# A Phase 3, multi-center, randomized, Double-Blind, double-dummy, active controlled, parallel group study to evaluate the efficacy and safety of RPC1063 administered orally to relapsing multiple sclerosis patients.

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Primary Objective:To assess whether the clinical efficacy of RPC1063 is superior to interferon (IFN) *-1a (Avonex®) inreducing the rate of clinical relapses in patients with RMS.Secondary Objectives:- To assess the effect of RPC1063 on the...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Neuromuscular disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON42145

**Source**
ToetsingOnline

**Brief title**
Sunbeam RPC01-301

### Condition

- Neuromuscular disorders

**Synonym**
Relapsing Multiple Sclerosis

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Receptos
**Source(s) of monetary or material Support:** sponsor/farmaceut

## Intervention

**Keyword:** Multiple Sclerosis, RPC1063

## Outcome measures

### Primary outcome

Primary Efficacy Endpoint:

ARR during the treatment period

### Secondary outcome

Secondary Efficacy Endpoints:

Key Secondary Endpoints (rank ordered):

- The number of new or enlarging hyperintense T2-weighted brain MRI lesions

over 12 months

- The number of GdE brain MRI lesions at Month 12

- Time to onset of disability progression as defined by a sustained worsening

in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months

Other Secondary Efficacy Endpoints

- Proportion of patients who are GdE lesion-free at Month 12

- Proportion of patients who are new or enlarging T2 lesion-free at Month12

- The percent change in normalized brain volume (atrophy) on brain MRI scans

from Baseline to Month 12

- Change in MSFC score from Baseline to Month 12 (including the Low-Contrast

Letter Acuity

Test [LCLA] measurement of visual function as a component)

- Change in MSQOL-54 score from Baseline to Month 12

Exploratory Endpoints:

- Changes in other MRI variables including number and volume of GdE T1 lesions,

volume of T2

lesions, number of new or enlarging T2 lesions, volume of unenhancing T1

lesions, number of new

unenhancing T1 lesions, and measures of brain atrophy

# Study description

**Background summary**

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central
nervous system (CNS), characterized by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier. Currently there is no cure for MS. The utility of treating MS with immune modulating drugs has been well-established. The goal of current treatment strategies for MS involves improving the quality of life of patients by managing symptoms and treating relapses.

Currently approved first-line immune-modulating therapies have moderate efficacy, reduce the relapse rate by approximately 30% and reduce disability accumulation compared to placebo. Natalizumab (Tysabri®), a humanized monoclonal antibody, has been shown to reduce relapse rates by 68% and reduces the risk of sustained progression of disability by 42% compared to placebo. Each of these drugs is characterized by a combination of limited therapeutic utility, safety concerns and/or drug compliance issues, suggesting the need for the development of effective, well tolerated orally active MS therapies.

Clinical experience with fingolimod (FTY720, Gilenya®) strongly supports the rationale for
therapeutically targeting S1PR in MS. Fingolimod, an oral drug recently approved for the

treatment of MS, has demonstrated a superior efficacy profile compared to IFN-*, reducing
relapse rates by 52%. Fingolimod is not specific for S1P1R. The compound also stimulates three other related receptors. Several toxicities associated with fingolimod treatment may be a consequence of the drug lacking specificity for S1P1R and potentially having pharmaceutics liabilities related to the drug*s structural class. RPC1063 is a small molecule compound that selectively and potently activates the sphingosine 1-phosphate 1 receptor (S1P1R), resulting in sequestration of lymphocytes in peripheral lymphoid organs and maintenance of endothelial barrier integrity.

**Study objective**

Primary Objective:
To assess whether the clinical efficacy of RPC1063 is superior to interferon (IFN) *-1a (Avonex®) in
reducing the rate of clinical relapses in patients with RMS.
Secondary Objectives:
- To assess the effect of RPC1063 on the proportion of patients with new/enlarging T2 lesions at
Month 12
- To evaluate whether the efficacy of RPC1063 is superior to IFN *-1a in delaying the
accumulation of disability, as assessed by the Multiple Sclerosis Functional Composite (MSFC)
and visual function as measured by the low-contrast letter acuity test (LCLA)
- To evaluate whether the efficacy of RPC1063 is superior to IFN *-1a in delaying The
accumulation of disability, as assessed by the Expanded Disability Status Scale (EDSS)
- To assess the effect of RPC1063 on brain atrophy over 12 months
- To evaluate the effect of RPC1063 on patient-reported quality of life as assessed by the Multiple
Sclerosis Quality of Life-54 (MSQOL-54)
- To assess the safety and tolerability of RPC1063 in patients with RMS
Exploratory Objectives:
To evaluate the effects of RPC1063 on other MRI outcomes including number and volume of GdE T1
lesions, volume of T2 lesions, number of new or enlarging T2 lesions, volume of unenhancing T1 lesions,
number of new unenhancing T1 lesions, and measures of brain atrophy

**Study design**

Study RPC01-301 is a multi-center, randomized, double-blind, double-dummy, active-controlled, parallel

group study to evaluate the efficacy and safety of RPC1063 administered orally to patients with RMS. In
this study two doses of RPC1063 will be administered daily for a 12 month period compared to an active
control, IFN *-1a (Avonex®). Patients will continue to receive randomized, blinded treatment until the last
active patient has been treated for at least 12 months, followed by a safety follow-up visit 28 days later.
This is a randomized, double-blind, double-dummy comparison of RPC1063 to an active control (IFN *-
1a) in patients with RMS, per revised 2010 McDonald criteria. Approximately 1200 patients who meet
eligibility criteria as assessed during the 30-day screening period will be randomly assigned 1:1:1 to receive
one of two doses of daily RPC1063 (0.5 mg or 1 mg) or IFN *-1a 30 *g intramuscular (IM) weekly for 12
months.
A *dual assessor* approach will be used to evaluate efficacy and safety to prevent potential unblinding as a
result of observed efficacy, AEs, or laboratory changes. Each site will have two investigators: a principal or
treating investigator (treating investigator) and a blinded evaluator (examining investigator or rater). The
treating investigator is the safety assessor and should be a neurologist experienced in the care of multiple
sclerosis (MS) patients. The treating investigator will have access to both safety and efficacy data and will
make all treatment decisions based on the patient*s clinical response and laboratory findings. The blinded
evaluator is the efficacy assessor and should be a neurologist or other health care practitioner trained in
administering the EDSS. The blinded evaluator will be responsible for administration of the EDSS. The
treating investigator and the blinded evaluator will not be allowed to switch roles.
Patients will be instructed to contact the treating investigator for any suspected relapses during the study.
The treating investigator will evaluate patients to confirm suspected relapses throughout the study as
necessary. A relapse is defined as the occurrence of new or worsening neurological symptoms attributable
to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days.
The new or worsening neurological symptoms must be accompanied by objective neurological worsening,
based on examination by the blinded evaluator, consistent with an increase of at least half a point on the

EDSS, or 2 points on one of the appropriate Functional System (FS) scores, or 1 point on two or more of
the appropriate FS scores. The change in FS scale scores should correspond to the patient*s symptoms (e.g.
patient reported change in visual acuity should correspond to a change in the vision FS score). Symptoms
must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever,
infection, injury, adverse reactions to concomitant medications).
Study assessments will include physical examination, vital signs, blood tests and MRI (without and with
Gadolinium contrast). Several of the AEs noted in fingolimod clinical studies may be a consequence of
S1P1R stimulation and will therefore be closely monitored in the study. These AEs include bradycardia and
heart conduction abnormalities (electrocardiogram [ECG] monitoring, vital signs), pulmonary toxicity
(forced expiratory volume at 1 second [FEV1], forced vital capacity (FVC) measurements, and lung
diffusion capacity testing [DLCO] measurements), macular edema (ophthalmic monitoring including
optical coherence tomography [OCT]), cutaneous malignancy (dermatological exams) and hepatotoxicity
(liver function tests [LFTs]).
Patients who experience a relapse may receive treatment with intravenous (IV) corticosteroids. The
following standardized treatment regimen should be used: as warranted, 1.0 g IV methylprednisolone per
day for a maximum of 5 consecutive days. A corticosteroid taper is not allowed. No deviation from the
standardized treatment regimen is allowed unless approved by the Medical Monitor. The Investigator
should attempt to maintain therapies or treatments for symptoms related to MS (e.g., spasticity,
incontinence, pain, fatigue) reasonably constant throughout the study. However, changes may be made if
appropriate for a patient*s well-being in the clinical judgment of the treating investigator.
All efforts will be made to follow patients who discontinue prematurely from the treatment due to lack of
response, AEs, or other reasons, even if alternative treatment is given. These patients will be followed for
collection of safety data, including lymphocyte recovery, and for the assessment of their disease status for a
minimum of 3 months.
The Cognitive Function subscale of the MSQOL-54 will be assessed to evaluate quality of life and

subjective cognitive impairment.

**Intervention**

For all patients, initial study treatment will consist of a 7-day dose titration regimen. For patients randomized to receive active treatment with RPC1063, this regimen will consist of 0.25 mg RPC1063 starting on Day 1 for 4 days, then 0.5 mg RPC1063 starting on Day 5 for 3 days, followed by the assigned treatment level beginning on Day 8.
Eligible patients will be randomized 1:1:1 to receive 1 of the following three regimens for 12 months:
- IFN *-1a 30 *g IM injection weekly
- 0.5 mg RPC1063 oral capsule daily
- 1 mg RPC1063 oral capsule daily
The randomization will be stratified by baseline EDSS (*3.5, >3.5) and country.
This study will use a double-dummy design. Thus, patients randomized to RPC1063 0.5 or 1 mg will also receive weekly matching placebo IM injections and patients randomized to IFN *-1a 30 *g will also receive daily matching placebo oral capsules.
RPC1063 and placebo will be provided as powder-filled capsules. RPC1063 drug substance is blended with Avicel PH-102 microcrystalline cellulose, Cabosil silicon dioxide, croscarmellose sodium and magnesium stearate in Capsugel Coni-Snap, Swedish orange opaque hard-gelatin capsules. Three RPC1063 dosage strengths have been prepared for the clinical investigations; 0.25 mg (size 4 capsule), 0.50 mg (size 4 capsule), and 1.0 mg (size 4 capsule).
For placebo, the same size 4 Capsugel Coni-Snap, Swedish orange opaque hard-gelatin capsules will contain the same blended excipients described above. All three doses of RPC1063 and placebo capsules are identical in appearance.
Study treatment IFN *-1a and matching placebo injections will be supplied in prefilled syringes, which will be dispensed to patients at each visit and will contain a sufficient supply of IFN *-1a (or matching placebo) for each dosing interval.

**Study burden and risks**

Several of the AEs noted in fingolimod clinical studies may be a consequence of S1P1R stimulation and will therefore be closely monitored in the study. These

AEs include bradycardia and heart conduction abnormalities (electrocardiogram [ECG] monitoring, vital signs), pulmonary toxicity
(forced expiratory volume at 1 second [FEV1], forced vital capacity (FVC) measurements, and lung diffusion capacity testing [DLCO] measurements), macular edema (ophthalmic monitoring including optical coherence tomography [OCT]), cutaneous malignancy (dermatological exams) and hepatotoxicity (liver function tests [LFTs]).

# Contacts

**Public**
Receptos

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San Diego CA 92121
US
**Scientific**
Receptos

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US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. MS, as diagnosed by the revised 2010 McDonald criteria
2. Exhibiting a relapsing clinical course consistent with RMS and history of brain MRI lesions consistent with MS

3. Ages 18-55 years, inclusive
4. EDSS score between 0 and 5.0 at baseline
5. Meet one of the following disease activity criteria:
o At least 1 documented relapse within the last 12 months prior to screening
OR
o At least 1 documented relapse occurred within the last 24 months prior to screening and documented evidence of at least 1 GdE lesion on brain MRI within the last 12 months prior to randomization
6. No history of relapse with onset from 30 days prior to screening until randomization; during this period, patients must have been clinically stable, without systemic corticosteroid treatment or adrenocorticotrophic hormone (ACTH)
7. Ability to provide written informed consent and to be compliant with the schedule of protocol assessments
8. Patients of reproduction potential (males and females) must practice an acceptable method of birth control (acceptable methods of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, vasectomy, or double-barrier method [condom or diaphragm with spermicide]) during study participation and for 30 days after their last dose of treatment of study medication or true sexual abstinence (periodic abstinence [calendar, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)
9. Patients must have documentation of positive Varicella zoster virus (VZV) IgG antibody status or complete VZV vaccination at least 30 days prior to randomization

## Exclusion criteria

1. Primary progressive MS at screening
2. Disease duration of more than 15 years in patients with an EDSS *2.0
3. Contraindications to MRI or Gadolinium contrast, such as known allergy to Gadolinium contrast dyes, renal insufficiency, claustrophobia, body size incompatible with the scanner, pacemaker, cochlear implants, intracranial vascular clips
4. Incompatibility with beta IFN use (e.g. intolerable side effects)
5. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (*-hCG) measured during screening
6. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, endocrine, renal, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the patient at risk by participating in the study in the opinion of treating investigator
7. Specific cardiac conditions are excluded, including history or presence of:
i. Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure, sick sinus syndrome, or severe untreated sleep apnea
ii. Prolonged QTcF interval (QTcF > 450 msec males, >470 msec females), or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT-prolonging drugs)
iii. Patients with other pre-existing stable cardiac conditions who have not been cleared for

the study by an appropriate cardiac evaluation by a cardiologist
iv. Other clinically significant conduction abnormalities or any other significant cardiac condition that could jeopardize a patient*s health or put them at significant safety risk during the course of the study in the opinion of treating investigator
8. Resting heart rate less than 55 bpm at Screening
9. Diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c > 9% , or diabetic patients with significant co-morbid conditions such as retinopathy or nephropathy
10. History of uveitis
11. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease [but excluding fungal infection of nail beds, minor upper respiratory tract infections [URTI] and minor skin infections]) or any major episode of infection that required hospitalization or treatment with IV antibiotics within 30 days of screening or oral antibiotics within 14 days prior to screening
12. History or known presence of recurrent or chronic infection; recurring urinary tract infections could be allowed
13. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved)
14. Suicide attempts in the past or current signs of major depression
15. History of alcohol or drug abuse within 1 year prior to randomization
16. History of or currently active primary or secondary immunodeficiency
17. Prior use of any investigational agent within 6 months prior to enrollment
18. Receipt of a live vaccine within 4 weeks prior to screening
19. Non-lymphocyte-depleting disease-modifying MS agents must be discontinued from signing of informed consent
20. Previous treatment with lymphocyte-depleting therapies
21. Treatment with other immunosuppressant agents such as azathioprine, cyclosporine, methotrexate, or mycophenolate within 6 months prior to randomization
22. Systemic corticosteroid therapy or ACTH use within 30 days prior to screening
23. Prior treatment with lymphocyte trafficking blockers
24. Treatment with intravenous immune globulin (IVIg) or plasmapheresis within 3 months prior to randomization
25. Treatment with other disease modifying therapies within 3 months prior to randomization
26. Intolerance of or contraindication to oral or IV corticosteroids
27. Use of therapies that are not allowed based on CYP3A4 metabolism within 4 weeks prior to randomization
28. Treatment with medications with a known impact on the cardiac conduction system are excluded
29. Positive rapid plasma reagin
30. Serum creatinine >1.4 mg/dL for women or >1.6 mg/dL for men
31. Liver function impairment or persisting elevations of aspartate aminotransferase (SGOT/AST) or alanine aminotransferase (SGPT/ALT) >1.5 times the upper limit of normal (ULN), or direct bilirubin >1.5 times the ULN
32. Platelet count <100,000/*L
33 Hemoglobin < 8.5 g/dL
34 Neutrophils < 1500/*L
35 Absolute white blood cell (WBC) count <3500/*L; absolute lymphocyte count <800/*L

36 Clinically significant findings on brain MRI scan consistent with conditions other than MS
37 ECG showing any clinically significant abnormality (e.g., acute ischemia, significant heart conduction abnormality (e.g., left bundle branch block)
38 FEV1 or FVC <70% of predicted values at screening)
39 Presence of >20 gadolinium-enhancing lesions on baseline brain MRI scan
Please refer to the protocol for the remaining Exclusion Criteria

# 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 |
| Enrollment: | 20 |
| Type: | Anticipated |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Avonex |
| Generic name: | INTERFERON BETA-1A |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | RPC1063 |
| Generic name: | Ozanimod |

# Ethics review

| | |
|---|---|
| Approved WMO Date: | 08-01-2015 |
| Application type: | First submission |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 28-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 15-09-2015 |
| Application type: | First submission |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 09-10-2015 |
| 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 | EUCTR2014-002320-27-NL |
| ClinicalTrials.gov | NCT01628393 |
| CCMO | NL51878.096.14 |