vaccine administration. If the intradermal route would be a safe and effective route for a fractional dose of the mRNA COVID vaccine, many more people could be vaccinated with the same limited amount of vaccine.

To enable the implementation of the intradermal injection technique in mass vaccination campaigns by relatively untrained technicians, we also will evaluate the performance of a needle specifically designed for highly accurate and easy-to-use intradermal administration.

An extra stage (stage 4) has been added in which participants from stage 3 (non-inferiority study) and an extra group of healthy volunteers, will receive a booster with mRNA-1273.

Study objective

Primary objectives:
- to describe tolerability, safety and immunogenicity in healthy adults of the intradermal delivery of one or two fractional doses of 10 µg and 20 µg mRNA-1273 LPN vaccine (Moderna).
- to compare the immunogenicity in healthy adults of the intradermal delivery of two fractional dosis of 20 µg mRNA-1273 LPN with that of two doses of 20 µg mRNA-1273 vaccine through intramuscular delivery on Day 43.
- to determine non-inferiority of the virus neutralising antibody response elicited by intradermal delivery by means of standard needle and syringe of mRNA-1273 vaccine in healthy adults after two fractional doses of 20 µg with the responses to two doses of 100 µg mRNA-1273 vaccine through intramuscular delivery on Day 43
- to determine non-inferiority of the virus neutralising antibody response elicited by intradermal delivery by means of U-needle and syringe of mRNA-1273 vaccine in healthy adults after two fractional doses of 20 µg with the responses to two doses of 100 µg mRNA-1273 vaccine through intramuscular delivery on Day 43*
- to determine the antibody-response after revaccination with standard dose (1/2 of primary dose) and fractional dose (1/5th of primary dose) of mRNA-1273 on Day 29 after revaccination

Secondary objectives:
- to describe the kinetics of the humoral immune responses elicited by intradermal or intramuscular delivery of mRNA-1273 vaccine in healthy adults after 1 and 2 fractional doses of 20 µg, and standard intramuscular delivery of 100 µg
- to compare the size of the dermal bleb after intradermal delivery with the standard needle and with the U-needle
- to document symptomatic and asymptomatic infection with SARS-CoV-2

Exploratory objectives:
- to describe the nasal mucosal immune response elicited by intradermal or intramuscular delivery of mRNA-1273 vaccine in healthy adults after 1 or 2 fractional doses of 20 µg, and standard intramuscular delivery of 100 µg
- to describe the glycosylation of SARS-CoV-2 antibodies elicited by intradermal or intramuscular delivery of mRNA-1273 vaccine in healthy adults after 1 or 2 fractional doses of 20 µg, and standard intramuscular delivery of 100 µg.
- to describe the T follicular helper cell kinetics elicited by intradermal or intramuscular delivery of mRNA-1273 vaccine in healthy adults after 1 or 2 fractional doses of 20 µg, and standard intramuscular delivery of 100 µg.
- to describe the memory B-cell and plasma cell response elicited by intradermal delivery of mRNA-1273 vaccine in healthy adults after 1 or 2 fractional doses of 20 µg, and standard intramuscular delivery of 100 µg.
- to describe several coagulation factors in response to the intradermal and intramuscular mRNA-1273 vaccination, such as fibrinogen, factors II, V, VII, VIII, IX, X, XI and inhibitors (protein C, protein S, antithrombin), activation/inhibition complexes, platelet factors and general coagulation and fibrinolysis tests. These will be measured with chromogenous coagulation tests, ELISA and mass spectrometry

Study design

This is a Phase 1/Phase 2a open-label, randomised- controlled, dose-escalation, proof-of-concept vaccine study in healthy adults.

This study will evaluate the safety, tolerability, and immunogenicity of the intradermal delivery two different fractional doses of mRNA-1273 vaccine:
- as a 2-dose schedule separated by 28 days
- up to 2 different dose levels: 10 and 20 µg

The study consists of 4 study stages.
- Stage 1: to establish tolerability, safety and immunogenicity of two doses of 10 µg of mRNA-1273 through intradermal injection
- Stage 2: to establish tolerability, safety and immunogenicity of two doses of 20 µg of mRNA-1273 through intradermal injection and to compare this with two fractional doses of 20 µg of mRNA-1273 administered through the intramuscular route
- Stage 3: to determine non-inferiority of two fractional doses of 20 µg of mRNA-1273 through the intradermal route (group a standard technique, group b u-needle) compared to two standard doses of 100 µg of mRNA-1273 administered through the intramuscular route.
- Stage 4: to determine the antibody-response of standard and fractional dose mRNA-1273 in participants of Stage 3, who received a fractional primary vaccins dose, and additionally recruited healthy participants who received a standard vaccine dose as primairy vaccination

The study is unblinded to the participant, investigator and other site staff as the route of administration differs. The study will blinded to the laboratory staff. Dependent upon safety generated during the course of this study, it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added at the same dose

Intervention

Stage 1-2-3
Intervention group:
group a: Participants will receive 10 µg or 20 µg mRNA-1273 vaccine followed by a second dose on day 28 through the intradermal route (standard technique).
group b: Participants will receive 10 µg or 20 µg mRNA-1273 vaccine followed by a second dose on day 28 through the intradermal route (U-needle).
Comparison group:
Participants will receive 20 µg or 100 µg mRNA-1273 vaccine followed by a second dose on day 28 through the intramuscular route

Booster study (stage 4)
Intervention group:
participants from stage 3 who received a fractional priming vaccine dose (n=90) are randomised 1:1 to receive again a fractional vaccine dose of a standard dose as booster
Comparison group:
Participants from stage 3 who received the standard vaccine dose (n=45) will receive the standard booster
Comparison group:
Participants who are recruited for stage 4 and who have received the standard vaccine dose as primary vaccine, will now receive the fractional dose as booster

Study burden and risks

The safety of COVID-19 Vaccine Moderna has been evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of COVID-19 Vaccine Moderna (n=15,185) or placebo (n=15,166) (NCT04470427). After intramuscular injection of 100 µg mRNA-1273, the most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/ tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or
moderate in intensity and resolved within a few days after vaccination.
Overall, there was a higher incidence of some adverse reactions in younger age

groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1. The frequency of anaphylactic reactions is estimated to be around 1:100,000 [CDC]. Three cases of Bell*s palsy have been reported in the vaccine group and one in the placebo group.

Since a smaller fractional dose is applied with intradermal injection, it is expected that the systemic side effects will be less. However, local side effects may be more pronounced with more redness, swelling, pain, and potentially necrosis and scarring at the injection site. Also swelling of the axillary lymph nodes may be more pronounced. The risk of anaphylactic reaction is probably lower because of the intradermal route. The participants may acquired virus neutralising antibodies after intradermal vaccination. Participation does not interfere with possible access to future COVID vaccinations.
The outcome of this study may have important health benefits for the population at large. If intradermal delivery of an one-fifth fractional dose of mRNA-1273 is safe and immunogenic, the population-wide benefits of higher vaccine coverage would outweigh the lower efficacy of fractionated dosing for individual vaccinees.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Male or female participants between the ages of 18 and 30 years, inclusive at randomisation.
- Stage 4 additional group: healthy male and female participants between the ages of 18 and 40 years, and having received the primary mRNA COVID-19 vaccine series approximately 6 months earlier
- Healthy participants who are determined by medical history and clinical judgment of the investigator to be eligible for inclusion in the study. Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrollment, can be included.
- Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.
- Females only: female volunteers of childbearing potential (i.e. have a uterus and are neither surgically sterilised nor postmenopausal) must not be pregnant or breastfeeding. They should agree to use adequate contraception at least up to four weeks following the final dose of mRNA-1273 vaccine.

Exclusion criteria

- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator*s judgment, make the participant inappropriate for the study.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
- Receipt of medications intended to prevent COVID-19.
- Previous clinical or microbiological diagnosis of COVID-19.
- Individuals at high risk for severe COVID-19, who are planned to receive COVID vaccine within the next two months.
- Immunosuppressed individuals with known or suspected immunodeficiency, as

determined by history.
- Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention.
- Receipt of systemic or topical corticosteroids.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding.
- Planned pregnancy within four weeks after the final injection.
- Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.
- SARS-CoV-2 PCR-positive nasopharyngeal/throat swab at the screening before receipt of first vaccine dose.
- Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-04-2021
Enrollment:	245
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	COVID-19 Vaccine Moderna

Ethics review

Approved WMO Date:	24-03-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	25-03-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	01-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	28-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	11-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	24-06-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	02-09-2021
Application type:	Amendment
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Approved WMO

Date:	17-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	13-01-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	27-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20603
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-000454-26-NL
CCMO	NL76702.058.21
OMON	NL-OMON20603

Study results