A two-year, double-blind, randomized, multicenter, active controlled, study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a i.m. once weekly in pediatric patients with multiple sclerosis with five-year fingolimod Extension Phase

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON53151

Source
ToetsingOnline

Brief title
CFTY720D2311 fingolimod in pediatric MS patients.

Condition

- Neurological disorders NEC

Synonym
multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: active controlled, fingolimod, multiple sclerosis, pediatric

Outcome measures

Primary outcome

EDSS, MRI, MS relapses.

Secondary outcome

Adverse events, Physical examination (including skin examination), sexual

development, ophthalmological examination, pulmonology, lab assessments, ECG,

Questionnaires.

Study description

Background summary

Fingolimod (FTY720) is an oral drug for the treatment of multiple sclerosis (MS), it is an immunosupperssivum. Fingolimod reduces the number of activated T-cells in the blood and in the CNS by the binding to sphingosine-1-phosphate receptor-1 {S1 P1) on circulating lymphocytes. This binding leads to a reversible sequestration of T cells, causing auto-aggressive T cells, as it were in peripheral lymphocyte tissue to be locked, and cannot migrate to sites of inflammation in the CNS.
Fingolimod gives a reduction of the number of MS relapse rate and leads to an improvement of the MRI image and of inflammatory markers.
The incidence of pediatric MS is not known, but it is estimated that approximately 5% (variously estimated range from 0.4 to 10.5%) of MS cases will

manifest in childhood and adolescence, and that less than 2% will do before the age of 10.

Study objective

The purpose of this study is to seek regulatory approval for use of fingolimod in a pediatric population with MS aged 10 to less than 18 years old. This study is conducted in line with the Pediatric Investigational Plan agreed with the EMA (under EU pediatric regulation (EC) No 1901/2006) and the post-marketing requirements in the US.

Study design

A study with a duration of 84-month (7 years).
The core phase (maximum 2 years) a double-blind, randomized, active-controlled, parallel-group multicenter study to evaluate the efficacy and safety of fingolimod compared to IFN β-1a in children/adolescent patients aged 10-17 (i.e. have not yet had their 18th birthday at randomization) with MS. Followed by a 5-year open-label extension phase with fingolimod.

The study consists of two phases: a pre-randomization phase consisting of screening and baseline periods and a double-blind treatment phase.

After obtaining informed consent, patients will enter the screening and baseline periods of the pre-randomization phase to confirm eligibility for the study. On Day 1, the first visit in the treatment phase, eligible patients will be randomized to one of the two treatment arms (fingolimod or IFN β-1a). The treatment phase will last up to 24 months.
Afterwards, the participant will have the opportunity to be treated for 5 years with (open label) fingolmod.

Intervention

Treatment with fingolimod or Interferon B 1-a (core phase, maximum 2 years) followed by treatment with fingolimod (extension phase, 5 years).

Study burden and risks

Risk:
Side effects of study medication.

Burden:
Core Phase:
Study visits: screening, baseline, day 1, 14 and 28, monthly for six months, then every 3 months.
(Almost) at all visits vital signs, blood test and pregnancy test (only if

relevant).
Monthly (partly home). pregnancy testing for sexually active girls.
Neurological and physical examination every 3 months.
Ophthalmological examination (including OCT measurement) during the first year every 3 months, then every half year
Lung function tests during screening, M1, 3, 6, and then every six months.
Dermatological examination at the beginning and end of the study.
ECG at screening, day 1, 1 month, then annually.
MRI annually.
X-ray of the left wrist and hand every 6 months.
Completing the C - SSRS (questionnaire to suicidal tendencies) by phone; each visit except visite M 1.5, 4 and 5.
Completion of Pediatric Quality of Life questionnaire annually.

Extensie fase:
17 visits; 8 visits in first year, as of year 2 twice a year plus 3 months after End Of Treatment (EOT) visit a Follow-Up (FU) visit.
Pregnancy test (if relevant): monthly (partly at home)
(Almost) at all visits: vital signs, blood collection
Physical examination: 3x in year 1, as of year 2 yearly and at FU visit
X-ray of the left wrist and hand: twice a year (not at EOT ann FU visit)
Skin examination: As of year 1 twice a year and at EOT visit
Ophthalmological examination: Month 3 (v19), month 6, year 1, as of year 2 if needed and at EOT visit
Lung function tests: Month 2 (v17), month 3, month 6, year 1, as of year 2 if needed and at EOT visit
ECG: Day 1, month 2, year 1, as of year 2 yearly and at EOT visit
MRI: Month 6, year 1, as of year 2 yearly and at EOT visit
EDSS: As of month 3 at every visit
Completion of C-SSRS: every visit
Completion of Pediatric Quality of Life questionnaire: yearly (not at FU visit).

Contacts

Public
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL
Scientific
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

Core phase:
1. Male and female patients aged 10-17 years old, inclusive (i.e., have not yet had their 18th birthday) at randomization.
2. A diagnosis of MS as defined by the revised consensus definition for pediatric MS (Krupp et al 2013, Polman et al 2011).
3. Central review of the diagnosis of pediatric MS will be required for all patients prior to randomization.
4. At least one MS relapse/attack during the previous year or two MS relapses in the previous two years prior to screening, or evidence of one or more Gd enhancing lesions on MRI within 6 months prior to randomization (including screening MRI).
5. Expanded Disability Status Scale (EDSS) score of 0 to 5.5, inclusive.,
Extension Phase:
Criterion applies to all patients entering the Extension Phase;
- Patients that originally met Core Phase Inclusion criteria and completed the Core phase on or off of study drug.

Criterion applies to patient newly recruited to participate in the Extension Phase:
Younger cohort is defined as the population of pediatric patients fulfilling any single one or a combination of the following criteria: being 12 or younger of age, weighing 40 kg or less, or being pre-pubertal (Tanner stage less than 2)
1. All newly recruited patients* that enroll directly into the Extension Phase must fulfill

the local country health authority product label approved for pediatric age group for
inclusion criteria. Countries that do not have the 0.25mg dose formulation of fingolimod
approved according to local label, may only enroll patients within the younger cohort who
have a body weight above 40 kg and be prescribed the 0.5mg dose level according to
local label.
2. Central review (including initial MRI report) of the diagnosis of pediatric MS
(Thompson et al 2018) will be required for all newly recruited patients.

Exclusion criteria

Core and extension phase:
1. Patients with progressive MS.
2. Patients with widespread and symmetric white matter alterations in the Screening MRI suggestive of other demyelinating disorders (e.g. metabolic disorders, mitochondrial disorders).
3. Patients meeting the definition of ADEM (Krupp et al 2013); patients meeting critieria for neuromyelitis optica (Wingerchuk et al 2006) or tested positive for aquaporin 4 (AQP4) at Screening. Patients who have tested positive for anti-MOG (applicable for patients enrolling in the new younger cohort in extension phase)
4. Patients with active systemic bacterial, viral or fungal infections, including tuberculosis.
5. Patients without acceptable evidence of immunity to varicella-zoster virus, mumps, measles, rubella, diphteria, tetanus and pertussis at randomization/ first dose in the extension phase.
6. Patients with any severe cardiac disease or significant findings on the screening ECG.
7. Positive results of screening period testing for serological markers for hepatitis A, B, C, and E indicating acute or chronic infection.,
Extension phase:
Criteria apply to patients who completed the Core Phase, but prematurely discontinued study drug;
- Premature discontinuation of the study drug during the Core Phase due to an adverse event, serious adverse event, laboratory abnormality or conditions leading to permanent study drug discontinuation due to safety reasons as described in the protocol.
- Patients with known new events or concomitant medications that would exclude them from the Core Phase exclusion criteria.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-01-2015
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gilenya
Generic name:	fingolimod
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-02-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-10-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-06-2015
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	17-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	07-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-10-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2011-005677-23-NL
ClinicalTrials.gov	NCT01892722
CCMO	NL45701.078.13