Multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose finding study to evaluate the efficacy, safety, and tolerability of three doses of ACT-128800, an oral S1P1 receptor agonist, administered for twenty-four weeks in patients with relapsing-remitting multiple sclerosis

Published: 07-07-2009
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Primary objective1. To demonstrate the efficacy of at least one of three doses of ACT-128800 as compared to placebo in patients withrelapsing-remitting multiple sclerosis (RRMS) on the cumulative number of new gadolinium-enhancing lesionsper patient...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Demyelinating disorders
Study type	Interventional

Summary

ID

NL-OMON35354

Source
ToetsingOnline

Brief title
protocol AC-058B201

Condition

- Demyelinating disorders

Synonym
ms, relapsing remitting multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals
Source(s) of monetary or material Support: Actelion Pharmaceuticals Ltd.

Intervention

Keyword: oral administration, Relapsing Remitting Multiple Sclerosis, selective S1P1receptor agonist

Outcome measures

Primary outcome

Primary efficacy endpoint

• Cumulative number of new gadolinium-enhancing lesions per patient recorded on

T1-weighted MRI scans at Weeks 12, 16, 20, and 24 after study drug initiation.

This endpoint is derived by summing the observed numbers of

new gadolinium-enhancing lesions on MRI scans at Weeks 12, 16, 20, and 24. A

reduction from 8 to 4 (50% decrease compared to placebo) in the mean cumulative

number of the lesions is to be detected.

Secondary outcome

Secondary efficacy endpoints

• Annualized confirmed relapse rate within 24 weeks of study drug initiation.

• Time to first confirmed relapse within 24 weeks of study drug initiation.

A relapse is defined as the occurrence of an acute episode of one or more new

symptoms, or worsening of existing

symptoms of MS, not associated with fever or infection, and lasting for at

least 24 hours after a stable period of at least

30 days.

A *confirmed relapse* is a relapse accompanied by an increase from baseline of

at least 0.5 point in the EDSS score, or

one point in the score for at least one of the Functional System (FS) scores,

excluding the bowel and bladder, and mental FS. The confirmatory EDSS must be

performed within 7 days of the onset of a new symptom or worsening of an

existing

symptom of MS. Symptoms of transient neurological worsening that do not meet

the criteria for *confirmed relapse* because unaccompanied by objective

findings but still judged to constitute a relapse by the treating neurologist,

will be recorded as *unconfirmed relapse* and included in the number of total

relapses.

Only confirmed relapses are included in the secondary efficacy analyses. For

exploratory efficacy endpoints both confirmed

and total relapses are analyzed.

Exploratory efficacy endpoints

1. Other MRI-related variables:

• Cumulative number of total gadolinium-enhancing lesions (a lesion may be

counted twice on two consecutive MRI scans) per patient recorded on T1-weighted

MRI scans at Weeks 12, 16, 20, and 24

after study drug initiation.

• Number of patients with no (new and total) gadolinium-enhancing lesions on

T1-weighted MRI scans at Weeks 12, 16, 20, and 24.

• Cumulative number of (new and total) gadolinium-enhancing lesions per patient on T1-weighted MRI scans at Weeks 4, 8, 12, 16, 20, and 24.

• Number of (new and total) gadolinium-enhancing lesions per patient on a T1-weighted MRI scan at Week 24.

• Number of patients with no (new or total) gadolinium-enhancing lesions on a T1-weighted MRI scan at Week 24.

• Total volume of (new and total) gadolinium-enhancing lesions per patient on T1-weighted MRI scans at Weeks 12, 16, 20, and 24.

• Cumulative number of new or enlarging lesions per patient on T2-weighted MRI scans at Weeks 12, 16, 20, and 24.

• Change from baseline to Week 24 in total lesion volume per patient on T2-weighted MRI scans.

• Cumulative number of combined unique active lesions (new gadolinium-enhancing lesions plus new or enlarging T2 lesions without gadolinium-enhancement) per patient on MRI scans at Weeks 12, 16, 20, and 24.

• Change from baseline to Week 24 in brain volume.

• Additional MRI parameters may be evaluated as appropriate.

2. Relapse over the 24-week treatment period:

• Annualized total relapse rate within 24 weeks of study drug initiation

• Time to first (total) relapse within 24 weeks of study drug initiation.

• Number of (confirmed and total) relapses.

• Number of patients without any (confirmed and total) relapse.

• Number of patients with a relapse requiring corticosteroid treatment.

3. Neurological assessments:

• Categorical change from baseline to Week 24 in EDSS and FS scores.

4. Ophthalmological assessments:

• Change from baseline to Week 24 of average retinal nerve fiber layer (RNFL)

thickness, central foveal

thickness and total macular volume as measured by optical coherence tomography

(OCT) at selected

centers.

• Change from baseline to Week 24 of average number of letters correctly read

in a best corrected visual acuity

test (recorded only at centers that also perform OCT).

5. Quality of life assessments:

• Change from baseline in quality of life based on the following two

questionnaires to be completed by the

patients at baseline, Week 12, and Week 24 (only in countries for which

validated translations are available):

* Multiple Sclerosis Impact Scale 29 (MSIS-29).

* Modified Fatigue Impact Scale (mFIS).

6. Additional exploratory endpoints:

• If appropriate, other exploratory endpoints derived from the clinical

database, will be analyzed based on

data-driven considerations. For safety and tolerability endpoints and

pharmacokinetic and pharmacodynamic endpoints see page 70-71 of protocol.

Study description

Background summary

Multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study to evaluate the efficacy, safety, and tolerability of three doses of ACT-128800, an oral S1P1 receptor agonist, administered for twenty-four weeks in
patients with relapsing-remitting multiple sclerosis.

Study objective

Primary objective
1. To demonstrate the efficacy of at least one of three doses of ACT-128800 as compared to placebo in patients with
relapsing-remitting multiple sclerosis (RRMS) on the cumulative number of new gadolinium-enhancing lesions
per patient, recorded on T1-weighted MRI scans at Weeks 12, 16, 20, and 24 after study drug initiation.
Secondary objectives
1. To evaluate the effects of ACT-128800 on the annualized confirmed relapse rate within 24 weeks of study drug initiation.
2. To evaluate the effects of ACT-128800 on time to first confirmed relapse within 24 weeks of study drug initiation.
3. To evaluate the safety and tolerability of ACT-128800.

Study design

Prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, four-arm, parallel group, dose-finding, Phase 2b superiority study.

Intervention

One capsule of ACT-128800, administered orally in the morning with or without breakfast (preferably always in the
same way and at approximately the same time).

• Group I: 10 mg for 24 weeks until EOT
• Group II: 10 mg from Day 1 to Day 7, 20 mg from Day 8 until EOT
• Group III: 10 mg from Day 1 to Day 7, 20 mg from Day 8 to Day 14, 40 mg from Day 15 until EOT
One capsule of matching placebo, administered orally in the morning with or without breakfast (preferably always in the
same way and at approximately the same time).
• Group IV: placebo for 24 weeks until EOT.

Study burden and risks

Hospital visits x13
Bloodsample x11 (average of 8 ml blood taken)
Physica examination x12
MRI x8
Chest X-ray x2
ECG x 31
Pulmonary function test x 10
Ophthalmological Assessment x 5
Questionnaire x3
Echocardiography x3 (in selected centers)
24-hour Holter ECG x5

Headache, dizziness, fatigue, a transient drop in heart rate after administration of the first dose of ACT-128800, asymptomatic, intermittent AV-block second degree Mobitz type I/Wenckebach after administration of first dose of 10 mg ACT-128800, QT prolongation after administration of first dose of 10 mg ACT-128800. A reduction in FEV1 (observed with the 40 mg dose) has been reported in previous clinical trials with ACT-128800. Due to immunosuppression in general there may be an increased risk of opportunistic infections and skin cancers. However, this has not been seen in previous clinical trials with ACT-128800.

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. Males and females aged 18 to 55 years (inclusive).
2. Women of childbearing potential must:
• Have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.
• Agree to use two methods of contraception from the screening visit until 8 weeks after study drug discontinuation.
Of the two contraceptive methods, one must be from Group 1, and one must be from Group 2, defined as follows:
* Group 1: Oral, implantable, transdermal or injectable hormonal contraceptives, intrauterine devices, female sterilization (tubal ligation), or partner*s sterilization (vasectomy). If a hormonal contraceptive will be chosen from this group, it must have been taken for at least 1 month prior to randomization.
* Group 2: Condoms, diaphragm or cervical cap, all in combination with spermicide.
Abstention and rhythm methods are not acceptable methods of contraception.
3. Presenting with a diagnosis of RRMS as defined by the revised (2005) McDonald Diagnostic Criteria for Multiple Sclerosis (MS).
4. Ambulatory and with an Expanded Disability Status Scale (EDSS) score between 0 and 5.5 (inclusive).
5. With at least one of the following characteristics of RRMS:
• One or more documented relapse(s) within 12 months prior to the screening visit,
• Two or more documented relapses within 24 months prior to the screening visit,
• At least one gadolinium-enhancing lesion detected on T1-weighted MRI at the Screening visit (based on central reading).
6. In a stable clinical condition:

• Without a clinical exacerbation of MS for at least 30 days prior to randomization (exacerbation of MS is defined as one or more new symptom(s), or worsening of existing symptoms, not associated with fever or infection, and lasting for at least 24 hours).
7. Signed informed consent prior to initiation of any study-mandated procedure.

Exclusion criteria

1. Breast-feeding women.
2. A diagnosis of MS categorized as primary progressive or
secondary progressive or progressive relapsing.
3. Treatment with
Within 30 days prior to randomization:
• Systemic corticosteroids or adrenocorticotropic hormone (ACTH)
• Treatment with β-blockers, diltiazem, verapamil, or digoxin or QTprolonging
drugs (as listed in Appendix 9), for any indication
Within 3 months prior to randomization:
• Interferon or glatiramer acetate
• Systemic immunosuppressive treatment (e.g., cyclosporine, sirolimus, mycophenolic acid)
• Vaccination with live vaccines
• Plasma exchange (plasmapheresis, cytapheresis)
• Treatment with an investigational drug (within 3 months or 5 half-lives of the drug, whichever is
longer), except biological agents (see below)
Within 6 months prior to randomization:
• Azathioprine or methotrexate
• Natalizumab (or previous failure to natalizumab)
• Intravenous immunoglobulin
• Non-lymphocyte-depleting biologic agents (e.g., daclizumab)
At any time prior to randomization:
• Cyclophosphamide, mitoxantrone, or cladribine
• Lymphocyte-depleting biologic agents such as alemtuzumab or rituximab
4. Patient currently treated for an autoimmune disorder other than MS.
5. Contraindications for MRI such as:
• Pacemaker, any metallic implants such as artificial heart valves, aneurysm/vessel clips and any metallic material in high-risk areas
• Known allergy to any gadolinium contrast agent
• Severe renal insufficiency defined as a creatinine clearance < 30 mL/min according to the Cockroft-Gault formula
• Claustrophobia
6. Ongoing bacterial, viral or fungal infection (with the exception of onychomycosis and dermatomycosis), positive hepatitis B surface antigen or hepatitis C antibody tests.
7. Congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection.
8. Negative antibody test for varicella-zoster virus at screening.
9. History or presence of malignancy (except for surgically excised basal or squamous cell

skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation or bone marrow transplantation.
10. Poorly controlled type I or type II diabetes.
11. Macular edema or diabetic retinopathy (as confirmed within 30 days prior to randomization).
12. History of clinically significant drug or alcohol abuse.
13. Any of the following cardiovascular conditions:
• Resting heart rate (HR) < 55 bpm, as measured by the pre-randomization ECG on Visit 3 (Day 1).
• History or presence of ischemic heart disease.
• History of or current valvular heart disease.
• History of or current heart failure (NYHA Class III or IV).
• History or presence of rhythm disorders (e.g., sino-atrial heart block, sick sinus syndrome, second or third-degree atrioventricular (AV) block, symptomatic bradycardia, atrial flutter or atrial
fibrillation) or ongoing anti-arrhythmic therapy.
• History of syncope.
• Uncontrolled arterial hypertension.
14. Any of the following pulmonary conditions:
• Moderate or severe bronchial asthma or chronic obstructive pulmonary disease (COPD) stage II-IV, i.e., forced expiratory volume in 1 second (FEV1) < 70% of forced vital capacity (FVC), i.e., FEV1/FVC ratio < 0.7.
• History of pulmonary fibrosis (scarring of the lung), pulmonary Langerhans*cell histiocytosis.
• History of tuberculosis, chest X-ray findings at screening or within the previous 3 months, suggestive of active or latent tuberculosis or absence of a negative test result for tuberculosis at screening based on an interferon gamma release assay.
15. Abnormal liver function tests as defined by elevations of ALT/SGPT or AST/SGOT > 2-fold the upper limit of the normal range (ULN) or total bilirubin > 1.5-fold ULN.
16. Any of the following abnormal laboratory values:
• White blood cell (WBC) count < 3,500/µL
• Hemoglobin (Hb) < 10 g/dL
• Lymphocyte count < 1,000/µL
• Platelets < 100,000/µL
17. Known allergy to any of the study drug excipients.
18. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the patient at risk by participating in the study.
19. Patients who are confined by order of either judicial or administrative authorities.
20. Patients unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits or known likelihood of not completing the study including mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study.

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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-04-2010
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ACT-128800
Generic name:	ACT-128800

Ethics review

Approved WMO Date:	07-07-2009
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	03-11-2009
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam

	(Amsterdam)
Approved WMO Date:	27-11-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	02-12-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	20-04-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	26-04-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	24-01-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	31-01-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

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	EUCTR2008-006786-92-NL
CCMO	NL27374.003.09