Information about participating in a scientific trial

English title: A Pragmatic Randomized Trial to Evaluate the Effect of Recombinant Herpes Zoster Vaccine on Major Adverse Cardiovascular Events and Dementia in Adults Aged 65 Years or Above (DAN-ZOSTER)

Danish title: Et pragmatisk, randomiseret forsøg til at evaluere effekten af herpes zoster vaccine på risikoen for alvorlig hjerte-kar-sygdom og demens hos voksne på 65 år eller derover (DAN-ZOSTER)

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Introduction

We would like to ask you whether you wish to take part in a scientific trial. The trial is being conducted at the clinics of the Danish Doctors' Vaccination Service (Danske Lægers Vaccinations Service) and its purpose is to examine the effect of the Shingrix® shingles vaccine on the risk of serious cardiovascular events and dementia in people aged 65 and above.

The trial is a randomised controlled trial, where approximately half of those taking part will receive a shingles vaccine (Shingrix®) and the other half will not receive a vaccine.

The trial has been organised by the research unit at the Department of Cardiology at Herlev and Gentofte Hospital, in collaboration with the Danish Doctors' Vaccination Service.

Before you decide whether you wish to take part in the trial, you will need to understand what is involved and how we are conducting the trial. We would therefore ask you to read this information for participants thoroughly.

The reason why you have received this information is either that you have been identified as a potential participant through the Danish health registers or that you have previously been vaccinated by the Danish Doctors' Vaccination Service. You may also have been made aware of the trial in some other way. The target group in this trial are Danes aged 65 years or above who have not been diagnosed with dementia, who are not undergoing treatment with immunosuppressant drugs for chronic inflammatory rheumatic disease, and who have not previously been vaccinated against shingles.

We would therefore point out that you will not be able to take part in this trial if you have previously been diagnosed with dementia, are undergoing treatment for chronic inflammatory rheumatic disease using immunosuppressant drugs, or have previously been vaccinated against shingles. It is a requirement for participating in the study that you understand Danish or English.

Purpose of the trial

The trial will examine whether the Shingrix® shingles vaccine can reduce the risk of serious cardiovascular events, such as blood clots in the heart or brain or brain haemorrhages, and whether

it can reduce the risk of developing dementia. We will compare people aged 65 or above who receive the vaccine with people of the same age who do not receive the vaccine.

Background of the trial

Shingles (herpes zoster) is caused by the reactivation of the varicella zoster virus, which most people have in their body after having had chickenpox. The risk of developing shingles increases with age and can lead to significant problems, including a painful rash and lasting nerve pain that can reduce a person's quality of life for months or years. In some people, shingles can lead to complications that will necessitate contacting the healthcare services or admission to hospital.

More recent research suggests that shingles does not only affect the skin and nervous system. Studies indicate that shingles may be associated with an increased risk of serious cardiovascular events, such as blood clots in the heart and brain and brain haemorrhages. Some studies also suggest a possible link between shingles and an increased risk of developing dementia. While more research is still needed in this area, these findings give reason to examine whether preventing shingles might also have a significant effect on the risk of developing cardiovascular disease and dementia.

Vaccination is the most effective way of preventing shingles. The Shingrix® vaccine has been shown to provide a high level of protection against shingles and lasting nerve pain. The vaccine is already used in Denmark to prevent shingles. Earlier studies have also indicated that the vaccine may perhaps reduce the risk of serious cardiovascular events, such as blood clots in the heart or stroke. Some studies also suggest that the vaccine may perhaps reduce the risk of developing dementia. However, it must be stressed that the scientific basis is insufficient, and we therefore lack any definite, concrete knowledge as to whether vaccination with the Shingrix® shingles vaccine – apart from preventing shingles – can also reduce the risk of serious cardiovascular events and the risk of developing dementia. The extensive health registers that we have in Denmark provide a unique opportunity to conduct a large, population-based trial and thus generate new, important knowledge.

The shingles vaccine is approved by the European Medicines Agency for the prevention of shingles (herpes zoster) and post-herpetic neuralgia (lasting pain once the rash has disappeared) in adults aged 50 and above, as well as in adults aged 18 and over who are at increased risk of developing

shingles. In Denmark, a conditional subsidy is given to people aged 50 with chronic inflammatory rheumatic disease who are being treated with immunosuppressant drugs. Everyone else must pay for the vaccine. You will not need to pay for the vaccine if taking part in this trial.

Organisation of the trial

The trial will be organised such that half of the participants will receive the shingles vaccine (Shingrix®) and the other half will not receive any vaccine. This allocation will be done at random by drawing lots. Shingrix® is given as an injection in a muscle, usually in the upper arm. This is not a blind trial, so the participants will know whether or not they have received the vaccine.

We expect to recruit up to around 162,000 participants in total. The trial includes two vaccinations with Shingrix®: one at the time of the first visit and one after 2–6 months. registering for the trial, participants will book both appointments at the same time, i.e. for the first dose and the subsequent dose. This is to ensure that the entire vaccination course is planned from the start and completed within the recommended timeframe.

The vaccinations will be given at the Danish Doctors' Vaccination Service's clinics. Following each vaccination, participants will be observed in accordance with current guidelines. Participants will then not be routinely contacted again. Participants will be monitored via their electronic patient record and extracts from the Danish health registers with regard to their medical history, cardiovascular events, dementia, admissions and deaths.

The trial will include participants throughout the period for which the vaccine is available, and all participants will be monitored for several years in order to establish the short-term and long-term effects of the vaccination.

If you are randomly assigned to the control group (i.e. you do not receive the shingles vaccine as part of the trial), you will still have the opportunity to be vaccinated outside the trial if you so wish. Taking part in the control group does not restrict your opportunity to receive the Shingrix® vaccination in another way.

Enrolment for the trial

There are two ways in which to enrol for the trial. You may either enrol for the trial online or ring our call centre and book an appointment to take part in the trial by telephone. Online enrolment is done on the Danish Doctors' Vaccination Service's website, where you will find further information, including this information for participants and an informational video. Once you have reviewed the material, you can book appointments to take part in the trial.

As part of the enrolment process, you will need to book two appointments straight away: one for the first visit and one for a follow-up visit 2–6 months later. Both appointments must have been booked before you give your consent to take part and before lots are drawn. This is so that the entire vaccination course has been planned in advance, even though only half of the participants will receive the vaccine as part of the trial.

Once you have booked your appointments, you will have the opportunity to sign the declaration of consent electronically at home. Once you have signed the declaration of consent electronically, an electronic draw will take place immediately to determine whether you will be assigned to the group that will receive the Shingrix® vaccine or the group that will not be offered the vaccine as part of the trial.

If you are assigned to the vaccination group, you will need to attend both planned appointments to receive two doses of the vaccine.
If you are assigned to the control group, you will be informed of this immediately and will not need to attend your appointments as part of the trial.

If you do not wish to sign the declaration of consent at home, you will also have the opportunity to give your informed consent by attending a vaccination clinic in person. If you wish to make use of this opportunity, you must book two appointments on the website – one for the first visit and one for the second visit 2–6 months later – without signing the declaration of consent electronically. The booked appointments will be retained, and at the first visit you will receive verbal information about the trial, have the chance to ask questions,, sign the declaration of consent electronically and then take part in the draw. It is also possible to book the appointments by telephone by ringing our call centre. You are welcome to bring along a family member, friend or acquaintance to the visit, and

you are entitled to time to consider before deciding whether you wish to sign the declaration of consent. If you then give your consent and are assigned to the vaccination group, you can receive your first dose of the vaccine at the same visit. It is important to be aware that, if the giving of consent and the random draw take place at the vaccination clinic rather than electronically at home, there is a chance that you will arrive at the clinic and not be offered the vaccination if you are assigned to the control group.

It is important for there to be a control group in the trial, as this will make it possible to compare the Shingrix® vaccination with no vaccination, with regard to both possible effects on cardiovascular disease and dementia and side effects. If you are assigned to the control group, you will therefore still be contributing important knowledge to the trial, even though you do not receive the vaccine.

Taking part in the trial is voluntary. You may withdraw you consent at any time and without giving a reason. There will be no consequences in terms of your future treatment.

Criteria for participation in the trial

You may take part in the trial if you are 65 years of age or older. You may not take part if you have been diagnosed with dementia, have previously been vaccinated against shingles, or have chronic inflammatory rheumatic disease that is being treated with immunosuppressant drugs (exept from painkillers).

You will not be able to receive the shingles vaccine (Shingrix®) in the trial if you have a known allergy to the vaccine.

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 time. This is in line with common vaccination practice.

Side effects and risks

It must be pointed out that there may be unforeseen risks and burdens associated with the trial. As with other vaccines, side effects may arise following vaccination. Most side effects are mild and temporary, such as soreness at the injection site, fatigue, headache or short-lasting fever. More

serious side effects are rare, and very serious side effects are very rate. The shingles vaccine used in this trial (Shingrix®) has already been approved for use in Denmark and abroad, and its side effects profile is therefore already well known.

Known side effects of the vaccine (Shingrix®, from the product's package leaflet) are given below:
Very common (more than 1 in 10 people): headache, nausea, vomiting, diarrhoea and/or abdominal pain, muscle pain, reactions at the injection site (pain, redness, swelling), fatigue, chills, fever
Common (up to 1 in 10 people): itching at the injection site, malaise
Uncommon (up to 1 in 100 people): swollen lymph nodes, joint pain
Rare (up to 1 in 1,000 people): allergic reactions, with rash, itchy red bumps (hives) or swelling of the skin and mucous membranes, e.g. in the face, lips and around the eyes
Very rare (fewer than 1 in 10,000 people): Guillain-Barré syndrome, a condition that may temporarily affect the nerves and produce muscle weakness

The description of both the disease shingles and vaccination with Shingrix® should provide you with the basis for considering the benefits and disadvantages of taking part in the trial. Both involve some risk, but for most people this risk is considered small, and the known risks of the vaccine are generally well documented. If any unforeseen risks or burdens arise in connection with the trial, the Principal Investigator will deal with this. 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 addition to the register-based safety monitoring, the study email address and a call center telephone number will be available to participants and treating physicians, allowing them to contact the study team regarding any concerns. Qualified physicians employed by the sponsor will be available to manage reported cases. The clinical management of any adverse events will take place within the public healthcare system.

Sensitive personal data

As a starting point, we record only your name, CPR (civil registration) number, whether or not you have received the Shingrix® vaccine, and the vaccine's batch number. Your CPR number is used to

identify you in the Danish registers. Register data can be accessed only by encrypted server access at the Danish Health Data Authority. No information is obtained that is unnecessary for the trial. All sensitive personal data is processed confidentially and in accordance with the rules of the General Data Protection Regulation (GDPR) and the rules of the Danish Data Protection Act, cf. CTR Article 7, 1(d).

With regard to the description of illnesses, etc., relevant information will be retrieved from the register for the period of up to 10 years before the start of the trial and up to the day before the trial visit. Following this, health data will be retrieved during the period of the trial with regard to monitoring the effects and safety of the vaccine. The data will include diagnosis codes, viral swab results, previous vaccinations, admissions, deaths and medical contacts. Register data will be collected for all participants, including the control group.

By giving your written informed consent, you are giving permission for the Principal Investigator, the scientific sponsor and their representatives to access relevant health information in your patient record for the purpose of conducting, monitoring and controlling the trial. No information will be obtained that is unnecessary for the trial. You are also giving your consent for the Danish Medicines Agency's inspectors, the Danish Health Research Ethics Committees and the trial's monitor to have direct access to information in your patient record – including electronic information – if this relates to the trial and the authorities' mandatory inspection of clinical trials.

Your consent also gives permission for relevant information on side effects to be reported to the manufacturer of the Shingrix® vaccine (GSK). Any participants not already registered on the Danish Doctors' Vaccination Service's internal database prior to recruitment may not be contacted in future for marketing purposes, and nor will their contact details be stored on the Danish Doctors' Vaccination Service's database.

Benefits of the trial

The purpose of the trial is to examine whether vaccination with Shingrix® does not merely prevent shingles but may also reduce the risk of serious cardiovascular events and dementia in people aged 65 and above. If it is shown that the vaccination has these additional beneficial effects, it may help towards better prevention of illness, fewer hospital admissions and improved quality of life for the

elderly. The results may therefore be important to the individual as well as the planning of future vaccination programmes.

Premature termination of the trial

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

Financial considerations

The trial has been financed by the pharmaceutical company GlaxoSmithKline (GSK), which developed the shingles vaccine called Shingrix® and which may therefore have a financial interest in a positive outcome of the trial. GSK is a co-sponsor of the trial, which in this study means that GSK has been involved in developing the study protocol, and that in the event of side effects, these are reported to the manufacturer of the vaccine (GSK). GSK has donated the Shingrix® vaccines and financed the other expenses involved in the trial to a total of approx. DKK 70,000,000. These funds will be transferred into a research account, which is subject to administration by the hospital and to public audit. The Danish Doctors' Vaccination Service is a private company and may have a financial interest in the trial. The Clinical Director of the Danish Doctors' Vaccination Service has received remuneration from GSK for training (approx. DKK 15,000) and has participated on advisory boards. The sponsor has received remuneration from GSK for presenting lectures (approx. DKK 20,000) and has participated in an advisory board meeting.

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

No financial compensation will be paid for taking part in the trial. Those in the vaccine group will be given the Shingrix® vaccine free of charge as part of the trial.

Publication of the results of the trial

The results of the trial will be processed in anonymised form and will be published irrespective of whether they are positive, negative or inconclusive. When the results are published, it will not be possible to identify individual participants in the trial. The results will be published in scientific

journals and will be presented at Danish and international congresses. The results are also expected to be published through patient organisations and interested news media.
A summary of the results of the trial 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 conclusion of the trial, a summary of the results aimed specifically at participants in the trial will be published at https://minvaccination.dk/forskning/resultater.

Rights of trial subjects

We would encourage you to read the leaflet 'Your rights as a subject in a clinical drug trial', which has been produced 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 participation 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, or if you have any other questions, you can contact us as follows:

Call centre for the Danish Doctors' Vaccination Service: 88 30 01 02

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NATIONALT CENTER FOR ETIK

10. maj 2023

Dine rettigheder som forsøgsperson i forsøg med medicin

Hvis du er deltager i et klinisk forsøg med medicin, så er det vigtigt, at du er opmærksom på dine rettigheder. Dem kan du læse om på denne side.

1. Din deltagelse i et klinisk forsøg er helt frivillig. Du har krav på både skriftlig og mundtlig information om forsøget, og du skal underskrive en samtykkeerklæring før du kan deltage.
2. Du har ret til at tage et familiemedlem, en ven eller en bekendt med til informationssamtalen.
3. Du har ret til betænkningstid før du underskriver samtykkeerklæringen.
4. Du kan til enhver tid trække dit samtykke tilbage og udgå af forsøget uden at give nogen begrundelse. Dette vil ikke påvirke din ret til patientbehandling eller andre rettigheder.
5. Oplysninger om dig, dit helbred, dine blodprøver mv. er omfattet af tavshedspligt, og skal behandles efter lovgivningen om databeskyttelse [1]. Den dataansvarlige for forsøget skal sikre, at du bliver orienteret om disse regler.
6. Dit samtykke til forsøget medfører, at den forsøgsansvarlige og sponsor må indhente oplysninger om dit helbred i journalsystemerne, når dette er nødvendigt for kvalitetskontrol og overvågning af forsøget.
7. Hvis de oplysninger om dit helbred, som er indsamlet under forsøget, senere anvendes af den forsøgsansvarlige til forskning eller statistik, kan du ikke gøre indsigelse imod behandling og udveksling af disse oplysninger.
8. Du har ret til at frabede dig potentiel viden om nye helbredsoplysninger som måtte fremkomme om dig i forsøget, og som ikke direkte har tilknytning til forsøget.
9. Hvis forsøget foregår i offentlig regi, har du ret til aktindsigt i dokumenter vedrørende afprøvningens tilrettelæggelse, bortset fra de dele, som indeholder forretningshemmeligheder eller fortrolige oplysninger om andre personer.
10. Hvis du bliver skadet under forsøget, kan du klage efter reglerne i lov om klage og erstatningsadgang inden for sundhedsvæsenet, se mere på www.patienterstatningen.dk
11. Når forsøget er afsluttet, har du ret til at få information om forsøgets resultater.
12. Den forsøgsansvarlige skal sikre, at der stilles en informationsenhed til rådighed for dig, hvorfra du kan få flere oplysninger om forsøget.

[1] Europa-Parlamentets og Rådets forordning nr. 2016/679 af 27. april 2016 om beskyttelse af fysiske personer i forbindelse med behandling af personoplysninger og om fri udveksling af sådanne oplysninger, og om ophævelse af direktiv 95/46/EF (generel forordning om databeskyttelse),
Lov nr. 502 af 23. maj 2018 om supplerende bestemmelser til forordning om beskyttelse af fysiske personer i forbindelse med behandling af personoplysninger og om fri udveksling af sådanne oplysninger (databeskyttelsesloven)
Europa-Parlamentets og Rådets Forordning (EU) 2017/745 af 5. april 2017 om medicinsk udstyr, om ændring af direktiv 2001/83/EF, forordning (EF) nr. 178/2002 og forordning (EF) nr. 1223/2009 og om ophævelse af Rådets direktiv 90/385/EØF og 93/42/EØF.
EUROPA-PARLAMENTETS OG RÅDETS FORORDNING (EU) Nr. 536/2014 af 16. april 2014 om kliniske forsøg med humanmedicinske lægemidler og om ophævelse af direktiv 2001/20/EF (EØS-relevant tekst).