Integrated Review

Table 1. Application Information

Application type	Efficacy Supplement
Application number(s)	BLA 761053/S-38
Priority or standard	Priority
Submit date(s)	11/10/2025
Received date(s)	11/10/2025
PDUFA goal date	5/10/2026
Division/office	Division of Neurology 2 (DN2)
Review completion date	5/7/2026
Established/proper name	Ocrelizumab
(Proposed) proprietary name	Ocrevus
Pharmacologic class	Anti-CD20 monoclonal antibody
Other product name(s)	Not applicable
Applicant	Genentech, Inc.
Dosage form(s)/formulation(s)	Solution for injection
Dosing regimen	Adults and pediatric patients (10 years of age and older, weighing 35 kg or more): • Start dose: 300 mg intravenous infusion, followed 2 weeks later by a second 300 mg intravenous infusion • Subsequent doses: 600 mg intravenous infusion every 6 months Pediatric patients (10 years of age and older) weighing less than 35 kg: • Start dose: 150 mg intravenous infusion, followed 2 weeks later by a second 150 mg intravenous infusion • Subsequent doses: 300 mg intravenous infusion every 6 months
Applicant-proposed indication(s)/ population(s)	The treatment of relapsing-remitting multiple sclerosis, in pediatric patients 10 years of age and older.
SNOMED CT code for proposed indication disease term(s)[1]	426373005 | Relapsing remitting multiple sclerosis (disorder) |
Regulatory action	Approval
Approved dosage (if applicable)	Adults and pediatric patients (10 years of age and older, weighing 35 kg or more): • Start dose: 300 mg intravenous infusion, followed 2 weeks later by a second 300 mg intravenous infusion • Subsequent doses: 600 mg intravenous infusion every 6 months Pediatric patients (10 years of age and older) weighing 25 kg to less than 35 kg: • Start dose: 150 mg intravenous infusion, followed 2 weeks later by a second 150 mg intravenous infusion • Subsequent doses: 300 mg intravenous infusion every 6 months
Approved indication(s)/ population(s) (if applicable)	The treatment of relapsing-remitting multiple sclerosis, in pediatric patients 10 years of age and older who weigh 25 kg or more
SNOMED CT code for approved indication disease term(s)[1]	426373005 | Relapsing remitting multiple sclerosis (disorder) |

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADA	antidrug antibodies
ADEM	acute disseminated encephalomyelitis
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AQP4	aquaporin-4
ARR	annualized relapse rate
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
CI	confidence interval
C_{max}	maximum plasma concentration
COD	cutoff date
COVID-19	coronavirus disease 2019
CPK	creatinine phosphokinase
CRP	C-reactive protein
CSR	clinical study report
DBP	double-blind period
DILI	drug-induced liver injury
DPMH	Division of Pediatrics and Maternal Health
EAER	exposure-adjusted event rate
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
FS	Functional System
GCP	good clinical practice
Gd	gadolinium
GGT	gamma (γ)-glutamyl transferase
HIV	human immunodeficiency virus
HLT	High-Level Term
HSV	herpes simplex virus
ICH	International Council for Harmonisation
IgA	immunoglobulin A
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IgM	immunoglobulin M
IND	investigational new drug
IPMSSG	International Pediatric Multiple Sclerosis Study Group

iPSP	initial Pediatric Study Plan
IV	intravenous
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MOA	mechanism of action
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
OCMQ	Office of New Drugs Custom Medical Query
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
PCR	polymerase chain reaction
PD	pharmacodynamic
PI	Prescribing Information
PK	pharmacokinetic
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement
PO	by mouth
PopPK	population pharmacokinetic
PPMS	primary progressive multiple sclerosis
PREA	Pediatric Research Equity Act
PT	preferred term
PY	patient-years
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SEE	substantial evidence of effectiveness
SFU	safety follow-up
SOC	system organ class
SPMS	secondary progressive multiple sclerosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
U.S.	United States
VZV	varicella zoster virus
WBC	white blood cell

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

The Applicant (Genentech, Inc.) submitted BLA 761053/S-38, an efficacy supplement for intravenously administered ocrelizumab (Ocrevus), an anti-CD20 monoclonal antibody, for the proposed treatment of relapsing remitting multiple sclerosis (RRMS) in pediatric patients 10 years of age and older. Ocrevus was originally approved on March 28, 2017, for the treatment of relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) in adults.

This efficacy supplement for the treatment of RRMS in pediatric patients 10 years of age and older was reviewed by a multidisciplinary review team that did not identify any issues that preclude approval. Each discipline has recommended approval. The signatory authority for this application concurs with those recommendations and agrees that the benefit-risk supports approval.

The Applicant submitted highly persuasive results from a single multicenter adequate and well-controlled study (Study WN42086), which was intended to demonstrate noninferiority of ocrelizumab to fingolimod on annualized relapse rate (ARR). Prior to this application, fingolimod was the only product approved for the treatment of RMS in pediatric patients 10 years of age and older. Based on prespecified and agreed-upon noninferiority criteria, the primary analysis of Study WN42086 demonstrated noninferiority of ocrelizumab to fingolimod in reducing ARR, which is considered a clinically meaningful endpoint. Findings on secondary endpoints included superiority in reducing the annualized rate of new/enlarging T2 hyperintense lesions over the double-blind period (DBP), and superiority in reducing the number of gadolinium (Gd)-enhancing T1 lesions at Week 12. The team concluded that the data were adequate to support approval for pediatric patients 10 years of age and older with RRMS.

The previous approval of Ocrevus for RMS in adults, which is considered a closely related indication, served as confirmatory evidence for this application. The approval in adults with RMS was based on a statistically significant reduction in ARR compared to an approved therapy (interferon beta-1a) in two adequate and well-controlled trials. Though there are some differences in clinical course and severity of adult and pediatric multiple sclerosis (MS), they represent phenotypes of the same autoimmune disease and are thought to have similar underlying pathophysiology.

The results of this single adequate and well-controlled study, plus confirmatory evidence from the prior approval in adults with RMS, provide substantial evidence of effectiveness of ocrelizumab for the proposed indication and therefore support approval for the treatment of RRMS in pediatric patients 10 years of age and older who weigh 25 kg or more. The Applicant did not propose specification of a lower limit of 25 kg for the 300 mg dose; this revision was recommended by the review team because Studies WA39085 and WN42086 only enrolled subjects weighing ≥25 kg.

The available safety data indicates that the safety profile of ocrelizumab in the pediatric population is consistent with that of the adult population, as discussed in current approved labeling. These risks are acceptable for the intended use in the indication under consideration. Identified risks can be mitigated through labeling and further evaluated via routine pharmacovigilance and ongoing postmarketing requirement (PMR) studies. No new PMRs or postmarketing commitments (PMCs) will be issued.

The final study reports for Studies WA39085 and WN42086 included in this submission are considered adequate to fulfill PMR 3194-14 for BLA 761053. Additionally, these studies were also conducted to fulfill a written request (WR), which will be considered fulfilled and pediatric exclusivity granted.

The overall benefit-risk is favorable as described in the benefit-risk framework (Section 2.1). For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this document.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

Study WN42086, a single adequate and well-controlled clinical study, along with confirmatory evidence from the prior approval of Ocrevus in adults with RMS, provide substantial evidence of effectiveness of ocrelizumab for the proposed indication and support the approval for the treatment of RRMS in pediatric patients 10 years of age and older who weigh 25 kg or more.

Study WN42086 was a randomized, double-blind, active-controlled, double-dummy, noninferiority multicenter study involving 185 subjects with RRMS between the ages of 10 and <18 years. Subjects were randomized 1:1 to receive ocrelizumab intravenously or fingolimod orally; ocrelizumab was administered at a dose of 300 mg for subjects with a body weight <35 kg or 600 mg for subjects with a body weight ≥35 kg. The primary efficacy analysis demonstrated that ocrelizumab is noninferior to fingolimod in reducing the frequency of relapses in patients ≥10 years and <18 years with RRMS, as measured by ARR. Secondary magnetic resonance imaging (MRI)-related endpoints indicated superiority of ocrelizumab in reducing the annualized rate of new/enlarging T2 hyperintense lesions over the DBP, and superiority in reducing the number of gadolinium-enhancing T1 lesions at Week 12, compared to fingolimod.

Confirmatory evidence was comprised of the previous approval of Ocrevus for RMS in adults, which is considered a closely related indication. The approval in adults with RMS was based on a statistically significant reduction in ARR compared to an approved therapy (interferon beta-1a) in two adequate and well-controlled trials. Though there are some differences in clinical course and severity of adult and pediatric MS, they represent phenotypes of the same autoimmune disease and are thought to have similar underlying pathophysiology.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disease affecting the central nervous system. • Relapsing forms of MS are defined by the occurrence of clinical relapses, which are events characterized by new onset neurological symptoms associated with disability, from which there is variable recovery. Relapsing forms of MS include clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS. Pediatric onset MS is almost always relapsing, and progressive forms of MS are rare in the pediatric population. • The prevention of relapses is paramount to the treatment of patients with relapsing forms of MS, in order to prevent new neurological symptoms that can lead to temporary or permanent disability.	Treatment of RMS is intended to reduce the frequency of clinical relapses. Clinical relapses can be permanently disabling and reduce quality of life.
Current treatment options	• There are over 20 products approved for treatment of relapsing forms of MS, but only Gilenya (fingolimod) is approved for use in the pediatric population with MS (≥10 years of age). • Currently approved MS therapeutics have demonstrated efficacy in reducing the risk of clinical relapse, which is presumed to be related to immunomodulatory or immunosuppressive mechanisms of action that impact the neuroinflammatory aspect of the disease.	Treatment of RMS generally involves immunomodulation or immunosuppression intended to reduce the frequency of clinical relapse. Many therapies approved for the treatment of relapsing forms of MS in adults are labeled to prevent accumulation of disability. Currently, only one treatment for MS (fingolimod) is indicated for use in patients ≥10 years of age. In a single adequate and well-controlled trial (Study CFTY720D2311), fingolimod was shown to have a statistically significant and clinically meaningful annualized relapse rate reduction compared to interferon beta-1a in patients with MS who were between 10 and 18 years old.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The basis for the original approval of intravenous ocrelizumab (Ocrevus) in adults with relapsing forms of MS was demonstration of a reduction in the frequency of relapses and in the rates of 12- and 24-week confirmed disability progression with Ocrevus, compared to interferon beta-1a, based on two adequate and well-controlled clinical trials. • The basis for the original approval of Ocrevus in adults with primary progressive MS was demonstration of a reduction in the occurrence of 12- and 24-week confirmed disability progression, as compared to placebo, based on one adequate and well-controlled clinical trial and using the studies conducted in RMS as supportive evidence. • One phase 3 trial in pediatric subjects aged ≥10 years and <18 years with RRMS, which was considered adequate and well-controlled, demonstrated that the ARR with Ocrevus was noninferior to that of fingolimod. Additionally, the trial indicated that Ocrevus was superior to that of fingolimod in terms of annualized rate of new or enlarging T2 MRI lesions over the DBP and number of T1 gadolinium-enhancing lesions at Week 12.	The benefits of treatment with Ocrevus on relapses in pediatric relapsing forms of MS are persuasive and justify the risk. The secondary endpoint results related to reduction in MRI lesion development are supportive of this finding.
Risk and risk management	• The risks of Ocrevus are known to include infusion reactions, serious (including life-threatening and fatal) infections (including respiratory tract infections, herpes infections, and hepatitis B virus reactivation), progressive multifocal leukoencephalopathy, reduction in immunoglobulins, malignancies, immune-mediated colitis, possible increased risk of immunosuppressant effects with other immunosuppressants, interference with the effectiveness of nonlive vaccines, and liver injury. • The Ocrevus phase 3 study in pediatric subjects with RRMS did not identify new risks. • Other uncertainties: The risks of long-term/chronic treatment with Ocrevus starting in childhood or adolescence and continuing through adulthood are unknown.	In patients ages ≥10 years to <18 years, the risks of Ocrevus are similar to those identified in adult patients. Current approved labeling for Ocrevus describes the known risks of treatment with intravenous ocrelizumab.

Abbreviations: MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis

2.2. Conclusions Regarding Benefit-Risk

Multiple sclerosis is a serious, disabling, chronic, immune-mediated, demyelinating, and neurodegenerative disease affecting the central nervous system. Although there are several treatments approved for the treatment of relapsing forms of MS in adults, only fingolimod products (Gilenya, Tascenso ODT, and generic fingolimod) are approved for the treatment of RMS in pediatric patients ≥10 years of age.

Ocrelizumab (Ocrevus) is an anti-CD20 monoclonal antibody approved for the treatment of RMS and PPMS in adults. Substantial evidence of effectiveness for ocrelizumab was established based on two adequate and well-controlled studies demonstrating a significant reduction in relapses compared to an active comparator (interferon beta-1a) in RMS, and a single adequate and well-controlled study in PPMS demonstrating delayed confirmed disability progression compared to placebo. The precise mechanism by which ocrelizumab exerts its therapeutic effects in MS is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

Substantial evidence of effectiveness for the current sBLA was established via a single adequate and well-controlled study plus confirmatory evidence, as described in Section 1.2. The efficacy of ocrelizumab for the treatment of RRMS in pediatric patients 10 to <18 years of age was demonstrated in Study WN42086, a flexible duration, randomized, double-blind, active-comparator (fingolimod) controlled, double-dummy, multicenter, noninferiority study. In Study WN42086, 187 subjects were randomized 1:1 in a blinded fashion to ocrelizumab or fingolimod. Ocrelizumab was noninferior to fingolimod in the reduction of clinical relapses as measured by ARR, and was superior to fingolimod in the reduction of the annualized rate of new or enlarging T2 hyperintense MRI lesions during the DBP, and in the reduction of the number of T1 gadolinium-enhancing lesions at Week 12.

The efficacy results from Study WN42086, in conjunction with the prior approval of ocrelizumab in RMS in adults as confirmatory evidence, support the approval of ocrelizumab for the treatment of RRMS in pediatric patients ≥10 years of age who weigh 25 kg or more. The dosing regimen proposed by the Applicant was supported by data from Studies WA39085 and WN42086. The Applicant originally proposed an indication of "the treatment of relapsing-remitting multiple sclerosis, in pediatric patients 10 years of age and older," but for safety reasons and to align with the eligibility criteria for Studies WA39085 and WN42086, the multidisciplinary review team determined that approval for an indication of "the treatment of relapsing-remitting multiple sclerosis, in pediatric patients 10 years of age and older ***who weigh 25 kg or more***" was appropriate.

The safety database for ocrelizumab was adequate for the intended population and proposed dosing regimen. Overall, the safety experience with ocrelizumab supports an acceptable risk/benefit profile. Any safety findings can be adequately addressed through labeling and pharmacovigilance. Safety concerns discussed in current approved labeling for Ocrevus are infections (including serious or life-threatening infections, hepatitis B reactivation, progressive multifocal leukoencephalopathy (PML), and herpes viral infections), infusion-related reactions, immune-mediated colitis, reduction in immunoglobulins, malignancies, and liver injury. Overall,

the safety profile for ocrelizumab in the pediatric population appeared similar to that in adults. No PMRs or PMCs will be issued.

In summary, based on the review of available efficacy and safety data, the benefits of ocrelizumab clearly outweigh the risks for the treatment of relapsing-remitting multiple sclerosis, in pediatric patients 10 years of age and older who weigh 25 kg or more. The availability of ocrelizumab for pediatric patients with RRMS will provide the second approved treatment option in this age group.

II. Interdisciplinary Assessment

3. Introduction

This review serves as the interdisciplinary assessment for BLA 761053/S-38 for intravenously administered ocrelizumab (Ocrevus). Ocrevus is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against CD20-expressing B-cells. The Applicant developed Ocrevus for the treatment of RRMS in pediatric patients aged 10 years and older.

Multiple sclerosis is a chronic, immune-mediated, demyelinating, and neurodegenerative disorder affecting the central nervous system. The cause of MS is unknown, but is hypothesized to be related to a complex interaction of genetic and environmental risk factors (International Multiple Sclerosis Genetics Consortium et al. 2013; Lublin et al. 2014). MS is the most common cause of nontraumatic neurologic disability in young adults, and it is estimated that approximately 1 million people in the United States (U.S.) have MS (Wallin et al. 2019). Disease manifestations can be diverse, and include weakness, incoordination, visual impairment, sensory loss, gait dysfunction, fatigue, cognitive impairment, and bowel/bladder dysfunction.

Relapsing forms of MS are defined by the occurrence of clinical relapses, which are events characterized by new onset neurological symptoms associated with disability, from which there is variable recovery. Relapsing forms of MS include clinically isolated syndrome, RRMS, and active secondary progressive MS. The prevention of relapses is paramount to the treatment of patients with relapsing forms of MS; relapses degrade the quality of life in patients with MS, and prevention of relapses prevents new neurological symptoms that can lead to disability.

RRMS is the most common MS phenotype, as it accounts for approximately 85% of MS cases at symptom onset (Deshpande et al. 2006). Patients with RRMS present with clinical relapses, from which there is a spectrum of recovery. The median age of RRMS onset is approximately 28 to 30 years (Weinshenker et al. 1989; Confavreux et al. 2003; Confavreux and Vukusic 2006b). In general, the frequency of relapse decreases over time (Tremlett et al. 2008b; Tremlett et al. 2009), with an estimate of relapse decrease by 17% for every 5 years of disease duration (Tremlett et al. 2008b). The decrease in relapse risk is thought to be more pronounced in patients with older age of onset.

Over time, the majority of patients with RRMS transition from predominantly inflammatory to more neurodegenerative driving forces of the disease, with development of secondary progressive multiple sclerosis (SPMS) (Leray et al. 2010). The transition to SPMS is an age-dependent process (Confavreux and Vukusic 2006a; Stankoff et al. 2007; Tutuncu et al. 2013), and it is estimated that approximately 30% to 40% of patients with SPMS have relapses superimposed upon this typical gradual decline (Confavreux et al. 2003; Paz Soldan et al. 2015). The time from RRMS diagnosis to SPMS conversion is age of onset-dependent, and ranges from 18.9 to 20 years for all patients per several natural history studies (Confavreux and Vukusic 2006a; Debouverie et al. 2008; Tremlett et al. 2008a; Tremlett et al. 2008b). Generally, the younger a patient is at the time of RRMS onset, the longer the disease duration prior to SPMS conversion. However, several studies have demonstrated that patients who receive MS treatments have substantially decreased risk of and delayed conversion to SPMS compared to

patients in the pretreatment era (Brown et al. 2007; Trojano et al. 2007; Tedeholm et al. 2013; Bergamaschi et al. 2016; Cree et al. 2016; Brown et al. 2019; Palace et al. 2019). Additionally, use of some therapies approved to treat MS has been shown to delay reaching disability milestones (Brown et al. 2007; Bergamaschi et al. 2016; Cree et al. 2016; Palace et al. 2019).

Patients with MS who have their first clinical event prior to the age of 18 years are considered to have pediatric onset MS. Onset of pediatric MS usually occurs in childhood and early adolescence, and comprises approximately 10% of adults with MS (Lee and Chitnis 2016). The median age of onset of pediatric MS is estimated to be approximately 14 to 16 years (Renoux et al. 2007; Harding et al. 2013).

Patients with pediatric onset MS generally present with similar syndromes as adults with MS, but ataxia, encephalopathy, seizures, and brainstem syndromes are more common in children below the age of 10 (Lee and Chitnis 2016). The majority of patients with pediatric onset MS have a relapsing-remitting course, similar to the natural history of most patients with adult-onset MS. Patients with pediatric onset MS tend to have more complete recovery from relapses despite relatively high relapse frequency early in the disease course compared to adults. Pediatric onset MS patients have longer time to disability milestones but younger median age at these milestones compared to those with adult-onset MS (Renoux et al. 2007; Harding et al. 2013).

There are over twenty products approved for treatment of RMS. Currently approved therapeutics indicated to treat RMS have demonstrated efficacy in reducing the risk of clinical relapse, which is presumed to be related to immunomodulatory mechanisms of action that impact the neuroinflammatory aspect of the disease. Treatments that have a robust benefit in RMS have for the most part been ineffective in the treatment of PPMS. Ocrevus is the only approved treatment for PPMS.

The overall treatment strategy for adult MS, immunomodulation to reduce relapse frequency, is thought to be applicable to the pediatric population as well. However, only fingolimod (Gilenya) is approved for use in pediatric patients ≥10 years of age.

The efficacy of Ocrevus was previously demonstrated in two double-blind, active comparator-controlled trials of subjects with RMS and in one double-blind, placebo-controlled trial of subjects with PPMS. These trials led to its approval on March 28, 2017, for the treatment of RMS (to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease) and PPMS, in adults.

For the current sBLA, the noninferiority of Ocrevus compared to fingolimod in clinical relapse prevention was demonstrated by Study WN42086, a phase 3, randomized, double-blind, double-dummy, parallel-group study that enrolled 187 pediatric subjects with RRMS aged ≥10 to <18 years. Subjects were randomized 1:1 to receive Ocrevus (300 mg for subjects weighing <35 kg or 600 mg for subjects weighing ≥35 kg) + oral placebo (Group A) or fingolimod orally daily + intravenous (IV) placebo (Group B) every 24 weeks, until the last randomized subject completed 24 weeks of double-blind treatment. Following completion of the primary analysis, subjects transitioned to an optional open-label extension (OLE) Period of at least 144 weeks in duration. The primary objective of Study WN42086 was to demonstrate the noninferiority of Ocrevus based on the primary endpoint of ARR, as determined by the number of protocol-defined relapses during the DBP, compared to fingolimod.

Based on current approved labeling for Ocrevus (Genentech 2025), there are several known safety risks for Ocrevus, which were relevant to and informed this sBLA review.

The established and anticipated risks of Ocrevus include:

- Infusion reactions
- Serious (including life-threatening and fatal) infections
  - Respiratory tract infections
  - Herpes infections
  - Hepatitis B virus reactivation
- Progressive multifocal leukoencephalopathy
- Reduction in immunoglobulins
- Malignancies
- Immune-mediated colitis
- Liver injury
- Possible increased risk of immunosuppressant effects with other immunosuppressants
- Interference with the effectiveness of nonlive vaccines

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Noninferiority of Ocrelizumab to Fingolimod

Evaluate whether ocrelizumab is noninferior to fingolimod based on the primary endpoint of ARR.

3.1.1.2. Protocol Deviations of Failure To Maintain Blinding

Evaluate the effects of reported protocol deviations related to failure to maintain blinding.

3.1.1.3. Data Quality Issues and Missing Data

Evaluate the impact of data quality concerns, which are primarily related to classification of pubertal status, timing of Expanded Disability Status Scale (EDSS) assessments in the setting of a reported relapse, and missing data on efficacy analyses.

3.1.2. Key Safety Review Issues

3.1.2.1. Infusion Reactions and Hypersensitivity

3.1.2.2. Infections

3.1.2.3. Reduction in Immunoglobulins

3.1.2.4. Malignancies

3.1.2.5. Immune-Mediated Colitis

3.1.2.6. Liver Injury

3.1.2.7. Cytopenias

3.2. Approach to the Clinical Review

The primary evidence of efficacy and safety for Ocrevus for the proposed indication of RRMS in pediatric patients aged 10 years of age and older was provided by Study WN42086, a single, randomized, noninferiority, double-blind, double-dummy, parallel-group study, which was considered adequate and well-controlled. The active comparator in Study WN42086 was fingolimod, which is the only product approved for the treatment of RMS in pediatric patients. The open-label, parallel-group, dose-finding, phase 2 Study WA39085 provided supportive safety data.

The safety assessment was based on the Applicant's reports and on clinical data scientist and clinical reviewer analyses of the submitted data. Safety analyses were provided by the clinical data scientist.

The efficacy assessment focused on the establishment of noninferiority of Ocrevus to fingolimod, which was evaluated in Study WN42086 based on the primary endpoint of ARR, based on the number of protocol-defined relapses during the DBP. Confirmation of the efficacy analyses was provided by the biometrics reviewer. Table 3 provides an overview of Studies WN42086 and WA39085.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

1. Verbatim indication:

   -the treatment of relapsing-remitting multiple sclerosis, in pediatric patients 10 years of age and older who weigh 25 kg or more

2. SEE was established with
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

   c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)[2]
3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established

1 FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, draft guidances will represent the FDA's current thinking on a topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998). Guidances are updated periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fdaguidance-documents.

[3] FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

Table 3. Clinical Studies Submitted in Support of Efficacy and/or Safety Determinations[1] for Ocrevus

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
WA39085/ NCT04075266	Pediatric subjects with RRMS aged ≥10 to <18 years	Phase 2 Control type: None Randomization: Actual enrolled Blinding: OL Biomarkers: N/A Innovative design features: None	Drug: Ocrelizumab Dosage: 300 mg or 600 mg IV infusion Number treated: 23 Duration: 24 weeks	Primary PK: Serum concentration of ocrelizumab at specified timepoints Primary PD: CD19+ B-cell counts Secondary: Safety	12 to 36 planned; 23 enrolled	12 sites, 3 countries (United States [5], Poland [4], and Italy [3])

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
WN42086/ NCT05123703	Pediatric subjects with RRMS aged ≥10 to <18 years	Phase 3 Control type: Active-controlled Randomization: R Blinding: DB Biomarkers: N/A Innovative design features: None	Drug: Ocrelizumab + PO placebo (Group A) or fingolimod + IV placebo (Group B) Dosage: Group A: Ocrelizumab 300 mg (body weight <35 kg) or 600 mg (body weight ≥35 kg) IV infusion every 24 weeks + PO placebo. Group B: fingolimod 0.25 mg (body weight ≤40 kg) or 0.5 mg (body weight >40 kg) PO daily + IV placebo Number treated: Group A: 93; Group B: 94 Duration: Flexible (at least 24 weeks)	Primary: Annualized relapse rate based on the number of protocol-defined relapses during the DBP (noninferiority) Secondary: Number of new or enlarging T2 hyperintense lesions during the DBP, number of T1 gadolinium-enhancing lesions at Week 12; protocol-defined ARR during DBP (superiority)	171 planned; 187 enrolled	79 sites, 25 countries (United States [10], Italy [7], Mexico [7], Brazil [6], Spain [6], Poland [5], France [4], Serbia [4], Germany [3], Greece [3], Portugal [3], Ukraine [3], Canada [2], Estonia [2], Hungary [2], India [2], Romania [2], Argentina [1], Australia [1], Austria [1], Belgium [1], Latvia [1], Morocco [1], Switzerland [1], and United Kingdom [1])

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled."
Abbreviations: ARR, annualized relapse rate; DB, double-blind; IV, intravenous; N/A, not applicable; NCT#, national clinical trial identifier; OCR, ocrelizumab; OL, open-label; PD, pharmacodynamic; PK, pharmacokinetic; PO, by mouth; R, randomized; RRMS, relapsing-remitting multiple sclerosis

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome (patient-reported Pediatric Quality of Life Inventory [PedsQL], PedsQL Multidimensional Fatigue Scale, Patient Global Impression of Change)	Data not discussed but provided general supportive background information.
☒	Observer-reported outcome (caregiver-reported Pediatric Quality of Life Inventory, Caregiver Global Impression of Change)	Data not discussed but provided general supportive background information.
☒	Clinician-reported outcome	In Study WN42086, protocol-defined relapses, which served as the basis for the primary endpoint of ARR, were defined based on changes in the EDSS score, a clinician-reported outcome. This study was the single adequate and well-controlled study that served as the basis for substantial evidence of effectiveness for this sBLA. This outcome is discussed in Sections 3, 6, and 16.
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Ocrelizumab is a humanized IgG1 monoclonal antibody that binds human and nonhuman primate CD20. As described in the nonclinical review to support the original approval of BLA 761053 (DARRTS ID: 4015041), in vitro and in vivo studies indicated that ocrelizumab depletes CD20+ B-cells through antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and/or apoptosis.

5.2. Clinical Pharmacology/Pharmacokinetics

Refer to current approved labeling for Ocrevus (ocrelizumab) for details on clinical pharmacology and pharmacokinetic (PK) characteristics of ocrelizumab (Genentech 2025). Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20-expressing B-cells, while preserving the capacity for B-cell reconstitution and preexisting humoral immunity. Ocrelizumab selectively depletes CD20-expressing B-cells through binding to the CD20 cell surface antigen, which is present on pre-B-cells, mature B-cells, and memory B-cells.

In the current sBLA, the Applicant seeks approval of ocrelizumab for pediatric patients 10 years of age and older with RRMS. This sBLA includes results from two clinical studies: Study WA39085, a dose-finding phase 2 study that evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of ocrelizumab in 23 pediatric subjects aged 10 to <18 years with RRMS; and Study WN42086, a phase 3 study comparing efficacy of ocrelizumab to fingolimod in 187 pediatric subjects (93 ocrelizumab; 94 fingolimod) aged 10 to <18 years with RRMS.

Pharmacokinetics in Pediatric Patients

Population pharmacokinetic (PopPK) analysis incorporating data from Studies WA39085 (n=23) and WN42086 (n=93) demonstrated that pediatric subjects aged 10 to <18 years receiving weight-based dosing (300 mg for subjects <35 kg; 600 mg for subjects ≥35 kg) achieved exposures comparable to adult exposures. Following administration of ocrelizumab 300 mg for subjects <35 kg or 600 mg for subjects ≥35 kg as two IV infusions given 14 days apart, followed by a single IV infusion every 6 months. The exposure parameters in pediatric subjects after the first dose are noted in Table 5 below.

Table 5. Ocrelizumab Exposure Parameters in Pediatric Subjects

Parameter	Median (Range)
AUC_{24W} (µg/mL·day)	3,130 (1,700-5,370)
C_{max} (µg/mL)	147 (95.4-223)

Source: Section 5.3.3 Pharmacometrics Assessment
Abbreviations: AUC_{24W}, area under the concentration-time curve from time 0 to Week 24; C_{max}, maximum plasma concentration

Pharmacodynamics in Pediatric Subjects

CD19+ B-cell count in blood serves as the pharmacodynamic (PD) biomarker for ocrelizumab. In Study WN42086, treatment with ocrelizumab led to rapid and sustained near-complete B-cell depletion in blood in pediatric subjects by 2 weeks after administration, which was maintained throughout the DBP.

Immunogenicity in Pediatric Subjects

In Study WA39085, no treatment-emergent antidrug antibodies (ADAs) to ocrelizumab were detected (0/23 subjects). In Study WN42086, two out of 90 evaluable pediatric subjects (2.2%) developed treatment-emergent ADAs to ocrelizumab. Given the low incidence, the impact of treatment-emergent ADAs on pharmacokinetics, pharmacodynamics, efficacy, and safety, could not be determined.

5.3. Clinical Pharmacology Assessment

The clinical pharmacology characteristics of ocrelizumab IV in adult patients with multiple sclerosis were previously reviewed and are detailed in the clinical pharmacology review of BLA 761053 dated September 16, 2016 (DARRTS ID: 3986651). The current pediatric supplement review focuses on the clinical pharmacology of ocrelizumab in pediatric subjects aged 10 to <18 years with RRMS, supported by data from Studies WA39085 and WN42086.

5.3.1. Individual Study Review

5.3.1.1. Study WA39085

Study WA39085 was an open-label, parallel arm, dose finding phase 2 study that evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of ocrelizumab in pediatric subjects with RRMS. Refer to Section 6.2.2 for study design and additional details. PK and PD results are described below.

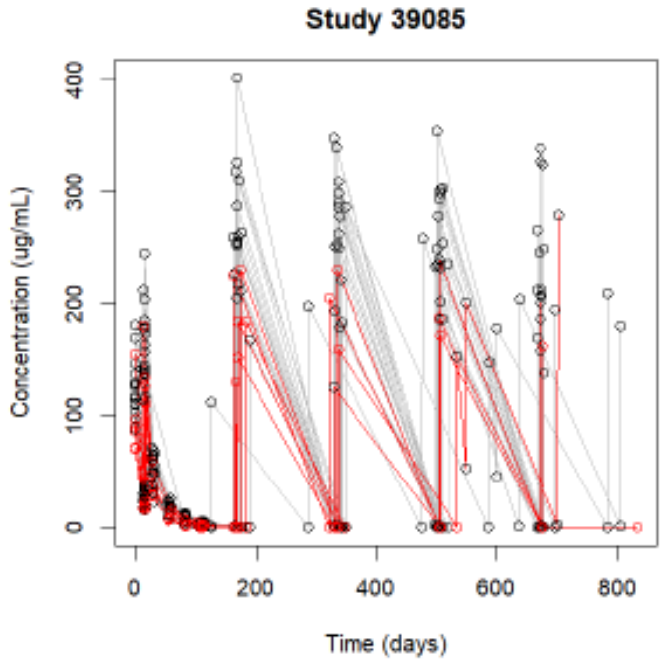
PK Results

Twenty-one of 23 enrolled subjects were included in the noncompartmental analysis. Two subjects were excluded due to a dosing protocol deviation (second infusion administered 126 days after the first infusion) and suspected sample mislabeling. Of the 21 subjects analyzed, five received 300 mg ocrelizumab (body weight <40 kg) and 16 received 600 mg ocrelizumab (body weight ≥40 kg).

Blood samples for PK analysis were drawn on Days 1, 15, 29, 57, 85, 113, 169, 337, 505, and 673 (before administration of premedication prior to ocrelizumab administration). On infusion visits, two serum samples were collected, the first sample 5 to 30 minutes prior to methylprednisolone premedication administration, and the second sample 30 (±10) minutes following the completion of the infusion of ocrelizumab. At noninfusion visits, samples were collected at any time during the visit. For all subjects, a sample was also drawn at delayed dosing visits and at withdrawal from treatment visits.

Observed individual plasma concentrations of ocrelizumab over time are presented in Figure 1, and a summary of ocrelizumab PK parameters calculated by noncompartmental analysis is presented in Table 6.

Figure 1. Observed Individual Plasma Ocrelizumab Concentrations vs. Time, Study WA39085



Source: Applicant's Clinical Pharmacology Summary, Page 22, Figure 8
Circles represent observed values. Black color indicates data from subjects administered 600-mg doses. Red color indicates data from subjects administered 300-mg doses.

Table 6. Summary of Ocrelizumab Serum PK Parameters Following IV Infusion of 300 mg (2×150 mg) and 600 mg (2×300 mg), Study WA39085

Treatment Arm PK Parameter	N	Mean (SD)	Median (Range)
Ocrelizumab 300 mg			
T_{max} (day)	5	13.5 (0.893)	14.1 (12.1-14.2)
C_{max} (µg/mL)	5	121 (40.9)	126 (77.8-180)
AUC_{24W} (µg/mL*day)	5	2680 (978)	2570 (1830-4220)
Ocrelizumab 600 mg			
T_{max} (day)	16	14.4 (1.13)	14.1 (13.1-17.1)
C_{max} (µg/mL)	16	164 (36.1)	160 (114-245)
AUC_{24W} (µg/mL*day)	16	3680 (859)	3780 (2120-5080)

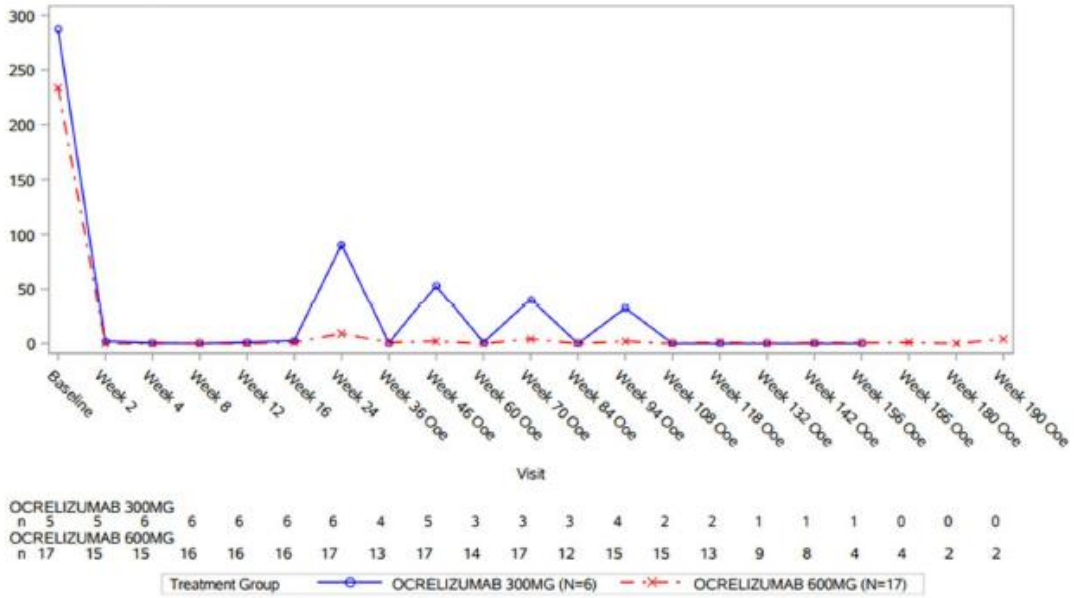
Source: Study WA39085, Primary clinical study report, Page 40, Table 4
Abbreviations: AUC_{24W}, area under the concentration-time curve from time 0 to Week 24; C_{max}, maximum plasma concentration; IV, intravenous; N, number of subjects in treatment arm; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum plasma concentration

Pharmacodynamics

Blood samples for obtaining CD19+ B-cell counts were collected at baseline and regular intervals through Week 190. However, this study is still ongoing. Ocrelizumab treatment led to rapid and near-complete B-cell depletion in blood by Week 2, which was sustained throughout

treatment until the last measured time point of Week 190. Median CD19+ B-cell count is presented in Figure 2.

Figure 2. Median CD19+ B-Cell Count in Blood Over Time, Study WA39085



Source: Primary clinical study report, Study WA39085, Page 52, Figure 11
Abbreviation: n, number of subjects with given characteristic; Ooe, optional ocrelizumab extension period

Immunogenicity

ADAs for ocrelizumab were not detected in this study up to Week 48 of the safety follow-up (SFU) Period.

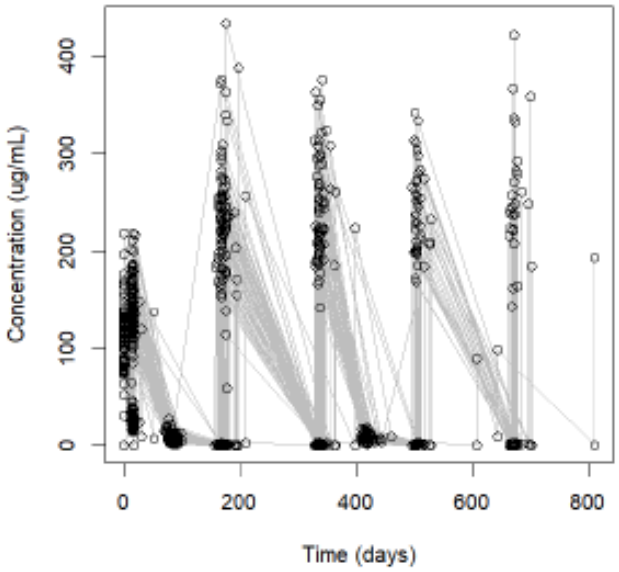
5.3.1.2. Study WN42086

Study WN42086 was a phase 3 study that evaluated safety and efficacy of ocrelizumab in comparison with fingolimod in pediatric subjects aged 10 to <18 years of age with RRMS. Refer to Section 6.2.1 for study design and additional details.

PK Results

Sparse PK samples were collected at Baseline, at Week 2, Week 12, every 12 weeks thereafter until Week 96, and at delayed dosing visits. PK data were analyzed using population pharmacokinetic analysis. Observed individual plasma concentrations of ocrelizumab versus time are presented in Figure 3. Refer to Section 5.3.3 for details.

Figure 3. Observed Individual Plasma Ocrelizumab Concentrations vs. Time, Study WN42086

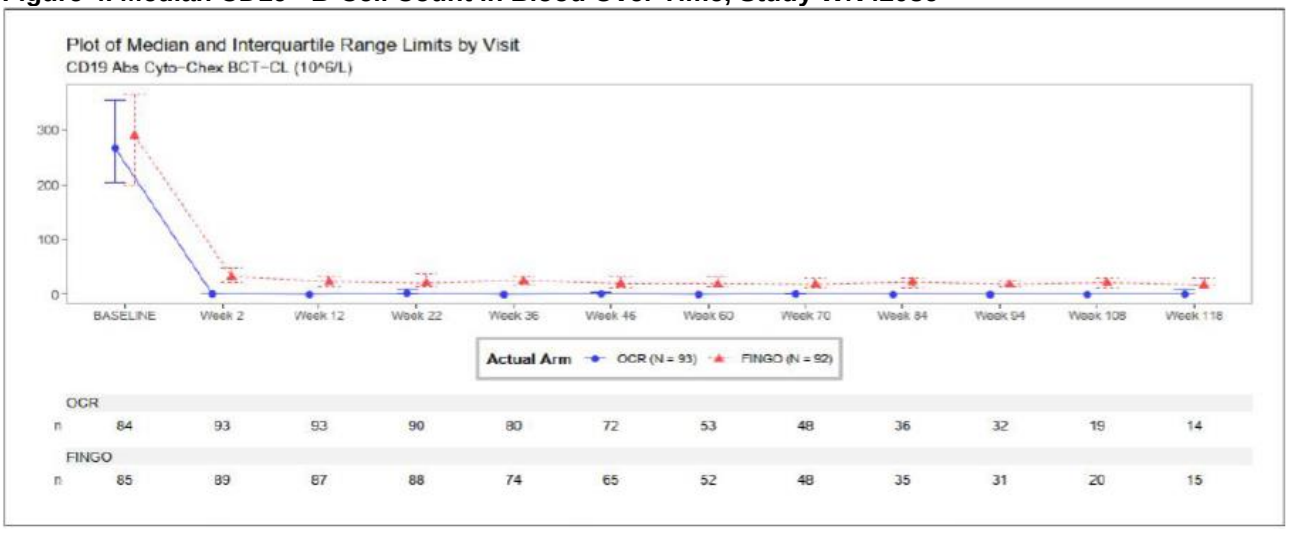


Source: Applicant's Clinical Pharmacology Summary, Page 22, Figure 8

Pharmacodynamics

Blood samples for CD19+ B-cells were collected at baseline, Week 2, Week 12, and every 12 weeks thereafter. Ocrelizumab treatment resulted in rapid and sustained near-complete CD19+ B-cell depletion through the clinical cutoff date (COD). In the fingolimod arm, CD19+ B-cell reduction was observed and remained stable throughout the DBP. Median CD19+ B-cell count over the DBP is presented in Figure 4.

Figure 4. Median CD19+ B-Cell Count in Blood Over Time, Study WN42086



Source: Study WN42086 primary clinical study report, Page 143, Figure 10
Abbreviations: FINGO, fingolimod; n, number of subjects with given characteristic; N, number of subjects in treatment arm; OCR, ocrelizumab

Immunogenicity

Immunogenicity was assessed at Baseline, Weeks 2, 12, 24, 48, 60, 72, 96, and at delayed dosing visits. ADA data were available from 90 evaluable subjects in the ocrelizumab arm. Two out of these 90 subjects (2.2%) developed treatment-emergent ADAs at some point during the treatment period. Given the low incidence of ADA development, these data are insufficient to analyze the impact of ADAs on the pharmacokinetics, efficacy, or safety of ocrelizumab in pediatric patients.

5.3.2. Bioanalytical Methods

5.3.2.1. Ocrelizumab Concentration in Serum

Ocrelizumab concentration in human serum was measured using a validated enzyme-linked immunosorbent assay (ELISA) with established immunoassay procedures. The assay was a quantitative indirect sandwich ELISA designed to detect ocrelizumab in human serum of pediatric subjects with RRMS. Samples and quality controls were diluted to a minimum required dilution (MRD) of 1/100 with sample diluent and transferred to an ELISA plate coated with goat anti-rhuMAb 2H7 polyclonal antibody, where ocrelizumab was captured during a one-hour incubation. Following washing, a solution of goat antihuman immunoglobulin G (IgG) antibody conjugated to horseradish peroxidase was added and incubated for one hour. After the final washing step, tetramethylbenzidine peroxidase substrate was added for color development, and the reaction was stopped with 1M phosphoric acid. The plate was read at 450 nm for detection absorbance and 630 nm for reference absorbance. The validation summary for the ocrelizumab concentration assay is presented in Table 7.

Table 7. Validation Summary for Ocrelizumab Concentration Assay, ELISA Method ICD 723 V 1.02

Parameter	Result
Analyte	Ocrelizumab (rhuMAb 2H7, Ocrevus, RO4964913)
Matrix	Human serum (multiple sclerosis study population)
Assay type	Quantitative indirect sandwich ELISA
Minimum sample volume	20.0 µL
Minimum required dilution (MRD)	1/100 in sample diluent
Quantification Range (LLOQ to ULOQ)	156-5000 ng/mL (neat serum); 1.56-50.0 ng/mL (in-well)
Calibration range	1.56 to 100 ng/mL (in-well) with anchor at 100 ng/mL
Calibration standards precision	1.70 to 6.42% CV (excluding anchor)
Calibration standards accuracy	−2.45 to 1.08% DFT (excluding anchor)
QC precision (interassay)	5.58 to 8.79% CV
QC accuracy (interassay)	−4.14 to 3.11% DFT
Dilutional linearity	Up to 1/640,000 (includes 1/100 MRD)
Hemolysis effect	No effect on quantification
Lipemia effect	No effect on quantification
Freeze/thaw stability	6 cycles at −80 °C
Bench-top stability	72.17 hours at room temperature

Parameter	Result
Long-term frozen storage stability	13 months at −25 °C; 4 years at −80 °C
Diluted sample stability	7 days at 2 °C to 8 °C
Delayed centrifugation stability	24 hours between draw and centrifugation
Assay pass rate (Study WN42086)	89.2% (33/37 runs acceptable)

Source: Interim Bioanalytical Report 1 for Analysis of Samples Using an ELISA Method for the Quantification of Ocrelizumab in Human Serum
Abbreviations: CV, coefficient of variation; DFT, diluted from top; ELISA, enzyme-linked immunosorbent assay; LLOQ, lower limit of quantitation; MRD, minimum required dilution; QC, quality control; ULOQ, upper limit of quantitation

The ocrelizumab concentration assay was previously reviewed and found to be acceptable for the adult ocrelizumab development program. The method, originally developed by Genentech (Method 2H7.011 PRO70769, December 2015), was successfully transferred to (b) (4) and was partially validated. The partial validation at (b) (4) demonstrates that the transferred method maintains adequate performance characteristics for supporting pediatric PK analyses in Studies WA39085 and WN42086.

5.3.2.2. Antidrug Antibodies to Ocrelizumab in Serum

ADAs to ocrelizumab in human serum were detected using a validated bridging ELISA with a tiered testing approach consisting of screening (Tier 1), confirmatory (Tier 2), and titration (Tier 3) steps. Samples and controls were diluted to an MRD of 1/20 and co-incubated overnight with 0.500 µg/mL biotinylated rhuMAb 2H7 and 0.700 µg/mL digoxigenin (DIG)-labeled rhuMAb 2H7. The formed immune complexes were transferred to a streptavidin-coated microtiter plate and incubated to immobilize the complexes via biotin-labeled rhuMAb 2H7. The bound complex was detected using horseradish peroxidase-conjugated chicken antidigoxigenin antibody, followed by tetramethylbenzidine substrate addition for color development and reaction termination with 1M phosphoric acid. The plate was read at 450 nm for detection absorbance and 630 nm for reference absorbance. The validation summary for the anti-ocrelizumab antibody assay is presented in Table 8.

Table 8. Validation Summary for Antiocrelizumab Antibody Assay, ELISA Method ICDIM 172 V 2.01

Parameter	Result
Validation project code	RBBW2, RBBW6, RBBW7, RBBW99
Analyte	Antibodies to ocrelizumab (ADAs)
Matrix	Human serum (multiple sclerosis study population)
Assay type	Bridging ELISA (tiered approach: screening, confirmatory, titration)
Minimum sample volume	20.0 µL
Minimum required dilution (MRD)	1/20
Assay format	Three-tier: Tier 1 (screening), Tier 2 (confirmatory), Tier 3 (titration)
Screening relative assay sensitivity	4.57 ng/mL (validation titer offset)
Confirmatory relative assay sensitivity	Validation CCP (38.0%): 7.71 ng/mL In-study CCP (19.5%): 3.19 ng/mL
Screening drug tolerance	100 ng/mL ADA detectable with up to 25.9 µg/mL ocrelizumab (validation) 100 ng/mL ADA detectable with up to 44.8 µg/mL ocrelizumab (RBBW7)
Hemolysis effect	No interference in screening or confirmatory assays
Lipemia effect	No interference in screening or confirmatory assays
Freeze/thaw stability	Screening: 5 cycles Confirmatory: 6 cycles at −80 °C

Parameter	Result
Bench-top stability	75.71 hours at room temperature
Assay pass rate (Study WN42086)	Overall: 81.0% (17/21 runs) Screening: 76.5% (13/17 runs) Confirmatory: 100% (2/2 runs) Titration: 100% (2/2 runs)

Source: Interim Bioanalytical Report 1 for Analysis of Samples Using an ELISA Method for the Detection of Antibodies to Ocrelizumab in Human Serum
Abbreviations: ADA, antidrug antibody; CCP, confirmatory cut point; ELISA, enzyme-linked immunosorbent assay; MRD, minimum required dilution

The ADA assay was previously reviewed and found acceptable for the adult ocrelizumab program. The method, originally developed by Genentech (Method 4.2H7.12 PRO70769, September 2010), was successfully transferred to [redacted] (b) (4) and partially validated. The partial validation at (b) (4), combined with the implementation of study-specific cut points for the pediatric population, appropriately supports immunogenicity assessment in Studies WA39085 and WN42086.

5.3.3. Pharmacometrics Assessment

5.3.3.1. Population Pharmacokinetic Modeling

The objectives of the PopPK analysis were to:

- Extend the earlier developed population PK model of ocrelizumab IV in adult patients with MS to the pediatric population using data from pediatric Studies WA39085 and WN42086.
- Determine and summarize individual PK parameters (e.g., clearance, steady state volume of distribution, etc.) and exposure measures (e.g., area under the concentration-time curve [AUC], maximum plasma concentration (C_{max}), etc.) following ocrelizumab IV administered in pediatric subjects from Study WN42086.

The Applicant developed a population PK analysis via nonlinear mixed-effects modeling to characterize ocrelizumab pharmacokinetics following intravenous administration in patients with MS (DARRTS ID: 3986651). The Applicant extended the initial PopPK model for ocrelizumab in adult patients with MS to pediatric patients. The final PK data set includes 1164 quantifiable observations from Studies WN39085 (847 concentrations from 93 subjects) and WN42086 (317 concentrations from 23 subjects). However, four postdose concentrations that were outliers and 47 concentrations (3.9%) that were below the limit of quantification were not included in the final analysis.

The analysis evaluated multiple covariates including body weight, age, sex, baseline CD19+ B-cell count, race, and markers of hepatic and renal function. The final model (Model 115) retained body weight effects on clearance and volume parameters (from the adult model via allometric scaling), and identified age as an independent covariate with a cutoff of 14.4 years, below which subjects exhibited higher weight-normalized clearance and lower volumes. Specifically, the model incorporated age-dependent adjustments to time-dependent clearance (CL_T) and central and peripheral volumes (V_C and V_P) using piecewise functions. Other evaluated covariates, including sex and baseline B-cell count, did not demonstrate statistically significant or clinically relevant effects on PK parameters. Parameter estimates of the pediatric PK model are shown in

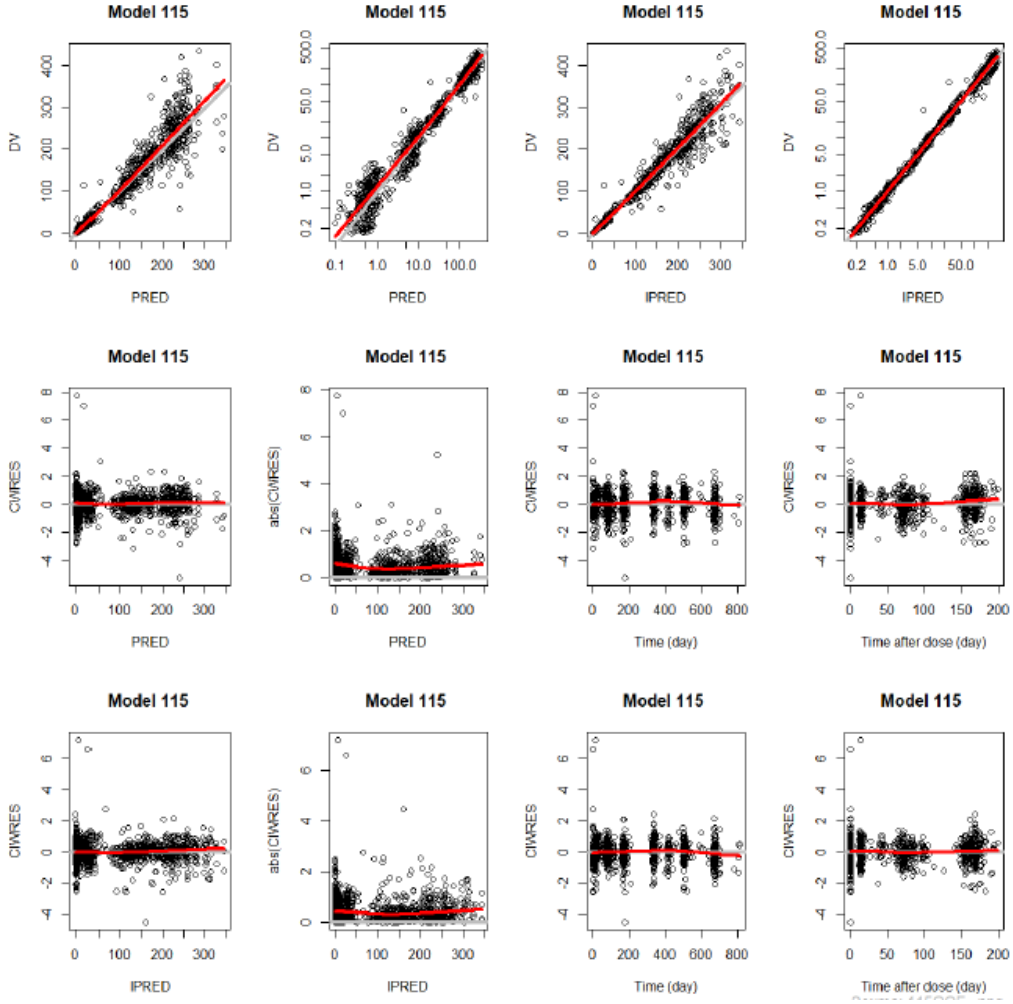
Table 9. Model diagnostics confirmed a robust fit of the final model across the dataset as shown in Figure 5 and Figure 6.

Table 9. Parameter Estimates of the Pediatric PK Model Based on Population PK Analyses

Parameter		Estimate	RSE (%)	95%CI
CL_{Tage}	θ(16)	4.56	34.1	1.51 ; 7.61
AGE_{cutoff}	θ(17)	14.4	3.81	13.4 ; 15.5
V_{age}	θ(18)	0.604	28.8	0.263 ; 0.945

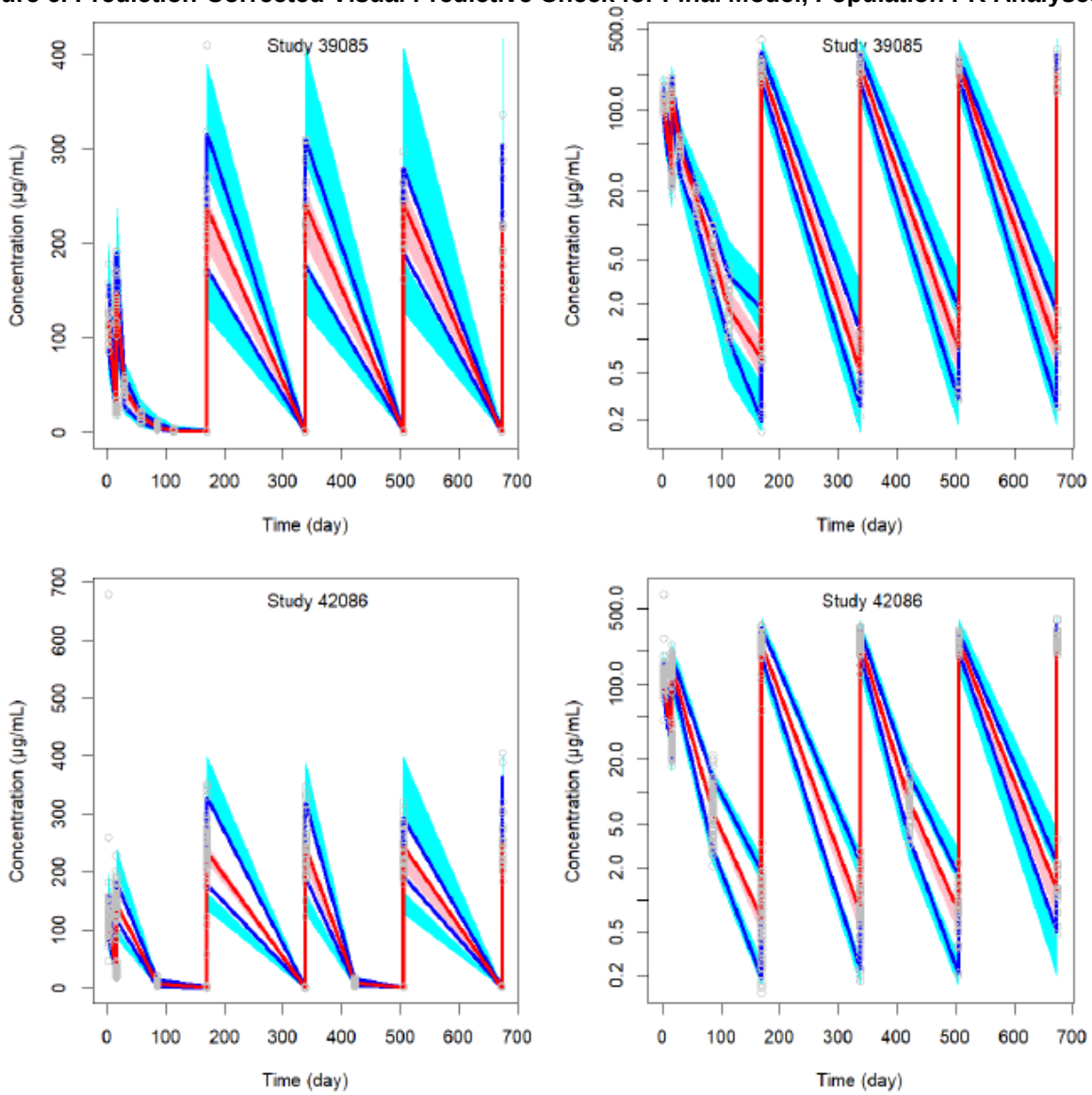
Source: Ocrelizumab pediatric PopPK report #1142975, page 33, Table 7
Abbreviations: AGE_{cutoff}, age threshold below which age-related effects on pharmacokinetic parameters become significant; CI, confidence interval; CL_{Tage}, magnitude of age effect on time-dependent clearance; PK, pharmacokinetic; PopPK, population pharmacokinetic; RSE, relative standard error; V_{age}, magnitude of the age effect on both central volume and peripheral volume

Figure 5. Goodness-of-Fit for Final Model, Population PK Analyses



Source: Ocrelizumab pediatric PopPK report #1142975, page 79, Figure 33
The grey solid y = x or y =0 lines are included for reference. The bold red lines are the LOWESS (local regression smoother) trend lines.
Abbreviations: CIWRES, conditional individual weighted residuals; CWRES, conditional weighted residuals; DV, observed concentrations; IPRED, individual predictions of the model; PopPK, population pharmacokinetic; PRED, population predictions of the model; Time, time after the first dose

Figure 6. Prediction-Corrected Visual Predictive Check for Final Model, Population PK Analyses



Source: Ocrelizumab pediatric PopPK report #1142975, page 83, Figure 37
The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations. The shaded regions show 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 1000 trials simulated using dosing, sampling, and the covariate values of the analysis dataset.

Predicted Exposures

The final PopPK model was used to simulate concentration-time courses and compute predicted individual values of exposure parameters for the subjects in Studies WA39085 and WN42086. Individual predicted exposures in Cycle 1 (AUC_{24W} in Table 5, and C_{max24W} in Table 6) in pediatric subjects from Studies WN42086 and WA39085 following per protocol dosing of Study WN42086 were summarized by weight groups (<35 kg, <40 kg, ≥40 kg, ≥40 & <60 kg, ≥60 & <80 kg, ≥80 kg) and compared with exposures of adult subjects with RMS from Studies WA21092 and WA21093, and those with PPMS from Study WA25046 following 600 mg IV ocrelizumab. See Table 10 and Table 11 for the results of these analyses for AUC_{24W} and C_{max24W}, respectively.

Table 10. Median (Range) AUC_{24W} (µg/mL*day) by Weight, Studies WA39085 and WN42086

Group / Dose	Weight Range (kg)						
	<35 kg	<40 kg	≥40 kg	≥40 &<60 kg	≥60 &<80 kg	≥80 kg	All
Pediatric (2 x 150 mg if WT <35 kg, 2 x 300 mg if WT ≥35 kg)	2640 (2160-3120) [N=2]	3320 (2160-5370) [N=6]	3080 (1700-4910) [N=110]	2950 (1700-4680) [N=50]	3210 (1740-4910) [N=38]	2810 (1790-4050) [N=22]	3130 (1700-5370) [N=116]
PPMS (2 x 300 mg)	-	-	2840 (369-6430) [N=482]	2870 (369-5860) [N=124]	2890 (720-6430) [N=208]	2670 (1050-5290) [N=150]	2840 (369-6430) [N=482]
RMS (2 x 300 mg)	-	3520 [N=1]	2830 (1260-8850) [N=781]	3550 (1860-8850) [N=156]	2990 (1410-6890) [N=343]	2370 (1260-4510) [N=282]	2840 (1260-8850) [N=782]

Source: Ocrelizumab pediatric PopPK report #1142975, page 40, Table 14
Abbreviations: AUC_{24W}, area under the concentration-time curve from time 0 to Week 24; N, number of subjects with given characteristic; PopPK, population pharmacokinetics; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; WT, weight

Table 11. Median (Range) C_{max24W} (µg/mL) by Weight, Studies WA39085 and WN42086

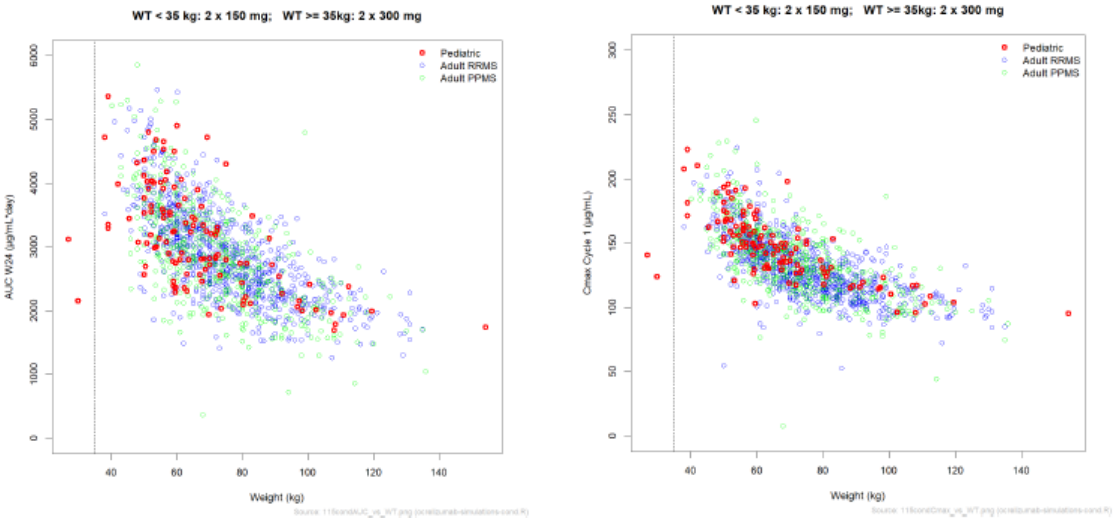
Group / Dose	Weight range (kg)						
	<35 kg	<40 kg	≥40 kg	≥40 &<60 kg	≥60 &<80 kg	≥80 kg	All
Pediatric (2 x 150 mg if WT <35 kg, 2 x 300 mg if WT ≥35 kg)	133 (124-141) [N=2]	176 (124-223) [N=6]	147 (95.4-210) [N=110]	147 (96.1-191) [N=50]	149 (95.4-198) [N=38]	139 (96.3-210) [N=22]	147 (95.4-223) [N=116]
PPMS (2 x 300 mg)	-	-	134 (7.77-246) [N=482]	137 (7.77-222) [N=124]	137 (76.6-229) [N=208]	130 (74.7-246) [N=150]	134 (7.77-246) [N=482]
RMS (2 x 300 mg)	-	163 [N=1]	129 (52.7-347) [N=781]	154 (54.6-347) [N=156]	134 (79.6-207) [N=343]	114 (52.7-204) [N=282]	129 (52.7-347) [N=782]

Source: Ocrelizumab pediatric PopPK report #1142975, page 42, Table 16
Abbreviations: C_{max24W}, maximum plasma concentration during the first 24 weeks; N, number of subjects with given characteristic; PopPK, population pharmacokinetic; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; WT, weight

Figure 7 and Figure 8 show AUC_{24W} and C_{max24W} versus body weight and age for pediatric subjects in Study WA39085 and WN42086, compared to adult MS patients.

Figure 7. Predicted AUC_{24W} and C_{max24W} vs. Body Weight for Pediatric Subjects in Studies WA39085 and WN42086 Compared to Adult MS Patients

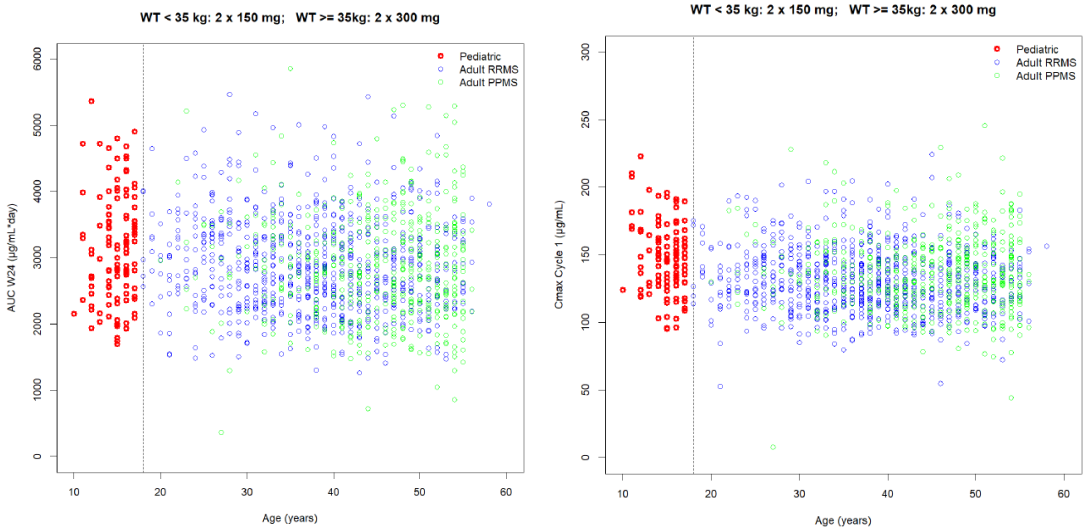
A. AUC_{24W} vs. Weight **B. C_{max} vs. Weight**



Source: Ocrelizumab pediatric PopPK report #1142975. A) page 107, Figure 61. B) Page 109, Figure 63
Vertical dashed line corresponds to 35 kg.
Abbreviations: AUC_{24W}, area under the concentration-time curve from time 0 to Week 24; MS, multiple sclerosis; PopPK, population pharmacokinetic; PPMS, primary progressive multiple sclerosis; RRMS, relapsing multiple sclerosis; WT, weight

Figure 8. Predicted AUC_{24W} and C_{max24W} vs. Body Age for the Pediatric Subjects in Studies WA39085 and WN42086 Compared to Adult MS Patients

A. Predicted AUC_{24W} vs. Age **B. Predicted C_{max24W} vs. Age**



Source: Ocrelizumab pediatric PopPK report #1142975. A) page 111, Figure 65. B) Page 112, Figure 66
Vertical dash line corresponds to 18 years
Abbreviations: AUC, area under the concentration-time curve; AUC_{24W}, AUC from time 0 to Week 24; C_{max24W}, maximum concentration during the first 24-weeks; MS, multiple sclerosis; PopPK, population pharmacokinetic; PPMS, primary progressive multiple sclerosis; RRMS, relapsing multiple sclerosis; WT, weight

The pediatric PopPK analysis appropriately extended the validated adult IV model to support weight-based dosing in pediatric patients with RRMS. The final model successfully demonstrated that the weight-based regimen (300 mg for <35 kg; 600 mg for ≥35 kg) achieves

pediatric exposures (median AUC_{24W}: 3,130 µg/mL·day; C_{max}: 147 µg/mL) consistent with adult exposures, thereby justifying the selected dosing strategy. The robust dataset (1,160 concentrations from 116 subjects) and rigorous model diagnostics support confidence in the model's predictive performance and its application for dose selection. The lowest body weight in the pediatric dataset was 27 kg (from Study WA39085), which aligns with the study inclusion criterion of ≥25 kg. While the PopPK model does not include an explicit lower weight limit, the 300 mg recommendation for patients <35 kg is supported by observed data down to 27 kg. For patients weighing <25 kg, model predictions would represent extrapolations beyond the observed data range; however, such patients would be rare in the target population of children aged ≥10 years, as this weight would represent significant underweight status for this age group. The 25 kg-lower limit established in the study inclusion criteria is considered reasonable and appropriate for the proposed pediatric indication.

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant's proposed dosing regimen of ocrelizumab is 300 mg for pediatric patients 10 years of age and older and weighing <35 kg, and 600 mg for adults and pediatric patients 10 years of age and older and weighing ≥35 kg, administered by IV infusion every 6 months. The initial dose is administered as two separate IV infusions of half the dose given 14 days apart (i.e., 2×150 mg for the 300 mg regimen or 2×300 mg for the 600 mg regimen). Subsequent doses are administered as a single IV infusion every 6 months.

The proposed dosing regimen was selected for the phase 3 Study WN42086, based on pharmacokinetics, pharmacodynamics, and safety data from the phase 2 Study WA39085. Study WA39085 evaluated two ocrelizumab dose levels, 300 mg for subjects weighing ≥25 kg to <40 kg, and 600 mg for patients weighing >40 kg. Following evaluation of the data, a body weight cutoff of 35 kg rather than 40 kg was selected by the Applicant, as this approach provided exposure values closer to the upper end of the adult exposure range for pediatric patients weighing 35 to 40 kg and ensured more consistent B-cell depletion throughout the dosing interval (Refer to Section 5.3.1.1 for details).

PK analysis incorporating data from both Studies WA39085 (n=23) and WN42086 (n=93) demonstrated that the median AUC_{24W} for pediatric patients was 3,130 µg/mL·day (range: 1,700 to 5,370), which overlapped with the exposure range observed in adult MS patients receiving 600 mg ocrelizumab. The median C_{max} was 147 µg/mL (range: 95.4 to 223), which is comparable to that in adult patients. Refer to Section 5.3.3.

In Study WN42086, consistent with the mechanism of action (MOA) and PD activity observed in adult subjects, treatment with ocrelizumab led to rapid and sustained near-complete B-cell depletion in pediatric subjects. Refer to Section 5.3.1.2.

In Study WN42086, ocrelizumab was noninferior to fingolimod based on the adjusted protocol-defined ARR, with a rate ratio of 0.517 (95% confidence interval [CI]: 0.193, 1.329). Additionally, ocrelizumab was superior to fingolimod in reducing the annualized rate of

new/enlarging T2 lesions, with a 47.8% (p=0.001) relative reduction compared to fingolimod. At Week 12, ocrelizumab also demonstrated superiority in reducing the number of T1 gadolinium-enhancing lesions compared to fingolimod, with an 87.2% (p=0.001) observed reduction. Refer to Section 6.2.1.4 for additional details.

Therefore, the proposed dose of 300 mg for pediatric patients 10 years of age and older and weighing ≥25 kg to <35 kg, and 600 mg for pediatric patients 10 years of age and older and weighing ≥35 kg administered every 6 months via intravenous infusion is considered appropriate. Of note, the Applicant did not propose specification of a lower limit of 25 kg for the 300-mg dose; this revision was recommended by the review team because Studies WA39085 and WN42086 only enrolled subjects ≥25 kg. The PK and safety data therefore only supported dosing subjects who weigh 25 kg or more.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

The efficacy portion of this review will focus on the phase 3 active-controlled, double-blind, randomized Study WN42086. Data from the flexible duration DBP of the trial will be reviewed to provide information regarding the safety and efficacy of ocrelizumab in children and adolescents ≥10 and <18 years of age for an indication of RRMS based on reduction in ARR, the primary endpoint.

The safety portion of this review will focus on the DBP of phase 3 Study WN42086 as well as its open-label extension. The results of phase 2 Study WA39085 will also be discussed. Refer to Section 7 for further details regarding the safety review strategy.

6.2.1. Study WN42086

6.2.1.1. Design, Study WN42086

Overview and Objective

Study WN42086 is an ongoing study intended to demonstrate noninferiority of ocrelizumab compared to fingolimod in children and adolescents between ≥10 and <18 years of age with RRMS. Subjects remained in the DBP of the study until the time of the primary analysis, which was conducted when the last randomized subject completed 24 weeks of double-blind treatment. The noninferiority analysis of the primary endpoint from the DBP has been completed. The study also assessed the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of ocrelizumab as compared to fingolimod. At the time of the sBLA data cutoff (June 9, 2025), Protocol WN42086 version 6 and statistical analysis plan (SAP) Version 2.0 were in effect and are therefore the protocol and SAP versions discussed in this BLA review.

The primary objective of the study was to demonstrate clinical noninferiority of ocrelizumab compared to fingolimod, based on protocol-defined ARR, as determined by the rate ratio of counts during the DBP.

Secondary objectives were to examine the effects of ocrelizumab, as compared to fingolimod, on the following:

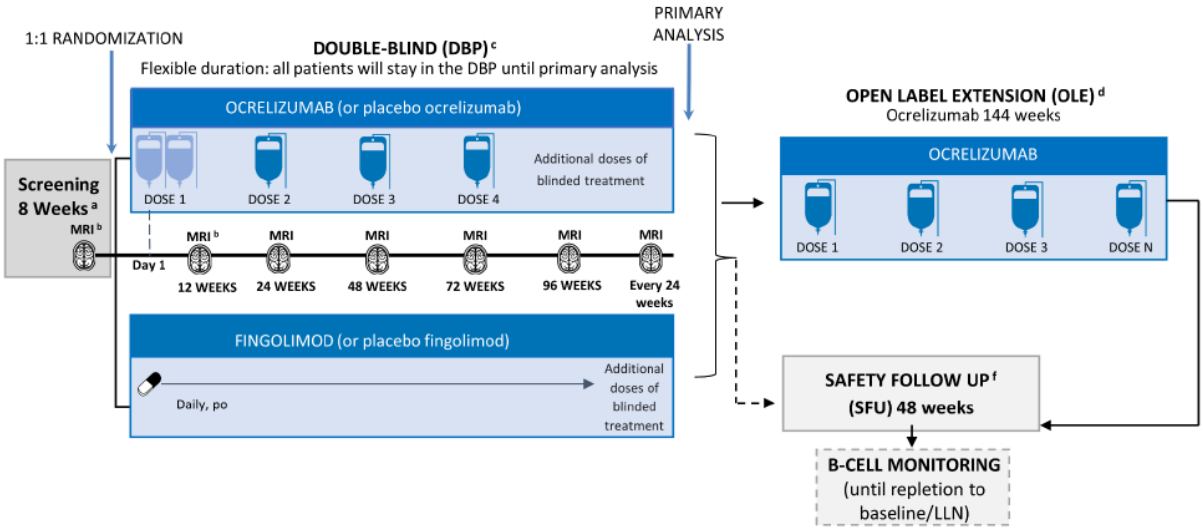
- To demonstrate the noninferiority of ocrelizumab compared to fingolimod, based on the number of new or enlarging T2 hyperintense brain MRI lesions during the DBP.
- To demonstrate the superiority of ocrelizumab compared to fingolimod, based on the following endpoints:
  - Number of T1 gadolinium-enhancing brain MRI lesions at week 12
  - Number of new or enlarging T2 hyperintense brain MRI lesions during the DBP
  - Protocol-defined ARR during the DBP

Study Design

Study WN42086 is an ongoing phase 3, randomized, double-blind, double-dummy, flexible duration (of at least 24 weeks), parallel-group, multicenter study designed to evaluate the clinical noninferiority of ocrelizumab as compared to fingolimod in pediatric subjects between the ages of 10 and <18 years, as per the revised McDonald 2017 Criteria (Thompson et al. 2018) or the International Pediatric Multiple Sclerosis Study Group (IPMSSG) 2012 Criteria for pediatric MS (Krupp et al. 2013). Subjects were required to have an EDSS score of 0.0 to 5.5 at screening. Subjects were randomized 1:1 to receive treatment with either ocrelizumab (Group A) or fingolimod (Group B) until 24 weeks after the last subject was randomized. Randomization was stratified by region (United States versus rest of the world), prepubertal status (yes versus no), and presence of T1 gadolinium-enhancing lesions at baseline (yes versus no). Following completion of the DBP, subjects continued to receive blinded treatment until the time of the primary analysis, and until the Applicant determined whether the OLE period would be opened for enrollment. Eligible subjects subsequently entered the 144-week OLE period. Subjects who completed the DBP but were not eligible for OLE Period enrollment and those who completed the OLE period subsequently entered a 48-week SFU Period.

The study schematic for Study WN42086 (protocol version 6) is presented in Figure 9. The study consisted of a screening period of up to 10 weeks, a flexible duration (of at least 24 weeks) DBP, a 144-week OLE period, and a 48-week SFU period.

Figure 9. Study Schematic, Study WN42086, Protocol Version 6



DBP = double-blind period; Gd = gadolinium; LLN = lower limit of normal; MRI = magnetic resonance imaging; OLE = open-label extension; SFU = safety follow-up.

[a] The screening period may be extended for relevant clinical, administrative, or operational reasons, but cannot exceed 10 weeks.

[b] Brain MRI with and without a Gd-contrast agent should be performed at Baseline and Week 12. Subsequent brain MRIs should be performed without Gd-contrast agent only. Please refer to the Schedule of Activities in Appendix 1 Table 2 regarding brain MRIs during the OLE.

[c] The double-blind period will continue for all patients until primary analysis (Section 3.1.2). The primary analysis will be conducted after the last patient randomized has completed 24 weeks since first blinded ocrelizumab/ocrelizumab placebo infusion.

[d] *Following database lock of the DBP, patients should continue to receive blinded treatment, as per Schedule of Assessments (Table 1), until the primary analysis is completed and the decision to start the OLE phase is communicated by the Sponsor*. The OLE period will last for at least 144 weeks and may be extended until the patient turns 18 years old (or as required per local regulation) or until commercial ocrelizumab is approved for children and available in the country for these patients, whichever occurs first (see Section 3.1.3).

[e] Patients in Group B switching from fingolimod to ocrelizumab must meet the *eligibility criteria as per Section 4.1.3*. The first dose of ocrelizumab will be administered as two half-dose IV infusions 14 days apart, and subsequent IV doses will be administered as single infusions every 24 weeks.

[f] Safety follow-up period will start after the double-blind period or the OLE period and last for at least 48 weeks, counting from the final ocrelizumab dose received (see Section 3.1.4).

Source: Study WN42086, protocol version 6
Abbreviations: DBP, double-blind period; Gd, gadolinium; LLN, lower limit of normal; MRI, magnetic resonance imaging; OLE, open-label extension; SFU, safety follow-up

Enrollment Adjudication Process

A subject diagnosis form was completed by the treating investigator or designee. Subsequently, an independent pediatric multiple sclerosis review committee confirmed a diagnosis of pediatric RRMS for all subjects prior to enrollment.

Study Treatment

Subjects received following treatments during the DBP:

- Group A (ocrelizumab arm):
  - Subjects weighing <35 kg: ocrelizumab 300 mg IV every 24 weeks + by mouth (PO) placebo daily
  - Subjects weighing ≥35 kg: ocrelizumab 600 mg IV every 24 weeks + PO placebo daily
- Group B (fingolimod arm):
  - Subjects weighing ≤40 kg: fingolimod 0.25 mg daily + IV placebo every 24 weeks
  - Subjects weighing >40 kg: fingolimod 0.50 mg daily + IV placebo every 24 weeks

The first dose of ocrelizumab or IV placebo was administered as two half-dose IV infusions, 14 days apart. For subsequent infusions, subjects were required to attend a study visit within 2 weeks prior to any planned infusions to undergo laboratory evaluations in order to ensure that ocrelizumab retreatment criteria were met. Refer to Section 4.3.3 *Criteria for Re-Treatment with Ocrelizumab/Placebo and Fingolimod/Placebo* of the protocol for specific retreatment criteria.

Subjects were required to undergo a first dose monitoring procedure for oral study treatment (either fingolimod or PO placebo). Refer to Section 4.3.2.2.3 *First-Dose Monitoring by a Blinded Independent Physician* of the protocol for a description of the first dose monitoring procedure for fingolimod and PO placebo, and to Section 4.3.2.2.4 *Monitoring with Reinitiation of Fingolimod/Fingolimod Placebo Therapy following Interruption [Blinded Independent Physician]* of the protocol for a description of first dose monitoring requirements for fingolimod reinitiation for subjects who interrupt treatment with fingolimod/PO placebo. Sections 4.3.2.2.3 and 4.3.2.2.4 of the protocol are in alignment with the first dose monitoring procedure described in current approved labeling for fingolimod.

Subjects receiving ocrelizumab/IV placebo with a body weight of <35 kg at study enrollment who reached a body weight of ≥35 kg over the course of the study were to be switched to the higher dose level of ocrelizumab/IV placebo (600 mg every 24 weeks). The first ocrelizumab infusion at the higher dose level was to be administered as two half-dose IV infusions, 14 days apart. However, there were no enrolled subjects with a body weight <35 kg.

Subjects receiving fingolimod/PO placebo with a body weight of ≤40 kg at study enrollment who reached a body weight of >40 kg over the course of the study (confirmed over two visits, at least 3 months apart) were to be switched to the higher dose level of fingolimod/IV placebo (0.5 mg daily). However, there were no enrolled subjects with a body weight ≤40 kg.

Upon transitioning to the OLE period, all subjects received two half-dose (according to body weight category) ocrelizumab IV infusions administered 14 days apart. All subsequent ocrelizumab doses were administered as a single IV infusion every 24 weeks. Group B subjects who transitioned to ocrelizumab during the OLE period were required to meet the eligibility criteria described in Section 4.1.3 *Eligibility Criteria for Optional Open-Label Extension Period* of the protocol.

Subjects were premedicated with methylprednisolone (or equivalent; mandatory), an antihistamine (e.g., diphenhydramine; mandatory), and with an oral analgesic/antipyretic (e.g., acetaminophen; recommended). Methylprednisolone was administered as an IV infusion (2 mg/kg for subjects weighing <40 kg, and 100 mg for subjects weighing ≥40 kg) to be completed approximately 30 minutes prior to study treatment administration. The mandatory antihistamine was administered approximately 30 to 60 minutes prior to study treatment administration.

Study Assessments and Procedures

For details regarding the timing of assessments and procedures, refer to the schedule of assessments in the protocol.

Blinding

In order to maintain the study blind, the protocol designated three separate blinded investigators: an independent physician, a treating investigator, and an examining investigator:

- The independent physician's role was to supervise the first dose of oral study treatment (i.e., first dose monitoring).
- The treating investigator, a neurologist with experience treating patients with pediatric MS, was responsible for the clinical care of each subject over the course of the study (except for first dose monitoring and fingolimod/PO placebo reinitiation). The treating investigator had access to blinded safety and efficacy data, performed neurological examinations, and made treatment decisions based on clinical findings.
- The examining investigator, a neurologist or other healthcare professional with experience treating patients with pediatric MS, was responsible for independently assessing and documenting EDSS scores. He or she was required to receive Neurostatus/EDSS training and certification prior to study initiation. Whenever possible, the same individual was to perform the assessments on a given subject for the entire study duration. Subjects were instructed not to discuss symptoms with the examining investigator. Results of the neurologic examinations, paraclinical findings, and EDSS scores could not be shared between the treating and examining investigators.

All MRI scans were performed by trained and certified blinded MRI technicians, and analyzed by a blinded centralized reading center. The centralized reader was blinded to the treatment assignment and scans were interpreted in the absence of clinical information. When a predefined deterioration on brain MRI scans was identified (≥5 new or enlarging T2 lesions at Week 48, compared to the most recent prior scan), the centralized reader notified the treating investigator. The information conveyed to the treating investigator included baseline T2 lesion count, new or enlarging T2 lesion count, baseline gadolinium-enhancing T1 lesion count, and associated MRI images. Treatment allocation remained blinded. Additionally, MRI scan reports containing unexpected findings of non-MS pathology were provided to the treating investigator, who did not have access to MRI scans. For situations in which the treating investigator needed to access MRI scans due to safety reasons, these events were documented as protocol deviations.

Laboratory parameters that could result in unblinding of treatment allocation (i.e., flow cytometry cell counts, white blood cell [WBC] count, lymphocyte counts, immunoglobulin levels, and markers of liver injury) remained blinded during the DBP. To ensure subject safety and to allow verification of ocrelizumab/IV placebo retreatment criteria, a central laboratory sent reflex messages to the treating investigator that were be triggered by critical blinded laboratory results. See Section 4.6.18.2 *Central Laboratory Assessments* of the protocol for the list of laboratory parameters that were unblinded when meeting critical thresholds.

An independent data monitoring committee monitored and evaluated safety data over the course of the study, until completion of the primary analysis. A blinded external steering committee provided general study guidance and served as liaison with investigators.

MS Relapse Assessment and Treatment

All subjects with new or worsening neurologic symptoms were "promptly" scheduled to undergo an evaluation by the treating investigator. Subjects with events suggestive of an MS relapse

subsequently underwent an EDSS evaluation by the examining investigator within 7 days of symptom onset, in order to confirm whether the event met the criteria for protocol-defined relapse.

Protocol-defined relapses were defined as the occurrence of new or worsening neurologic symptoms attributable to MS that persisted for at least 24 hours, could not be attributed to other conditions (e.g., fever, infection, injury, or adverse reactions to medications), were immediately preceded by at least 30 days of neurological stability, and were accompanied by objective neurologic findings (a ≥0.5 step increase in EDSS, a ≥2 point increase in 1 Functional System [FS] score, or a ≥1 point increase in 2 FS scores). Changes in FS scores were required to impact the pyramidal, ambulation, cerebellar, brainstem, sensory, or visual domains.

The protocol allowed use of methylprednisolone IV 30 mg/kg/day (maximum daily dose of 1000 mg) for 3 to 5 days, with or without an up to 10-day taper, for the treatment of MS relapses (as per the treating investigator's discretion). Per the Applicant, MRI did not play a role in the relapse confirmation process.

Stopping Criteria

Subjects were permanently discontinued from study treatment (but not from study participation) for any of the following reasons:

- Any medical condition that in the opinion of the investigator could impact subject safety.
- Determined to be in the best interest of the subject.
- Life-threatening (Grade 4) infusion reactions or a severe allergic or anaphylactic reaction to an ocrelizumab infusion.
- Active hepatitis B or C infection or hepatitis B infection reactivation.
- Severe liver injury (as defined by Hy's law) that cannot be attributed to an alternative etiology.
- Macular edema.
- PML.
- Life-threatening (Grade 4) infections.

Subjects were permanently discontinued from the study for any of the following reasons:

- Subject withdrawal of consent or assent
- Parent or legal guardian withdrawal of consent
- Study termination or site closure
- Determined to be in the best interest of the subject
- Subject noncompliance

Adverse Events of Special Interest

The following adverse events (AEs) were designated as adverse events of special interest:

- Cases of potential drug-induced liver injury (DILI), as defined by Hy's law.
- Suspected transmission of infectious agent by the study drug due to contamination.

Protocol Amendments

For details regarding protocol amendments, refer to Section 3.1.2 *Changes in Study Conduct* of the clinical study report (CSR) for Study WN42086.

Assessment of Study WN42086 Design

Overall, the design of Study WN42086 was considered acceptable by the multidisciplinary review team. The noninferiority design and analysis was previously agreed upon by the Division of Neurology 2 (the Division). The study population (pediatric subjects between the ages of 10 and <18 years with RRMS), eligibility criteria, and endpoints are acceptable to support the study objectives and review of this sBLA.

6.2.1.2. Eligibility Criteria, Study WN42086

Key eligibility criteria are summarized below.

Key Inclusion Criteria

- Age ≥10 to <18 years at randomization.
- Body weight ≥ 25 kg.
- Up to date with local vaccination schedule.
- Completion of chickenpox vaccination series if negative serology for varicella zoster virus (VZV).
- Agreement to remain abstinent or implement a highly effective contraceptive method (female subjects of childbearing potential only).

MS-Specific Inclusion Criteria:

- Diagnosis of RRMS, according to the 2012 IPMSSG criteria for pediatric MS or the 2017 Revised McDonald Criteria.
- Pediatric MS diagnosis confirmed by an independent pediatric multiple sclerosis review committee.
- EDSS score of 0 to 5.5, inclusive.
- At least 1 relapse in the year prior to screening or 2 relapses in the previous 2 years or evidence of ≥ 1 gadolinium-enhancing brain MRI lesion in the last 6 months (including screening MRI). If a new MRI is required for rescreening, the identification of a new or enlarging T2 hyperintense brain MRI lesion compared to the prior screening MRI is

sufficient to demonstrate recent radiologic disease if both MRIs were performed within the last 6 months.

Key Exclusion Criteria:

- Pregnant or lactating subjects.
- Presence or suspicion of a neurologic disorder that could potentially mimic MS or of any other condition that could interfere with cognitive function or neurologic development.
- For subjects with initial MS relapse consistent with acute disseminated encephalomyelitis (ADEM), a second relapse with classic MS features is required.
- Positive anti-aquaporin-4 (AQP4) and/or anti-myelin oligodendrocyte glycoprotein (MOG) antibodies.
- Atypical findings for MS at initial presentation, such as signs of infection or encephalopathy.
- Cerebrospinal fluid at initial presentation with protein > 100 mg/dL, pleocytosis > 50 cells/mm^3, or with presence of neutrophils or eosinophils above the reference range or of atypical cells (Cerebrospinal fluid sampling at Screening was not mandatory).
- Atypical findings on MRI, such as ADEM-like lesions, location of lesions atypical for MS, bilateral optic neuritis, or spinal cord lesions spanning ≥3 spinal segments.
- Known active infection, excluding fungal nailbed infections.
- Infection requiring hospitalization or treatment with IV anti-infectives within the last 4 weeks or oral anti-infectives within the last 2 weeks.
- History or presence of recurrent or chronic infection, such as human immunodeficiency virus (HIV), syphilis, or tuberculosis.
- History of vaccination in the last 6 weeks.
- Coagulation disorder requiring medical treatment.
- History of malignancy at any time, except for basal cell or squamous cell carcinoma of the skin that has been definitely treated.

Fingolimod-Specific Exclusion Criteria:

- History of symptomatic bradycardia, recurrent syncope, or QT prolongation (QTc >460 msec [for pediatric females] or >450 msec [for pediatric males]). Presence of risk factors for QT prolongation (e.g., hypokalemia, congenital QT prolongation, or uncontrolled hypertension).
- History of myocardial infarction, unstable angina, stroke, transient ischemic attack, heart failure exacerbation requiring inpatient treatment, or New York Heart Association Class III/IV heart failure in the last 6 months.
- Severe cardiac arrhythmia requiring treatment with Class Ia or Class III antiarrhythmics.
- Second-degree Mobitz type II or third-degree atrioventricular (AV) block, sick-sinus syndrome, or sinoatrial heart block.
- Baseline QTc interval ≥ 500 msec.

- Macular edema.
- Presence of any pulmonary conditions, as determined by the investigator, including severe asthma (2010 World Health Organization uniform definition on severe asthma).
- History of seizures, including nonepileptic seizures, in the last 12 months.
- History of chronic liver or biliary disease (except for Gilbert's syndrome) or acute or chronic pancreatitis.

Medication-Specific Exclusion Criteria:

- History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies or known hypersensitivity to ocrelizumab or any of its excipients.
- Premedication (i.e., corticosteroids, antihistamines, or antipyretics) contraindication or intolerance.
- Treatment with any investigational agents within the last 24 weeks or within five half-lives, whichever is longer.
- History of treatment with any B-cell depleting therapies.
- History of treatment with alemtuzumab, anti-CD4 antibodies, cladribine, mitoxantrone, daclizumab, laquinimod, total body irradiation, or bone marrow transplantation.
- History of treatment with any other immunomodulatory or immunosuppressive therapies without undergoing an appropriate washout period, as described in the local label or at least five times the half-life of the medication. The PD effects of each therapy must also be considered when determining an appropriate for washout period.
- History of treatment with natalizumab with in the last 12 months.
- History of treatment with teriflunomide within the last 4 weeks (for subjects who completed an accelerated elimination procedure and do not have confirmation of a teriflunomide plasma level of <0.02 mg/L). For subjects who have not completed an accelerated washout procedure, treatment with teriflunomide within the last 24 weeks.
- History of treatment with fingolimod.
- History of treatment with any other S1P receptor modulators within the last 24 weeks.
- History of treatment with dimethyl fumarate within the last 4 weeks and absolute lymphocyte count (ALC) below the lower limit of normal (LLN).
- History of treatment with intravenous immunoglobulin within the last 12 weeks.
- History of treatment with plasmapheresis within the last 4 weeks.
- History of treatment with corticosteroids within the last 7 days.

Medication-Specific Exclusion Criteria Related to Fingolimod Treatment:

- History of severe allergic reaction or known hypersensitivity to fingolimod or any of its excipients.
- Current treatment with beta-blockers and/or heart rate-lowering calcium channel blockers (e.g., verapamil, diltiazem, or ivabradine).
- Current treatment with digoxin, anticholinesterase agents, or pilocarpine.
- Current treatment with Class Ia (e.g., quinidine, disopyramide) and Class III (e.g., amiodarone, sotalol) antiarrhythmics.
- Current treatment with QT prolonging medications with additional risk factors for QT prolongation (e.g., hypokalemia or congenital QT prolongation).

Laboratory-Based Exclusion Criteria:

- Positive β-hCG at Screening or a positive pregnancy test prior to receiving the first dose of study treatment.
- Positive Hepatitis B surface antigen or positive Hepatitis B core antibody confirmed by a positive Hepatitis B DNA polymerase chain reaction (PCR).
- Positive Hepatitis C antibody.
- Positive plasma rapid plasma reagin confirmed by a microhemagglutination assay or fluorescent treponema antibody absorption test.
- Positive anti-MOG antibody.
- Positive anti-AQP4 antibody.
- Positive serology for HIV.
- Negative serology for varicella zoster virus (vaccination should be considered for eligibility, except for subjects who have already completed a full vaccination course against VZV).
- CD4+ lymphocytes <30%.
- IgG 18% <LLN.
- Immunoglobulin M (IgM) 8% <LLN.
- Absolute neutrophil count (ANC) $<1.5\times10^3/\mu L$.
- ALC <LLN for age- and sex-specific range.
- Liver laboratory evaluations:
  - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma(γ)-glutamyl transferase (GGT) >2× the upper limit of normal (ULN). For prepubertal subjects, >1× ULN or >2× ULN if currently treated with beta interferons or

glatiramer acetate. Isolated ALP elevations are not automatically exclusionary, and investigator discretion should be applied.
- Total and conjugated bilirubin elevation >1.5× ULN, except for subjects with history of Gilbert's syndrome. For prepubertal subjects, >1× ULN or >1.5× ULN if currently treated with beta interferons or glatiramer acetate.

6.2.1.3. Statistical Analysis Plan, Study WN42086

SAP Version 2.0 was submitted under IND 100593 on February 11, 2025, which was prior to the data cutoff date of June 9, 2025. The SAP prespecified the following statistical methods.

All efficacy analyses were conducted using the full analysis set (FAS), which included all randomized subjects, with subjects grouped according to their randomized treatment assignment.

The following estimand was used for analyzing the primary endpoint:

- **Treatment**: Ocrelizumab administered by IV infusion every 24-weeks or fingolimod taken orally once a day.
- **Target population**: Subjects with RRMS aged between ≥10 and <18 years.
- **Primary endpoint**: ARR of the number of protocol-defined relapses during the DBP.
- **Population-level summary for the primary endpoint**: The protocol-defined ARR ratio.
- **Strategies for handling potential intercurrent events**:
  - ***Premature discontinuation from treatment***: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, with the exception of subsequent data used to confirm protocol-defined relapse; assuming the future event rate follows the behavior observed in the period before withdrawing from treatment, hence no imputation will be performed.
  - ***Initiation of another MS treatment***: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis and no imputation will be performed.

The Agency agreed upon the use of the hypothetical strategy for these intercurrent events because data collected after treatment discontinuation or initiation of another medication may look more similar "for reasons that are unrelated to the similarity of the initially randomized treatments," as discussed in the International Council for Harmonisation (ICH) guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021). As such, a treatment policy strategy could be anticonservative for testing the hypothesis of noninferiority.

To control the study-wise type I error rate, a hierarchical testing strategy was used. The five hypotheses were tested in the following order, if all previous hypotheses were significant using a two-sided type I error rate of 5%:

- Noninferiority of ocrelizumab compared with fingolimod based on the ARR of protocol-defined relapses during the DBP.
- Noninferiority of ocrelizumab compared with fingolimod based on the number of new or enlarging T2-hyperintense lesions during the DBP.

- Superiority of ocrelizumab compared with fingolimod based on the number of new or enlarging T2 lesions during the DBP.
- Superiority of ocrelizumab compared with fingolimod based on the number of T1 Gd-enhancing lesions during the DBP.
- Superiority of ocrelizumab compared with fingolimod based on the ARR of protocol-defined relapses during the DBP.

The primary endpoint of the ARR was estimated using a negative binomial model adjusted for the randomization stratification variables of region (United States versus rest of the world), prepubertal status (yes versus no), and presence of T1 Gd lesions at baseline (yes versus no). The log-transformed follow-up time for each subject was included in the model as an offset term. Data collected after the intercurrent events were not included in the model and no imputation of missing data were performed. The resulting estimated ratio of the protocol-defined ARR and the 95% CI was used to test the hypothesis of noninferiority. Noninferiority was concluded if the upper bound of the 95% CI of the ARR ratio was smaller than the prespecified noninferiority margin of 3. The noninferiority margin was prespecified and was justified using the lower bound of the 95% CI of the estimated ARR ratio comparing fingolimod to interferon beta from the pediatric Study CFTY720D2311, which served as the basis for the approval of fingolimod for RMS in pediatric patients 10 years of age and older (Chitnis et al. 2018). No discounting was necessary because superiority to interferon is sufficient. The superiority test used the same analysis model but tested superiority using the p-value.

To assess sensitivity to the assumption that data missing after treatment discontinuation was missing at random, a tipping point analysis was conducted. For the tipping point analysis, relapse rates were predicted for subjects within treatment arms, the predicted relapse rates in the ocrelizumab arm were multiplied by a penalty to reduce the treatment effect, and the number of relapses for the missing follow-up time was simulated using a negative binomial distribution given the penalized relapse rate. This process was repeated 100 times and the results were combined using Rubin's rules to estimate the rate ratio and corresponding uncertainty. The multiple imputation process was repeated for increasing values of the penalty term to assess if the conclusion of noninferiority would change.

The rate ratio of new or enlarging T2 hyperintense lesions was estimated using a negative binomial model adjusted for the randomization stratification variables of region (United States versus rest of the world), prepubertal status (yes versus no), and presence of T1 Gd-enhancing lesions at baseline (yes versus no). The log-transformed count of MRI scans for each subject was included in the model as an offset term. Noninferiority was concluded if the upper bound of the 95% CI of the new or enlarging T2 hyperintense lesion rate ratio was smaller than the prespecified noninferiority margin of 1.27. The noninferiority margin was justified using the lower bound of the 95% confidence interval of the ratio of T2 lesions comparing fingolimod to interferon beta from the pediatric Study CFTY720D2311 with 50% discounting. The same strategies for handling intercurrent events that were used for the primary endpoint were used for analyzing T2 hyperintense lesions. The superiority test used the same analysis model but tested superiority using the p-value.

The rate ratio of T1 Gd-enhancing lesions was estimated using a negative binomial model adjusted for the randomization stratification variables of region (United States versus rest of the world), prepubertal status (yes versus no), and presence of T1 Gd-enhancing lesions at baseline

(yes versus no). No offset term was included in the model because subjects had at most one MRI at Week 12. Superiority was tested using the p-value.

The ratio of the ARR comparing treatment arms was also estimated within the following subgroups:

- Region (United States versus rest of the world)
- Prepubertal status (yes versus no)
- Presence of T1 Gd-enhancing lesions at baseline (yes versus no)
- Baseline weight (≥35 kg versus <35 kg)
- Baseline age (≥14 years old versus <14 years old)
- Early versus late enrollment time (randomized 1 year prior to the last patient last visit date versus within a year of the last patient last visit date)
- Washout period of prior corticosteroids use (>30 days prior to randomization versus ≤30 days prior to randomization)

6.2.1.4. Results of Analyses, Study WN42086

This section presents subject disposition, baseline demographics, and results of the efficacy analyses for the primary and secondary efficacy endpoints.

Subject Disposition

The number (%) of subjects screened, screen failed, and enrolled are shown in Table 12. The number (%) of subjects randomized and discontinued for each arm are shown in Table 13. There were 254 unique subjects screened, with 66 screen failures. The first subject was randomized on May 19, 2022, and the last subject was randomized on November 7, 2024. A total of 187 subjects were enrolled and randomized in the study, with 93 subjects randomized to OCR and 94 subjects randomized to fingolimod. Due to the variable DBP duration, a total of 145 and 71 subjects were anticipated to be followed for at least 48 and 96 weeks, respectively. A total of four subjects in the ocrelizumab arm and 13 subjects in the fingolimod arm were prematurely discontinued from study treatment, including two subjects randomized to fingolimod who discontinued from the study prior to study treatment initiation. All 15 subjects who discontinued study treatment prematurely did not participate in additional safety and efficacy follow-up assessments (See Table 12 and Table 13 for additional details. In the fingolimod arm, three subjects discontinued study treatment due to AEs and four due to lack of efficacy. There were no subjects in the ocrelizumab arm that discontinued study treatment due to AEs or lack of efficacy. As of the data cutoff date (June 9, 2025), study participation was ongoing for 89 subjects in the ocrelizumab arm and 81 subjects in the fingolimod arm.

Table 12. Subject Screening and Enrollment, Study WN42086

Disposition	Study WN42086
Subjects screened, N	254
Screening failures, n (%)	0 (0.0%)
Inclusion/exclusion criteria not met	47 (18.5%)
Subject noncompliance	0 (0.0%)
Consent withdrawn	2 (0.8%)
Withdrawal by investigator	1 (0.4%)
Other	16 (6.3%)
Subjects randomized, n (%)	187 (73.6%)

Source: Clinical study report for Study WN42086
Abbreviations: N, number of subjects; n, number of subjects with given characteristic

Table 13. Subject Disposition, Study WN42086

Parameter	Ocrelizumab N=93 n (%)	Fingolimod N=94 n (%)
Subjects randomized	93 (100)	94 (100)
Randomized, not treated	0 (0.0)	2 (2.1)
ITT population	93 (100)	94 (100)
Safety population	93 (100)	92 (97.9)
Completed DBP	89 (95.7)	81 (86.2)
Discontinued study drug	4 (4.3)	13 (13.8%)
Adverse event	0 (0.0)	3 (3.2%)
Lack of efficacy	0 (0.0)	4 (4.3%)
Lost to follow-up	0 (0.0)	1 (1.1%)
Protocol deviation	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	1 (1.1)
Death	0 (0.0)	0 (0.0)
Withdrawal by subject	3 (3.2)	3 (3.2)
Other	1 (1.1)	1 (1.1)
Discontinued study	4 (4.3)	13 (13.8)
Adverse event	0 (0.0)	1 (1.1)
Death	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	1 (1.1)
Withdrawal by subject	3 (3.2)	8 (8.5)
Physician decision	0 (0.0)	2 (2.1)
Protocol deviation	0 (0.0)	0 (0.0)
Other	1 (1.1)	1 (1.1)

Source: Table 7 in the clinical study report for Study WN42086 and ADSL for WN42086; DCP01RS (tabulated by ARM) and DCT01RS (tabulated by ACTARM) and verified by the statistical reviewer
Abbreviations: DB, double-blind; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with given characteristic

Protocol Deviations

Major protocol deviations occurred in a higher proportion of subjects in the fingolimod arm (75.5%) compared to the ocrelizumab arm (67.7%). The difference between the groups was mostly accounted for by subjects with retreatment criteria not reviewed/met, failure to maintain blinding procedures, and failure to perform ophthalmological assessments and pre/postdose electrocardiograms in the fingolimod arm. The number (%) of subjects per arm who experienced a major protocol deviation during Study WN42086 are depicted in Table 14.

According to the CSR, major deviations due to EDSS assessments not being performed as per protocol, though relatively frequent in both groups, were infrequent in subjects experiencing

relapses. Of particular concern, 26 subjects experienced a major protocol deviation of failure to maintain blinding procedures. Deviations due to failure to maintain the study blind were more common in the fingolimod arm. For more details, see the clinical inspection summary, dated April 13, 2026 (DARRTS ID: 5779527). The evaluation of the potential impact of the failure to maintain study blind is discussed in Section 6.3.2. Overall, the review team did not find evidence that such deviations had an impact on the results of primary outcome analyses.

Table 14. Major Protocol Deviations, Efficacy-Evaluable Population, Study WN42086[1]

Category	Deviation	Ocrelizumab N=93 n (%)	Fingolimod N=94 n (%)
All	Any major deviation	63 (67.7)	71 (75.5)
Exclusion	Current disease or condition not met or not reviewed	1 (1.1)	3 (3.2)
	Serologies missed or not met as per protocol	1 (1.1)	1 (1.1)
	History of exclusionary disease/condition	0 (0.0)	2 (2.1)
	Inability to complete MRI or contraindication to Gd contrast administration	0 (0.0)	1 (1.1)
	Laboratory criteria not met, or central laboratory result unavailable prior to randomization	6 (6.5)	3 (3.2)
	Pregnant, lactating or missing pregnancy test at Screening	2 (2.2)	1 (1.1)
	Previous treatment with prohibited therapies	0 (0.0)	1 (1.1)
	Vaccination within 6 weeks prior to randomization	1 (1.1)	1 (1.1)
Inclusion	Unmet/unconfirmed EDSS criteria	1 (1.1)	2 (2.1)
	Failure to obtain informed consent prior to study procedure initiation	4 (4.3)	3 (3.2)
	Negative serological testing for VZV with no confirmed vaccination	1 (1.1)	0 (0.0)
	No neurological stability for at least 30 days	0 (0.0)	1 (1.1)
Medication	Retreatment criteria not reviewed or not met	12 (12.9)	18 (19.1)
	Received prohibited concomitant medication	11 (11.8)	10 (10.6)
	Noncompliance with study treatment	8 (8.6)	9 (9.6)
	Administration of drug that has exceeded stability criteria	4 (4.3)	1 (1.1)
	Medication error (e.g., frequency, dose, route, delays)	2 (2.2)	1 (1.1)
	Mandatory premedication missed or not administered as per protocol	1 (1.1)	0 (0.0)
	Minimum interval between infusions not met	1 (1.1)	0 (0.0)

Category	Deviation	Ocrelizumab N=93 n (%)	Fingolimod N=94 n (%)
Procedural	Violations of the informed consent process	28 (29.8)	16 (17.2)
	EDSS assessments not performed as per protocol	17 (18.3)	19 (20.2)
	Failure to maintain blinding procedures	9 (9.7)	17 (18.1)
	First-dose monitoring not performed as per protocol	10 (10.8)	12 (12.8)
	Telephone interview not performed within 24 hours following an infusion or failure to perform any interview in between study visits	9 (9.7)	11 (11.7)
	MRI procedures not performed as per protocol	8 (8.6)	11 (11.7)
	Failure to perform any safety assessment	10 (10.8)	6 (6.4)
	Stratification factors unavailable or incorrectly captured	7 (7.5)	6 (6.4)
	Failure to perform pre/post dose ECGs as per protocol	3 (3.2)	7 (7.4)
	Failure to perform ophthalmological assessments	2 (2.2)	8 (8.5)
	Incomplete telephone interview	6 (6.4)	2 (2.2)
	Fingolimod restart not performed as per protocol	0 (0.0)	4 (4.3)
	Delayed reporting of SAEs, AESIs, or pregnancy	0 (0.0)	3 (3.2)
	Failure to perform pregnancy test	1 (1.1)	2 (2.1)

Source: Clinical study report for Study WN42086 and addv.xpt for Study WN42086, EEPFL=Y; tabulated by ACTARM
[1] Duration=At least 24 weeks of DB treatment.
Abbreviations: AESI, adverse events of special interest; DB, double-blind; ECG, electrocardiogram; EDSS, Expanded Disability Status Scale; Gd, gadolinium; MRI, magnetic resonance imaging; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SAE, serious adverse event; VZV, *varicella zoster* virus

Baseline Demographic Characteristics

Baseline demographic characteristics for the randomized population (FAS) stratified by treatment arm are presented in Table 15. Continuous covariates were summarized by mean, standard deviation (SD), median, minimum, and maximum. Categorical variables were summarized by count and percentage. A total of 187 subjects were included in the FAS (all randomized) for Study WN42086. Most subjects were female, ≥14 years of age, White, not Hispanic, and from countries outside of the United States. Overall, there appears to be an acceptable balance of demographic characteristics between the ocrelizumab and fingolimod arms.

Table 15. Baseline Demographics and Clinical Characteristics, Full Analysis Set, Study WN42086

Characteristic	Ocrelizumab N=93 n (%)	Fingolimod N=94 n (%)	Total N=187 n (%)
Age (years)			
Mean (SD)	15.0 (1.5)	15.0 (1.5)	15.0 (1.5)
Median	15	15	15
Min, max	11.0, 17.0	12.0, 17.0	11.0, 17.0
Age group			
<12	1 (1.1)	0	1 (<1)
≥12 to <14	13 (14.0)	19 (20.2)	32 (17.1)
≥14	79 (84.9)	75 (79.8)	154 (82.4)
Sex			
Male	26 (28.0)	32 (34.0)	58 (31.0)
Female	67 (72.0)	62 (66.0)	129 (69.0)

Characteristic	Ocrelizumab N=93 n (%)	Fingolimod N=94 n (%)	Total N=187 n (%)
Ethnicity			
Hispanic or Latino	26 (28.0)	18 (19.1)	44 (23.5)
Not Hispanic or Latino	50 (53.8)	55 (58.5)	105 (56.1)
Unknown	0	2 (2.1)	2 (1.1)
Not reported	17 (18.3)	19 (20.2)	36 (19.3)
Race			
American Indian or Alaska Native	4 (4.3)	3 (3.2)	7 (3.7)
Asian	1 (1.1)	1 (1.1)	2 (1.1)
Black or African American	3 (3.2)	6 (6.4)	9 (4.8)
Native Hawaiian or other Pacific Islander	0	0	0
White	63 (67.7)	60 (63.8)	123 (65.8)
Multiple	6 (6.5)	4 (4.3)	10 (5.3)
Unknown	1 (1.1)	1 (1.1)	2 (1.1)
Not reported	15 (16.1)	19 (20.2)	34 (18.2)
Region (stratification variable)			
United States	11 (11.8)	10 (10.6)	21 (11.2)
Rest of world	82 (88.2)	84 (89.4)	166 (88.8)
Country			
Brazil	12 (12.9)	11 (11.7)	23 (12.3)
France	10 (10.8)	11 (11.7)	21 (11.2)
Poland	11 (11.8)	14 (14.9)	25 (13.4)
United States	11 (11.8)	10 (10.6)	21 (11.2)
Other	49 (52.7)	48 (51.1)	97 (51.9)

Source: Table 9 in the clinical study report for Study WN42086, verified by the statistical reviewer; ADSL dataset, FASFL=Y; tabulated by TRT01P
Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

Baseline Clinical, Disease, and MRI Characteristics

Baseline clinical characteristics for the FAS are presented in Table 16. The treatment groups appeared to be similar in terms of height, weight, body mass index, and Tanner stage.

Table 16. Baseline Clinical Characteristics, Full Analysis Set, Study WN42086

Characteristic	Ocrelizumab N=93	Fingolimod N=94	Total N=187
Height (cm)			
Mean (SD)	167.0 (8.6)	166.6 (8.3)	166.8 (8.4)
Median	166.7	166.1	166.4
Min, max	144.5, 189.0	145.0, 188.0	144.5, 189.0
Missing	0	2	2
Weight (kg)			
Mean (SD)	69.0 (18.5)	67.6 (17.2)	68.3 (17.8)
Median	63.1	63.5	63.1
Min, max	50.0, 154.2	42.3, 123.0	42.3, 154.2
Missing	0	2	2
BMI (kg/m^2)			
Mean (SD)	24.7 (6.5)	24.3 (5.5)	24.5 (6.0)
Median	23.2	22.9	23.1
Min, max	16.4, 59.5	16.8, 46.3	16.4, 59.5
Missing	0	2	2

Characteristic	Ocrelizumab N=93	Fingolimod N=94	Total N=187
Tanner stage (verified value)			
<2	1 (1.1)	2 (2.1)	3 (1.6)
≥2	90 (96.8)	89 (94.7)	179 (95.7)
Missing	2 (2.2)	3 (3.2)	5 (2.7)
Prepubertal status (prerandomization value)			
Yes	7 (7.5)	6 (6.4)	13 (7.0)
No	86 (92.5)	88 (93.6)	174 (93.0)

Source: Table 9 in the clinical study report for Study WN42086, verified by the statistical reviewer; ADSUB, FASFL=Y; tabulated by TRT01P
Abbreviations: BMI, body mass index; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

Baseline disease characteristics for the safety population are presented in Table 17 and Table 18. Overall, the treatment arms appeared to be similar in terms of MS disease characteristics. However, a higher proportion of subjects in the fingolimod arm had previously been treated with an approved MS therapy. The difference was primarily driven by a higher proportion of subjects previously treated with dimethyl fumarate in the fingolimod arm. The proportion of subjects in each treatment arm with history of treatment with systemic corticosteroids for MS relapse, chronic use for MS, and for other indications were clarified with the Applicant via an information request.

Table 17. Baseline MS Disease Characteristics, Safety Population, Study WN42086

Characteristic	Ocrelizumab N=93	Fingolimod N=92	Total N=185
Time since MS diagnosis (years)			
n (%)	93 (100)	92 (100)	185 (100)
Mean (SD)	0.6 (0.7)	0.7 (0.8)	0.7 (0.7)
Median (IQR)	0.4 (0.5)	0.5 (0.6)	0.4 (0.5)
Min, max	0.1, 4.4	0.1, 4.8	0.1, 4.8
Time since MS symptom onset (years)			
n (%)	93 (100)	91 (98.9)	184 (99.5)
Mean (SD)	1.1 (1.1)	1.3 (1.2)	1.2 (1.1)
Median (IQR)	0.7 (1.2)	0.9 (1.2)	0.8 (1.2)
Min, max	0.1, 6.7	0.1, 6.9	0.1, 6.9
Time since last relapse (months)			
n (%)	93 (100)	91 (98.9)	184 (99.5)
Mean (SD)	5.8 (4.9)	6.1 (4.1)	5.9 (4.5)
Median (IQR)	4.0 (3.4)	4.9 (4.6)	4.4 (3.9)
Min, max	0.7, 33.5	0.9, 21.8	0.7, 33.5
Baseline EDSS score			
n (%)	93 (100)	92 (100)	185 (100)
Mean (SD)	1.5 (1.1)	1.4 (1.2)	1.5 (1.2)
Median (IQR)	1.5 (1.2)	1.5 (2.0)	1.5 (2.0)
Min, max	0, 4.5	0, 5.5	0, 5.5

Source: ADSUB for WN42086, SAFFL=Y; tabulated by ACTARM
Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range; max, maximum; min, minimum; MS, multiple sclerosis; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

Table 18. Prior MS Treatments, Safety Population, Study WN42086

MS Treatment	Ocrelizumab N=93 n (%)	Fingolimod N=92 n (%)	Total N=185 n (%)
Any prior MS therapy	13 (14.0)	20 (21.7)	33 (17.8)
Glatiramer acetate	5 (5.4)	7 (7.6)	12 (6.5)
Interferon beta-1a	4 (4.3)	5 (5.4)	9 (4.9)
Dimethyl fumarate	2 (2.2)	7 (7.6)	9 (4.9)
Interferon beta-1b	1 (1.1)	0 (0.0)	1 (0.5)
Teriflunomide	1 (1.1)	0 (0.0)	1 (0.5)
Peginterferon beta-1a	0 (0.0)	1 (1.1)	1 (0.5)
Previous treatment with corticosteroids	17 (18.3)	16 (17.4)	33 (17.8)
Acute treatment of MS relapse	12 (12.9)	14 (15.2)	26 (14.1)
Chronic use for MS	5 (5.4)	5 (5.4)	10 (5.4)
Other indications	0 (0.0)	1 (1.1)	1 (0.5)

Source: adsub.xpt for Study WN42086, SAFFL=Y; tabulated by ACTARM and Applicant's response to information request, dated March 20, 2026
Abbreviations: MS, multiple sclerosis; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

Baseline MRI characteristics for the FAS are presented in Table 19. The number and volume of Gd-enhancing and T2 hyperintense lesions at baseline were comparable between the groups.

Table 19. Baseline MRI Characteristics, Full Analysis Set, Study WN42086

Characteristic	Ocrelizumab N=93	Fingolimod N=94	Total N=187
Presence of T1 gadolinium-enhancing lesions at baseline[1]			
Yes	44 (47.3)	44 (46.8)	88 (47.1)
No	49 (52.7)	50 (53.2)	99 (52.9)
Number of T1 gadolinium-enhancing lesions[2]			
Mean (SD)	2.5 (4.8)	2.3 (4.5)	2.4 (4.6)
Median	0	0	0
Min, max	0.0, 28.0	0.0, 24.0	0.0, 28.0
0	48 (51.6)	49 (52.1)	97 (51.9)
1	15 (16.1)	11 (11.7)	26 (13.9)
2	6 (6.5)	9 (9.6)	15 (8.0)
3	4 (4.3)	8 (8.5)	12 (6.4)
≥4	20 (21.5)	16 (17.0)	36 (19.3)
Missing	0	1 (1.1)	1 (<1)
Volume of T1 gadolinium-enhancing lesions (mL)			
Mean (SD)	2.0 (3.1)	1.8 (2.3)	1.9 (2.7)
Median	0.9	0.8	0.9
Min, max	0.0, 16.9	0.0, 10.7	0.0, 16.9
Missing	0	1	1
Number of T2 lesions			
Mean (SD)	57.4 (46.6)	57.4 (48.2)	57.4 (47.3)
Median	42	42	42
Min, max	5.0, 237.0	2.0, 216.0	2.0, 237.0
Missing	0	1	1

Characteristic	Ocrelizumab N=93	Fingolimod N=94	Total N=187
Volume of T2 lesions (mL)			
Mean (SD)	11.0 (10.8)	11.8 (12.4)	11.4 (11.6)
Median	8.5	8.9	8.7
Min, max	0.6, 61.0	0.2, 72.6	0.2, 72.6
Missing	0	1	1

Source: Table 9 in the clinical study report for Study WN42086, verified by the statistical reviewer; ADSUB for and ADMRI for WN42086, FASFL=Y; tabulated by TRT01P
[1] Prerandomization value used for stratification.
[2] Verified value.
Abbreviations: IQR, interquartile range; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

General medical history for subjects enrolled in Study WN42086 by arm was reviewed as well. Ongoing medical disorders (defined by MHENRTPT=ONGOING) occurring in >5% of subjects in either treatment arm are presented in Table 20. A higher proportion of subjects in the fingolimod arm had an ongoing medical history of myopia. A higher proportion of subjects in the ocrelizumab arm had an ongoing medical history of drug hypersensitivity and headache.

Table 20. Concurrent Medical Disorders Reported in >5% of Either Treatment Arm, Safety Population, Study WN42086

System Organ Class	Dictionary-Derived Term[1]	Ocrelizumab (N=93) n (%)	Fingolimod (N=92) n (%)
Eye disorders	Hypermetropia	5 (5.4)	2 (2.2)
	Myopia	4 (4.3)	11 (12.0)
General disorders and admin. site conditions	Asthenia	5 (5.4)	2 (2.2)
Immune system disorders	Drug hypersensitivity	6 (6.5)	3 (3.3)
	Seasonal allergy	5 (5.4)	4 (4.3)
Metabolism and nutrition disorders	Obesity	2 (2.2)	5 (5.4)
	Vitamin D deficiency	9 (9.7)	7 (7.6)
Nervous system disorders	Headache	10 (10.8)	6 (6.5)
	Migraine	3 (3.2)	6 (6.5)
Psychiatric disorders	Anxiety	10 (10.8)	9 (9.8)
	Depression	5 (5.4)	4 (4.3)
Reproductive system and breast disorders	Dysmenorrhea	5 (5.4)	2 (2.2)
Skin and subcutaneous tissue disorders	Acne	6 (6.5)	6 (6.5)

Source: ADMH for WN42086, SAFFL=Y, MHENRTPT=ONGOING; tabulated by ACTARM
[1] MHDECOD in ADMH.
Abbreviations: admin., administration; N, number of subjects in treatment arm; n, number of subjects with given characteristic

Treatment Compliance

Of the 187 subjects randomized (n=93 ocrelizumab; n=94 fingolimod), two subjects in the fingolimod arm were excluded prior to treatment initiation. Although there were no subjects excluded from the ocrelizumab arm, the number of subjects in each group remained balanced. The remaining 185 subjects received at least one dose of ocrelizumab (n=93) or fingolimod (n=92). Compliance with ocrelizumab and fingolimod in the DBP appeared to be similar between treatment arms. According to the CSR, treatment compliance for ocrelizumab/IV placebo infusions was 100%. For fingolimod/PO placebo, overall treatment compliance was ≥80%.

Concomitant Medications

Per the Applicant's CSR, the most commonly used concomitant medication classes were analgesics, anti-inflammatory and antirheumatic products, ophthalmologicals, other dermatological preparations, other gynecologicals, and topical products for joint and muscular pain. The frequency of subjects receiving concomitant medications for each drug category was reviewed. Concomitant medications used by ≥5% of subjects in the safety population during the DBP are shown in Table 21.

Table 21. Selected Concomitant Medications Used by ≥5% of Either Treatment Arm, Safety Population, Study WN42086, Double-Blind Period

Medication Class	Medication Name	Ocrelizumab (N=93) n (%)	Fingolimod (N=92) n (%)
Analgesics	Paracetamol	43 (46.2)	36 (39.1)
	Metamizole sodium	8 (8.6)	9 (9.8)
Antibacterials for systemic use	Amoxicillin	10 (10.8)	8 (8.7)
	Azithromycin	7 (7.5)	6 (6.5)
Antiemetics and antinauseants	Ondansetron	5 (5.4)	5 (5.4)
Anti-inflammatory and antirheumatic products	Ibuprofen	32 (34.4)	22 (23.9)
Corticosteroids for systemic use	Methylprednisolone	8 (8.6)	9 (9.8)
	Prednisone	7 (7.5)	6 (6.5)
Drugs for acid related disorders	Omeprazole	5 (5.4)	7 (7.6)
Vitamins	Cholecalciferol	8 (8.6)	7 (7.6)

Source: ADCM for Study WN42086, where ATIREL="CONCOMITANT," CMCAT="CONCOMITANT MEDICATIONS," ONTRFL=Y; ATC2 and CMDECOD tabulated by ACTARM and Applicant's response to information request, dated March 20, 2026
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given characteristic

Rescue Medication Use

The number of subjects in the safety population who received treatment with systemic corticosteroids for the acute treatment of an MS relapse during the DBP of Study WN42086 were clarified with the Applicant via an information request and are presented in Table 22. According to the Applicant, the ADCM dataset variables and/or flag(s) used to tabulate the number of subjects who received systemic corticosteroids for the acute treatment of MS relapses were ATC2="CORTICOSTEROIDS FOR SYSTEMIC USE," ANL01FL="Y," and C_{MIN}DC="RELAPSE." A higher proportion of subjects in the fingolimod arm received rescue medication compared to the ocrelizumab arm.

Table 22. Summary of Subjects Who Received Concomitant Steroids for the Treatment of MS Relapses, Study WN42086, Double-Blind Period

Relapse Parameter	Ocrelizumab N=93	Fingolimod N=92	Total N=185
Protocol-defined MS relapse	7 (7.5)	12 (13.0)	19 (10.3)
Clinical relapse	8 (8.6)	13 (14.1)	21 (11.4)

Source: Applicant's response to information request, dated March 20, 2026
Abbreviations: MS, multiple sclerosis; N, number of subjects in treatment arm; n, number of subjects given characteristic

Efficacy Results, Study WN42086

Primary Efficacy Results

The primary endpoint was the protocol-defined ARR during the DBP. The estimated annualized protocol-defined relapse rates per arm (unadjusted and adjusted) are shown in Table 23. Subjects randomized to the ocrelizumab arm had an estimated 48.3% lower (relative risk 0.517; 95% CI: 0.193, 1.329) ARR compared to subjects randomized to the fingolimod arm. The upper bound of the 95% confidence interval for the rate ratio was less than 3; therefore, ocrelizumab is noninferior to fingolimod at reducing the ARR. The results of the tipping point analysis and other sensitivity analyses were similar; see Section 6.3.3. The p-value for testing superiority is also shown in Table 23. This study did not provide evidence of superiority for ocrelizumab over fingolimod at reducing the ARR.

Table 23. Ratio of the Annualized Relapse Rate, Full Analysis Set, Study WN42086, Double-Blind Period

Parameter	Ocrelizumab N=93	Fingolimod N=94
Number (%) of subjects who experienced a protocol-defined relapse during the DBP	9 (9.7)	13 (13.8)
Number of protocol-defined relapses experienced per subject during the DBP		
0 (n (%))	84 (90.3)	81 (86.2)
1 (n (%))	8 (8.6)	10 (10.6)
2 (n (%))	1 (1.1)	3 (3.2)
Early discontinuations		
Number (%) who discontinued treatment early	4 (4.3)	13 (13.8)
Number (%) with 0 weeks of follow-up	0 (0)	2 (2.1)
Total patient-years missing after treatment discontinuation	3.45	14.08
DBP follow-up time (weeks)		
Mean (SD)	76.7 (35.7)	72.2 (37.9)
Median (IQR)	72.1 (59.6)	70.9 (67.8)
Min, max	24, 158.9	0, 141.7
Unadjusted annualized relapse rate		
Total number of protocol-defined relapses	10	16
Total patient-years followed	136.76	130.04
Unadjusted ARR	0.073	0.123
Adjusted annualized relapse rate[1]	0.07	0.135
95% CI	(0.034, 0.144)	(0.075, 0.243)

Parameter	Ocrelizumab N=93	Fingolimod N=94
Adjusted annualized relapse rate ratio	0.517	
95% CI[2]	(0.193, 1.329)	
p-Value[3]	0.159	

Source: Table 16 in the CSR and verified by the statistical reviewer
Protocol-defined relapses were calculated using the ADRLP dataset, where FASFL=Y, PARAMCD=PDR; AVALC=Y; I01E01FL !=Y; I01E02FL !=Y.
The analysis used the full analysis set (FAS). Follow-up time was defined as the time on treatment. A hypothetical strategy was used for the intercurrent events of treatment discontinuation and initiation of any other MS disease modifying treatment where data collected after the intercurrent events was excluded. The adjusted ARR ratio was estimated using a negative binomial model adjusted for region (U.S. versus rest of the world), verified (postrandomization) prepubertal status, and presence of T1 Gd lesions at baseline. The log-transformed follow-up time for each subject was included in the model as an offset term. The model was fit using the glm.nb function from the MASS package in R version 4.5.3.
[1] The adjusted annualized relapse rate was estimated using a negative binomial model only adjusted for region and presence of T1 Gd lesions at baseline. Prepubertal status was removed from the model due to convergence issues.
[2] Noninferiority evaluation, noninferiority was established if the upper bound of the 95% CI was less than the prespecified noninferiority margin of 3
[3] Superiority evaluation.
Abbreviations: ARR, annualized relapse rate; CI, confidence interval; CSR, case study report; DBP, double-blind period; FAS, full analysis set; IQR, interquartile range; max, maximum; min, minimum; N, number of subjects in treatment arm; SD, standard deviation

Secondary Efficacy Results

Secondary efficacy outcomes were evaluated according to the prespecified hierarchical order to control for multiplicity. For details, see Section 6.2.1.3.

New or Enlarging T2 Hyperintense Lesions

Though the study was not formally powered for testing secondary efficacy outcomes, one of the secondary radiologic efficacy endpoints was the annualized rate of the number of new or enlarging T2 hyperintense lesions. The number of subjects with an MRI for assessing the number of new or enlarging T2 hyperintense MRI lesions, the number of subjects with a new or enlarging T2 hyperintense lesion, and a summary of the counts of T2 hyperintense lesions per visit is shown in Table 24.

Table 24. Summary of the Number of New and/or Newly Enlarging T2 Hyperintense Lesions as Detected by Brain MRI by Visit, Full Analysis Set, Study WN42086, Double-Blind Period

	Ocrelizumab (N=93)					Fingolimod (N=94)				
Visit	n With MRI	n With T2 Lesions	# of T2 Lesions	Mean (SD) # T2 Lesions	Min, Max # T2 Lesions	n With MRI	n With T2 Lesions	# of T2 Lesions	Mean (SD) # T2 Lesions	Min, Max # T2 Lesions
Baseline/ Screening	93	93	5337	57.4 (46.6)	5, 237	93	93	5342	57.4 (48.2)	2, 216
Week 12	93	72	479	5.2 (7.6)	0, 33	89	63	611	6.9 (13.8)	0, 114
Week 24	93	6	9	0.1 (0.4)	0, 2	87	37	111	1.3 (2.4)	0, 13
Week 48	72	4	4	0.1 (0.2)	0, 1	65	31	100	1.5 (3)	0, 17
Week 72	48	3	3	0.1 (0.2)	0, 1	47	20	46	1 (1.5)	0, 7
Week 96	32	0	0	0 (0)	0, 0	29	12	40	1.4 (2.8)	0, 12

Source: Table 18 in the clinical study report, modified by the statistical reviewer
Abbreviations: max, maximum; min, minimum; MRI, magnetic resonance imaging; N, number of subjects in treatment arm; SD, standard deviation; n, number of subjects with given characteristic

Analysis of the count of new or enlarging hyperintense T2-weighted lesions was performed in the FAS (see Table 25). The estimated adjusted rate of new or enlarging T2 lesions during the DBP was lower in the ocrelizumab arm compared to the fingolimod arm. Subjects in the ocrelizumab arm had a 47.8% reduction (risk ratio 0.522; 95% CI: 0.359, 0.760) in the adjusted T2 lesion rate ratio during the DBP. The criteria for noninferiority and superiority were met; the results provide evidence that ocrelizumab is superior to fingolimod at reducing the rate of new or enlarging T2 hyperintense lesions.

Table 25. Rate Ratio of the Number of New or Enlarging Hyperintense T2-Weighted MRI Lesions, Full Analysis Set, Study WN42086, Double-Blind Period

Lesion Parameter	Ocrelizumab N=93	Fingolimod N=94
Number of subjects with new or enlarging T2 lesions during the DBP	73 (78.5%)	71 (75.5%)
Number of new or enlarging T2 lesions during the DBP	495	908
Total patient-years observed	121.79	116.07
Unadjusted rate	4.064	7.823
Adjusted lesion rate	3.778	7.235
95% CI	(2.896, 4.929)	(5.578, 9.383)
Adjusted lesion rate ratio	0.522	
95% CI[1]	(0.359, 0.760)	
p-Value[2]	0.0006	

Source: Table 18 in the CSR and 20260331-clin-amend.pdf submitted in eCTD 1915; verified by the statistical reviewer
The count of T2 lesions were calculated using the ADMRI dataset, where FASFL=Y, PARAMCD=T2COUNT, ANL01FL=Y, AVISIT="Week 12," "Week 24," "Week 48," "Week 72," and "Week 96."
The analysis used the full analysis set (FAS). A hypothetical strategy was used for the intercurrent events of treatment discontinuation and initiation of any other MS disease modifying treatment where data collected after the intercurrent events was excluded. The adjusted ARR ratio was estimated using a negative binomial model adjusted for region (U.S. versus rest of the world), verified (postrandomization) prepubertal status, and presence of T1 Gd lesions at baseline. The log-transformed number of MRI scans for each patient was included in the model as an offset term. The model was fit using the glm.nb function from the MASS package in R version 4.5.3.
[1] Noninferiority evaluation, the upper bound of the 95% CI was compared to the prespecified noninferiority margin of 1.27.
[2] Superiority evaluation
Abbreviations: CI: confidence interval; CSR, clinical study report; DBP: double-blind period; Gd, gadolinium; IQR, interquartile range; MRI, magnetic resonance imaging; N, number of subjects in treatment arm; U.S., United States

Gadolinium-Enhancing T1 Lesions

Though the study was not formally powered for testing secondary efficacy outcomes, an additional secondary radiologic efficacy endpoint was the number of Gd-enhancing T1 lesions at Week 12. Analysis of this endpoint was performed in the FAS population (see Table 26). Refer to Table 19 for a summary of baseline Gd-enhancing lesions per treatment arm. The total number of Gd-enhancing lesions at Week 12 was five in the ocrelizumab arm and 33 in the fingolimod arm. Subjects in the ocrelizumab arm had an 87.2% reduction (risk ratio 0.128; 95% CI: 0.034, 0.414) in the adjusted Gd-enhancing T1 lesion rate ratio during the DBP. The criterion for superiority was met; the results provide evidence that ocrelizumab is superior to fingolimod at reducing the Gd-enhancing T1 lesion rate.

Table 26. Gadolinium-Enhancing T1-Weighted MRI Lesions at Week 12, Full Analysis Set, Study WN42086

Lesion Parameter	Ocrelizumab N=93	Fingolimod N=94
Number of subjects with available data at Week 12 visit	93 (100%)	88 (93.6%)
Number of subjects with T2 Gd-enhancing lesions at Week 12 visit	4	14
Number of T1 Gd-enhancing lesions at Week 12 visit	5	33
Total patient-years between Baseline and Week 12 visit	30.44	30.41
Mean (SD) of T1 Gd-enhancing lesions	0.1 (0.27)	0.4 (1.12)
Min, max of T1 Gd-enhancing lesions	0, 2	0, 6
Unadjusted rate	0.054	0.375
Adjusted rate[1]	0.031	0.243
95% CI	(0.01, 0.1)	(0.121, 0.488)
Adjusted Rate Ratio	0.128	
95% CI	(0.034, 0.414)	
p-Value	0.0012	

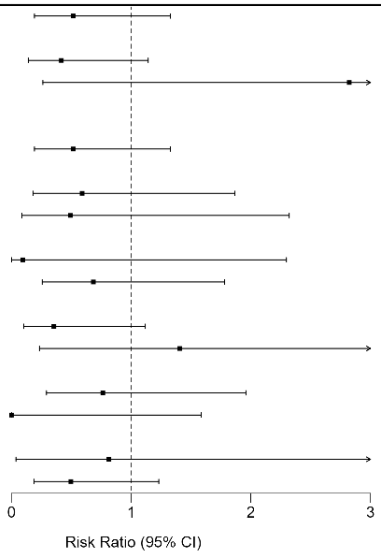
Source: Table "Total Number of T1 Gadolinium-Enhancing Lesions as Detected by Brain MRI at Week 12, Full Analysis Set Protocol: WN42086" in the CSR and 20260331-clin-amend.pdf submitted in eCTD 1915. Verified by the statistical reviewer.
The count of T1 Gd lesions were calculated using the ADMRI dataset, where FASFL=Y, PARAMCD=T1COUNT, ANL01FL=Y, AVISIT="Week 12."
The analysis used the full analysis set (FAS). A hypothetical strategy was used for the intercurrent events of treatment discontinuation and initiation of any other MS disease modifying treatment where data collected after the intercurrent events was excluded. The adjusted ARR ratio was estimated using a negative binomial model adjusted for region (U.S. versus rest of the world), verified (postrandomization) prepubertal status, and presence of T1 Gd lesions at baseline. No offset term was included in the model because subjects had at most one MRI scan from Week 12. The model was fit using the glm.nb function from the MASS package in R version 4.5.3.
[1] The adjusted annualized relapse rates were estimated using a negative binomial model only adjusted for presence of T1 Gd lesions at baseline. Region and prepubertal status was removed from the model due to convergence issues.
Abbreviations: CI: confidence interval; CSR, clinical study report; Gd: gadolinium; max, maximum; min, minimum; MRI, magnetic resonance imaging; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

Subgroup Analyses

The estimated adjusted relapse rates per arm and the corresponding estimated ratio of the relapse rates (95% CI) are shown in Table 27. The point estimate of the risk ratio for subjects from the United States numerically favored the fingolimod arm. Similarly, the point estimate of the risk ratio for subjects who enrolled within 1 year of the study end (and thus had shorter follow-up time) numerically favored the fingolimod arm. However, the CIs across subgroups for both were overlapping. There was not sufficient information to make definitive conclusions about these subgroups.

Table 27. Annualized Protocol-Defined Relapse Rate Ratio by Subgroup, Study WN42086, Double-Blind Period

Variable	N total	OCR n	OCR PY	OCR PDR	FINGO n	FINGO PY	FINGO PDR	RR (95% CI)
FAS	187	93	136.76	10	94	130.04	16	0.52 (0.19, 1.33)
Region								
Rest of World	166	82	118.75	7	84	115.74	15	0.42 (0.14, 1.14)
United States	21	11	18.02	3	10	14.3	1	2.82 (0.26, 67.44)
Tanner Stage								
<2	3	1	1.2	0	2	1.23	0	NE (NE, NE)
>=2	184	92	135.56	10	92	128.81	16	0.52 (0.19, 1.33)
Presence of T1-Gd lesions								
Yes	88	44	64.43	7	44	57.07	9	0.59 (0.18, 1.86)
No	99	49	72.33	3	50	72.96	7	0.49 (0.09, 2.32)
Age Group								
<14 years old	33	14	20.54	1	19	30.08	5	0.10 (0.00, 2.30)
>=14 years old	154	79	116.22	9	75	99.95	11	0.68 (0.26, 1.78)
Time of Enrollment								
Early	135	67	117.53	7	68	111.99	14	0.36 (0.10, 1.12)
Late	52	26	19.23	3	26	18.05	2	1.41 (0.23, 10.69)*
Corticosteroid use								
>30 days prior to randomization	171	85	127.62	10	86	116.76	11	0.76 (0.29, 1.96)
<= 30 days prior to randomization	16	8	9.14	0	8	13.28	5	0.00 (0.00, 1.586)**
DMT prior to baseline								
Yes	34	13	18.29	1	21	29.85	2	0.82 (0.04, 8.52)*
No	153	80	118.47	9	73	100.19	14	0.50 (0.19, 1.23)



Source: Figure 3 in the Study WN42086 clinical study report, modified by the statistical reviewer
The rate ratio, confidence intervals, and dispersion parameter are estimated using a Negative Binomial regression model for the total number of events adjusted for region, prepubertal status, and presence of T1 Gd-enhancing lesions at baseline. The prepubertal status was removed for subgroups with convergence issues. All randomized subjects were ≥35 kg and thus the prespecified baseline weight subgroup analysis was not conducted. Note that for each subgroup, the review team used the model most similar to the negative binomial model with all three adjustment variables that would still converge.
* In the case that removing all adjustment covariates could not solve convergence issues, a Poisson model was used instead.
** If there were zero counts in one arm, an exact Poisson model was used.
Abbreviations: CI, confidence interval; DMT, disease modifying therapy; FAS, full analysis set; FINGO, fingolimod; Gd, gadolinium; N, number of subjects in treatment arm; n, number of subjects with given characteristic; NE, not estimable; OCR, ocrelizumab; PDR, protocol-defined relapses; PY, patient-years; RR, relapse rate

6.2.2. Study WA39085

Overview and Objective

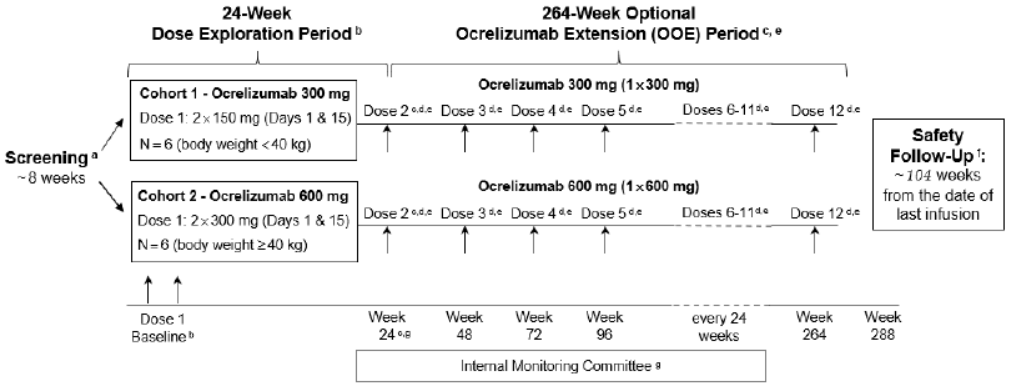
Study WA39085 was a phase 2, multicenter, open-label, parallel-group, dose-ranging study that evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of ocrelizumab, in pediatric subjects with RRMS aged ≥10 to <18 years.

The primary objectives of the study were to characterize the ocrelizumab PK (as determined by the serum concentration of ocrelizumab) and to evaluate relationship between drug exposure and PD (as measured by CD19+ B-cell counts) to identify an ocrelizumab dose that results in the same exposure and PD in children and adolescents as that observed in adults with MS with the approved 600-mg dose. The selected dose was subsequently evaluated in the phase 3 Study WN42086. The secondary objectives were to evaluate the safety and immunogenicity of ocrelizumab in this subject population based on incidence and severity of AEs (Common Terminology Criteria for Adverse Events version 5.0), change from baseline in vital signs, laboratory evaluations (including circulating B-cells, T-cells, natural killer-cells, leukocyte, serum immunoglobulin levels, and vaccine antibody titers), developmental milestones, non-MS brain pathology, and incidence of treatment-emergent ADAs.

Study Design

Subjects with a body weight of ≥25 kg to <40 kg (Cohort 1; n=6) received treatment with ocrelizumab 300 mg IV and subjects with a body weight ≥40 kg (Cohort 2; n=6) received treatment with ocrelizumab 600 mg IV. The initial dose of ocrelizumab was administered as two separate IV infusions given 14 days apart. All subsequent doses were administered as a single infusion every 24 weeks. The study (Figure 10) consisted of an 8-week screening period, a 24-week dose-exploration period, followed by a 264-week optional OCR extension period, and a ~104-week SFU period. The total duration of study participation for individual subjects was ~402 weeks (~8 years).

Figure 10. Study Schematic, Study WA39085, Protocol Version 10



IMC = Internal Monitoring Committee; OOE = Optional Ocrelizumab Extension.

[a] Screening for the study may be extended but cannot exceed 10 weeks for relevant clinical, administrative, or operational reasons.

[b] Eligible patients will be allocated into one of two treatment groups depending on their body weight at screening. The first dose of ocrelizumab for the 24-week period must be administered as two infusions of half the dose 14 days apart. Patients who receive a partial or complete dose of ocrelizumab and discontinue from the 24–week period will enter the safety follow-up period (at least *104* weeks).

[c] At Week 24, patients will have the opportunity to continue with ocrelizumab treatment by entering a 264–week optional ocrelizumab extension period. For patients continuing the extension, subsequent doses of ocrelizumab will be administered if all re-treatment criteria are met.

[d] Treating investigator must ensure patients meet criteria for re-treatment with ocrelizumab before each subsequent infusion (Section 4.3.6).

[e] It is planned that patients will continue in the optional ocrelizumab extension period with the dose corresponding to their initial treatment regimen until the appropriate dosing regimen is selected by the IMC. At that time, patients will be assigned to this selected dose level. In a situation where a subsequent dose is higher than the initial treatment regimen, that dose must be administered as two infusions of half the dose 14 days apart.

[f] Patients completing the 288–week treatment period, or patients who discontinue treatment prematurely for any reason at any time during the study, will enter the safety follow–up period (for more details see Section 3.1.1.4).

[g] The IMC will review all data obtained in each cohort (for more details see Section 3.1.1).

Source: Applicant's protocol, version 10, Study WA39085
Abbreviation: N, number of subjects in treatment arm

Eligibility Criteria

Inclusion Criteria

Key inclusion criteria were as follows: age between ≥10 and <18 years, body weight ≥25 kg, diagnosis of RRMS according to the 2012 IPMSSG Criteria for pediatric MS or the Revised 2017 McDonald Criteria, and EDSS score of 0 to 5.5. Subjects naïve to treatment with MS therapies and those with <6 months of exposure to an MS therapy in the last 6 months must have experienced ≥2 relapses in the last 2 years (including 1 in the last year) OR ≥2 relapses in the last 2 years and ≥1 gadolinium-enhancing T1 lesion on brain MRI in the last year. Subjects with at least 6 months of continuous treatment with an MS therapy in the prior year must have evidence

of disease activity after 6 months of continuous treatment (i.e., ≥1 relapse or ≥1 gadolinium-enhancing T1 lesion).

Exclusion Criteria

Key exclusion criteria were presence or suspicion of other neurologic disorders that may mimic MS (e.g., ADEM, neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein associated disease), anti-AQP4 or anti-MOG antibody positivity, atypical MRI findings (e.g., ADEM-like CNS lesions, lesions in atypical locations for MS, bilateral optic neuritis, spinal cord lesions spanning ≥3 segments), and history of a severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies or to OCR or any of its excipients. Subjects with history of treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, obinutuzumab, atacicept, belimumab, or ofatumumab) were also excluded.

Overall Assessment of Phase 2 Study Design

Study WA39085 was appropriately designed to meet its stated dose-finding objective. Refer to Section 5.3.

Baseline Clinical Characteristics

Baseline demographic characteristics for the safety population stratified by treatment arm are presented in Table 28. Continuous covariates were summarized by mean, SD, median, minimum, and maximum. Categorical variables were summarized by count and percentage. A total of 23 subjects were included in the safety population (all randomized) for Study WA39085. Most subjects were female, ≥14 years of age, White, not Hispanic, and from countries outside of the United States. Overall, there appears to be an acceptable balance of demographic characteristics between the ocrelizumab 300 mg and 600 mg arms.

In terms of baseline clinical characteristics, subjects in the ocrelizumab 300 mg arm had lower baseline height and weight compared to the ocrelizumab 600 mg arm, which was expected due to the weight-based dosing cutoffs for ocrelizumab in pediatric subjects. Of note, the lowest baseline weight among subjects enrolled in Study WA39085 was 27 kg.

Table 28. Demographic and Baseline Clinical Characteristics, Safety Population, Study WA39085

Characteristic	Ocrelizumab 300 mg N=6	Ocrelizumab 600 mg N=17
Sex, n (%)		
Female	5 (83.3)	10 (58.8)
Male	1 (16.7)	7 (41.2)
Age, years		
Mean (SD)	11.2 (0.8)	15.3 (1.8)
Median (min, max)	11 (10, 12)	16 (11, 17)
Age group, years, n (%)		
9 to 13	6 (100)	2 (11.8)
14 to 17	0	15 (88.2)
Age group ≥65, years, n (%)		
<65	6 (100)	17 (100)
Age group ≥75, years, n (%)		
<75	6 (100)	17 (100)

Characteristic	Ocrelizumab 300 mg N=6	Ocrelizumab 600 mg N=17
Height (cm)		
Mean (SD)	146.6 (8.6)	166.2 (12.0)
Median (min, max)	148 (136.2, 158)	164.9 (141, 191.5)
Weight (kg)		
Mean (SD)	35.3 (5.4)	63.6 (18.6)
Median (min, max)	38.5 (27, 39)	62.4 (42.1, 108.4)
Race, n (%)		
Asian	1 (16.7)	0
Black or African American	0	1 (5.9)
White	5 (83.3)	16 (94.1)
Ethnicity, n (%)		
Hispanic or Latino	0	3 (17.6)
Not Hispanic or Latino	6 (100)	14 (82.4)
Country of participation, n (%)		
Italy	3 (50.0)	4 (23.5)
Poland	2 (33.3)	5 (29.4)
United States	1 (16.7)	8 (47.1)
Is in United States, n (%)		
United States	1 (16.7)	8 (47.1)
Outside the United States	5 (83.3)	9 (52.9)

Source: adsl.xpt and adsub.xpt; Software: R and JMP
Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

6.3. Key Efficacy Review Issues

6.3.1. Noninferiority of Ocrelizumab to Fingolimod

Issue

The primary efficacy review issue is the assessment of noninferiority of ocrelizumab to the active comparator, fingolimod.

Background

The noninferiority of ocrelizumab to fingolimod was evaluated using the primary endpoint of the annualized rate of protocol-defined relapses during the DBP of Study WN42086. The study design and analysis plan was agreed upon with the Division prior to database lock. The analysis of the primary endpoint was the relative ARR across arms. As discussed in Section 6.2.1.3, the noninferiority margin was prespecified and set to 3 based on the lower bound of the 95% CI of the estimated ARR ratio comparing fingolimod to interferon beta from the pediatric Study CFTY720D2311, which served as the basis for the approval of fingolimod for RMS in pediatric patients 10 years of age and older (Chitnis et al. 2018). No discounting was necessary because superiority to interferon beta is sufficient.

Assessment

Subjects randomized to the ocrelizumab arm had an estimated 48.3% lower (relative risk 0.517; 95% CI: 0.193, 1.329) ARR compared to subjects randomized to the fingolimod arm (see Table 23). The upper bound of the 95% CI for the rate ratio was less than 3, indicating that ocrelizumab

is noninferior to fingolimod at reducing the ARR. The prespecified and post hoc sensitivity analyses did not identify any concerns about the robustness of the conclusions. The assessment of the potential impact of missing data are summarized in Section 6.3.3.

Conclusion

The review team concluded that Study WN42086 provides evidence of noninferiority of ocrelizumab to fingolimod in reducing the ARR of protocol-defined relapses in pediatric patients with RRMS.

6.3.2. Protocol Deviations of Failure To Maintain Blinding

Issue

There were 26 subjects (9 in the ocrelizumab arm and 17 in the fingolimod arm) with a protocol deviation of a failure to maintain blinding. Unblinding of the investigators could have introduced bias into the endpoint evaluations.

Background

The CSR indicates the protocol deviation of a failure to maintain the study blind occurred most frequently due to procedural deviations resulting from study staff accessing results of Day 1 electrocardiogram, MRI, or blinded laboratory data, which may have not practically resulted in unblinding.

Assessment

For additional details of the prevalence and types of protocol deviations of a failure to maintain blinding procedures, see the Clinical Inspection Summary, dated April 13, 2026 (DARRTS ID: 5779527). To assess the impact of the major protocol deviation of a failure to maintain blinding procedures, the review team conducted a sensitivity analysis repeating the analysis of the primary endpoint while excluding subjects who experienced a protocol deviation of "failure to maintain study blind." The conclusions (shown in Table 29) of the analysis excluding subjects who experienced this protocol deviation were similar to the conclusions using the FAS.

Table 29. Sensitivity Analysis To Assess the Impact of Unblinding Protocol Deviations for the Rate Ratio of the Annualized Relapse Rate, Full Analysis Set, Study WN42086, Double-Blind Period

	N Subjects		Rate		
Analysis Set	OCR	FINGO	Ratio	95% CI	p-Value
Full analysis set	93	94	0.517	(0.193, 1.329)	0.159
No protocol deviation of failure to maintain blinding	84	77	0.896	(0.331, 2.445)	0.825
Protocol deviation of failure to maintain blinding	9	17			

Source: Table 16 in the CSR and analyses conducted by the statistical reviewer
Protocol-defined relapses were calculated using the ADRLP dataset, where FASFL=Y, PARAMCD=PDR; AVALC=Y; I01E01FL !=Y; I01E02FL !=Y.
The analysis used the full analysis set (FAS). Follow-up time was defined as the time on treatment. A hypothetical strategy was used for the intercurrent events of treatment discontinuation and initiation of any other MS disease modifying treatment where data collected after the intercurrent events was excluded. The adjusted ARR ratio was estimated using a negative binomial model adjusted for region (U.S. versus rest of the world), verified (postrandomization) prepubertal status, and presence of T1 Gd lesions at baseline. The log-transformed follow-up time for each subject was included in the model as an offset term. The model was fit using the glm.nb function from the MASS package in R version 4.5.3.
Noninferiority was established if the upper bound of the 95% CI was less than the prespecified noninferiority margin of 3.
Abbreviations: ARR, annualized relapse rate; CI, confidence interval; CSR, clinical study report; FINGO, fingolimod; N, number of subjects in treatment arm; OCR, ocrelizumab

Conclusion

The review team concluded it was unlikely that major protocol deviations of unblinding led to bias in the efficacy evaluation.

6.3.3. Data Quality Issues and Missing Data

Issue

There were several concerns with data quality issues and missing data.

Background

Prepubertal Status

The review team identified issues with the randomization stratification variable of prepubertal status. The Applicant recorded prerandomization values of prepubertal status, but there were some discrepancies with the verified values of prepubertal status. Table 15 summarizes the verified values that were based on the Tanner Stage and the prerandomization value of prepubertal status used for stratifying randomization. The CSR states “Thirteen major protocol deviations were recorded for patients incorrectly stratified at randomization due to inaccurate prepubertal status data reported by the site in IxRS. The correct prepubertal status, based on Tanner Stage, was accurately captured in the electronic case report form (eCRF) and used for the primary analyses.” As shown in Table 16, there were five subjects who were missing Tanner Stage values. The Applicant imputed these missing values with a status of “No” for the verified prepubertal status variable.

EDSS Assessments Conducted More Than 7 Days After a Reported Clinical Relapse

Per protocol, all subjects with new or worsening neurologic symptoms were “promptly” scheduled to undergo an evaluation by the treating investigator. Subjects with events suggestive of an MS relapse subsequently underwent an EDSS evaluation by the examining investigator within 7 days of symptom onset, in order to confirm whether the event met the criteria for

protocol-defined relapse. As discussed in the clinical inspection summary (DARRTS ID: 5779527), two subjects (one from the ocrelizumab arm and one from the fingolimod arm) had their EDSS assessment 37 and 81 days, respectively, after the start date of the clinical relapse. These assessments also occurred more than 7 days after the documented end date of the clinical relapse. The subject randomized to the ocrelizumab arm did not meet criteria for a protocol-defined relapse based on the EDSS assessment conducted after the clinical relapse, but the subject randomized to the fingolimod arm did meet relapse criteria.

Missing Data

Seventeen subjects (four from the ocrelizumab arm and 13 from the fingolimod arm) from the FAS discontinued treatment (see Table 13). All 17 of these subjects discontinued the study: 13 discontinued treatment and study on the same day, and the remaining four discontinued the study within 2 weeks of discontinuing treatment. The protocol specified that subjects who discontinued treatment should be followed through the end of the DBP. Three subjects from the fingolimod arm initiated another MS therapy after discontinuing the study treatment. A summary of missing data in the analysis of the primary endpoint is provided in Table 23.

Assessment

Prepubertal Status

An information request was sent to the Applicant on March 30, 2026, regarding the verification process for prepubertal status. The Applicant responded on April 1, 2026, and explained that the discrepancies were identified by reconciliation between the IxRS and eCRF; it appears that incorrect values were entered into the IxRS system. Twelve subjects were classified as prepubertal at screening, but were later defined as not prepubertal based on Tanner stage. Two subjects were classified as not prepubertal at screening, but were later defined as prepubertal. The Applicant used the verified value of the prepubertal status, instead of the prerandomization value of the prepubertal status as a covariate in the analysis of the primary endpoint.

The review team repeated the primary analysis using the prerandomization value of prepubertal status, and also using the verified value of prepubertal status with the imputation for subjects missing Tanner Stage changed to "Yes." The results for both sensitivity analyses are presented in Table 30. The results of the primary analysis were similar, regardless of using the verified prepubertal status with the Applicant's imputation strategy, the screening prepubertal status, or the verified prepubertal status with the alternative imputation strategy.

Table 30. Sensitivity Analyses of the Primary Endpoint, Ratio of the Annualized Relapse Rate, Assessing the Impact of Analysis Decision for the Prepubertal Status Stratification Variable, Full Analysis Set, Study WN42086

Value of Prepubertal Status	Rate Ratio	95% CI
Verified prepubertal status (primary analysis)	0.517	(0.193, 1.329)
Prerandomization prepubertal status	0.531	(0.199, 1.355)
Verified prepubertal status with alternative imputation strategy	0.525	(0.196, 1.346)

Source: Table 16 in the CSR and the statistical reviewer
Abbreviations: CI, confidence interval; CSR, clinical study report

EDSS Assessments Conducted More Than 7 Days After Clinical Relapse

To assess the impact of the EDSS assessments conducted more than 7 days after clinical relapse, the review team conducted a sensitivity analysis repeating the analysis of the primary endpoint while excluding the two subjects who had late EDSS assessments after clinical relapses (37 and 81 days, respectively). The conclusions of the analysis excluding subjects with an EDSS assessment conducted substantially longer than 7 days after clinical relapse were similar to those using the FAS (Table 31).

Table 31. Sensitivity Analysis To Assess the Impact of EDSS Assessments Conducted Well After 7 Days After Clinical Relapse for the Rate Ratio of the Annualized Relapse Rate, Full Analysis Set, Study WN42086, Double-Blind Period

	N Subjects		Rate		
Analysis Set	Ocrelizumab	Fingolimod	Ratio	95% CI	p-Value
Full analysis set	93	94	0.517	(0.193, 1.329)	0.159
Excluding subjects with a late EDSS assessment	92	93	0.575	(0.212, 1.504)	0.244

Source: Table 16 in the Study WN42086 CSR and the statistical reviewer
Abbreviations: CI, confidence interval; CSR, clinical study report; EDSS, Expanded Disability Status Scale; N, number of subjects in treatment arm

Missing Data

To assess the sensitivity of the results of the analysis of the primary endpoint to the assumption that data are missing at random, the statistical reviewer conducted a tipping point analysis as prespecified in the SAP. First, the relapse rates for each subject were predicted within treatment arms. The predicted relapse rates in the ocrelizumab arm were then multiplied by a value delta, which ranged from one to ten. Relapse counts were then simulated for the time between treatment discontinuation and study end using a negative binomial model with the penalized relapse rates. Next, 100 complete datasets were imputed per value of delta, and the rate ratio and corresponding uncertainty estimates were estimated using Rubin's rules. Even when the imputed relapse rates were 10-fold higher than relapse rates from the observed subjects in the ocrelizumab arm, noninferiority could still be concluded. The results of the primary analysis seemed to be robust to deviations from the missing at random assumption.

Conclusion

The review team did not find evidence that the data quality issues or missing data impacted the conclusions of the study.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No new nonclinical studies were submitted with this sBLA.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Ocrelizumab is an anti-CD20, IgG1, cytolytic, monoclonal antibody. The known risks associated with ocrelizumab (Ocrevus, BLA 761053) described in current approved labeling include infusion reactions, infections (including serious and potentially fatal infections), PML, reduction in immunoglobulins, malignancies (including breast cancer), immune-mediated colitis, and liver injury. These safety concerns are further described in Section 7.7.

In clinical trials of ocrelizumab in adults, the most common adverse reactions that occurred in ≥10% of subjects treated with ocrelizumab for RMS, and at a higher frequency than reported for interferon beta-1a, included upper respiratory tract infections and infusion reactions. The most common adverse reactions that occurred in ≥10% of adult subjects treated with ocrelizumab for PPMS, and at a higher frequency than reported for placebo, included upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Ocrelizumab was approved on March 28, 2017, under BLA 761053. As of March 27, 2025, ocrelizumab has been approved in over 100 countries worldwide. Since approval, and until March 31, 2025, the estimated cumulative postmarket exposure to ocrelizumab (either IV or subcutaneous ocrelizumab and hyaluronidase-ocsq [approved as Ocrevus Zunovo]) is (b) (4) patients, corresponding to an estimated (b) (4) patient-years (PY) of exposure. Based on the postmarketing safety data, no new safety concerns for ocrelizumab (compared to current approved labeling) were identified by the Applicant.

Ocrelizumab is not approved for pediatric use in the United States or in any foreign market; however, the Applicant estimates that (b) (4) pediatric patients receive ocrelizumab off-label.

7.3.1. Adverse Events Identified in Postmarket Experiences

AEs identified in the postmarket experience and discussed in Section 6.3 (Adverse Reactions - Postmarketing Experience) of current approved labeling for ocrelizumab include immune-mediated colitis, liver injury, serious infections, PML, babesiosis, and pyoderma gangrenosum. Identification of these safety signals has led to the Division issuing Safety Labeling Change Notifications and labeling revisions for Ocrevus. Refer to Section 7.7 for a discussion of key safety review issues.

7.3.2. Expectations on Safety

The clinical review team expects that the use of ocrelizumab in pediatric patients will have a similar safety profile to that of ocrelizumab in adults.

7.3.3. Additional Safety Issues From Other Disciplines

Not applicable.

7.4. FDA Approach to the Safety Review

Clinical study data were independently analyzed by the clinical data scientist support team. Additional analyses were performed by the clinical review team using JMP software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. No major data quality or integrity issues were identified that would preclude a safety review of this sBLA. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for the events reported in Studies WN42086 and WA39085 were reviewed and found to be acceptable. All AEs in the reviewed trials were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5).

Data from the ongoing phase 3, randomized, double-blind, double-dummy Study WN42086 formed the basis of the clinical safety evaluation. Data from the ongoing phase 2, open-label, parallel-group, dose-finding Study WA39085 provided supportive evidence of safety. A summary of the study designs can be found in Sections 6.2.1.1 and 6.2.2, respectively.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of ocrelizumab for the proposed indication, patient population, dosage regimen, and duration. When considered in conjunction with the adult safety data for ocrelizumab, the pediatric safety database for ocrelizumab data meets the sample size requirements outlined in the ICH guidance for industry, *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995). Per this ICH guidance, the safety database should include at least 1500 individuals exposed to the investigational product in short-term trials, 300 to 600 individuals with at least 6 months of exposure, and 100 individuals with at least 1 year of exposure.

The safety database is adequate in terms of size and duration of exposure. The duration of exposure by dose in the pediatric safety database for ocrelizumab is presented in Table 32. At the time of the sBLA data cutoff, 116 pediatric subjects had been exposed to at least 1 dose of ocrelizumab 300 mg or 600 mg and 50 pediatric subjects to at least 24 months of treatment.

The initial ocrelizumab BLA included a safety database of 2147 subjects (4485 PY of exposure), with data pooled from several studies involving adult subjects with RMS and PPMS. Additionally, since approval (March 28, 2017) and until March 31, 2025, the estimated cumulative postmarket exposure to ocrelizumab (subcutaneous or IV) is (b) (4) patients (corresponding to (b) (4) PY of exposure). Therefore, in addition to the establishment of the safety profile of ocrelizumab in adults via clinical trials and further characterization in the postmarket setting, the safety of ocrelizumab for pediatric use is also supported by safety data collected during the pediatric ocrelizumab development program.

Table 32. Duration of Treatment Exposure, Safety Population, Pooled Analyses, Studies WN42086 and WA39085

	Number of Subjects Exposed to Ocrelizumab					
Dosage	≥1 Dose (n)	<6 Months (n)	≥6 Months (n)	≥12 Months (n)	≥18 Months (n)	≥24 Months (n)
Proposed dosing regimen[1]	116	0	27	20	19	50
300 mg (<35 kg)[2]	6	0	0	2	2	2
600 mg (≥35 kg)[3]	115	2	28	20	18	47
Cohort 1[4]	5	2	1	0	0	2
Cohort 2[4]	17	0	0	0	0	17
Study WN42086[5]	93	0	27	20	18	28
Other dosing regimens[6]	0	0	0	0	0	0

Source: Applicant's response to information request, dated March 20, 2026
[1] All doses.
[2] Exposure to ocrelizumab 300 mg in Study WA39085 was defined as the duration between date of the first ocrelizumab 300-mg dose administration and the date of switch to the 600-mg dose or the COD February 20, 2025, whichever was earlier +1 day.
[3] Subjects received at least one ocrelizumab 600-mg dose in Study WA39085 Cohort 1 and Cohort 2, or in Study WN42086.
[4] Exposure to ocrelizumab 600 mg in Study WA39085 was defined as the duration between the date of the first ocrelizumab 600-mg dose administration and the date of withdrawal from treatment or the COD of February 20, 2025, whichever was earlier +1 day.
[5] Exposure to ocrelizumab 600 mg in Study WN42086 was defined as the duration between the date of the first ocrelizumab 600-mg dose administration and the date of withdrawal from treatment or the COD of June 9, 2025, whichever was earlier +1 day.
[6] By weight category.
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Abbreviations: COD, cutoff date; n, number of subjects with given characteristic

7.6. Safety Results

7.6.1. Safety Results, Studies WN42086 and WA39085

Treatment-emergent adverse events (TEAEs) were defined as AEs with an observed or imputed date of onset on or after the start date of study treatment and were coded according to MedDRA version 28.0. Serious adverse events (SAEs) were defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect. Due to the flexible duration of the DBP, TEAEs were summarized using the count of events and the exposure-adjusted event rate (EAER). The EAER was defined as the number of events per 100 patient-years (events/100 PY) of follow-up time among subjects at risk at the beginning of the study.

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Studies WN42086 and WA39085

Study WN42086

The frequency of TEAEs during the DBP of the ongoing phase 3 Study WN42086 is shown in Table 33. The EAER for any TEAE was higher in the ocrelizumab arm (507.9 events/100 PY) compared to the fingolimod arm (490.1 events/100 PY). However, the EAER for severe TEAEs was higher in the fingolimod arm (22 events/100 PY) compared to the ocrelizumab arm (10.2 events/100 PY), in which the EAER for TEAEs of mild severity (323.6 events/100 PY) was higher. The EAER for SAEs was higher in the fingolimod arm (13.7 events/100 PY), as compared to the ocrelizumab arm (5.1 events/100 PY). There were no SAEs that had a fatal

outcome in either treatment arm, but the EAER for events that were life-threatening or required hospitalization was higher in the fingolimod arm (1.5 and 12.2 events/100 PY, respectively) compared to the ocrelizumab arm (0.0 and 4.4 events/100 PY, respectively). Additionally, EAER for TEAEs that led to permanent discontinuation of study treatment or to treatment interruption was higher in the fingolimod arm (3.0 and 12.2 events/100 PY, respectively) compared to the ocrelizumab arm (0.0 and 5.8 events/100 PY, respectively).

Table 33. Overview of Treatment-Emergent Adverse Events, Safety Population, Study WN42086

Adverse Event Category	Ocrelizumab PY =137.8 E =700 Event (EAER)	Fingolimod PY =131.6 E =645 Event (EAER)	EAER Difference (95% CI)
Any SAE	7 (5.1)	18 (13.7)	−8.6 (−17.1, −1.4)*
Death	0	0	0.0 (−2.9, 2.8)
Life-threatening	0	2 (1.5)	−1.5 (−5.5, 1.3)
Initial or prolonged hospitalization	6 (4.4)	16 (12.2)	−7.8 (−15.8, −1.1)*
Other	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
AE leading to permanent discontinuation of treatment	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Dose not changed	699 (507.2)	641 (487.0)	20.2 (−33.2, 73.5)
AE leading to interruption of treatment	8 (5.8)	16 (12.2)	−6.4 (−14.5, 0.8)
Not applicable	1 (0.7)	0	0.7 (−2.2, 4.1)
Any TEAE	700 (507.9)	645 (490.1)	17.9 (−35.6, 71.3)
Severe and worse	14 (10.2)	29 (22.0)	−11.9 (−22.4, −2.4)*
Moderate	240 (174.2)	204 (155.0)	19.2 (−11.6, 49.9)
Mild	446 (323.6)	411 (312.3)	11.4 (−31.4, 54.0)

Source: adae.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Subjects may be counted more than once in the AE leading to action taken of treatment analysis.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; E, number of events; EAER, exposure-adjusted event rate; PY, patient-years; SAE, serious adverse event; TEAE, treatment-emergent adverse event

90-Day Safety Update

The 90-day safety update for Study WN42086 had a data cutoff date of September 9, 2025. TEAEs that occurred in subjects who received at least one dose of ocrelizumab were analyzed as part of the 90-day safety update, and subjects who received ocrelizumab during the DBP and continued to receive ocrelizumab during the OLE period were compared to subjects who received fingolimod during the DBP and subsequently transitioned to ocrelizumab during the OLE period (“switchers”). Therefore, this analysis included TEAEs that occurred during the DBP and the OLE period. Among switchers (n=22), the mean ocrelizumab exposure was 1.9 weeks, which, except for infusion reactions, precludes meaningful safety analyses due to the short exposure duration. Overall, the safety data contained in the 90-day safety update appeared consistent with that included in the initial sBLA submission.

Study WA39085

The frequency of TEAEs that occurred during the phase 2 Study WA39085 is shown in Table 34. The EAER for any TEAE was higher in the ocrelizumab 300 mg arm (655.6 events/100 PY) compared to the ocrelizumab 600 mg arm (620.0 events/100 PY). However, the EAER for

severe TEAEs was higher in the ocrelizumab 600 mg arm (37.7 events/100 PY) compared to the ocrelizumab 300 mg arm (22.0 events/100 PY), in which the EAER for TEAEs of mild severity (396.7 events/100 PY) was higher. The EAER for any SAE was higher in the ocrelizumab 600 mg arm (26.1 events/100 PY) compared to the ocrelizumab 300 mg arm (16.5 events/100 PY). No SAEs had a fatal outcome in either treatment arm, but the EAER for events that required hospitalization was higher in the ocrelizumab 600 mg arm (21.8 events/100 PY) compared to the ocrelizumab 300 mg arm (16.5 events/100 PY, respectively). There were no events leading to permanent treatment discontinuation or treatment interruption in the ocrelizumab 300 mg arm; however, the EAERs for TEAEs that led to permanent treatment discontinuation or to treatment interruption were higher in the ocrelizumab 600 mg arm (1.5 and 5.8 events/100 PY, respectively).

Table 34. Overview of Adverse Events, Safety Population, Study WA39085

Adverse Event Category	Ocrelizumab 300 mg PY =18.2 E =119 Event (EAER)	Ocrelizumab 600 mg PY =68.9 E =427 Event (EAER)
Any SAE	3 (16.5)	18 (26.1)
Death	0	0
Life-threatening	1 (5.5)	2 (2.9)
Initial or prolonged hospitalization	3 (16.5)	15 (21.8)
Other	0	3 (4.4)
AE leading to permanent discontinuation of treatment	0	1 (1.5)
Dose not changed	119 (655.6)	424 (615.6)
AE leading to interruption of treatment	0	4 (5.8)
Not applicable	10 (55.1)	42 (61.0)
Any TEAE	119 (655.6)	427 (620.0)
Severe and worse	4 (22.0)	26 (37.7)
Moderate	43 (236.9)	220 (319.4)
Mild	72 (396.7)	181 (262.8)

Source: adae.xpt; Software: R
Duration is a median of 147.6 weeks (ocrelizumab 300 mg) and 185.7 weeks (ocrelizumab 600 mg).
Subjects may be counted more than once in the AE leading to action taken of treatment analysis.
Abbreviations: AE, adverse event; E, number of events; EAER, exposure-adjusted event rate; PY, patient-years; SAE, serious adverse event; TEAE, treatment-emergent adverse event

90-Day Safety Update

The 90-day safety update for Study WA39085 had a data cutoff of September 9, 2025, and focused on the analysis of TEAEs that occurred in subjects who received at least one dose of ocrelizumab. Overall, the safety data contained in the 90-day safety update appeared consistent with that included in the initial submission of the sBLA.

7.6.1.2. Deaths, Studies WN42086 and WA39085

There were no deaths reported in Study WN42086, either in the original sBLA submission or in the 90-day safety update. No deaths were reported for Study WA39085 in the original sBLA submission. However, one death due to methamphetamine intoxication following several recurrent opportunistic infections and development of HIV infection was reported in a Study WA39085 Cohort 2 subject as part of the 90-day safety update. The narrative for this case is presented below.

Subject (b) (6)

Subject (b) (6) (a 17-year-old male adolescent with RRMS and a body weight of 62.6 kg who received ocrelizumab on Study Days 1, 16, 170, 339, 520, 675, 845, 1009, 1173, and 1340) experienced the SAEs candida infection (Grade 3, serious), gonococcal infection (Grade 3, serious), pneumonia (Grade 3, serious), abscess limb (Grade 3, serious), HIV infection (Grade 2, nonserious), and anal abscess (Grade 3, serious). His past medical history included latent tuberculosis (reportedly resolved prior to study entry), tinea versicolor, oral herpes, vitamin D deficiency, and hypertension. Concomitant medications included acetylsalicylic acid/caffeine/paracetamol, cholecalciferol, oxiconazole nitrate, bisacodyl, and *Hippophae rhamnoides*.

On Study Day 382, the subject developed pain with swallowing. On Study Day 387, he noticed an anal lesion, along with fecal urgency, hematochezia, and mucus in stool. He presented to the emergency department on Study Day 388 and reported significant pain in the anal region, which appeared to worsen with movement and radiated to his scrotum. He also reported numbness and tingling in his groin, left thigh, and leg. Physical examination demonstrated an erythematous fluctuant mass around his anus of ~1 cm in diameter. The mass was reportedly tender to palpation. The subject was diagnosed with perianal fistula and perianal abscess, which required incision and drainage (I&D) under sedation. The procedure yielded bloody, nonpurulent drainage and the wound was packed. Digital rectal examination yielded purulent material. A wound culture grew “moderate mixed gastrointestinal tract microorganisms with moderate polymorphonuclear neutrophils (PMNs) and rare gram-positive cocci on Gram stain.” Therefore, a gonococcal infection was suspected. A CT scan of the abdomen and pelvis demonstrated an incidental finding of “nonspecific left lung base pulmonary nodule.” He received treatment with ibuprofen, sodium chloride, ketamine hydrochloride, hydrocodone bitartrate/paracetamol, and clindamycin.

On Study Day 390 he experienced odynophagia and decreased oral intake, which were thought to be due to his prior diagnosis of candida infection. On that same day, his surgical wound was evaluated, packing was removed, and reportedly no purulence, fluctuance, or induration were noted. On Study Day 393, he reported that the anal region pain had not improved, and he continued to experience severe pain with movement and persistent left foot and groin numbness. On Study Day 402, he developed pyrexia (body temperature of 38.8 °C) and worsening throat pain. “Streptococcal test, COVID-19, and monospot tests” were negative on Study Day 403. He presented to the emergency department on Study Day 404 due to worsening odynophagia, inability to tolerate oral intake, and ongoing fever. A CT scan of the neck with contrast was performed and revealed “inflammatory lymph nodes and no abscess.” Laboratory evaluations were notable for elevated C-reactive protein (CRP) to 22.2, WBC count to 16.1, and ANC to

12.2 (units and reference ranges not provided). Herpes simplex virus PCR oral swab test, "respiratory virus panel," and "histoplasma test" were negative. A candida swab culture (site not reported) was positive for *Candida dubliniensis* and he was therefore diagnosed with candida infection and treated with sodium chloride, lidocaine, ketorolac and diphenhydramine/aluminum hydroxide/magnesium hydroxide/simethicone.

On Study Day 405, he developed ~5 "oral thrush lesions on his mouth and tongue" and therefore received treatment with valaciclovir. A repeat herpes simplex virus PCR test was negative on Study Day 406 and was discharged on that same day with diphenhydramine/aluminum hydroxide/magnesium hydroxide/simethicone and fluconazole as treatments. The subject's throat pain worsened on Study Day 410 and he was diagnosed with another episode of candidiasis. Oxycodone was added to his treatment regimen for pain management. On that same day, he reported blood and mucus in his stool.

The subject then experienced two episodes of fever (body temperature 38 °C) on Study Day 414 and reported a 5.85 kg weight loss since the onset of odynophagia (Study Day 390). Laboratory evaluations were notable for elevated WBC count to 17.6, ANC to 12.4, ALC to 2.7, and CRP to 82.7 (units and reference ranges not reported). A CT scan of the chest revealed "bilateral lower lobe airspace (left greater than right)," which led to a diagnosis of pneumonia, resulting in hospitalization. Infectious work-up was negative and he received treatment with lidocaine, sodium chloride, morphine, oxycodone, ketorolac, ibuprofen, glucose/potassium chloride/sodium chloride, paracetamol, and ampicillin sodium/sulbactam sodium.

On Study Day 415, the subject reported worsening odynophagia and increased blood and mucus in stool. Laboratory evaluations were notable for positive Epstein-Barr virus viral capsid antigen IgG and negative IgM. Testing for cytomegalovirus and syphilis was negative (tests not specified). Throat and rectal swabs were positive for *Neisseria gonorrhoeae* and negative for *Chlamydia trachomatis*. The subject was therefore diagnosed with a gonococcal infection. HIV-1 RNA PCR was negative. He received treatment with ceftriaxone, fluconazole, acyclovir, senna, macrogol/potassium chloride/sodium bicarbonate/sodium chloride/sodium sulfate, ondansetron, and oxycodone. He was discharged from the hospital on Study Day 422 with a 7-day course of fluconazole and valaciclovir.

On Study Day 730, the subject developed swelling, tenderness, and erythema on the left gluteal region and was diagnosed with "abscess limb," which subsequently worsened on Study Day 733 and were thought to be consistent with left gluteal abscess measuring ~3 cm in diameter. Laboratory evaluations on Study Day 734 were notable for elevated WBC count to 10.4, ANC to 5.5, ALC to 3.8, and CRP to 18.0 (units and reference ranges not provided). He was hospitalized, underwent I&D, and was discharged on treatment with clindamycin.

On Study Day 1383, the subject was diagnosed with HIV infection and received treatment with bictegravir sodium/emtricitabine/tenofovir alafenamide fumarate. Due to this event, the study treatment was permanently discontinued on Study Day 1424 and the subject entered the SFU period. The subject was then switched to commercially available ocrelizumab on Study Day 1508. On Study Day 1614, the subject was again diagnosed with anal abscess, but antibiotics were not prescribed. He was then hospitalized on Study Day 1637 due to lack of improvement, received treatment with amoxicillin, and was discharged on Study Day 1639.

The subject was also diagnosed with an event of febrile neutropenia on Study Day 1701, which resolved by Study Day 1710. The subject died due to methamphetamine intoxication on Study

Day 1698. It was unclear whether this was an intentional overdose. The subject had last been dosed with commercially available ocrelizumab on Study Day 1698.

Discussion

This fatal case involves recurrent infections, including opportunistic infections, in an ocrelizumab-treated pediatric subject, who was later diagnosed with HIV. The risk of serious (including life-threatening or fatal) bacterial, viral, parasitic and fungal infections is discussed in Section 5.2 (Warnings and Precautions) of current approved labeling for ocrelizumab. Immunosuppression from HIV infection and ocrelizumab treatment are likely to be additive due to the impact of these conditions on T-cells and B-cells, respectively. Therefore, a causal association between this case of recurrent infections can at least partially be attributed to ocrelizumab treatment. Although study treatment was discontinued, treatment with commercially available ocrelizumab was initiated following his HIV diagnosis, which likely contributed to the occurrence of additional serious and opportunistic infections with ocrelizumab in this subject. It is unclear whether ocrelizumab could have contributed to the event of methamphetamine overdose in this subject, because it is unclear whether it was intentional.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Studies WN42086 and WA39085

Study WN42086

Treatment-emergent SAEs in Study WN42086 are summarized by system organ class (SOC) and PT in Table 35. Review of treatment-emergent SAEs using the Office of New Drugs Custom Medical Query (OCMQ, Narrow) demonstrated similar findings (results not shown).

Table 35. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study WN42086

System Organ Class Preferred Term	Ocrelizumab PY =137.8 E =7 Event (EAER)	Fingolimod PY =131.6 E =18 Event (EAER)	EAER Difference (95% CI)
Any SAE	7 (5.1)	18 (13.7)	−8.6 (−17.1, −1.4)*
Blood and lymphatic system disorders (SOC)	0	2 (1.5)	−1.5 (−5.5, 1.3)
Neutropenia	0	2 (1.5)	−1.5 (−5.5, 1.3)
Cardiac disorders (SOC)	0	1 (0.8)	−0.8 (−4.3, 2.0)
Sinus bradycardia	0	1 (0.8)	−0.8 (−4.3, 2.0)
General disorders and administration site conditions (SOC)	0	1 (0.8)	−0.8 (−4.3, 2.0)
General physical health deterioration	0	1 (0.8)	−0.8 (−4.3, 2.0)
Infections and infestations (SOC)	4 (2.9)	4 (3.0)	−0.1 (−5.2, 4.8)
Pneumonia	3 (2.2)	1 (0.8)	1.4 (−2.3, 5.7)
Peritonitis	1 (0.7)	0	0.7 (−2.2, 4.1)
Conjunctivitis	0	1 (0.8)	−0.8 (−4.3, 2.0)
Dengue fever	0	1 (0.8)	−0.8 (−4.3, 2.0)
Influenza	0	1 (0.8)	−0.8 (−4.3, 2.0)
Injury, poisoning and procedural complications (SOC)	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Infusion related reaction	1 (0.7)	0	0.7 (−2.2, 4.1)
Toxicity to various agents	0	2 (1.5)	−1.5 (−5.5, 1.3)

System Organ Class Preferred Term	Ocrelizumab PY =137.8 E =7 Event (EAER)	Fingolimod PY =131.6 E =18 Event (EAER)	EAER Difference (95% CI)
Investigations (SOC)	0	2 (1.5)	−1.5 (−5.5, 1.3)
Electrocardiogram QT prolonged	0	1 (0.8)	−0.8 (−4.3, 2.0)
Transaminases increased	0	1 (0.8)	−0.8 (−4.3, 2.0)
Nervous system disorders (SOC)	1 (0.7)	0	0.7 (−2.2, 4.1)
Headache	1 (0.7)	0	0.7 (−2.2, 4.1)
Psychiatric disorders (SOC)	1 (0.7)	5 (3.8)	−3.1 (−8.2, 0.7)
Suicidal ideation	1 (0.7)	0	0.7 (−2.2, 4.1)
Anxiety disorder	0	1 (0.8)	−0.8 (−4.3, 2.0)
Conversion disorder	0	1 (0.8)	−0.8 (−4.3, 2.0)
Mental disorder	0	1 (0.8)	−0.8 (−4.3, 2.0)
Psychotic disorder	0	2 (1.5)	−1.5 (−5.5, 1.3)
Renal and urinary disorders (SOC)	0	1 (0.8)	−0.8 (−4.3, 2.0)
Nephrolithiasis	0	1 (0.8)	−0.8 (−4.3, 2.0)

Source: adae.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; E, number of events; EAER, exposure-adjusted event rate; PY, patient-years; QT, QT interval; SAE, serious adverse event; SOC, system organ class

The EAER for any SAEs was higher in the fingolimod arm (13.7 events/100 PY) compared to the ocrelizumab arm (5.1 events/100 PY). This difference was mainly driven by higher EAERs of events coded to PTs contained within the SOCs Blood and lymphatic system disorders (1.5 versus 0.0 events/100 PY), Investigations (1.5 versus 0.0 events/100 PY), and Psychiatric disorders (3.8 versus 0.7) in the fingolimod arm compared to the ocrelizumab arm. The EAER for SAEs that were coded to PTs contained within the SOC Infections and Infestations was balanced between the groups.

Overall, the SAEs reported with ocrelizumab appear to be consistent with its known safety profile discussed in current approved labeling. However, a selected narrative for a subject treated with ocrelizumab who experienced an SAE of suicidal ideation is discussed below.

Subject (b) (6)

Subject (b) (6) (a 17-year-old male adolescent with RRMS and a body weight of 105.4 kg who received ocrelizumab on Study Days 1, 15, 195, 365, 609, 644, 812, and 973) experienced the SAE suicidal ideation (Grade 2, serious) on Study Day 1025. His medical history included seasonal allergies and fatigue. On Study Day 1025, the subject "expressed verbally the desire to be no longer alive." Subsequently, he reported suicidal ideation on Study Day 1063 during the Week 132 visit. Contributing factors were noted to be "recent interpersonal conflict and feelings of isolation after a recent move." A psychiatrist was consulted, and a safety plan was developed, including arrangements for the subject to begin counseling services via telemedicine. The event was considered resolved on Study Day 1086. No changes were made to the study treatment in response to this event. The investigator assessed the event as unrelated to treatment with ocrelizumab.

Discussion

This event appears to be a case of suicidal ideation in a pediatric subject without prior psychiatric history that occurred in the setting of ongoing life stressors. The association of monoclonal antibody treatment with suicidal ideation and behavior has been described in the extant medical literature. Cases of depression and suicide occurred in adult clinical trials of ocrelizumab. In the PPMS phase 3 trial, SAEs of depression suicidal, suicide attempt, and suicidal ideation occurred only in ocrelizumab-treated adult subjects, but not in those receiving placebo. TEAEs of depression occurred less frequently in ocrelizumab-treated adult subjects with PPMS compared to those receiving placebo, but in the adult RMS controlled trials TEAEs of depression occurred slightly more frequently in the ocrelizumab arm than in interferon beta-1a group. Of note, interferon beta-1a has a Warnings and Precautions subsection for depression and suicide in labeling. Because this was the only case of suicidal ideation or behavior in Study WN42086 and no cases of depression occurred in either treatment arm, it is not possible to comprehensively assess the causal relationship between ocrelizumab and this event of suicidal ideation.

Overall, the SAEs reported with fingolimod appear to be consistent with its known safety profile discussed in current approved labeling. A selected narrative for a subject treated with fingolimod who experienced psychosis and seizures is discussed below.

Subject (b) (6)

Subject (b) (6) (a 19-year-old male adolescent with RRMS and a body weight of 71.6 kg who received fingolimod 0.5 mg daily) experienced the SAE psychotic disorder (Grade 2, serious) on Study Day 281. His medical history included anxiety. Concomitant medications included clonazepam, escitalopram, and quetiapine. On Study Day 281 the subject experienced a "psychotic episode with hallucinations, and seizure." He was found in his bedroom, unresponsive and covered in vomit and urine. He was taken to the emergency room, where he received treatment with valproic acid. He was transferred to the intensive care unit on Study Day 282. A CT scan of the chest demonstrated "early bronchopneumonia in the left lower lobe." An EEG was performed on Study Day 282, which demonstrated "nonsignificant generalized epileptiform activity." On Study Day 282, the subject experienced the TEAE schizophrenia (Grade 1, nonserious). The events were considered resolved on Study Day 287. No changes were made to the study treatment. The investigator assessed the events as unrelated to treatment with fingolimod.

On Study Day 845, the subject experienced an additional TEAE of psychotic episode (Grade 2, serious) described as a 10-day history of "irritability and aggressiveness including walking and sleeping with a knife, auditory hallucinations, and delusional thoughts." At the time, the subject also reported *Cannabis sativa* dependence. He was hospitalized and received treatment with promethazine and haloperidol. The investigator assessed the event as unrelated to treatment with fingolimod. The event remained unresolved. The subject was withdrawn from the study on Day 883, as it was deemed unsafe for the subject to continue with study participation.

Discussion

This appears to be an event of seizure and psychosis requiring treatment with antiepileptics and antipsychotics. It is unclear whether the event of psychosis was associated with fingolimod treatment. However, Section 6.1 (Clinical Trials Experience) of current approved labeling for fingolimod states that in the pediatric phase 3 study, cases of seizures were reported in 5.6% of Gilenya-treated patients compared to 0.9% of interferon beta-1a-treated patients. It is therefore possible that this subject's seizure could have occurred in the setting of a decreased seizure threshold given CT chest findings and fingolimod use.

90-Day Safety Update

In addition to the SAEs that occurred prior to the sBLA submission data cutoff (discussed above), there was 1 additional SAE (neuralgic amyotrophy [Grade 3]) experienced by a subject who switched from double-blind fingolimod to open-label ocrelizumab, approximately 27 days following the first ocrelizumab dose.

Study WA39085

Treatment-emergent SAEs in Study WA39085 are summarized by SOC and PT in Table 36. Review of treatment-emergent SAEs using the OCMQ (Narrow) demonstrated similar findings (results not shown).

Table 36. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study WA39085

System Organ Class Preferred Term	Ocrelizumab 300 mg PY =18.2 E =3 Event (EAER)	Ocrelizumab 600 mg PY =68.9 E =18 Event (EAER)
Any SAE	3 (16.5)	18 (26.1)
Blood and lymphatic system disorders (SOC)	1 (5.5)	0
Neutropenia	1 (5.5)	0
Gastrointestinal disorders (SOC)	0	1 (1.5)
Abdominal pain	0	1 (1.5)
General disorders and administration site conditions (SOC)	0	1 (1.5)
Peripheral swelling	0	1 (1.5)
Infections and infestations (SOC)	1 (5.5)	6 (8.7)
Pneumonia	0	1 (1.5)
Gonococcal infection	0	1 (1.5)
Candida infection	0	2 (2.9)
Appendicitis	1 (5.5)	0
Anal abscess	0	1 (1.5)
Abscess limb	0	1 (1.5)
Investigations (SOC)	0	2 (2.9)
Blood creatine phosphokinase increased	0	1 (1.5)
Alanine aminotransferase increased	0	1 (1.5)
Metabolism and nutrition disorders (SOC)	0	1 (1.5)
Dehydration	0	1 (1.5)
Musculoskeletal and connective tissue disorders (SOC)	0	4 (5.8)
Pain in extremity	0	1 (1.5)
Musculoskeletal pain	0	1 (1.5)
Muscular weakness	0	2 (2.9)

System Organ Class Preferred Term	Ocrelizumab 300 mg PY =18.2 E =3 Event (EAER)	Ocrelizumab 600 mg PY =68.9 E =18 Event (EAER)
Nervous system disorders (SOC)	1 (5.5)	0
Syncope	1 (5.5)	0
Psychiatric disorders (SOC)	0	1 (1.5)
Conversion disorder	0	1 (1.5)
Skin and subcutaneous tissue disorders (SOC)	0	1 (1.5)
Rash	0	1 (1.5)
Vascular disorders (SOC)	0	1 (1.5)
Hypotension	0	1 (1.5)

Source: adae.xpt; Software: R
Duration is a median of 147.6 weeks (ocrelizumab 300 mg) and 185.7 weeks (ocrelizumab 600 mg).
Abbreviations: E, number of events; EAER, exposure-adjusted event rate; PY, patient-years; SAE, serious adverse event; SOC, system organ class

The EAER for SAEs was higher in the ocrelizumab 600 mg arm (26.1 events/100 PY) compared to the ocrelizumab 300 mg arm (16.5 events/100 PY). Overall, the EAERs for SAEs by SOC and PT appeared balanced between the groups. Selected narratives are discussed below.

Subject (b) (6)

Subject (b) (6) (a 16-year-old male adolescent with RRMS and a body weight of 56.7 kg who received ocrelizumab on Study Days 1, 127, 288, 477, 638, 806, 974, 1142, 1318, and 1486) experienced the SAEs. ALT increased (Grade 4, serious) on Study Day 1 and blood creatinine phosphokinase (CPK) increased (Grade 4, serious) on Study Day 435. His medical history included CD4+ and CD8+ lymphocytes decreased, leukopenia, and serum immunoglobulin G decreased. No concomitant medications were reported.

On Study Day 1, prior to the first ocrelizumab infusion, he was noted to have elevated AST to 94 U/L (normal range: 10 to 40 U/L) and ALT to 227 U/L (normal range: 6 to 43 U/L) with normal ALP, GGT, and total bilirubin. The subject received treatment with ocrelizumab as planned on Study Day 1. The premedication regimen included pantoprazole 40 mg IV, methylprednisolone 100 mg IV, paracetamol 500 mg PO, and chlorphenamine 10 mg IV. Transaminase levels were again obtained on Study Day 8 (ALT: 1315 U/L and AST: 533 U/L). On Study Day 11, the subject experienced the events GGT increased (Grade 1, value not reported) and ALP increased (Grade 1, value not reported). On Study Day 14, ALT became elevated to 1795 U/L, AST to 684 U/L, and lactate dehydrogenase (LDH) to 434 U/L. Direct bilirubin was 0.25 mg/dL.

Hepatitis B surface antigen, hepatitis C virus antibody, and HIV antibodies were negative. MR cholangiography was performed on an unspecified date and "showed negative results." The subject received treatment with ursodeoxycholic acid and phosphatidylcholine/silibinin/vitamin E (dose and treatment duration not specified). Transaminase levels normalized by Study Day 95. Due to these events, the second 300 mg infusion (dose 1) was delayed until Study Day 127. Of note, aside from methylprednisolone for premedication, the subject did not receive additional corticosteroids throughout the study. The investigator assessed the events as unrelated to study treatment administration. However, the etiology for this subject's transaminase elevation was not specified.

He subsequently experienced the SAE Grade 4 blood CPK elevation to 6907 U/L (RR: 39 to 308

U/L) on Study Day 435. A liver ultrasound was performed and was found to be "normal." No treatment was administered for this event. CPK decreased to 299 U/L by Study Day 441 and the event resolved by Study Day 455. The study treatment was temporarily interrupted due to this event and the subject received the next study treatment dose on Study Day 477. The investigator assessed the event as related to treatment with ocrelizumab, because no other potential etiologies were identified. Of note, this subject experienced additional nonserious events of CPK elevation on Study Days 38 and 1296.

Discussion

- This subject's AST and ALT were elevated prior to the first ocrelizumab treatment administration, as per the ADLB dataset. It appears that GGT remained within normal limits and LDH was elevated around the time transaminase levels peaked. This Grade 4 SAE of transaminase elevation does not appear related to treatment with ocrelizumab. However, a contribution of ocrelizumab to worsening of this adverse event cannot be excluded. The etiology for transaminase elevation remains unclear.
- Upon review of the ADLB dataset, this subject's CPK elevation to 6907 U/L on Study Day 435 was also accompanied by elevated ALT and AST to 85 U/L and 220 U/L, respectively, and by elevated LDH to 288 U/L. AST was higher than ALT, which appears consistent with muscular tissue damage. Of note, this subject also experienced isolated CPK elevations on Study Days 1296 (1293 U/L) and 1345 (379 U/L) that did not appear to be temporally associated with ocrelizumab infusions. This Grade 4 SAE of CPK elevation does not appear related to treatment with ocrelizumab.

Subject (b) (6)

Subject (b) (6) (an 11-year-old female with RRMS and a body weight of 39 kg who received ocrelizumab on Study Days 1, 14, 170, 331, 345, 505, 673, 841, 1010, 1178, and 1347) experienced the SAE neutropenia (Grade 4, serious) on Study Day 883. Her medical history included type 1 diabetes, mitral valve prolapse, unilateral hypoacusis, and constipation. Concomitant medications included insulin and cholecalciferol. On Study Day 883 the subject was hospitalized due to unspecified "skin lesions and for diagnostic purposes." Laboratory evaluations demonstrated neutropenia to $0.43\times10^3/\mu L$ (RR: $1.8\text{-}8\times10^3/\mu L$) and she was therefore diagnosed with Grade 4 neutropenia. Treatment was not administered for this event. The event of neutropenia was considered resolved by Study Day 890 and the subject was discharged from the hospital.

Discussion

This TEAE of neutropenia appears to be potentially complicated by skin infection, although there are insufficient details regarding this subject's clinical course. Neutropenia is discussed in Section 6.1 (Clinical Trials Experience) of current approved labeling for Ocrevus, which states that in the adult PPMS clinical trial, decreased neutrophil counts occurred in 13% of ocrelizumab-treated subjects compared to 10% of placebo-treated subjects. In the adult PPMS clinical trial, the majority of the decreased neutrophil counts were only observed once for a given subject treated with ocrelizumab, and were between the LLN $-1.5\times10^9/L$ and $1.0\times10^9/L$. Additionally, 1% of ocrelizumab-treated subjects had neutrophil counts $<1.0\times10^9/L$; the observed cases of neutropenia were not associated with an infection. Therefore, this case of

neutropenia appears to be more severe compared to the cases observed in adult PPMS clinical trials of ocrelizumab.

90-Day Safety Update

The Applicant indicated that the EAER of SAEs for subjects who received at least one dose of ocrelizumab remained consistent between the initial sBLA submission COD and the 90-day safety update COD. In addition to the SAEs that occurred prior to the initial sBLA submission data cutoff, there were 3 additional SAEs that occurred between the sBLA submission COD and the 90-day safety update COD. One subject experienced an SAE of joint dislocation (Grade 3). Another subject experienced two SAEs (febrile neutropenia [Grade 3] and death [Grade 5]); the narrative for this case is described in Section 7.6.1.2.

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Studies WN42086 and WA39085

Study WN42086

TEAEs in Study WN42086 leading to permanent discontinuation of study treatment are reported by SOC and PT in Table 37. Review of these TEAEs by OCMQ (Narrow) demonstrated similar findings (data not shown). There were no subjects in the ocrelizumab arm who experienced TEAEs leading to permanent treatment discontinuation. TEAEs leading to study treatment discontinuation in the fingolimod arm (EAER of 0.8 events /100 PY) included toxicity to various agents, alanine aminotransferase increased, transaminases increased, and mental disorder.

Table 37. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study WN42086

System Organ Class Preferred Term	Ocrelizumab PY =137.8 E =0 Event (EAER)	Fingolimod PY =131.6 E =4 Event (EAER)	EAER Difference (95% CI)
At least one AE leading to treatment discontinuation	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Injury, poisoning and procedural complications (SOC)	0	1 (0.8)	−0.8 (−4.3, 2.0)
Toxicity to various agents	0	1 (0.8)	−0.8 (−4.3, 2.0)
Investigations (SOC)	0	2 (1.5)	−1.5 (−5.5, 1.3)
Alanine aminotransferase increased	0	1 (0.8)	−0.8 (−4.3, 2.0)
Transaminases increased	0	1 (0.8)	−0.8 (−4.3, 2.0)
Psychiatric disorders (SOC)	0	1 (0.8)	−0.8 (−4.3, 2.0)
Mental disorder	0	1 (0.8)	−0.8 (−4.3, 2.0)

Source: adae.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; E, number of events; EAER, exposure-adjusted event rate; PY, patient-years; SOC, system organ class

90-Day Safety Update

No additional subjects enrolled in Study WN42086 experienced TEAEs leading to study treatment discontinuation after the sBLA COD.

Study WA39085

TEAEs in Study WA39085 leading to permanent discontinuation of study treatment are reported by PT in Table 38. There was one TEAE of HIV infection in the ocrelizumab 600 mg arm (see Section 7.6.1.2) and no TEAEs leading to study treatment discontinuation in the ocrelizumab 300 mg arm.

Table 38. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study WA39085

System Organ Class Preferred Term	Ocrelizumab 300 mg PY =18.2 E =0 Event (EAER)	Ocrelizumab 600 mg PY =68.9 E =1 Event (EAER)
At least one AE leading to treatment discontinuation	0	1 (1.5)
Infections and infestations (SOC)	0	1 (1.5)
HIV infection	0	1 (1.5)

Source: adae.xpt; Software: R
Duration is a median of 147.6 weeks (ocrelizumab 300 mg) and 185.7 weeks (ocrelizumab 600 mg).
Abbreviations: AE, adverse event; E, number of events; EAER, exposure-adjusted event rate; HIV, human immunodeficiency virus; PY, patient-years; SOC, system organ class

90-Day Safety Update

No additional subjects enrolled in Study WA39085 experienced AEs leading to study treatment discontinuation after the sBLA COD.

7.6.1.5. Treatment-Emergent Adverse Events, Studies WN42086 and WA39085

Study WN42086

Table 39 provides a summary of the TEAEs that occurred in ≥5.5% of subjects in either treatment arm. The EAER for any TEAE was higher in the ocrelizumab arm (507.9 events/ 100 PY) compared to the fingolimod arm (490.1 events/100 PY). This difference was primarily driven by events of infusion related reactions (56.6 events/100 PY OCR versus 27.4 events/100 PY fingolimod), which are expected with ocrelizumab. TEAEs with a higher EAER in the OCR arm compared to the fingolimod arm were infusion related reaction, headache, nasopharyngitis, influenza, sinusitis, insomnia, upper respiratory tract infection, pain in extremity, and vomiting. TEAEs with risk difference 95% confidence intervals that did not include zero and had higher EAERs in the ocrelizumab arm included infusion related reaction, influenza, sinusitis, insomnia, pain in extremity, and panic attack. TEAEs of neutropenia, hypoesthesia, white blood cell count decreased, neutrophil count decreased, viral upper respiratory tract infection, cystitis, rhinorrhea, pruritus, and gastroenteritis viral had higher EAERs in the fingolimod arm and risk difference 95% confidence intervals that did not include zero.

Table 39. Treatment-Emergent Adverse Events Occurring at ≥5.5% Frequency by Preferred Term, Safety Population, Study WN42086

Preferred Term	Ocrelizumab PY =137.8 E =700 Event (EAER)	Fingolimod PY =131.6 E =645 Event (EAER)	EAER Difference (95% CI)
Any TEAE	700 (507.9)	645 (490.1)	17.9 (−35.6, 71.3)
Infusion related reaction	78 (56.6)	36 (27.4)	29.2 (14.0, 45.3)*
Headache	57 (41.4)	39 (29.6)	11.7 (−2.6, 26.4)
Nasopharyngitis	30 (21.8)	17 (12.9)	8.9 (−1.2, 19.4)
Influenza	14 (10.2)	5 (3.8)	6.4 (0.0, 13.7)*
Sinusitis	11 (8.0)	3 (2.3)	5.7 (0.3, 12.3)*
Insomnia	6 (4.4)	0	4.4 (1.4, 9.5)*
Upper respiratory tract infection	51 (37.0)	43 (32.7)	4.3 (−10.0, 18.7)
Pain in extremity	7 (5.1)	1 (0.8)	4.3 (0.3, 9.8)*
Vomiting	10 (7.3)	4 (3.0)	4.2 (−1.4, 10.7)
Panic attack	5 (3.6)	0	3.6 (0.7, 8.5)*
Dry eye	4 (2.9)	0	2.9 (−0.0, 7.5)
Paresthesia	8 (5.8)	6 (4.6)	1.2 (−4.8, 7.4)
Fatigue	11 (8.0)	9 (6.8)	1.1 (−5.9, 8.3)
Urinary tract infection	12 (8.7)	10 (7.6)	1.1 (−6.3, 8.5)
Gastroenteritis	9 (6.5)	9 (6.8)	−0.3 (−7.2, 6.4)
Nausea	10 (7.3)	11 (8.4)	−1.1 (−8.5, 6.0)
Dizziness	6 (4.4)	9 (6.8)	−2.5 (−9.1, 3.5)
Diarrhea	7 (5.1)	10 (7.6)	−2.5 (−9.5, 3.8)
Gastroenteritis viral	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Pruritus	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Rhinorrhea	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Cystitis	0	5 (3.8)	−3.8 (−8.9, −1.0)*
Viral upper respiratory tract infection	0	5 (3.8)	−3.8 (−8.9, −1.0)*
Neutrophil count decreased	0	6 (4.6)	−4.6 (−9.9, −1.8)*
Oropharyngeal pain	4 (2.9)	10 (7.6)	−4.7 (−11.4, 0.9)
Dysmenorrhea	10 (7.3)	16 (12.2)	−4.9 (−13.3, 2.7)
White blood cell count decreased	0	7 (5.3)	−5.3 (−11.0, −2.5)*
Hypoaesthesia	1 (0.7)	8 (6.1)	−5.4 (−11.3, −1.3)*
Neutropenia	0	12 (9.1)	−9.1 (−15.9, −5.2)*

Source: adae.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; E, number of events; EAER, exposure−adjusted event rate; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years; TEAE, treatment-emergent adverse event

Table 40 provides a summary of the TEAEs that occurred in ≥1.5% of subjects in either treatment arm by SOC and PT. The EAER for any TEAE was higher in the ocrelizumab arm (507.9/100 PY) compared to the fingolimod arm (490.1/100 PY). This difference was primarily driven by PTs contained within the SOCs Infections and infestations (PTs nasopharyngitis, influenza, sinusitis, upper respiratory tract infection, and respiratory tract infection); Injury, poisoning and procedural complications (PT infusion related reaction); Psychiatric disorders (PTs insomnia and panic attack), and musculoskeletal and connective tissue disorders (PT pain in extremity).

Table 40. Subjects With Adverse Events That Occurred in ≥1.5% of Subjects by System Organ Class and Preferred Term, Safety Population, Study WN42086

System Organ Class Preferred Term	Ocrelizumab PY =137.8 E =700 Event (EAER)	Fingolimod PY =131.6 E =645 Event (EAER)	EAER Difference (95% CI)
Any AE	700 (507.9)	645 (490.1)	17.9 (−35.6, 71.3)
Blood and lymphatic system disorders (SOC)	5 (3.6)	22 (16.7)	−13.1 (−22.0, −5.9)*
Iron deficiency anemia	3 (2.2)	0	2.2 (−0.7, 6.4)
Lymphopenia	0	2 (1.5)	−1.5 (−5.5, 1.3)
Anemia	0	3 (2.3)	−2.3 (−6.7, 0.5)
Leukopenia	0	3 (2.3)	−2.3 (−6.7, 0.5)
Neutropenia	0	12 (9.1)	−9.1 (−15.9, −5.2)*
Cardiac disorders (SOC)	3 (2.2)	10 (7.6)	−5.4 (−12.0, −0.2)*
Palpitations	1 (0.7)	5 (3.8)	−3.1 (−8.2, 0.7)
Eye disorders (SOC)	15 (10.9)	10 (7.6)	3.3 (−4.3, 11.2)
Dry eye	4 (2.9)	0	2.9 (−0.0, 7.5)
Eye pain	3 (2.2)	3 (2.3)	−0.1 (−4.8, 4.4)
Astigmatism	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Myopia	0	2 (1.5)	−1.5 (−5.5, 1.3)
Gastrointestinal disorders (SOC)	56 (40.6)	63 (47.9)	−7.2 (−23.6, 8.7)
Vomiting	10 (7.3)	4 (3.0)	4.2 (−1.4, 10.7)
Dyspepsia	3 (2.2)	0	2.2 (−0.7, 6.4)
Abdominal pain	7 (5.1)	5 (3.8)	1.3 (−4.4, 7.1)
Constipation	2 (1.5)	2 (1.5)	−0.1 (−4.2, 3.9)
Dental caries	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Abdominal pain upper	5 (3.6)	6 (4.6)	−0.9 (−6.7, 4.5)
Nausea	10 (7.3)	11 (8.4)	−1.1 (−8.5, 6.0)
Flatulence	0	2 (1.5)	−1.5 (−5.5, 1.3)
Tooth malformation	0	2 (1.5)	−1.5 (−5.5, 1.3)
Mouth ulceration	0	3 (2.3)	−2.3 (−6.7, 0.5)
Toothache	0	3 (2.3)	−2.3 (−6.7, 0.5)
Odynophagia	3 (2.2)	6 (4.6)	−2.4 (−8.0, 2.4)
Diarrhea	7 (5.1)	10 (7.6)	−2.5 (−9.5, 3.8)
General disorders and admin. site conditions (SOC)	39 (28.3)	41 (31.2)	−2.9 (−16.3, 10.4)
Chest discomfort	4 (2.9)	1 (0.8)	2.1 (−1.6, 6.8)
Pain	4 (2.9)	2 (1.5)	1.4 (−2.9, 6.1)
Fatigue	11 (8.0)	9 (6.8)	1.1 (−5.9, 8.3)
Influenza like illness	3 (2.2)	2 (1.5)	0.7 (−3.6, 5.0)
Peripheral swelling	0	2 (1.5)	−1.5 (−5.5, 1.3)
Asthenia	3 (2.2)	5 (3.8)	−1.6 (−7.0, 3.1)
Pyrexia	4 (2.9)	6 (4.6)	−1.7 (−7.4, 3.5)
Malaise	0	3 (2.3)	−2.3 (−6.7, 0.5)
Chest pain	4 (2.9)	7 (5.3)	−2.4 (−8.4, 2.8)
Immune system disorders (SOC)	3 (2.2)	6 (4.6)	−2.4 (−8.0, 2.4)
Drug hypersensitivity	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Seasonal allergy	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Infections and infestations (SOC)	204 (148.0)	152 (115.5)	32.5 (5.1, 60.2)*
Nasopharyngitis	30 (21.8)	17 (12.9)	8.9 (−1.2, 19.4)
Influenza	14 (10.2)	5 (3.8)	6.4 (0.0, 13.7)*
Sinusitis	11 (8.0)	3 (2.3)	5.7 (0.3, 12.3)*
Upper respiratory tract infection	51 (37.0)	43 (32.7)	4.3 (−10.0, 18.7)
Respiratory tract infection	5 (3.6)	1 (0.8)	2.9 (−1.0, 7.8)
Oral herpes	7 (5.1)	3 (2.3)	2.8 (−2.2, 8.5)

System Organ Class Preferred Term	Ocrelizumab PY =137.8 E =700 Event (EAER)	Fingolimod PY =131.6 E =645 Event (EAER)	EAER Difference (95% CI)
Tonsillitis	3 (2.2)	0	2.2 (−0.7, 6.4)
Pharyngitis	4 (2.9)	1 (0.8)	2.1 (−1.6, 6.8)
Viral infection	4 (2.9)	1 (0.8)	2.1 (−1.6, 6.8)
Conjunctivitis	5 (3.6)	2 (1.5)	2.1 (−2.3, 7.2)
Bronchitis	3 (2.2)	1 (0.8)	1.4 (−2.3, 5.7)
Pneumonia	4 (2.9)	2 (1.5)	1.4 (−2.9, 6.1)
Urinary tract infection	12 (8.7)	10 (7.6)	1.1 (−6.3, 8.5)
Rhinitis	7 (5.1)	6 (4.6)	0.5 (−5.5, 6.5)
Ear infection	2 (1.5)	2 (1.5)	−0.1 (−4.2, 3.9)
Gastroenteritis	9 (6.5)	9 (6.8)	−0.3 (−7.2, 6.4)
Fungal skin infection	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Lower respiratory tract infection	2 (1.5)	3 (2.3)	−0.8 (−5.4, 3.3)
COVID−19	4 (2.9)	5 (3.8)	−0.9 (−6.3, 4.1)
Dengue fever	0	2 (1.5)	−1.5 (−5.5, 1.3)
Paronychia	0	2 (1.5)	−1.5 (−5.5, 1.3)
Pertussis	0	2 (1.5)	−1.5 (−5.5, 1.3)
Pharyngotonsillitis	0	2 (1.5)	−1.5 (−5.5, 1.3)
Skin infection	0	2 (1.5)	−1.5 (−5.5, 1.3)
Gastroenteritis viral	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Cystitis	0	5 (3.8)	−3.8 (−8.9, −1.0)*
Viral upper respiratory tract infection	0	5 (3.8)	−3.8 (−8.9, −1.0)*
Injury, poisoning and procedural complications (SOC)	98 (71.1)	57 (43.3)	27.8 (9.8, 46.3)*
Infusion related reaction	78 (56.6)	36 (27.4)	29.2 (14.0, 45.3)*
Ligament sprain	4 (2.9)	3 (2.3)	0.6 (−4.1, 5.4)
Ligament rupture	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Limb injury	0	2 (1.5)	−1.5 (−5.5, 1.3)
Toxicity to various agents	0	2 (1.5)	−1.5 (−5.5, 1.3)
Investigations (SOC)	22 (16.0)	40 (30.4)	−14.4 (−26.8, −3.0)*
Aspartate aminotransferase increased	3 (2.2)	2 (1.5)	0.7 (−3.6, 5.0)
Alanine aminotransferase increased	4 (2.9)	3 (2.3)	0.6 (−4.1, 5.4)
Blood creatine phosphokinase increased	4 (2.9)	3 (2.3)	0.6 (−4.1, 5.4)
Amylase increased	0	2 (1.5)	−1.5 (−5.5, 1.3)
Gamma-glutamyl transferase increased	0	2 (1.5)	−1.5 (−5.5, 1.3)
Lipase increased	0	2 (1.5)	−1.5 (−5.5, 1.3)
Lymphocyte count decreased	0	2 (1.5)	−1.5 (−5.5, 1.3)
Neutrophil count decreased	0	6 (4.6)	−4.6 (−9.9, −1.8)*
White blood cell count decreased	0	7 (5.3)	−5.3 (−11.0, −2.5)*
Metabolism and nutrition disorders (SOC)	10 (7.3)	7 (5.3)	1.9 (−4.6, 8.7)
Hypertriglyceridemia	4 (2.9)	2 (1.5)	1.4 (−2.9, 6.1)
Decreased appetite	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Musculoskeletal and connective tissue disorders (SOC)	35 (25.4)	23 (17.5)	7.9 (−3.3, 19.5)
Pain in extremity	7 (5.1)	1 (0.8)	4.3 (0.3, 9.8)*
Arthralgia	7 (5.1)	3 (2.3)	2.8 (−2.2, 8.5)
Back pain	5 (3.6)	3 (2.3)	1.3 (−3.5, 6.5)
Muscle spasms	2 (1.5)	2 (1.5)	−0.1 (−4.2, 3.9)
Myalgia	2 (1.5)	3 (2.3)	−0.8 (−5.4, 3.3)
Neck pain	1 (0.7)	4 (3.0)	−2.3 (−7.2, 1.3)

System Organ Class Preferred Term	Ocrelizumab PY =137.8 E =700 Event (EAER)	Fingolimod PY =131.6 E =645 Event (EAER)	EAER Difference (95% CI)
Nervous system disorders (SOC)	97 (70.4)	96 (72.9)	−2.6 (−23.1, 17.8)
Headache	57 (41.4)	39 (29.6)	11.7 (−2.6, 26.4)
Restless legs syndrome	3 (2.2)	0	2.2 (−0.7, 6.4)
Syncope	4 (2.9)	2 (1.5)	1.4 (−2.9, 6.1)
Paresthesia	8 (5.8)	6 (4.6)	1.2 (−4.8, 7.4)
Multiple sclerosis pseudo relapse	2 (1.5)	2 (1.5)	−0.1 (−4.2, 3.9)
Multiple sclerosis	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Post herpetic neuralgia	0	2 (1.5)	−1.5 (−5.5, 1.3)
Somnolence	0	2 (1.5)	−1.5 (−5.5, 1.3)
Presyncope	1 (0.7)	3 (2.3)	−1.6 (−6.0, 2.0)
Migraine	5 (3.6)	7 (5.3)	−1.7 (−7.8, 3.8)
Seizure	0	3 (2.3)	−2.3 (−6.7, 0.5)
Dizziness	6 (4.4)	9 (6.8)	−2.5 (−9.1, 3.5)
Hypoaesthesia	1 (0.7)	8 (6.1)	−5.4 (−11.3, −1.3)*
Psychiatric disorders (SOC)	32 (23.2)	16 (12.2)	11.1 (1.0, 21.8)*
Insomnia	6 (4.4)	0	4.4 (1.4, 9.5)*
Panic attack	5 (3.6)	0	3.6 (0.7, 8.5)*
Depression	3 (2.2)	1 (0.8)	1.4 (−2.3, 5.7)
Anxiety	6 (4.4)	4 (3.0)	1.3 (−4.0, 6.8)
Anxiety disorder	0	2 (1.5)	−1.5 (−5.5, 1.3)
Psychotic disorder	0	2 (1.5)	−1.5 (−5.5, 1.3)
Reproductive system and breast disorders (SOC)	12 (8.7)	21 (16.0)	−7.2 (−16.6, 1.2)
Menstruation irregular	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Heavy menstrual bleeding	0	2 (1.5)	−1.5 (−5.5, 1.3)
Dysmenorrhea	10 (7.3)	16 (12.2)	−4.9 (−13.3, 2.7)
Respiratory, thoracic and mediastinal disorders (SOC)	24 (17.4)	37 (28.1)	−10.7 (−22.8, 0.7)
Rhinitis allergic	5 (3.6)	2 (1.5)	2.1 (−2.3, 7.2)
Dyspnea	2 (1.5)	2 (1.5)	−0.1 (−4.2, 3.9)
Epistaxis	4 (2.9)	6 (4.6)	−1.7 (−7.4, 3.5)
Rhinorrhea	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Cough	2 (1.5)	7 (5.3)	−3.9 (−9.7, 0.6)
Oropharyngeal pain	4 (2.9)	10 (7.6)	−4.7 (−11.4, 0.9)
Skin and subcutaneous tissue disorders (SOC)	24 (17.4)	32 (24.3)	−6.9 (−18.5, 4.1)
Acne	4 (2.9)	2 (1.5)	1.4 (−2.9, 6.1)
Eczema	4 (2.9)	3 (2.3)	0.6 (−4.1, 5.4)
Alopecia	5 (3.6)	5 (3.8)	−0.2 (−5.7, 5.2)
Urticaria	0	2 (1.5)	−1.5 (−5.5, 1.3)
Rash	2 (1.5)	4 (3.0)	−1.6 (−6.5, 2.6)
Pruritus	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Vascular disorders (SOC)	4 (2.9)	3 (2.3)	0.6 (−4.1, 5.4)
Flushing	3 (2.2)	0	2.2 (−0.7, 6.4)

Source: adae.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
The preferred terms in the table are ordered by descending risk difference.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: admin., administration; AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; E, number of events; EAER, exposure-adjusted event rate; PY, patient-years; SOC, system organ class

TEAEs grouped using OCMQs (narrow) were also reviewed and demonstrated similar findings (data not shown). OCMQs that had a higher EAER in the ocrelizumab arm compared to the fingolimod arm and a EAER difference 95% CI that did not include zero were local administration reaction and insomnia.

The EAER for PTs contained within the OCMQs were numerically higher in the OCR arm versus the fingolimod arm:

- Nasopharyngitis: OCR: 71.8 events/100 PY versus fingolimod: 53.9 events/100 PY
- Viral infection: OCR: 24.7 events/100 PY versus fingolimod: 22.0 events/100 PY
- Arthralgia: OCR: 5.1 events/100 PY versus fingolimod: 2.3 events/100 PY
- Headache: OCR: 45.0 events/100 PY versus fingolimod: 35.7 events/100 PY
- Anxiety: OCR: 9.4 events/100 PY versus fingolimod: 6.1 events/100 PY

Although TEAEs reported with ocrelizumab in Study WN42086 overall appeared consistent with the known safety profile in adults, the following differences were noted:

- Events of lower respiratory tract infection, herpes virus infections, and back pain, while discussed in current approved labeling for Ocrevus, were infrequent in pediatric subjects in Study WN42086. Instead, upper respiratory tract infections were the most common events coded to PTs (nasopharyngitis, influenza, sinusitis, and upper respiratory tract infection) contained within the MedDRA SOC Infections and infestations in pediatric subjects.
- According to current approved labeling for Ocrevus, AEs of depression were reported in 8% of ocrelizumab-treated adult subjects pooled from the phase 3 RMS studies; however, such events were only reported in 2.2% of pediatric subjects in Study WA42086.
- Events coded to the PT insomnia occurred in 6.5% of pediatric subjects; however, the risk of insomnia is not discussed in current approved labeling for Ocrevus.

90-Day Safety Update

TEAEs reported in the 90-day safety update were consistent with those reported in the initial sBLA submission.

Study WA39085

TEAEs occurring in ≥1.5% of subjects in either treatment arm are listed by PT in Table 41. The EAER for any TEAE was higher in the ocrelizumab 300 mg arm (655.6 events/100 PY) compared to the ocrelizumab 600 mg arm (620.0 events/100 PY). The incidence of some TEAEs appeared to differ between treatment arms; however, these findings are difficult to interpret in the setting of a relatively low frequency of events, small sample size, and lack of a true comparator arm. Review of TEAEs using OCMQs (narrow) demonstrated similar findings (results not shown).

The EAERs for TEAEs of pyrexia and headache were higher in the ocrelizumab 300 mg arm (27.5 events/100 PY and 82.6 events/100 PY, respectively), as compared to the ocrelizumab 600 mg arm (11.6 events/100 PY and 49.4 events/100 PY, respectively). The EAER for PTs coded under the SOC infections and infestations was higher in the ocrelizumab 600 mg arm

(142.3 events/100 PY) compared to the ocrelizumab 300 mg arm (99.2 events/100 PY). This difference was primarily driven by events coded to the PTs upper respiratory tract infection (ocrelizumab 600 mg: 24.7 events/100 PY, ocrelizumab 300 mg: 11.0 events/100 PY) and nasopharyngitis (ocrelizumab 600 mg: 18.9 events/100 PY, ocrelizumab 300 mg: 0.0 events/100 PY). Additionally, the EAER for TEAEs of infusion reaction was higher in the ocrelizumab 600 mg arm (78.4 events/100 PY) compared to the ocrelizumab 300 mg arm (44.1 events/100 PY).

Table 41. Subjects With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 1.5% of Subjects in Any Treatment Arm, Safety Population, Study WA39085

System Organ Class Preferred Term	Ocrelizumab 300 mg PY =18.2 E =119 Event (EAER)	Ocrelizumab 600 mg PY =68.9 E =427 Event (EAER)
Any AE	119 (655.6)	427 (620.0)
Blood and lymphatic system disorders (SOC)	1 (5.5)	8 (11.6)
Neutropenia	1 (5.5)	1 (1.5)
Lymphopenia	0	2 (2.9)
Leukopenia	0	4 (5.8)
Cardiac disorders (SOC)	2 (11.0)	1 (1.5)
Tachycardia	1 (5.5)	0
Bundle branch block left	1 (5.5)	0
Ear and labyrinth disorders (SOC)	0	3 (4.4)
Ear pain	0	2 (2.9)
Eye disorders (SOC)	0	4 (5.8)
Chalazion	0	2 (2.9)
Gastrointestinal disorders (SOC)	16 (88.1)	26 (37.7)
Vomiting	2 (11.0)	3 (4.4)
Nausea	3 (16.5)	1 (1.5)
Mouth ulceration	1 (5.5)	0
Irritable bowel syndrome	0	2 (2.9)
Gastroesophageal reflux disease	0	2 (2.9)
Diarrhea	2 (11.0)	6 (8.7)
Dental caries	1 (5.5)	1 (1.5)
Constipation	1 (5.5)	3 (4.4)
Abdominal pain upper	2 (11.0)	3 (4.4)
Abdominal pain	4 (22.0)	3 (4.4)
General disorders and admin. site conditions (SOC)	11 (60.6)	25 (36.3)
Vessel puncture site pain	1 (5.5)	0
Pyrexia	5 (27.5)	8 (11.6)
Peripheral swelling	0	2 (2.9)
Pain	0	3 (4.4)
Malaise	1 (5.5)	1 (1.5)
Fatigue	3 (16.5)	6 (8.7)
Asthenia	1 (5.5)	1 (1.5)
Immune system disorders (SOC)	1 (5.5)	4 (5.8)
Hypersensitivity	1 (5.5)	4 (5.8)

System Organ Class Preferred Term	Ocrelizumab 300 mg PY =18.2 E =119 Event (EAER)	Ocrelizumab 600 mg PY =68.9 E =427 Event (EAER)
Infections and infestations (SOC)	18 (99.2)	98 (142.3)
Viral infection	0	5 (7.3)
Urinary tract infection	0	6 (8.7)
Upper respiratory tract infection	2 (11.0)	17 (24.7)
Tooth infection	0	2 (2.9)
Sinusitis	0	2 (2.9)
Rhinitis	2 (11.0)	6 (8.7)
Pharyngitis	0	3 (4.4)
Oral herpes	0	3 (4.4)
Nasopharyngitis	0	13 (18.9)
Nasal herpes	0	2 (2.9)
Influenza	2 (11.0)	4 (5.8)
Herpes zoster	1 (5.5)	1 (1.5)
Herpes virus infection	4 (22.0)	0
Gastrointestinal infection	1 (5.5)	3 (4.4)
Gastroenteritis	1 (5.5)	0
Fungal infection	1 (5.5)	0
COVID-19	3 (16.5)	12 (17.4)
Candida infection	0	2 (2.9)
Bronchitis	0	2 (2.9)
Appendicitis	1 (5.5)	0
Anal abscess	0	5 (7.3)
Injury, poisoning and procedural complications (SOC)	14 (77.1)	69 (100.2)
Upper limb fracture	1 (5.5)	0
Torus fracture	1 (5.5)	0
Muscle strain	1 (5.5)	0
Limb injury	1 (5.5)	0
Infusion related reaction	8 (44.1)	54 (78.4)
Fall	2 (11.0)	2 (2.9)
Arthropod sting	0	2 (2.9)
Investigations (SOC)	7 (38.6)	40 (58.1)
Weight decreased	1 (5.5)	1 (1.5)
Neutrophil count decreased	0	3 (4.4)
Lymphocyte count decreased	0	3 (4.4)
Lipase increased	0	4 (5.8)
Gamma-glutamyl transferase increased	0	2 (2.9)
Fungal test positive	1 (5.5)	0
CD8 lymphocytes decreased	0	2 (2.9)
Blood triglycerides increased	0	4 (5.8)
Blood immunoglobulin M decreased	2 (11.0)	2 (2.9)
Blood immunoglobulin G decreased	1 (5.5)	1 (1.5)
Blood creatine phosphokinase increased	0	4 (5.8)
Aspartate aminotransferase increased	1 (5.5)	2 (2.9)
Alanine aminotransferase increased	1 (5.5)	2 (2.9)
Metabolism and nutrition disorders (SOC)	4 (22.0)	5 (7.3)
Vitamin D deficiency	1 (5.5)	0
Hypertriglyceridemia	0	3 (4.4)
Hypernatremia	1 (5.5)	0
Hypercholesterolemia	1 (5.5)	1 (1.5)
Hyperamylasemia	1 (5.5)	0

System Organ Class Preferred Term	Ocrelizumab 300 mg PY =18.2 E =119 Event (EAER)	Ocrelizumab 600 mg PY =68.9 E =427 Event (EAER)
Musculoskeletal and connective tissue disorders (SOC)	5 (27.5)	25 (36.3)
Scoliosis	1 (5.5)	0
Pain in extremity	1 (5.5)	7 (10.2)
Myalgia	1 (5.5)	0
Muscular weakness	0	5 (7.3)
Back pain	2 (11.0)	3 (4.4)
Arthralgia	0	8 (11.6)
Nervous system disorders (SOC)	25 (137.7)	65 (94.4)
Syncope	1 (5.5)	2 (2.9)
Presyncope	0	2 (2.9)
Paresthesia	0	3 (4.4)
Migraine	2 (11.0)	6 (8.7)
Headache	15 (82.6)	34 (49.4)
Dizziness	5 (27.5)	5 (7.3)
Disturbance in attention	2 (11.0)	1 (1.5)
Psychiatric disorders (SOC)	11 (60.6)	9 (13.1)
Suicidal ideation	1 (5.5)	0
Self-destructive behavior	1 (5.5)	0
Restlessness	1 (5.5)	0
Insomnia	2 (11.0)	1 (1.5)
Initial insomnia	1 (5.5)	0
Depressed mood	2 (11.0)	0
Conversion disorder	0	3 (4.4)
Anxiety	3 (16.5)	4 (5.8)
Renal and urinary disorders (SOC)	0	4 (5.8)
Micturition urgency	0	3 (4.4)
Reproductive system and breast disorders (SOC)	0	4 (5.8)
Dysmenorrhea	0	3 (4.4)
Respiratory, thoracic and mediastinal disorders (SOC)	3 (16.5)	20 (29.0)
Rhinorrhea	0	2 (2.9)
Oropharyngeal pain	1 (5.5)	4 (5.8)
Nasal congestion	0	2 (2.9)
Epistaxis	1 (5.5)	0
Cough	1 (5.5)	7 (10.2)
Skin and subcutaneous tissue disorders (SOC)	1 (5.5)	9 (13.1)
Urticaria	0	2 (2.9)
Rash	0	2 (2.9)
Pruritus	0	2 (2.9)
Acne	1 (5.5)	0
Surgical and medical procedures (SOC)	0	2 (2.9)
Wisdom teeth removal	0	2 (2.9)

Source: adae.xpt; Software: R
Duration is a median of 147.6 weeks (ocrelizumab 300 mg) and 185.7 weeks (ocrelizumab 600 mg).
Abbreviations: admin, administration; AE, adverse event; COVID-19, coronavirus disease 2019; E, number of events; EAER, exposure-adjusted event rate; PY, patient-years; SOC, system organ class

90-Day Safety Update

TEAEs reported in the 90-day safety update were consistent with those reported in the initial sBLA submission.

7.6.1.6. Laboratory Findings, Study WN42086

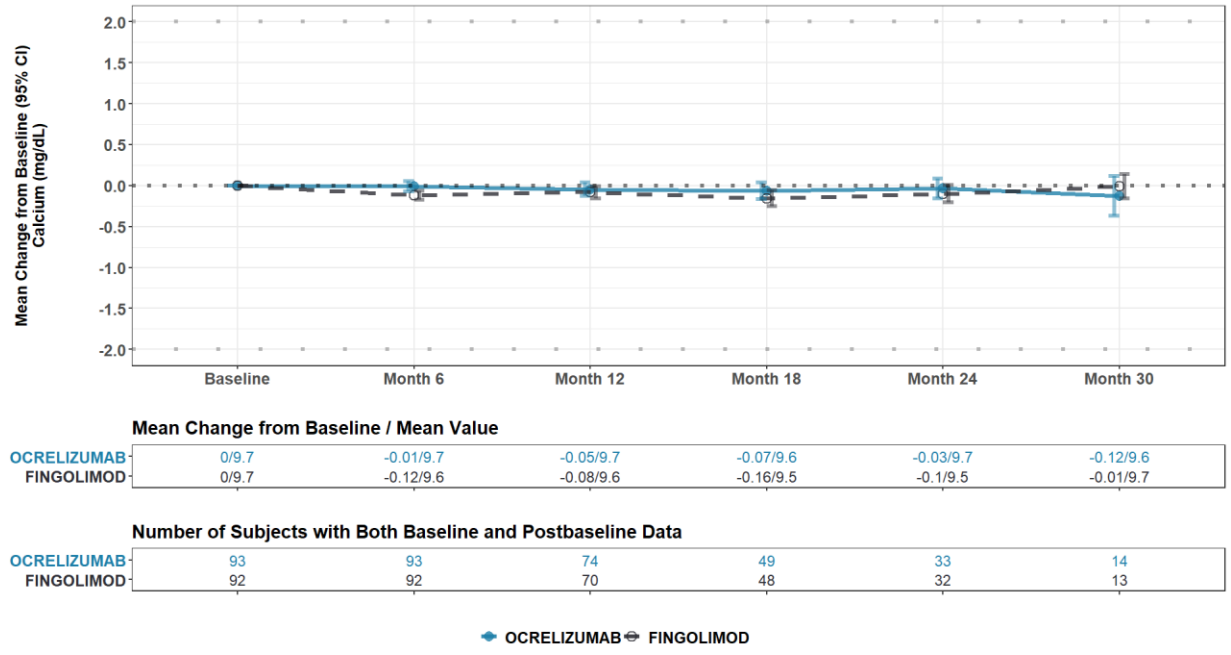
Results of the analysis of laboratory value abnormalities for subjects enrolled in Study WN42086 (DBP) were evaluated at each scheduled timepoint. In general, laboratory abnormalities consistent with the known safety profile and pharmacodynamic effects of ocrelizumab. The results are presented below, with additional discussion of reductions in immunoglobulins, liver injury, and cytopenias in Sections 7.7.3, 7.7.6, and 7.7.7, respectively.

Chemistry

Mean change from baseline and outlier analyses were conducted for sodium, potassium, chloride, protein, albumin, lipase, amylase, and blood urea nitrogen. No consistent trends or concerning findings were noted in these analyses (Table 42).

Serum calcium appeared to have a similar change from baseline in the ocrelizumab arm compared to the fingolimod arm (Figure 11). However, a higher proportion of subjects in the ocrelizumab arm experienced Level 1 (>10.5 mg/dL) and 2 (>11.0 mg/dL) hypercalcemia (15.1% and 2.2%, respectively) at any point after baseline compared to subjects in the fingolimod arm (2.2% and 0.0%, respectively; Table 42). No subjects in either treatment arm experienced TEAEs of hypercalcemia. There does not appear to be a clinically significant change in calcium values or increase in calcium-related TEAEs with ocrelizumab in pediatric subjects.

Figure 11. Mean Calcium (mg/dL) Change From Baseline Over Time by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period

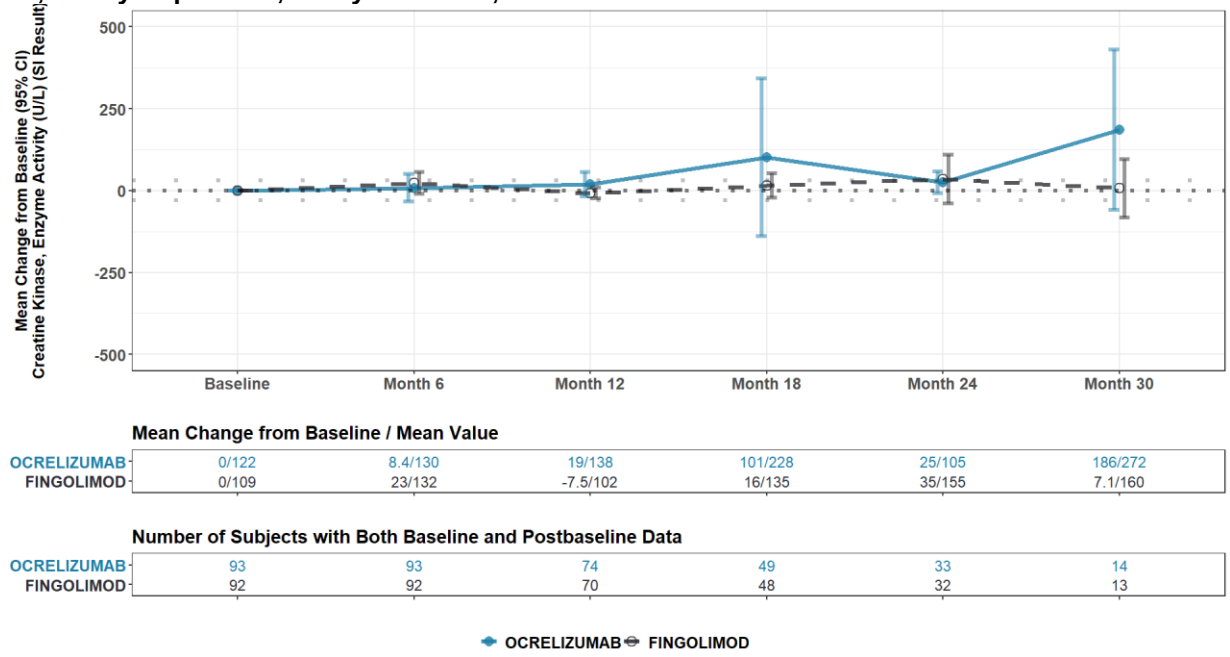


Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
The vertical bars shown on the plotted lines indicate the 95% CI of the mean change at the corresponding time points.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

Subjects in the ocrelizumab arm had a higher increase from baseline in serum CPK compared to the fingolimod arm at Months 12 and 30 (Figure 12). However, a consistent trend was not

observed over time. A higher proportion of subjects in the ocrelizumab arm experienced Level 1 (>3× ULN) and 2 (>5× ULN) CPK elevation (14.0% and 5.4%, respectively) at any point after Baseline compared to subjects in the fingolimod arm (5.4% and 4.3%, respectively; Table 42). There was one SAE of blood CPK abnormal in the ocrelizumab arm and none in the fingolimod arm; see Section 7.6.1.3. Four subjects (4.3%) in the ocrelizumab arm experienced TEAEs of blood CPK increased compared to three subjects (3.3%) in the fingolimod arm. There does not appear to be a clinically significant change in CPK values or increase in CPK-related TEAEs with ocrelizumab versus fingolimod in pediatric subjects.

Figure 12. Mean Creatine Phosphokinase (U/L) Change From Baseline Over Time by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period



Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
The vertical bars shown on the plotted lines indicate the 95% CI of the mean change at the corresponding time points.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

There were no other clinically significant differences or trends between the groups in abnormalities of other blood chemistry values, including sodium, potassium, chloride, protein, albumin, amylase, lipase, or blood urea nitrogen (data not shown).

Table 42. Subjects With One or More Selected General Chemistry Analyte Values Above or Below Specified Levels, Safety Population, Study WN42086, Double-Blind Period

Laboratory Parameter	Ocrelizumab N=93 n/N_w (%)	Fingolimod N=92 n/N_w (%)	Risk Difference (%) (95% CI)
Calcium, low (mg/dL)			
Level 1 (<8.4)	3/93 (3.2)	6/92 (6.5)	−3.3 (−10.7, 3.4)
Level 2 (<8)	1/93 (1.1)	3/92 (3.3)	−2.2 (−8.2, 2.9)
Level 3 (<7.5)	1/93 (1.1)	1/92 (1.1)	−0.0 (−4.9, 4.9)

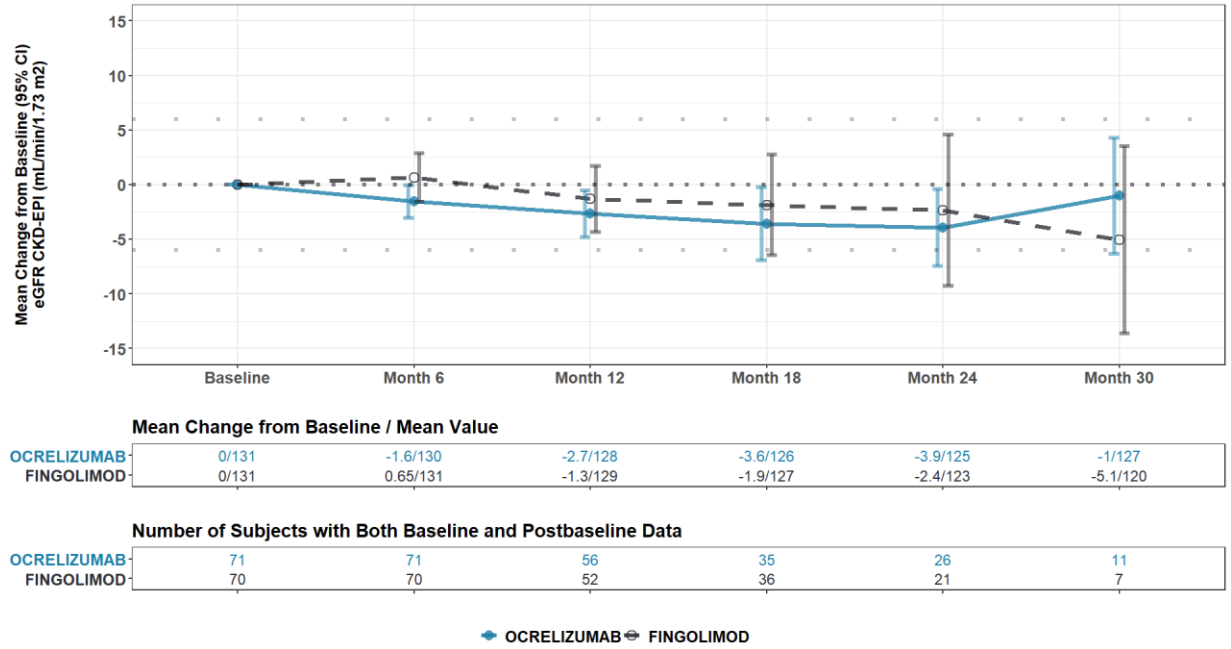
Laboratory Parameter	Ocrelizumab N=93 n/N_w (%)	Fingolimod N=92 n/N_w (%)	Risk Difference (%) (95% CI)
Calcium, high (mg/dL)			
Level 1 (>10.5)	14/93 (15.1)	2/92 (2.2)	12.9 (5.4, 21.8)*
Level 2 (>11)	2/93 (2.2)	0/92 (0)	2.2 (−1.9, 7.5)
Level 3 (>12)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)
CPK, high (U/L)			
Level 1 (>3× ULN)	13/93 (14.0)	5/92 (5.4)	8.5 (−0.0, 17.8)
Level 2 (>5× ULN)	5/93 (5.4)	4/92 (4.3)	1.0 (−6.0, 8.2)
Level 3 (>10× ULN)	3/93 (3.2)	3/92 (3.3)	−0.0 (−6.4, 6.2)

Source: adlb.xpt; Software: R
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria) (FDA 2025).
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Subject counts are cumulative for each abnormality threshold.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects with given characteristic; N_w, number of subjects with data; ULN, upper limit of normal

Kidney Function

Mean change from baseline and outlier analyses were conducted for kidney function analytes. There was a higher decrease from Baseline in estimated glomerular filtration rate (eGFR) in the fingolimod arm compared to the ocrelizumab arm (Figure 13), particularly at Months 24 and 30. However, this decrease in eGFR is unlikely to have resulted in a clinically significant decrease in kidney function. A higher proportion of subjects in the ocrelizumab arm (9.9%) experienced a Level 1 (≥25%) decrease in eGFR at any point after baseline compared to subjects in the fingolimod arm (4.3%). One subject (1.1%) in the ocrelizumab arm experienced a TEAE of blood creatinine abnormal, versus none in the fingolimod arm. However, there does not appear to be a clinically significant change in eGFR values or increase in kidney function-related TEAEs with ocrelizumab versus fingolimod in pediatric subjects.

Figure 13. Mean Glomerular Filtration Rate (mL/Minute/1.73 m^2), Change From Baseline Over Time by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period



Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
The vertical bars shown on the plotted lines indicate the 95% CI of the mean change at the corresponding time points.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate

There were no other clinically significant differences between the groups observed during the DBP in kidney function analyte values (creatinine and eGFR) exceeding specified levels (Table 43).

Table 43. Subjects With Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Study WN42086, Double-Blind Period

Laboratory Parameter	Ocrelizumab N=93 n/N_w (%)	Fingolimod N=92 n/N_w (%)	Risk Difference (%) (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5× baseline)	0/93 (0)	2/92 (2.2)	−2.2 (−7.6, 1.9)
Level 2 (≥2× baseline)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)
Level 3 (≥3× baseline)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)

Laboratory Parameter	Ocrelizumab N=93 n/N_w (%)	Fingolimod N=92 n/N_w (%)	Risk Difference (%) (95% CI)
eGFR, low (mL/minute/1.73 m^2)			
Level 1 (≥25% decrease)	7/71 (9.9)	3/70 (4.3)	5.6 (−3.4, 15.4)
Level 2 (≥50% decrease)	0/71 (0)	0/70 (0)	0.0 (−5.2, 5.2)
Level 3 (≥75% decrease)	0/71 (0)	0/70 (0)	0.0 (−5.2, 5.2)

Source: adlb.xpt; Software: R
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria) (FDA 2025).
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Subject counts are cumulative for each abnormality threshold.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects with given characteristic; N_w, number of subjects with data

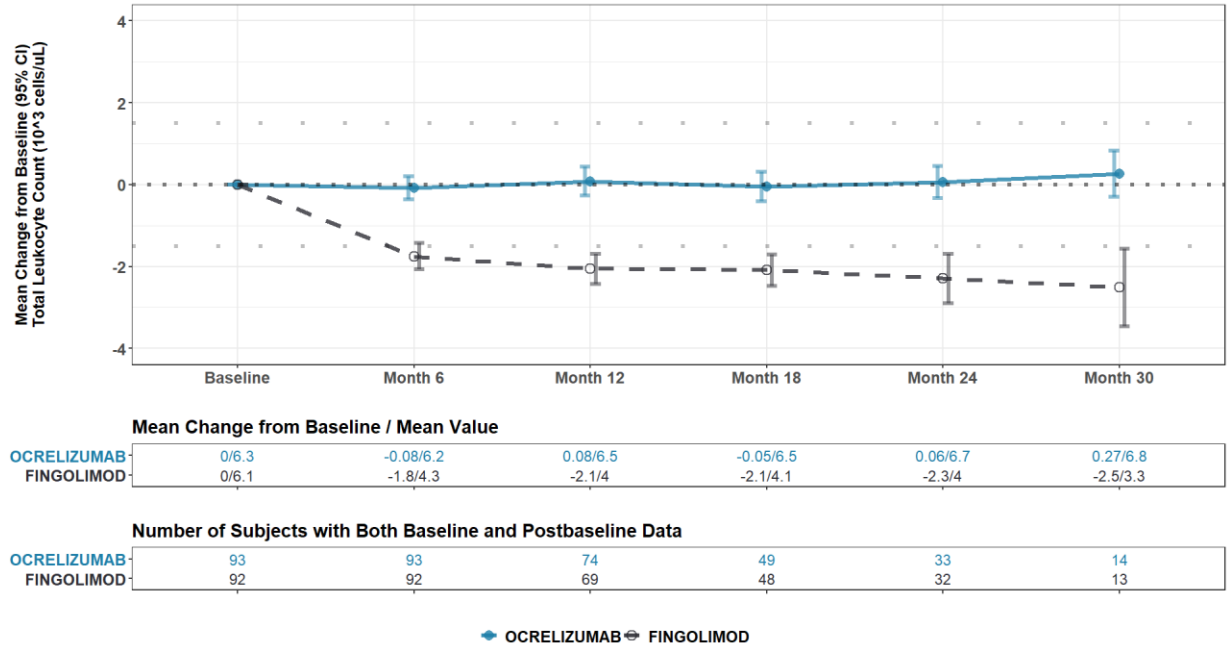
Hematology

Mean change from baseline and outlier analyses were conducted for hemoglobin, platelets, eosinophils, prothrombin time, and partial thromboplastin time (Table 44).

A greater decrease from baseline in WBC count was observed in the fingolimod arm compared to the ocrelizumab arm (Figure 14), with a consistent downtrend over time in the fingolimod arm. A higher proportion of subjects in the fingolimod arm (65.2% and 56.5%, respectively) experienced a Level 1 ($<3.5\times10^3$ cells/µL) or Level 2 ($<3\times10^3$ cells/µL) decrease in WBC count at any point after Baseline compared to subjects in the ocrelizumab arm (14.0% and 5.4%, respectively; Table 44). One subject (1.1%) in the fingolimod arm experienced a TEAE of WBC count decreased (versus none in the ocrelizumab arm). Additionally, two subjects (2.2%) in the fingolimod arm experienced a TEAE of leukopenia (versus none in the ocrelizumab arm). Decreases in WBC count are not unexpected with fingolimod given its MOA (i.e., sequestration of lymphocytes in lymphoid tissue) and known safety profile discussed in current approved labeling.

A higher proportion of subjects in the ocrelizumab arm (11.8%) experienced a Level 1 ($<10.8\times10^3$ cells/µL) increase in WBC count at any point after baseline compared to subjects in the fingolimod arm (6.5%; Table 44). Although there were no TEAEs of leukocytosis or WBC count increased reported in Study WN42086, TEAEs coded to PTs within the SOC Infections and Infestations were more common in the ocrelizumab arm compared to the fingolimod arm, which could potentially explain this imbalance. Refer to Section 7.7.2 for additional details regarding TEAEs of infection.

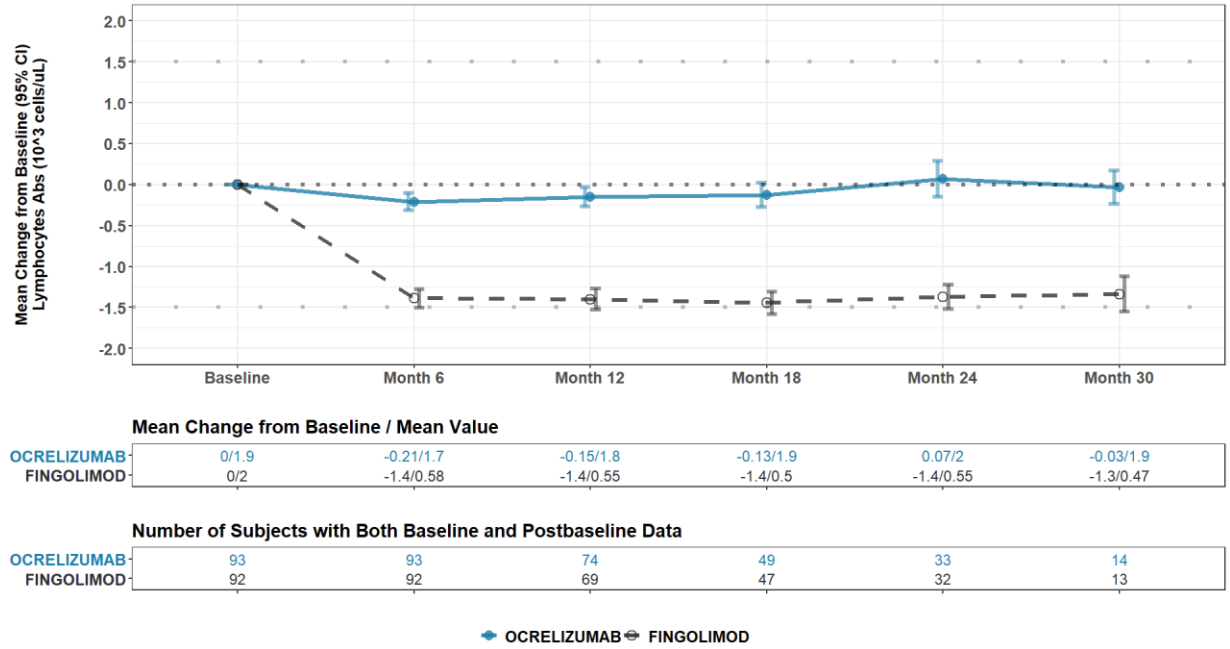
Figure 14. Mean Leukocyte Count (×10^3 Cells/µL), Change From Baseline Over Time by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period



Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
The vertical bars shown on the plotted lines indicates the 95% CI of the mean change at the corresponding time points.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

There was a greater decrease from baseline in ALC in the fingolimod arm compared to the ocrelizumab arm (Figure 15), which was identified at Month 6 and remained consistent over time. A higher proportion of subjects in the fingolimod arm (97.8%, 97.8%, and 78.3%, respectively) experienced Level 1 (<1.0×10^3 cells/µL), Level 2 (<0.75×10^3 cells/µL), and Level 3 (<0.50×10^3 cells/µL) decreases in ALC at any point after baseline compared to subjects in the ocrelizumab arm (22.6%, 6.5%, and 2.2%, respectively; Table 44). TEAEs of lymphocyte count decreased and lymphopenia (two subjects [2.2%] each) were reported in the fingolimod arm but not in the ocrelizumab arm. Decreases in ALC are expected with fingolimod given its MOA (i.e., sequestration of lymphocytes in lymphoid tissue). Compared to fingolimod, there does not appear to be a clinically significant change in ALC or an increase in lymphopenia-related TEAEs with ocrelizumab. Refer to Section 7.7.7 for an assessment of cytopenias with ocrelizumab.

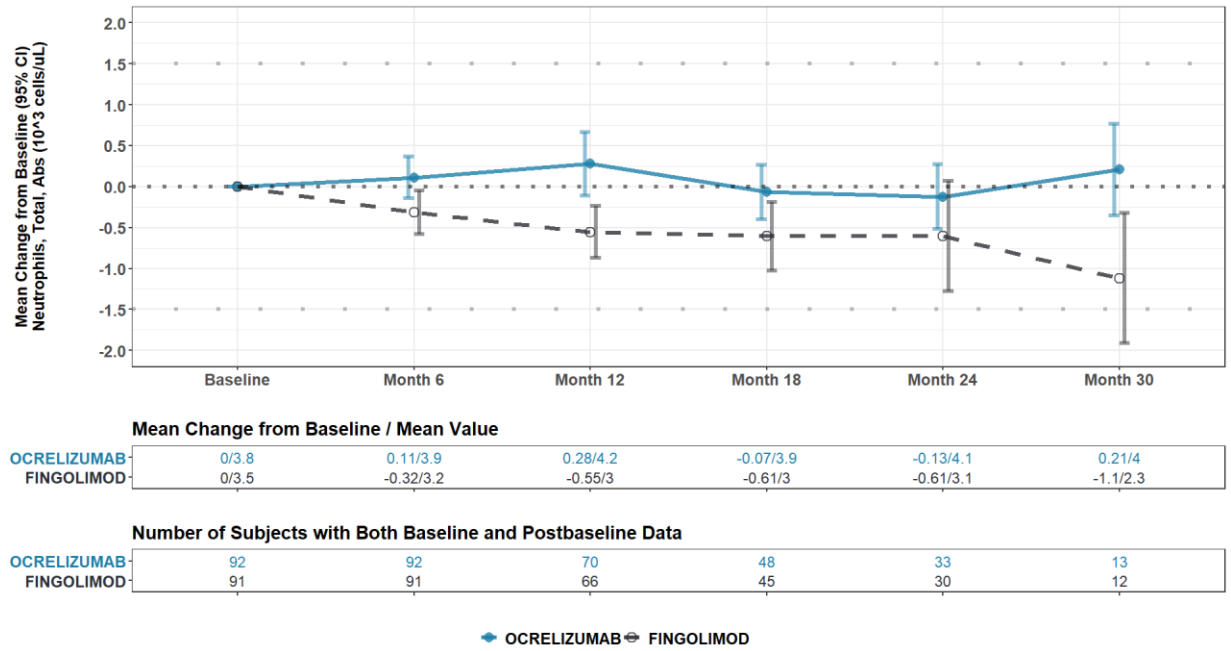
Figure 15. Mean Absolute Lymphocyte Count (×10^3 cells/µL), Change From Baseline Over Time by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period



Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
The vertical bars shown on the plotted lines indicates the 95% CI of the mean change at the corresponding time points.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

Subjects in the fingolimod arm experienced a greater decrease over time from baseline in ANC compared to the ocrelizumab arm (Figure 16). A higher proportion of subjects in the fingolimod arm (47.8%, and 6.5%, respectively) experienced Level 1 (<2.0×10^3 cells/µL) and Level 2 (<1×10^3 cells/µL) decreases in ANC at any point after Baseline compared to subjects in the ocrelizumab arm (16.1%, and 1.1%, respectively; Table 44). TEAEs of neutrophil percentage increased (n=1 [1.1%]), neutrophil percentage decreased (n=3 [3.3%]) and neutropenia (n=7 [7.6%]) were reported in the fingolimod arm but not in the ocrelizumab arm. Decreases in ANC are expected with fingolimod; as discussed in current approved labeling, "chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline." Compared to fingolimod, there does not appear to be a clinically significant change in ANC or an increase in neutropenia-related TEAEs with ocrelizumab. Refer to Section 7.7.7 for an assessment of cytopenias with ocrelizumab.

Figure 16. Mean Absolute Neutrophil Count (×10³ cells/µL), Change From Baseline Over Time by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period



Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
The vertical bars shown on the plotted lines indicates the 95% CI of the mean change at the corresponding time points.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

There were no other clinically significant differences between the groups observed during the DBP in hemoglobin, platelets, or eosinophils exceeding specified levels (data not shown).

Table 44. Subjects With Selected Hematology Analyte Values Exceeding Specified Levels, Safety Population, Study WN42086, Double-Blind Period

Laboratory Parameter	Ocrelizumab N=93 n/N_w (%)	Fingolimod N=92 n/N_w (%)	Risk Difference (%) (95% CI)
WBC, low (×10³ cells/µL)			
Level 1 (<3.5)	13/93 (14.0)	60/92 (65.2)	−51.2 (−62.3, −38.3)*
Level 2 (<3)	5/93 (5.4)	52/92 (56.5)	−51.1 (−61.7, −39.5)*
Level 3 (<1)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)
WBC, high (×10³ cells/µL)			
Level 1 (>10.8)	11/93 (11.8)	6/92 (6.5)	5.3 (−3.3, 14.3)
Level 2 (>13)	2/93 (2.2)	1/92 (1.1)	1.1 (−4.0, 6.6)
Level 3 (>15)	1/93 (1.1)	1/92 (1.1)	−0.0 (−4.9, 4.9)
Lymphocytes, low (×10³ cells/µL)			
Level 1 (<1)	21/93 (22.6)	90/92 (97.8)	−75.2 (−83.0, −65.0)*
Level 2 (<0.75)	6/93 (6.5)	90/92 (97.8)	−91.4 (−95.6, −83.5)*
Level 3 (<0.5)	2/93 (2.2)	72/92 (78.3)	−76.1 (−83.8, −66.0)*
Lymphocytes, high (×10³ cells/µL)			
Level 1 (>4)	1/93 (1.1)	0/92 (0)	1.1 (−3.0, 5.9)
Level 2 (>10)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)
Level 3 (>20)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)

Laboratory Parameter	Ocrelizumab N=93 n/N_w (%)	Fingolimod N=92 n/N_w (%)	Risk Difference (%) (95% CI)
Neutrophils, low ($\times 10^3$ cells/µL)			
Level 1 (<2)	15/93 (16.1)	44/92 (47.8)	−31.7 (−43.9, −18.6)*
Level 2 (<1)	1/93 (1.1)	6/92 (6.5)	−5.4 (−12.6, 0.1)
Level 3 (<0.5)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)

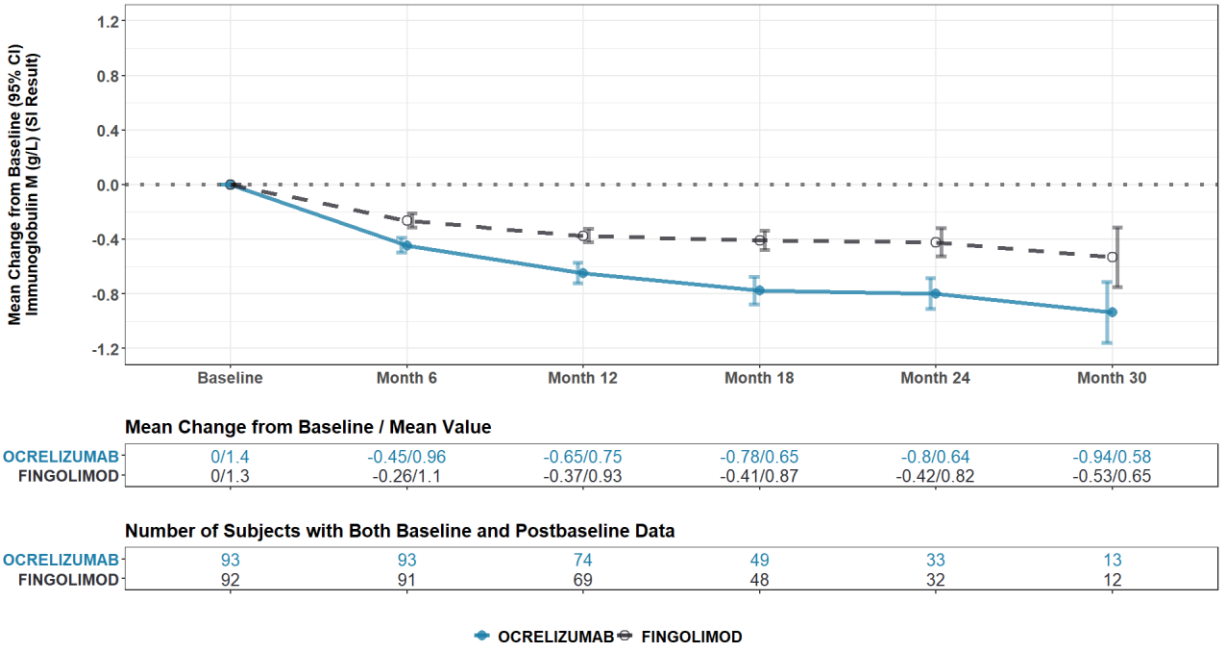
Source: adlb.xpt; Software: R
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria) (FDA 2025).
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Subject counts are cumulative for each abnormality threshold.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; dec., decrease; inc., increase; N, number of subjects in treatment arm; n, number of subjects meeting the specified laboratory criteria; N_w, total number of subjects with data available for the laboratory test of interest; WBC, white blood cells

Serum Immunoglobulin Levels

Mean change from baseline and outlier analyses were conducted for serum IgG, immunoglobulin A (IgA), and IgM. There were no clinically significant differences observed between the groups during the DBP in serum IgG or IgA levels (see Section 7.7.3). Overall, there does not appear to be a clinically significant change over time in serum IgG and IgA with ocrelizumab versus fingolimod in pediatric subjects.

Both treatment arms experienced a decrease in serum IgM from baseline over time, but the decrease was more pronounced in the ocrelizumab arm compared to the fingolimod arm (Figure 17). A higher proportion of subjects in the ocrelizumab arm experienced serum IgM levels below the LLN at any point after Baseline compared to subjects in the fingolimod arm (see Section 7.7.3). There were no TEAEs related to decreased immunoglobulin levels in either treatment arm. Compared to fingolimod, there appeared to be a clinically significant decrease in serum IgM levels over time, which is consistent with results of adult clinical trials of ocrelizumab, as described in current approved labeling. Refer to Section 7.7.3 for an assessment of hypogammaglobulinemia with ocrelizumab.

Figure 17. Mean Serum Immunoglobulin M Levels (g/L), Change From Baseline Over Time by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period



Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
The vertical bars shown on the plotted lines indicates the 95% CI of the mean change at the corresponding time points.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

Lipid Analytes

There were no clinically significant differences observed between the groups during the DBP in lipid analyte values. Mean change from baseline and outlier analyses were conducted for cholesterol and triglycerides. Overall, there does not appear to be a clinically significant change in lipid analyte values with ocrelizumab versus fingolimod in pediatric subjects.

Study WA39085

There did not appear to be any clinically significant changes over time for chemistry, hematology, kidney function, or lipid analyte values between subjects receiving ocrelizumab 300 mg versus 600 mg IV every 24 weeks. Outlier analyses for these analytes revealed a higher proportion of subjects in the ocrelizumab 300 mg arm (83.3%, 66.7%, and 33.3%) with Level 1 (>200 mg/dL), Level 2 (>210 mg/dL), and Level 3 (>225 mg/dL) cholesterol elevation compared to the ocrelizumab 600 mg arm (47.1%, 35.3%, and 23.5%). Subjects in the ocrelizumab 300 mg arm had lower mean age and weight (11.2 years and 34.8 kg) as compared to the ocrelizumab 600 mg arm (15.3 years and 62.3 kg). The lack of a comparator arm precludes the interpretation of this finding.

7.6.1.7. Assessment of Drug-Induced Liver Injury

Study WN42086

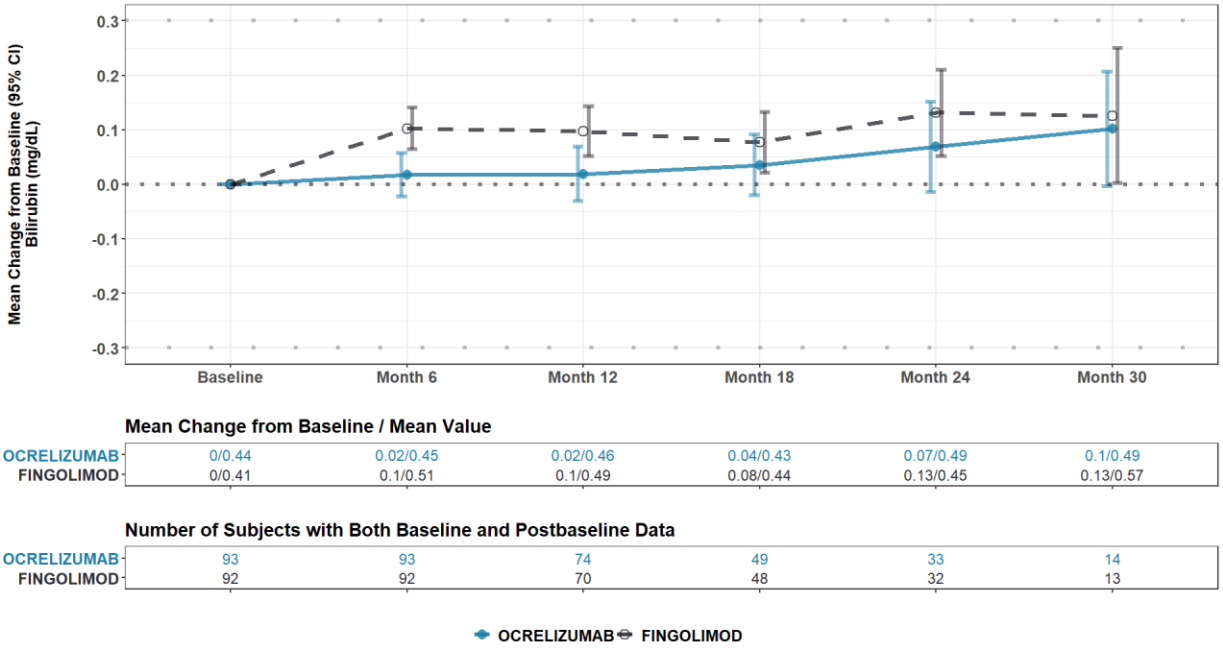
Results of analyses of liver laboratory abnormalities for subjects enrolled in Study WN42086 during the DBP are shown in Table 45. Liver injury is a known risk of both ocrelizumab and fingolimod and is discussed in the Warnings and Precautions section of labeling for each product.

Both treatment arms experienced a decrease over time in ALP, which was not clinically significant (data not shown). A higher proportion of subjects in the ocrelizumab arm (6.5%) experienced a Level 1 (>1.5× ULN) increase in ALP at any point after baseline compared to subjects in the fingolimod arm (1.1%; Table 45).

No clinically significant differences were observed between the groups in the proportion of subjects with ALT or AST exceeding specified levels (Table 47).

Both treatment arms experienced a slight increase over time in total bilirubin levels, which was not clinically significant (Figure 18). A higher proportion of subjects in the fingolimod arm (3.3%) experienced a Level 1 (>1.5× ULN) increase in total bilirubin at any point after baseline compared to subjects in the ocrelizumab arm (1.1%; Table 45).

Figure 18. Mean Total Bilirubin (mg/dL), Change From Baseline Over Time by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period



Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
The vertical bars shown on the plotted lines indicates the 95% CI of the mean change at the corresponding time points.
Only central laboratory data are included in the analysis.
Abbreviation: CI, confidence interval

TEAEs potentially concerning for liver injury reported during the DBP of Study WN42086 included hepatic enzyme increased (ocrelizumab n=1 [1.1%]; fingolimod n=0 [0.0%]), aspartate aminotransferase increased (ocrelizumab n=3 [3.2%]; fingolimod n=2 [2.2%]), alanine

aminotransferase increased in both treatment arms (ocrelizumab n=2 [2.2%]; fingolimod n=2 [2.2%]), blood bilirubin increased (ocrelizumab n=0 [0.0%]; fingolimod n=1 [1.1%]), transaminases increased (ocrelizumab n=0 [0.0%]; fingolimod n=1 [1.1%]), gamma-glutamyl transferase increased (ocrelizumab n=0 [0.0%]; fingolimod n=2 [2.2%]).

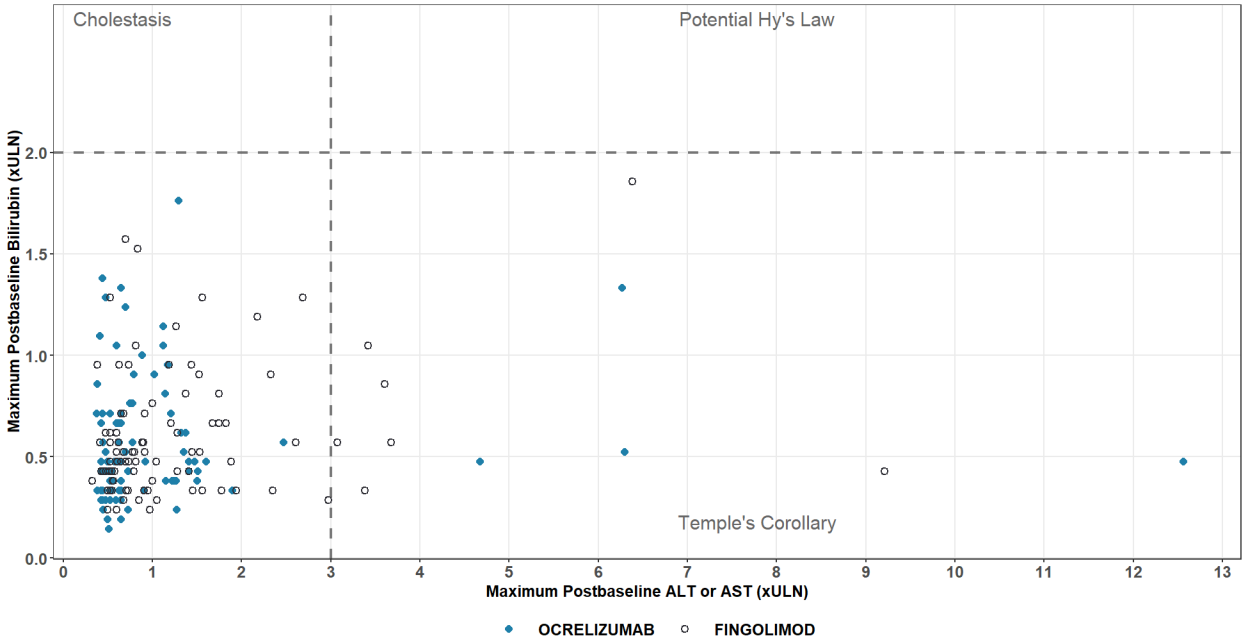
Table 45. Subjects With Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study WN42086

Laboratory Parameter	Ocrelizumab N=93 n/N_w (%)	Fingolimod N=92 n/N_w (%)	Risk Difference (%) (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5× ULN)	6/93 (6.5)	1/92 (1.1)	5.4 (−0.2, 12.5)
Level 2 (>2× ULN)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)
Level 3 (>3× ULN)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)
Alanine aminotransferase, high (U/L)			
Level 1 (>3× ULN)	3/93 (3.2)	6/92 (6.5)	−3.3 (−10.7, 3.4)
Level 2 (>5× ULN)	2/93 (2.2)	2/92 (2.2)	−0.0 (−5.7, 5.6)
Level 3 (>10× ULN)	1/93 (1.1)	0/92 (0)	1.1 (−3.0, 5.9)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3× ULN)	3/93 (3.2)	2/92 (2.2)	1.1 (−4.8, 7.2)
Level 2 (>5× ULN)	1/93 (1.1)	1/92 (1.1)	−0.0 (−4.9, 4.9)
Level 3 (>10× ULN)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5× ULN)	1/93 (1.1)	3/92 (3.3)	−2.2 (−8.2, 2.9)
Level 2 (>2× ULN)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)
Level 3 (>3× ULN)	0/93 (0)	0/92 (0)	0.0 (−4.0, 4.0)

Source: adlb.xpt; Software: R
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria) (FDA 2025).
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Subject counts are cumulative for each abnormality threshold.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For specific evaluation of drug-induced liver injury (DILI), see the figures “Hepatocellular Drug-Induced Liver Injury Screening Plot.” and “Cholestatic Drug-Induced Liver Injury Screening Plot.” and the tables “Subjects in Quadrant of Interest for Potential Hepatocellular DILI Screening Plot...” and “Subjects in Each Quadrant for Cholestatic DILI Screening Plot…”
Abbreviations: CI, confidence interval; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects with given characteristic; N_w, total number of subjects with data; ULN, upper limit of normal

Figure 19 shows a screening assessment for potential cases of serious DILI. There were no potential Hy’s Law cases.

Figure 19. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study WN42086



Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN.
The within 30 days analysis window rule does not apply to cholestasis and Temple's corollary quadrants.
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Overall, there does not appear to be a clinically significant change in liver biochemistry values or increase in liver-related TEAEs with ocrelizumab versus fingolimod in pediatric subjects in Study WN42086. Refer to Section 7.7.3 for further discussion of liver injury.

Study WA39085

There did not appear to be any clinically significant changes over time or differences in outliers for markers of liver injury between subjects receiving ocrelizumab 300 mg versus 600 mg IV every 24 weeks.

7.6.1.8. Vital Signs, Studies WN42086 and WA39085

Study WN42086

Vital signs, specifically blood pressure (systolic and diastolic), heart rate, and temperature, were reviewed at each scheduled visit for the safety population during the DBP. There were no clinically significant changes over time for any of these parameters in either treatment arm. No notable differences in postbaseline outlier values from normal baseline values were identified between the groups. Vital sign-related TEAEs are presented in Table 46; there were no imbalances in the proportion of subjects who experienced vital sign-related TEAEs. Overall,

there does not appear to be a clinically significant change in vital signs or increase in vital sign-related TEAEs with ocrelizumab versus fingolimod in pediatric subjects.

Table 46. Subjects With Vital Sign-Related Adverse Events by Preferred Term, Safety Population, Study WN42086

Preferred Term	Ocrelizumab N=93 n (%)	Fingolimod N=92 n (%)
Pyrexia	4 (4.3)	4 (4.3)
Dyspnea	2 (2.2)	2 (2.2)
Palpitations	1 (1.0)	3 (3.3)
Hypotension	1 (1.0)	1 (1.0)
Temperature regulation disorder	1 (1.0)	0 (0.0)
Blood pressure increased	0 (0.0)	1 (1.0)
Heart rate increased	0 (0.0)	1 (1.0)
Orthostatic hypotension	0 (0.0)	1 (1.0)
Extraventricular extrasystoles	0 (0.0)	1 (1.0)
Respiratory rate increased	0 (0.0)	1 (1.0)
Sinus bradycardia	0 (0.0)	1 (1.0)
Tachycardia	0 (0.0)	1 (1.0)

Source: Reviewer; adlb.xpt for Study WN42086
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given characteristic

The Division of Pediatrics and Maternal Health (DPMH) was consulted for review of this efficacy supplement. DPMH conducted a review of the safety data to determine whether any effects of ocrelizumab on growth and development were evident. DPMH did not identify any concerns related to growth or development associated with ocrelizumab in Study WN42086. Refer to the DPMH consultation memorandum dated April 3, 2026 (DARRTS ID: 5774905).

Study WA39085

Given the open-label nature of Study WA39085 and lack of a comparator arm, a detailed review of vital signs will not be presented for that study. Overall, there were no clinically significant changes over time of vital sign parameters in either treatment arm, and no notable differences in postbaseline outlier values from normal baseline values were identified between the groups.

7.6.1.9. Subgroups, Study WN42086

Results of analyses of TEAEs by demographic subgroup for subjects enrolled in Study WN42086 are shown in Table 47. Results of subgroup analyses appear consistent with the overall safety results presented in Sections 7.6.1.1 and 7.6.1.5; a higher proportion of subjects receiving ocrelizumab across demographic subgroups experienced any TEAE, as compared to those receiving fingolimod. Hispanic or Latino subjects in both treatment arms were more likely to experience a TEAE (92.3% ocrelizumab, 88.9% fingolimod), compared to non-Hispanic or Latino subjects (84% ocrelizumab, 70.9% fingolimod).

Table 47. Overview of Adverse Events by Demographic Subgroups, Safety Population, Study WN42086

Characteristic	Ocrelizumab N=93 n/N_S (%)	Fingolimod N=92 n/N_S (%)	Risk Difference (%) (95% CI)
Any AE	83/93 (89.2)	72/92 (78.3)	11.0 (0.3, 21.9)*
Sex			
Female	60/67 (89.6)	47/60 (78.3)	11.2 (−1.6, 24.7)
Male	23/26 (88.5)	25/32 (78.1)	10.3 (−10.5, 29.8)
Age group 1, years			
10 to 11	1/1 (100)	0/0 (N/A)	N/A
12 to 17	82/92 (89.1)	72/92 (78.3)	10.9 (0.2, 21.8)*
Age group 2, years			
<14	12/14 (85.7)	13/19 (68.4)	17.3 (−14.1, 43.9)
≥14	71/79 (89.9)	59/73 (80.8)	9.1 (−2.3, 20.9)
Age group ≥65, years			
<65	83/93 (89.2)	72/92 (78.3)	11.0 (0.3, 21.9)*
Age group ≥75, years			
<75	83/93 (89.2)	72/92 (78.3)	11.0 (0.3, 21.9)*
Race			
American Indian or Alaska Native	3/4 (75.0)	1/3 (33.3)	41.7 (−33.4, 84.7)
Asian	0/1 (0)	0/1 (0)	0.0 (−88.5, 88.5)
Black or African American	2/3 (66.7)	6/6 (100)	−33.3 (−80.7, 18.5)
Multiple	6/6 (100)	4/4 (100)	0.0 (−41.6, 51.6)
Not reported	15/15 (100)	16/17 (94.1)	5.9 (−15.7, 27.4)
Unknown	1/1 (100)	1/1 (100)	0.0 (−88.5, 88.5)
White	56/63 (88.9)	44/60 (73.3)	15.6 (1.8, 29.6)*
Ethnicity			
Hispanic or Latino	24/26 (92.3)	16/18 (88.9)	3.4 (−15.5, 26.6)
Not Hispanic or Latino	42/50 (84.0)	39/55 (70.9)	13.1 (−3.2, 28.8)
Not reported	17/17 (100)	16/17 (94.1)	5.9 (−13.6, 27.4)
Unknown	0/0 (N/A)	1/2 (50.0)	N/A
Is in United States			
United States	10/11 (90.9)	10/10 (100)	−9.1 (−38.6, 21.1)
Outside the United States	73/82 (89.0)	62/82 (75.6)	13.4 (1.8, 25.2)*

Source: adae.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with given characteristic; N/A, not applicable; N_S, number of subjects in subgroup

7.7. Key Safety Review Issues

7.7.1. Infusion Reactions and Hypersensitivity

Issue

Infusion reactions are listed in Section 5.1 of current approved labeling for Ocrevus and are expected with intravenously-administered monoclonal antibodies. Hypersensitivity is a potential risk with monoclonal antibody administration. Section 5.1 (Warnings and Precautions [Infusion Reactions] of current approved labeling for Ocrevus discusses anaphylaxis in the context of infusion reactions. Symptoms of infusion reactions in adult clinical trials of ocrelizumab

included pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis. In adult MS clinical trials, the incidence of infusion reactions in Ocrevus-treated subjects (who received methylprednisolone [or an equivalent steroid] and possibly other premedication to reduce the risk of infusion reaction prior to each infusion) was 34% to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of Ocrevus-treated MS patients experienced infusion related reactions that were serious, some requiring hospitalization. Ocrevus labeling recommends that patients be observed for infusion reactions during each infusion and for at least 1 hour after completion of the infusion. Infusion reactions can occur up to 24 hours after the infusion. Premedication (e.g., methylprednisolone or an equivalent corticosteroid, and an antihistamine) should be administered to reduce the frequency and severity of infusion reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered.

Background

Definition of Infusion Related Reaction

According to Section 5.3.5.1 *Infusion-Related Reactions* of the protocol for Study WN42086 (version 6), infusion related reactions were defined as “adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion.” Per the protocol, signs and symptoms associated with infusion related reactions were recorded on a dedicated eCRF.

Reporting of Adverse Events of Infusion Related Reaction

Section 5.3.5.1 *Infusion-Related Reactions* of Protocol WN42086 (version 6) recommended that events of infusion related reaction “be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF” and that ambiguous terms be avoided.

Premedication Administration Window and Postinfusion Monitoring

Subjects received mandatory premedication prior to blinded IV study treatment (ocrelizumab or IV placebo) administration to reduce the frequency of infusion related reactions. According to Section 4.3.2.1.5 *Premedication for Infusion-Related Reactions* of Protocol WN42086 (version 6), premedication included “methylprednisolone, administered by slow IV infusion to be completed approximately 30 minutes before the start of each ocrelizumab/ocrelizumab placebo infusion” at the weight-adjusted dose of 2 mg/kg for subjects weighing <40 kg and at a dose of 100 mg for subjects weighing ≥40 kg. Premedication also included administration of “an antihistaminic drug (e.g., diphenhydramine) approximately 30 to 60 minutes before each infusion” and “the addition of an analgesic/antipyretic (e.g., acetaminophen/paracetamol) […could] also be considered.”

The review team requested that the Applicant provide a data-driven justification for the proposed methylprednisolone dose for premedication for pediatric patients aged 10 years and older with a body weight <40 kg and for pediatric patients aged 10 years and older with a body weight ≥40 kg via information request. According to the Applicant, a weight-based dose was proposed for pediatric patients aged 10 years and older weighing <40 kg to ensure adequate receptor occupancy and avoid supraphysiological steroid exposure, which could occur with

administration of adult fixed doses in lower weight individuals. According to the Applicant, the transition to the adult methylprednisolone 100 mg fixed dose was justified by allometric scaling models, which demonstrated that the drug clearance and volume of distribution in that weight bracket were statistically comparable to those observed in adults.

The review team also requested that the Applicant propose and justify a maximum dose of methylprednisolone IV for premedication of pediatric patients aged 10 years and older with a body weight <40 kg. The Applicant proposed a maximum methylprednisolone dose of (b) (4) mg IV in this group. According to the Applicant, the maximum dose was justified by the principle of receptor saturation.

Assessment

Infusion related reactions were observed during the DBP of Study WN42086 in pediatric subjects receiving ocrelizumab. TEAEs of infusion related reactions were common in the ocrelizumab arm and occurred in 48.4% of subjects, compared to 23.9% of fingolimod-treated subjects. Per the CSR of Study WN42086, there were no confirmed events of hypersensitivity reactions.

Table 48 presents the frequency of TEAEs of infusion related reaction, as defined in the study protocol (i.e., those that occurred within the first 24 hours following administration of IV study treatment and that were considered by the investigator to be related to the study drug) that occurred in the safety population. There were no life-threatening or fatal events of infusion related reaction in either treatment arm, and no events resulted in study treatment discontinuation. Three subjects (3.2%) experienced severe events of infusion related reaction in the ocrelizumab arm and none in the fingolimod arm. The duration of the reported infusion related reaction events for both treatment arms was from 1 to 8 days, with a median of 1 day. The proportion of subjects experiencing infusion related reactions decreased over time in both treatment arms.

Table 48. Adverse Events of Injection-Related Reaction That Occurred Within 24 Hours After Ocrelizumab or IV Placebo Infusion, Safety Population, Study WN42086, Double-Blind Period

Preferred Term	Ocrelizumab N=93 n (%)	Fingolimod N=92 n (%)
Infusion related reaction	45 (48.4)	22 (23.9)
Maximum severity		
Death	0 (0.0)	0 (0.0)
Life-threatening	0 (0.0)	0 (0.0)
Severe	3 (3.2)	0 (0.0)
Moderate	23 (24.7)	4 (4.3)
Mild	33 (35.5)	27 (29.3)
Serious	1 (1.1)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)
Resulting in treatment discontinuation	0 (0.0)	0 (0.0)
Duration, days (from AE start date to AE end date)		
Mean (SD)	1.5 (1.1)	1.8 (1.5)
Median (IQR)	1 (1)	1 (1)
Min, max	1, 8	1, 8

Source: adae.xpt; Software: JMP
Abbreviations: AE, adverse event; IQR, interquartile range; IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects given characteristic; SD, standard deviation

Subject (b) (6) (a 15-year-old female with a body weight of 114.8 kg) experienced the SAE infusion related reaction (Grade 3) on Study Day 1. The subject was premedicated with methylprednisolone 100 mg IV, dimenhydrinate 50 mg PO, and paracetamol 1 g IV. Preinfusion vital signs included body temperature 36.2 °C, blood pressure 110/87 mm Hg, heart rate 80 beats/min, and respiratory rate 21 breaths/min. Approximately 2 hours following infusion initiation, the subject developed pruritus, cough, flushing, and throat irritation and therefore the infusion was interrupted. The subject received treatment with desloratadine and dimenhydrinate and her symptoms resolved approximately 1 hour and 20 minutes after onset, at which point the infusion was resumed. The subject remained hospitalized overnight for observation and was discharged the next day.

Discussion

This is a serious event of infusion related reaction requiring hospitalization that did not result in study treatment discontinuation. The subject was premedicated and the infusion related reaction was treated according to the protocol. Infusion related reactions are a known risk of ocrelizumab.

Table 49 presents the frequency of signs and symptoms of events of infusion related reaction that occurred in 3 or more subjects in either treatment arm. Symptoms of infusion related reaction reported by each subject were coded to a PT. The most common symptoms included headache, erythema, nausea, rash, fatigue, pruritus, flushing, and throat irritation. These symptoms are similar to those reported with infusion related reactions in the adult population.

Table 49. Symptoms of Adverse Events of Injection Related Reaction, Safety Population, Study WN42086, Double-Blind Period

Preferred Term	Ocrelizumab N=93 n (%)	Fingolimod N=92 n (%)
Headache	15 (16.1)	10 (10.9)
Erythema	8 (8.6)	2 (2.2)
Nausea	8 (8.6)	1 (1.1)
Rash	8 (8.6)	1 (1.1)
Fatigue	7 (7.5)	6 (6.5)
Pruritus	7 (7.5)	2 (2.2)
Flushing	6 (6.5)	2 (2.2)
Throat irritation	5 (5.4)	1 (1.1)
Chills	3 (3.2)	2 (2.2)
Oropharyngeal pain	3 (3.2)	0 (0.0)
Rash erythematous	3 (3.2)	0 (0.0)
Blood pressure diastolic decreased	2 (2.2)	3 (3.3)
Hypotension	2 (2.2)	3 (3.3)

Source: adirr.xpt; Software: JMP
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given characteristic

The review team requested that Applicant provide a summary of the doses and route of administration for diphenhydramine administered in Study WN42086, stratified by age and weight. A summary of the rate of infusion reactions based on the dose of diphenhydramine administered was also requested. According to the Applicant's response, diphenhydramine for premedication "was administered 191 times at dosages between 10 mg and 100 mg during the double-blind period" of Study WN42086. The diphenhydramine dose most commonly administered was 50 mg (166/191 [86.9%] doses), of which 78.3% (130/166 doses) were orally-

administered and 21.7% (36/166 doses) were intravenously-administered. Per the Applicant, "the median age of subjects at diphenhydramine administration (50 mg) was 16.4 (range: 11.2 to 20.3) years and the median weight was 65.5 (range: 48.4 to 163.7) kg." In terms of the rate of injection related reactions among subjects who received premedication with diphenhydramine 50 mg prior to an ocrelizumab infusion, 29.7% (11/37) of subjects experienced an infusion related reaction with the first infusion (dose 1, Day 1), 8.1% (3/37) of subjects experienced an infusion related reaction with the second infusion (dose 1, Day 15); and 17.1% (6/35) of subjects experienced an infusion related reaction with the third infusion (dose 2). The proportion of subjects experiencing infusion related reactions decreased with subsequent doses.

Conclusion

Infusion related reactions were common in subjects treated with ocrelizumab in Study WN42086. The risk of infusion related reactions is expected in pediatric patients given the known safety profile of ocrelizumab in adults, and is discussed in current approved labeling for Ocrevus. Based on the results from Study WN42086, there is no evidence of a differential risk for infusion-related reactions in adult versus pediatric patients. Labeling recommendations regarding postinfusion monitoring for at least one hour after completion of the infusion are also applicable to the pediatric population. The premedication specified in Protocol WN42086 (i.e., methylprednisolone 2 mg/kg IV for subjects weighing <40 kg and 100 mg IV for subjects weighing ≥40 kg [to be completed ~30 minutes before the start of each ocrelizumab infusion], an antihistaminic [to be administered 30 to 60 min prior to each ocrelizumab infusion], and an optional analgesic/antipyretic) were discussed by the multidisciplinary review team, and will also be recommended in labeling.

7.7.2. Infections

Issue

Ocrelizumab carries a risk of serious (including life-threatening or fatal) infections, as described in current approved labeling for Ocrevus. The risk of infections (including progressive multifocal leukoencephalopathy) is also discussed in current approved labeling for fingolimod.

Background

Section 5.2 (Warnings and Precautions, Infections) of current approved labeling for Ocrevus discusses the risk of serious, including life-threatening or fatal, bacterial, viral, parasitic, and fungal infections with Ocrevus and other anti-CD20 monoclonal antibodies. Clinical trials of ocrelizumab in adult subjects demonstrated a higher risk of upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections with Ocrevus, as compared to subjects taking Rebif or placebo. Additionally, hepatitis B reactivation has been reported in MS patients treated with Ocrevus in the postmarketing setting, and cases of fulminant hepatitis, hepatic failure, and death caused by hepatitis B reactivation have occurred in patients treated with anti-CD20 monoclonal antibodies. Cases of PML have also been reported in patients with MS treated with Ocrevus in the postmarketing setting.

Assessment

Table 50 presents the results of the division's analyses of TEAEs of infection (PTs contained within the MedDRA SOC Infections and Infestations) that occurred in the safety population of Study WN42086. The EAER for any TEAEs coded to PTs contained within the MedDRA SOC Infections and Infestations was higher in the ocrelizumab arm (148.0 events/100 PY) compared to the fingolimod arm (115.5 events/100 PY). The risk difference between the groups was largest for TEAEs of nasopharyngitis, influenza, sinusitis, and upper respiratory tract infection, which were more common in the ocrelizumab arm. The proportion of subjects who experienced infection-related SAEs was similar between the groups and the majority of events were mild or moderate in severity in both arms. The EAER for any SAEs coded to PTs contained within the MedDRA SOC Infections and Infestations was similar between the groups. Refer to Section 7.6.1.3 for a discussion of SAEs that occurred during Study WN42086.

Table 50. Subjects With Adverse Events Coded to Preferred Terms Contained Within the MedDRA System Organ Class Infections and Infestations, Showing Terms Occurring in at Least 1.5% of Subjects in Any Treatment Arm, Safety Population, Study WN42086, Double-Blind Period

System Organ Class Preferred Term	Ocrelizumab PY =137.8 E =700 Event (EAER)	Fingolimod PY =131.6 E =645 Event (EAER)	EAER Difference (95% CI)
Infections and infestations (SOC)	204 (148.0)	152 (115.5)	32.5 (5.1, 60.2)*
Nasopharyngitis	30 (21.8)	17 (12.9)	8.9 (−1.2, 19.4)
Influenza	14 (10.2)	5 (3.8)	6.4 (0.0, 13.7)*
Sinusitis	11 (8.0)	3 (2.3)	5.7 (0.3, 12.3)*
Upper respiratory tract infection	51 (37.0)	43 (32.7)	4.3 (−10.0, 18.7)
Respiratory tract infection	5 (3.6)	1 (0.8)	2.9 (−1.0, 7.8)
Oral herpes	7 (5.1)	3 (2.3)	2.8 (−2.2, 8.5)
Tonsillitis	3 (2.2)	0	2.2 (−0.7, 6.4)
Pharyngitis	4 (2.9)	1 (0.8)	2.1 (−1.6, 6.8)
Viral infection	4 (2.9)	1 (0.8)	2.1 (−1.6, 6.8)
Conjunctivitis	5 (3.6)	2 (1.5)	2.1 (−2.3, 7.2)
Bronchitis	3 (2.2)	1 (0.8)	1.4 (−2.3, 5.7)
Pneumonia	4 (2.9)	2 (1.5)	1.4 (−2.9, 6.1)
Urinary tract infection	12 (8.7)	10 (7.6)	1.1 (−6.3, 8.5)
Rhinitis	7 (5.1)	6 (4.6)	0.5 (−5.5, 6.5)
Ear infection	2 (1.5)	2 (1.5)	−0.1 (−4.2, 3.9)
Gastroenteritis	9 (6.5)	9 (6.8)	−0.3 (−7.2, 6.4)
Fungal skin infection	1 (0.7)	2 (1.5)	−0.8 (−4.9, 2.7)
Lower respiratory tract infection	2 (1.5)	3 (2.3)	−0.8 (−5.4, 3.3)
COVID-19	4 (2.9)	5 (3.8)	−0.9 (−6.3, 4.1)
Dengue fever	0	2 (1.5)	−1.5 (−5.5, 1.3)
Paronychia	0	2 (1.5)	−1.5 (−5.5, 1.3)
Pertussis	0	2 (1.5)	−1.5 (−5.5, 1.3)
Pharyngotonsillitis	0	2 (1.5)	−1.5 (−5.5, 1.3)
Skin infection	0	2 (1.5)	−1.5 (−5.5, 1.3)
Gastroenteritis viral	0	4 (3.0)	−3.0 (−7.8, −0.3)*
Cystitis	0	5 (3.8)	−3.8 (−8.9, −1.0)*
Viral upper respiratory tract infection	0	5 (3.8)	−3.8 (−8.9, −1.0)*

System Organ Class Preferred Term	Ocrelizumab PY =137.8 E =700 Event (EAER)	Fingolimod PY =131.6 E =645 Event (EAER)	EAER Difference (95% CI)
Maximum severity			
Death, n (%)	0	0	N/A
Life-threatening, n (%)	0	0	N/A
Severe, n (%)	3 (3.2)	3 (3.3)	N/A
Moderate, n (%)	74 (79.6)	51 (55.4)	N/A
Mild, n (%)	87 (93.5)	67 (72.8)	N/A
Serious	4 (2.9)	4 (3.0)	−0.1 (−5.2, 4.8)
Deaths	0	0	N/A
Resulting in treatment discontinuation	0	0	N/A

Source: adae.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
The preferred terms in the table are ordered by the descending risk difference.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; E, number of events; EAER, exposure-adjusted event rate; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with given characteristic; N/A, not applicable; PY, patient-years; SOC, system organ class

The EAER for TEAEs coded to the PT oral herpes was higher in the ocrelizumab arm (5.1 events/100 PY) compared to the fingolimod arm (2.3 events/100 PY). One subject in the fingolimod arm experienced an event of herpes zoster, of which there were no events in the ocrelizumab arm. None of the reported herpes virus infection-related TEAEs were serious. There were no reported events of tick-borne infection, hepatitis B reactivation, or PML reported in either Studies WN42086 or WA39085.

Conclusion

Current approved labeling for Ocrevus discusses the risk of serious, including life-threatening or fatal, infections in Section 5.2 (Warnings and Precautions, Infections), including herpes viral infections, which is also expected in the pediatric population. The risk of serious infections with ocrelizumab in pediatric subjects appeared comparable to that of adults.

7.7.3. Reduction in Immunoglobulins

Issue

Ocrelizumab carries a known risk of reduction in immunoglobulins, as discussed in current approved labeling for Ocrevus.

Background

Sections 5.4 (Warnings and Precautions, Reduction in Immunoglobulins) and 6.1 (Adverse Reactions - Clinical Trials Experience) of current approved labeling for Ocrevus discuss the risk of reduction in immunoglobulins, which is expected with any B-cell depleting therapy. The pooled data of Ocrevus clinical studies in adults (RMS [Studies WA21092 and WA21093] and PPMS [Study WA25046]) and their open-label extensions (up to approximately 7 years of exposure) showed an association between decreased levels of immunoglobulin G (IgG <LLN) and increased rates of serious infections. The type, severity, latency, duration, and outcome of

serious infections observed during episodes of immunoglobulin levels below the LLN were consistent with the overall serious infections observed in patients treated with Ocrevus.

In the adult active-controlled (RMS) trials (Studies WA21092 and WA21093), the pooled proportion of subjects at baseline reporting IgG, IgA, and IgM below the LLN in OCR-treated subjects was 0.5%, 1.5%, and 0.1%, respectively. Following treatment, the proportion of ocrelizumab-treated subjects reporting IgG, IgA, and IgM below the LLN at 96 weeks was 1.5%, 2.4%, and 16.5%, respectively. In the placebo-controlled PPMS trial (Study WA25046), the proportion of ocrelizumab-treated subjects at baseline reporting IgG, IgA, and IgM below the LLN was 0.0%, 0.2%, and 0.2%, respectively. Following treatment, the proportion of ocrelizumab-treated subjects reporting IgG, IgA, and IgM below the LLN at 120 weeks was 1.1%, 0.5%, and 15.5%, respectively.

Therefore, currently approved Ocrevus labeling recommends monitoring the levels of quantitative serum immunoglobulins during Ocrevus treatment and after discontinuation of treatment, until B-cell repletion, and especially in the setting of recurrent serious infections. Additionally, discontinuation of treatment with Ocrevus should be considered in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with IV immunoglobulins.

Assessment

Table 51 presents subjects with serum immunoglobulin levels below the lower limit of normal at any point during Study WN42086. A higher proportion of subjects in the ocrelizumab arm (40.9%) experienced serum IgM levels below the LLN compared to the fingolimod arm (16.3%). There were no TEAEs of hypogammaglobulinemia reported in Study WN42086.

The following events of decreased serum immunoglobulin levels occurred in association with TEAEs of serious or opportunistic infections:

- Subject (b) (6) (ocrelizumab arm) experienced an SAE of pneumonia (Grade 3) on Study Day 534, which occurred in close temporal association with serum IgM <LLN (Study Day 534).
- Subject (b) (6) (ocrelizumab arm) experienced events coded to PTs contained within the MedDRA HLT Herpes viral infections (Grade 1, nonserious) on Study Days 182 and 416 and also experienced serum IgA and IgG levels <LLN on Study Day 498.
- Subject (b) (6) (ocrelizumab arm) experienced events coded to PTs contained within the MedDRA HLT Herpes viral infections (Grades 1 and 2, Nonserious) on Study Days 134 and 168 and also experienced serum IgM levels <LLN on Study Day 193.

Table 51. Subjects With Serum Immunoglobulin Levels Below the Lower Limit of Normal, Safety Population, Study WN42086

Parameter	Ocrelizumab N=93 n (%)	Fingolimod N=92 n (%)
Immunoglobulin A (g/L) <LLN	16 (17.2)	18 (19.6)
Immunoglobulin G (g/L) <LLN	11 (11.8)	12 (13)
Immunoglobulin M (g/L) <LLN	38 (40.9)	15 (16.3)

Source: adlb.xpt; Software: R
Duration is a median of 76.7 weeks (ocrelizumab) and 73.9 weeks (fingolimod).
Abbreviations: LLN, lower limit of normal; N, number of subjects in treatment arm; n, number of subjects with given characteristic

Table 52 presents subjects with serum immunoglobulin levels below the LLN at any point during Study WA39085. A higher proportion of subjects in the ocrelizumab 300 mg group (100%) experienced serum IgM levels below the LLN compared to the 600 mg group (70.6%); however, these results should be interpreted with caution due to the small sample size.

The following events of decreased serum immunoglobulin levels occurred in association with TEAEs of serious or opportunistic infections:

- Subject (b) (6) experienced a TEAE of blood IgM decreased (Grade 1, nonserious) on Study Day 488.
- Subject (b) (6) experienced a TEAE of blood IgM decreased (Grade 1, nonserious) on Study Day 493, followed by nonserious events of COVID-19 (Grade 2) and gastroenteritis (Grade 1) on Study Days 500 and 518, respectively. Subject (b) (6) also experienced a TEAE of blood IgG decreased on Study Day 1189, followed by a TEAE of influenza (Grade 2, nonserious) on Study Day 1240.
- Subject (b) (6) experienced TEAEs of nasal herpes on Study Days 179 and 520, along with serum IgG levels <LLN on Study Days 171 and 466.
- Subject (b) (6) experienced TEAEs of herpesvirus infection on Study Days 153, 1189, and 1365, along with serum IgM levels <LLN on Study Days 995, 1164, and 1332.
- Subject (b) (6) experienced a TEAE of oral herpes (Grade 2, nonserious) on Study Day 1009, along with serum IgA levels <LLN on Study Day 1159.
- Subject (b) (6) experienced a TEAE of herpes zoster (Grade 2, nonserious) on Study Day 166, along with serum IgG levels <LLN on Study Day 85.

Table 52. Subjects With Serum Immunoglobulin Levels Below the Lower Limit of Normal, Safety Population, Study WA39085

Parameter	Ocrelizumab 300 mg	Ocrelizumab 600 mg
Immunoglobulin A (g/L) <LLN	0 (0.0)	2 (11.8)
Immunoglobulin G (g/L) <LLN	2 (33.3)	4 (23.5)
Immunoglobulin M (g/L) <LLN	6 (100)	12 (70.6)

Source: adlb.xpt; Software: R
Duration is a median of 147.6 weeks (ocrelizumab 300 mg) and 185.7 weeks (ocrelizumab 600 mg).
Abbreviations: LLN, lower limit of normal; N, number of subjects in treatment arm; n, number of subjects with given characteristic

A clinically meaningful difference in mean IgA or IgG levels over time between the groups was not observed in either study. However, a trend was identified for declining IgM in subjects receiving ocrelizumab during Studies WN42086 and WA39085, which is consistent with the known safety profile of ocrelizumab (refer to Section 7.6.1.6).

Conclusion

A trend for declining IgM in ocrelizumab-treated subjects was observed in Studies WN42086 and WA39085, but no changes in IgA or IgG were noted. Though decreases in IgG are also expected with B-cell depleting therapies, the duration of the reviewed studies is likely not sufficient to observe this phenomenon. There were several events coded to PTs contained within the MedDRA HLT Herpes viral infections that occurred in close temporal association with instances of decreased serum immunoglobulin levels, particularly IgG and IgM.

Currently approved labeling for Ocrevus discusses the risk of reduction in immunoglobulins in Sections 5.4 (Warnings and Precautions, Reduction in Immunoglobulins) and 6.1 (Adverse Reactions, Clinical Trials Experience). Therefore, the risk of reduction in immunoglobulins is characterized for ocrelizumab and is also expected in the pediatric population.

7.7.4. Malignancies

Issue

Malignancy is a known potential safety risk with immunosuppressant therapies, including anti-CD20 therapies, especially with long-term use. As discussed in current approved labeling, ocrelizumab may increase the risk of malignancies. The risk of malignancy is also discussed in current approved labeling for fingolimod.

Background

Section 5.5 (Warnings and Precautions, Malignancies) of current approved labeling for Ocrevus states that an increased risk of malignancy with Ocrevus may exist. In controlled trials of Ocrevus in adults, malignancies, including breast cancer, occurred more frequently in OCR-treated subjects. Breast cancer occurred in 6 out of 781 female subjects treated with Ocrevus and in none of the 668 female subjects treated with interferon beta-1a or placebo. Labeling recommends that OCR-treated patients follow standard breast cancer screening guidelines. Additionally, a study intended to fulfill PMR 3194-2, evaluating the risk of breast cancer and other malignancies with ocrelizumab, is ongoing.

Assessment

There were no TEAEs with PTs contained within the SMQ Malignant tumors in Studies WN42086 or WA39085. Two subjects in Study WA39085 experienced TEAEs coded to PTs contained within the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) (benign neoplasm of thyroid gland [n=1] and skin papilloma [n=1]).

Conclusion

Malignancies are less common in pediatric patients, and the duration of exposure was short and may limit the interpretation of these data regarding this safety signal. Currently approved labeling for Ocrevus discusses the risk of malignancies, including breast cancer, in Section 5.5 (Warnings and Precautions, Malignancies). Although it is unclear whether there is a differential risk of malignancy between adult and pediatric patients, a potential risk with long-term exposure to ocrelizumab cannot be ruled out for the pediatric population. A PMR study intended to evaluate this risk is ongoing.

7.7.5. Immune-Mediated Colitis

Issue

Ocrelizumab carries a risk of immune-mediated colitis, as described in current approved labeling for Ocrevus.

Background

Sections 5.6 (Warnings and Precautions, Immune Mediated Colitis) and 6.3 (Adverse Reactions - Postmarketing Experience) of current approved labeling for Ocrevus discuss the risk of immune-mediated colitis, which can present as a severe and acute-onset form of colitis. Some of the cases of immune-mediated colitis, which were reported in adults in the postmarketing setting were serious, requiring hospitalization, with a few patients requiring surgical intervention. Additionally, systemic corticosteroids were required in many of these patients. The time from treatment initiation to onset of symptoms in these cases ranged from a few weeks to years.

Assessment

There was one TEAE coded to a PT contained within the MedDRA High-Level Term (HLT) Colitis (excluding infective) in Study WN42086. Details regarding this case were clarified with the Applicant via information request.

Subject (b) (6)

Subject (b) (6), an 18-year-old male subject receiving ocrelizumab, developed a TEAE of colitis (Grade 1, nonserious). On Study Day 133, the subject developed flatulence and abdominal distention that were thought to be related to "bad eating habits." No diagnostic evaluations (e.g., colonoscopy or intestinal biopsy) were performed. Per the Applicant's response to information request, a clinical diagnosis of noninfectious colitis was made. The subject received treatment with pinaverium bromide and dimethicone. The event was considered resolved on Study Day 137.

Discussion

This appears to be an acute event of colitis triggered by food consumption that resolved completely after 5 days. This event does not appear consistent with immune-mediated colitis.

There were no TEAEs coded to PTs contained within the MedDRA High-Level Term Colitis (excluding infective) in Study WA39085.

Conclusion

Currently approved labeling for Ocrevus discusses the risk of immune-mediated colitis in Section 5.6 (Warnings and Precautions, Immune-Mediated Colitis). Although it is unclear whether there is a differential risk of immune-mediated colitis between adult and pediatric patients, this risk cannot be ruled out for the pediatric population.

7.7.6. Liver Injury

Issue

Ocrelizumab carries a risk of liver injury, as described in current approved labeling for Ocrevus. The risk of liver injury is also discussed in current approved labeling for fingolimod.

Background

Sections 5.7 (Warnings and Precautions, Liver Injury) and 6.3 (Adverse Reactions - Postmarketing Experience) of current approved labeling for Ocrevus discuss the risk of liver injury. Clinically significant liver injury, without findings of viral hepatitis, has been reported in the postmarketing setting in patients treated with anti-CD20 B-cell depleting therapies approved for the treatment of MS, including Ocrevus. Signs of liver injury, including markedly elevated serum hepatic enzymes with elevated total bilirubin, have occurred from weeks to months after administration.

Assessment

Table 53 presents TEAEs coded to PTs contained within the OCMQs (narrow) hepatic injury or hepatic failure that occurred during Study WN42086. The number of subjects experiencing liver-related TEAEs and the EAER for these events appeared to be balanced between the groups.

Table 53. Adverse Events by Preferred Term in Hepatic Injury or Hepatic Failure OND Custom Medical Queries (Narrow) by Treatment Arm, Safety Population, Study WN42086, Double-Blind Period

OND Custom Medical Query Preferred Term	Ocrelizumab N=93 n (%)	Fingolimod N=92 n (%)	Ocrelizumab PY =137.8 E =7 Event (EAER)	Fingolimod PY =131.6 E =5 Event (EAER)	EAER Difference (95% CI)
Hepatic injury (narrow OCMQ)	3 (3.2)	4 (4.3)	7 (5.1)	5 (3.8)	1.3 (−4.4, 7.1)
Aspartate aminotransferase increased	3 (3.2)	2 (2.2)	3 (2.2)	2 (1.5)	0.7 (−3.6, 5.0)
Alanine aminotransferase increased	2 (2.2)	2 (2.2)	4 (2.9)	3 (2.3)	0.6 (−4.1, 5.4)
Hepatic failure (narrow OCMQ)	0	0	0	0	0.0 (−2.9, 2.8)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; E, number of events; EAER, exposure-adjusted event rate; N, number of subjects in treatment arm; n, number of subjects with given characteristic; OCMQ, Office of New Drugs custom medical query; OND, Office of New Drugs; PY, patient-years

Refer to Section 7.6.1.4 for details regarding liver-related TEAEs leading to study treatment discontinuation in Study WN42086, none of which occurred in the ocrelizumab arm. There were no liver-related TEAEs leading to study treatment discontinuation in Study WA39085. There were no subjects in Studies WN42086 or WA39085 who experienced TEAEs coded to PTs contained within the MedDRA SOC Hepatobiliary disorders. There were no cases meeting Hy's Law laboratory criteria in Studies WN42086 or WA39085. For additional details regarding laboratory findings, refer to Section 7.6.1.7.

Conclusion

Current approved labeling for Ocrevus discusses the risk of liver injury in Section 5.7 (Warnings and Precautions, Liver Injury). No cases of DILI were reported in the pediatric development program for ocrelizumab. Although it is unclear whether there is a differential risk of liver injury between adult and pediatric patients, this risk cannot be ruled out for the pediatric population.

7.7.7. Cytopenias

Issue

Ocrelizumab carries a known risk of decreased neutrophil levels, as discussed in current approved labeling for Ocrevus. Additionally, decreases in lymphocyte counts are expected based on the MOA of ocrelizumab and other anti-CD20 monoclonal antibodies. Lymphopenia and leukopenia are discussed in current approved labeling for fingolimod. Additionally, chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline.

Background

Section 6.1 (Adverse Reactions - Clinical Trials Experience) of current approved labeling for Ocrevus discusses the risk of decreased neutrophil levels. In the adult PPMS clinical trial (Study WA25046), decreased neutrophil counts occurred in 13% of ocrelizumab-treated subjects, compared to 10% in placebo-treated subjects. The majority of the decreased neutrophil counts were only observed once for a given subject treated with ocrelizumab and were between the LLN and 1.0×10^9/L. Overall, 1% of subjects in the ocrelizumab-treated group had neutrophil counts $<1.0\times10^9$/L at any point after Baseline; these laboratory abnormalities were not associated with infections.

Assessment

Table 54 summarizes the frequency of TEAEs related to cytopenias that occurred in the safety population during the DBP of Study WN42086. TEAEs with PTs pertaining to cytopenias were manually selected. Laboratory results for Study WN42086 are reviewed in Section 7.6.1.6.

Table 54. Cytopenia-Related Treatment-Emergent Adverse Events, Safety Population, Study WN42086, Double-Blind Period

Preferred Term	Ocrelizumab N=93 n (%)	Fingolimod N=92 n (%)
Iron deficiency anemia	3 (3.2)	0 (0.0)
Neutrophil count decreased	1 (1.1)	3 (3.3)
White blood cell count decreased	1 (1.1)	1 (1.1)
Hemoglobin decreased	1 (1.1)	0 (0.0)
Monocyte count decreased	1 (1.1)	0 (0.0)
Neutropenia	0 (0.0)	7 (7.6)
Anemia	0 (0.0)	3 (3.3)
Leukopenia	0 (0.0)	2 (2.2)
Lymphocyte count decreased	0 (0.0)	2 (2.2)
Lymphopenia	0 (0.0)	2 (2.2)

Source: ADAE, SAFFL=Y, TRTEMFL=Y, by ACTARM
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given characteristic

TEAEs related to leukopenia, lymphopenia, and neutropenia were more common in the fingolimod arm. The number of TEAEs related to decreased hemoglobin appeared comparable between the groups. There were no subjects in either treatment arm who experienced TEAEs related to decreased platelets.

Conclusion

Currently approved labeling for Ocrevus discusses the risk of neutropenia in Section 6.1 (Adverse Events - Clinical Trials Experience). Although there were more subjects in the fingolimod arm who experienced TEAEs related to neutropenia, neutropenia appears to be associated with both anti-CD20 therapies and S1P receptor modulators (including fingolimod). The risk of neutropenia with ocrelizumab does not appear to be differential between adult and pediatric subjects.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Except for body weight, age, sex, baseline B-cell count, race and markers of hepatic and renal function did not affect ocrelizumab pharmacokinetics. The body weight-tiered dosing regimen (300 mg for <35 kg; 600 mg for ≥35 kg) achieved AUC and C_{max} (median AUC_{24W}: 3,130 µg/mL·day; median C_{max}: 147 µg/mL) in pediatric subjects who are comparable to adult subjects. Refer to Section 5.3.

8.2. Extrinsic Factors

Not applicable; no new analyses were presented by the Applicant.

8.3. Plans for Pediatric Drug Development

This sBLA is intended to support approval for a pediatric population and fulfill the outstanding Pediatric Research Equity Act (PREA) PMR 3194-14 and WR for BLA 761053. The multidisciplinary review team and the Pediatric Research Committee (PeRC) agreed that PMR 3194-14 can be fulfilled by this sBLA submission. Additionally, the Pediatric Exclusivity Board, in agreement with the multidisciplinary review team, determined that this submission meets the terms of the WR; therefore, pediatric exclusivity will be granted.

DPMH was consulted for review of this efficacy supplement. DPMH provided input on labeling and conducted a review of the safety data to determine whether any effects of ocrelizumab on growth and development were evident. Additionally, DN2 requested that DPMH evaluate any pediatric-specific considerations regarding vaccinations in patients receiving ocrelizumab. DPMH did not identify any concerns related to growth or development associated with ocrelizumab. This sBLA did not include any new data regarding response to vaccinations in the setting of ocrelizumab, but DPMH provided input regarding terminology for age-appropriate vaccinations in labeling. Refer to the DPMH consultation memorandum dated April 3, 2026 (DARRTS ID: 5774905).

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

According to the protocol deviation log for Study Site 336122, a pregnancy was reported on February 6, 2026, for Subject (b) (6) while enrolled in the OLE period of Study WN42086. The review team requested that the Applicant provide all available information regarding this case including, but not limited to, dates of exposure to the study treatment and event outcome. The Applicant also confirmed that there were no other events of pregnancy reported as part of the pediatric OCR development program.

Subject (b) (6)

The reported pregnancy occurred in a 19-year-old female subject had a positive pregnancy test on February (b) (6), during the Week 22 visit of the OLE Period. The subject's last menstrual period had been (b) (6). The subject and her male partner used condoms as a contraceptive method. The subject experienced a TEAE of acute tubulointerstitial nephritis (Grade 3) requiring oral antibiotic treatment from (b) (6) through (b) (6). The subject was also hospitalized from (b) (6), through (b) (6), due to an SAE of Bartholin's abscess (Grade 3), which required incision and drainage and oral antibiotic treatment. On (b) (6), an ultrasound confirmed the subject's pregnancy and provided a gestational age of 6 weeks and 1 day. The subject was hospitalized again on (b) (6), due to abdominal pain and bleeding thought to be consistent with threatened miscarriage. An abdominal ultrasound was performed at the time and was reportedly "normal." On (b) (6), the subject received marsupialization treatment for Bartholin's cyst and was also treated with oral antibiotics. On (b) (6), the subject experienced another SAE of Bartholin's cyst and then, on (b) (6), experienced vaginal bleeding due to an SAE of spontaneous abortion. On that same day, "emptying of the uterus" was performed, along with marsupialization of Bartholin's cyst.

Discussion

According to version 6 of the protocol for Study WN42086, "female patients must remain abstinent or use two methods of contraception, including at least one method with a failure rate of <1% per year, during the treatment period and for at least 24 weeks after the final dose of ocrelizumab/ocrelizumab placebo and for 2 months after the final dose of fingolimod/fingolimod placebo." Subject (b) (6) was only using 1 method of contraception, which did not include a contraceptive method with a failure rate of <1% per year. This was recorded as a protocol deviation.

Current approved labeling for Ocrevus indicates that there are no adequate data on the developmental risk associated with use of Ocrevus in pregnant women. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to Ocrevus have not been studied in clinical trials. The potential duration of B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness, is unknown. Following administration of ocrelizumab to pregnant monkeys at doses similar to or greater than those used clinically, increased perinatal mortality, depletion of B-cell populations, and renal, bone marrow, as well as testicular toxicity were observed in the offspring in the absence of maternal toxicity. Women of childbearing potential should use effective contraception while receiving Ocrevus and for 6 months after the last infusion of Ocrevus.

Upon approval of BLA 761053, PMRs 3194-3 and 3194-4 were issued and required the Applicant to conduct a pregnancy registry study and a pregnancy outcomes study of a different design, respectively, to evaluate the potential risk of embryofetal toxicity associated with Ocrevus. Studies intended to fulfill these PMRs are ongoing, and the PMRs remain outstanding.

Regarding lactation, there is no data on the presence of ocrelizumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. However, ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ocrevus and any potential adverse effects on the breastfed infant from Ocrevus or from the underlying maternal condition.

9. Product Quality

Approval

The Office of Pharmaceutical Quality (OPQ) review team has assessed BLA 761053/S-38 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this sBLA from a quality perspective.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Review of the financial disclosures did not raise any concerns about the validity or reliability of the data (see Section 18).

Refer to the clinical inspection summary, dated April 13, 2026 (DARRTS ID: 5779527). Bioresearch monitoring review-based good clinical practice (GCP) inspections of three clinical investigators were conducted for the pivotal study (Study WN42086) supporting BLA 761053/S-38. Additionally, an inspection of the Applicant was conducted via center-led remote regulatory assessment (CLRRA). See Sections 6.3.2, 6.3.3, and 15 for discussion of the inspection findings and evaluation of any impact on study results.

Based on the inspection findings, the study appears to have been conducted in observance of GCP principles and in compliance with FDA regulations. The data generated by the clinical investigators appear to be acceptable for use in support of the indication.

11. Advisory Committee Summary

An advisory committee meeting was not held during this marketing application review.

III. Additional Information

12. Summary of Regulatory History

Ocrevus (ocrelizumab, RO4964913) injection for IV administration was developed by Genentech, Inc. under IND100593 and approved for adults under BLA 761053 on March 28, 2017. Ocrevus is a CD20-directed cytolytic recombinant humanized monoclonal antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis.

An initial Pediatric Study Plan (iPSP) with a request for waiver of pediatric studies was submitted on March 5, 2015, under IND 100593. The Division issued a written response on June 5, 2015. The Applicant submitted an agreed iPSP on September 2, 2015. On October 2, 2015, the Division issued an agreed iPSP with a partial waiver for children under 10 years of age with pediatric RRMS, a deferral for children 10 years to <18 years of age with pediatric RRMS, and a full waiver for children with secondary progressive MS and PPMS.

At the time of approval on March 28, 2017, several PMRs were issued, including PREA PMR 3194-1. This PMR required Genentech, Inc. to conduct a two-part study of ocrelizumab in pediatric patients with RMS at least 10 years and <17 years of age. Part A was an open-label study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of ocrelizumab in pediatric patients, including two cohorts based on body weight (<40 kg and 40 kg or more). The objective of Part A was to determine a dose of ocrelizumab achieving PK and PD effects that are comparable to the adult 600-mg dose (300 mg given twice, 14 days apart). Safety assessments were to continue for at least 2 years after the last dose of ocrelizumab. Part B was a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ocrelizumab compared to an appropriate comparator.

On April 20, 2017, the initial protocol and associated study documents for Study WA39085, "An Open-Label, Parallel-Group Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Effects of Ocrelizumab in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis," were submitted.

On August 2, 2017, studies in pediatric patients being conducted under the IND were placed on a partial clinical hold due to premature animal deaths in Study 15-3109, an immunotoxicity study in juvenile cynomolgus monkeys. This hold was removed on April 26, 2019, after further examination of the cause of these deaths.

On April 28, 2020, Type C Written Responses were issued regarding phase 3 study design, including the primary and secondary endpoints, and proposed flexible study duration. The Division advised the Applicant that a flexible duration study design "may result in significant variability and skew in treatment duration across the trial population…[which] has the potential to affect the adequacy and interpretation of a safety database." The Division also indicated that it would be open to considering a noninferiority trial in pediatric RMS using an active comparator, with ARR as the primary endpoint. The Division provided feedback on the proposed noninferiority margin as well.

On November 4, 2020, additional Type C Written Responses were issued regarding phase 3 study design, including the primary endpoint and statistical methodology. The Division advised the Applicant to use a noninferiority margin no greater than 2 and provided additional feedback on the proposed intercurrent event and imputation strategies.

An amended PSP was received on March 10, 2021, and a PSP closure form was issued on May 4, 2021.

On April 11, 2022, in response to the Applicant's proposed pediatric study request dated July 16, 2021, the Division issued a WR under the Best Pharmaceuticals for Children Act for pediatric studies investigating ocrelizumab for the treatment of patients 10 years to <18 years of age with RMS.

On May 4, 2022, the initial protocol and associated study documents for Study WN42086, "A Phase III Multicenter, Randomized, Double-Blind, Double-Dummy Study to Evaluate Safety and Efficacy of Ocrelizumab in Comparison with Fingolimod in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis," was submitted for the Division's review. The Division sent comments regarding this submission on July 18, 2022, including a recommendation that the Applicant revise the noninferiority margin (b) (4) to 3.0.

On September 30, 2022, proposed changes to WR for pediatric studies were received. On January 24, 2023, an inadequate proposed amendment to WR letter was issued. (b) (4) .

On March 31, 2023, a request to revise the milestone dates for PMR 3194-1 was received, citing delays in study start due to the imposed partial clinical hold (resolved in 2019), and recruitment difficulties.

On April 3, 2023, proposed changes to WR for pediatric studies were received. On August 1, 2023, WR – Amendment 1 was issued. The WR was revised to reflect the Agency's evolving thinking regarding dose selection for the pediatric multiple sclerosis population, and to align studied weight categories across therapies approved for relapsing forms of multiple sclerosis. Also on August 1, 2023, Genentech, Inc. sent correspondence notifying the Division of and explaining the missed study completion milestone for PMR 3194-1. A PMR notification of missed milestone letter was issued by the FDA on September 8, 2023, designating this PMR as delayed.

On September 14, 2023, Proposed Changes to WR – Amendment 1 for pediatric studies were received.

On September 15, 2023, Genentech, Inc. was released from PMR 3194-1, and PMR 3194-14 was issued to align studied weight categories across therapies approved for RMS. The study completion and final report submission dates were revised to May 2025 and November 2025, respectively. PMR 3194-14 specified that the open-label study was to be completed in pediatric patients weighing 40 kg or less.

On January 31, 2024, WR – Amendment 2 was issued to reach agreement on specific aspects of the WR following Amendment 1.

On February 29, 2024, Protocol Version 10 of Study WA39085 was submitted. On May 10, 2024, Protocol Version 6 of Study WN42086 was submitted. These protocols were acknowledged as the final protocols for PMR 3194-14 on June 28, 2024.

On August 16, 2024, a proposed amendment to WR was received. On December 6, 2024, an inadequate proposed amendment to WR letter was issued. (b) (4)

No pre-sBLA meeting was held under IND 100593 for this application. Supplement 38 was submitted and received on November 10, 2025, with the proposed indication of treatment of relapsing-remitting MS in pediatric patients 10 years of age and older. This submission was intended to fulfill PREA PMR 3194-14 and to address Studies 1 and 2 of the WR. The supplement contains the open-label phase 2 Study WA39085 and the phase 3 Study WN42086.

A priority review determination letter was sent to the Applicant on January 9, 2026. The supplement was filed on January 22, 2026. At the time of filing, a potential review issue was identified. While the comparative dissolution data for the U.S. and European comparator products (Gilenya, fingolimod capsules) were provided, the dissolution method and test conditions utilized were found questionable due to lack of justification for the test conditions and inadequate demonstration of the suitability for the comparator products. Additionally, the claim for comparable formulation composition of the two comparator products was not adequately supported with quantitative information. According to the biopharmaceutics assessment, “the Applicant provided data including comparative dissolution profile data, capsule composition, and appearance assessment to establish the equivalency of the comparators and support the pooling of clinical trial results from these different regions.” (Patel 2026).

13. Clinical Virology

Not applicable.

14. Clinical Microbiology

Not applicable.

15. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Refer to the clinical inspection summary, dated April 13, 2026 (DARRTS ID: 5779527).

The Office of Scientific Investigations conducted inspections for 3 clinical investigator sites and the Applicant (Genentech/Roche) for this sBLA. None of the inspected sites had any violations of the applicable statutory requirements or FDA regulations that justified compliance or enforcement action. However, the clinical inspection summary indicated that there were a significant number of protocol deviations at Site 336952 that resulted in the Applicant

implementing a site improvement plan that resulted in improvement in site compliance. Additionally, the site inspections did not indicate under-reporting of adverse events at any of the sites.

The clinical investigator sites selected for inspection were as follows:

- Site 336952 (France; Dr. Deiva)
- Site 337741 (U.S.; Dr. Soe Mar)
- Site 336122 (Poland; Dr. Steinborn)

The Office of Scientific Investigations also conducted a CLRRA of the Applicant focused on EDSS scores, maintenance of study blinding, and database access. The CLRRA "identified significant gaps in oversight of critical data, electronic systems, processes, and service provider oversight."

Specifically, the following issues were identified:

1. Approximately 62% of EDSS data were recorded on paper forms that were later transcribed into TrialManager; the protocol stipulates that paper forms were to be used as a backup only in the setting of electronic device unavailability. Concerns were raised about potential transcription errors and delays, as well as recall errors by the EDSS rater if the University Hospital Basel expert EDSS review was delayed. During the CLRRA, the Applicant indicated that 42% of EDSS data were entered into TrialManager on the same day; however, 11% were entered 14 to 52 weeks later. Assessment of the EDSS data for subjects who experienced a protocol-defined relapse led the reviewer to conclude that the delayed data entry did not appear to impact the EDSS scores in these subjects or data integrity overall.
2. EDSS assessments in the setting of a relapse evaluation were to be conducted within 7 days of relapse symptom onset. However, two subjects had their EDSS assessment 37 and 81 days after onset of a potential relapse. See Section 6.3.3 for sensitivity analyses and discussion of this issue.
3. Thirty-two major protocol deviations of "failure to maintain study blind" occurred in 26 subjects (9 ocrelizumab, 17 fingolimod), 5 of whom experienced a protocol-defined relapse. See Section 6.3.2 for sensitivity analyses and further discussion of these protocol deviations.

Except as noted above, based on the inspection findings, the study appears to have been conducted in observance of the GCP principles and in compliance with the FDA regulations.

Despite the identified issues, the study results appeared robust to sensitivity analyses (see Section 6.3.2 and Section 6.3.3). The data generated by the clinical investigators appear to be acceptable in support of the indication.

16. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the PI as compared to the currently approved PI and the Applicant's draft PI (Table 55). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 55. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to PI[2] Compared to Currently Approved PI and Applicant's Draft PI
BOXED WARNING	Not applicable.
1 INDICATIONS AND USAGE	The Applicant proposed an indication for the treatment of relapsing-remitting MS in pediatric patients 10 years of age and older, to which the Agency agrees. The Agency added a lower weight distinction (i.e., "who weigh 25 kg or more") to the Applicant proposed new indication to align with the inclusion criteria for Study WN42086 (Study 5). To note, according to the current CDC growth charts for both boys and girls 10 years of age and 0 months, approximately 95% of children in the U.S. at this age will weigh above 25 kg.
2 DOSAGE AND ADMINISTRATION	2.1 Assessments Prior to First Dose of OCREVUS: The phrase "age-appropriate" was added to sections of labeling relevant to vaccinations due to differing immunization recommendations for pediatric and adult patients. 2.2 Preparation Before Every Infusion: The Applicant proposed to include a table to include information regarding premedication in adult and pediatric patients prior to administration of Ocrevus. The Agency had concerns with the proposed organization and presentation of the premedication information in table format (e.g., combining population descriptors, body weight criteria, dosing statements, and cross-references within the Dose column), which could increase the potential for medication errors. Therefore, the Agency revised to a narrative format to present the premedication information in a clear manner that allows the healthcare provider to easily identify the appropriate premedication dosing and administration instructions. 2.3 Recommended Dosage and Dose Administration: The Applicant proposed to include the recommended dosage information for the new patient population. To reduce redundant information, the Agency removed text from the narrative description of the recommended dosage that is also presented in the recommended dosage table. The Applicant added a further clarifying description of the initial dose. The Agency added the lower weight distinction (i.e., "who weigh 25 kg or more") in alignment with the addition to the indication. 2.4 – 2.5: There were no substantial changes.

Full PI Sections[1]	Rationale for Major Changes to PI[2] Compared to Currently Approved PI and Applicant's Draft PI
	2.6 Preparation and Storage of the Dilute Solution for Infusion: The Applicant proposed inclusion of a table presentation for the dilution information, including for the new 150 mg dose. The Applicant also proposed to include the instruction to discard any unused portion left in the vial.
4 CONTRAINDICATIONS	There were no changes proposed by the Applicant nor added by the Agency.
5 WARNINGS AND PRECAUTIONS	5.1 Infusion Reactions: The Applicant proposed inclusion of the safety information regarding infusion reactions from the pediatric study. Instead of presenting all of the pediatric infusion reaction information separately from the adult information, the Agency revised the presentation of the information to include an introductory paragraph that describes information that applies to both adult and pediatric patients (e.g., the symptoms and timing of infusion reactions that were seen with Ocrevus and the premedication of patients in the studies). The case of the serious infusion reaction requiring hospitalization that occurred in a pediatric patient was added. 5.2 Infections: The Applicant proposed inclusion of the safety information regarding infections from the pediatric study. The Agency deleted the sentence, "(b) (4) ", to avoid minimizing the risk of serious infections. Other editorial revisions were included in this subsection. 5.3 – 5.7: There were no substantial changes.
6 ADVERSE REACTIONS	6.1 Clinical Trials Experience: The Applicant proposed to include the safety information from the pediatric study in patients 10 years of age and older with relapsing-remitting MS. The Agency added the outcome of the serious infusion reaction. The Applicant proposed (b) (4) ; however, the Agency revised to note that serious infections did occur in 3% of patients in each study arm. The Applicant proposed (b) (4) ; however, the Agency deleted the information because it did not qualify as an adverse reaction. 6.2 Immunogenicity: The Agency relocated this information to the Clinical Pharmacology section, as recommended in the draft Guidance for Industry, Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format. 6.3 Postmarketing Experience: There were no changes proposed by the Applicant nor added by the Agency.
7 DRUG INTERACTIONS	There were no changes proposed by the Applicant nor added by the Agency.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential,	8.1 Pregnancy and 8.2 Lactation: There were no changes proposed by the Applicant nor added by the Agency.

Full PI Sections[1]	Rationale for Major Changes to PI[2] Compared to Currently Approved PI and Applicant's Draft PI
Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.3 Females and Males of Reproductive Potential: No change from the minor Applicant proposed revision. 8.4 Pediatric Use: The Applicant proposed revisions to the standard pediatric use statements and inclusion of pediatric safety information. The Agency added the entire new indication to the statement noting that safety and effectiveness have been established. In addition to noting that this indication was established by the controlled clinical study (Study 5), the Agency added that additional pharmacokinetic data in pediatric patients was also used to support the indication. The Agency removed the proposed (b) (4) because the information is described in the Adverse Reactions section. The Agency added the weight cutoff of less than 25 kg to the statement noting that safety and effectiveness have not been established. 8.5 Geriatric Use: There were no changes proposed by the Applicant nor added by the Agency.
9 DRUG ABUSE AND DEPENDENCE	Not applicable.
10 OVERDOSAGE	Not applicable.
12 CLINICAL PHARMACOLOGY:	12.1 Mechanism of Action: There were no changes proposed by the Applicant nor added by the Agency. 12.2 Pharmacodynamics: Text was added to clarify whether the data being described was from adult or adult and pediatric patients. 12.3 Pharmacokinetics: The Applicant proposed to include pediatric exposure information (i.e., AUC and C_{max}), to which the Agency agrees. The Agency deleted the Applicant's proposed sentence (b) (4) because it is not relevant to the proposed indicated population. 12.6 Immunogenicity: The Agency relocated the immunogenicity information that was previously in the Adverse Reactions section, per current recommendations in the draft Guidance for Industry, Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling — Content and Format. The Agency revised the introductory paragraph to align with the text recommended in the guidance. To the newly proposed pediatric data, the Agency revised the denominator from the proposed (b) (4) patients to 90 patients because only 90 had anti-drug antibody data available.
13 NONCLINICAL TOXICOLOGY	There were no changes proposed by the Applicant nor added by the Agency.
14 CLINICAL STUDIES	The Applicant proposed to include the pediatric study data that supports the new indication. The Agency revised the study description to describe the flexible duration of the study, provide treatment duration using median (range), and the racial background of study participants. The Applicant proposed clinical

Full PI Sections[1]	Rationale for Major Changes to PI[2] Compared to Currently Approved PI and Applicant's Draft PI
	endpoints were deemed acceptable for inclusion; however, the Agency revised the MRI endpoint results to the values presented by the Applicant in a response to an information request in which different models were used to obtain the values.
17 PATIENT COUNSELING INFORMATION	The Agency revised text under the headings to refer to counseling of patients or caregivers, to account for the addition of pediatric patients to the indication.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	There were no changes proposed by the Applicant nor added by the Agency.

Source: Last approved Ocrevus PI dated August 18, 2025; Applicant proposed PI submitted November 10, 2025
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the PI is the PI that will be approved or is close to being approved.
Abbreviation: PI, Prescribing Information

16.1. Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide

17. Postmarketing Requirements and Commitments

No new PMRs or PMCs were issued with approval of this sBLA.

18. Financial Disclosure

Table 56. Covered Clinical Studies: WA39085 and WN42086

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Study WA39085: 120 investigators; Study WN42086: 627 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 investigators		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Study WA39085: 1 investigator; Study WN42086: 2 investigators		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 investigators (1 participated in Studies WA39085 and WN42086) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: CFR, Code of Federal Regulations; FDA, Food and Drug Administration

19. References

19.1. Guidances for Industry

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ICH Guidance for Industry: *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021). https://www.fda.gov/media/148473/download.

19.2. Literature

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19.3. Product Labels

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19.4. Other

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20. Review Team

Table 57. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Elaine Gettelman, PharmD, PhD Sandra Folkendt
Nonclinical Reviewer	Elizabeth Khoury, PhD
Nonclinical Team Leader	David Carbone, PhD
OCP Reviewer(s)	Ramakrishna Samala, PhD
OCP Team Leader(s)	Anantha Ram Nookala, PhD Atul Bhattaram, PhD
Clinical Reviewer	Daniela Pimentel Maldonado, MD, MSCR
Clinical Team Leader	Laura Baldassari, MD, MHS
Biometrics Reviewer	Olivia Morgan, PhD
Biometrics Team Leader	John Lawrence, PhD
Associate Director for Labeling	Tracy Peters, PharmD
Cross-Discipline Team Leader	Laura Baldassari, MD, MHS
Division Director (Pharm/tox)	Dan Mellon, PhD
Division Director (OCP)	Mehul Mehta, PhD
Division Director (OB)	Hsien Ming (Jim) Hung, PhD
Deputy Director for Safety	Alice Hughes, MD
Signatory Division Director (Clinical)	Laura Jawidzik, MD, FAAN

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 58. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Milos Dokmanovic, PhD (OPQA III) Andrea George, PhD (OPQA III) Hardikkumar Patel, PhD (Biopharmaceutics) Ta-Chen Wu, PhD (Biopharmaceutics) Hyung Lee, PhD (OPMA Facility) Zhong Li, PhD (OPMA Facility) Musse Olani, PharmD (RBPM)
Microbiology	N/A
DPMH	Sonaly McClymont, MD Shetarra Walker, MD, MSCR John Alexander, MD, MPH
OPDP	Emily Foltz, PharmD Taylor Burnett Mmagu, PharmD, RAC
DMPP	Lonice Carter, MS, RN, CNL, NHDP-BC Marcia Williams, PhD
OSI	Cara Alfaro, PharmD Philip Kronstein, MD Jenn Sellers, MD, PhD
OSE/DEPI	Cassidi McDaniel, PhD Steven Bird, PhD, PharmD, MS
OSE/DMEPA	Stephanie DeGraw, PharmD Beverly Weitzman, PharmD
OSE/DPV	Karen Long, PharmD Leah Herity, PharmD, MPH, BCPS
Clinical Data Scientists	Zachary Moldwin, Pharm D Deangelo McKinley, PharmD, PhD
Medical Editors	Priyanka Joseph Irum Syed, PhD
Other	Christine Phipps, PharmD

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH: Division of Pediatrics and Maternal Health; DPV: Division of Pharmacovigilance; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

20.1. Reviewer Signatures

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Laura Baldassari ON DNII	Sections: 1, 2, 3, 4, 6, 7, 8.4, 17, 18, 19	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Laura Baldassari			**Digitally signed by Laura Baldassari** **Date: 5/6/2026 3:56 PM EDT** **GUID: 20265619560**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Anantha Ram Nookala OCP DNP	Sections: 5, 6, 8	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Anantha Ram Nookala			**Digitally signed by Anantha Ram Nookala** **Date: 5/6/2026 3:59 PM EDT** **GUID: 202656195920**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Hsien Ming Hung OB	Sections: 1.1, 1.2, 6.2, 6.3	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Hsien Ming Hung			**Digitally signed by Hsien Ming Hung** **Date: 5/6/2026 4:04 PM EDT** **GUID: 2026562046**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Hsien Ming Hung OB DBI	Sections: 1.1, 1.2, 6.2, 6.3	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Hsien Ming Hung			**Digitally signed by Hsien Ming Hung** **Sign on behalf of I signed off for John Lawrence.** **Date: 5/6/2026 4:12 PM EDT** **GUID: 202656201230**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Primary Reviewer	Tracy Peters ON DNI	Sections: 16 Labeling: Key Changes	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Tracy Peters			**Digitally signed by Tracy Peters** **Date: 5/6/2026 4:15 PM EDT** **GUID: 202656201526**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director of Labeling Discipline Secondary Reviewer	Tracy Peters ON DNI	Sections: 16 Labeling: Key Changes	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Tracy Peters			**Digitally signed by Tracy Peters** **Date: 5/6/2026 4:16 PM EDT** **GUID: 20265620166**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline RPM	Elaine Gettelman ORO DRON	Sections: 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Elaine Gettelman			**Digitally signed by Elaine Gettelman** **Date: 5/6/2026 4:20 PM EDT** **GUID: 202656202010**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Secondary Reviewer	Andrea George OPQAIII DPQAXIII	Sections: 5, 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Andrea George			**Digitally signed by Andrea George** **Date: 5/6/2026 4:26 PM EDT** **GUID: 202656202621**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Venkatesh Bhattaram OCP DPM	Sections: 5.2, 5.3, 6.1, 8	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Venkatesh Bhattaram			**Digitally signed by Venkatesh Bhattaram** **Date: 5/6/2026 4:37 PM EDT** **GUID: 202656203753**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Ramakrishna Samala OCP DNP	Sections: 5.2, 5.3, 6.1, and 8	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Ramakrishna Samala			**Digitally signed by Ramakrishna Samala** **Date: 5/6/2026 4:42 PM EDT** **GUID: 202656204252**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Ramakrishna Samala OCP DNP	Sections: 5.2, 5.3, 6.1, and 8	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Ramakrishna Samala			**Digitally signed by Ramakrishna Samala** **Date: 5/6/2026 4:43 PM EDT** **GUID: 202656204326**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Primary Reviewer	Milos Dokmanovic OPQAIII DPQAXIII	Sections: Section 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Milos Dokmanovic			**Digitally signed by Milos Dokmanovic** **Date: 5/6/2026 4:48 PM EDT** **GUID: 202656204824**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline CPMS	Stephanie Parncutt ORO DRON	Sections: 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Stephanie Parncutt			**Digitally signed by Stephanie Parncutt** **Date: 5/7/2026 9:39 AM EDT** **GUID: 202657133949**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Olivia Morgan OB DBI	Sections: 6	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Olivia Morgan			**Digitally signed by Olivia Morgan** **Date: 5/7/2026 10:06 AM EDT** **GUID: 20265714651**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Richard Mellon ON DPTN	Sections: 5.1, 7.1	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Richard Mellon			**Digitally signed by Richard Mellon** **Date: 5/7/2026 10:24 AM EDT** **GUID: 20265714243**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	David Carbone ON DPTN	Sections: 5.1, 7.1	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:David Carbone			**Digitally signed by David Carbone** **Date: 5/7/2026 12:45 PM EDT** **GUID: 202657164517**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Daniela Pimentel Maldonado ON DNII	Sections: 1, 2, 3, 4, 6, 7, 8.4, 17, 18, 19	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Daniela Pimentel Maldonado			**Digitally signed by Daniela Pimentel Maldonado** **Date: 5/7/2026 2:09 PM EDT** **GUID: 20265718930**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Elizabeth Khoury ON DPTN	Sections: 5.1, 7.1	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature:Elizabeth Khoury			**Digitally signed by Elizabeth Khoury** **Date: 5/7/2026 3:07 PM EDT** **GUID: 2026571978**	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAURA E BALDASSARI
05/08/2026 10:21:16 AM

LAURA A JAWIDZIK
05/08/2026 10:26:18 AM