EMR 200136-532: A three-arm, randomized, double-blind, placebo controlled, multicenter, phase II study to evaluate the efficacy of Vigantol® oil as add-on therapy in subjects with Relapsing-Remitting Multiple Sclerosis receiving treatment with Rebif®

Published: 24-09-2010
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Primary objective: To assess the efficacy of Vigantol oil versus placebo as add-on therapy in subjects with relapsing-RemittingMultiple sclerosis receiving treatment with Rebif.Secondary objective:To assess changes on clinical parametersto assess...

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

Summary

ID

NL-OMON34154

Source
ToetsingOnline

Brief title
SOLAR

Condition

- Central nervous system infections and inflammations

Synonym
MS, Multiple Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: Bedrijf: Merck BV

Intervention

Keyword: Multiple Sclerosis, Rebif, Vigantol-oil, Vitamin D

Outcome measures

Primary outcome

The primary endpoint is a composite endpoint of MRI and clinical variables:

the primary MRI endpoint is the mean change from baseline in the total volume

of T2 lesions at week 48

the primary clinical endpoint is the proportion or relapse free subject at week

96

(at randomization, subjects may be stratified according to (1=most important)

1. BMI

2. Gender

3. number of relapses in the past two years

Secondary outcome

Relapses:

-proportion of relapse-free subjects at week 48

-time to first documented relapse

-annualized relapse rate at week 48 and 96

-total of number of reported relapses at all time points

-requirement for treatment with glucocorticoids due to relapses (during 96

weeks)

EDSS:

-proportions of subject with stable EDSS at week 48 and 96

-time to 24 week sustained disability progression on EDSS

-proportions of subjects with 24 weeks sustained disability progression on EDSS

at week 48 an d96

MRI:

-Mean number of new T1 gadolinium enhancing lesions per subject per scan at

Week 48 and week 96

-Cumulative number of T1 gadolinium enhancing lesions at Week 48 and week 96

-Mean number of new CU lesions per subject per scan at Week 48 and week 96

-Cumulative number of new combined unique CU lesions at Week 48 and week 96

-Mean number of new T2 lesions per subject per scan at Week 48 and week 96

-Cumulative number of new T2 lesions at Week 48 and week 96

-Mean change from baseline in the total volume of T2 lesions at Week 48 and

Week 96 (T2 Burden of disease) [mm3].

-Proportion of subjects free from T1 gadolinium enhancing lesions at week 48

and week 96

-Proportion of subjects free from T1 lesions at week 48 and week 96

-Percentage of new T1 lesions at week 48 and 96 within the subgroup of new

non-enhancing T2 lesions

Other Efficacy endpoints:

-Proportion of subjects free from disease activity: relapse-free, free of

sustained disability progression, no new Gd+ lesions and no active T2 lesions

at week 48 and 96

-Change in cognitive function at week 48 and 96 with respect to baseline as

measured by Symbol Digit Test.

-Proportion of T1 gadolinium-enhancing lesions at SD1 that transform into black

holes at Weeks 48 and 96.

-Percent Brain Volume Change (PBVC) at Weeks 48 and 96 with respect to baseline

and at Week 96 with respect to week 48

Study description

Background summary

Multiple sclerosis is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) and is one of the most common causes of neurological disability in young adults. It characterized by multi focal recurrent events of neurological symptoms and signs, with variable recovery.
The exact cause of multiple sclerosis is unknown, although an autoimmune process has been implicated.
There are four clinical forms of MS, primary progressive, progressive-relapsing, secondary progressive and relapsing-remitting.
Pathalogy change occurs in MS and include blood-brain barriere breakdown with edema, leukocyte infiltration with cytokine release, demyelination, and axonal transection.
It affects up to 2.5 million people worldwide.

Study objective

Primary objective:
To assess the efficacy of Vigantol oil versus placebo as add-on therapy in subjects with relapsing-RemittingMultiple sclerosis receiving treatment with Rebif.

Secondary objective:
To assess changes on clinical parameters
to assess changes in MRI parameters
To investigate the safety profile upp to the end of the treatment Period (week 96)
To explore pharmacogenetics/pharmacogenomics (PGx) biomarkers and to evalute whether ther is a possible relationship to Vigantol oil traetment outcomes

Study design

The study consists of a screening visit, a baseline visit (SD1), a treatment period with 9 subsequent visits and a follow-up visit.

The treatment period has a duration of 96 weeks and will consist of three arms:
Treatment Group 1: Vigantol ® oil 7.000 IU/d (175 *g/d) for 4 weeks followed by 14.000 IU/d (350 *g/d) for 92 weeks on top of Rebif® 44 *g tiw in subjects with 25-hydroxy-vitamin D plasma levels below 150 nmol/L (174 subjects)

Treatment Group 2: Matching placebo daily on top of Rebif® 44 *g tiw in subjects with 25-hydroxy-vitamin D plasma levels below 150 nmol/L (174 subjects)

Treatment Group 3: Subjects with 25-hydroxy-vitamin D plasma levels equal or higher than 150 nmol/L will continue administration of Rebif® 44 *g tiw without add-on therapy

Two parallel populations will be recruited, one with 25-hydroxy-vitamin D plasma levels equal or higher than 150 nmol/L, and one with 25-hydroxy-vitamin D plasma levels lower than 150 nmol/L.

Randomization will be done only for subjects with 25-hydroxy-vitamin D plasma levels lower than 150 nmol/L by means of IVRS. These subjects will randomly be assigned to Vigantol® oil (Treatment Group 1) and placebo treatment (Treatment Group 2) in a 1:1 ratio on top of the preexisting treatment with Rebif®.
Subjects with 25-hydroxy-vitamin D plasma levels equal or higher than 150 nmol/L will be assigned automatically by means of IVRS to Treatment Group 3.
Recruitment will be concluded once the requested number of subjects for the Treatment Groups 1 and 2 are included in the study.
The analyses planned for Treatment Group 3 will be limited to the number of subjects assigned to this group during the recruitment period needed for Treatment Groups 1 and 2.
During the whole treatment period efficacy and safety will be evaluated by means of anti-inflammatory and neurodegenerative effects assessed by MRI parameters and clinical outcomes, safety, and tolerability of Vigantol® oil at the dose of 7.000 IU/d (175 *g/d) for 4 weeks followed by 14.000 IU/d (350 *g/d) for 92 weeks in combination with Rebif® compared to placebo in combination with Rebif® in subjects with RRMS according to the revised McDonald criteria

for the diagnosis of Multiple Sclerosis from 2005.

Intervention

Additional treatment with Vitamin D (Vigantol-oil)

Study burden and risks

(From the Patient information form:)

As with any drug, Vigantol® oil can also have side effects. Generally speaking, Vigantol® oil is well tolerated Studies have been conducted to see to what extent vitamin D supplementation, such as Vigantol®, affects blood pressure or cholesterol, but to date no effects have been reported. Long-term treatment with high doses of vitamin D has proven to cause high calcium concentrations in the blood. Very high calcium concentrations may be connected with reduced appetite, nausea, vomiting, fatigue, increased urine production, joint pain, bone decalcification (with an increased risk of bone fractures), general loss of strength and disorientation. At the vitamin D dose you receive in this trial, it is very unlikely that you will receive calcium concentrations leading to any of the symptoms listed.
The vitamin D dose you receive in connection with participation in this trial may be up to 14 times higher than the dose you would take for a vitamin D deficiency. Earlier studies suggest that the dose may have favourable effects in the treatment of multiple sclerosis. In another, recent trial, a dose was tested that was even higher than the dose you receive in this trial; namely 20 times higher than the dose you would take for a vitamin D deficiency. Data from this trial do not indicate patient risks associated with such a high dose. In total, about 320 ml blood will be taken throughout the clinical trial. The pricking of a vein does not generally entail any risks. In rare cases, bleeding in the surrounding tissue, a very rare inflammation of the vein or thrombosis (formation of blood clots) may occur, or in rare cases a nerve may be affected.

MRI scan:
MRI is generally regarded as very safe imaging. In an MRI, no ionising radiation is released and to date no notable side effects have been recorded for the magnetic fields and radio waves used on the human body. The contrast fluid gadolinium most used has proven to be safe, but may have the following, short-term side effects: headache, irritation at the insertion site, nausea, vomiting, dizziness, rash and a numb or tingling sensation in hands and feet. MRI must, however, not be used for people with metal objects in their bodies, such as:
* Patients with a pacemaker, hearing implants (inner ear or cochlea) or implanted spinal cord stimulator
* Patients with a metal object (metal splinter) in the eye, inner ear implants or an aneurysm clip in the brain (because the magnetic field may displace the

metal).
* Patients with metal objects in their back (such as screws and plates) may undergo an MRI scan, but the resolution of the scan is often seriously disturbed by the metal object and the backbone is not reproduced properly.
There are other conditions that may prevent the making of an MRI scan, such as pregnancy and/or the presence of other kinds of metal in your body. Patients with claustrophobia (i.e. people who are afraid in small spaces) may possibly be unable to cope with an MRI scan, although more open scanners are now available. A sedative may also simplify undergoing the test.
If you are allergic to gadolinium or do not want to undergo an MRI for other reasons, you should notify your study doctor.
The further investigations do not entail any health risks for you.

Contacts

Public
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Scientific
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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. Males and females between 18 and 50 years of age
2. Diagnosis of a relapsing- remitting form of MS, according to teh revised Mc Donald criteria.
3. Brain and / or spinal MRI with findings typical of MS
4. A first clinical occuring within 5 years prior to screening
5. Disease activity by;
At least one MS lesion within the 12 months prior to Screening
One or more Gd-enhancing MRI lesions within the 12 months prior to Screening
EDSS score <<= 4.0 at Screening.
7. Currently and for the first time treated with interferon-beta-la (tiw) s.c., and having received this treatment for a minimum of 90 days and for not longer than 12 months before baseline visit (including titration period).
8. Willingness and ability to comply with the protocol for the duration of the trial.
9. Written informed consent given prior to any trial-related procedures not part of the normal medical practice.

Exclusion criteria

10. Pregnancy and lactation period
11. Any disease other than MS that could better explain signs and symptoms.
12. Complete transvere meylitis or bilateral optic neuritis.
13. Currently receiving or use at any time of monoclonal antibodies, mitoxantrone, cytotoxic or immunosupressive therapy (excluding systemic steroids and adrenocortocotrophic hormone [ACTH], B cell modulating therapies (e.g. RituxiMab or BelimuMab), total lymphoid irradiation or bone marrow transplantation.
14. Use of any cytokine or anti-cytokine therapy, intravenous immunoglobulin, plasmapheresis, or any investigational drug or experimental procedure within 12 months prior to Screening.
15. use of oral or systemic corticosteroids or ACTH
16. Have experienced a relapse within 30 days before the SDI visit
17. Have abnormalities of Vitamin D related hormonal system other than low dietary intake or decreased sun exposure, e.e. primary hyperparathyroidism or granulomatous disorder.
18. Have an urine calcium/ creatinine (mmol.mmol) ratio grater than 1.0 or hypercalcaemia (11 mg/100cc (5.5 mEq./l.)
19. Are taking medication that influence Vitamin D metabolism other than corticosteroids, e.g., phenytoin, barbiturates, thiszide diuretcs and cardiac glycosides
20. Have a conditions with increase susceptibilty to to hypercalcaemia, e.g., known arrhythmia or heart disease , treatment with Digilis, or Hydrochlorothiazide and those who suffer from nephroliathiasis.
21. Have inadequate liver function, defined by alanine aminotransferase (ALT) 3 times upper limit of normal (ULN), aspartate sminotransferase (AST) 3 times upper limit of normal (ULN) or alkanine phosphatase > 2.5 times ULN, or total bilirubin > 1.5 times ULN, if assiciated with any elevation of ALT or alkanine phosphatase

22. Moderate to servere renal impairment (estimate of glomurlar filtration rate [GFR] <50 mL/min/1.73 m2 [based on creatinine clearance according to Cockcroft-Gault aquation])
23. Inadequate bone marrow reserve, defined by a WBC count <0,50 times the lower limit of normal.
24. History or presence of serious or acute heart disease such as controlled cardiac dysrhythmia or arrthythmia, uncontrolled cardiac dysrhythmia or arrthythmia, uncontrolled angina pectoris, cardiomyopathy, or uncontrolled congestive heart failure (NYHA class 3 or 4).
25. History or presence of severe depression, history of suicide attempt, or current suicidal ideation.
26. Epilepsy or seizures not adequately controlled by treatment.
27. Current or past (within the last 2 years) alcohol or drug abuse.
28. Any major medical or psychiatric illness (such as psychosis, bipolar disorder)
that in the opinionof the investigator could create undue risk to the subject or could affect adherence with the trial protocol.
29. known contra-indication to treatment with vitam D (according to SPC)
30. Known hypersentivity to IFN or its excipient(s) (according to SPC).
31. Known hypersentivity to gadolinium.
32. any other condition that would prevent the subject from undergoing an MRI scan
33. Signs and sympoms suggestive of transmissible spongiform encephalopathy, or family members who suffer(ed) from such.
34. Positive HIV, hepatitis C, or hepatitis B (HBsAg and HBc antibody) serology (test perfomed at screening).
35. Legal incapacity or limited legal capacity.
36. Another current autoimmune disease, except diabetes.

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):	15-02-2011
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Vigantol oil
Generic name:	Cholecalciferol

Ethics review

Approved WMO Date:	24-09-2010
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	06-01-2011
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	22-03-2012
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	25-06-2012
Application type:	Amendment

Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	20-08-2013
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	EUCTR2010-020328-23-NL
CCMO	NL33417.096.10