A Double-masked, Placebo-controlled Study with Open-label Period to Evaluate the Efficacy and Safety of MEDI-551 in Adult Subjects with Neuromyelitis Optica and Neuromyelitis Optica Spectrum Disorders.

Published: 16-04-2018
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Primary Objective: To compare the efficacy of MEDI-551 versus placebo in reducing the risk of an NMO/NMOSD attack in subjects with NMO/NMOSD.Secondary Objectives:1. To compare the efficacy of MEDI-551 versus placebo on the reduction of EDSS...

Ethical review	Approved WMO
Status	Completed
Health condition type	Central nervous system infections and inflammations
Study type	Interventional

Summary

ID

NL-OMON46416

Source
ToetsingOnline

Brief title
N-MOmentum

Condition

- Central nervous system infections and inflammations

Synonym
Neuromyelitis optica; NMO

Research involving

Human

Sponsors and support

Primary sponsor: MedImmune LLC
Source(s) of monetary or material Support: Industry;Sponsor

Intervention

Keyword: MEDI-551, Neuromyelitis Optica, Neuromyelitis Optica Spectrum Disorders

Outcome measures

Primary outcome

Primary Endpoint:

The primary endpoint is the time (days) from Day 1 to onset of an Adjudication Committee (AC)-determined NMO/NMOSD attack on or before Day 197. The definition of an NMO/NMOSD attack is the presence of a new symptom(s) or worsening of an existing symptom(s) related to NMO/NMOSD that meets at least ONE of the protocol-defined criteria for an NMO/NMOSD attack.

Secondary outcome

Secondary Endpoints:

Endpoints 1, 2, 3, and 4 are key secondary endpoints to be considered for studywise Type I error control.

1. Worsening from baseline in EDSS at last visit during the RCP.

2. Change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart, at last visit during RCP.

3. Cumulative total active MRI lesions (new Gd-enhancing or new/enlarging T2) during the RCP.

4. Number of NMO/NMOSD-related in-patient hospitalizations. In-patient

hospitalization is defined as more than an overnight stay.

5. Annualized attack rate (total number of AC-determined NMO/NMOSD attacks normalized by person years) during any exposure to MEDI-551.

6. Treatment-emergent adverse events (TEAEs), including treatment-emergent serious adverse events (TESAEs). Laboratory measurements as well as their changes or shift from baseline over time.

7. Pharmacokinetic profile of MEDI-551.

8. Incidence of anti-drug antibodies (ADAs) directed against MEDI-551 for the duration of the study, both predose and postdose for each subject.

Exploratory Endpoints:

1. Change from baseline in the 4-week recall SF-36 PCS and MCS at the last visit during the RCP.

2. Change from baseline in pain NRS in 5 locations at the last visit during the RCP.

3. B-cell counts (total and subsets).

4. Change from baseline in plasma cell gene signature.

5. Serum AQP4-IgG titers.

Study description

Background summary

Neuromyelitis optica (NMO; also known as Devic*s syndrome) is a rare, chronic, autoimmune, inflammatory, demyelinating disorder of the central nervous system (CNS) characterized by attacks of predominantly optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM). Commonly reported symptoms

include unilateral and bilateral loss of visual acuity, ocular pain, loss of sensation, severe paraplegia, bladder and bowel dysfunction, paroxysmal tonic spasms of the trunk and limbs, and Lhermitte*s phenomenon. Brain and brain stem involvement are rare but can occur, usually as an extension of a severe cervical myelitis, and may cause symptoms such as nausea, intractable vomiting, hiccups, and acute neurogenic respiratory failure. Up to 90% of patients with NMO have relapsing episodes of ON and myelitis rather than a monophasic course .Relapses occur within 1 year of onset in 60% of patients and within 3 years in 90%. Relapses can be severe and result in blindness, paralysis, and even death due to neurogenic respiratory failure (Oh and Levy, 2012). Incomplete recovery from attacks is typical, and accumulative disabilities arise from the severity and frequency of attacks. By some estimates, within 5 years, > 50% of patients are blind in one or both eyes or require ambulatory help. Historically, mortality in NMO was as high as 30% at 5 years, but a more recent study suggests 9% at 6 years.

Once thought to be a variant of multiple sclerosis (MS), NMO/neuromyelitis optica spectrum disorders (NMOSD) are now recognized as a distinct disease (Wingerchuk et al, 2007). A defining feature of NMO is the presence of serum autoantibodies against aquaporin-4 (AQP4) (ie, AQP4 immunoglobulin G [IgG] or NMO-IgG), which is detected in 60% to 90% of NMO/NMOSD patients (Jarius and Wildemann, 2010). Aquaporin-4 is the most abundant water channel expressed on the plasma membrane of astrocytes throughout the CNS. AQP4-IgG is thought to be pathogenic by causing astrocyte loss through activation of lytic complement components, antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC) and/or by unfavorably altering astrocyte physiology by reducing expression of key water channel proteins. AQP4-IgG is produced by CD19 positive (CD19+) B-lineage plasmablasts, and that the presence of these plasmablasts correlates with disease activity in NMO. It has been demonstrated that subpopulations of CD19+ and CD20 negative (CD20-) B cells showing morphological and phenotypical properties of plasmablasts are increased selectively in the peripheral blood of NMO patients and that anti AQP4 antibodies are produced by these cells. These subsets of B cells have shown to expand in the 2 weeks prior to and during NMO attacks.

MEDI-551 is a humanized, affinity-optimized, afucosylated IgG1* mAb that binds to the B-cell specific surface antigen CD19 resulting in the depletion of B cells. It is currently in clinical development in diseases such as B-cell malignancies and relapsing forms of MS, where B-cell depletion may have or has been shown to have a therapeutic effect.

Study objective

Primary Objective:
To compare the efficacy of MEDI-551 versus placebo in reducing the risk of an NMO/NMOSD attack in subjects with NMO/NMOSD.

Secondary Objectives:
1. To compare the efficacy of MEDI-551 versus placebo on the reduction of EDSS worsening in subjects with NMO/NMOSD.
2. To compare the efficacy of MEDI-551 versus placebo on the change from baseline of low-contrast visual acuity score in subjects with NMO/NMOSD.
3. To compare the efficacy of MEDI-551 versus placebo in reducing the cumulative active MRI lesion count (new gadolinium [Gd]-enhancing or new/enlarging T2).
4. To compare the efficacy of MEDI-551 versus placebo in reducing NMO/NMOSD-related in-patient hospitalizations in subjects with NMO/NMOSD.
5. To characterize the long-term efficacy of MEDI-551 by means of annualized attack rate.
6. To evaluate the safety and tolerability of a single course of MEDI-551 in subjects with NMO/NMOSD in the Randomized-controlled Period (RCP) and repeated doses of MEDI-551 in the Open label Period (OLP).
7. To characterize the pharmacokinetic (PK) profile and immunogenicity of MEDI-551 in NMO/NMOSD subjects.

Exploratory Objectives:
1. To compare the effect of MEDI-551 versus placebo on health-related quality of life (HRQoL) as measured by the 4-week recall Short Form-36 (SF-36) Health Survey physical component score (PCS) and mental component score (MCS) in NMO/NMOSD subjects.
2. To compare the effect of MEDI-551 versus placebo on pain as measured using the pain numeric rating scale (NRS).
3. To characterize the pharmacodynamic (PD) profile (B cells and plasma cell signature) of MEDI-551 in NMO/NMOSD subjects.
4. To compare the effect of MEDI-551 versus placebo on aquaporin-4-antibody (AQP4-IgG) titer.
5. To compare the effect of MEDI-551 versus placebo on soluble biomarkers (eg, cytokines, chemokines, and immunoglobulins) and genomic (ribonucleic acid [RNA; microRNA]) biomarkers and other relevant cells (eg, T cells, astrocytes) in NMO/NMOSD subjects.

Study design

This is a multicenter, multinational, randomized, double-masked, placebo controlled study with an open-label extension period to evaluate the efficacy and safety of intravenous (IV) MEDI-551 in adult subjects with AQP4-IgG seropositive and seronegative NMO and NMOSD. Enrollment of subjects into the study will stop when a total of 67 AC-determined NMOSD attacks have occurred or when 252 subjects have been randomized,

Subjects receive IV MEDI-551 (300 mg at Day 1 and 300 mg at Day 15) or placebo for a period of 197 days (RCP).
Subjects who complete the RCP without experiencing an NMO/NMOSD attack will be given the option to enroll into an OLP and will initiate or continue treatment

with MEDI-551. Subjects who experience an AC determined NMO/NMOSD attack during the RCP will be given the option to enroll into the OLP following rescue therapy. Subjects for whom the NMO/NMOSD attack is not determined by the AC will continue in the RCP until Day 197 (or until another attack occurs that is determined by the AC).

The OLP will continue for a minimum of 1 year and a maximum of 3 years after the last subject enters the OLP, or until regulatory approval for MEDI-551 as treatment for NMO in the participating country, or until the Sponsor discontinues development of MEDI 551 in this indication, whichever occurs first.

Subjects can choose to exit the OLP at any time, they will enter the Safety Follow-up Period (SFP; unless consent is withdrawn).
All subjects will continue in the SFP for a total of 12 months from last dose to evaluate the long-term safety of the investigational product.

Two hundred and fifty-two subjects will be randomized into the study in a 3:1 ratio to receive IV MEDI-551 or placebo.
On Day 1, subjects will be treated with MEDI-551 or placebo on Day 1 and Day 15. An oral corticosteroid course will be initiated on Day 1 (prednisone 20 mg/day or equivalent oral glucocorticoid) and continue until Day 14. Tapering the oral corticosteroids will occur from Day 15 to Day 21. By Day 21, tapering must be completed.
The planned duration of the RCP for each subject will be 197 days. All subjects who complete the RCP without experiencing an NMO/NMOSD attack will be given the option to enter the OLP. Subjects who are in the RCP when a total of 67 AC-determined NMOSD attacks have occurred will discontinue the RCP within 14 days and be given the option to enter the OLP.

When a possible new or worsening symptom(s) related to NMO/NMOSD is identified, subjects will be required to inform the site. If an Assessment Visit is deemed necessary, this must be scheduled as soon as possible but within 72 hours of reporting of the symptom to the site. At the Assessment Visit, subjects will initially undergo evaluations to determine if the symptoms are related to NMO/NMOSD; if related, the subjects will undergo further evaluations to determine if the symptoms meet at least ONE of the protocol-defined criteria for an NMO/NMOSD attack. In cases where a new or worsening symptom(s) does not meet at least one of the protocol-defined criteria for an NMO/NMOSD attack, the subject will continue in the RCP.

Enrollment of subjects into the study will stop when a total of 67 AC-determined NMOSD attacks have occurred or when 252 subjects have been randomized, whichever occurs first.

Open-label Period
Subjects will be given the option to enter the OLP if they 1) complete 197 days

of the RCP, or 2) experience an AC-determined NMO/NMOSD attack during the RCP, or 3) are in the RCP at the time that 67 AC-determined attacks have occurred.

The first day of the OLP will be Day 1 (OLP Day 1). Upon entering the OLP, subjects will receive MEDI-551. During the OLP, subjects will be followed at scheduled study visits and will continue on MEDI-551 therapy. The OLP will continue for minimum of 1 year and a maximum of 3 years (after the last subject enters), or until regulatory approval for MEDI-551 in the participating country, or until the Sponsor discontinues development of MEDI-551 in this indication, whichever occurs first. Subjects can choose to exit the OLP at any time for any reason, including seeking alternative treatment options, at which point they will enter the SFP (unless consent is withdrawn).
Subjects will be followed for NMO/NMOSD attacks in the same fashion as in the RCP and events will be centrally adjudicated.

Intervention

Randomized-controlled Period
• Treatment Arm 1: 300 mg IV MEDI-551 on Day 1 and Day 15
• Treatment Arm 2: IV Placebo on Day 1 and Day 15
Additionally, all subjects entering the RCP will be treated for 2 weeks (Day 1 to Day 14) with oral corticosteroids (prednisone 20 mg/day or equivalent oral glucocorticoid). A tapering schedule will be implemented from Day 15 to Day 21.

Open-label Period
Subjects randomized to Treatment Arm 1 during the RCP will receive:
• 300 mg IV MEDI-551 on OLP Day 1, masked IV placebo on OLP Day 15, then 300 mg IV MEDI-551 every 26 weeks (Q26W) thereafter
Subjects randomized to Treatment Arm 2 during the RCP will receive:
• 300 mg IV MEDI-551 on OLP Day 1, masked 300 mg IV MEDI-551 on OLP Day 15, then 300 mg IV MEDI-551 Q26W thereafter

Dosing of subjects enrolling into the OLP following an adjudicated NMO/NMOSD attack, and following the occurrence of the 67th adjudicated NMO/NMOSD attack, will follow the OLP dosing regimen described.

For both the RCP and the OLP, investigational product will be administered as a 90-minute IV infusion via an infusion pump. All subjects will be premedicated on Day 1 and Day 15 (OLP Day 1 and OLP Day 15) and at subsequent dosing visits with IV methylprednisolone (100 mg or equivalent glucocorticoid), oral (PO) diphenhydramine (25 50 mg or equivalent antihistamine), and PO paracetamol (acetaminophen; 500-650 mg) prophylactically to prevent infusion reactions.
On Day 1, subjects will be treated with MEDI-551 or placebo on Day 1 and Day 15. An oral corticosteroid course will be initiated on Day 1 (prednisone 20 mg/day or equivalent oral glucocorticoid) and continue until Day 14. Tapering the oral corticosteroids will occur from Day 15 to Day 21. By Day 21,

Study burden and risks

Vaak voorkomende bijwerkingen:
De vaakst voorkomende bijwerkingen die in onderzoeken naar MEDI-551 met mensen zijn waargenomen waren vermoeidheid (een vermoeid gevoel), pijn in de armen en benen, gewrichtspijn, misselijkheid en hoesten. Minder vaak voorkomende bijwerkingen waren brandend maagzuur en spijsverteringsklachten, braken, herpes simplex, huidzweer, geïnfecteerde huidzweer, infectie van de bovenste luchtwegen (inclusief verkoudheid), nachtelijk zweten, blozen, koorts, rood oog, gewrichtszwelling, schimmelinfectie, huiduitslag en afwijkende levertests.

Verspreid over alle locaties waren de meest voorkomende infecties bij voor dit NMO/NMOSD-onderzoek aangemelde patiënten opportunistische infecties (bij ongeveer 10%), infecties van de urinewegen (bij ongeveer 8%) en infecties van de bovenste luchtwegen (bij ongeveer 5%).

Bijwerkingen die voornamelijk in kanker gerelateerde onderzoeken met MEDI-551 werden waargenomen waren lage neutrofielen- en lage bloedplaatjestellingen in het bloed. Deze ongewenste voorvallen werden ook (minder vaak) waargenomen bij proefpersonen in de niet kanker gerelateerde onderzoeken die MEDI-551 kregen, inclusief dit geblindeerde onderzoek.

Andere mogelijke risico*s van MEDI-551:

Infectie
Omdat MEDI-551 het aantal B-cellen in het bloed verlaagt, kan door toediening van MEDI-551 het risico toenemen op infectie. In klinische onderzoeken gemelde infecties waarvan wordt aangenomen dat ze het gevolg waren van MEDI-551 omvatten herpes van de mond, longontsteking en bloedinfectie.

Infusiegerelateerde reactie
De mogelijkheid bestaat dat de proefpersoon binnen enkele minuten tot enkele uren nadat het via intraveneuze infusie onderzoeksgeneesmiddel toegediend heeft gekregen, een infusiereactie krijgt. Infusiereacties zijn een risico bij MEDI-551, maar ze kunnen ook optreden bij toediening van een placebo via IV-infusie. Symptomen van een infusiereactie omvatten koorts, (koude) rillingen, kortademigheid, toename of afname van de bloeddruk, duizeligheid, braken en hoofdpijn. De infusiereacties die tot op heden in onderzoeken met mensen zijn waargenomen waren over het algemeen licht tot matig van ernst en traden op wanneer het onderzoeksgeneesmiddel voor de eerste keer werd toegediend; de reacties verdwenen binnen een paar uur. De preofpersoon zalt voordat het onderzoeksgeneesmiddel wordt toegediend intraveneuze en orale medicijnen krijgen om de kans op een infusiereactie te helpen verlagen.

Het onderzoeksgeneesmiddel en de premedicatie methylprednisolon zullen intraveneus worden toegediend dit kan de volgende problemen veroorzaken:

- irritatie van de ader
- beschadiging van de ader
- beschadiging van de huid of het weefsel rond de injectieplaats
- stijging of daling van de elektrolytenconcentratie, wat gezondheidsproblemen veroorzaakt
- er kan een bloedstolsel of luchtbel ontstaan, waardoor een bloedvat in een ander deel van uw lichaam kan worden afgesloten
Sommige van deze problemen kunnen zeer ernstig zijn.
Na verloop van tijd kan toediening van veel injecties ervoor zorgen dat een ader hard wordt of littekens gaat vertonen, waardoor het moeilijk kan worden een naald in de ader te brengen om een injectie te geven of bloed af te nemen.

Allergische reactie
Er bestaat ook een kans dat de proefpersoon een ernstige allergische reactie op MEDI-551 krijgt. Symptomen zijn onder andere een daling van de bloeddruk, ademhalingsproblemen, ernstige netelroos en soms kan dit zelfs overlijden tot gevolg hebben. De proefpersoon zal nadat hij/zij het onderzoeksgeneesmiddel toegediend heeft gekregen gedurende ten minste 2 uur zeer nauwlettend worden gecontroleerd en er zullen onmiddellijk medicijnen beschikbaar zijn om eventuele allergische reacties te behandelen. Binnen uren tot dagen na toediening van het onderzoeksgeneesmiddel kunnen minder ernstige allergische reacties optreden, waaronder huiduitslag met of zonder jeuk en zwelling. Deze effecten verdwijnen meestal zonder behandeling vanzelf.

Progressieve multifocale leuko-encefalopathie
Van met MEDI-551 vergelijkbare geneesmiddelen, zoals rituximab, is (hoewel dit zelden is gebeurd) gemeld dat ze progressieve multifocale leuko-encefalopathie (PML) veroorzaken, een zeldzame hersenziekte die wordt veroorzaakt door reactivatie van een virus die fataal kan zijn. Deze aandoening is op dit moment niet te genezen. Het is niet bekend of MEDI-551 PML kan veroorzaken; tot op heden zijn er geen gevallen van PML bij gebruik van MEDI-551 bevestigd. Eén patiënt in dit onderzoek overleed aan complicaties als gevolg van de ontwikkeling van nieuwe hersenlaesies waarvan werd vermoed (maar niet werd bevestigd) dat het PML betrof. Resultaten van procedures die doorgaans worden gebruikt voor diagnose van PML (MRI van de hersenen en testen van cerebrospinaalvocht (CSF) op het JC-virus) leverden onvoldoende informatie op om een duidelijke diagnose te kunnen stellen. Mogelijke alternatieve diagnoses waren acute gedissemineerde hersenontsteking en een atypische NMO-aanval. .

Reactivatie van virale hepatitis
Met MEDI-551 vergelijkbare geneesmiddelen, zoals rituximab, kunnen terugkeer van het hepatitisvirus veroorzaken bij mensen die in het verleden hepatitis hebben gehad of die het hepatitisvirus bij zich dragen. Dit kan ernstige leverproblemen (inclusief leverfalen) en overlijden veroorzaken. Het is niet bekend of MEDI-551 reactivatie van virale hepatitis kan veroorzaken. De preofpersoon zal tijdens de screeningsperiode op hepatitis B en C worden gecontroleerd en mag zich niet voor het onderzoek mogen aanmelden als hij/zij

hepatitis B of C heeft gehad.

De patient kan ongemak en hinder ondervinden van de studieprocedures, deze zijn meestal van tijdelijke aard.

Benefit:
Neuromyelitis optica/NMOSD is a rare, chronic, relapsing disorder with debilitating effects. There are currently no medicinal products approved for the prevention of NMO/NMOSD relapses or the treatment of acute relapses. Off-label medications are currently being used for the prevention and treatment of NMO/NMOSD relapse based on low-level evidence and unproven efficacy. There is a high unmet medical need for more effective therapies in this patient population. Furthermore, to date, no randomized-controlled clinical trials have been conducted in this patient population.

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) Men and women 18 years or older with diagnosis of NMO/NMOSD.
2) Confirmation of NMO/NMOSD status:
a.) AQP4-IgG sero-positive NMO/NMOSD with at least one attack requiring rescue therapy in the last year or two attacks requiring rescue therapy in the last 2 years.
b.) AQP4-IgG sero-negative NMO with at least one attack requiring rescue therapy in the last year or two attacks requiring rescue therapy in the last 2 years.
3) EDSS <= 7.5 (8 in special circumstances).
4) Men and women of reproductive potential must agree to use a highly effective method of birth control from screening to 6 months after final dose of the investigational product.

Exclusion criteria

1) Lactating and pregnant females.
2) Treatment with any investigational agent within 4 weeks of screening.
3) Known history of a severe allergy or reaction to any component of the investigational product formulation or history of anaphylaxis following any biologic therapy.
4) Known active severe bacterial, viral, or other infection or any major episode of infection requiring hospitalization.
5) History of of alcohol, drug, or chemical abuse, or a recent history of such abuse < 1 year prior to randomization.
6) Receipt of the following at any time prior to randomization:
a) Alemtuzumab
b) Total lymphoid irradiation
c) Bone marrow transplant
d) T-cell vaccination therapy
7) Receipt of rituximab or any experimental B-cell depleting agent within 6 months prior screening and B-cells below the lower limit of normal.
8) Receipt of IVIG within 1 month prior to randomization.
9) Receipt of any of the following within 3 months prior to randomization:
a) Natalizumab (Tysabri®)
b) Cyclosporin
c) Methotrexate
d) Mitoxantrone
e) Cyclophosphamide
f) Tocilizumab
g) Eculizumab
10) History of Hepatitis B and/or Hepatitis C (Hep B/C at screening).
11) Known history of a primary immunodeficiency (congenital or acquired) or an underlying condition such as human immunodeficiency virus (HIV) infection.
12) History of malignancies, apart from squamous cell or basal cell carcinoma of the skin

treated with documented success of curative therapy > 3 months prior to randomization. 13) Any concomitant disease other than NMO/NMOSD that required treatment with oral or intravenous steroids at doses over 20 mg a day for over 21 days.

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:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-11-2011
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MEDI-551
Generic name:	MEDI-551

Ethics review

Approved WMO

Date:	16-04-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	07-09-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-000253-36-NL
ClinicalTrials.gov	NCT02200770
CCMO	NL65012.078.18

Study results

Date completed:	25-09-2018
Results posted:	05-01-2022

Summary results
Trial ended prematurely

First publication
09-06-2021