A Phase II Randomized, Placebo-Controlled Clinical Trial to Study the Safety and Immunogenicity of V212 in Adult Patients with Autoimmune Disease

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The primary objective of the study is to assess the safety and immunogenicity of V212 in a population of adults with autoimmune disease.

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

Summary

ID

NL-OMON37443

Source
ToetsingOnline

Brief title
V212-009

Condition

- Autoimmune disorders

Synonym
shingles, skin laesions

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme

Intervention

Keyword: Auto-immune diseases, Shingles, V212

Outcome measures

Primary outcome

The primary objective is to determine whether V212 is immunogenic when

administered to adult patients with autoimmune disease and to assess the safety

and tolerability of V212 in adult patients with autoimmune disease.

Secondary outcome

N.A.

Study description

Background summary

HZ, known also as shingles, is a manifestation of reactivation of VZV, which, as a primary infection, results in chickenpox (varicella). Following initial infection, the virus remains latent in the spinal dorsal root or cranial sensory ganglia until it reactivates and replicates, resulting in clinical HZ. ZOSTAVAX 1 is the only currently licensed intervention that can reduce the risk of developing HZ, postherpetic neuralgia (PHN), and the acute and chronic pain associated with HZ. ZOSTAVAX Merck Research Laboratories (MRL) for the prevention of HZ and its complications, especially HZ-related pain. However ZOSTAVAX a live attenuated vaccine, is contraindicated in immunocompromised patients.

The incidence of HZ in immunocompetent older adults (i.e., >=60 years of age) is 7 to 11 per 1000 person-years (PY). Immunocompromised individuals have a higher incidence of HZ that can often be recurrent, and are at increased risk for developing severe and sometimes life-threatening complications. Patients with one of the more than 80 known or suspected autoimmune diseases are often immunocompromised, sometimes because of the underlying disease itself, but more often due to the increasing use of immunocompromising therapy. Published data suggest that depending on their treatment, patients with systemic lupus erythematosus (SLE) tend to have a risk of HZ approximately 10 times that of the general population of the same age. Patients with other autoimmune diseases potentially requiring immunocompromising treatment tend to have a risk of HZ on

average approximately double that of the general population of the same age. This risk can increase up to 5 to 7 times when very immunocompromising treatments are used. For example, studies in the rheumatoid arthritis (RA) population show that HZ typically occurs as a complication of immunocompromising treatment. HZ was shown to be more frequent after treatment with tumor necrosis factor (TNF) alpha inhibitors (10/1000 PY) than after conventional disease-modifying anti-rheumatic drugs (DMARDs) (5.6/1000 PY). Prevention of HZ in patients with an autoimmune disease and/or receiving immunosuppressive therapies represent an area of significant unmet medical need since these immunocompromised individuals are at increased risk of HZ and cannot receive ZOSTAVAX.

Two proof-of-concept (PoC) studies in hematopoietic cell transplant (HCT) recipients using heat-inactivated Oka/Merck varicella vaccine demonstrated: 1) reduced morbidity (i.e., extent and severity of HZ) following a 3-dose vaccine regimen and, 2) a decreased incidence of disease due to VZV reactivation, following a 4-dose vaccine regimen. The heat-treated VZV vaccine appeared generally safe. Overall, these two studies demonstrated that inactivated VZV vaccine given to recipients of HCT had a significant impact on the development of HZ.

Based on the favorable safety and efficacy profiles observed in these PoC studies, V212 Protocol 002, a randomized, double-blind, multicenter, immunogenicity and safety Phase I clinical study was conducted in 4 distinct immunocompromised populations: recipients of HCT (allogeneic and autologous), patients infected with human immunodeficiency virus (HIV) with CD4 counts <=200 cells/mm3, patients with hematologic malignancy (HM) and patients with solid tumor malignancy (STM) receiving chemotherapy. The study demonstrated promising immunogenicity following a 4-dose regimen in the autologous-HCT, STM and HM populations, less robust responses in the HIV population, and poor responses in the allogeneic-HCT study population. No safety signals were identified in any of the immunocompromised populations studied.

Protocol 009 is a Phase II study to assess the safety and immunogenicity of V212 in a population of adults with autoimmune disease. The study will be conducted using a 4-dose regimen with doses administered ~30 days apart, consistent with the vaccine regimen used in Protocol 002. This protocol will expand upon the experience of the earlier V212 studies by providing information on the safety and immunogenicity of 4 doses of the inactivated VZV vaccine, and will expand the vaccine to a patient population chronically immunocompromised due to their chronic immunosuppressive therapies. Protocol 009 will inform the dosing schedule and candidate measures of cell-mediated immunity (glycoprotein enzyme-linked immunosorbent assay [gpELISA] and/or interferon-gamma enzyme-linked immunospot assay [IFN-γ ELISPOT]).

Study objective

The primary objective of the study is to assess the safety and immunogenicity of V212 in a population of adults with autoimmune disease.

Study design

This is a randomized, double-blind (with in-house blinding procedures), placebocontrolled, multicenter study to evaluate the safety and immunogenicity of V212 in adults with autoimmune disease. Approximately 340 individuals 18 years of age or older will be randomized to receive either V212 (~180 patients), V212 containing a higher quantity of Ag (~100 patients), or placebo (~60 patients) given as a 4-dose regimen with doses administered ~30 days apart. V212, V212 containing a higher quantity of Ag, or placebo Dose 1 will be administered at the time of enrollment (Day 1). Doses 2 through 4 will be administered approximately 30 days following each previous dose. Each dose of V212, V212 containing a higher quantity of Ag, or placebo will be administered as a 0.5-mL subcutaneous injection preferably in the deltoid region, alternating arms for each study vaccine or placebo dose, if possible.
Another important goal of the study is to evaluate the safety and tolerability of V212 in patients with autoimmune disease. Adverse experiences will be collected from the time the consent form is signed (Visit 1) through Visit 5 using a standard Vaccination Report Card (VRC). All patients will receive a VRC at each vaccination visit (Visits 1 through 4). The VRC will be used to collect safety information during each postvaccination
period (minimum 21 days Postdose 1 through Dose 3, and through 28 days Postdose 4). The VRC will be returned by the patient and reviewed by study site personnel at the next scheduled study visit.
Daily oral temperature readings and injection-site and systemic adverse experiences occurring through 28 days Postdose 4 will be recorded on the VRC. In addition, patients will be actively prompted to record on the VRC injection-site adverse experiences for 5 days after each vaccination dose. All patients will be followed for exposure to varicella or HZ and development of any varicella/varicella-like or HZ/HZ-like rashes, or other symptoms suggestive of HZ through 28 days Postdose 4. For the evaluation of immune responses to vaccination, all patients will have blood samples collected on Day 1 (prior to Dose 1) and Visit 5 (~Day 118, 28 to 35 days Postdose 4). Additionally, one half of the study population (~170 patients) will be assigned to have blood collected at Visit 3 (~Day 60, 21 to 35 days Postdose 2), and the other half of the population (~170 patients) will be assigned to have blood collected at Visit 4 (~Day 90, 21 to 35 days Postdose 3). Blood draws at Visit 3 (Postdose 2) and Visit 4 (Postdose 3) will be randomly assigned and identified by the Interactive Voice Response System (IVRS) at the time of randomization into the study. A total of 65 mL of blood will be drawn at each of the 3 visits, with 5 mL designated for the gpELISA and 60 mL for the IFN-γ ELISPOT assay.

Intervention

Approximately 340 individuals 18 years of age or older will be randomized to receive either V212 (~180 patients), V212 containing a higher quantity of Ag (~100 patients), or placebo (~60 patients) given as a 4-dose regimen with doses administered ~30 days apart. Each dose of V212, V212 containing a higher quantity of Ag, or placebo will be administered as a 0.5-mL subcutaneous injection, preferably in the deltoid region, alternating arms for each study vaccine or placebo dose, if possible. Placebo will be the vaccine stabilizer for the VZV vaccine with no virus Ag.

Study burden and risks

Risks of possible side effects of the vaccination:
• headache
• rash that looks like chicken pox
• fever
• muscle aches
• joint pain
• nausea
• vomiting
• sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage

Some burdens of the study procedures:
• Blood samples: drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely, infection.
• Rash samples: having a sample taken from your rash may cause discomfort and, rarely, bruising.
• Reactions at the injection site such as: redness, swelling, pain, itching, bruising, warmth, hardening of the area around the injection site, discoloration, rash, and a bump on the skin

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient is >=18 years of age on the day of signing informed consent.
2. Patient has been diagnosed with an autoimmune disease, including but not limited to RA, PSA, PSO, IBD, SLE, MS, or other similar diseases.
3. Patient is not likely to undergo HCT during the study period (through 28 days Postdose 4).
4. Patient must be on at least one biologic agent, such as a TNF alpha inhibitor, or a non-biologic therapy, at a stable dose for >=3 months, with no planned or anticipated changes in treatment regimen at the time of enrollment. Treatment route of administration must be parenteral or oral; topical administration alone is not sufficient.
5. Minimum doses are required for the following treatments if taken as monotherapy:
5.1 methotrexate, >0.4 mg/Kg/week;
5.2 sulfasalazine, or mycophenolate mofetil: >=2g/day;
5.3 azathioprine, >3.0 mg/Kg/day;
5.4 6-mercaptopurine, >1.5 mg/Kg/day;
5.5 prednisone or equivalent of >20 mg/day.
No minimum doses are required for patients receiving combination therapy including two or more non-biologic agents.
6. Patient has clinically stable disease for >=30 days prior to enrollment.
7. Patient understands the study procedures, alternative treatments available and risks involved with the study, and voluntarily agrees to participate by giving written informed consent. The patient may also provide consent for future biomedical research. However, the patient may participate in the main trial without participating in future biomedical research.
8. Patient has prior history of varicella, antibodies to VZV (documented prior to receipt of blood products), or residence (for >=30 years) in a country with endemic VZV infection, or if participant is 30 years old, attended primary or secondary school in a

country with endemic VZV infection.
9. Patient is able to read, understand and complete questionnaires and diaries.
10. All female patients of childbearing potential (as defined under Criterion #11) must have a negative serum or urine pregnancy test (sensitive to 25IU beta human chorionic gonadotropin [β-hCG]) prior to each vaccine dose.
11. Patient is highly unlikely to conceive during the time period starting 2 weeks prior to enrollment through 6 months from the last vaccination dose, as indicated by at least one "yes" answer to the following questions:
- Patient is male.
- Patient is a female who agrees to remain abstinent or use (or have their partner use) adequate contraception during the time period starting 2 weeks prior to enrollment through 6 months from the last vaccination dose. Note that simultaneous use of two reliable forms of contraception is recommended.
- Patient is a female who is not of reproductive potential.

Exclusion criteria

1. A history of allergic reaction to any vaccine component (including gelatin) or an anaphylactic/anaphylactoid reaction to neomycin (a history of contact dermatitis to neomycin is not a criterion for study exclusion).
2. Prior history of HZ within 1 year of enrollment.
3. Prior receipt of any varicella or zoster vaccine.
4. Patient has active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebritis or CNS vasculitis) requiring therapeutic intervention within 90 days of enrollment.
5. Patient is receiving or expected to receive therapy containing rituximab or any other anti-CD20 monoclonal antibodies at any time during the time period beginning 3 months prior to enrollment through 28 days Postdose 4.
6. Patient is receiving systemic corticosteroid therapy, prednisone or prednisone equivalent >40 mg/day at the time of enrollment.
7. Patient has received systemic prednisone or prednisone equivalent >=50 mg/day for >=30 days within 6 months of enrollment.
8. Patient has participated in a study of investigational drug or vaccine or received investigational products within 30 days prior to enrollment or is expected to receive an investigational product (other than the study vaccine) throughout the duration of the study.
9. Patient is pregnant or breastfeeding or expecting to conceive within the period of 2 weeks prior to enrollment through 6 months after last vaccination dose.
10. Any live virus vaccine administered or scheduled in the period from 4 weeks prior to Dose 1 through 28 days Postdose 4.
11. Any inactivated vaccine administered or scheduled within the period from 7 days prior to, through 7 days following, any dose of study vaccine.
12. Patient has immunoglobulin or any blood products administered or scheduled in the period from 3 months prior to Visit 1 through 28 days Postdose 4.
13. Patient is unlikely to adhere to the study procedures or attend study visits.
14. Any other reason that in the opinion of the investigator might interfere with the

evaluation required by the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-07-2012
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable

Ethics review

Approved WMO Date:	02-01-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-05-2012

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-11-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-002313-11-NL
ClinicalTrials.gov	NCT01527383
CCMO	NL38876.000.11