

Novartis announces NEJM publication of landmark PARADIGMS study demonstrating significant benefit of Gilenya® in children and adolescents with MS

- *Treatment with Gilenya (fingolimod) substantially reduced the debilitating impact of MS, with significant decreases in key measures of disease activity vs. interferon beta-1a*
- *MS severely affects the everyday lives of children and adolescents with the disease and carries a significant impact throughout their lifetime*
- *Gilenya, a leading oral therapy for relapsing MS, is the only treatment approved by the US FDA for patients from 10 years of age through to adulthood*

Basel, September 12, 2018 – Novartis today announced that *The New England Journal of Medicine (NEJM)* has published full results from the landmark Phase III Gilenya® (fingolimod) PARADIGMS study, the first-ever controlled, randomized study specifically designed for children and adolescents (aged 10 to 17) with relapsing forms of MS (RMS). Children and adolescents with MS experience more frequent and often more severe relapses than those seen in adults with MS¹. The negative effect of relapses on movement, memory and thinking prevents patients from enjoying their childhood and adolescent years to the full, often leaving them feeling isolated and anxious². PARADIGMS met the primary endpoint of significantly reducing the rate of relapses when compared to interferon beta-1a intramuscular injections over a period of up to two years³. The study also met several secondary clinical and imaging endpoints³.

“I’d like to thank all the children who participated in the PARADIGMS study, and their families, who have helped transform the outlook for pediatric patients living with relapsing MS,” said Dr. Tanuja Chitnis, Principle Investigator for PARADIGMS and Director of the Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, Boston, US, and Scientist, Ann Romney Center, Brigham and Women’s Hospital, Boston, US. “These data, published today, will go a long way in helping to advance knowledge and understanding amongst the MS community of how to evaluate and treat pediatric patients with MS.”

Results from PARADIGMS show that, compared to interferon beta-1a, Gilenya³:

- Significantly reduced relapse rates by 82% (p<0.001) and delayed 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 (p<0.001)
- Significantly reduced the number of new or newly enlarged T2 lesions up to 24 months by 53% (p<0.001). Also, it significantly reduced the average number of gadolinium enhancing T1 (Gd+) lesions per scan at 24 months by 66.0% (p<0.001). The number and volume of lesions are associated with increased relapse rates and disability progression
- In additional analyses, significantly reduced the annualized rate of brain volume loss (brain shrinkage) by 40%

The safety profile of Gilenya in this study was overall consistent with that seen in previous clinical trials in adults³.

“PARADIGMS exemplifies Novartis’ commitment to reimagining care for young patients with neurological conditions,” said Danny Bar-Zohar, Global Head, Neuroscience Development for Novartis. “It is pioneering in every sense of the word, demonstrating the collaborative approach taken with all stakeholders and disciplines to bring the understanding of the unique attributes of pediatric MS to the next level. Our priority now is to continue discussions with worldwide health authorities to bring Gilenya to young patients in need, as soon as possible.”

Gilenya is a well-established treatment for MS in the adult population, having been used to treat more than 255,000 patients in both clinical trials and the post-marketing setting, with approximately 566,000 years of patient experience⁴.

About the Phase III PARADIGMS study

The Phase III PARADIGMS study (NCT01892722) is a flexible duration (up to two years), double-blind, randomized, multi-center study to evaluate the safety and efficacy of oral Gilenya[®] (fingolimod) compared to interferon beta-1a in children and adolescents with a confirmed diagnosis of multiple sclerosis (MS), followed by a five-year open label extension phase³. The study enrolled 215 children and adolescents with MS, 10 to less than 18 years of age with an Expanded Disability Status Scale (EDSS) score between 0 and 5.5³. Patients were randomized to receive once-daily oral Gilenya (0.5 mg or 0.25 mg, dependent on patients’ body weight) or intramuscular interferon beta-1a once weekly³.

The primary endpoint of the study was the frequency of relapses in patients treated up to 24 months (annualized relapse rate)³. Secondary endpoints include the number of new or newly enlarged T2 lesions, gadolinium-enhancing T1 lesions, safety and the pharmacokinetic properties of Gilenya, all measured throughout the treatment period³.

The Phase III PARADIGMS study was conducted in 80 centers in 25 countries, and was designed in partnership with the US Food and Drug Administration, the European Medicines Agency and the International Pediatric Multiple Sclerosis Study Group³.

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS) that disrupts the normal functioning of the brain, optic nerves and spinal cord through inflammation and tissue loss⁵. In adults, there are three types of MS: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS)⁶. Approximately 85% of people with MS have RRMS, where the immune system attacks healthy tissue⁷. In children and adolescents, RRMS accounts for nearly all cases (approximately 98 percent)¹.

The evolution of MS results in an increasing loss of both physical and cognitive (e.g. memory) function. This has a substantial negative impact on the lives of the approximately 2.3 million people worldwide affected by MS, of which between three and five percent are estimated to be children or adolescents^{7,8}.

About Gilenya (fingolimod)

Gilenya[®] (fingolimod) is an oral disease-modifying therapy (DMT) that is highly efficacious at controlling disease activity in relapsing multiple sclerosis (RMS)⁹. Gilenya has a reversible lymphocyte redistribution effect targeting both focal and diffuse central nervous system (CNS) damage caused by MS^{10,11}. Long-term clinical trial and real-world evidence and experience has shown Gilenya treatment to be convenient for individuals to incorporate into everyday life, leading to high treatment satisfaction, long-term persistence, and ultimately, improved long-term outcomes for people with RMS^{12,13}.

Gilenya impacts four key measures of RMS disease activity: relapses, MRI lesions, brain shrinkage (brain volume loss) and disability progression^{14,15}. Its effectiveness on all of these measures has been consistently shown in multiple controlled clinical studies and in the real-

world setting. Studies have shown its safety and high efficacy to be sustained over the long term, demonstrating that switching to Gilenya treatment as early in the disease course as possible can be beneficial in helping to preserve individuals' function^{16,17}.

Gilenya is approved in the US for the first-line treatment of relapsing forms of MS in adults, and children and adolescents ages 10 to less than 18 years of age⁹. 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 RRMS¹⁸. Gilenya is currently under review with the European Medicines Agency as a treatment for children and adolescents with MS.

About Novartis in Multiple Sclerosis

Alongside Gilenya[®] (fingolimod, a modulator of the S1P receptor subtypes 1,3,4 and 5), Novartis' multiple sclerosis (MS) portfolio includes Extavia[®] (interferon beta-1b for subcutaneous injection) which is approved in the US for the treatment of relapsing forms of MS. In Europe, Extavia is approved to treat people with relapsing-remitting MS, secondary progressive MS (SPMS) with active disease and people who have had a single clinical event suggestive of MS.

Investigational compounds include siponimod (BAF312, a selective modulator of the S1P receptor subtypes 1 and 5), for SPMS, and ofatumumab (OMB157), a fully human monoclonal antibody in development for relapsing MS. Ofatumumab targets CD20, and is currently being investigated in two Phase III pivotal studies.

In the US, the Sandoz Division of Novartis markets Glatopa[®] (glatiramer acetate injection) 20 mg/mL and 40 mg/mL, generic versions of Teva's Copaxone[®].

*Copaxone[®] is a registered trademark of Teva Pharmaceutical Industries Ltd.

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Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 125,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit <http://www.novartis.com>.

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References

1. Waldman A et al. Pediatric multiple sclerosis. *Neurology*. 2016; 87(9): S74-S81.
2. MS Society. Children and MS. <https://www.mssociety.org.uk/what-is-ms/types-of-ms/ms-in-children#MS%20and%20school> (link is external). Accessed September 2018.
3. Chitnis T et al. Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis. *NEJM* 2018; 379(11): 1017-1027.
4. Novartis data on file.
5. PubMed Health. Multiple Sclerosis (MS). <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001747/> (link is external). Accessed September 2018.
6. MS Society. Types of MS. <https://www.mssociety.org.uk/what-is-ms/types-of-ms> (link is external). Accessed September 2018.
7. Multiple sclerosis International Federation. Atlas of MS 2013. <https://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf> (link is external). Accessed September 2018.
8. Patel Y et al. Pediatric multiple sclerosis. *Ann Indian Acad Neurol*. 2009; 12(4): 238-245.
9. Gilenya US Prescribing Information. <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gilenya.pdf> (link is external). Accessed September 2018.
10. Brinkmann V et al. FTY720 (fingolimod) in Multiple Sclerosis: therapeutic effects in the immune and the central nervous system. *Br J Pharmacol*. 2009; 158(5): 1173-1182.
11. De Stefano N et al. Effect of fingolimod on diffuse brain tissue damage in relapsing-remitting multiple sclerosis patients. *Mult Scler Relat Disord*. 2016; 7: 98-101.
12. Warrender-Sparkes M et al. The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis. *Mult Scler*. 2016; 22(4): 520-532.
13. Khatri B et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. *Lancet Neurol*. 2011; 10(6): 520-529.
14. Giovannoni G et al. "No evident disease activity": The use of combined assessments in the management of patients with multiple sclerosis. *Mult Scler*. 2017. Doi 10.1177/1352458517703193.
15. De Stefano N et al. Effect of Fingolimod on Brain Volume Loss in Patients with Multiple Sclerosis. *CNS Drugs*. 2017; 31(4): 289-305.
16. Kappos L et al. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. *Mult Scler*. 2016; 22(10): 1297-1305.
17. Lizac N et al. Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2017; 88(3): 196-203.
18. Gilenya EMA Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf (link is external). Accessed September 2018.

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