**Referenced submission (with links) for Ocrevus (ocrelizumab)**

**Background information and need for innovation**

Nearly 1 million people in the U.S. are living with MS.[[1]](#footnote-1) They are most often diagnosed as young or middle-aged adults — in their 20s through 40s — and experience cognitive impairment, physical disabilities and mobility issues that can significantly impact their lives.

The disease’s impact on quality of life cannot be overstated; instead of focusing on building their families or careers, they contend with symptoms such as fatigue, difficulty walking, impaired vision and bladder issues. Many lose their jobs as the disease progresses due to physical and neurological impairments.[[2]](#footnote-2) It’s not uncommon for people with MS to need wheelchairs, mobility aids and caregivers just to meet their daily needs.

While we’ve seen progress in the fight against MS, there remains no cure for the disease. Historically, MS treatments focused on reducing relapses in relapsing MS (RMS). Still, people with this form of the disease frequently had to choose between higher efficacy medicines that came with serious risks or medicines that provided limited efficacy to slow underlying, chronic disease progression.

Meanwhile, the 15% of people with MS who had the primary progressive form of the disease (PPMS) were left without a disease-modifying medicine at all. But this form is one of the most disabling forms of MS marked by steadily worsening symptoms, typically without distinct relapses or periods of remission, and are most in need of safe and effective treatment options to slow disease progression.[[3]](#footnote-3)

Before the introduction of Ocrevus, there clearly remained a significant need for an innovative medicine that offered the potential for more effective control of disease symptoms and progression so people living with MS could live more independent and fuller lives.

**History of the development of your innovation**

T cells were long believed to be the main culprit in the underlying biology of MS. However, based on a growing body of evidence suggesting a pivotal role for B cells in the immunopathology of MS, Dr. Stephen Hauser, then Chair of the Department of Neurology at University of California, San Francisco (UCSF) and current Director of the UCSF Weill Institute for Neurosciences, began discussions to test B-cell depletion in MS in 2001.[[4]](#footnote-4)

Dr. Hauser wanted to test this theory with an existing CD20-targeted B-cell depleting therapy; however, the MS research community was skeptical and an attempt to obtain public funding to conduct a clinical trial failed.

Genentech recognized the need for innovative medicines in MS and supported Dr. Hauser’s Phase 2 studies in RMS and PPMS. Insights from these proof-of-concept studies clearly demonstrated that Dr. Hauser was onto something — selective depletion of CD20-expressing B-cells appeared to be a potential approach to treating MS.

Inspired by this compelling data, Roche and Genentech launched a large clinical trial program comprised of three Phase 3 trials – two in RMS and one in PPMS – to thoroughly test the new treatment approach with a next-generation B-cell targeting drug — the anti-CD20 antibody, Ocrevus.

The pivotal results in RMS were astounding. Inflammatory lesion activity in the brain was nearly completely suppressed, the annualized relapse rate was dramatically reduced, and disability progression was cut by nearly half when compared to interferon beta-1a.[[5]](#footnote-5) The first-ever positive data slowing disability progression in PPMS were also game-changing.[[6]](#footnote-6) When these data were initially presented at an international congress, neurologists were astonished by the compelling results.

The first-of-their-kind results led to Ocrevus being the first approved anti-CD20 medicine for MS and the first and only medicine approved in the U.S., and other countries around the world, to treat both RMS and PPMS.[[7]](#footnote-7)

**Why your product is innovative**

Our approach to targeting B cells began a new era for the MS community and has redefined our understanding of MS biology. Our trials showed that B cells play a central role in the disease, and that underlying disease progression occurs in all forms of MS.

The FDA recognized the potential of Ocrevus and granted Breakthrough Therapy designation for PPMS in Feb 2016 and a Priority Review of the licensing application for RMS and PPMS in June 2016. Ocrevus was the first and only medicine for both RMS and PPMS approved by the FDA. Five years later, it remains the only disease-modifying medicine for PPMS in the U.S.

Ocrevus’ potential was proven in three Phase 3 trials.5,6 In two RMS trials, Ocrevus demonstrated superior efficacy in three major markers of disease activity and progression vs. high-dose interferon beta-1a.5 In the PPMS trial, Ocrevus was the first to significantly slow disability progression and reduce signs of disease activity in the brain vs. placebo.6

In all pivotal studies, the Ocrevus group experienced a low rate of serious adverse events.5,6

The RMS indication was updated in 2019 to include clinically isolated syndrome and active secondary progressive MS. A shorter, two-hour infusion was approved in 2020.[[8]](#footnote-8) We are advancing its development across more than 30 ongoing clinical trials. Long-term data continue to demonstrate a consistent benefit-risk profile for Ocrevus over nine years.

Today, Ocrevus has treated 300,000 people globally and is approved in over 100 countries. And we remain dedicated to expanding access to new patient groups with our ongoing Ocrevus trial program. We are studying higher dose and subcutaneous formulas in Phase 3 trials and the safety of Ocrevus in pregnant and breastfeeding women.

Ocrevus — and its unique mechanism of action — has transformed the MS treatment landscape.

**Pubmed Links for Ocrevus publications**

[Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet*. 2011;378(9805):1779-1787.](https://pubmed.ncbi.nlm.nih.gov/22047971/)

[Hauser S, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *New England Journal of Medicine* 2017; 376:221-234 DOI: 10.1056/NEJMoa1601277.](https://pubmed.ncbi.nlm.nih.gov/28002679/)

[Montalban X, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *New England Journal of Medicine* 2017; 376:209-220 DOI: 10.1056/NEJMoa1606468](https://pubmed.ncbi.nlm.nih.gov/28002688/)

[Havrdová E, Arnold DL, Bar-Or A, et al. No evidence of disease activity (NEDA) analysis by epochs in patients with relapsing multiple sclerosis treated with ocrelizumab vs interferon beta-1a. *Mult Scler J Exp Transl Clin*. 2018;4(1):2055217318760642.](https://pubmed.ncbi.nlm.nih.gov/29568544/)

[Wolinsky JS, Montalban X, Hauser SL, et al. Evaluation of no evidence of progression or active disease (NEPAD) in patients with primary progressive multiple sclerosis in the ORATORIO trial. *Ann Neurol*. 2018;84(4):527-536.](https://pubmed.ncbi.nlm.nih.gov/30155979/)

[Fox EJ, Markowitz C, Applebee A, et al. Ocrelizumab reduces progression of upper extremity impairment in patients with primary progressive multiple sclerosis: Findings from the phase III randomized ORATORIO trial. *Mult Scler*. 2018;24(14):1862-1870.](https://pubmed.ncbi.nlm.nih.gov/30415593/)

[Turner B, Cree BAC, Kappos L, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. *J Neurol*. 2019;266(5):1182-1193.](https://pubmed.ncbi.nlm.nih.gov/30820738/)

[Mayer L, Kappos L, Racke MK, et al. Ocrelizumab infusion experience in patients with relapsing and primary progressive multiple sclerosis: Results from the phase 3 randomized OPERA I, OPERA II, and ORATORIO studies. *Mult Scler Relat Disord*. 2019;30:236-243.](https://interpublic-my.sharepoint.com/personal/dmalkin_webershandwick_com/Documents/Microsoft%20Teams%20Chat%20Files/pubmed.ncbi.nlm.nih.gov/30844611/)

[Barkhof F, Kappos L, Wolinsky JS, et al. Onset of clinical and MRI efficacy of ocrelizumab in relapsing multiple sclerosis. *Neurology*. 2019;93(19):e1778-e1786.](https://pubmed.ncbi.nlm.nih.gov/31484710/)

[Elliott C, Belachew S, Wolinsky JS, et al. Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis. *Brain*. 2019;142(9):2787-2799.](https://pubmed.ncbi.nlm.nih.gov/31497864/)

[Wolinsky JS, Engmann NJ, Pei J, Pradhan A, Markowitz C, Fox EJ. An exploratory analysis of the efficacy of ocrelizumab in patients with multiple sclerosis with increased disability. *Mult Scler J Exp Transl Clin*. 2020;6(1):2055217320911939.](https://pubmed.ncbi.nlm.nih.gov/32206332/)

[Hartung HP; ENSEMBLE Steering Committee members and study investigators. Ocrelizumab shorter infusion: Primary results from the ENSEMBLE PLUS substudy in patients with MS. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e807.](https://pubmed.ncbi.nlm.nih.gov/32503093/)

[Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. *JAMA Neurol*. 2020;77(9):1132-1140.](https://pubmed.ncbi.nlm.nih.gov/32511687/)

[Hauser SL, Kappos L, Arnold DL, et al. Five years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. *Neurology*. 2020;95(13):e1854-e1867.](https://pubmed.ncbi.nlm.nih.gov/32690791/)

[Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: The VELOCE study. *Neurology*. 2020;95(14):e1999-e2008.](https://pubmed.ncbi.nlm.nih.gov/32727835/)

[Wolinsky JS, Arnold DL, Brochet B, et al. Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: a post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2020;19(12):998-1009.](https://pubmed.ncbi.nlm.nih.gov/33129442/)

[Hartung HP, Berger T, Bermel RA, et al. Shorter infusion time of ocrelizumab: Results from the randomized, double-blind ENSEMBLE PLUS substudy in patients with relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord*. 2020;46:102492.](https://pubmed.ncbi.nlm.nih.gov/33039944/)

[Bermel RA, Waubant E, Pardo G, et al. Safety evaluation of shorter infusion for ocrelizumab in a substudy of the Phase IIIb CHORDS trial. *Ann Clin Transl Neurol*. 2021;8(3):711-715.](https://pubmed.ncbi.nlm.nih.gov/33621404/)

[Gibiansky E, Petry C, Mercier F, et al. Ocrelizumab in relapsing and primary progressive multiple sclerosis: Pharmacokinetic and pharmacodynamic analyses of OPERA I, OPERA II and ORATORIO. *Br J Clin Pharmacol*. 2021;87(6):2511-2520.](https://pubmed.ncbi.nlm.nih.gov/33202059/)

[Cree BAC, Pradhan A, Pei J, Williams MJ; OPERA I and OPERA II clinical investigators. Efficacy and safety of ocrelizumab vs interferon beta-1a in participants of African descent with relapsing multiple sclerosis in the Phase III OPERA I and OPERA II studies. *Mult Scler Relat Disord*. 2021;52:103010.](https://pubmed.ncbi.nlm.nih.gov/34147885/)

[Hauser SL, Kappos L, Montalban X, et al. Safety of Ocrelizumab in Patients With Relapsing and Primary Progressive Multiple Sclerosis. *Neurology*. 2021;97(16):e1546-e1559.](https://pubmed.ncbi.nlm.nih.gov/34475123/)

[Vermersch P, Oreja-Guevara C, Siva A, et al. Efficacy and safety of ocrelizumab in patients with relapsing-remitting multiple sclerosis with suboptimal response to prior disease-modifying therapies: A primary analysis from the phase 3b CASTING single-arm, open-label trial. *Eur J Neurol*. 2022;29(3):790-801.](https://pubmed.ncbi.nlm.nih.gov/34748672/)

[Giovannoni G, Kappos L, de Seze J, et al. Risk of requiring a walking aid after 6.5 years of ocrelizumab treatment in patients with relapsing multiple sclerosis: Data from the OPERA I and OPERA II trials. *Eur J Neurol*. 2022;29(4):1238-1242.](https://pubmed.ncbi.nlm.nih.gov/33724637/)

[Butzkueven H, Spelman T, Horakova D, et al. Risk of requiring a wheelchair in primary progressive multiple sclerosis: Data from the ORATORIO trial and the MSBase registry. *Eur J Neurol*. 2022;29(4):1082-1090.](https://pubmed.ncbi.nlm.nih.gov/33724638/)

[Arnold DL, Sprenger T, Bar-Or A, et al. Ocrelizumab reduces thalamic volume loss in patients with RMS and PPMS. *Mult Scler*. 2022;28(12):1927-1936.](https://pubmed.ncbi.nlm.nih.gov/35672926/)

[Longbrake EE, Hua LH, Mowry EM, et al. The CELLO trial: Protocol of a planned phase 4 study to assess the efficacy of Ocrelizumab in patients with radiologically isolated syndrome. *Mult Scler Relat Disord*. 2022;68:104143.](https://pubmed.ncbi.nlm.nih.gov/36031693/)

[Garcia A, Dugast E, Shah S, et al. Immune Profiling Reveals the T-Cell Effect of Ocrelizumab in Early Relapsing-Remitting Multiple Sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(3):e200091.](https://pubmed.ncbi.nlm.nih.gov/36810163/)

[Hauser SL, Bar-Or A, Weber MS, et al. Association of Higher Ocrelizumab Exposure With Reduced Disability Progression in Multiple Sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(2):e200094.](https://pubmed.ncbi.nlm.nih.gov/36792367/)

**Supplemental information**

Although there were 15 medicines available for RMS at the time Ocrevus was approved, hundreds of prescriptions for Ocrevus were received each day for both RMS and PPMS soon after its launch. Today, ~60% of new therapy starts or switches in MS are to an anti-CD20 treatment. These statistics highlight the obvious need that Ocrevus continues to fill and speak to how truly transformative Ocrevus has been for patient care in MS.

When Ocrevus was approved, MS medicines were given by a daily pill, injections multiple times per week, or monthly IV infusions. People with MS had a frequent treatment burden. Ocrevus was the first MS medicine to be given every 6 months, which is important for people living with a chronic disease like MS. Less frequent dosing is also important to healthcare professionals, as it can lead to higher adherence and persistence to medications. Claims data have shown that patients on Ocrevus have the highest persistence and superior adherence compared to patients initiating other classes of MS disease-modifying therapies.

1. Walton C, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult Scler*. 2020 Dec;26(14):1816-1821. [↑](#footnote-ref-1)
2. Lorefice L, Fenu G, Frau J, Coghe G, Marrosu MG, Cocco E. The impact of visible and invisible symptoms on employment status, work and social functioning in Multiple Sclerosis. *Work*. 2018;60(2):263-270. [↑](#footnote-ref-2)
3. Raghavan K., et al. Progression rates and sample size estimates for PPMS based on the CLIMB study population. *Mult Scler*. 2015;21(2):180-8. [↑](#footnote-ref-3)
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5. Hauser S, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *New England Journal of Medicine* 2017; 376:221-234. [↑](#footnote-ref-5)
6. Montalban X, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *New England Journal of Medicine* 2017; 376:209-220. [↑](#footnote-ref-6)
7. OCREVUS (ocrelizumab) Prescribing Information. Genentech, Inc., 2017. [↑](#footnote-ref-7)
8. OCREVUS (ocrelizumab) Prescribing Information. Genentech, Inc., 2023. [↑](#footnote-ref-8)