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MINERAL (Magnetic-resonance Image of Nutraceutical Efficacy on Relapsing-ms Autoimmune Lesions) study: a novel nutraceutical formula NEUROASPIS PLP10® for the treatment of relapsing-remitting multiple sclerosis

Submission date
09/03/2013

Recruitment status
No longer recruiting

Registration date
19/03/2013

Overall study status
Completed

Last Edited
11/11/2022

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Multiple sclerosis (MS) affects nerves in the brain and spinal cord, causing problems with muscle movement, balance and vision. In relapsing-remitting MS, people have distinct attacks of symptoms which then either partially or completely fade away. This study is the last stage of testing the effect of the new drug PLP10 on patients with relapsing-remitting MS. We have previously tested PLP10 on a smaller number of patients and the results showed a positive effect without any strong side effects. Now we want to re-examine the activity and safety of the treatment on a larger population.

Who can participate?
Relapsing-remitting MS patients aged between 18 and 55 years from Cyprus and Greece.

What does the study involve?
Patients will be randomly allocated to either receive PLP10 orally once a day for 30 months, or to receive a placebo (dummy) drug. Patients will be clinically examined at the time of entering the study. There will then be a 6-month period for the PLP10 ingredients to exert their beneficial effect. Patients will then be examined again at the baseline (starting point), at 6, 12, 18 and 24 months after baseline, and at 12 months after completion of the study. Patients will also give blood at enrolment, baseline, 12 and 24 months. We will examine the number of relapses per patient, carry out Magnetic Resonance Imaging (MRI) scans of the patients brain lesions, measure any increases in disability, and look at markers in the patients blood.

What are the possible benefits and risks of participating?
The possible benefits are a decreased relapse rate, a decreased development of new or

enlarging brain lesions, and a decreased risk of disability accumulation. No severe side effects are expected based on our previous study and from what is already known from the published literature.

Where is the study run from?
This study has been set up by PALUPA Medical Ltd. The clinical sites involved are the Cyprus Institute of Neurology and Genetics, Nicosia Cyprus (the lead center); Medical School, Aristotelion University Thessaloniki, Greece; Medical School, University of Thessaly, Greece; Medical School, University of Ioannina, Greece.

When is the study starting and how long is it expected to run for?
April 2013 to December 2018

Who is funding the study?
The study has been granted funds from the Cyprus Ministry of Commerce Industry and Tourism.

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
Novel oral nutraceutical intervention NEUROASPIS PLP10® for the treatment of relapsing-remitting multiple sclerosis: A multicenter, parallel-group, phase III, double-blind, randomized, placebo-controlled, add-on with Interferon Beta, trial of efficacy and safety

Acronym
MINERAL

Study objectives
1. Docosahexaenoic acid (DHA)/eicosapentaenoic acid (EPA)/gamma-linolenic acid (GLA)/linoleic acid (LA) polyunsaturated fatty acids along with specific monounsaturated fatty acids, minor quantity of specific saturated fatty acids and specific antioxidant vitamins (E and A) and gamma-tocopherol within a specific ratio, quantity and quality can possibly interfere with all known pathophysiological mechanisms in multiple sclerosis (MS)
2. This could result in increased treatment efficacy, reduction of annual relapse rate (ARR) and T1 /T2 MRI lesions and disability accumulation and can possibly trigger remyelination and neuroprotection.

This is for efficacy and safety of PLP10, composed and formulated based on natural structural and functional bio-molecules such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), linoleic acid (LA) and gamma (γ)-linolenic acid (GLA), gamma-tocopherol and other specific omega-3, monounsaturated, saturated fatty acids and antioxidant vitamins compared to placebo, on multiple sclerosis (MS) patients when it is used for a 6-month normalization period (oral essential fatty acids need about 6 months to exert their beneficial effect) until entry baseline plus 24 months on-treatment period (total 30 months).

Trial questions:
1. Whether the interventions are effective for those patients who adhere to the assigned treatment, the per-protocol analysis
2. What happened to all MS patients who are placed on the interventions, the effect of assignment, the intention to treat (ITT) analysis?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Cyprus National Bioethics Committee (CNBC), 27/03/2014, ref: ΕΕΒΚ/ΕΠ/2013/18

Study design
Multicenter Phase III interventional randomized double-blind placebo-controlled parallel clinical trial of efficacy and safety

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Relapsing-remitting multiple sclerosis

Interventions
Update as of 26/09/2018:
In case where there are changes and alteration of the local clinical practice guidelines, making difficult the enrolment due to difficulties to find patients in accordance to the designed protocol

inclusion criteria, to participate in a reasonable time (meaning the study participants' recruitment rates for these centers are severely hindered) the study should continue to completion and be ended according to the protocol if the total enrolled number of patients can be considered as able to produce statistically meaningful results by the independent statistician of the project, positive or negative.

1. The daily oral liquid formula dose of intervention PLP10, is a mixture of:
1.1. EPA (about 1650 mg)
1.2. DHA (about 4650 mg)
1.3. GLA (about 2000 mg)
1.4. LA (about 3850 mg)
1.5. Total other omega-3 (about 600 mg)
1.6. Total monounsaturated fatty acids (MUFA) (about 1700 mg)
1.7. Total saturated fatty acids (SFA) (18:0 about 160 mg, 16:0 about 650 mg)
1.8. Vitamin A (about 0.6 mg)
1.9. Vitamin E (about 22 mg)
2. Pure γ-tocopherol (760 mg)
3. Placebo is composed of virgin olive oil (16930 mg).
4. Food grade lemon-aroma is in each intervention formula to make up a total dosage of 20 ml of solution per day once daily for a total of 30 months
5. The first 6 months of the study is used as a normalization period for the interventions agents to exert their beneficial effect
6. All preparations and the placebo have identical appearance and smell
7. The bottles containing the syrup are labeled with medication code numbers unidentifiable for patients as well as investigators

The intervention dosage: 20 ml, per os, daily, 30 minutes before dinner, for the 6-month normalization period and for the 24-month on-treatment period (total 30 months).

A 12-month extension, free of drug (washout) period is included in the clinical trial design.

Note: The design of the study includes a 6-month normalization (essential fatty acids and antioxidant vitamins) period:

Specifically the normalization period begins at enrolment and continues for 6 months with regular consumption of the assigned intervention (for both study arms). The end of this period is denoted as the entry baseline. The period between entry baseline and the 24 months of treatment until the study completion (end) is the 'on treatment' period.

The 'normalization period' will be a 6-month period between enrolment and entry baseline (the first 6 months of the trial that patients will be on the intervention treatment for only normalization purposes). For the results analysis this 6-month period will be considered as a period before entry baseline for both treatment arms.
Due to the nature of the intervention ingredients/agents the protocol of the clinical study is considering a normalization period for the interventions agents to exert their beneficial effect.

Intervention Type
Other

Phase
Phase III

Primary outcome(s)

Primary outcome measures as of 31/03/2016:
At 2 years the primary end points will be the annual relapse rate (ARR)

1. The study is designed to end 30 months after enrollment (plus 12-month washout period) and neurological and clinical assessments should be scheduled at entry baseline (6 months after enrollment, the end of normalization period) and at 6, 12, 18 and 24 months on-treatment. Another assessment should be scheduled 6 months after the end of the study if a patient is reported with an increased EDSS score during the 24th month assessment , otherwise at 12 months after the end of the study.
2. Patients should be examined within 48 hours after the onset of new neurological symptoms for the treating physician to confirm and record a relapse as per protocol

Original primary outcome measures:
At 2 years the primary end points will be the annual relapse rate (ARR) and the number of new or enlarging brain lesions (evaluated by MRI)

1. The study is designed to end 30 months after enrollment (plus 12-month washout period) and neurological and clinical assessments should be scheduled at entry baseline (6 months after enrollment, the end of normalization period) and at 6, 12, 18 and 24 months on-treatment. Another assessment should be scheduled 6 months after the end of the study if a patient is reported with an increased EDSS score during the 24th month assessment.
2. Patients should be examined within 48 hours after the onset of new neurological symptoms for the treating physician to confirm and record a relapse as per protocol.
3. MRI scans should be scheduled at enrollment and at the end (completion) of the study.
4. Number of T1 gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing lesions, number of new or enlarged lesions on T2-weighted MRI scans, proportion of patients free from new or enlarged lesions on T2-weighted scans, volumes of hyperintense lesions on T2-weighted scans and hypointense lesions on T1-weighted scans, change in brain volume between baseline and 24 months, and safety and tolerability measures.
5. Magnetization transfer (MTR) and diffusion-weighted images (the total enrolled population will be investigated by these techniques to demonstrate possible remyelination) for proportion of patients exhibiting remyelination.

MRI
MRI protocol should include a dual-echo, a 3D T1w and a post-contrast T1- and T2-weighted sequence, for quantification of disease activity (number of new T2 lesions, gadolinium-enhancing lesions) and magnetization transfer and diffusion images for remyelination.

Relapses are defined as new neurologic symptoms or worsening of pre-existing symptoms (that are stable for at least 1 month) not associated with fever or infection that lasts for at least 24 hours and characterized by new or worsening neurological signs on examination.

Total MRI scans will be centrally analyzed (Medical School, University of Vita-Salute San Raffaele, Milan, Italy, Massimo Philippi).

Key secondary outcome(s))

Secondary end points at 2 years will be the time to confirmed disability progression and quantity changes of inflammatory/anti-inflammatory markers in the blood

Time to confirmed disability progression is defined as an increase of 1.0 on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0.0,

confirmed after 6 months, with an absence of an ongoing relapse at the time of assessment (progression cannot be confirmed during a relapse) and with no documented relapse during the 6-month period needed for the confirmation. Under the same conditions as previously discussed, the final EDSS score should also be confirmed 6 months after the end of the study.

Blood samples should be collected at enrollment, baseline, 12 and 24 months (total of 30 months including normalization) for specific pharmacodynamic/pharmacokinetic experimental investigations (markers in the blood).

1. Evaluation of the hematological (full blood count) and biochemical analyses at enrollment, baseline (6 months after enrollment), 12 months and 24 months on treatment and compared to enrollment and baseline.
2. Compare changes of inflammatory markers, cytokines, chemokines, adhesion molecules and lipid metabolite markers in plasma at enrollment, baseline, 12, 24 months on treatment and compared to enrollment and baseline.
3. Specific antioxidant vitamin counts in serum at enrollment, baseline, 12, 24 months on treatment compared to enrollment and baseline.
4. Changes of antioxidant activity and fatty acids in the serum and red blood cells at enrollment, baseline, 12, 24 months on treatment and compared to enrollment and baseline.

Safety adverse events:
Hematological (full blood count) and biochemical analyses at enrolment, baseline, 12 months and at study completion.
Serious adverse events are defined as those that result in admission to hospital, cause prolonged disability or death, or are judged to be life threatening or otherwise medically significant.

Drop outs:
The drop outs, at any time and even the drop outs that never received the assigned interventions should be followed like all other participants as required for intention-to-treat analyses (ITT).

Missing data handling:
All patients who prematurely discontinue the study drug will be encouraged to continue in the study until the end of the planned treatment period, regardless of the treatments received. The data collected will be included for analyses. The main analysis of ARR will include all confirmed relapses during the study, including relapses reported after study drug discontinuation.

As of 31/03/2016, the following secondary outcome measures have been added (originally primary outcome measures):
1. MRI scans should be scheduled at baseline and at the end (completion) of the study
2. Number of T1 gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing lesions, number of new or enlarged lesions on T2-weighted MRI scans, proportion of patients free from new or enlarged lesions on T2-weighted scans, volumes of hyperintense lesions on T2-weighted scans and hypointense lesions on T1-weighted scans, change in brain volume between baseline and 24 months, and safety and tolerability measures
3. Magnetization transfer (MTR) and diffusion-weighted images (the total enrolled population will be investigated by these techniques to demonstrate possible remyelination) for proportion of patients exhibiting remyelination

MRI
MRI protocol should include a dual-echo, a 3D T1w and a post-contrast T1- and T2-weighted

sequence, for quantification of disease activity (number of new T2 lesions, gadolinium-enhancing lesions) and magnetization transfer and diffusion images for remyelination.

Relapses are defined as new neurologic symptoms or worsening of pre-existing symptoms (that are stable for at least 1 month) not associated with fever or infection that lasts for at least 24 hours and characterized by new or worsening neurological signs on examination.

Total MRI scans will be centrally analyzed (Ayios Therissos Radiology Center, Nicosia Cyprus).

Completion date
31/12/2018

Eligibility

Key inclusion criteria
1. Men and women
2. Aged between 18 and 55 years
3. Diagnosis of relapsing remitting multiple sclerosis (RRMS) according to revised McDonald criteria
4. A score of 0.0 to 5.0 on the Expanded Disability Status Scale (EDSS)
5. At least one medically documented relapse within the 18 months before enrolment
6. Cranial MRI scan demonstrating lesion(s) consistent with MS
7. On interferon beta (IFN-β) treatment for the last 6 continuous months or more

Note: If a clinical documented relapse (see primary outcomes) is reported during the 'normalization' period the entry baseline EDSS for that patient will be reported as the EDSS score documented at least 4 weeks after the last relapse during this period.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Prior immunosuppressants or monoclonal antibodies therapy (prior or concomitant use of cladribine, mitoxantrone, copaxone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporin, methotrexate, mycophenolate, fingolimod or natalizumab [Tysabri]) or Tecfidera/BG-12)
3. Prior use in the 3 months preceding randomization of cytokine therapy, glatiramer acetate or intravenous immunoglobulins, or concomitant use of these treatments
3. Pregnancy or nursing

4. A clinically significant infectious illness within 30 days prior to randomization
5. Primary progressive, secondary progressive or progressive relapsing MS
6. Patients known to have a history of recent drug or alcohol abuse
7. Any severe disease other than MS compromising organ function, meaning: history of or abnormal laboratory results indicative of any significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, renal and /or other major disease, that in the opinion of the investigator would preclude the administration of PLP10 for 30 months.
8. History of severe allergic or anaphylactic reactions or known specific nutritional hypersensitivity.

As of 31/03/2016 the following exclusion criteria have been added:
9. Consumption of any additional food supplement formula (prior use in the 3 months preceding randomization, of any type of vitamin including vitamin D, or 6 months preceding randomization, of any form of polyunsaturated fatty acid (PUFA), or concomitant use of these treatments)
10. Prior or concomitant use of statins

Note: During intervention treatment it is strongly suggested for the patients to continue only on the interferon beta treatment. If a patient changes therapy to immunosuppressant or monoclonal antibody or fingolimode or any other treatment on physicians decision then he/she will be considered as a drop-out, but will continue to be medically followed for the purpose of the intention-to-treat analyses.

Date of first enrolment
01/02/2016

Date of final enrolment
31/12/2016

Locations

Countries of recruitment
Cyprus

Greece

Study participating centre
The Cyprus Institute of Neurology and Genetics
Nicosia
Cyprus
1683

Sponsor information

Organisation
Ministry of Commerce, Industry and Tourism (Cyprus)

ROR
https://ror.org/016bxe465

Funder(s)

Funder type
Government

Funder Name
Cyprus Ministry of Commerce Industry and Tourism (Cyprus)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	17/04/2013		Yes	No
Results article		04/11/2022	11/11/2022	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes