About the Phase III PARADIGMS study
Media Fact Sheet

Background

- Approximately 2.3 million people worldwide are affected by multiple sclerosis (MS), of which **3-5% are estimated to be children** (pediatric MS).[1,2]
- Pediatric MS is the appearance of MS symptoms in young people **aged up to 18 years old**.[3]
- Pediatric MS is associated with **more frequent relapses than adults with MS**[4], resulting in:
    - **Physical and cognitive (e.g. memory) disabilities** which severely limit patients' ability to go about daily activities, like going to school.[5]
    - **An earlier accumulation of physical disability**, compared to those diagnosed as adults.[1,6]
- **Progression to secondary progressive MS** (SPMS), a highly disabling form of MS, occurs on average **10 years earlier** in pediatric MS patients than in those diagnosed as adults.[4]
- There is currently **no treatment indicated for children and adolescents living with MS, based on randomized, controlled, clinical study data**; there is a **significant unmet need for new, safe and effective treatments** for these patients.
- Sponsored by Novartis, the Phase III PARADIGMS study was initiated to investigate whether **Gilenya® (fingolimod) is a safe and effective treatment option for children and adolescents with MS**.

PARADIGMS study design

- PARADIGMS (**NCT01892722**) is the **first ever controlled, randomized trial specifically designed for pediatric MS**.
- Initiated in 2013, PARADIGMS was conducted in **87 sites over 25 countries**.
- PARADIGMS was designed in partnership with the **US Food and Drug Administration**, **European Medicines Agency** and the **International Pediatric Multiple Sclerosis Study Group**.

PARADIGMS study design: key information[7]

Aim:	Evaluate the safety and efficacy of daily oral fingolimod versus weekly interferon beta-1a intramuscular injections in children and adolescents with MS
Design:	Flexible duration (up to two years), double-blind, randomized, multi-center study, followed by a five-year open label extension phase
Enrollment:	Two hundred and fifteen children and adolescents with MS, aged between 10 and 17 years. Patients had an Expanded Disability Status Scale (EDSS) score between 0 and 5.5
Randomization:	Oral fingolimod once daily (0.5 mg or 0.25 mg, dependent on body weight) versus intramuscular interferon beta-1a, once weekly
Primary endpoint:	Frequency of relapses (annualized relapse rate) over the course of up to two years

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Secondary endpoints:	• Number of new or newly enlarged T2 lesions and Gd-enhancing T1 lesions in the brain, per year (annualized rate) • Safety • Pharmacokinetic properties of fingolimod

PARADIGMS results

- In October 2017, Novartis announced **positive full results from the Phase III PARADIGMS study**, **also presented at the 7th Joint European and Americas Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS-ACTRIMS) meeting** in Paris, France.
- **The study met its primary and secondary endpoints**, showing that Gilenya treatment resulted in:
    - **An 82% reduction in the rate of relapses** (annualized relapse rate) over a period of up to two years versus interferon beta-1a (p <0.001).[8]
    - A **significant reduction in the number of new / newly enlarging T2 and Gd-enhancing T1 lesions in the brain**, as measured by magnetic resonance imaging (MRI). The number and volume of lesions are associated with increased relapses and disability progression.[8]
    - Individuals treated with fingolimod had **significantly less brain shrinkage** (measured by MRI as brain volume loss), compared to those treated with interferon beta-1a[8]. Brain shrinkage in adults is associated with the loss of physical and cognitive function[9].
    - The **safety profile** of Gilenya was overall **consistent with that seen in previous clinical trials, with more adverse events reported in the interferon group**.[8]
    - In an additional analysis, Gilenya **significantly delayed disability progression**, defined as Confirmed Disability Progression (CDP), compared to interferon beta-1a[8].

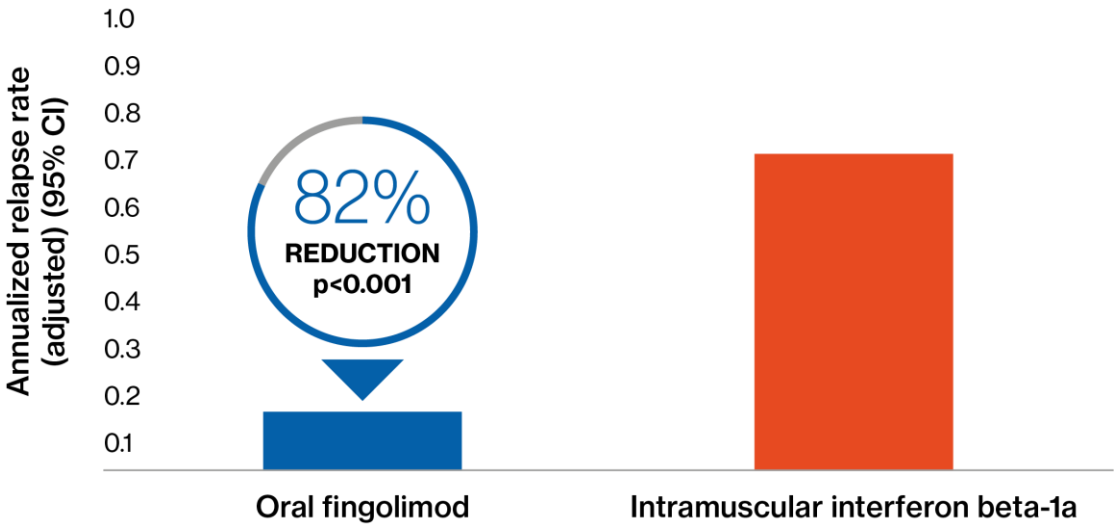

Figure 1: PARADIGMS study results (primary endpoint data)

Next steps

Based on these data, Novartis is working with health authorities to discuss regulatory submissions for fingolimod in pediatric patients.

About Gilenya® (fingolimod)

- Gilenya is not currently approved for the treatment of pediatric MS.
- Gilenya is approved in the US and Switzerland for the first-line treatment of relapsing forms of MS in adults and in the EU for adult patients with highly-active relapsing-remitting MS (RRMS) defined as either high disease activity despite treatment with at least one DMT, or rapidly-evolving severe RRMS.[10,11]

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