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 onset MS).[1,2]
- Pediatric onset MS is the appearance of MS symptoms in young people **aged up to 18 years old**.[3]
- MS in children and adolescents 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]

In May 2018 the US Food and Drug Administration (FDA) approved Gilenya® (fingolimod) for the treatment of children and adolescents, ages 10 to less than 18, with relapsing forms of MS (RMS).[6] This approval makes Gilenya **the first disease-modifying therapy (DMT) indicated for these patients in the US**.

The approval was based on data from the Phase III PARADIGMS study of **Gilenya in children and adolescents with MS**. PARADIGMS was the **first ever controlled, randomized trial specifically designed for children and adolescents with relapsing forms of MS**.[7,8]

Gilenya has been approved in the US for the first-line treatment of adults with RMS since 2010.[6]

PARADIGMS study design

- The **PARADIGMS study** (**NCT01892722**) was initiated in 2013 and enrolled 215 patients at **80 centers in 25 countries**.[9]
- PARADIGMS was designed in partnership with the **US FDA**, the **European Medicines Agency** and the **International Pediatric Multiple Sclerosis Study Group**.

PARADIGMS study design: key information[9]

Aim:	Evaluate the safety and efficacy of daily oral Gilenya 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, ages 10 to less than 18. Patients had an Expanded Disability Status Scale (EDSS) score between 0 and 5.5
Randomization:	Oral Gilenya once daily (0.5 mg, or 0.25 mg for patients with a body weight ≤40 kg) versus once weekly intramuscular interferon beta-1a (30 µg)
Primary endpoint:	Frequency of relapses (annualized relapse rate) over the course of active treatment, up to two years
Key Secondary endpoint:	• Number of new or newly enlarged T2 lesions and gadolinium (Gd)-enhancing T1 lesions in the brain, per year (annualized rate)
Other secondary endpoints	• Time to first confirmed relapse • The percentage of patients free of relapse up to 24 months

- The volume of Gd-enhancing T1 lesions and percentage of patients free of these lesions up to 24 months
- Percentage change in brain volume from baseline (pre-specified exploratory endpoint)
- Safety and side-effect profile of Gilenya and interferon beta-1a in all the patients who received treatment for up to 24 months

PARADIGMS results

- Full results from the Phase III PARADIGMS study **showed the study met its primary and secondary endpoints**, showing that Gilenya treatment resulted in:
  - **An 82% relative reduction in the rate of relapses** (annualized relapse rate) over a period of up to two years versus interferon beta-1a ($p<0.001$)
  - **A delay in the time to first relapse;** an estimated 85.7% of patients treated with Gilenya were relapse-free at 24 months, versus 38.8% of patients treated with interferon beta-1a[7,8]
  - A **significant relative reduction in the number of new or newly enlarging T2 and Gd-enhancing T1 lesions in the brain** versus interferon beta-1a, as measured by magnetic resonance imaging (MRI). Compared to patients receiving interferon beta-1a, T2 lesions were reduced by 53% ($p<0.001$) and Gd+ lesions by 66% ($p<0.001$) with Gilenya.[8] The number and volume of lesions are associated with increased relapses and disability progression.[7]
  - Individuals treated with Gilenya had **significantly less brain shrinkage,** measured by MRI as brain volume loss (40% reduction in annualized rate of brain volume loss), compared to those treated with interferon beta-1a.[7] Brain shrinkage in adults is associated with the loss of physical and cognitive function.[10]
  - The **safety profile** of Gilenya was overall **consistent in this study with that seen in previous clinical trials.**[7]

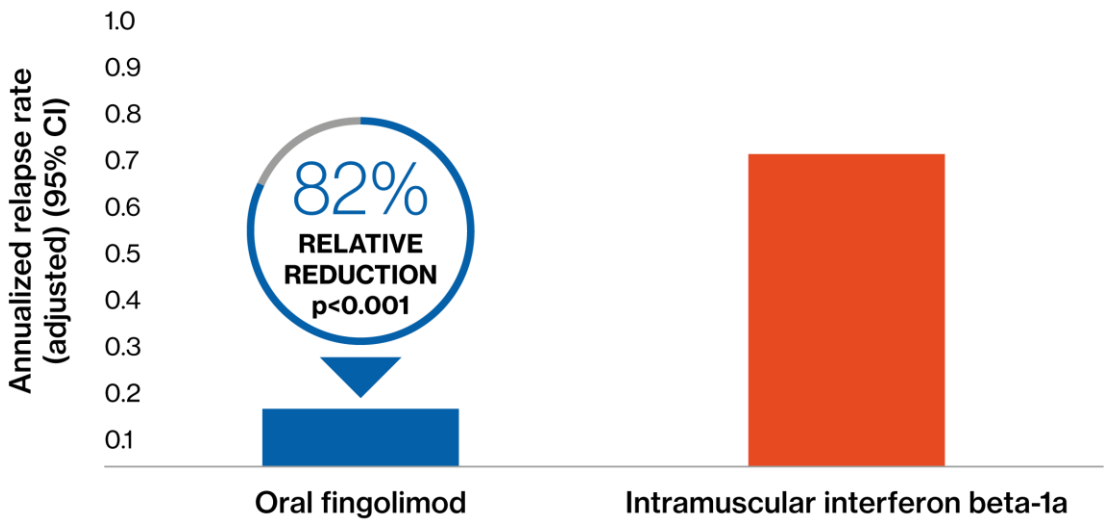

Figure 1: PARADIGMS study results (primary endpoint data)

About Gilenya® (fingolimod)

- Gilenya is approved in the US for the first-line treatment of relapsing forms of MS in adults, and in children and adolescents ages 10 to less than 18 years of age.[11]
- In the EU, Gilenya is approved 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.[11,12]
- Gilenya is currently under review with the European Medicines Agency as a treatment for children and adolescents with MS.

References

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