Information about participation in a scientific trial

Engelsk titel: A Phase 4, Pragmatic, Randomized Trial to Evaluate the Effectiveness of An Influenza/COVID-19 Vaccine (mCombriax [mRNA-1083]) in Adults ≥ 65 Years (DAN-COMBO)

Dansk titel: Et fase 4, pragmatisk, randomiseret forsøg til at undersøge effekten af en influenza/COVID-19-vaccine (mCombriax [mRNA-1083]) hos personer ≥65 år (DAN-COMBO)

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We would like to ask you whether you wish to take part in a clinical trial. The trial is looking to examine the effect of a combination vaccine against influenza (flu) and COVID-19, given as a single injection (mCombriax®), on the risk of being admitted to hospital because of flu or COVID-19 in people aged 65 years and over.

The trial is a randomized trial, where about half the participants will receive a combined flu and COVID-19 vaccine (mCombriax®) in a single injection, while the other half will simultaneously receive a high-dose flu vaccine as well as a COVID-19 vaccine in two separate injections. You will be told which group you have been assigned to on the day of your vaccination.

The trial is organized by the research unit at the Department of Cardiology at Herlev and Gentofte Hospital, in collaboration with Danske Lægers Vaccinations Service. It will be carried out at clinics run by the Danske Lægers Vaccinations Service.

Before deciding whether to take part in the trial, you must gain an understanding of what is involved in the trial and why we are conducting it. We therefore ask you to read this Participant Information thoroughly.

The trial targets people aged 65 years and over as health authorities recommend annual vaccination against flu and COVID-19 for this group.
You are receiving this information because you belong to the target group of the trial, or because you have been made aware of the trial in some other way.

You do not need to participate in this trial to receive the recommended influenza and COVID-19 vaccinations. You can also receive these vaccinations outside the trial through the national vaccination program, for example at pharmacies or from other vaccination providers.

Purpose of the trial

The purpose of the trial is to find out whether a combined flu and COVID-19 (mCombriax®) vaccine can reduce the risk of being admitted to hospital with flu and/or COVID-19 and of complications and death related to these infections in people aged 65 or over. The effect will be

compared with vaccination with a high-dose flu vaccine and a COVID-19 vaccine administered simultaneously in separate injections.

Background of the trial

Flu and COVID-19 are infectious diseases that mainly affect the airways. Every year, many people, especially older ones, become seriously ill or die from these diseases. Both diseases can cause serious complications, including hospital admission and, in some cases, death. In addition, when flu and SARS-CoV-2 are both spreading at the same time in the winter months, they can put a heavy burden on the healthcare system.

Vaccination is the most effective way of preventing flu and COVID-19 and to reduce the risk of disease-related complications. In Denmark, annual vaccination against both diseases is recommended in people aged 65 and over. The COVID-19 vaccine is given as a separate vaccine and can be administered at the same time as the flu vaccine. People aged 70 and over are usually given an enhanced flu vaccine (e.g., a high-dose or a flu vaccine containing an ingredient that helps the body's immune system produce a stronger response) as these vaccines can produce a better immune response and provide better protection than standard-dose vaccines. In this trial, participants who do not receive the combination vaccine will receive a high-dose flu vaccine together with a COVID-19 vaccine, whatever their age.

A combination vaccine, consisting of both an enhanced flu vaccine and a COVID-19 vaccine in the same injection, has now been developed. Such a vaccine could potentially simplify vaccination programmes and possibly encourage more people to vaccinate. Although combination vaccines are already used for other diseases, our knowledge of their effects in larger groups of elderly people is limited. Studies have already shown that the combination vaccine provides an immune response against both flu and COVID-19 that is comparable to, or better than, that of the flu and COVID-19 vaccines currently used, including the high-dose influenza vaccine.

The Danish health registers provide a unique opportunity to carry out large, pragmatic randomized trials, thus generating reliable knowledge about the effect of new vaccination strategies in the general population. This trial is therefore being carried out to examine whether a combination vaccine can be an effective and practical alternative to the current separate vaccinations against flu and COVID-19.

Organization of the trial

The trial is organized so that half of the participants will receive a combination vaccine against flu and COVID-19, while the other half will receive separate vaccinations with a high-dose flu vaccine and an mRNA COVID-19 vaccine. Allocation to the different groups will be done at random by drawing lots. The vaccines are administered in a muscle, usually in the upper arm. This is not a blind trial, so the participants will know which type of vaccination they have been given.

We expect to recruit up to around 410,000 participants in total. The trial will involve one vaccination visit, which will take place at one of the clinics run by Danske Lægers Vaccinations Service. Following vaccination, participants will be monitored in accordance with current guidelines. Participants will not routinely be contacted again, apart from being given a short questionnaire. Information from participants' electronic health records and the Danish health registries will be used to obtain information about their medical conditions and medication use, and to monitor whether participants develop influenza or COVID-19 infections, are admitted to hospital, or die.

The trial will include participants during the 2026/2027 and 2027/2028 winter seasons.
Vaccinations will start from 1 October in each season. It is possible to take part in both seasons. For each season, there will be new randomization for the vaccines.
Follow-up of all participants will be conducted using information obtained from the Danish health registries for up to 20 years after vaccination. The information includes what is relevant to the purpose of the study and the areas being investigated.
The information will be used to investigate any long-term effects and safety of the vaccine, including the occurrence of infections, related hospital admissions, and death.
As part of the routine vaccination scheme, people over 70 years of age are generally a flu vaccine containing an ingredient that helps the body's immune system produce a stronger response rather than a standard-dose flu vaccine. This vaccine has been selected by the Danish Health Authority because it may provide better protection in the elderly. If you are randomized to be vaccinated with two separate injections, you will receive a high-dose flu vaccine along with a COVID-19 vaccine. Like the flu vaccine containing this additional ingredient, the high-dose flu vaccine is considered an enhanced flu vaccine that gives better protection to the elderly. The high-dose flu vaccine will be used in this trial regardless of your age.

During your appointment, you will be asked to confirm that you still wish to take part in the trial.

A sub-group of up to 10,000 participants will be invited to take part in a sub-trial where they will have to swab themselves for flu and COVID-19 from home when they develop symptoms of a respiratory illness and report their symptoms in a questionnaire over a period of 7–21 days. Participation in the sub-trial will be offered to you electronically before or during your vaccination visit. If you wish to take part in the sub-trial, you will need to give a separate consent for this, either electronically before your vaccination visit or during the vaccination visit itself. Participants will receive the results of their swab test once it has been analysed. Only participants who have already provided consent to the main trial may participate in the sub-study.

The trial will also include participants in Galicia, Spain, where the eligibility criteria for participation are the same as those described in this participant information sheet. This is done to ensure that the trial includes the number of participants required to obtain robust results, even if the influenza/COVID-19 season is mild in one of the countries.

Enrolling for the trial

There are two ways to book an appointment for the trial. You can either enrol for the trial online or ring our call centre to book an appointment by telephone. Online enrolment for the trial is done on Danske Lægers Vaccinations Service´s website, where you can also find additional information, including this Participant Information Sheet and an information video. Once you have reviewed the material, you can book an appointment to take part in the trial.

You will also have the option to sign the informed consent form electronically from home before the visit. The draw to determine which vaccination you receive will take place when you attend your agreed appointment.

If you prefer, you can instead give your consent during the actual visit to the vaccination clinic, where you can also receive information verbally and ask questions before deciding whether to take part. You are welcome to bring along a family member, friend or acquaintance with you. If you decide to take part in the trial, we will ask you to sign an informed consent form. Remember that you are entitled to time to consider your decision before signing the informed consent form. If, following the discussion, you feel ready to sign the informed consent form, you may be vaccinated

immediately.

Taking part in the trial is voluntary. You may withdraw your consent at any time and without giving a reason. This will not affect any future medical care you may have.

Criteria for participation in the trial

You may take part in the trial if you are 65 years of age or older. A requirement for taking part in the trial is that you understand Danish or English.

In line with standard vaccination practice, you cannot receive the trial vaccines if you have a known allergy to flu and/or COVID-19 vaccines or their ingredients.

If, on the day of your vaccination, you have a fever, signs of an active infection or anything else that means that you should not receive the vaccine on that day, the vaccination will be postponed to a later date. This is in line with common vaccination practice.

Side effects and risks

Note that the trial may be associated with unforeseen risks and inconveniences. As with other vaccines, side effects may arise following vaccination. Most side effects are mild and temporary, such as soreness at the injection site, tiredness, headache or a short-lasting fever. More serious side effects are rare, and very serious side effects are very rare. All the vaccines used in this trial have already been approved for use in Denmark and abroad.

Known side effects of the combined flu and COVID-19 vaccine, borrowed from the Summary of Product Characteristics (product summary) of the mRNA-1083 (mCombriax®) vaccine:

Very common (may affect more than 1 in 10 people): pain at the injection site, fever, tiredness, headache, muscle ache, joint ache, swelling/tenderness in the underarm, feeling sick, vomiting and chills.

Common (may affect up to 1 in 10 people): swelling and redness at the injection site.

Uncommon (may affect up to 1 in 100 people): diarrhoea, itching at the injection site.

Known side effects of the high-dose flu vaccine, borrowed from the Efluelda® Summary of Product Characteristics (product summary):

Very common (may affect more than 1 in 10 people): Reactions and discomfort at the injection site, malaise, muscle pains, headache.

Common (may affect up to 10 in 100 people): Chills.

Uncommon (may affect up to 1 in 100 people): Fever, tiredness, muscle weakness, cough, diarrhoea, feeling sick, heartburn, night sweats, rash, dizziness.

Rare (may affect up to 1 in 1,000 people): Joint pains, pain in the arms and legs, vomiting, itching, hives, redness.

Frequency not known: Chest pain, nerve inflammation, seizures, fever fits, inflammation of the brain and spinal cord, facial paralysis, inflammation of the optic nerve, fainting, changes to skin sensitivity, increased tendency for bleeding due to a fall in the number of platelets, inflammation of the lymph nodes, shortness of breath, wheezing, narrowing of the throat, throat pain, runny nose, anaphylaxis, other allergic reactions, hypersensitivity reactions, inflammation of the blood vessels, redness of the eyes.

Known side effects of the COVID-19 vaccine, borrowed from the mRNA-1273 Spikevax® vaccine's Summary of Product Characteristics (product summary):

Very common (may affect more than 1 in 10 people): swelling/tenderness in the armpit, headache, nausea, vomiting, muscle pains, joint pains and stiffness, pain or swelling at the injection site, redness at the injection site, tiredness, chills, fever.

Common (may affect up to 1 in 10 people): Diarrhoea, rash, rash or hives at the injection site.

Uncommon (may affect up to 1 in 100 people): Itching at the injection site, dizziness, stomach pain, raised itchy rash (hives).

Rare (may affect up to 1 in 1,000 people): Temporary drooping of the face on one side (Bell's palsy), facial swelling (swelling of the face can occur in people who have received cosmetic injections to the face), reduced feeling or sensation, sensory disturbances in the skin such as a prickly or tingling sensation (paraesthesia).

Very rare (may affect fewer than 1 in 10,000 people): inflammation of the heart muscle (myocarditis) or of the membrane surrounding the heart (pericarditis).

Unknown frequency: severe allergic reactions with breathing difficulties (anaphylaxis), hypersensitivity, skin reaction involving red spots or marks on the skin that may resemble a target

(erythema multiforme), severe swelling in the arm where the vaccine was administered, severe menstrual bleeding, rashes caused by external impacts such as firm stroking, scratching or pressure to the skin (mechanical hives), a swollen, itchy rash lasting more than six weeks (chronic hives)

If any unforeseen risks or inconveniences arise in connection with the trial, the Principal Investigator will take care of them. The contact details of the trial team and the Principal Investigator can be found on the last page. The Principal Investigator is responsible for reporting any new unexpected and serious side effects to the Danish Medicines Agency and the Danish Health Research Ethics Committees in the course of the trial.
In addition to the register-based safety monitoring, participants and their physicians may contact the trial team with any concerns by e-mail and telephone. Qualified doctors employed by the sponsor will be available to deal with any reported cases. Clinical treatment of any side effects will take place within the public healthcare system.

Sensitive personal data
As a general rule, we will only record your name, CPR (civil registration) number, vaccine/vaccines received and its/their respective batch numbers. Your CPR number will be used to identify you in the Danish registers. Register data will only be accessed via encrypted server access at the Danish Health Data Authority. No information that is unnecessary for the trial. All sensitive personal data will be processed in confidence and in accordance with the GDPR (General Data Protection Regulation) and the Danish Data Protection Act. As regards medical information, etc., register information covering the period from 10 years before the trial visit and up to the day of the trial visit will be retrieved. Following this, medical data about hospital visits, etc. will be retrieved during the course of the trial for the purpose of monitoring the effects and safety of the vaccine. The information collected include diagnosis codes, results of viral swab tests, previous vaccinations, hospital admissions, deaths, and healthcare contacts. By signing the written informed consent, you are giving the Principal Investigator, the scientific sponsor and their representatives permission to access relevant health data in your medical records for the purpose of conducting, monitoring and controlling the trial. No information that is unnecessary for the trial. You also give consent to the Danish Medicines Agency's inspectors, the Danish Health Research Ethics Committees and the trial monitor to directly access relevant information, including electronic information, in your medical records if it is of relevance for the trial and the statutory inspections of

clinical trials by the authorities. Your consent also permits relevant information on side effects to be reported to the manufacturer of the combination vaccine (Moderna). Participants not already registered in Danske Lægers Vaccinations Service's internal database prior to recruitment may not be contacted in the future for marketing purposes, nor will their contact details be stored in Danske Lægers Vaccinations Service's database.

Benefits of the trial

Flu and COVID-19 continue to cause serious illness and death among the elderly. This trial will investigate if a combined flu and COVID-19 vaccine provides equivalent protection to that of the two vaccines currently given in separate injections. The results of this trial may provide important knowledge if vaccination against flu and COVID-19 can be simplified by combining the vaccines into one injection. Simplifying this may make vaccination easier, thus raising vaccination take-up in the population.

Therefore, it is a matter of strong public interest to investigate the value of a combined flu and COVID-19 vaccine and assess the possible benefits for both the healthcare service and the population as a whole.

Early termination of the trial

The sponsor of the trial may decide to terminate the trial at any time. This may also be demanded by the authorities. You will be informed of this immediately, and any options for further treatment will be discussed with you.

Financial considerations

The trial is financed by the pharmaceutical company Moderna, which developed the mCombriax® (mRNA-1083) combination vaccine and which may therefore have a financial interest in a positive outcome of the trial. Moderna is a co-sponsor of the trial, which, in this specific trial means that Moderna has helped develop the trial protocol and that any side effects will be reported to Moderna. Moderna has donated the vaccines and covered the other expenses of the trial, which amount to approximately DKK 140 million. These funds will be transferred into a research account administered by the hospital and subject to public audit. Danske Lægers Vaccinations Service is a private company.

The sponsor has previously received remuneration from Moderna for presenting lectures (approx. DKK 27,000).

If any further funding is received for the trial, the participants and the Danish Health Research Ethics Committees will be informed.

Participants will not receive any financial consideration for taking part in the trial. All vaccines will be given free of charge as part of the trial.

Publication of the results of the trial

The results of the trial will be processed in anonymized form and published regardless of whether they are positive, negative or inconclusive. Individual participants in the trial will not be identifiable when the results are published. The results will be published in scientific journals and presented at Danish and international congresses. The results are also expected to be published through patient organizations and interested news media.

A summary of trial results will be published at www.euclinicaltrials.eu within a year of the conclusion of the trial and can be found by searching for the trial's CT number, which can be found in the footnote to this document.

You have a right to be informed of the progress and final results of the trial. At the end of the trial, a summary of results, specifically meant for the participants in it will be published at https://minvaccination.dk/forskning/resultater.

Rights of trial subjects

We encourage you to read the leaflet 'Your rights as a subject in a medical trial', which has been prepared by the Danish Health Research Ethics Committees. The leaflet is also attached as an annex to this document. You have the right to withdraw your consent for participating in the trial at any time. As a participant in this trial, you will be covered by the Danish Patient Compensation Scheme (Patienterstatningen).

Contacts

For more information about the trial, you can contact us, as follows:

Call centre for Danske Lægers Vaccinations Service: 88 30 01 02

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Your rights as a participant in a clinical trial with medical products

If you are a participant in a clinical trial involving a medicine, it is important that you are aware of your rights. You can read about them on this page.

1. Your participation in a clinical trial is completely voluntary. You are entitled to both written and verbal information about the trial, and you must sign a consent form before you can participate.
2. You have the right to bring a family member, friend or acquaintance to the information session.
3. You have the right to a reflection period before signing the consent form.
4. You can withdraw your consent at any time and withdraw from the trial without giving any reason. This will not affect your right to patient treatment or other rights.
5. Information about you, your health, your blood samples, etc. is subject to confidentiality and must be processed in accordance with data protection legislation [1]. The data controller for the trial must ensure that you are informed of these rules.
6. Your consent to the trial means that the data controller and sponsor may obtain information about your health in the medical record systems when this is necessary for quality control and monitoring of the trial.
7. If the information about your health collected during the trial is later used by the investigator for research or statistical purposes, you cannot object to the processing and sharing of this information.
8. You have the right to opt-out of potential knowledge of new health information that may emerge about you in the trial that is not directly related to the trial.
9. If the trial is conducted under public auspices, you have the right of access to documents relating to the organization of the trial, except for those parts that

contain trade secrets or confidential information about other persons.

10. If you are injured during the trial, you can complain according to the rules in the Danish Act on Complaints and Compensation in the Healthcare Sector, see more at www.patienterstatningen.dk
11. When the trial is completed, you have the right to receive information about the results of the trial.
12. The trial coordinator must ensure that an information unit is made available to you from which you can obtain more information about the trial.

[1] Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation),
Act no. 502 of May 23, 2018 on supplementary provisions to the Regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (Data Protection Act)
Regulation (EU) 2017/745 of the European Parliament and of the Council of April 5, 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.
REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of April 16, 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC (Text with EEA relevance).