A phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial of Rebif New Formulation (44 mcg tiw and 44 mcg ow) in subjects at high risk of converting to Multiple Sclerosis

Published: 21-09-2006
Last updated: 10-05-2024

The primary objective of the study is to evaluate the effect of Rebif New Formulation 44 mcg (tiw and ow) versus placebo on the time to conversion to McDonald MS in patients with a first clinical demyelinating event at high risk of converting to MS...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Central nervous system infections and inflammations
Study type	Interventional

Summary

ID

NL-OMON30517

Source
ToetsingOnline

Brief title
Rebif FLEXible dosing in early Multiple Sclerosis (REFLEX)

Condition

- Central nervous system infections and inflammations

Synonym
disease of the central nervous system, multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Clinical Research Assistance
Source(s) of monetary or material Support: Serono internationalSA;15 bis Chemin des mines;1202 Geneva;Zwitserland

Intervention

Keyword: CIS-Clinical Isolated Syndrome, Conversion, MS-Multiple sclerose, Rebif-Interferon-beta-1a

Outcome measures

Primary outcome

The primary endpoint is the time to conversion to MS (from randomization),

according to the revised McDonald criteria (2005).

Secondary outcome

The time to conversie to CDMS

Number of combined unique active MS lesions

Number of new T2 lesions

Number of new T1 lesions

Number of new Gd-enhancing lesions

Cognition by means of PASAT

Relapse rate

EDSS

MSFC

Development of BAbs and NAbs

safety including AE's, SAE's and laboratory parameters

Study description

Background summary

The Rebif new formulation RNF is a HSA-Free formulation and a new formulation subcutaneous which will be test in a frequency of 3x per week and 1x per week
This formulation is well tolerated in a dosage of 44 mcg and the reported side effects were consistent with the known to the safety profile of Rebif
Over the last years, various clinical trials have demonstrated that early treatment of MS could be beneficial for the patient special for the time to conversion to develop a progression.
Patients who have A clinically Isolated Syndrome (CIS) for MS e.g optic neuritis, myelopathy or a brainstem syndrome is a isolated syndrome in the central nervous system at a single site do not yet comply with a diagnosis of MS.
They will undergo a period of time till the diagnosis MS as per McDonald criteria is reached, unless there is a better parameter as a new MRI lesion or a second attack implicating a different location
In order to invest the period to the definitive diagnosis of MS and possible to delay this progression this trial has been prepared in which the two dosages of RNF will be used compared to placebo
In addition to the procedures described in the main part all patients entering the study 27025 who DO NOT suffer from conditions of the eye such as glaucoma, hypoplasia of the optic nerve, macular hole, vitreomacular traction, diabetes, other diseases of the optic nerve, which are not related to multiple sclerosis, are proposed to undergo Optical Coherence Tomography (OCT), low contrast letter acuity (Sloan chart) and Contrast Sensitivity (Pelli-Robson charts). In addition to the aforementioned, subjects who suffer with severe myopia, superior to 5 diopters, will be excluded from this substudy

Study objective

The primary objective of the study is to evaluate the effect of Rebif New Formulation 44 mcg (tiw and ow) versus placebo on the time to conversion to McDonald MS in patients with a first clinical demyelinating event at high risk of converting to MS.
The aim of these extra procedures for the OCT study is to investigate any degeneration to the nerve fibres (axons) in the retina of the eye, following the first attack suggestive of multiple sclerosis (MS) and at regular intervals throughout the study, It also aims to examine the effect of Rebif® New Formulation on nerve degeneration compared with placebo and to establish whether there is any link between nerve degeneration and other MS related assessments such as Magnetic Resonance Imagining (MRI) or the Neurological assessments done by the Evaluating Physician

Study design

This study will be a randomised, double-blind, placebo-controlled, multicenter, clinical trial comparing 2 dosage regimens of Rebif (Rebif New Formulation; 44 mcg tiw and ow) in a 1:1:1 randomisation of subjects with a single demyelinating event at high risk of converting to a diagnosis of MS. When subjects reach CDMS, they will be re-titrated to open-label treatment with Rebif, 44 mcg tiw. The duration of study treatment will be a total 24 months from randomisation except for subjects who do not convert to CDMS within the 24 months, who will be offered an additional 12-month open-label treatment period with Rebif 44 mcg tiw.

Intervention

Investigational Medicinal Product:
- Rebif New Formulation 44 mcg sc tiw.
- Rebif New Formulation 44 mcg sc ow (+ placebo twice weekly to ensure appropriate blinding).
- Matching placebo sc tiw.
All patients will be titrated at the beginning of the study over 4 weeks. For the first 2 weeks clip-on spacers for the syringes will be provided which will ensure that patients receive 20% of the total dose; the following 2 weeks clip-on spacers that will allow for 50% of the dose to be dispensed will be provided. When subjects reached CDMS they will be re-titrated to 44 mcg tiw For patients who have not converted to CDMS within the 24 months, an optional 12-month open-label extended treatment with RNF 44 mcg tiw will be offered.

Study burden and risks

The duration of the study is 24 months in which in total 11 visits will be performed, in addition a option extended observation period of 12 months in which 4 visits will be performed. When subjects during the study reach CDMS, they will be re-titrated to open-label treatment with Rebif, 44 mcg tiw. The first visit, screening visit will take 2-3 hours, the other visits will take 2 hours. During the study visits a MRI scan will be performed.
During the screening vsit there is an optional liquor sample (15ml) and a Cervix MRI, during the study period an Optic Coherence Tomography (OCT) can be requested at the sites that are selected by the sponsor. During the visit day1, month 6, 12, 18 and 24 blood samples for the Immunological biomarkers can be drawn. During visit day 1 and visit month 24 or early termination visit a blood sample for pharmacogenetic analysis can be drawn, for this a separate patient information and consent form is developed. In order to reduce the risks the standard procedures which will be used for the used assessments, will be done as clean and sterile as possible.it is recommended to telephone contact with the subject within 10 days after SD1 to ensure compliance to study medication. it is recommended to offer prophylaxis and treatment of flu like symptoms with

Iboprofen and/or paracetamol. The patients will be offered to use the Rebiject® in order to be of help for the subcutaneous self injections. The patients will receive the self injection instructions from the research nurse and there will be guidance offered for the self injection procedures performed at their home .
Possible side effects of Rebif as described on page 15 of the protocol (most mentioned) flu like symptoms, tiredness, skin reactions at the injection site, (also reported) decrease of white blood cells, also decrease of red blood cells as well as decrease of platelets.
Changes in liver enzyme Transaminase is reported (increase of value), in some cases liver function disorders, in which jaundice and in two cases a liver transplantation was requested. Most side effects are mild. Rebif can be of influence on thyroid and course depression, there are also notifications for miscarriages during the use of Rebif. Finally Rebif can course just as other medications an allergic reaction. Possible side effect due to the misuse of the Rebiject® can give blood extravasations. Possible side effects due to Blood dawns are site located pain, blood extravasations and swelling, also possible are a light feeling in the head, dizziness, and in some rare cases faint and/ or local infection.
Possible side effects of the liquor drawn are incidental headache after the drawn, this will disappear after a few hours. Possible side effects of the MRI assessments, during the MRI assessment Gadolinium will be added, this can give a headache, disturbance on the injection site, disgusting, vomiting, dizziness, irritation of the skin and e deaf feeling or itching of hands and feet*s. The patients will be asked in advance if they are allergic to Gadolinium.
If the patient is suffering from a renal disease, the contrast dye that is injected while the MRI scan is taken may be poorly tolerated and the following possible signs and symptoms may occur: swelling and tightening of the skin; difficulty extending the joints of arms, hands, legs, and feet; weakness, reddened or darkened areas on the skin; burning or itching of the skin; and deep bone pain in the hips and ribs. Gradual improvement of these effects may occur over time if the renal function improves, but complete recovery has not yet been reported. Therefore, it is important to advise the treating physician if the patient is suffering from a renal (kidney) disease, as depending on the severity of the illness, the patient may not be allowed to participate to this study.
Female subjects must use a highly effective method of birth control as explained by the Treating Doctor. A highly effective method of contraception is defined as those which result in low failure rate (i.e. less than 1% per year or 1 in every 100 per year) when used consistently and correctly such as implants, injectables, combined oral contraceptive, some IUDs (Intra Uterine Devices), sexual abstinence or vasectomised partner.
The following additional tests for the oCT substudy will be asked for 8x for the participants,
Optical Coherence Tomography (OCT) is a relatively new, non-invasive test that measures the thickness of the nerve fibres in the retina of the eye as they enter the optic nerve. The test is very similar to having a photograph taken. You will see a red background with a rotating gold circle. The test takes about

2 to 3 minutes per eye (4 to 6 minutes in total). OCT is completely painless and non-invasive. There is no injection of any dye into the vein or into the eye. No adverse events or side effects have been associated with OCT.
Low-contrast letter acuity (Sloan charts). You will be asked to read letters from a chart. The letters on the chart get progressively smaller in size but all of the letters on the chart are of the same contrast (darkness). Different charts of varying contrast may be used. This test takes about 5 minutes per eye (10 minutes in total).
Contrast sensitivity (Pelli-Robson charts). You will be asked to read out letters from a chart. The letters on the chart decrease in contrast (darkness) but not in size. The letters are arranged in groups of 3, successive groups of 3 letters decrease in contrast. This test takes about 5 minutes per eye (10 minutes in total).
Although there are no risks associated with any of the above tests, no direct benefits can be promised from your participation in this additional testing, other than contributing to scientific knowledge of Clinically Isolated Syndrome.
Smoking Habits. You will be asked about your previous smoking habits and your smoking habits during the course of the study.

Contacts

Public
Clinical Research Assistance

Blikkertweg 3A
7451JK Holten-Rijssen
Nederland
Scientific
Clinical Research Assistance

Blikkertweg 3A
7451JK Holten-Rijssen
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subject with a single, first clinical event suggestive of MS within the last 60 days (clock starts 24 hours after onset). The event must be a new neurological abnormality present for at least 24 hours, either mono-polysymptomatic, other than a paresthesia, vegetative or cerebral dysfunction

Exclusion criteria

Subject has a diagnosis of Multiple Sclerosis (per Mc Donald creteria 2005)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	29-09-2006
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Rebif NF
Generic name:	RNF Interferon-beta-1a

Ethics review

Approved WMO Date:	21-09-2006
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-01-2007
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-03-2007
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-05-2007
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-05-2007
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-05-2007
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	13-07-2007
Application type:	Amendment
Approved WMO Date:	24-07-2007
Application type:	Amendment
Approved WMO Date:	18-03-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-03-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2006-002982-38-NL
CCMO	NL13892.068.06