Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on cladribine tablets − CLARION

First published: 27/06/2018

Last updated: 26/10/2026

Study Ongoing

Administrative details

EU PAS number

EUPAS24484

Study ID

47525

DARWIN EU® study

No

Study countries

Australia

Belgium

- Canada
- Croatia
- Czechia
- Denmark
- Finland
- Germany
- Italy
- Kuwait
- Lebanon
- Netherlands
- Norway
- Sweden
- Switzerland
- Türkiye
- United States

Study description

This Post-authorisation safety study (PASS) is a multi-country, multi-center, long-term, prospective, observational study evaluating the safety in patients with highly active relapsing remitting multiple sclerosis (R(R)MS) newly initiating cladribine tablets (cladribine cohort) as compared to R(R)MS patients newly initiating fingolimod (comparator cohort).

The study is projected to last for a maximum of 15 years, with a maximum 5-year recruitment period until both cohorts have reached 4,000 patients and with a follow-up of 10 years for each patient.

The study will only use pre-existing registries or databases and is based on a mixed data collection model relying on secondary use of data and additional (primary) data collection. For each patient, data collection will begin after the signature of the informed consent form – noting that patient consent applies to countries where primary data collection will be conducted and to some

countries where secondary use of data will be performed –and will continue during 10 years, as each patient will be followed-up for a period of 10 years, except if s/he is lost to follow-up, or withdrawn his/her consent, or dies before the end of the follow-up period.
Follow-up will continue regardless of cladribine tablet or fingolimod discontinuation.

Study status

Ongoing

Research institutions and networks

Institutions

IQVIA

United Kingdom

First published: 12/11/2021

Last updated: 22/04/2024

Institution **Non-Pharmaceutical company** **ENCePP partner**

Contact details

Study institution contact

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Primary lead investigator

Mickael Arnaud

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 05/10/2017

Actual: 05/10/2017

Study start date

Planned: 14/09/2018

Actual: 25/09/2018

Data analysis start date

Planned: 01/09/2033

Date of interim report, if expected

Planned: 30/09/2021

Actual: 30/09/2021

Date of final study report

Planned: 30/09/2034

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Merck KGaA

Study protocol

20180626_MS700568-0002 CLARION protocol v1.0__Redacted.pdf (1.52 MB)

MS700568_0002-Protocol-Version 6.0_Redacted.pdf (1.63 MB)

MS700568_0002-Protocol-Version 6.0_Redacted.pdf (1.63 MB)

MS700568_0002-Protocol-CLARION-v4.0_Redacted.pdf (3.13 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

EU RMP category 3 (required)

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Combined primary data collection and secondary use of data

Study design:

Multi-country, multi-center, long-term, prospective, observational cohort study. The study is projected to last 15 years, with an anticipated 5-year recruitment period until both cohorts have reached 4,000 patients and with a follow-up of 10 years for each patient.

Main study objective:

To further characterize and compare the risk, in terms of incidence of AESI (malignancies [all], severe infections, herpes zoster, tuberculosis, PML, other opportunistic infections, and seizures) in patients with highly active R(R)MS newly initiating cladribine tablets or fingolimod.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

MAVENCLAD

GILENYA

Study drug International non-proprietary name (INN) or common name

CLADRIBINE

FINGOLIMOD

Anatomical Therapeutic Chemical (ATC) code

(L04AA40) cladribine

cladribine

(L04AE01) fingolimod

fingolimod

Medical condition to be studied

Multiple sclerosis

Relapsing multiple sclerosis

Population studied

Short description of the study population

Patients newly initiating cladribine tablets or fingolimod according to the local label for MS, after the date of cladribine tablets launch in the relevant country.

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)

- Adults (75 to < 85 years)
- Adults (85 years and over)

Estimated number of subjects

8.000

Study design details

Setting

The study will only use pre-existing registries or databases and is based on a mixed data collection model relying on secondary use of data and primary data collection.

Comparators

R(R)MS patients newly initiating fingolimod.

Outcomes

Primary outcomes (on cohort level):

• Number of AESIs (malignancies [all], severe infections, herpes zoster, tuberculosis, PML, other opportunistic infections, and seizures) in patients with highly active R(R)MS newly initiating cladribine tablets or fingolimod.

Secondary outcomes (on cohort level):

• Number of AESIs in patients with highly active R(R)MS newly initiating cladribine tablets or fingolimod by prior use of immunomodulatory/ immunosuppressive agents;

• Number of severe lymphopenia events in patients with highly active R(R)MS newly initiating cladribine tablets;

• Number of patients by DMT (immunosuppressive or immunomodulatory agents) after cladribine tablets treatment in patients with highly active R(R)MS

newly initiating oral cladribine;
• Number of AESIs in patients with highly active R(R)MS by first subsequent use of DMT (immunomodulatory / immunosuppressive agents) after cladribine tablets treatment.
Exploratory outcomes (on cohort level):
• Number of patients switching treatment, overall and by reasons for stopping study drug in patients with highly active R(R)MS newly initiating cladribine tablets or fingolimod;
• Number and time points of severe lymphopenia events and AESI in patients with highly active R(R)MS newly initiating cladribine tablets.

Data analysis plan

Data analysis will be performed using a pooled aggregated dataset based on the data source specific aggregated datasets.
In the primary analysis, using the intention-to-treat (ITT) exposure definition, the crude and adjusted incidence rates of the different AESIs along with 95% CIs will be estimated in both cladribine patients and fingolimod patients.
To compare the adjusted incidence of AESI between cladribine and fingolimod patients, the incidence rates ratios of the AESI together with the 95% CIs will be estimated by Poisson regression models adjusted for the key risk factors (including prior use of immunomodulatory/ immunosuppressive agents).
The impact of the prior use of DMT classified as immunomodulatory/ immunosuppressive agents on the incidence of AESI in patients initiating cladribine or fingolimod will be assessed by stratifying the analyses.
The impact of first subsequent DMT used on the incidence of AESI in patients after cladribine tablets treatment will be assessed grouping DMT as IM or IS.
In the secondary analyses, using the on-treatment exposure definition, the crude and adjusted incidence rate of severe lymphopenia among cladribine patients as well as the 95% CI will be estimated using Poisson regression models. As for the primary analysis, the adjustments will be done for the key

risk factors and results displayed by means of forest plots.

Documents

Study publications

The CLARION study design and status update: a long-term, registry-based study e...

The CLARION study: first report on safety findings in patients newly initiating...

Harmonized Data Quality Indicators Maintain Data Quality in Long-Term Safety St...

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

Conflict(s) of interest of investigators.pdf (782.08 KB)

Composition of steering group and observers

MS700568-0002 CLARION protocol v1.9_Composition of Steering Committee and Observers.pdf (8.37 KB)

MS700568-0002 CLARION_Composition of Steering Committee_v4.0.pdf (364.42 KB)

Signed code of conduct

2018-0051_Declaraton compliance with Code.pdf (415.96 KB)

ENCePPCoCAnnex3_DeclarationofcompliancewiththeENCePPCodeofConduct__signed_IB_R (361.19 KB)

Signed code of conduct checklist

2018-0051_CoC checklist.pdf (2.44 MB)

ENCePPCoCAnnex2_ChecklistofCodeofConduct__signed IB 11JUN2021.pdf (530.36 KB)

Signed checklist for study protocols

2018-0051_Checklist for Study Protocol.pdf (296.45 KB)

CLARION_v4.0.Checklist for Study Protocol_Redacted.pdf (212.19 KB)

Data sources

Data source(s), other

• Multiple sclerosis management system 3 Dimension, Germany
• Italian multiple sclerosis and related disorders Registry
• MSBase: Australia, Belgium, Canada, Croatia, Kuwait, Lebanon, the Netherlands and Turkey
• The national healthcare and MS registers in Denmark, Finland, Norway, and Sweden
• The Swiss MS Cohort (Switzerland)
• US DOD

Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No