CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761371Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761371
Priority or standard	Standard
Submit date(s)	11/10/2023
Received date(s)	11/13/2023
PDUFA goal date	9/13/2024
Division/office	Division of Neurology II (DNII)
Review completion date	9/13/2024
Established/proper name	Ocrelizumab and hyaluronidase-ocsq
(Proposed) proprietary name	OCREVUS ZUNOVO
Pharmacologic class	Anti-CD20 monoclonal IgG1 antibody
Other product name(s)	N/A
Applicant	Genentech, Inc.
Dosage form(s)/formulation(s)	Injection, solution
Dosing regimen	920 mg subcutaneously every 6 months
Applicant-proposed indication(s)/ population(s)	Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults Primary progressive MS, in adults
SNOMED CT code for proposed indication disease term(s)[1]	Relapsing forms of multiple sclerosis - Clinically isolated syndrome [445967004] - Relapsing-remitting multiple sclerosis [426373005] - Active secondary progressive multiple sclerosis [general SPMS: 425500002; SNOMED CT code does not exist for active SPMS specifically] Primary progressive multiple sclerosis [420700003]
Regulatory action	Approval
Approved dosage (if applicable)	920 mg/23,000 units administered as a single 23-mL subcutaneous injection in the abdomen over approximately 10 minutes every 6 months.
Approved indication(s)/ population(s) (if applicable)	Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults Primary progressive MS, in adults
SNOMED CT code for approved indication disease term(s)[1]	Relapsing forms of multiple sclerosis - Clinically isolated syndrome [445967004] - Relapsing-remitting multiple sclerosis [426373005] - Active secondary progressive multiple sclerosis [general SPMS: 425500002; SNOMED CT code does not exist for active SPMS specifically] Primary progressive multiple sclerosis [420700003]

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

Table of Contents

Table of Tables

Table of Figures

Glossary

ADA	antidrug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{W1-12}	area under the concentration-time curve from Week 1 to Week 12
BLA	biologics license application
C_{max}	maximum plasma concentration
CSR	clinical study report
DBP	diastolic blood pressure
DILI	drug-induced liver injury
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
IND	investigational new drug
iPSP	Initial Pediatric Study Plan
IV	intravenous
IV OCR	intravenously administered ocrelizumab
LLN	lower limit of normal
MARS	Modeling Approaches to Reimagine Stability
MedDRA	Medical Dictionary for Regulatory Activities
MS	multiple sclerosis
PD	pharmacodynamic
PI	Prescribing Information
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement
PopPK	population pharmacokinetics
PPMS	primary progressive multiple sclerosis
PT	preferred term
PY	patient-years
rFC	recombinant factor C
RMS	relapsing forms of multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
RTRT	Real Time Release Testing
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SC OCR	subcutaneously administered ocrelizumab
SD	standard deviation

SMQ	Standard Medical Dictionary for Regulatory Activities Query
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Biologic license application (BLA) 761371 for ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo) was reviewed by the multidisciplinary review team. Each discipline recommends approval, and I, the signatory authority for this application, concur with those recommendations.

The review team recommends, and I concur with, traditional approval of this 351(a) BLA for the proposed indications of (1) relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults, and (2) primary progressive multiple sclerosis (PPMS), in adults.

Substantial evidence of effectiveness for Ocrevus Zunovo was established using data from a single adequate study (Study CN42097), along with the prior approval that established substantial evidence of effectiveness for Ocrevus (intravenously administered ocrelizumab (IV OCR), BLA 761053).

In Study CN42097, the Applicant successfully demonstrated pharmacokinetic (PK) non-inferiority of subcutaneously administered ocrelizumab (SC OCR) to IV OCR. Other than the expected signal of local injection-related reactions given the new subcutaneous route of administration, no clinically meaningful differences in the efficacy or safety profiles of SC OCR and IV OCR were identified in this study.

The overall benefit-risk is favorable, as described in the Benefit-Risk Framework (Table 2). For detailed information supporting the basis for this approval, refer to the detailed reviews included in Part II (the Interdisciplinary Assessment) and the Product Quality review.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with evidence that supported SEE from a prior approval.

SC OCR (proposed proprietary name Ocrevus Zunovo) was developed for the treatment of RMS and PPMS. The Applicant submitted a 351(a) BLA for SC OCR, which included a single adequate and well-controlled study, Study CN42097, and was supported by the substantial evidence of effectiveness established via the prior approval of the IV OCR BLA.

Data from the ongoing Phase 3 Study CN42097 established the PK non-inferiority of SC OCR, compared to IV OCR, based on the serum concentration of ocrelizumab. This finding was supported by secondary endpoint data, which demonstrated a similar total number of T1 gadolinium-enhancing and new or newly enlarging T2 MRI lesions in subjects treated with SC OCR, compared to IV OCR. Data from the ongoing Phase 1 Study CN41144 provided

supportive evidence of safety. Based on the findings of PK non-inferiority from Study CN42097, SC OCR is expected to have similar efficacy and safety to that of IV OCR, for which substantial evidence of effectiveness has been established.

The data submitted with this BLA and the previous findings for IV OCR support the proposed indications of the treatment of RMS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (in adults), and the treatment of primary progressive MS (in adults). Traditional approval for BLA 761371 for SC OCR was recommended based on the establishment of substantial evidence of effectiveness via one adequate clinical investigation and the prior approval for ocrelizumab.

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 – 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. – 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 disability. • Primary progressive MS – Primary progressive MS (PPMS) is considered a distinct phenotype of MS characterized by steady progression of disability, perhaps especially because of involvement of the spinal cord. Relapses are either absent or very infrequent. – Treatments that have demonstrated a treatment benefit in RMS have for the most part been ineffective in trials of patients with PPMS. Intravenously administered ocrelizumab (IV OCR, Ocrevus) is the only treatment approved for the treatment of PPMS.	• Treatment of relapsing forms of multiple sclerosis is intended to reduce the frequency of clinical relapses. Clinical relapses can be permanently disabling and reduce quality of life. Treatment of primary progressive MS is intended to slow clinical disease progression. Clinical disease progression can result in disability due to mobility impairment over time and reduced quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Relapsing forms of MS – There are over twenty products approved for the treatment of relapsing forms of MS. – Currently approved therapies to treat MS 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. • Primary progressive MS – IV ocrelizumab is the only approved treatment for primary progressive MS. IV ocrelizumab was shown to reduce the risk of confirmed disability progression in subjects with primary progressive MS.	• Treatment of relapsing forms of multiple sclerosis generally involves immunomodulation intended to reduce the frequency of clinical relapse. Many therapies approved for the treatment of relapsing forms of MS are labeled to prevent accumulation of disability. • Treatment of primary progressive MS involves immunomodulation to reduce the risk of confirmed disability progression.
Benefit	• The basis for the original approval of IV OCR (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 Rebif, based on two adequate and well-controlled clinical trials. • The basis for the original approval of IV OCR (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. • Hyaluronidase (Hylenex, also referred to as rHuPH20 or PH20) was initially approved in 2005 as a tissue permeability modifier indicated as an adjuvant to increase the dispersion and absorption of other injected drugs. Hyaluronidase is not detected in the plasma after SC administration. • One Phase 3, open-label trial in adults with relapsing forms of MS and primary progressive MS, which was considered adequate, demonstrated that subcutaneously administered ocrelizumab (SC OCR) achieved a similar ocrelizumab serum concentration, compared to IV OCR (Ocrevus). Additionally, though not powered for efficacy outcomes, the	• The comparable pharmacokinetic profile of SC OCR to that of IV OCR in Study CN42097, as well as the established substantial evidence of effectiveness for IV OCR, provides substantial evidence of effectivness of SC OCR for the proposed indications (RMS and PPMS). The PK findings were also supported by a similar total number of T1 gadolinium-enhancing and new or enlarging T2 MRI lesions seen between subjects treated with SC OCR and IV OCR.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	trial indicated that the benefit of SC OCR was comparable to that of IV OCR (Ocrevus) in terms of total number of T1 gadolinium-enhancing and new or enlarging T2 MRI lesions.	
Risk and risk management	• The risks of IV OCR (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, and interference with the effectiveness of non-live vaccines. • The SC OCR Phase 3 study identified the new but expected risk of local and systemic injection-related reactions. None were serious or severe. However, the injection-related reactions that occurred in the submitted studies were not adequately characterized in terms of signs and symptoms.	• Overall, the safety of SC OCR appears comparable to that of IV OCR, with the exception of injection reactions. Approval is recommended, as the benefits of SC OCR outweigh its risks, based on the adequate capture of the seriousness and severity of injection reactions. However, the data limitations resulting from a lack of detailed investigator-reported accounting of signs and symptoms of injection reactions warrant a PMR to further evaluate and characterize this risk. • Additionally, as was done for IV OCR (Ocrevus), a PMR will be issued for SC OCR to determine the incidence and mortality rates of breast cancer and all malignancies. Patients receiving SC OCR may be enrolled in the ongoing study intended to fulfill PMR 3194-2 for Ocrevus. A separate study is not required.

Abbreviations: IV OCR, intravenously administered ocrelizumab; MRI, magnetic resonance imaging; MS, multiple sclerosis; PH20, hyaluronidase; PK, pharmacokinetic; PMR, postmarketing requirement; PPMS, primary progressive multiple sclerosis; rHuPH20, recombinant human hyaluronidase; RMS, relapsing forms of multiple sclerosis; SC OCR, subcutaneously administered ocrelizumab

2.2. Conclusions Regarding Benefit-Risk

Multiple sclerosis (MS) is a serious, disabling, chronic, immune-mediated, demyelinating, and neurodegenerative disease affecting the central nervous system. The cause of MS is unknown, but the etiology of MS is hypothesized to be related to a complex interaction of genetic and environmental risk factors. 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 have MS. Disease manifestations can be diverse, and include weakness, incoordination, visual impairment, sensory loss, gait dysfunction, fatigue, cognitive impairment, and bowel/bladder dysfunction.

RMS include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. In the relapsing forms of MS, patients experience episodes of focal neurological deficits and disseminated lesions of demyelination within the central nervous system. Symptoms of relapsing forms of MS commonly include recurrent episodes, or relapses, of diminished sensory or motor function that can be temporarily or permanently disabling. Many, but not all, patients with relapsing forms of MS experience some degree of persistent disability that may gradually worsen over years. Over twenty unique therapies have been approved for the treatment of relapsing forms of MS, and all of these approved therapies share a basic common feature of modifying the immune response.

Approximately 15% of patients with MS are diagnosed with PPMS, which is characterized by progressive disability worsening in the absence of relapses. However, patients with PPMS can also experience relapses. Ocrelizumab (Ocrevus) currently is the only approved therapy for PPMS.

Ocrelizumab (Ocrevus) is an anti-CD20 monoclonal antibody approved for the treatment of RMS and PPMS in adults. Substantial evidence of effectiveness for intravenous ocrelizumab was established based on two adequate and well-controlled studies demonstrating a significant reduction in relapses compared to an active comparator 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.

The benefit of SC OCR was established via Study CN42097, which demonstrated noninferior PK of SC OCR to IV OCR, and the prior approval establishing substantial evidence of effectiveness for Ocrevus (IV OCR) for the indications of RMS and PPMS.

Safety concerns for ocrelizumab discussed in current approved labeling for Ocrevus are infections (including serious or life-threatening infections, hepatitis B reactivation, progressive multifocal leukoencephalopathy, and herpes viral infections), infusion-related reactions, immune-mediated colitis, reduction in immunoglobulins, and malignancies. These risks are expected to apply to the subcutaneous formulation of ocrelizumab as well, with the added risk of local and systemic injection-related reactions.

Overall, the safety profile of SC OCR appeared consistent with that of IV OCR based on the results of Studies CN41144 and CN42097. However, injection-related reactions, both local and

systemic, were common in subjects treated with SC OCR. None were serious or severe, but the review team noted that the study protocols led to suboptimal ascertainment and characterization of injection-related reactions. Specifically, rather than capturing detailed information regarding the signs and symptoms of an injection-related reaction (e.g., injection site erythema, injection site pain), investigators were instructed to code all events using the preferred term injection reaction. The Applicant was not able to provide the detailed data regarding investigator-reported symptoms of injection-related reactions requested by the Division of Neurology 2 (DN2, the Division). Though this issue did not affect approvability, as the seriousness and severity of events appear to have been adequately and reliably captured, the Division determined that a postmarketing requirement (PMR) for the comprehensive characterization of local and systemic injection-related reactions with SC OCR should be issued. Labeling will also serve to mitigate the uncertainty regarding this potentially serious risk, as labeling will recommend that patients receive premedication at least 30 minutes prior to SC OCR administration, and that patients be monitored for 1 hour after every injection.

Due to the outstanding PMR related to malignancy risk for Ocrevus, and the ongoing study intended to fulfill this PMR, an identical PMR will be issued for SC OCR. A new or separate study will not be required, but patients receiving SC OCR in the postmarket setting may be enrolled in the ongoing study, if necessary. The results of this ongoing study are expected to inform labeling decisions for both IV and SC OCR.

Additionally, the chemistry, manufacturing, and controls review team recommends issuing a postmarketing commitment related to drug product commercial container closure system leachate studies.

In summary, we conclude that the benefits of ocrelizumab and hyaluronidase-ocsq outweigh its risks when used according to the agreed-upon labeling in the indicated populations. The availability of a subcutaneous formulation of ocrelizumab provides a more convenient treatment option for patients with RMS and PPMS.

II. Interdisciplinary Assessment

3. Introduction

This review serves as the interdisciplinary assessment for biologics license application (BLA) 761371 for subcutaneously administered ocrelizumab (SC OCR, Ocrevus Zunovo). Intravenously administered ocrelizumab (IV OCR, Ocrevus) is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against CD20-expressing B-cells. The Applicant has developed a subcutaneously administered formulation of ocrelizumab (referred to as SC OCR) that is coformulated with recombinant human hyaluronidase, an approved tissue permeability modifier. The Applicant developed SC OCR for the treatment of relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) in adults. The proposed indications align with the indications of the approved product, Ocrevus (IV OCR, BLA 761053), on which the Applicant is partially relying on safety and efficacy data as confirmatory evidence for the current BLA.

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 multiple sclerosis (RRMS), and active secondary progressive MS. PPMS is considered a distinct phenotype of MS characterized by steady progression of disability, perhaps due to more extensive involvement of the spinal cord. Relapses are either absent or infrequent in PPMS.

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. IV OCR is the only approved treatment for PPMS.

The efficacy of IV OCR was previously demonstrated in two double-blind, placebo-controlled trials of subjects with RMS and in one double-blind, placebo-controlled trial of subjects with PPMS. These trials led to its approval in 2017 for the treatment of RMS (to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease) and PPMS in adults. Hyaluronidase (Hylenex, also referred to as rHuPH20 or PH20) was initially approved in 2005 as a tissue permeability modifier, indicated as an adjuvant to increase the dispersion and absorption of other injected drugs. In SC OCR, coadministration with hyaluronidase allows for a larger volume to be injected subcutaneously.

For the current BLA, the pharmacokinetic (PK) noninferiority of SC OCR compared to IV OCR was demonstrated by Study CN42097, a Phase 3, randomized, open-label, parallel-group study that enrolled 236 subjects with RMS and PPMS. Subjects were randomized 1:1 to receive treatment with either SC OCR 920 mg or IV OCR 600 mg (two 300-mg intravenous (IV) infusions administered 14 days apart) for 24 weeks. Subjects randomized to IV OCR then

transitioned to SC OCR, for a total planned treatment duration of 72 weeks (last SC OCR injection at Week 48). The primary objective of Study CN42097 was to demonstrate the PK noninferiority of SC OCR based on the primary endpoint serum ocrelizumab area under the concentration-time curve (AUC) from Week 1 to Week 12 (AUC_{W1-12}), compared to IV OCR.

Based on current approved labeling for IV OCR (Ocrevus) (Genentech 2024), several known safety risks were identified for SC OCR, which were relevant to and informed this BLA review. The established, and anticipated, risks of SC OCR include:

- Systemic injection reactions, local injection reactions
- Serious (including life-threatening and fatal) infections
  - Respiratory tract infections
  - Herpes infections
  - Hepatitis B virus reactivation
- Progressive multifocal leukoencephalopathy (PML)
- Reduction in immunoglobulins
- Malignancies
- Immune-mediated colitis
- Possible increased risk of immunosuppressant effects with other immunosuppressants
- Interference with the effectiveness of non-live vaccines.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Demonstration of PK Noninferiority to IV Ocrelizumab

3.1.2. Key Safety Review Issues

3.1.2.1. Injection-Related Reactions

3.1.2.2. Hypersensitivity

3.1.2.3. Headache

3.1.2.4. Infections

3.1.2.5. Reduction in Immunoglobulins

3.1.2.6. Cytopenias

3.1.2.7. Malignancy

3.1.2.8. Immune-Mediated Colitis

3.1.2.9. Comparability of Safety Profile to IV OCR

3.2. Approach to the Clinical Review

The primary evidence of efficacy and safety for SC OCR for the proposed indications of RMS and PPMS in adults was provided by Study CN42097, a single, randomized, noninferiority, open-label, parallel-group study, which was considered adequate. The active comparator in Study CN42097 was IV OCR. Additionally, the Applicant partially relied on evidence of safety and efficacy from BLA 761053 for IV OCR (Ocrevus) as confirmatory evidence. The open-label, dose-ranging, Phase 1b Study CN41144 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 clinical data scientist Elizabeth Booth, PharmD.

The effectiveness assessment focused on the establishment of PK noninferiority between SC OCR and IV OCR (Ocrevus), which was evaluated in Study CN42097 based on the primary endpoint serum ocrelizumab AUC_{W1-12}. Table 3 provides an overview of studies CN42097 and CN41144.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

   Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

   Primary progressive MS, in adults

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*

   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

      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) (May 1998)

3. Complete response, if applicable

   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for SC Administered OCR

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
CN41144/ NCT03972306	Adults with RMS or PPMS	Phase 1b, randomized, open-label.	Drug: ocrelizumab (OCR) with hyaluronidase (SC OCR), IV OCR Dosage: • Dose escalation: SC OCR 40 mg, 200 mg, 600 mg, 920 mg, or 1200 mg and IV OCR 600 mg • Dose continuation: SC OCR 920 mg Number treated: 134 Duration (quantity and units): 146 wk	Primary: OCR AUC following a single-dose administration (IV vs. SC) Secondary: AEs, vital signs, ECG parameters, safety laboratory evaluations, immunogenicity	135 planned; 135 enrolled	20 sites, 1 country (USA)
CN42097/NCT04544449	Adults with RMS or PPMS	Phase 3, noninferiority, randomized, open-label, parallel group, active-control.	Drug: SC OCR, IV OCR Dosage: • Initial dosing: SC OCR 920 mg x1 or IV OCR 300 mg x2 (2 weeks apart). • Weeks 24 and 48 dosing: SC OCR 920 mg (all subjects) Number treated: 236 Duration (quantity and units): 96 wk	Primary: Ocrelizumab AUC_{w1-12} (SC OCR vs. IV OCR) Secondary: Cmax, total number of gadolinium-enhancing T1 MRI lesions at Weeks 8 and 24, total number of new or enlarging T2 MRI lesions at Weeks 12 and 24 (compared to prior scan).	232 planned; 236 enrolled	37 sites, 8 countries (Czech Republic [8], USA [7], Spain [5], Turkey [5], Italy [4], Poland [4], Brazil [2], and New Zealand [2])

Source: Reviewer.
[1] Includes all submitted clinical trials
Abbreviations: AE, adverse event; AUC_{w1-12}, area under the concentration-time curve from Week 1 to Week 12; C_{max}, maximum plasma concentration; ECG, electrocardiogram; IV, intravenous; MRI, magnetic resonance imaging; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing forms of multiple sclerosis; SC, subcutaneous; wk, week(s)

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	Data not discussed but provided general supportive background information.
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Data not discussed but provided general supportive background information.
☐	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	Data not discussed but provided general supportive background information.
☐	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

Ocrevus Zunovo is a fixed dose combination of ocrelizumab and hyaluronidase developed for the treatment of RMS and primary progressive MS. Ocrelizumab is a humanized IgG1 monoclonal antibody that binds human and non-human primate CD20. Primary pharmacology studies were conducted under BLAs 761053 (ocrelizumab, IV infusion) and 021859 (Hylenex; hyaluronidase); right of reference provided). Based on the nonclinical review of BLA 761053, studies conducted in human-derived cells as well as in non-human primate indicated that ocrelizumab depletes $CD20^{+}$ B cells through antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis. Incorporation of hyaluronidase is intended to increase drug absorption following subcutaneous administration by facilitating drug dispersion through the tissue.

5.2. Clinical Pharmacology / Pharmacokinetics

Refer to Section 12 for regulatory history and the approval of IV OCR.

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	See the EPC text phrases for active moieties on the Prescription Drug Labeling Resources .
Mechanism of action	The precise mechanism by which ocrelizumab exerts its therapeutic effects in multiple sclerosis 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. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan.
Active moieties	Ocrelizumab
QT prolongation	Not applicable (ocrelizumab is a monoclonal antibody).
	General Information
Bioanalysis	A validated enzyme-linked immunosorbent assay (ELISA)-based method was used to quantify ocrelizumab concentrations in human plasma, which was used to measure ocrelizumab plasma concentrations in the previously approved IV ocrelizumab. Method validation characteristics and performance meet the FDA recommendations.
Healthy subjects versus patients	Pharmacokinetics of ocrelizumab and hyaluronidase-ocsq were not characterized in healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	C_{max} and AUC_{w1-12} following a single 920 mg ocrelizumab and hyaluronidase-ocsq subcutaneous injection was reported to be 132 µg/mL and 3,730 µg/mL*day, respectively.
Range of effective dose(s) or exposure	NA: Single effective dose-level (i.e., 920 mg ocrelizumab and 23,000 units of hyaluronidase subcutaneously in the abdomen every 6 months).
Maximally tolerated dose or exposure	NA
Dose proportionality	NA
Accumulation	No accumulation is expected following multiple dosing.

Characteristic	Drug Information
Bridge between to-be-marketed and clinical trial/study formulations	The to-be-marketed formulation was used in the pivotal bridging study.
	Absorption
Bioavailability	Estimated absolute bioavailability of ocrelizumab following subcutaneous administration is 81%.
T_{max}	About 4 days (range 2 to 13 days)
Food effect (fed/fasted) Geometric least squares mean and 90% CI	Ocrelizumab and hyaluronidase-ocsq is administered subcutaneously. Therefore, a food effect is not relevant.
	Distribution
Volume of distribution	Central compartment volume is 2.78 L. Peripheral compartment volume is 2.68 L. Intercompartmental clearance is 0.55 L/day.
Plasma protein binding	Protein binding was not determined.
Drug as substrate of transporters	Ocrelizumab is a monoclonal antibody. It is unlikely to be affected by drug transporters; therefore, no transporter-mediated drug interactions were conducted.
	Elimination
Mass balance results	NA
Clearance	Clearance is 0.17 L/day. Initial time-dependent clearance is 0.05 L/day.
Half-life	20 days.
Metabolic pathway(s)	The metabolic pathway has not been studied. Antibodies are expected to be cleared by catabolism.
	Intrinsic Factors and Specific Populations
Body weight	Population pharmacokinetic analysis of intravenous ocrelizumab identified bodyweight as a covariate. No dose adjustment is recommended.
Renal impairment	Current approved labeling for intravenous ocrelizumab indicates that no dosage adjustment is necessary in patients with mild renal impairment. No significant changes in dosage recommendations in patients with mild renal impairment are expected with SC ocrelizumab.
Hepatic impairment	Current approved labeling for intravenous ocrelizumab indicates that no dosage adjustment is necessary in patients with mild hepatic impairment. No significant changes in dosage recommendations in patients with mild hepatic impairment are expected with SC ocrelizumab.
	Drug Interaction Liability
Inhibition/induction of metabolism	Ocrelizumab is not expected to be an object or precipitant of major CYP450 enzyme systems. Therefore, no CYP450-mediated drug interaction studies were conducted.
Inhibition/induction of transporter systems	Ocrelizumab is not expected to be an object or precipitant of major transporter systems. Therefore, no transporter-mediated drug interactions were conducted.

Characteristic	Drug Information
	Immunogenicity (if Applicable)
Bioanalysis	A tiered testing approach (screening, confirmatory, and titration assays) was used to detect antidrug antibodies (ADAs) to ocrelizumab and rHuPH20 (hyaluronidase). A validated bridging ELISA was used to measure ADAs to ocrelizumab in human serum, and a validated bridging ECLA was used to measure anti-rHuPH20 antibodies in human plasma.
Incidence	No treatment-emergent ADAs to ocrelizumab were observed.
Clinical impact	Not applicable.

Source: Section 14, Clinical Pharmacology
Abbreviations: ADA, antidrug antibody; AUC_{w1-12}, area under the concentration-time curve from week 1 to week 12; C_{max}, maximum plasma concentration; CYP450, cytochrome P450; ECLA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; EPC, established pharmacologic class; NA, not available; PK, pharmacokinetic; QT, QT interval; rHuPH20, recombinant human hyaluronidase; SC, subcutaneous; T_{max}, time to maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant conducted Study CN41144 (OCARINA I) to evaluate the PK and safety of single ascending doses of ocrelizumab ranging from 40 mg to 1200 mg, administered subcutaneously (SC). Based on results from Study CN41144, the Applicant concluded that 920 mg ocrelizumab SC is expected to yield exposures comparable to those following the approved 600 mg ocrelizumab IV dose (two 300-mg infusions given two weeks apart). In addition, the Applicant noted that the 25th percentile in the exposures (AUC during the dosing interval) following a 920-mg SC dose matched the 25th percentile in the exposure following a 600-mg IV dose, ensuring adequate coverage at the lower exposures as well. Therefore, the Applicant selected this dose level for subsequent evaluation in the Phase 3 study CN42097 (OCARINA II).

The results from Study CN42097 demonstrated that ocrelizumab exposures following a 920-mg SC dose were comparable to those following a 600-mg IV dose, consistent with the findings from Study CN41144. Therefore, the selected dose appears appropriate to provide the same exposure as 600-mg IV dose of OCR and is anticipated to provide similar efficacy to that of IV OCR.

The Applicant noted that splitting the first dose (600 mg) into two doses (300 mg) taken two weeks apart, which is the approved dosing regimen for IV OCR, is not necessary for SC administration of ocrelizumab because treatment-naive subjects tolerated up to 1200 mg of ocrelizumab SC.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Study CN42097

At the time of data cutoff for the BLA submission (March 3, 2023), version 2 of Protocol CN42097 was in effect and is therefore the protocol version discussed in this BLA review. Wherever applicable, revisions implemented in the most recent version of Protocol CN42097 (version 4, dated July 13, 2023) will be discussed.

6.2.1.1. Design, Study CN42097

Study CN42097 is an ongoing Phase 3, randomized, noninferiority, open-label, parallel-group study intended to evaluate the PK, pharmacodynamics (PD), safety, immunogenicity, and clinical and radiological effects of SC OCR compared to IV OCR in subjects with RMS or PPMS. Note that “efficacy” in the context of this section refers to demonstration of comparable/noninferior PK of SC OCR to that of IV OCR, which is anticipated to result in the

same efficacy as the approved IV OCR, for which safety and effectiveness in RMS and PPMS are established.

The primary objective of Study CN42097 is to demonstrate the PK noninferiority of SC OCR in subjects with RMS or PPMS based on the serum ocrelizumab AUC_{W1-12}, compared to IV OCR.

Secondary objectives were to examine the effects of SC OCR as compared to IV OCR on the following:

- Maximum serum concentration (maximum plasma concentration)
- Total number of T1 gadolinium-enhancing brain MRI lesions
- Total number of new or enlarging T2 brain MRI lesions
- Other MRI parameters
- Annualized relapse rate
- Expanded Disability Status Scale (EDSS)
- Treatment Administration Satisfaction Questionnaires
- Subject satisfaction and preference of SC OCR over other previously received MS treatments
- Patient Preference Questionnaire
- Safety of SC OCR compared to IV OCR, as determined by adverse events (AEs), vital signs, and laboratory safety evaluations
- Evaluation of immune response, as determined by treatment-emergent antidrug antibodies (ADAs)
- Proportion of subjects with $CD19^+$ B lymphocytes level of $\leq$5 cells/μL
- Serum neurofilament light (NfL) levels

Study Design

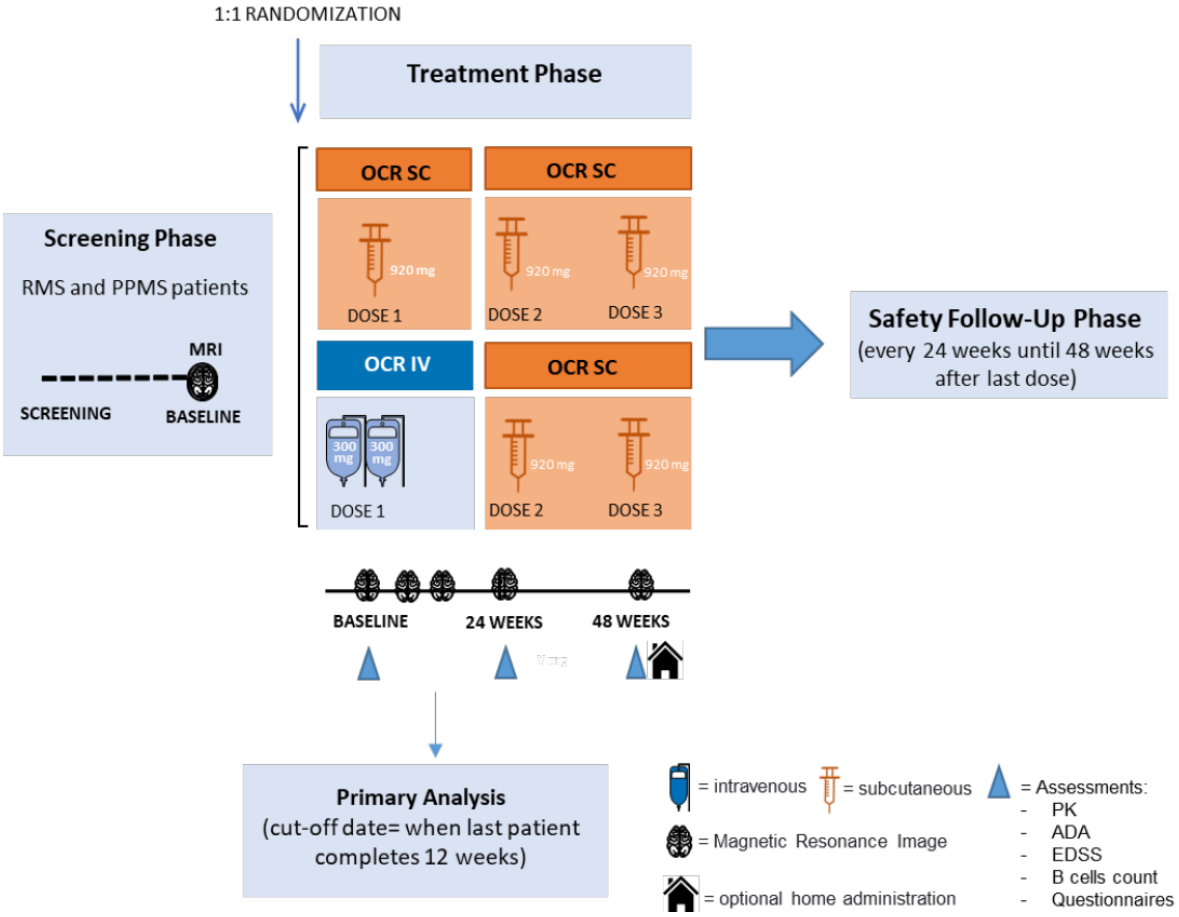
Study CN42097 is a 96-week, Phase 3, randomized, multicenter, open-label, noninferiority study, designed to evaluate the PK, PD, safety, immunogenicity, and clinical and radiological effects of SC OCR compared to IV OCR in subjects with RMS and PPMS, per the 2017 McDonald revised diagnostic criteria (Thompson et al. 2018). The planned sample size was 232 subjects, and 236 subjects were randomized 1:1 to receive treatment with either SC OCR 920 mg or IV OCR 600 mg (two 300-mg IV infusions administered 14 days apart) for 24 weeks. Randomization was stratified according to baseline body weight (<70 kg versus ≥70 kg), disease phenotype (RMS versus PPMS), and country/geographical region (United States versus rest of the world). Subjects randomized to IV OCR then transitioned to SC OCR at Week 24, for a total treatment duration of 72 weeks (last SC OCR injection at Week 48). Study CN42097 did not have a relapse adjudication committee. In Protocol CN42097 version 4, the Treatment Period duration was increased to 96 weeks (last SC OCR injection at Week 96 [total treatment duration: 120 weeks]) and the Safety Follow-Up Period was reduced to 24 weeks.

There were 232 subjects in the PK-evaluable analysis set (n=116 SC OCR, n=116 IV OCR) and 236 subjects in the safety-evaluable and efficacy-evaluable analysis sets (n=118 SC OCR, n=118

IV OCR). The study included 213 subjects with RMS (n=210 RRMS, n=3 active secondary progressive MS) and 23 subjects with PPMS.

The study schematic for Study CN42097 is presented in Figure 1. The study consisted of a Screening Period of up to 6 weeks, a 48-week Treatment Period, and a 48-week Safety Follow-Up Period. Subjects received a total of 3 ocrelizumab doses during the Treatment Period. The Treatment Period consisted of a 24-week Controlled Period and a 24-week SC Ocrelizumab Treatment Period. During the Controlled Period (1:1 randomization), SC OCR was administered as a single 920-mg SC injection at Week 1 (Dose 1) and IV OCR was administered as two 300-mg IV infusions administered 2 weeks apart (Weeks 1 and 2, Dose 1). During the SC Ocrelizumab Treatment Period, SC OCR was administered to all subjects as a single 920-mg SC injection at Weeks 24 (Dose 2) and 48 (Dose 3). See details above regarding revisions to the treatment duration and safety follow-up period implemented in Protocol CN42097 version 4. Refer to Section 15 (Study/Trial Design) for additional details regarding the design of Study CN42097.

Figure 1.Study Schematic, Study CN42097 (Protocol Version 2)



Source: Applicant's Clinical Study Report, Study CN42097.
Abbreviation: ADA, antidrug antibody; EDSS, Expanded Disability Status Scale; IV, intravenous; MRI, magnetic resonance imaging; OCR, ocrelizumab; PK, pharmacokinetic; PPMS, primary progressive multiple sclerosis; RMS, relapsing-remitting multiple sclerosis; SC, subcutaneous

Study CN42097 Endpoints

Refer to Section 15.1.1 (Study Design) for a detailed description of study endpoints. The primary endpoint for Study CN42097 was AUC_{W1-12} after administration of SC OCR, compared to that with IV OCR. Secondary endpoints included an additional PK endpoint (maximum plasma concentration) and MRI-based, safety, immunogenicity, and PD endpoints.

Assessment of Study CN42097 Design

Overall, the design of Study CN42097 was considered acceptable by the multidisciplinary review team. The noninferiority design and analysis was previously agreed upon by the Division of Neurology II (the Division). The study population (adults with RMS and PPMS), eligibility criteria, and endpoints are acceptable to support the study objectives and review of this BLA.

6.2.1.2. Eligibility Criteria, Study CN42097

Key eligibility criteria are summarized in this section.

Key Inclusion Criteria

- Diagnosis of RMS or PPMS per the 2017 McDonald revised criteria.
- Age 18 to 65 years, inclusive.
- EDSS score 0.0 to 6.5, inclusive.
- Neurological stability for ≥30 days.
- MS disease duration of <15 years for subjects with EDSS score <2.0.

Key Exclusion Criteria

- Known or suspected active infection or infection requiring hospitalization or treatment with IV antimicrobials within the previous 8 weeks or infection requiring treatment with oral antimicrobials within the previous 2 weeks.
- History of PML.
- History of malignancy within 10 years prior to screening, except for successfully treated skin basal or squamous cell carcinoma or in situ carcinoma of the cervix that has been successfully treated >1 year prior to screening.
- Immunocompromised state (CD4 count <250/µL, absolute neutrophil count (ANC) $<1.5\times10^3$/µL, or serum IgG <4.6 g/L).
- Live-attenuated vaccine administration within the previous 6 weeks.
- Presence of other neurologic or systemic disorder that could interfere with study conduct.
- Treatment with systemic corticosteroids within the previous 4 weeks.

Refer to Section 15 (Study/Trial Design) for a full list of eligibility criteria for Study CN42097.

6.2.1.3. Statistical Analysis Plan, Study CN42097

The primary efficacy analysis is based on the comparison of PK exposures (AUC_{W1-12}) between SC OCR and IV OCR using a noninferiority margin. Therefore, the Clinical Pharmacology review team conducted the analysis of the primary endpoint, and the Office of Biostatistics was not involved in the review of this BLA.

Specifically, noninferiority was defined as the lower end of the two-sided 90% CI of the geometric mean ratio of AUC_{W1-12} being >0.8. The Applicant selected the noninferiority margin of 0.8, as it corresponds to a maximal 20% loss in AUC following SC administration compared with IV. The Division previously agreed with this margin; refer to Section 12 for discussion of regulatory history.

The Clinical review team conducted analyses of the secondary efficacy endpoints, relapses, and MRI lesions, as discussed in Section 1.1, including negative binomial regression and descriptive analyses. Formal hypothesis testing was not conducted for the secondary efficacy endpoints.

6.2.1.4. Results of Analyses, Study CN42097

This section presents subject disposition, baseline demographics, and results of the efficacy analyses for the primary and secondary efficacy endpoints. Note that "efficacy" in the context of this section refers to demonstration of noninferior PK of SC OCR to that of IV OCR, which is anticipated to result in the same efficacy as the approved IV OCR, for which safety and effectiveness in RMS and PPMS are established.

6.2.1.5. Disposition and Baseline Demographic, Clinical, and MS Disease Characteristics

Subject Disposition

Subject disposition is presented in Table 6 and Table 7. A total of 236 subjects were enrolled, of whom 118 were randomized to SC OCR and 118 to IV OCR. Two subjects (1.7%) randomized to IV OCR withdrew from the Controlled Period and entered the Safety Follow-Up Period (one due to pregnancy and one due to withdrawal of consent). As of the BLA data cutoff date, 126 subjects (53.3%; 63 SC OCR and 63 IV OCR) had completed the 24-week Controlled Period and entered the Subcutaneous Treatment Period. Three subjects (2.5%; two SC OCR and one IV OCR) discontinued treatment prematurely and entered the Safety Follow-Up period due to withdrawal of consent (one SC OCR and one IV OCR) or lack of efficacy (two SC OCR). Of the five subjects (2.1%) who entered the Safety Follow-Up Period due to premature study drug discontinuation, as of the BLA cutoff date (March 10, 2023), one subject (0.8%) in the IV OCR group discontinued the study due to withdrawal of consent. At the time of the BLA data cutoff, 108 subjects (45.8%) remained in the ongoing Controlled Period.

Table 6. Subject Screening and Enrollment, Study CN42097

Disposition	n (%)
Subjects screened	267
Screening failures	42* (15.7%)
Inclusion/exclusion criteria not met	31 (11.6%)
Subject noncompliance	0 (0.0%)
Consent withdrawn	0 (0.0%)
Other	11 (4.1%)
Subjects enrolled	236 (88.4%)
Subjects randomized	236 (88.4%)

Source: Clinical Study Report for Study CN42097.
*11 subjects we rescreened and subsequently enrolled.
Abbreviation: n, number of subjects

Table 7. Subject Disposition, Safety Population, Study CN42097

Parameter	SC OCR 920 mg N=118 n (%)	IV OCR 600 mg N=118 n (%)
Subjects randomized	118 (100)	118 (100)
PK population	116 (98.3)	116 (98.3)
Safety population	118 (100)	118 (100)
Efficacy population	118 (100)	118 (100)
Discontinued study drug	2 (1.7)[1]	3 (2.5)[1,2]
Adverse event	0 (0.0)	0 (0.0)
Lack of efficacy	1 (0.8)[1]	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)
Withdrawal by subject	1 (0.8)[1]	2 (1.7)[1,2]
Other	0 (0.0)	1 (0.8)[2]
Discontinued study	0 (0.0)	1 (0.8)[3]
Death	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)
Withdrawal by subject	0 (0.0)	1 (0.8)[3]
Physician decision	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)

Source: Clinical Study Report for Study CN42097.
[1] Discontinued during the Subcutaneous Treatment Period
[2] Discontinued during the Controlled Treatment Period
[3] Discontinued during the Safety Follow-Up Period
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given characteristic; OCR, ocrelizumab; PK, pharmacokinetic; SC, subcutaneous

Protocol Deviations

Major protocol deviations occurred in a higher proportion of subjects in the SC OCR group (16.9%) compared to the IV OCR group (12.7%). The difference between the groups was mostly accounted for by subjects with missed PK and ADA assessments in the SC OCR group. Major protocol deviations that occurred during Study CN42097 are listed in Table 8.

Table 8. Major Protocol Deviations, Safety Population, Study CN42097

Category	Deviation	OCR SC N=118 n (%)	OCR IV N=118 n (%)
All	Any major deviation	20 (16.9)	15 (12.7)
Inclusion/exclusion criteria	Active infection	1 (0.8)	0 (0.0)
	Pregnant or breastfeeding	1 (0.8)	0 (0.0)
	Prior treatment with prohibited therapy	0 (0.0)	1 (0.8)
Study medication	Retreated without meeting retreatment criteria	0 (0.0)	2 (1.7)
Study procedure or assessment	Incorrect stratification	1 (0.8)	1 (0.8)
	MRI not performed	3 (2.5)	3 (2.5)
	Safety assessment not performed	3 (2.5)	5 (4.2)
	MRI not performed as per protocol	3 (2.5)	4 (3.4)
	PK/ADA assessment repeatedly not collected	6 (5.1)	0 (0.0)
	Repeat minor deviations at same site	0 (0.0)	1 (0.8)
Informed consent	Any major deviation	4 (3.4)	3 (2.5)

Source: ADDV for CN42097, SAFFL = Y; tabulated by TRT01A.
Abbreviations: ADA, antidrug antibody; IV, intravenous; MRI, magnetic resonance imaging; N, number of subjects in treatment arm; n, number of subjects with given deviation; OCR, ocrelizumab; PK, pharmacokinetic; SC, subcutaneous

Per the clinical study report (CSR), Subject (b) (6) experienced an eligibility criteria-related major protocol deviation described as “pregnant or lactating,” but additional details regarding this event were not provided. The Applicant clarified via Information Request that the serum pregnancy test required at screening was not collected for this subject due to incorrect completion of the laboratory requisition form. However, urine pregnancy testing was completed per protocol and this subject was not pregnant at screening and was not pregnant during study participation.

Baseline Demographic Characteristics

Baseline demographic characteristics for the safety population are presented in Table 9. A total of 236 subjects were enrolled and randomized in Study CN42097. Most subjects were female, ≥40 years of age, White, non-Hispanic, and from Central Europe. Overall, there appears to be an acceptable balance of demographic characteristics between the SC OCR and IV OCR groups.

Table 9. Baseline Demographic Characteristics, Safety Population, Study CN42097

Characteristic	OCR SC N=118 n (%)	OCR IV N=118 n (%)	Total (N=236) n (%)
Sex, n (%)			
Male	41 (34.7)	48 (40.7)	89 (37.7)
Female	77 (65.3)	70 (59.3)	147 (62.3)

Characteristic	OCR SC N=118 n (%)	OCR IV N=118 n (%)	Total (N=236) n (%)
Age at randomization, years			
Mean (SD)	39.9 (11.4)	40.0 (11.9)	39.9 (11.6)
Median (IQR)	40 (16.2)	40 (18)	40 (18)
Min, max	17, 65	18, 64	17, 65
Age group at randomization (years), n (%)			
<18 years	1 (0.8)	0 (0.0)	1 (0.4)
≥18 to <30 years	20 (16.9)	25 (21.2)	45 (19.1)
≥30 to <40 years	35 (29.7)	30 (25.4)	65 (27.5)
≥40 years	62 (52.5)	63 (53.4)	125 (53.0)
Race, n (%)			
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	1 (0.8)	1 (0.4)
Black or African American	7 (5.9)	1 (0.8)	8 (3.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.8)	1 (0.4)
White	102 (86.4)	109 (92.4)	211 (89.4)
Multiple	3 (2.5)	1 (0.8)	4 (1.7)
4 (unknown)	6 (5.1)	5 (4.2)	11 (4.7)
Ethnicity, n (%)			
Hispanic	7 (5.9)	8 (6.8)	15 (6.4)
Non-Hispanic	95 (80.5))	93 (78.8)	188 (79.7)
Unknown	2 (1.7)	2 (1.7)	4 (1.7)
Not reported	14 (11.9)	15 (12.7)	29 (12.3)
Country of participation, n (%)			
Brazil	4 (3.4)	4 (3.4)	8 (3.4)
Czech Republic	46 (39.0)	44 (37.3)	90 (38.1)
Spain	10 (8.5)	4 (3.4)	14 (5.9)
Italy	9 (7.6)	10 (8.5)	19 (8.1)
New Zealand	2 (1.7)	4 (3.4)	6 (2.5)
Poland	21 (17.8)	25 (21.2)	46 (19.5)
Turkey	10 (8.5)	11 (9.3)	21 (8.9)
United States	16 (13.5)	16 (13.5)	32 (13.5)

Source: ADSL for CN42097, SAFFL = Y; tabulated by TRT01A.
Abbreviations: IQR, interquartile range; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given characteristic; OCR, ocrelizumab; SC, subcutaneous; SD, standard deviation

Baseline Clinical, Disease, and MRI Characteristics

Baseline clinical characteristics for the safety population are presented in Table 10. The treatment groups appeared to be similar in terms of height, weight, and body mass index.

Table 10. Baseline Clinical Characteristics, Safety Population, Study CN42097

Characteristic	OCR SC N=118	OCR IV N=118	Total (N=236) n (%)
Height (cm)			
n (%)	116 (98.3)	115 (97.5)	231 (97.9)
Mean (SD)	170.3 (9.2)	171.0 (9.8)	170.7 (9.5)
Median (IQR)	169 (15)	170 (13)	170 (13.8)
Min, max	152.4, 193.0	152, 203	152, 203

Characteristic	OCR SC N=118	OCR IV N=118	Total (N=236) n (%)
Weight (kg)			
n (%)	118 (100)	118 (100)	236 (100)
Mean (SD)	75.4 (16.6)	76.1 (22.7)	75.8 (19.8)
Median (IQR)	75 (22.1)	72 (30.2)	73 (26.7)
Min, max	47.0, 132.0	42.0, 194.1	42, 194.1
BMI (kg/m^2)[1]			
n (%)	116 (98.3)	115 (97.5)	231 (97.9)
Mean (SD)	25.9 (5.2)	25.8 (6.1)	25.9 (5.7)
Median (IQR)	25.1 (6.4)	24.5 (7.8)	24.9 (7.4)
Min, max	17.3, 43.6	15.9, 47.1	15.9, 47.1

Source: ADSUB for CN42097, SAFFL = Y; tabulated by TRT01A.
[1] Source: Response to Information Request received 2/6/2024, ADVS2 for CN42097, SAFFL = Y; tabulated by TRT01A.
Abbreviations: BMI, body mass index; IQR, interquartile range; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given characteristic; OCR, ocrelizumab; SC, subcutaneous; SD, standard deviation

Baseline disease characteristics for the safety population are presented in Table 11 and Table 12. The treatment groups appeared to be similar in terms of MS disease characteristics.

Table 11. Baseline MS Disease Characteristics, Safety Population, Study CN42097

Characteristic	OCR SC N=118	OCR IV N=118	Total (N=236) n (%)
Time since MS diagnosis (years)			
n (%)	118 (100)	118 (100)	236 (100)
Mean (SD)	5.7 (6.8)	4.8 (5.8)	5.2 (6.3)
Median (IQR)	3.1 (9.1)	2.3 (6.6)	2.7 (8.3)
Min, max	0.1, 41.8	0.1, 28.7	0.1, 41.8
Time since MS symptom onset (years)			
n (%)	117 (99.2)	117 (99.2)	234 (99.2)
Mean (SD)	7.7 (8.3)	6.8 (7.1)	7.3 (7.7)
Median (IQR)	4.2 (9.7)	4.4 (9.3)	4.4 (9.4)
Min, max	0.3, 41.8	0.2, 38.7	0.2, 41.8
Time since last relapse (months)			
n (%)	85 (72.0)	89 (75.4)	174 (73.7)
Mean (SD)	2.3 (3.0)	1.8 (2.4)	2.0 (2.7)
Median (IQR)	0.6 (2.8)	0.6 (2.6)	0.6 (2.6)
Min, max	0.1, 11.2	0.1, 10.6	0.1, 11.2
Baseline EDSS score[1]			
n (%)	111 (94.1)	113 (95.8)	224 (94.9)
Mean (SD)	2.9 (1.6)	3.0 (1.7)	2.9 (1.6)
Median (IQR)	2.5 (2.5)	3.0 (2.5)	2.5 (2.5)
Min, max	0, 6.5	0, 6.5	0, 6.5
≤3.5 (n [%])	82 (69.5)	82 (69.5)	164 (69.5)
>3.5 (n [%])	29 (24.6)	31 (26.3)	60 (25.4)

Source: ADSUB for CN42097, SAFFL = Y; tabulated by TRT01A.
[1] Source: Response to Information Request received 2/8/2024, ADQS for CN42097, SAFFL = Y, ANL01FL = Y; tabulated by TRT01A.
Abbreviations: EDSS, Expanded Disability Status Scale Score; IQR, interquartile range; IV, intravenous; MS, multiple sclerosis; N, number of subjects in treatment arm; n, number of subjects with given characteristic; OCR, ocrelizumab; SC, subcutaneous; SD, standard deviation

Table 12. Prior MS Treatments, Safety Population, Study CN42097

Characteristic	OCR SC N=118 n (%)	OCR IV N=118 n (%)	Total (N=236) n (%)
Interferon beta-1a	21 (17.8)	17 (14.4)	38 (16.1)
Dimethyl fumarate*	19 (16.1)	17 (14.4)	35 (14.8)
Teriflunomide	15 (12.7)	15 (12.7)	30 (12.7)
Glatiramer acetate	14 (11.9)	15 (12.7)	29 (12.3)
Peginterferon beta-1a	5 (4.2)	7 (5.9)	12 (5.1)
Natalizumab	5 (4.2)	6 (5.1)	11 (4.7)
Fingolimod hydrochloride	5 (4.2)	4 (3.4)	9 (3.8)
Interferon beta-1b*	5 (4.2)	2 (1.7)	6 (2.5)
Fingolimod	2 (1.7)	6 (5.1)	8 (3.4)
Azathioprine*	4 (3.4)	0 (0.0)	2 (0.8)
Cyclophosphamide	2 (1.7)	0 (0.0)	2 (0.8)
Ocrelizumab	1 (0.8)	1 (0.8)	2 (0.8)
Diroximel fumarate	1 (0.8)	0 (0.0)	1 (0.4)
Immunostimulants	1 (0.8)	0 (0.0)	1 (0.4)
Methotrexate	1 (0.8)	0 (0.0)	1 (0.4)
Opicinumab	1 (0.8)	0 (0.0)	1 (0.4)
Siponimod fumarate	1 (0.8)	0 (0.0)	1 (0.4)
Mitoxantrone	0 (0.0)	2 (1.7)	2 (0.8)
Daclizumab	0 (0.0)	1 (0.8)	1 (0.4)
Immunoglobulins (not otherwise specified)	0 (0.0)	1 (0.8)	1 (0.4)
Interferon beta	0 (0.0)	1 (0.8)	1 (0.4)
Ozanimod	0 (0.0)	1 (0.8)	1 (0.4)
Rituximab	0 (0.0)	1 (0.8)	1 (0.4)
Previous episodic (≤30 days) corticosteroid treatment for MS symptoms or relapse**	9 (7.6)	7 (5.9)	20 (8.5)

Source: ADCM for CN42097, SAFFL = Y; CMMDMST = Y; PREFL = Y; CMDECOD, tabulated by TRT01A.
* Tabulated without CMMDMST flag.
** Source: Applicant's response to Information Request, dated 2/6/2024.
Abbreviations: IV, intravenous; MS, multiple sclerosis; N, number of subjects in treatment arm; n, number of subjects with given characteristic; OCR, ocrelizumab; SC, subcutaneous

Section 4.5.1.1 (Previous Medications) of the CSR for Study CN42097 indicated that prior corticosteroids for systemic use were reported in 11.9% (n=14) of subjects on SC OCR and in 7.6% (n=9) of those on IV OCR. The Applicant clarified via Information Request that these percentages pertained to the indications "acute treatment of MS symptoms" and "other indications" (n=1, "itching"), and included subjects who received episodic (≤30 days) and chronic (≥31 days) systemic corticosteroid treatment. The Applicant provided the percentage of subjects in each treatment group with history of episodic (≤30 days) systemic corticosteroid use for the acute treatment of MS symptoms or relapses (SC OCR n=9 [7.6%] and IV OCR n=7 [5.9%]). The proportion of subjects in the entire cohort with prior systemic corticosteroid use for the acute treatment of MS symptoms and relapses is much lower than expected in the general MS population, which could be due to underreporting. Additionally, this proportion was slightly higher in the SC OCR group, which could be consistent with the slightly longer disease duration and time since MS symptom onset in the SC OCR group.

Baseline MRI characteristics for the safety population are presented in Table 13. Baseline MRI characteristics were missing for 29 subjects (14 on SC OCR and 15 on IV OCR). Although the presence of gadolinium-enhancing T1 lesions at baseline appeared to be comparable between the groups, subjects in the IV OCR group had a higher gadolinium-enhancing T1 lesion burden at

baseline (i.e., 3 lesions and 4 or more lesions), compared to the SC OCR group. The treatment groups appeared to be similar in terms of baseline T2 lesion volume; however, subjects in the IV OCR group had a higher T2 lesion count, compared to those in the SC OCR group.

Table 13. Baseline MRI Characteristics, Safety Population, Study CN42097

Characteristic	OCR SC N=118	OCR IV N=118	Total N=236
Gadolinium-enhancing lesions			
n (%)	104 (88.1)	103 (87.3)	207 (87.7)
Mean (SD)	0.5 (1.7)	1.0 (2.5)	0.8 (2.1)
Median (IQR)	0 (0)	0 (0)	0 (0)
Min, max	0, 14	0, 19	0, 19
0	82 (78.8)	78 (75.7)	160 (77.3)
1	11 (10.6)	5 (4.8)	16 (7.7)
2	4(3.8)	4 (3.8)	8 (3.9)
3	2 (1.9)	5 (4.8)	7 (3.4)
≥4	5 (4.8)	11 (10.7)	16 (7.7)
T2 lesion count[1]			
n (%)	104 (88.1)	103 (87.3)	207 (87.7)
Mean (SD)	44.5 (32.3)	49.8 (34.6)	47.1 (33.4)
Median (IQR)	38 (34)	39 (44)	38 (37)
Min, max	3, 174	0, 190	0, 190
T2 lesion volume (mL)			
n (%)	104 (88.1)	103 (87.3)	207 (87.7)
Mean (SD)	9.7 (9.5)	9.7 (9.3)	9.7 (9.4)
Median (IQR)	6.8 (12.1)	6.0 (11.1)	6.4 (11.1)
Min, max	0.4, 54.6	0.0, 38.4	0, 54.6

Source: ADMRI for CN42097, SAFFL = Y; tabulated by TRT01A.
[1] Source: Response to Information Request received 2/6/2024, T2MRI for CN42097, SAFFL = Y; tabulated by TRT01A.
Abbreviations: IQR, interquartile range; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given characteristic; OCR, ocrelizumab; SC, subcutaneous; SD, standard deviation

General medical history for subjects enrolled in Study CN42097 was reviewed as well. There did not appear to be any clinically meaningful differences between the treatment groups. Ongoing medical disorders (defined by MHENRTPT = ONGOING) occurring in >5% of subjects in either treatment group are presented in Table 14. No major or clinically relevant differences in medical history were observed between the treatment groups.

Table 14. Concurrent Medical Disorders Reported in >5% of Either Treatment Group, Safety Population, Study CN42097

System Organ Class	Dictionary-Derived Term[1]	SC OCR (N=118) n (%)	IV OCR (N=118) n (%)
Endocrine disorders	Hypothyroidism	12 (10.2)	5 (4.2)
Gastrointestinal disorders	Gastroesophageal reflux disease	7 (5.9)	6 (5.1)
General disorders and administration site conditions	Fatigue	6 (5.1)	7 (5.9)
Immune system disorders	Drug hypersensitivity	7 (5.9)	6 (5.1)
	Seasonal allergy	9 (7.6)	6 (5.1)
Metabolism and nutrition disorders	Vitamin D deficiency	13 (11.0)	10 (8.5)
Musculoskeletal and connective tissue disorders	Back pain	7 (5.9)	9 (7.6)
Nervous system disorders	Headache	8 (6.8)	5 (4.2)
	Migraine	9 (7.6)	11 (9.3)
Psychiatric disorders	Anxiety	9 (7.6)	6 (5.1)
	Depression	14 (11.9)	16 (13.6)
	Insomnia	4 (3.4)	6 (5.1)
Vascular disorders	Hypertension	16 (13.6)	13 (11.0)

Source: Study CN42097, ADMH, where SAFFL = Y, MHENRTPT = ONGOING, by TRT01A
[1] MHDECOD in ADMH
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given medical history; OCR, ocrelizumab; SC, subcutaneous

Body mass index data, baseline MRI T2-weighted lesion counts, and Expanded Disability Status (EDSS) scores for Study CN42097 were not included in the original BLA submission, but were submitted by the Applicant upon Information Request.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All 236 subjects received at least one dose of SC OCR (n=118) or IV OCR (n=118). Four subjects were excluded from the PK analysis population, two in the SC OCR group (1 due to incomplete dose and 1 due to “impossible concentration-time profile”), and two in the IV OCR group (one due to delay in administration of second IV infusion and one due to incomplete dose). The number of excluded subjects was balanced between the groups and compliance with SC and IV OCR in the Controlled Period appeared to be similar between treatment arms.

Concomitant Medications

Per the Applicant’s CSR, the most commonly used concomitant medication classes were vitamins, analgesics, and ophthalmological and psychiatric medications. Concomitant medications used by ≥5% of subjects in the safety population during the Controlled Period are shown in Table 15.

Table 15. Selected Concomitant Medications Used by ≥5% of Either Treatment Group of Safety Population During the Controlled Period, Study CN42097

Medication Class	Medication Name	SC OCR N=118 n (%)	IV OCR N=118 n (%)
Vitamins	Cholecalciferol	41 (34.7)	33 (28.0)
	Vitamin D NOS	6 (5.1)	7 (5.9)
Anti-inflammatory and antirheumatic products	Ibuprofen	18 (15.3)	12 (10.2)
Analgesics	Paracetamol	18 (15.3)	20 (16.9)
	Gabapentin	11 (9.3)	9 (7.6)
	Pregabalin	9 (7.6)	6 (5.1)
Thyroid therapy	Levothyroxine sodium	13 (11.0)	4 (3.4)
Other nervous system drugs	Baclofen	9 (7.6)	7 (5.9)
	Vitamin B12 NOS	6 (5.1)	4 (3.4)
Drugs for acid-related disorders	Omeprazole	6 (5.1)	3 (2.5)
Lipid modifying agents	Atorvastatin calcium	6 (5.1)	0 (0.0)
Antibacterials for systemic use	Amoxicillin	2 (1.7)	6 (5.1)
	Azithromycin	3 (2.5)	6 (5.1)

Source: ADCM for Study CN42097, where ATIREL= "PRIOR_CONCOMITANT" or "CONCOMITANT," ANL02FL = Y, SEALLFL = Y, ATC2 and CMDECOD by TRT01A and Applicant's response to Information Request, dated 2/22/2024.
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with given medical history; NOS, not otherwise specified; OCR, ocrelizumab; SC, subcutaneous

Rescue Medication Use

Rescue medication use in Study CN42097 was tabulated using the CMINDC variable in the ADCM dataset, which indicated treatment for an MS relapse ("MS relaps," "MS relapse," "MS exacerbation," and "pseudo MS exacerbation secondary to influenza"), and the SDG01NAM variable indicated "corticosteroids." Per these flags, four subjects on SC OCR (3.4%) and four on IV OCR (3.4%) received systemic corticosteroids for relapse treatment during the Controlled Period (APERIODC = Controlled Period).

According to the Applicant's analysis submitted via Information Request, during the Controlled Period, two subjects (0.8%; one SC OCR [0.8%], one IV OCR [0.8%]) received systemic corticosteroids for treatment of a protocol-defined relapse, five subjects (2.1%; three SC OCR [2.5%], two IV OCR [1.7%]) received systemic corticosteroids for treatment of a suspected MS relapse, and seven subjects (3.0%; four SC OCR [3.4%], three IV OCR [2.5%]) received systemic corticosteroids for treatment of any MS relapse (Table 16).

Table 16. Summary of Subjects Who Received Concomitant Steroids for the Treatment of MS Relapses, Study CN42097, Controlled Period

Relapse Parameter	SC OCR N=118 n (%)	IV OCR N=118 n (%)	All (N=236) n (%)
Protocol-defined MS relapse	1 (0.8)	1 (0.8)	2 (0.8)
Suspected MS relapse	3 (2.5)	2 (1.7)	5 (2.1)
Any MS relapse	4 (3.4)	3 (2.5)	7 (3.0)

Source: Applicant's Response to Information Request, dated 2/22/2024.
Abbreviations: IV, intravenous; MS, multiple sclerosis; N, number of subjects in treatment arm; n, number of subjects with given medical history; OCR, ocrelizumab; SC, subcutaneous

The overall proportion of subjects who received systemic corticosteroids for treatment of MS relapse in both groups during the Controlled Period was low, which is not unexpected given the short follow-up time and the known efficacy of ocrelizumab.

Efficacy Results, Study CN42097

Primary Efficacy Results

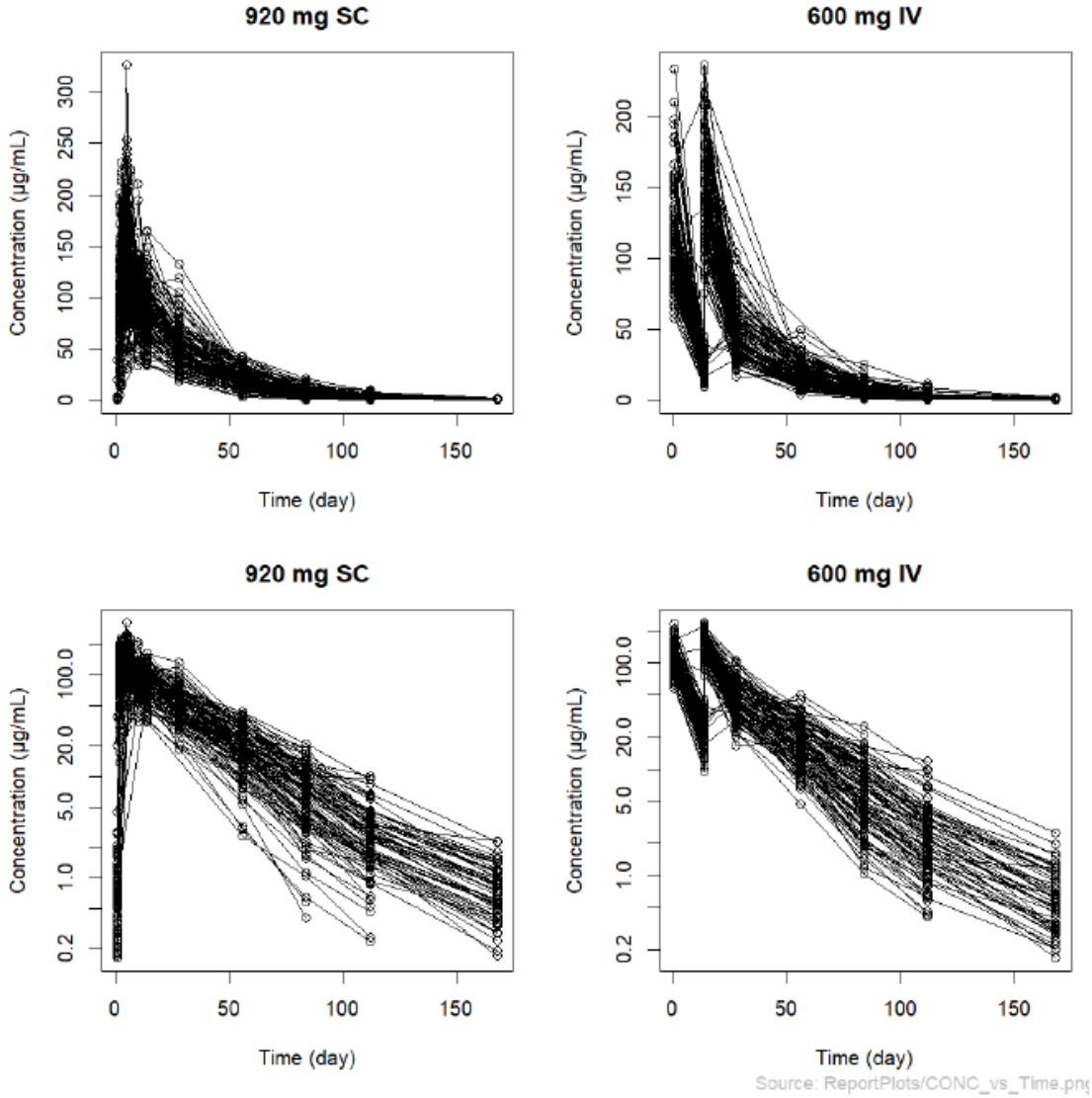
The observed individual concentration vs. time profiles by treatment are presented in Figure 2, and the geometric mean ratio for $AUC_{W1–12}$, the primary endpoint, are presented in Table 17. These results indicate that the exposures ($AUC_{W1–12}$) following SC injection of 920 mg ocrelizumab were noninferior to the 600-mg IV administration (two 300-mg infusions given two weeks apart). Ocrelizumab concentrations in human serum samples was measured using a validated enzyme-linked immunosorbent assay method. Refer to Section 14.3 (Bioanalytical Method Validation and Performance) for details.

Table 17. Estimated Ratios of Geometric Mean and 90% Confidence Intervals for AUC From Week 1 to Week 12 of SC OCR in Comparison With IV OCR

PK Parameter	Comparison	n	Geometric Mean Ratio [1]	90% CI Lower Bound	90% CI Upper Bound
AUC over the first 12 weeks (day*mcg/mL)	OCR SC vs OCR IV	116 vs 116	1.2851	1.2258	1.3473

Source: Clinical Study Report for Study CN42097. Page 118, Table 32.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; IV, intravenous; OCR, ocrelizumab; PK, pharmacokinetic; SC, subcutaneous

Figure 2. Observed Individual Concentration vs. Time Profiles by Treatment



Source: Clinical Study Report for Study CN42097. Page 119, Figure 3.
Abbreviations: IV, subcutaneous; SC, subcutaneous

Secondary Efficacy Results

Gadolinium-Enhancing Lesions

Though the study was not powered for efficacy outcomes, one of the secondary radiologic efficacy endpoints was the total number of gadolinium-enhancing lesions on brain MRI at Weeks 8 and 24. The "Efficacy-Evaluable – MRI" population included subjects who had an MRI and received at least one infusion or injection (partial or complete) of study drug during the Controlled Period, which was identical to the Safety Population (SC OCR n=118; IV OCR n=118). Refer to Table 13 for a summary of baseline gadolinium-enhancing lesions per treatment group. Although slightly higher in the IV OCR group, the total number of gadolinium-enhancing lesions at Weeks 8 and 24 was similar between the groups and was low overall (see Table 18).

Gadolinium-enhancing lesions were identified in subjects with RMS, but not in those with PPMS.

The total number of gadolinium-enhancing lesions at Week 8 was 17 in the SC OCR group and 24 in the IV OCR group. The mean (standard deviation (SD)) total number of gadolinium-enhancing lesions was 0.15 (0.45) for the SC OCR group and 0.21 (0.98) for the IV OCR group. At Week 24, the total number of gadolinium-enhancing lesions was two in the SC OCR group and zero in the IV OCR group; the mean (SD) total number of gadolinium-enhancing lesions was 0.03 (0.18) in the SC OCR group, and no lesions were seen in the IV OCR group. Unadjusted lesion rates (total number of lesions/number of subjects with a readable MRI) were provided by the Applicant and were reproduced as part of this BLA review. The Applicant's adjusted lesion rates yielded similar results, indicating no clinically significant difference in the total number of gadolinium-enhancing lesions between the SC OCR and IV OCR groups.

Table 18. Gadolinium-Enhancing Lesions, Efficacy-Evaluable. MRI Population, Study CN42097

Lesion Parameter	SC OCR N=118	IV OCR N=118
Total # of gadolinium-enhancing lesions at Week 8		
n	112	112
Total number of lesions detected	17	24
Unadjusted lesion rate	0.15	0.21
Mean (SD)	0.15 (0.45)	0.21 (0.98)
Median	0	0
Min, max	0, 2	0, 9
Total # gadolinium-enhancing lesions at Week 24		
n	61	65
Total number of lesions detected	2	0
Unadjusted lesion rate	0.03	0.0
Mean (SD)	0.03 (0.18)	0.00 (0.00)
Median	0	0
Min, max	0, 1	0, 0

Source: Study CN42097, ADMRI, where EMRIFL = Y, PARAMCD = GADELSC by TRT01A (VISIT = WEEK 8 and WEEK 24)
Abbreviations: IV, intravenous; MRI, magnetic resonance imaging; N, number of subjects in treatment arm; n, number of subjects with readable MRI; OCR, ocrelizumab; SC, subcutaneous; SD, standard deviation

New or Enlarging T2 Lesions

Though the study was not powered for efficacy outcomes, another secondary radiologic efficacy endpoint was the total number of new or enlarging T2 lesions on brain MRI at Weeks 12 and 24, compared to the prior scan. Analysis of this endpoint was performed in the Efficacy-Evaluable – MRI population, described above (Table 18). Refer to Table 13 for a summary of baseline T2 lesion count per treatment group. Overall, the number of new or enlarging T2 lesions, compared to the prior scan, was low in both groups (see Table 19).

The total number of new or enlarging T2 lesions at Week 12 was 6 in the SC OCR group and 7 in the IV OCR group. The mean (SD) total number of T2 lesions was 0.05 (0.3) for the SC OCR group and 0.06 (0.4) for the IV OCR group. At Week 24, the total number of T2 lesions was 2 in the SC OCR group and 0 in the IV OCR group; the mean (SD) total number of T2 lesions was 0.03 (0.2) in the SC OCR group, and no lesions were seen in the IV OCR group. Additionally, no new or enlarging T2 lesions were identified in subjects with PPMS at 12 or 24 weeks. Unadjusted lesion rates (total number of lesions/number of subjects with a readable MRI) were provided by the Applicant and were reproduced as part of this BLA review. The Applicant's

adjusted lesion rates yielded similar results, indicating no clinically significant difference in the total number of new or enlarging T2-weighted MRI lesions between the SC OCR and IV OCR groups.

Table 19. Number of New or Enlarging T2-Weighted MRI Lesions, Efficacy-Evaluable, MRI Population, Study CN42097

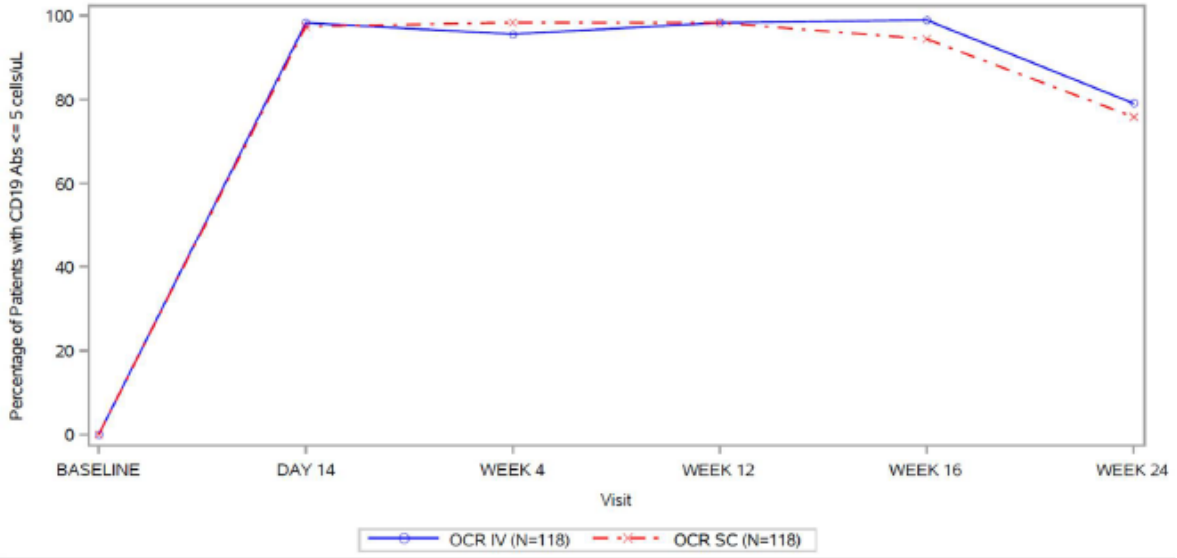
Lesion Parameter	SC OCR N=118	IV OCR N=118
New or enlarging T2 lesions at Week 12		
n	116	116
Total number of new or enlarging T2 lesions	6	7
Unadjusted lesion rate	0.05	0.06
Mean (SD)	0.05 (0.3)	0.06 (0.4)
Median	0	0
Min, max	0, 2	0, 3
New or enlarging T2 lesions at Week 24		
n	61	65
Total number of new or enlarging T2 lesions	2	0
Unadjusted lesion rate	0.03	0.0
Mean (SD)	0.03 (0.2)	0.00 (0.00)
Median	0	0
Min, max	0, 1	0, 0

Source: Study CN42097, ADMRI, where EMRIFL = Y, PARAMCD = NEWT2 by TRT01A (VISIT = WEEK 12 and WEEK 24)
Abbreviations: IV, intravenous; MRI, magnetic resonance imaging; N, number of subjects in treatment arm; n, number of subjects with readable MRI; OCR, ocrelizumab; SC, subcutaneous; SD, standard deviation

Pharmacodynamic Results

The B-cell count in blood was measured using flow cytometry and CD19 expression. Ocrelizumab binds to CD20, and its presence at receptors interferes with measurement of the B-cell count using the surface antigen CD20 itself. Therefore, expression of CD19, which has overlapping expression profiles with that of CD20, was used to quantitate B-cells. The proportion of subjects with B-cell depletion over time is presented in Figure 3.

Figure 3. Proportion of Subjects With CD19 Abs Results Below or Equal to 5 cells/μL Over Time by Visit During Controlled Period



Abs = Absolute Value.
Baseline: the last assessment before the first exposure.
Only scheduled visit results contribute to the results summary.
For one patient in the SC arm, the sample was collected both at baseline and at 'Day 1' visit.
The 'Day 1' visit assessment has been removed from the plot for this patient.

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/
g_lb_propn_cdl9.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/
g_lb_propn_cdl9_CP_SEALL.pdf
31JUL2023 10:08

Source: Clinical Study Report for Study CN42097. Page 124, Figure 6.
Abbreviations: IV, intravenous; OCR, ocrelizumab; SC, subcutaneous

6.3. Key Efficacy Review Issues

6.3.1. Demonstration of PK Noninferiority to IV Ocrelizumab

Issue

In order to rely upon the established effectiveness of IV OCR, the results of Study CN42097 would need to demonstrate that ocrelizumab 920 mg SC dose results in noninferior exposures compared to the ocrelizumab 600 mg (2 × 300 mg given two weeks apart) IV dose.

Background

Ocrelizumab 600 mg for IV infusion (Ocrevus) was approved on March 28, 2017, for the treatment of RMS and PPMS in adults. The approved dose of ocrelizumab 600 mg IV is administered every 6 months. The initial 600-mg dose is administered as two separate IV infusions, i.e., a 300-mg infusion followed 2 weeks later by a second 300-mg infusion. Subsequent doses of ocrelizumab IV are administered as a single 600-mg IV infusion every 6 months.

The Applicant developed a subcutaneous (SC) formulation of ocrelizumab containing recombinant human hyaluronidase (rHuPH20), which they claim acts as a permeation enhancer. The SC route of administration of ocrelizumab would provide an additional delivery option to accommodate the individual needs of patients and healthcare professionals.

Study CN41144 (OCARINA I) assessed initial safety and tolerability of ocrelizumab SC and determined the bioavailability of ocrelizumab after SC injection. Study results showed that a 920 mg SC dose would provide PK exposures comparable to the exposures after 600 mg IV OCR given as 2 doses of 300 mg 2 weeks apart.

Study CN42097 (OCARINA II) was conducted to demonstrate noninferiority in exposures following the 920-mg SC dose relative to exposures following 600-mg IV dose (2 doses of 300 mg 2 weeks apart). Study CN41144 data suggested that the absorption of ocrelizumab will be completed within 12 weeks post-SC-injection, and AUC up to Week 12 was considered representative of the overall ocrelizumab exposure over the 6-month dosing interval, AUC over the first 24 weeks (AUC_{W1-12} is >90% of the area under the ocrelizumab serum concentration time curve over 24 weeks postdose). Therefore, ocrelizumab AUC_{W1-12} was selected as the primary endpoint for the PK bridging in Study CN42097. The maximum plasma concentration is presented as the secondary PK endpoint. Serum $CD19^+$ B-cell count served as the PD parameter, and immunogenicity was assessed.

Assessment

The Clinical Pharmacology review team independently verified the Applicant's results and agrees with the following conclusions of the Applicant:

- Study CN42097 demonstrated noninferiority in exposures (geometric mean ratio for AUC_{W1-12} was 1.285, with 90% CI interval: 1.2258 to 1.3473) following 920 mg ocrelizumab SC relative to exposures following 600 mg ocrelizumab IV (2 × 300 mg infusions given 2 weeks apart).
- Ocrelizumab SC administration led to a rapid and sustained depletion of $CD19^+$ B-cells in blood, consistent with the trends observed following ocrelizumab IV administration.
- No subjects had treatment-emergent ADAs to ocrelizumab or rHuPH20 in Study CN42097.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical studies conducted to support clinical development of Ocrevus Zunovo consisted of local toxicity assessments in rat and minipig. Drug-related toxicity in both rat and minipig consisted of minimal to mild perivascular infiltrate, fibroplasia, and edema. The potential for systemic toxicity was reviewed under BLAs 761053 (ocrelizumab) and 021859 (hyaluronidase).

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 the IV form (ocrelizumab [Ocrevus] injection, BLA 761053) described in current approved labeling for OCR IV include infusion reactions, infections (including serious infections), PML, reduction in immunoglobulins, malignancies (including breast cancer), and immune-mediated colitis. These safety concerns are further described in Section 7.7 of this review.

In clinical trials of OCR IV, the most common adverse reactions that occurred in ≥10% of subjects treated with OCR IV for RMS, and at a higher frequency than reported for Rebif, included upper respiratory tract infections and infusion reactions. The most common adverse reactions that occurred in ≥10% of subjects treated with OCR IV 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.

Hyaluronidase human injection (Hylenex recombinant, BLA 021859) is a glycosylated single-chain protein produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase is a tissue permeability modifier that temporarily degrades hyaluronan and is used to increase the dispersion and absorption of subcutaneously administered drug solutions. The known risks associated with hyaluronidase, discussed in current approved labeling of Hylenex recombinant (Halozyme 2024), include spread of localized infection, ocular damage (if applied directly to cornea), and enzyme inactivation with IV administration. Allergic and anaphylactic-like reactions have been reported but have been rare.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

OCR IV was approved on March 28, 2017, under BLA 761053. As of March 27, 2023, OCR IV has been approved in over 100 countries worldwide. Since approval, and until March 31, 2023, the estimated cumulative postmarket exposure to OCR IV 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 OCR IV were identified by the Applicant.

OCR SC is not approved in the U.S. market or in any foreign market; therefore, no postmarketing experience is available for OCR SC.

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 OCR IV include immune-mediated colitis, 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 OCR IV. Refer to Section 7.7 of this review for a discussion of key review safety issues.

Adverse reactions have also been identified during postapproval use of hyaluronidase products. According to current approved labeling for Hylenex recombinant, the most frequently reported postmarketing adverse reactions have been mild local injection site reactions such as erythema and pain (Halozyme 2024). Additionally, hyaluronidase has been reported to enhance the adverse reactions associated with coadministered drug products. Edema has been reported most frequently in association with subcutaneous fluid administration. Allergic reactions (urticaria or angioedema) have been reported in less than 0.1% of subjects receiving hyaluronidase. Anaphylactic-like reactions following retrobulbar block or IV injections have occurred, rarely.

7.3.2. Expectations on Safety

The Clinical review team expects OCR SC will have a similar safety profile to that of OCR IV. However, it is expected that local injection-related reactions and injection site reactions will occur at a higher frequency with OCR SC given its route of administration. Infusion-related reactions are not expected with OCR SC; however, systemic postinjection reactions are likely to occur.

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 using JMP software. Additional analyses were provided by the Clinical Data Scientist support team. 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 BLA. 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 CN41144 and CN42097 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).

However, the protocols for Studies CN41144 and CN42097 did not direct investigators to capture comprehensive information for injection-related reactions. Refer to further discussion in Section 7.7.1.

Data from the ongoing Phase 3, randomized, open-label, parallel-group, active-control Study CN42097 formed the basis of the clinical safety evaluation. Data from the ongoing Phase 1, randomized, open-label, dose-escalation, and dose continuation Study CN41144 provided some supportive evidence of safety. A summary of the study designs can be found in Section 6 and Section 15.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of OCR SC for the proposed indications, patient populations, dosage regimen, and duration. When considered in conjunction with the safety data for OCR IV, the safety database for OCR SC data meets the sample size requirements outlined in the International Conference on Harmonisation E1A Guidance for chronically administered medications for non-life-threatening conditions (March 1995). Per this 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 safety database for SC OCR is presented in Table 20. At the time of BLA data cutoff, 312 subjects had been exposed to at least 1 dose of SC OCR 920 mg or 1200 mg. Note that subjects in Study CN41144 could have received multiple different doses of SC OCR, and therefore the rows of this table are not mutually exclusive. As of the data cutoff for the 120-Day Safety Update (November 15, 2023, and December 4, 2023, for Studies CN41114 and CN42097, respectively), 364 subjects had been exposed to at least one dose of SC OCR 920 mg or 1200 mg.

The initial IV OCR BLA included a safety database of 2147 subjects (4485 PY of exposure), with data pooled from several studies involving subjects with RMS and PPMS. Additionally, since approval (March 28, 2017) and until March 31, 2023, the estimated cumulative postmarket exposure to IV OCR is (b) (4) patients (corresponding to (b) (4) PY of exposure). Therefore, given the establishment of comparable PK with IV OCR, the safety of SC OCR is also supported by safety data collected during the IV OCR development program and postmarketing experience.

Table 20. Duration of Exposure, Safety Population, Pooled Analyses, Studies CN42097 and CN41144

	Number of Subjects Exposed to SC Ocrelizumab				
Dosage*	**≥1 Dose**	**≥6 Months**	**≥12 Months**	**≥18 Months**	**≥24 Months**
Proposed dosing regimen (920 mg)	N=299	N=172	N=7	N=5	N=0
Other dosing regimens (40 mg)	N=7	N=0	N=0	N=0	N=0
Other dosing regimens (200 mg)	N=7	N=0	N=0	N=0	N=0
Other dosing regimens (600 mg)	N=7	N=1	N=0	N=0	N=0
Other dosing regimens (1200 mg)	N=125	N=109	N=75	N=45	N=7
Other dosing regimens (total)	N=126	N=109	N=76	N=51	N=21

Source: Applicant's response to Information Request, dated 2/6/2024.
* Subjects can be counted in multiple dosage categories.
Abbreviations: N, number of subjects with given treatment duration; SC, subcutaneous

7.6. Safety Results

7.6.1. Safety Results, Studies CN42097 and CN41144

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Studies CN42097 and CN41144

Study CN42097

Treatment-emergent adverse events (TEAEs) that occurred during the Controlled Period of the ongoing Phase 3 Study CN42091 are shown in Table 21. A higher proportion of subjects (73.7%) in the SC OCR group experienced TEAEs compared to subjects in the IV OCR group (45.8%). However, TEAEs in the SC OCR group were more frequently of mild severity (40.7%) compared to the IV OCR group, which had a higher frequency of TEAEs of moderate severity (27.1%). There were no serious adverse events (SAEs) that were life-threatening or had a fatal outcome in either treatment group. The number of SAEs requiring hospitalization appeared to be balanced between the groups. Additionally, 6.8% of subjects in the IV OCR group experienced TEAEs leading to dose modification of study drug, while none of these events occurred in the SC OCR group.

Table 21. Overview of Treatment-Emergent Adverse Events, Safety Population, Study CN42097, Controlled Period (Weeks 0 to 24)

Event Category	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Any TEAE	87 (73.7)	54 (45.8)	28.0 (15.6, 39.5)*
Severe or worse	4 (3.4)	7 (5.9)	-2.5 (-8.8, 3.3)
Moderate	35 (29.7)	32 (27.1)	2.5 (-9.0, 14.0)
Mild	48 (40.7)	15 (12.7)	28.0 (17.0, 38.5)*
SAE	3 (2.5)	4 (3.4)	-0.8 (-6.2, 4.3)
SAEs with fatal outcome	0	0	0.0 (-3.2, 3.2)
Life-threatening SAEs	0	0	0.0 (-3.2, 3.2)
SAEs requiring hospitalization	3 (2.5)	4 (3.4)	-0.8 (-6.2, 4.3)
TEAE leading to permanent discontinuation of study drug	0	0	0.0 (-3.2, 3.2)
TEAE leading to dose modification of study drug	0	8 (6.8)	-6.8 (-12.8, -3.5)*
TEAE leading to interruption of study drug	0	4 (3.4)	-3.4 (-8.4, -0.2)*
TEAE leading to reduction of study drug	0	4 (3.4)	-3.4 (-8.4, -0.2)*
TEAE leading to dose delay of study drug	0	0	0.0 (-3.2, 3.2)

Source: adae.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with at least one event; OCR, ocrelizumab; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event

120-Day Safety Update

The 120-Day Safety Update for Study CN42097 had a data cutoff date of December 4, 2023. TEAEs that occurred in subjects who received at least one dose of SC OCR were analyzed as part of the 120-Day Safety Update, and subjects who received SC OCR during the Controlled Period and continued to receive SC OCR during the SC Treatment Period (SC/SC arm) were

compared to subjects who received IV OCR during the Controlled Period and were subsequently switched to SC OCR during the SC Treatment Period (IV/SC arm). Therefore, this analysis included TEAEs that occurred during the Controlled Period, the SC OCR Treatment Period (Treatment Period), and the Safety Follow-Up Period. Overall, the safety data contained in the 120-Day Safety update was consistent with that included in the BLA.

Study CN41144

An overview of TEAEs that occurred during Study CN41144 is shown in Table 22. Of note, the safety analyses of Study CN41144 focused on subjects who received at least one dose of SC OCR 920 mg (the target dose). However, some of these subjects could have also received other dosing regimens, including SC OCR 1200 mg and/or IV OCR, over the course of the study. Due to significant subject overlap, safety data for subjects who received at least one dose of SC OCR 1200 mg at any point during the study will only be discussed when substantially different from those reported for subjects who received at least one dose of SC OCR 920 mg at any point during the study. Therefore, the safety data of Study CN41144 should be interpreted in the setting of those limitations.

Overall, a higher proportion of OCR-naive subjects (Group B, 82.1%) treated with SC OCR 920 mg experienced TEAEs, when compared to subjects previously treated with ocrelizumab (Group A, 78.5%). However, most of the subjects who had TEAEs in the OCR-naive group (Group B) experienced mild events (46.2%), while most of those who had TEAEs in the previously treated group (Group A) experienced events of moderate severity (41.8%).

In subjects who received at least one dose of SC OCR 920 mg, the frequency of SAEs appeared to be similar between Groups A and B, and there were no SAEs that were life-threatening or had a fatal outcome. Additionally, a higher proportion of subjects in the OCR-naive group (Group B) who received at least one dose of SC OCR 920 mg (10.3%) experienced TEAEs leading to interruption of study drug (versus 0% in Group A).

Of note, when compared to OCR-naive subjects (4.4%, Group B), a higher proportion of subjects previously treated with ocrelizumab (12.5%, Group A) who received at least one dose of SC OCR 1200 mg at any point during the study experienced SAEs, including one event that resulted in a fatal outcome. Refer to Section 7.6.1.2 for additional details.

Table 22. Overview of Treatment-Emergent Adverse Events, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
Event Category	**Group A N=79 n (%)**	**Group B N=39 n (%)**	**Group A N=80 n (%)**	**Group B N=45 n (%)**
Any TEAE	62 (78.5)	32 (82.1)	73 (91.2)	44 (97.8)
Severe and worse	6 (7.6)	4 (10.3)	14 (17.5)	9 (20.0)
Moderate	33 (41.8)	10 (25.6)	39 (48.8)	19 (42.2)
Mild	23 (29.1)	18 (46.2)	20 (25.0)	16 (35.6)
SAE	2 (2.5)	2 (5.1)	10 (12.5)	2 (4.4)
SAEs with fatal outcome	0	0	1 (1.2)	0
Life-threatening SAEs	0	0	0	0
SAEs requiring hospitalization	2 (2.5)	1 (2.6)	10 (12.5)	1 (2.2)
SAEs resulting in substantial disruption of normal life functions	0	0	1 (1.2)	0
Other	1 (1.3)	1 (2.6)	0	1 (2.2)
TEAE leading to permanent discontinuation of study drug	0	1 (2.6)	0	1 (2.2)
TEAE leading to dose modification of study drug	0	4 (10.3)	2 (2.5)	1 (2.2)
TEAE leading to interruption of study drug	0	4 (10.3)	2 (2.5)	1 (2.2)
TEAE leading to reduction of study drug	0	0	0	0
TEAE leading to dose delay of study drug	0	0	0	0

Source: adae.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during Study CN41144.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during Study CN41144, either in the dose escalation phase or in the dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Duration is up to 3 years.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with at least one event; OCR, ocrelizumab; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event

120-Day Safety Update

The 120-Day Safety Update for Study CN41144 had a data cutoff of November 15, 2023, and focused on the analysis of TEAEs that occurred in subjects who received at least one dose of SC OCR 920 mg. Overall, the safety data contained in the 120-Day Safety update was consistent with that included in the BLA.

7.6.1.2. Deaths, Studies CN42097 and CN41144

There were no deaths reported in Study CN42097, either in the original BLA submission or in the 120-Day Safety Update. However, two deaths occurred in Study CN41144. One death occurred during the Dose Escalation Phase in a subject previously treated with ocrelizumab who received at least one dose of SC OCR 1200 mg (Cohort A5) and experienced COVID-19 pneumonia. See Table 23. The second death occurred during the Dose Escalation Phase in a subject previously treated with ocrelizumab who received one dose of IV OCR 600 mg (Cohort AA) and experienced cerebral infarction. Note that only one death is listed in Table 23, as the second subject did not receive treatment with SC OCR.

Table 23. Deaths, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
Preferred Term	Group A N=79 n (%)	Group B N=39 n (%)	Group A N=80 n (%)	Group B N=45 n (%)
Any TEAE leading to death	0	0	1 (1.2)	0
COVID-19 pneumonia	0	0	1 (1.2)	0

Source: adae.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during Study CN41144.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during Study CN41144, either in the dose escalation phase or in the dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Duration is up to 3 years.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous; TEAE, treatment-emergent adverse event

The two reported deaths in the SC OCR development program are discussed below:

Subject (b) (6)

Subject (b) (6) was a 56-year-old man with history of hypercholesterolemia, unspecified headache, "left eye blindness," erectile dysfunction, and prior tobacco use receiving SC OCR 1200 mg who experienced the SAE **COVID-19 pneumonia** and died on Study Day 422. He received SC OCR 1200 mg on Study Days 1, 170, and 338.

He developed fever (body temperature not specified) and sore throat on Study Day 404 and was therefore started on treatment with azithromycin (dosing regimen not specified). He then experienced symptom worsening and shortness of breath on Study Day 412, which prompted an emergency department visit on the same day. A COVID-19 PCR test was performed, which was positive. He was diagnosed with "COVID 19 pneumonia" (Grade 2), which led to hospitalization. He received treatment with salbutamol, fluticasone, enoxaparin, dexamethasone, and remdesivir (dosing regimen not specified). Of note, the subject had been vaccinated against COVID-19 on Study Day 110 (Janssen COVID-19 vaccine) and Study Day 354 (Pfizer COVID-19 vaccine). The subject's immune response to vaccination administration was not evaluated.

On Study Day 414, a chest X-ray demonstrated "widespread bilateral infiltrates" and a CT scan revealed "extensive ground glass opacities." "Abnormal right kidney function" was noted on Study Day 419 (details unknown). Additionally, the subject was admitted to the Intensive Care Unit, intubated, and mechanically ventilated. A chest X-ray was repeated on Study Day 421, which revealed a "small pneumothorax on the right side." The subject's condition further deteriorated, and he developed oliguria requiring renal replacement therapy. Per his family's wishes, he was switched to a "do not resuscitate" status. The subject died on Study Day 422 due to COVID-19 pneumonia complicated by pneumothorax and renal failure. The investigator assessed this AE as unrelated to treatment with SC OCR.

Discussion: This SAE of COVID-19 pneumonia leading to death appears related to long-term treatment with OCR, in the setting of treatment with IV OCR prior to study enrollment and the COVID-19 public health emergency that was ongoing at the time of study conduct. Additionally, this subject had decreased serum IgM levels to <0.20 g/L prior to enrolling in Study CN41144.

This subject's serum IgM (but not IgG) levels remained low throughout the duration of his study participation. Current approved labeling for IV OCR (Ocrevus) includes a warning for serious (including life-threatening and fatal) infections with IV OCR treatment, where ocrelizumab interference with the effectiveness of non-live vaccines is also discussed (Genentech 2024).

Subject (b) (6)

Subject (b) (6) was a 51-year-old man with RMS, obesity, type 2 diabetes (reportedly poorly controlled), hypertension, congestive heart failure, obstructive sleep apnea, carpal tunnel syndrome, "bariatric sleeve surgery," and cholecystectomy receiving IV OCR 600 mg who experienced the SAE cerebral infarction and died on Study Day 192. He received IV OCR 600 mg on Study Day 1.

He experienced aphasia and a "suspected seizure" on Study Day 159. Additionally, he experienced right face, arm, and leg weakness. The subject was unable to "look to the left side." His NIH Stroke Scale score was reported as 26. "CT-scan of head and neck showed left common carotid and left internal carotid artery occlusion with left middle cerebral artery syndrome." He was diagnosed with cerebral infarction (Grade 4) and was treated with alteplase and intracranial thrombectomy with carotid stent placement.

On Study Day 162, the subject underwent decompressive hemicraniectomy due to cerebral edema in the setting of middle cerebral artery infarction and was placed on a ventilator (Glasgow Coma Scale score unknown). He then underwent tracheotomy and open gastrotomy tube placement on Study Day 165. On Study Day 169, he underwent another CT scan of the head, but results were not provided. The subject was transferred to a long-term care facility for ventilator wean on Study Day 190. He died on Study Day 192, reportedly due to aspiration from cerebral infarction. It is unclear if autopsy was performed. The investigator assessed this AE as unrelated to treatment with SC OCR.

Discussion: It appears that this SAE of cerebral infarction with fatal outcome is unrelated to treatment with SC OCR. Per the reported past medical history, this subject had several comorbidities and risk factors that placed him at high risk for developing a stroke. Additionally, this subject was treated with IV OCR, but not with SC OCR. There is no labeled risk of stroke for IV OCR, and there is no known nor suspected mechanism to explain how OCR might confer an increased risk of stroke.

120-Day Safety Update

No additional deaths were reported in the 120-Day Safety Update for Study CN411144.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Studies CN42097 and CN41144

Study CN42097

Treatment-emergent SAEs in Study CN42097 are summarized by system organ class (SOC) and PT in Table 24 and by SOC and Food and Drug Administration Medical Dictionary for Regulatory Activities query (FMQ) in Table 25.

Table 24. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study CN42097, Controlled Period

System Organ Class Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Any SAE	3 (2.5)	4 (3.4)	-0.8 (-6.2, 4.3)
Eye disorders (SOC)	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Eye pain	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Infections and infestations (SOC)	0 (0.0)	4 (3.4)	-3.4 (-8.4, -0.2)*
Appendicitis	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Cellulitis staphylococcal	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Pneumonia	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Subcutaneous abscess	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Upper respiratory tract infection	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Metabolism and nutrition disorders (SOC)	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Diabetes mellitus	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Nervous system disorders (SOC)	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Multiple sclerosis pseudo relapse	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Multiple sclerosis relapse	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Psychiatric disorders (SOC)	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Anxiety	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)

Source: adae.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class

Overall, the proportion of subjects who experienced SAEs was balanced between the groups; however, a higher proportion of subjects in the IV OCR arm experienced SAEs with PTs within the SOC Infections and Infestations (3.4% versus 0%).

Table 25. Subjects With Serious Adverse Events by System Organ Class and FDA Medical Query, Safety Population, Study CN42097, Controlled Period

System Organ Class FMQ (Narrow)	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Endocrine disorders (SOC)			
Hyperglycemia	0	1 (0.8)	-0.8 (-4.7, 2.3)
Infections and infestations (SOC)			
Nasopharyngitis	0	1 (0.8)	-0.8 (-4.7, 2.3)
Pneumonia	0	1 (0.8)	-0.8 (-4.7, 2.3)
Purulent material	0	1 (0.8)	-0.8 (-4.7, 2.3)
Bacterial infection	0	2 (1.7)	-1.7 (-6.0, 1.5)
Psychiatric disorders (SOC)			
Anxiety	1 (0.8)	0	0.8 (-2.3, 4.7)

Source: adae.xpt; Software: R.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; PT, preferred term; SC, subcutaneous; SOC, system organ class

Selected narratives for subjects treated with SC OCR are discussed below:

Subject (b) (6)

Subject (b) (6) (a 24-year-old woman receiving SC OCR) experienced the SAE eye pain (Grade 3) on Study Day 60 through Study Day 62. She began treatment with SC OCR on Study Day 1 and received a second SC OCR injection on Study Day 169 (after the SAE). Her medical history included depression, anxiety, migraine, muscle spasticity, blurred vision, and cataract.

She underwent vitrectomy on Study Day 55 due to decreased vision (additional details were not provided). She was hospitalized on Study Day 60 due to experiencing eye pressure and eye pain. She received docusate sodium (unknown dosing regimen) to prevent constipation that could lead to Valsalva maneuver leading to eye straining during bowel movements. She was discharged from the hospital on Study Day 61 and received treatment with butalbital/caffeine/paracetamol (unknown dosing regimen) for headache. The event of eye pain resolved on Study Day 62. The investigator assessed the event as unrelated to treatment with SC OCR.

Discussion: This event of eye pain in a subject receiving SC OCR is consistent with a postsurgical complication and appears unrelated to SC OCR administration. However, the indication for the vitrectomy was not reported, so there can be no assessment of whether SC OCR contributed to the etiology of the ocular disorder that the surgery intended to correct.

Subject (b) (6)

Subject (b) (6) (a 37-year-old woman receiving SC OCR) experienced the SAEs MS pseudo-relapse (Grade 2) and anxiety (Grade 2) on Study Days 99 (through Study Day 106) and 109 (through Study Day 111), respectively. She began treatment with SC OCR on Study Day 1 and received a second SC OCR injection on Study Day 173 (after the SAEs). Her medical history included migraine, anxiety, drug hypersensitivity (hydrocodone), vitamin D deficiency, fibromyalgia, ovarian cyst, ligament rupture (unspecified), bilateral ankle repair, and oophorectomy.

She was diagnosed with MS pseudorelapse on Study Day 99. Additional details regarding symptoms and diagnostic evaluation were not provided. She presented to the emergency department on Study Day 103 due to experiencing chest pain, shortness of breath, and “Grade 2 influenza.” “All cardiac and respiratory work up was negative” and her symptoms were attributed to her history of anxiety and migraine. She received treatment with lorazepam, alprazolam, paracetamol, prochlorperazine, and diphenhydramine (dosing regimen not specified).

On Study Day 104, she presented again to the emergency department with similar symptoms and was hospitalized due to MS pseudorelapse, thought to be secondary to influenza infection. She received treatment with methylprednisolone 1000 mg IV daily for 3 days. A test for influenza A was positive on Study Day 105. She was discharged from the hospital on Study Day 106.

The subject returned to the hospital on Study Day 109 with similar symptoms, which were thought to be secondary to anxiety and she was again hospitalized. She received treatment with hydroxyzine (unknown dosing regimen). Laboratory evaluations, electrocardiograms, EEG, chest X-ray, and CT scan of the head were reportedly normal. MRI of the brain, cervical, and thoracic spine did not demonstrate any abnormalities that could be consistent with new MS lesions. The event resolved on Day 111, and she was discharged from the hospital. The investigator assessed the events as unrelated to treatment with SC OCR.

Discussion: These events of MS pseudorelapse secondary to influenza infection and anxiety in a subject receiving SC OCR appear to unrelated to SC OCR administration. The influenza infection experienced by this subject could potentially be related to treatment with SC OCR; however, this is unlikely given the short treatment duration at the time of SAE occurrence and this subject's relatively normal WBC count, ALC, ANC, and immunoglobulin levels from Study Day -21 to Study Day 159. Current approved labeling for IV OCR (Ocrevus) includes a warning for serious (including life-threatening and fatal) infections with ocrelizumab treatment (Genentech 2024).

120-Day Safety Update

Per the Applicant's analyses, the proportion of subjects who experienced at least one SAE during the Treatment or Safety Follow-Up Period was lower in the SC/SC arm (n=3 [2.5%]) compared to the IV/SC arm (n=7 [5.9%]). In addition to the SAEs that occurred prior to the BLA submission data cutoff (discussed above), additional SAEs experienced by subjects in the SC/SC arm (n=1 [0.8%] each) included MS pseudorelapse and intentional self-injury. Additional SAEs experienced by subjects in the IV/SC arm (n=1 [0.8%] each) included urinary tract infection, leukopenia, neutropenia, pyrexia, and hemorrhagic ovarian cyst.

Study CN41144

Treatment-emergent SAEs in Study CN42097 are summarized by SOC and PT in Table 26. Refer to Section 7.7.4 for further discussion of the higher frequency of SAEs within the SOC Infections and Infestations (particularly of COVID-19 infection-related SAEs) seen in Group A subjects (compared to Group B subjects) who received at least one 1 dose of SC OCR 1200 mg, and in subjects who received at least one dose of SC OCR 1200 mg (compared to those who received at least one dose of SC OCR 920 mg).

Table 26. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
System Organ Class Preferred Term	Group A N=79 n (%)	Group B N=39 n (%)	Group A N=80 n (%)	Group B N=45 n (%)
Any SAE	2 (2.5)	2 (5.1)	10 (12.5)	2 (4.4)
General disorders and administration site conditions (SOC)	0	0	1 (1.2)	0
Asthenia	0	0	1 (1.2)	0
Infections and infestations (SOC)	2 (2.5)	0	10 (12.5)	1 (2.2)
COVID-19	1 (1.3)	0	4 (5.0)	0
COVID-19 pneumonia	1 (1.3)	0	3 (3.8)	1 (2.2)
Pneumonia	1 (1.3)	0	3 (3.8)	0
Encephalitis	0	0	1 (1.2)	0
Musculoskeletal and connective tissue disorders (SOC)	0	0	1 (1.2)	0
Muscular weakness	0	0	1 (1.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	1 (2.6)	0	0
Papillary thyroid cancer	0	1 (2.6)	0	0
Nervous system disorders (SOC)	0	0	1 (1.2)	1 (2.2)
Multiple sclerosis relapse	0	0	1 (1.2)	1 (2.2)

System Organ Class Preferred Term	SC OCR 920 mg Group A N=79 n (%)	SC OCR 920 mg Group B N=39 n (%)	SC OCR 1200 mg Group A N=80 n (%)	SC OCR 1200 mg Group B N=45 n (%)
Renal and urinary disorders (SOC)	0	1 (2.6)	0	0
Nephrolithiasis	0	1 (2.6)	0	0
Respiratory, thoracic and mediastinal disorders (SOC)	0	0	1 (1.2)	0
Acute respiratory failure	0	0	1 (1.2)	0
Pulmonary embolism	0	0	1 (1.2)	0

Source: adae.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during Study CN41144.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during Study CN41144, either in the dose escalation phase or in the dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Duration is up to 3 years.
Abbreviations: incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class

Selected narratives are discussed below:

Subject (b) (6)

Subject (b) (6) (a 47-year-old woman previously treated with IV OCR who received SC OCR 1200 mg on Study Days 1, 164, 329, 497, 730, 891, and 1080) experienced the SAEs COVID-19 pneumonia (Grade 2, Study Day 702), acute respiratory failure (Grade 2, Study Day 702), and pulmonary embolism (Grade 3, Study Day 767). Her medical history included vitamin B12 deficiency, anemia, peripheral edema ophthalmoplegia, spasticity, gastroesophageal reflux disease, hypokalemia, and anxiety. She received her first and second doses of SARS-CoV-2 vaccine (Moderna) on Study Days 14 and 595, respectively.

The subject presented to the emergency department on Study Day 695 with lower extremity weakness and back pain. Her laboratory evaluations (complete blood count [CBC] and comprehensive metabolic panel [CMP]) were reportedly only remarkable for hypokalemia (potassium 2.8 [units and reference range not provided]), which had been ongoing since Study Day 688. Her erythrocyte sedimentation rate and C-reactive protein (CRP) were found to be elevated at 107 and 6.1, respectively (units and reference range not provided). She was hospitalized with a diagnosis of MS relapse. MRI of the brain and cervical and thoracic spine did not reveal new or enhancing lesions. She was treated with prednisone, acetaminophen/hydrocodone, and potassium (unknown dosing regimen). The subject was discharged home with a prednisone taper (unknown dosing regimen) on Study Day 697. The event of MS relapse was considered resolved on Study Day 722. The investigator assessed the event as unrelated to treatment with SC OCR.

On Study Day 702, the subject was again hospitalized due to a 2-day history of shortness of breath that worsened on exertion and a positive COVID-19 test (unspecified). She was diagnosed with COVID-19 pneumonia (Grade 2) and acute respiratory failure (Grade 2). Upon hospital admission, an arterial blood gas showed a pH of 7.45 and oxygen saturation of 92%. She was also diagnosed with SARS-CoV-2 sepsis (Grade 3, nonserious). Of note, her son had been recently diagnosed with COVID-19 infection. An electrocardiogram demonstrated sinus tachycardia and a chest CT revealed a “fairly extensive pattern of diffuse ground glass and

interstitial infiltrates." She received treatment with O_2 at 3L via nasal cannula and dexamethasone. She was discharged home on Study Day 714 and the event was considered resolved on that day. The investigator assessed the events as unrelated to treatment with SC OCR.

Discussion: These SAEs in a subject previously treated with IV OCR for at least 1 year prior to study enrollment appear to be related to long-term treatment with OCR, in the setting of the COVID-19 public health emergency that was ongoing at the time of study conduct, and the known risks of ocrelizumab. Except for an ALC of 0.84×10^9/L (reference range 0.85 to 3.9×10^9/L) on Study Day 29 and a serum IgM ranging from 0.21 to 0.43 g/L over the course of the study, this subject's serum IgG, IgA, ANC, and total WBC count remained within the reference range of normal throughout Study Day 1080. However, current approved labeling for IV OCR (Ocrevus) includes a warning for serious (including life-threatening and fatal) infections with ocrelizumab treatment, where ocrelizumab interference with the effectiveness of non-live vaccines is also discussed (Genentech 2024).

The subject experienced dyspnea on Study Day 767. She received an outpatient diagnosis of deep vein thrombosis (Grade 3, nonserious) but presented to the emergency department due to worsening dyspnea. CT angiogram of the chest, troponin, prothrombin time, and additional laboratory evaluations (unspecified) were performed (results not provided). She was diagnosed with pulmonary embolism (Grade 3, serious) and was hospitalized for further evaluation and management. A bilateral pulmonary artery embolectomy was performed. She received treatment with apixaban due to lower limb deep vein thrombosis. Thrombectomy was performed on Study Day 768. She was discharged from the hospital on Study Day 770 and the event was considered resolved.

Discussion: This event of deep vein thrombosis leading to the SAE pulmonary embolism is unlikely to be related to treatment with SC OCR. Per the narrative, this subject's dyspnea that resulted from SAE COVID-19 pneumonia did not completely resolve, which could have led to decreased mobility and ambulation, potentially leading to a deep vein thrombosis.

Subject (b) (6)

Subject (b) (6) (a 29-year-old man previously treated with IV OCR who received SC OCR 1200 mg on Study Days 1, 175, and 384 and SC OCR 920 mg on Study Days 657 and 818) experienced the SAEs pneumonia (Grade 3, Study Day 476) and encephalitis ("meningoencephalitis," Grade 3, Study Day 492). His medical history included asthma and carpal tunnel syndrome.

On Study Day 461, the subject developed pyrexia (Grade 3, nonserious) and was diagnosed with hand-foot-mouth disease (Grade 1, nonserious). He received treatment with paracetamol and ibuprofen. He then received the first dose of SARS-CoV-2 vaccine (Moderna) on Study Day 472. On Study Day 476, the subject developed fever (reportedly ongoing for 1 month), intermittent nasal congestion, headache, and dry couth. COVID-19 PCR test was negative. He received a diagnosis of pneumonia (Grade 3, serious) and received treatment with paracetamol, ibuprofen, levofloxacin, and doxycycline. It is unclear if additional diagnostic evaluations were performed. He reportedly remained febrile (body temperature not reported) despite treatment with antibiotics. He was discharged from the hospital on Study Day 478.

On Study Day 492, he presented to the hospital again with fever (body temperature 104.3°F) and altered mental status. He was hospitalized with a diagnosis of encephalitis (Grade 3, serious). On that same day, a chest X-ray was performed and showed "improved bibasilar interstitial pneumonia with residual infiltrate in the right lower lobe." During this hospitalization, he was also diagnosed with hyperthyroidism due to a TSH of 0.25 and free T4 of 1.16 (units and reference range not provided). Reportedly, the event hyperthyroidism had been ongoing since Study Day 469.

A lumbar puncture was performed on Study Day 493 and enterovirus was found to be present in CSF, presumably on PCR testing. Laboratory evaluations were remarkable for low serum IgG (461 mg/dL), WBC count 3.39, and RBC count of 4.31 (units and reference range not provided). An echocardiogram and blood cultures were reportedly normal. A CT scan of the chest demonstrated "mild to moderate multi lobar ground glass infiltrates, consistent with pneumonia." He was treated with "immunoglobulins." The subject was discharged from the hospital on Study Day 501 and the events of pneumonia and encephalitis were considered resolved. The investigator assessed events of encephalitis and pneumonia as related to treatment with SC OCR. Study treatment was interrupted due to the event of encephalitis but was subsequently restarted.

Discussion: These SAEs of pneumonia and enterovirus encephalitis in a subject previously treated with IV OCR for at least one year prior to study enrollment appear to be related to treatment with SC OCR. Current approved labeling for IV OCR (Ocrevus) includes a warning for serious (including life-threatening and fatal) infections with ocrelizumab treatment (Genentech 2024).

Subject (b) (6)

Subject (b) (6) (a 51-year-old woman, OCR-naive, who received SC OCR 40 mg on Study Day 1 and IV OCR 300 mg on Study Days 84 and 99) experienced the SAEs road traffic accident (Grade 3, Study Day 185), peritonitis (Grade 3, Study Day 195), and acute respiratory failure (Grade 3, Study Day 197). Her medical history included neurogenic bladder, tremor, insomnia, dyspnea, dysphagia, fatigue, unspecified migraine, visual impairment, and current tobacco use.

The subject presented to the emergency department on Study Day 185 after experiencing a road traffic accident (Grade 3, serious) and was hospitalized. At the time, she reported back pain. She underwent chest X-ray, X-ray of the lumbar and thoracic spine, CT scan of the lumbar, thoracic, and cervical spine, CT abdomen and pelvis, and CT head with and without contrast. She was diagnosed with spinal compression fracture ("acute compression fracture at T12 and L3," Grade 3, nonserious) and rib fracture ("fractures of the right fourth and fifth ribs," Grade 2, nonserious). She was treated with paracetamol, hydromorphone, and oxycodone for pain. On Study Day 186, she was treated with alprazolam and lorazepam for anxiety (Grade 1, nonserious). She was discharged home on Study Day 193 with and was prescribed outpatient rehabilitation and a back brace.

The subject returned to the emergency department on Study Day 195 due to fever (body temperature unknown) and altered mental status. Abdominal and chest X-rays were performed, but results were not provided. A CT scan of the abdomen and pelvis demonstrated "perforated bowel," which prompted a diagnosis of peritonitis (Grade 3, serious). She underwent small bowel resection and intra-abdominal abscess drainage. The event peritonitis was considered

resolved on the same day. The subject experienced dyspnea and anxiety on Study Day 196, which prompted transfer to the intensive care unit for overnight monitoring.

A chest X-ray was performed on Study Day 197, and she was diagnosed with acute respiratory failure (Grade 3, serious) and chronic obstructive pulmonary disease (Grade 2, nonserious). It is unclear if additional diagnostic evaluations were performed. At the time, she was reportedly lethargic, appeared weak, and was unable to communicate. She was placed on a 100% nonrebreather mask. A chest X-ray was performed on Study Day 214, but results were not available. She was discharged from the hospital on an unknown date to an acute rehabilitation facility. The events of chronic obstructive pulmonary disease, anxiety, acute respiratory failure, spinal compression fracture, and rib fracture remained unresolved as of the clinical cutoff date. The investigator assessed the events of road traffic accident, peritonitis, and acute respiratory failure as unrelated to treatment with SC OCR.

Discussion: The SAEs of road traffic accident, peritonitis, and acute respiratory failure in a subject treated with a subtherapeutic dose of SC OCR (40 mg) without prior exposure to ocrelizumab appear unrelated to treatment with study drug. It appears that the event peritonitis occurred as a result of a bowel perforation that appeared to be a complication of the road traffic accident experienced by this subject. Additionally, this subject was at high risk for experiencing acute respiratory failure due to her history of current smoking, chronic obstructive pulmonary disease, and recent rib fractures. However, the possibility that immunosuppression due to treatment with ocrelizumab contributed to the severity of the infection (peritonitis) cannot be excluded.

120-Day Safety Update

The Applicant indicated that the proportion of subjects who received at least one dose of SC OCR 920 mg and experienced a SAE was higher as of the 120-Day Safety Update cutoff date (n=11 [9.3%]), compared to the cutoff date of the BLA submission (n=4 [3.4%]). SAEs reported after the BLA submission cutoff date (n=1 [0.8%] each) included pilonidal disease, acute myocardial infarction, intentional overdose, muscular weakness, MS pseudorelapse, and pulmonary embolism.

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Studies CN42097 and CN41144

Study CN42097

There were no subjects who experienced TEAEs leading to permanent treatment discontinuation in Study CN42097.

Study CN41144

TEAEs in Study CN41144 leading to permanent discontinuation of study treatment are reported by PT in Table 27. No subjects experienced TEAEs leading to permanent treatment discontinuation in the Dose Escalation Phase. One subject who received at least one dose of SC OCR 1200 mg experienced the SAE MS relapse and one subject who received at least one dose of SC OCR 920 mg experienced a TEAE of MS ("worsening MS," Grade 2). The narratives for these two cases are discussed below.

Table 27. Subjects With Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
System Organ Class Preferred Term	Group A N=79 n (%)	Group B N=39 n (%)	Group A N=80 n (%)	Group B N=45 n (%)
Any TEAE leading to discontinuation	0	1 (2.6)	0	1 (2.2)
Nervous system disorders (SOC)	0	1 (2.6)	0	1 (2.2)
Multiple sclerosis	0	1 (2.6)	0	0
Multiple sclerosis relapse	0	0	0	1 (2.2)

Source: adae.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during Study CN41144.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during Study CN41144, either in the dose escalation phase or in the dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Duration is up to 3 years.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous; SOC, system organ class; TEAE, treatment-emergent adverse event

Subject (b) (6)

Subject (b) (6) (a 42-year-old OCR-naive man who received SC OCR 1200 mg on Study Days 1, 169, and 344) experienced the SAE MS relapse (Grade 3, serious) on Study Day 406. His medical history included attention deficit hyperactivity disorder, vitamin D deficiency, and dysesthesia. On Study Day 406, the subject experienced transient bilateral lower extremity and right hand pain, and "difficulties with fine motor skills using his hands and erections." Additionally, he reported a three-week history of worsening fatigue, difficulties with short-term memory, and irritability. His physical exam reportedly revealed "worsening of numbness and balance." He was diagnosed with MS relapse (Grade 3, serious) and received treatment with IV methylprednisolone for three days. The event was considered resolved on Study Day 463. Study

treatment was permanently discontinued due to the event and the subject entered the Safety Follow-Up Period. The investigator assessed the event as unrelated to treatment with SC OCR.

Discussion: This appears to be an event of MS relapse requiring treatment with IV methylprednisolone. Of note, this subject's $CD19^+$ B-cell counts remained appropriately suppressed throughout the duration of this subject's participation in the study at <10/μL from Study Day 14 through Study Day 674. Events of MS relapse are typically not categorized as AEs and are typically considered as part of analyses of efficacy. Protocol Section 5.3.5.10 (Lack of Efficacy or Worsening of Multiple Sclerosis) states that "medical occurrences or symptoms of deterioration that are anticipated as part of MS should be recorded as an AE if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study." Additionally, protocol Section 5.3.11 (Hospitalization or Prolonged Hospitalization) indicates that "hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone" should not be reported as an AE. Therefore, based on the procedures outlined by the protocol, it appears that this event of MS relapse was appropriately reported as a TEAE leading to study treatment discontinuation but was inappropriately reported as a SAE. It is unclear whether other potential causes for MS symptom worsening were ruled out prior to diagnosing this subject with an MS relapse, particularly in the setting of appropriately suppressed $CD19^+$ B-cell counts over time. Additionally, it appears that MRI was not performed, which contributes to the uncertainty regarding this event.

Subject (b) (6)

Subject (b) (6) (a 21-year-old OCR-naive man who received SC OCR 1200 mg on Study Days 1 and 169 and SC OCR 920 mg on Study Days 337 and 547) experienced the SAE MS ("worsening MS," Grade 2, nonserious) on Study Day 603. He was diagnosed with relapsing MS on Study Day -48. His medical history included attention deficit hyperactivity disorder. He was found to be positive for anti-rHuPH20 antibodies on Study Day 168 and was diagnosed with "ADA positive to rHuPH20." He again was found to be positive for anti-rHuPH20 antibodies on Study Day 336. He was diagnosed with worsening MS ("worsening MS," Grade 2, nonserious) on Study Day 603. A neurological exam was performed on Study Day 616, and he was diagnosed with MS disease progression. No treatment was administered for the event and the Applicant indicated that presenting symptoms and details regarding diagnostic evaluations were not reported. Study treatment was permanently discontinued, and the subject entered the Safety Follow-Up Period. The event remained unresolved as of the data cutoff date. The investigator assessed the event as unrelated to treatment with SC OCR.

Discussion: This appears to be a case of MS disease worsening in a subject recently diagnosed with relapsing MS who developed ADAs to hyaluronidase, although it is unclear if additional causes for MS disease worsening were ruled out. Despite ADA positivity, this subject's $CD19^+$ B-cell count remained appropriately suppressed throughout the duration of his participation in the study at <5/μL from Study Day 14 through Study Day 616. Section 12.3 (Pharmacokinetics) of current approved labeling for rHuPH20 states that hyaluronidase is antigenic and that repeated injections of relatively large amounts of hyaluronidase preparations may result in the formation of neutralizing antibodies (Halozyme 2024). Refer to Section 14.4 for the Clinical Pharmacology discussion of immunogenicity. Refer to the discussion above regarding reporting of events of MS relapses or MS worsening as TEAEs.

120-Day Safety Update

Per the Applicant's 120-Day Safety Update, one subject receiving SC OCR 920 mg experienced a TEAE with the PT microscopic colitis (PT subsequently updated to collagenous colitis), which led to study treatment discontinuation. This TEAE of microscopic colitis was not reported as a SAE. Refer to Section 7.7.8 (Immune-Mediated Colitis) for additional details.

7.6.1.5. Treatment-Emergent Adverse Events, Studies CN42097 and CN41144

Study CN42097

Table 28 provides an overview of the TEAEs that occurred in ≥1% of subjects in either treatment group. A higher proportion of subjects in the SC OCR group (73.7%) experienced any TEAE, as compared to subjects in the IV OCR group (45.8%). This difference was primarily driven by injection-related reactions, which are expected with SC OCR due to the route of administration (46.6% SC OCR versus 0.0% IV OCR). The most common TEAEs in the SC OCR group that also occurred at a higher frequency compared to the IV OCR group were injection-related reactions, headache, COVID-19, nasopharyngitis, and oral herpes. TEAEs with risk difference 95% confidence intervals that did not include zero and occurred at higher frequencies in the SC OCR group included injection-related reaction and headache. Additionally, 16.9% of subjects in the IV OCR group experienced infusion-related reactions, which are a known risk of IV OCR, but are not expected with SC OCR.

Table 28. Subjects With Common Adverse Events Occurring at ≥1% Frequency, Safety Population, Study CN42097, Controlled Period (Weeks 0 to 24)

Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Any AE	87 (73.7)	54 (45.8)	28.0 (15.6, 39.5)*
Injection-related reaction	55 (46.6)	0 (0.0)	46.6 (37.8, 55.6)*
Headache	12 (10.2)	3 (2.5)	7.6 (1.6, 14.7)*
Upper respiratory tract infection	8 (6.8)	9 (7.6)	-0.8 (-8.0, 6.2)
COVID-19	8 (6.8)	5 (4.2)	2.5 (-3.7, 9.1)
Nasopharyngitis	5 (4.2)	2 (1.7)	2.5 (-2.3, 8.1)
Oral herpes	4 (3.4)	1 (0.8)	2.5 (-1.6, 7.7)
Urinary tract infection	3 (2.5)	5 (4.2)	-1.7 (-7.3, 3.5)
Pharyngitis	3 (2.5)	3 (2.5)	-0.0 (-5.0, 5.0)
Contusion	3 (2.5)	2 (1.7)	0.8 (-3.7, 5.7)
Influenza	3 (2.5)	1 (0.8)	1.7 (-2.4, 6.5)
Rhinitis	3 (2.5)	1 (0.8)	1.7 (-2.4, 6.5)
Injection site erythema	3 (2.5)	0 (0.0)	2.5 (-0.7, 7.2)
Arthralgia	2 (1.7)	5 (4.2)	-2.5 (-8.1, 2.3)
Bronchitis	2 (1.7)	6 (5.1)	-3.4 (-9.2, 1.5)
Dizziness	2 (1.7)	4 (3.4)	-1.7 (-6.9, 3.0)
Fall	2 (1.7)	4 (3.4)	-1.7 (-6.9, 3.0)
Eye pain	2 (1.7)	2 (1.7)	-0.0 (-4.5, 4.5)
Cough	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Pain in extremity	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Rash	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Toothache	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Anxiety	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Back pain	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Constipation	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Foot fracture	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Injection site reaction	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Paresthesia	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Sinusitis	1 (0.8)	3 (2.5)	-1.7 (-6.5, 2.4)
Arthropod bite	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Migraine	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Pyrexia	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Viral infection	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Infusion-related reaction	0 (0.0)	20 (16.9)	-16.9 (-24.8, -11.2)*
Asthenia	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Depression	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Gait disturbance	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Multiple sclerosis	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Myalgia	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Neutropenia	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Sinus congestion	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Skin abrasion	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)

Source: adae.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous

TEAEs that are grouped using the FMQ (narrow) are shown in Table 29. The only FMQ that had a risk difference 95% confidence interval that did not include zero was Local Administration Reactions; however, these events appear to have occurred at a higher frequency in the IV OCR

group because the FMQ Local Administration Reactions includes the PT infusion related reaction (which is not expected to occur in the SC OCR group), but not the PT injection related reaction (which is not expected to occur in the IV OCR group). Therefore, TEAEs with the PT injection related reaction are not accounted for in the referenced table.

PTs within the FMQ Nasopharyngitis occurred at a higher frequency in subjects receiving SC OCR (16.1%), as compared to those receiving IV OCR (12.7%). The FMQ Nasopharyngitis contains the PTs nasopharyngitis and rhinitis, both of which were more common in the SC OCR group (4.2% and 2.5%, respectively) compared to the IV OCR group (1.7% and 0.8%, respectively). PTs within the FMQ Viral Infection occurred at a higher frequency in subjects receiving SC OCR (13.6%), as compared to those receiving IV OCR (10.2%). The FMQ Viral Infection contains the PTs COVID-19, oral herpes, and influenza, all of which were more common in the SC OCR group (6.8%, 3.4%, and 2.5%, respectively) compared to the IV OCR group (4.2%, 0.8%, and 0.8%, respectively).

The Applicant's draft labeling includes a warning for infections, indicating a risk of upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections with SC OCR administration, based on current approved labeling for IV OCR.

PTs within the FMQ Headache occurred at a higher frequency in subjects receiving SC OCR (11%), as compared to those receiving IV OCR (4.2%). The Applicant's draft labeling includes a warning for injection reactions and states that headache and nausea are common symptoms of injection reactions.

Table 29. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study CN42097, Controlled Period (Weeks 0 to 24)

System Organ Class FMQ (Narrow)	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Cardiac disorders (SOC)			
Systemic hypertension	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Palpitations	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Endocrine disorders (SOC)			
Hyperglycemia	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Gastrointestinal disorders (SOC)			
Abdominal pain	3 (2.5)	1 (0.8)	1.7 (-2.4, 6.5)
Constipation	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Diarrhea	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Dyspepsia	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Nausea	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
General disorders and administration site conditions (SOC)			
Fatigue	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Peripheral edema	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Pyrexia	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Dizziness	2 (1.7)	4 (3.4)	-1.7 (-6.9, 3.0)
Fall	2 (1.7)	4 (3.4)	-1.7 (-6.9, 3.0)
Local administration reaction^	6 (5.1)	20 (16.9)	-11.9 (-20.3, -4.1)*
Immune system disorders (SOC)			
Hypersensitivity	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)

System Organ Class FMQ (Narrow)	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Infections and infestations (SOC)			
Nasopharyngitis	19 (16.1)	15 (12.7)	3.4 (-5.7, 12.6)
Viral infection	16 (13.6)	12 (10.2)	3.4 (-5.1, 12.0)
Bacterial infection	8 (6.8)	8 (6.8)	-0.0 (-6.9, 6.9)
Fungal infection	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Purulent material	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Pneumonia	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Metabolism and nutrition disorders (SOC)			
Lipid disorder	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Musculoskeletal and connective tissue disorders (SOC)			
Back pain	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Fracture	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Myalgia	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Arthralgia	2 (1.7)	5 (4.2)	-2.5 (-8.1, 2.3)
Nervous system disorders (SOC)			
Headache	13 (11.0)	5 (4.2)	6.8 (-0.0, 14.3)
Paresthesia	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Syncope	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Tremor	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Psychiatric disorders (SOC)			
Anxiety	3 (2.5)	0 (0.0)	2.5 (-0.7, 7.2)
Insomnia	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Depression	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Renal and urinary disorders (SOC)			
Urinary retention	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Renal & urinary tract infection	4 (3.4)	6 (5.1)	-1.7 (-7.7, 4.0)
Reproductive system and breast disorders (SOC)			
Abnormal uterine bleeding	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Erectile dysfunction	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Sexual dysfunction	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Respiratory, thoracic and mediastinal disorders (SOC)			
Cough	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Bronchospasm	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Skin and subcutaneous tissue disorders (SOC)			
Erythema	4 (3.4)	1 (0.8)	2.5 (-1.6, 7.7)
Rash	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Urticaria	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Alopecia	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Vascular disorders (SOC)			
Hemorrhage	3 (2.5)	3 (2.5)	-0.0 (-5.0, 5.0)

Source: adae.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
^ Indicates that the PT *injection related reaction* is not included in the Local Administration Reaction FMQ.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; PT, preferred term; SC, subcutaneous; SOC, system organ class

TEAEs that are grouped using the FMQ (broad) are shown in Table 30. See comment above regarding the FMQ Local Administration Reaction. The only broad FMQ that had a risk difference 95% confidence interval that did not include zero and included PTs of TEAEs that occurred at a higher frequency in subjects who received SC OCR was the FMQ Hypersensitivity (broad). However, Table 29 did not show an imbalance between the groups for the FMQ Hypersensitivity (narrow). The FMQ Hypersensitivity (broad) also contains the PT injection related reaction, which occurred at a higher frequency in subjects receiving SC OCR (46.6%), compared to those receiving IV OCR (0.0%, not expected to occur with IV administration). Of note, the PT infusion related reaction is also included in the FMQ Hypersensitivity (broad), which occurred in 16.9% of subjects in the IV OCR group.

The Applicant's draft labeling includes a warning for injection reactions, including injection site reactions (erythema, pain, swelling, and pruritus) and systemic injection-related reactions (headache and nausea).

Table 30. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad), Safety Population, Study CN42097, Controlled Period (Weeks 0 to 24)

System Organ Class FMQ (Broad)	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)			
Leukopenia	1 (0.8)	4 (3.4)	-2.5 (-7.7, 1.6)
Cardiac disorders (SOC)			
Systemic hypertension	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Heart failure	0	1 (0.8)	-0.8 (-4.7, 2.3)
Palpitations	0	1 (0.8)	-0.8 (-4.7, 2.3)
Arrhythmia	3 (2.5)	5 (4.2)	-1.7 (-7.3, 3.5)
Ear and labyrinth disorders (SOC)			
Vertigo	2 (1.7)	4 (3.4)	-1.7 (-6.9, 3.0)
Endocrine disorders (SOC)			
Hyperglycemia	0	1 (0.8)	-0.8 (-4.7, 2.3)
Gastrointestinal disorders (SOC)			
Abdominal pain	3 (2.5)	1 (0.8)	1.7 (-2.4, 6.5)
Constipation	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Dyspepsia	3 (2.5)	2 (1.7)	0.8 (-3.7, 5.7)
Diarrhea	3 (2.5)	3 (2.5)	-0.0 (-5.0, 5.0)
Nausea	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Vomiting	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
General disorders and administration site conditions (SOC)			
Fatigue	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Pyrexia	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Dizziness	2 (1.7)	4 (3.4)	-1.7 (-6.9, 3.0)
Peripheral edema	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Fall	4 (3.4)	8 (6.8)	-3.4 (-9.9, 2.5)
Local administration reaction^	6 (5.1)	20 (16.9)	-11.9 (-20.3, -4.1)*
Hepatobiliary disorders (SOC)			
Hepatic injury	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Immune system disorders (SOC)			
Hypersensitivity	56 (47.5)	22 (18.6)	28.8 (17.1, 39.9)*
Anaphylactic reaction	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Angioedema	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)

System Organ Class FMQ (Broad)	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Infections and infestations (SOC)			
Nasopharyngitis	19 (16.1)	15 (12.7)	3.4 (-5.7, 12.6)
Viral infection	24 (20.3)	22 (18.6)	1.7 (-8.5, 11.9)
Fungal infection	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Opportunistic infection	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Purulent material	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Bacterial infection	11 (9.3)	13 (11.0)	-1.7 (-9.8, 6.3)
Pneumonia	3 (2.5)	5 (4.2)	-1.7 (-7.3, 3.5)
Metabolism and nutrition disorders (SOC)			
Lipid disorder	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Musculoskeletal and connective tissue disorders (SOC)			
Back pain	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Fracture	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Myalgia	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Arthralgia	3 (2.5)	7 (5.9)	-3.4 (-9.5, 2.1)
Arthritis	3 (2.5)	7 (5.9)	-3.4 (-9.5, 2.1)
Nervous system disorders (SOC)			
Headache	13 (11.0)	5 (4.2)	6.8 (-0.0, 14.3)
Paresthesia	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Tremor	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Somnolence	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Confusional state	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Syncope	3 (2.5)	4 (3.4)	-0.8 (-6.2, 4.3)
Psychiatric disorders (SOC)			
Anxiety	3 (2.5)	0 (0.0)	2.5 (-0.7, 7.2)
Psychosis	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Insomnia	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Depression	0 (0.0)	2 (1.7)	-1.7 (-6.0, 1.5)
Renal and urinary disorders (SOC)			
Urinary retention	2 (1.7)	2 (1.7)	-0.0 (-4.5, 4.5)
Renal & urinary tract infection	4 (3.4)	6 (5.1)	-1.7 (-7.7, 4.0)
Reproductive system and breast disorders (SOC)			
Amenorrhea	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Decreased menstrual bleeding	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Erectile dysfunction	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Sexual dysfunction	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Abnormal uterine bleeding	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Respiratory, thoracic and mediastinal disorders (SOC)			
Cough	2 (1.7)	1 (0.8)	0.8 (-3.1, 5.2)
Bronchospasm	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Skin and subcutaneous tissue disorders (SOC)			
Erythema	4 (3.4)	1 (0.8)	2.5 (-1.6, 7.7)
Rash	3 (2.5)	2 (1.7)	0.8 (-3.7, 5.7)
Urticaria	2 (1.7)	2 (1.7)	-0.0 (-4.5, 4.5)
Alopecia	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)

System Organ Class FMQ (Broad)	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Vascular disorders (SOC)			
Hemorrhage	3 (2.5)	4 (3.4)	-0.8 (-6.2, 4.3)

Source: adae.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
^ Indicates that the PT *injection-related reaction* is not included in the Local Administration Reaction FMQ.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; PT, preferred term; SC, subcutaneous; SOC, system organ class

120-Day Safety Update

TEAEs that occurred in ≥3% of subjects during the Treatment or Safety Follow-up Periods are presented in Table 31. Per the Applicant's 120-Day Safety Update, most TEAEs were Grade 1 and 2 in severity, the number of Grade 3 TEAEs was balanced between the groups, and there were no Grade 4 or 5 TEAEs.

A higher proportion of subjects in the SC/SC arm (86.4%) experienced at least one TEAE during the Treatment and Safety Follow-Up Periods, as compared to the IV/SC arm (75.4%). Per the Applicant, this difference appeared to be primarily driven by TEAEs with PTs belonging to the SOC Injury, Poisoning, and Procedural Complications (the most frequent PT was injection related reaction), which were mild and moderate in severity. The Applicant indicated that subjects in the SC/SC arm had received up to 4 SC OCR injections, while subjects in the IV/SC arm had received up to 3 injections of SC OCR. Therefore, the Applicant stated that the observed difference between the groups in terms of subjects who experienced at least one injection-related reaction (SC/SC group 59.3% [56.8% at least one local and 15.3% at least one systemic injection-related reaction] versus IV/SC group 42.4% [42.4% at least one local and 7.6% at least one systemic injection-related reaction) was primarily driven by the difference in total number of injections received in each group.

TEAEs that occurred at a frequency of >10% in either treatment group included injection related reaction (58.5% OCR SC/SC, 42.4% OCR IV/SC), COVID-19 (11.0% OCR SC/SC, 5.1% OCR IV/SC), headache (10.2% OCR SC/SC, 2.5% OCR IV/SC), upper respiratory tract infection (9.3%% OCR SC/SC, 11.9% OCR IV/SC), and infusion related reaction (0.0% OCR SC/SC, 16.9% OCR IV/SC). Overall, AEs reported in the 120-Day Safety Update remained consistent with those reported in the BLA submission.

Table 31. Adverse Events That Occurred in ≥3% of Subjects in Either Treatment Group by Preferred Term, Safety Population, Study CN42097

Preferred Term	OCR SC/SC N=118 n (%)	OCR IV/SC N=118 n (%)
Any AE	102 (86.4)	89 (75.4)
Injection-related reaction	69 (58.5)	50 (42.4)
COVID-19	13 (11.0)	6 (5.1)
Headache	12 (10.2)	3 (2.5)
Upper respiratory tract infection	11 (9.3)	14 (11.9)
Urinary tract infection	7 (5.9)	9 (7.6)
Nasopharyngitis	7 (5.9)	4 (3.4)
Bronchitis	5 (4.2)	7 (5.9)
Pain in extremity	5 (4.2)	3 (2.5)
Oral herpes	5 (4.2)	1 (0.8)
Rhinitis	5 (4.2)	1 (0.8)
Rash	5 (4.2)	1 (0.8)
Dizziness	4 (3.4)	5 (4.2)
Pharyngitis	4 (3.4)	4 (3.4)
Influenza	4 (3.4)	3 (2.5)
Sinusitis	4 (3.4)	3 (2.5)
Back pain	3 (2.5)	4 (3.4)
Arthralgia	2 (1.7)	6 (5.1)
Fall	2 (1.7)	5 (4.2)
Injection site reaction	2 (1.7)	4 (3.4)
Infusion-related reaction	0 (0.0)	20 (16.9)

Source: Applicant's 120-Day Safety Update, received 3/15/2024
Abbreviations: AE, adverse event; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous

Study CN41144

TEAEs occurring in ≥2.5% of subjects in any treatment group are listed by PT in Table 32. A higher proportion of Group A (91.2%, previously treated with OCR) and Group B (97.8%, OCR-naive) subjects who received at least one dose of SC OCR 1200 mg (higher dose) experienced any TEAEs, as compared to Group A (78.5%) and Group B (82.1%) subjects who received at least one dose of SC OCR 920 mg (lower dose). Upper respiratory tract infection appeared to occur more frequently in subjects who received at least one dose of SC OCR 920 mg. TEAEs that appeared to occur more frequently in OCR-naive subjects included injection site reaction, fatigue, headache, and hypokalemia, while pneumonia appeared to occur more frequently in subjects previously treated with OCR. TEAEs that were more frequent in subjects who received at least one dose of SC OCR 1200 mg included injection site reaction, COVID-19, injection related reaction, urinary tract infection, fatigue, headache, arthralgia, back pain, injection site pain, injection site bruising, injection site erythema, dizziness, muscle spasms, and tooth infection.

Table 32. Subjects With Common Adverse Events Occurring at ≥2.5% Frequency, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
	Group A N=79	Group B N=39	Group A N=80	Group B N=45
Preferred Term	n (%)	n (%)	n (%)	n (%)
Any AE	62(78.5)	32 (82.1)	73 (91.2)	44 (97.8)
Injection site reaction	36 (45.6)	26 (66.7)	50 (62.5)	40 (88.9)
COVID-19	17 (21.5)	8 (20.5)	24 (30.0)	18 (40.0)
Injection related reaction	12 (15.2)	1 (2.6)	16 (20.0)	10 (22.2)
Urinary tract infection	6 (7.6)	2 (5.1)	9 (11.2)	5 (11.1)
Bronchitis	4 (5.1)	2 (5.1)	1 (1.2)	0 (0.0)
Acute sinusitis	3 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	3 (3.8)	4 (10.3)	7 (8.8)	13 (28.9)
Headache	3 (3.8)	3 (7.7)	7 (8.8)	10 (22.2)
Nasopharyngitis	3 (3.8)	2 (5.1)	6 (7.5)	3 (6.7)
Upper respiratory tract infection	3 (3.8)	2 (5.1)	2 (2.5)	0 (0.0)
Muscular weakness	2 (2.5)	0 (0.0)	4 (5.0)	6 (13.3)
Paresthesia	2 (2.5)	1 (2.6)	1 (1.2)	4 (8.9)
Cough	2 (2.5)	1 (2.6)	0 (0.0)	1 (2.2)
Urinary incontinence	2 (2.5)	1 (2.6)	0 (0.0)	0 (0.0)
Pneumonia	2 (2.5)	0 (0.0)	5 (6.2)	0 (0.0)
Tooth abscess	2 (2.5)	0 (0.0)	0 (0.0)	1 (2.2)
Diarrhea	0 (0.0)	3 (7.7)	0 (0.0)	1 (2.2)
Vomiting	0 (0.0)	2 (5.1)	1 (1.2)	1 (2.2)
Anxiety	0 (0.0)	2 (5.1)	0 (0.0)	4 (8.9)
Arthralgia	1 (1.3)	1 (2.6)	8 (10.0)	3 (6.7)
Back pain	1 (1.3)	1 (2.6)	7 (8.8)	3 (6.7)
Fall	1 (1.3)	1 (2.6)	4 (5.0)	8 (17.8)
Pain in extremity	1 (1.3)	1 (2.6)	5 (6.2)	2 (4.4)
Vertigo	1 (1.3)	1 (2.6)	1 (1.2)	1 (2.2)
Contusion	1 (1.3)	1 (2.6)	0 (0.0)	1 (2.2)
Asthma	1 (1.3)	1 (2.6)	0 (0.0)	0 (0.0)
Facial bones fracture	1 (1.3)	1 (2.6)	0 (0.0)	0 (0.0)
Hepatic steatosis	1 (1.3)	1 (2.6)	0 (0.0)	0 (0.0)
Injection site pain	1 (1.3)	0 (0.0)	5 (6.2)	4 (8.9)
Depression	1 (1.3)	0 (0.0)	3 (3.8)	2 (4.4)
COVID-19 pneumonia	1 (1.3)	0 (0.0)	3 (3.8)	1 (2.2)
Abdominal pain	1 (1.3)	0 (0.0)	2 (2.5)	2 (4.4)
Anemia	1 (1.3)	0 (0.0)	2 (2.5)	0 (0.0)
Asthenia	1 (1.3)	0 (0.0)	2 (2.5)	0 (0.0)
Blood potassium decreased	1 (1.3)	0 (0.0)	2 (2.5)	0 (0.0)
Hypoaesthesia	1 (1.3)	0 (0.0)	2 (2.5)	1 (2.2)
Pain	1 (1.3)	0 (0.0)	1 (1.2)	2 (4.4)
Edema peripheral	1 (1.3)	0 (0.0)	0 (0.0)	3 (6.7)
Skin laceration	0 (0.0)	1 (2.6)	3 (3.8)	1 (2.2)
Neck pain	0 (0.0)	1 (2.6)	2 (2.5)	0 (0.0)
Abdominal pain upper	0 (0.0)	1 (2.6)	1 (1.2)	2 (4.4)
Hypokalemia	0 (0.0)	1 (2.6)	1 (1.2)	3 (6.7)
Flushing	0 (0.0)	1 (2.6)	1 (1.2)	1 (2.2)
Vertebral foraminal stenosis	0 (0.0)	1 (2.6)	1 (1.2)	0 (0.0)
Mammogram abnormal	0 (0.0)	1 (2.6)	1 (1.2)	0 (0.0)
Nephrolithiasis	0 (0.0)	1 (2.6)	1 (1.2)	0 (0.0)
Road traffic accident	0 (0.0)	1 (2.6)	1 (1.2)	0 (0.0)
Arthropathy	0 (0.0)	1 (2.6)	0 (0.0)	2 (4.4)
Memory impairment	0 (0.0)	1 (2.6)	0 (0.0)	2 (4.4)

	SC OCR 920 mg		SC OCR 1200 mg	
	Group A N=79	Group B N=39	Group A N=80	Group B N=45
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Micturition urgency	0 (0.0)	1 (2.6)	0 (0.0)	2 (4.4)
Vision blurred	0 (0.0)	1 (2.6)	0 (0.0)	2 (4.4)
Concussion	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.2)
Disease progression	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.2)
Multiple sclerosis pseudo relapse	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.2)
Atrioventricular block first degree	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Blood glucose increased	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Chest pain	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Conjunctivitis	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Dysphonia	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Erectile dysfunction	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Eye pain	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Flatulence	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Hiccups	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Intervertebral disc degeneration	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Intervertebral disc protrusion	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Ligament sprain	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Lymphopenia	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Multiple sclerosis	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Papillary thyroid cancer	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Physical assault	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Post-depletion B-cell recovery	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Rhinovirus infection	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Skin disorder	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	6 (7.5)	0 (0.0)
Muscle spasms	0 (0.0)	0 (0.0)	5 (6.2)	6 (13.3)
Injection site erythema	0 (0.0)	0 (0.0)	5 (6.2)	1 (2.2)
Dizziness	0 (0.0)	0 (0.0)	3 (3.8)	5 (11.1)
Blood cholesterol increased	0 (0.0)	0 (0.0)	3 (3.8)	0 (0.0)
Injection site bruising	0 (0.0)	0 (0.0)	2 (2.5)	1 (2.2)
Pyrexia	0 (0.0)	0 (0.0)	2 (2.5)	1 (2.2)
Tooth infection	0 (0.0)	0 (0.0)	2 (2.5)	1 (2.2)
Benign breast neoplasm	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Blood sodium decreased	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Chills	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Dyspnea	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Temporomandibular joint syndrome	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
White blood cell count increased	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Neuralgia	0 (0.0)	0 (0.0)	1 (1.2)	3 (6.7)
Arthropod bite	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)
Swelling face	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)

	SC OCR 920 mg		SC OCR 1200 mg	
Preferred Term	Group A N=79 n (%)	Group B N=39 n (%)	Group A N=80 n (%)	Group B N=45 n (%)
White blood cell count decreased	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)

Source: adae.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during Study CN41144.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during Study CN41144, either in the dose escalation phase or in the dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Duration is up to 3 years.
Abbreviations: AE, adverse event; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous

TEAEs that occurred in Study CN41144 are listed in Table 33 by SOC and FMQ (narrow). The FMQs (narrow) Local Administration Reaction and Fatigue were more frequent in OCR-naive subjects who received at least one dose of SC OCR 920 mg (66.7% versus 45.6% and 10.3% versus 5.1%, respectively) and at least one dose of SC OCR 1200 mg (88.9% versus 62.5% and 31.1% versus 10.0%, respectively), as compared to those who had received treatment with ocrelizumab prior to study enrollment.

PTs within the FMQs (narrow) Viral Infection, Bacterial Infection, Headache, and Renal and Urinary Tract Infection were reported more frequently in subjects who received at least one dose of SC OCR 1200 mg, compared to those who received at least one dose of SC OCR 920 mg. Additionally, PTs within the following FMQs (narrow) occurred at higher frequencies in subjects treated with at least one dose of SC OCR 1200 mg, as compared to those treated with at least one dose of SC OCR 920 mg: Abdominal Pain, Local Administration Reaction, Fatigue, Dizziness, Fall, Pyrexia, Hepatic injury, Hypersensitivity, Viral Infection, Bacterial Infection, Pneumonia, Lipid Disorder, Back Pain, Arthralgia, Headache, Paresthesia, Depression, Anxiety, Renal and Urinary Tract Infection, Rash, Erythema, Pruritus, and Hemorrhage.

Table 33. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
System Organ Class FMQ (Narrow)	Group A N=79 n (%)	Group B N=39 n (%)	Group A N=80 n (%)	Group B N=45 n (%)
Blood and lymphatic system disorders (SOC)				
Anemia	1 (1.3)	0 (0.0)	3 (3.8)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.7)
Cardiac disorders (SOC)				
Arrhythmia	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Cardiac conduction disturbance	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.2)
Palpitations	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Systemic hypertension	0 (0.0)	0 (0.0)	1 (1.2)	1 (2.2)
Tachycardia	0 (0.0)	0 (0.0)	1 (1.2)	1 (2.2)
Ear and labyrinth disorders (SOC)				
Vertigo	2 (2.5)	1 (2.6)	1 (1.2)	1 (2.2)
Endocrine disorders (SOC)				
Hyperglycemia	2 (2.5)	1 (2.6)	0 (0.0)	1 (2.2)

	SC OCR 920 mg		SC OCR 1200 mg	
System Organ Class **FMQ (Narrow)**	**Group A** **N=79** **n (%)**	**Group B** **N=39** **n (%)**	**Group A** **N=80** **n (%)**	**Group B** **N=45** **n (%)**
Gastrointestinal disorders (SOC)				
Abdominal pain	1 (1.3)	1 (2.6)	4 (5.0)	5 (11.1)
Constipation	1 (1.3)	0 (0.0)	0 (0.0)	1 (2.2)
Diarrhea	0 (0.0)	3 (7.7)	0 (0.0)	1 (2.2)
Dry mouth	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Dyspepsia	0 (0.0)	1 (2.6)	1 (1.2)	2 (4.4)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Vomiting	0 (0.0)	2 (5.1)	1 (1.2)	1 (2.2)
General disorders and administration site conditions (SOC)				
Local administration reaction	36 (45.6)	26 (66.7)	50 (62.5)	40 (88.9)
Fatigue	4 (5.1)	4 (10.3)	8 (10.0)	14 (31.1)
Dizziness	2 (2.5)	1 (2.6)	5 (6.2)	6 (13.3)
Fall	1 (1.3)	1 (2.6)	4 (5.0)	8 (17.8)
Peripheral edema	1 (1.3)	0 (0.0)	0 (0.0)	3 (6.7)
Pyrexia	0 (0.0)	0 (0.0)	2 (2.5)	1 (2.2)
Hepatobiliary disorders (SOC)				
Hepatic injury	1 (1.3)	0 (0.0)	2 (2.5)	1 (2.2)
Immune system disorders (SOC)				
Hypersensitivity	0 (0.0)	0 (0.0)	1 (1.2)	2 (4.4)
Infections and infestations (SOC)				
Viral infection	20 (25.3)	8 (20.5)	31 (38.8)	19 (42.2)
Bacterial infection	11 (13.9)	2 (5.1)	12 (15.0)	8 (17.8)
Nasopharyngitis	9 (11.4)	4 (10.3)	9 (11.2)	4 (8.9)
Fungal infection	2 (2.5)	0 (0.0)	1 (1.2)	1 (2.2)
Pneumonia	2 (2.5)	0 (0.0)	5 (6.2)	0 (0.0)
Purulent material	2 (2.5)	0 (0.0)	0 (0.0)	1 (2.2)
Metabolism and nutrition disorders (SOC)				
Cachexia	1 (1.3)	0 (0.0)	1 (1.2)	0 (0.0)
Lipid disorder	0 (0.0)	0 (0.0)	3 (3.8)	0 (0.0)
Musculoskeletal and connective tissue disorders (SOC)				
Back pain	2 (2.5)	1 (2.6)	7 (8.8)	3 (6.7)
Fracture	2 (2.5)	1 (2.6)	0 (0.0)	1 (2.2)
Arthralgia	1 (1.3)	1 (2.6)	8 (10.0)	3 (6.7)
Osteoporosis	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Arthritis	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Myalgia	0 (0.0)	0 (0.0)	1 (1.2)	1 (2.2)
Tendinopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)				
Malignancy	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.2)
Nervous system disorders (SOC)				
Headache	4 (5.1)	5 (12.8)	7 (8.8)	12 (26.7)
Paresthesia	3 (3.8)	1 (2.6)	4 (5.0)	4 (8.9)
Seizure	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Syncope	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Tremor	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)

System Organ Class FMQ (Narrow)	SC OCR 920 mg Group A N=79 n (%)	SC OCR 920 mg Group B N=39 n (%)	SC OCR 1200 mg Group A N=80 n (%)	SC OCR 1200 mg Group B N=45 n (%)
Psychiatric disorders (SOC)				
Depression	1 (1.3)	0 (0.0)	3 (3.8)	2 (4.4)
Insomnia	1 (1.3)	2 (5.1)	1 (1.2)	1 (2.2)
Self-harm	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	2 (5.1)	0 (0.0)	5 (11.1)
Renal and urinary disorders (SOC)				
Renal & urinary tract infection	6 (7.6)	2 (5.1)	9 (11.2)	5 (11.1)
Urinary retention	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Reproductive system and breast disorders (SOC)				
Abnormal uterine bleeding	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Erectile dysfunction	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Sexual dysfunction	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.2)
Respiratory, thoracic and mediastinal disorders (SOC)				
Cough	2 (2.5)	1 (2.6)	0 (0.0)	2 (4.4)
Bronchospasm	1 (1.3)	1 (2.6)	0 (0.0)	0 (0.0)
Dyspnea	1 (1.3)	0 (0.0)	2 (2.5)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Skin and subcutaneous tissue disorders (SOC)				
Rash	1 (1.3)	0 (0.0)	5 (6.2)	1 (2.2)
Urticaria	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	0 (0.0)	0 (0.0)	1 (1.2)	1 (2.2)
Erythema	0 (0.0)	1 (2.6)	7 (8.8)	2 (4.4)
Pruritus	0 (0.0)	0 (0.0)	2 (2.5)	1 (2.2)
Vascular disorders (SOC)				
Hemorrhage	2 (2.5)	1 (2.6)	3 (3.8)	2 (4.4)
Thrombosis	1 (1.3)	0 (0.0)	1 (1.2)	0 (0.0)
Thrombosis venous	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)

Source: adae.xpt; Software: R
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during Study CN41144.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during Study CN41144, either in the dose escalation phase or in the dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Duration is up to 3 years.
Each FMQ is aligned to a single SOC based on clinical judgment. Some FMQs may contain PTs from more than one SOC.
Abbreviations: FMQ, FDA medical query; incl, including; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; PT, preferred term; SC, subcutaneous; SOC, system organ class.

120-Day Safety Update

TEAEs that occurred in ≥3% of subjects who received at least one dose of SC OCR 920 mg as of the 120-Day Safety Update cutoff date (November 15, 2023) are shown in Table 34. Per the 120-Day Safety Update, the proportion of overall subjects who received at least one dose of SC OCR 920 mg and experienced at least one TEAE had increased from 79.7% to 89.0%, of which 84.8% were Grade 1 or 2 in severity. The Applicant indicated that the proportion of subjects who experienced injection-related reactions (any, local, and systemic) as of the 120-Day Safety Update cutoff date (59.3%, 55.1%, and 11.0%, respectively) remained consistent with that of the BLA submission (57.6%, 52.5%, and 11.0%, respectively). TEAEs of infection were reported in 19 additional subjects after the BLA submission, 5 of whom experienced serious infections

(pneumonia, COVID-19, COVID-19 pneumonia, and pilonidal disease). There were no confirmed cases of hypersensitivity or anaphylaxis, which was also consistent with the BLA submission. TEAEs that occurred at a frequency ≥10% in subjects who received at least one dose of SC OCR 920 mg included injection site reaction (55.1%), COVID-19 (30.5%), and urinary tract infection (11.9%). Overall, AEs reported in the 120-Day Safety Update remained consistent with those reported in the BLA submission.

Table 34. Treatment-Emergent Adverse Events Occurring in ≥3% of Subjects Who Received ≥1 SC OCR 920-mg Dose, 120-Day Safety Update, Study CN41144

	SC OCR 920 mg N=118
Preferred Term	**n (%)**
Injection site reaction	65 (55.1)
COVID-19	36 (30.5)
Urinary tract infection	14 (11.9)
Headache	10 (8.5)
Fatigue	9 (7.6)
Upper respiratory tract infection	9 (7.6)
Cough	8 (6.8)
Bronchitis	7 (5.9)
Nasopharyngitis	7 (5.9)
Sinusitis	7 (5.9)
Fall	6 (5.1)
Pneumonia	6 (5.1)
Arthralgia	5 (4.2)
Back pain	5 (4.2)
Migraine	5 (4.2)
Anxiety	4 (3.4)
Contusion	4 (3.4)
Diarrhea	4 (3.4)
Multiple sclerosis pseudo relapse	4 (3.4)
Paresthesia	4 (3.4)
Vulvovaginal mycotic infection	4 (3.4)

Source: Applicant's 120-Day Safety Update, received 3/15/2024
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; PT, preferred term; SC, subcutaneous

7.6.1.6. Laboratory Findings, Study CN42097

Results of the analysis of laboratory value abnormalities for subjects enrolled in Study CN42097 (Controlled Period) are shown in the following tables. Overall, there were no clinically significant differences between the groups in abnormalities in blood chemistry values (Table 35). Refer to Section 17 for additional details regarding individual analytes, including mean/median values at individual timepoints and change over time, and for a discussion of outlier values.

Table 35. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Study CN42097, Controlled Period

Laboratory Parameter	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 2 (<130)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 3 (<125)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Sodium, high (mEq/L)			
Level 1 (>150)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 2 (>155)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 3 (>160)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Potassium, low (mEq/L)			
Level 1 (<3.6)	0/115 (0)	2/115 (1.7)	-1.7 (-6.1, 1.5)
Level 2 (<3.4)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 3 (<3)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Potassium, high (mEq/L)			
Level 1 (>5.5)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 2 (>6)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 3 (>6.5)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Amylase, high (U/L)			
Level 1 (>1.1× ULN)	6/117 (5.1)	7/116 (6.0)	-0.9 (-7.5, 5.5)
Level 2 (>1.5× ULN)	2/117 (1.7)	1/116 (0.9)	0.8 (-3.2, 5.3)
Level 3 (>3× ULN)	0/117 (0)	0/116 (0)	0.0 (-3.2, 3.2)

Source: adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous; ULN, upper limit of normal

There were no clinically significant differences between the groups observed during the Controlled Period in kidney function analyte values (Table 36). Refer to Section 17 for additional details regarding creatinine mean/median values at individual timepoints and change over time, and for a discussion of outlier values.

Table 36. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Study CN42097, Controlled Period

Laboratory Parameter	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5× baseline)	0/115 (0)	2/115 (1.7)	-1.7 (-6.1, 1.5)
Level 2 (≥2× baseline)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 3 (≥3× baseline)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
eGFR, low (mL/min/1.73 m^2)			
Level 1 (≥25% decrease)	1/106 (0.9)	3/109 (2.8)	-1.8 (-7.0, 2.7)
Level 2 (≥50% decrease)	0/106 (0)	0/109 (0)	0.0 (-3.4, 3.5)
Level 3 (≥75% decrease)	0/106 (0)	0/109 (0)	0.0 (-3.4, 3.5)

Source: adlb.xpt; Software: R.
Threshold levels 1, 2, and 3, as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
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; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab, SC, subcutaneous

There were no clinically significant differences observed between the groups during the Controlled Period in hematology analyte values (Table 37). Refer to Section 17 for additional details regarding individual analytes, including mean/median values at individual timepoints and change over time, and for a discussion of outlier values.

Table 37. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Study CN42097, Controlled Period

Laboratory Parameter	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
Complete blood count			
WBC, low (10^3 cells/µL)			
Level 1 (<3.5)	8/114 (7.0)	5/113 (4.4)	2.6 (-3.9, 9.4)
Level 2 (<3)	1/114 (0.9)	3/113 (2.7)	-1.8 (-6.8, 2.4)
Level 3 (<1)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
WBC, high (10^3 cells/µL)			
Level 1 (>10.8)	0/114 (0)	3/113 (2.7)	-2.7 (-7.5, 0.7)
Level 2 (>13)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
Level 3 (>15)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	3/114 (2.6)	2/112 (1.8)	0.8 (-4.0, 5.9)
Level 3 (>2 g/dL dec. from baseline)	1/114 (0.9)	0/112 (0)	0.9 (-2.5, 4.8)
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	1/114 (0.9)	1/112 (0.9)	-0.0 (-4.1, 4.0)
Level 3 (>3 g/dL inc. from baseline)	0/114 (0)	1/112 (0.9)	-0.9 (-4.9, 2.4)
Platelets, low (10^3 cells/µL)			
Level 1 (<140)	0/114 (0)	1/112 (0.9)	-0.9 (-4.9, 2.4)
Level 2 (<125)	0/114 (0)	0/112 (0)	0.0 (-3.3, 3.3)
Level 3 (<100)	0/114 (0)	0/112 (0)	0.0 (-3.3, 3.3)

Laboratory Parameter	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
WBC differential			
Lymphocytes, low (10^3 cells/µL)			
Level 1 (<1)	15/114 (13.2)	20/113 (17.7)	-4.5 (-14.2, 5.0)
Level 2 (<0.75)	4/114 (3.5)	7/113 (6.2)	-2.7 (-9.2, 3.3)
Level 3 (<0.5)	1/114 (0.9)	1/113 (0.9)	-0.0 (-4.1, 4.0)
Lymphocytes, high (10^3 cells/µL)			
Level 1 (>4)	0/114 (0)	1/113 (0.9)	-0.9 (-4.9, 2.4)
Level 2 (>10)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
Level 3 (>20)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
Neutrophils, low (10^3 cells/µL)			
Level 1 (<2)	10/114 (8.8)	9/113 (8.0)	0.8 (-6.8, 8.5)
Level 2 (<1)	0/114 (0)	2/113 (1.8)	-1.8 (-6.2, 1.5)
Level 3 (<0.5)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
Eosinophils, high (10^3 cells/µL)			
Level 1 (>0.65)	1/114 (0.9)	3/113 (2.7)	-1.8 (-6.8, 2.4)
Level 2 (>1.5)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
Level 3 (>5)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)

Source: adlb.xpt; Software: R.
Threshold levels 1, 2, and 3, as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; dec., decrease; inc., increase; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous; WBC, white blood cells

7.6.1.7. Assessment of Drug-Induced Liver Injury, Study CN42097

Results of analyses of liver laboratory abnormalities for subjects for subjects enrolled in Study CN42097 during the Controlled Period are shown in Table 38. There were no clinically significant differences observed between the groups during the Controlled Period in liver biochemistry analyte values. Refer to Section 17 for additional details regarding individual analytes, including mean/median values at individual timepoints and change over time, and for a discussion of outlier values.

Table 38. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study CN42097, Controlled Period

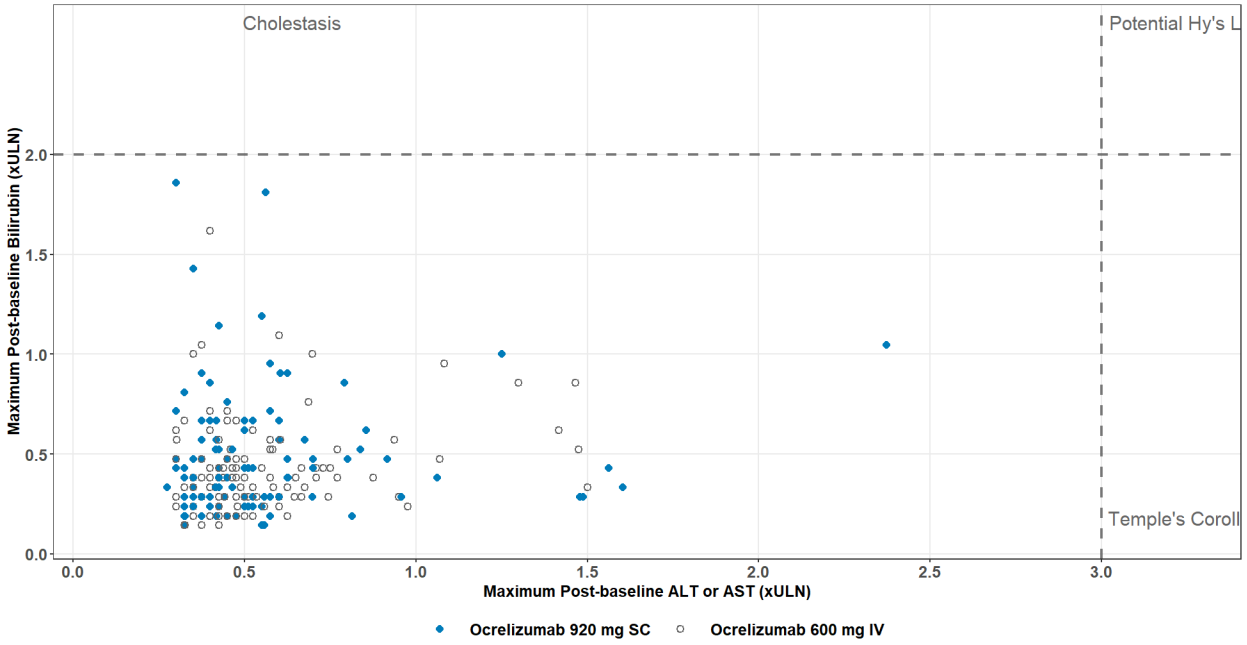
Laboratory Parameter	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5× ULN)	1/115 (0.9)	0/115 (0)	0.9 (-2.4, 4.8)
Level 2 (>2× ULN)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Level 3 (>3× ULN)	0/115 (0)	0/115 (0)	0.0 (-3.2, 3.2)
Alanine aminotransferase, high (U/L)			
Level 1 (>3× ULN)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
Level 2 (>5× ULN)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)
Level 3 (>10× ULN)	0/114 (0)	0/113 (0)	0.0 (-3.3, 3.3)

Laboratory Parameter	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3× ULN)	0/117 (0)	0/116 (0)	0.0 (-3.2, 3.2)
Level 2 (>5× ULN)	0/117 (0)	0/116 (0)	0.0 (-3.2, 3.2)
Level 3 (>10× ULN)	0/117 (0)	0/116 (0)	0.0 (-3.2, 3.2)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5× ULN)	2/112 (1.8)	1/112 (0.9)	0.9 (-3.3, 5.5)
Level 2 (>2× ULN)	0/112 (0)	0/112 (0)	0.0 (-3.3, 3.3)
Level 3 (>3× ULN)	0/112 (0)	0/112 (0)	0.0 (-3.3, 3.3)

Source: adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For specific evaluation of drug-induced liver injury (DILI), see Figure 4 and Figure 5 and Table 39 and Table 40.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; DILI, drug-induced liver injury; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous; ULN, upper limit of normal

Figure 4 shows the results of a screening assessment for potential cases of drug-induced liver injury (DILI). There were no potential Hy's Law cases, as shown in Table 39.

Figure 4. Hepatocellular DILI Screening Plot, Safety Population, Study CN42097, Controlled Period



Source: adlb.xpt; Software: R.
Each datapoint 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 within 30 days after a postbaseline ALT or AST equal to or exceeding 3× ULN, and ALP less than 2× ULN (note ALP values are not circled). All subjects with at least one postbaseline ALT or AST and bilirubin are plotted. The within-30 days analysis window rule does not apply to cholestatic DILI and Temple's Corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; IV, intravenous; SC, subcutaneous; ULN, upper limit of normal

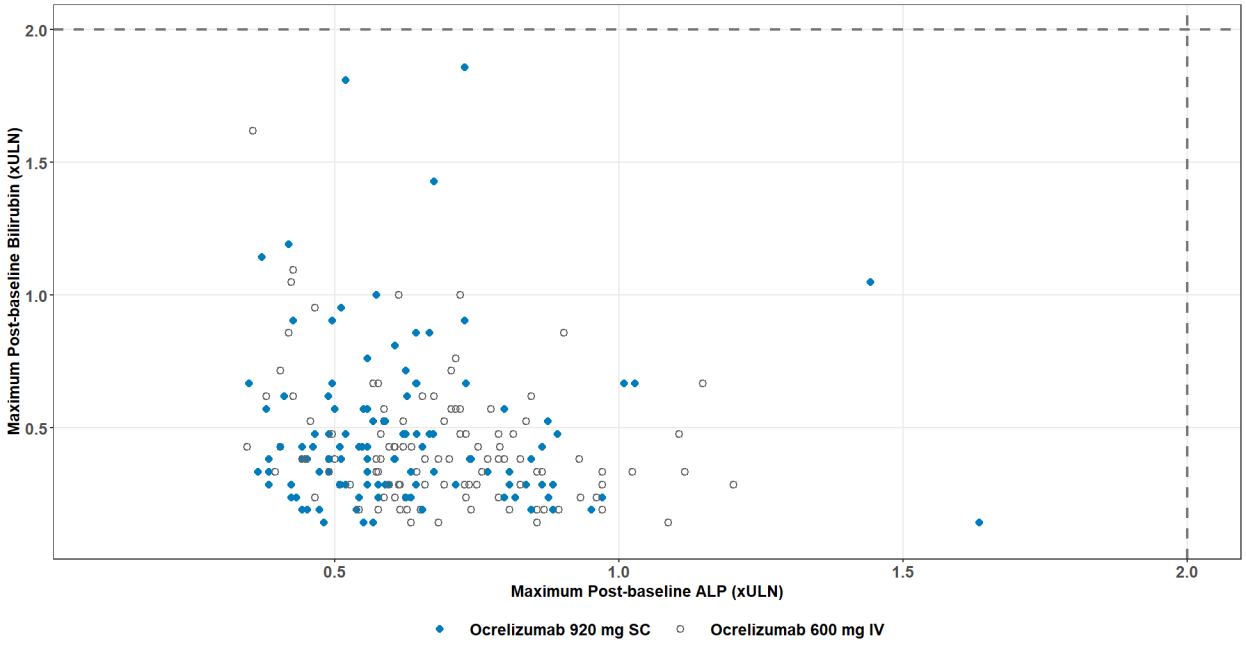
Table 39. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Study CN42097, Controlled Period

Quadrant	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)
Potential Hy's Law (right upper)	0/112 (0)	0/112 (0)
Cholestasis (left upper)	0/112 (0)	0/112 (0)
Temple's Corollary (right lower)	0/112 (0)	0/112 (0)
Total	0/112 (0)	0/112 (0)

Source: adlb.xpt; Software: R.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3× ULN, and ALP less than 2× ULN. The within-30 days analysis window rule does not apply to cholestatic DILI and Temple's Corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous; ULN, upper limit of normal

Figure 5 shows the results of a screening assessment for potential cases of cholestatic DILI. There were no cases potentially consistent with cholestatic DILI, as shown in Table 40.

Figure 5. Cholestatic DILI Screening Plot, Safety Population, Study CN42097, Controlled Period



Source: adlb.xpt; Software: R.
Each datapoint represents a subject plotted by their maximum ALP versus their maximum total bilirubin values in the postbaseline period.
A potential cholestatic DILI case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after postbaseline ALP became equal to or exceeding 2× ULN. The within-30 days analysis window rule does not apply to cholestatic DILI cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; IV, intravenous; SC, subcutaneous; ULN, upper limit of normal

Table 40. Subjects in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, Study CN42097, Controlled Period

Quadrant	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)
Bilirubin ≥2× ULN and ALP ≥2× ULN (right upper)	0/111 (0)	0/112 (0)
Bilirubin ≥2× ULN and ALP <2× ULN (left upper)	0/111 (0)	0/112 (0)
Bilirubin <2× ULN and ALP ≥2× ULN (right lower)	0/111 (0)	0/112 (0)
Total	0/111 (0)	0/112 (0)

Source: adlb.xpt; Software: R.
A potential cholestatic DILI case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after postbaseline ALP became equal to or exceeding 2× ULN. The within-30 days analysis window rule does not apply to cholestatic DILI cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous; ULN, upper limit of normal

7.6.1.8. Vital Signs, Study CN42097

Study CN42097

Vital signs, specifically blood pressure (systolic and diastolic), heart rate, and temperature, were reviewed at each scheduled visit (i.e., ANL02FL=Y) for the safety population during the Controlled Period. Postbaseline (Visits 12 and 24) outlier values from normal baseline values (BNRIND=Y) are presented below. Vital-sign-related TEAEs are also discussed in this section and additional analyses are presented for subjects meeting specific blood pressure parameters.

Blood Pressure

Postbaseline systolic blood pressure (SBP) values below 90 mm Hg or above 160 mm Hg following normal baseline values were infrequent in both treatment groups. SBP <90 mm Hg following normal baseline values occurred in 1.7% (n=2) of subjects on SC OCR and in 0.0% (n=0) of subjects on IV OCR. SBP >160 mm Hg following normal baseline values did not occur in any subjects in either treatment group.

Table 41 presents analyses of maximum SBP levels experienced by subjects at any point after baseline during the Controlled Period, regardless of baseline SBP values. Overall, there was a trend for a higher proportion of subjects with maximum SBP ≥140, 160, and 180 mm Hg in the IV OCR group as compared to the SC OCR group.

Table 41. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Study CN42097, Controlled Period

Systolic Blood Pressure (mm Hg)	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
<90	0/118 (0)	0/118 (0)	0.0 (-3.2, 3.2)
≥90	118/118 (100)	118/118 (100)	0.0 (-3.2, 3.2)
≥120	93/118 (78.8)	96/118 (81.4)	-2.5 (-12.8, 7.8)
≥140	21/118 (17.8)	26/118 (22.0)	-4.2 (-14.5, 6.1)
≥160	1/118 (0.8)	4/118 (3.4)	-2.5 (-7.7, 1.6)
≥180	0/118 (0)	1/118 (0.8)	-0.8 (-4.7, 2.3)

Source: advs.xpt; Software: R.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous

Postbaseline diastolic blood pressure (DBP) values below 60 mm Hg following normal baseline values occurred in 0.8% (n=1) of subjects on SC OCR compared to 1.7% (n=2) of subjects on IV OCR, indicating similar frequencies. DBP >90 mm Hg from normal baseline values occurred in 3.4% (n=4) of subjects on SC OCR and in 3.4% (n=4) of subjects on IV OCR, also indicating similar frequencies.

Table 42 presents analyses of maximum DBP levels experienced by subjects at any point after baseline during the Controlled Period, regardless of baseline DBP levels. A higher proportion of subjects in the IV OCR group experienced maximum DBP ≥90 mm Hg (32.2%) compared to the SC OCR group (19.5%). However, there were no subjects in either treatment group who experienced maximum DBP ≥110 mm Hg.

Table 42. Percentage of Subjects With Maximum Diastolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Study CN42097, Controlled Period

Diastolic Blood Pressure (mm Hg)	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
<60	0/118 (0)	0/118 (0)	0.0 (-3.2, 3.2)
≥60	118/118 (100)	118/118 (100)	0.0 (-3.2, 3.2)
≥90	23/118 (19.5)	38/118 (32.2)	-12.7 (-23.7, -1.5)*
≥110	0/118 (0)	0/118 (0)	0.0 (-3.2, 3.2)
≥120	0/118 (0)	0/118 (0)	0.0 (-3.2, 3.2)

Source: advs.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous

Table 43 presents analyses of subjects meeting specific hypotension levels at any point after baseline, regardless of baseline systolic and DBP levels, during the Controlled Period. Compared to those receiving SC OCR (1.7%), a higher proportion of subjects receiving IV OCR (12.7%) experienced DBP <60 mm Hg at any point after baseline during the Controlled Period. The reason for this difference is not clear; however, the risk of hypotension is discussed in current approved labeling for Ocrevus within the context of infusion reactions.

Table 43. Percentage of Subjects Meeting Specific Hypotension Levels Postbaseline, Safety Population, Study CN42097, Controlled Period

Blood Pressure (mm Hg)	SC OCR N=118 n/N_w (%)	IV OCR N=118 n/N_w (%)	Risk Difference % (95% CI)
SBP <90	3/118 (2.5)	3/118 (2.5)	-0.0 (-5.0, 5.0)
DBP <60	2/118 (1.7)	15/118 (12.7)	-11.0 (-18.5, -5.0)*

Source: advs.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SBP, systolic blood pressure; SC, subcutaneous

The TEAE hypertension occurred in 0.8% (n=1) of subjects on SC OCR and in 0.0% (n=0) of subjects on IV OCR. There were no subjects in either treatment group who experienced TEAEs of blood pressure increased, hypertensive crisis, hypotension, or blood pressure decreased.

Although there appeared to be a trend for higher SBP and DBP levels in the IV OCR group, as compared to the SC OCR group, there did not appear to be any clinically significant changes in blood pressure in either treatment group. Section 5.1 (Warnings and Precautions, Infusion Reactions) of current approved labeling for Ocrevus discusses the risk of hypotension in the context of infusion reactions. Because the Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus, the risk of hypotension within the context of infusion and systemic injection reactions will also be included as a warning in labeling for SC OCR, should approval be granted. Refer to Section 7.7.1 for a discussion of injection-related reactions that occurred in subjects treated with SC OCR during the Controlled Period of Study CN42097.

Heart Rate

There were no subjects in either treatment group with postbaseline HR below 50 beats per minute (bpm) or above 120 bpm following normal baseline values. Additionally, there were no subjects in either treatment group that experienced TEAEs of tachycardia, sinus tachycardia, heart rate increased, bradycardia, sinus bradycardia, or heart rate decreased.

Overall, there did not appear to be any clinically significant changes in heart rate in subjects treated with SC OCR compared to IV OCR. However, Section 5.1 (Warnings and Precautions, Infusion Reactions) of current approved labeling for Ocrevus discusses the risk of tachycardia in the context of infusion reactions. Because the Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus, the risk of tachycardia in the context of infusion and systemic injection reactions will also be included as a warning in labeling for SC OCR, should approval be granted. Refer to Section 7.7.1 for a discussion of injection-related reactions that occurred in subjects treated with SC OCR during the Controlled Period of Study CN42097.

Temperature

There were no subjects in either treatment group that experienced postbaseline temperature >38.1°C following normal baseline values. Postbaseline temperature <36°C following normal baseline values occurred in 0.8% (n=1) of subjects on IV OCR. There were no occurrences of postbaseline temperature <36°C following normal baseline values in subjects receiving SC OCR.

The TEAE pyrexia occurred in 0.8% (n=1) of subjects on SC OCR compared to 1.7% (n=2) of subjects on IV OCR. There were no subjects in either treatment group who experienced the TEAEs body temperature increased, hyperthermia, body temperature decreased, or hypothermia. Overall, there did not appear to be any clinically significant differences in temperature in subjects treated with SC OCR compared to IV OCR.

Study CN41144

Given the adaptive design and open-label nature of Study CN41144, a detailed review of vital signs will not be presented for that trial.

7.6.1.9. Subgroups, Study CN42097

Results of analyses of TEAEs by demographic subgroup for subjects enrolled in Study CN42097 are shown in Table 44. Results of subgroup analyses appear consistent with the overall results presented in Sections 7.6.1.1 and 7.6.1.5, as a higher proportion of subjects receiving SC OCR across demographic subgroups experienced any TEAE, as compared to those receiving IV OCR.

Table 44. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study CN42097

Characteristic	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Sex			
Female	59/77 (76.6)	34/70 (48.6)	28.1 (12.5, 42.4)*
Male	28/41 (68.3)	20/48 (41.7)	26.6 (5.8, 45.1)*
Age group, years			
18 to 65	87/118 (73.7)	54/118 (45.8)	28.0 (15.6, 39.5) *
Race			
Asian	0/0 (NA)	1/1 (100)	NA
Black or African American	5/7 (71.4)	1/1 (100)	-28.6 (-66.1, 61.3)
Multiple	1/3 (33.3)	0/1 (0)	33.3 (-66.9, 82.7)
Native Hawaiian or other Pacific Islander	0/0 (NA)	1/1 (100)	NA
Unknown	1/6 (16.7)	0/5 (0)	16.7 (-33.5, 58.1)
White	80/102 (78.4)	51/109 (46.8)	31.6 (18.9, 43.4) *
Ethnicity			
Hispanic or Latino	6/7 (85.7)	7/8 (87.5)	-1.8 (-43.6, 38.2)
Non-Hispanic or Latino	73/95 (76.8)	40/93 (43.0)	33.8 (20.1, 46.3)*
Not reported	7/14 (50.0)	7/15 (46.7)	3.3 (-31.8, 37.7)
Unknown	1/2 (50.0)	0/2 (0)	50.0 (-46.8, 92.4)
Is in United States			
United States	13/16 (81.2)	11/16 (68.8)	12.5 (-18.5, 41.7)
Non-United States	74/102 (72.5)	43/102 (42.2)	30.4 (17.0, 42.7)*

Source: adae.xpt; Software: R.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N, number of subjects; OCR, ocrelizumab; SC, subcutaneous

7.7. Key Safety Review Issues

7.7.1. Injection-Related Reactions

Issue

Local injection-related reactions are expected with subcutaneously administered drugs. Adverse reactions of local injection site reactions, such as erythema and pain, have been reported with postmarket use of recombinant hyaluronidase and are listed in Section 6 (Adverse Reactions) of current approved labeling for Hylenex recombinant (Halozyme 2024).

Background

Injection-related reactions (local and systemic) were observed during the Controlled Period of Study CN42097 in subjects receiving SC OCR. TEAEs of local and systemic injection-related reactions were common in the SC OCR group and occurred in 47.5% and 11.0% of subjects, respectively, following the first injection. Overall, 49.2% of subjects experienced an injection reaction with the first dose of SC OCR.

Definition of Injection- and Infusion-Related Reactions

The CSR for Study CN42097 and Protocol CN42097 (version 2) Section 5.3.5.1 (Infusion-Related Reactions or Injection Reactions) indicated that "Injection reactions (IRs) comprise AEs with the MedDRA [Preferred Terms (PTs)] Injection related reaction and Injection site reaction which occurred during or within 24 hours after ocrelizumab SC administration and which were judged by the investigator to be related to the ocrelizumab SC injection," and that "Infusion related reactions (IRRs) comprise AEs with the MedDRA PTs Infusion related reaction which occurred during or within 24 hours after ocrelizumab IV administration and which were judged by the investigator to be related to the ocrelizumab IV infusion." Per the protocol, signs and symptoms associated with infusion-and injection-related reactions were recorded on a dedicated electronic case report form.

Reporting of Adverse Events of Injection- and Infusion-Related Reactions

Section 5.3.5.2 (Diagnosis vs. Signs and Symptoms) of Protocol CN42097 (version 2) recommended that a diagnosis (rather than individual signs and symptoms) should be recorded on the electronic case report form for any AE unless the presenting signs and symptoms could not be consolidated under an individual diagnosis at the time of AE reporting. Once the final diagnosis was established, the protocol recommended to "nullify" the initially reported signs and symptoms and to replace them with a single diagnosis-based AE report.

Premedication Administration Window and Postinjection Monitoring

Prior to the BLA submission, on February 21, 2023, the Sponsor submitted amendments for Protocols CN41144 (version 6) and CN42097 (version 3) to shorten the premedication administration window from one to two hours to "shortly before initiating the ocrelizumab SC injection" and to remove the mandatory one-hour postinjection monitoring period following SC OCR administration, reportedly based on safety data from Study CN41144.

Current approved labeling for Ocrevus also indicates that patients should be closely monitored during and for at least one hour after each infusion. Per Ocrevus labeling, patients should also be premedicated "with 100 mg of methylprednisolone (or an equivalent corticosteroid) administered IV approximately 30 minutes prior" and with "an antihistamine (e.g., diphenhydramine) approximately 30-60 minutes prior to each OCREVUS infusion to further reduce the frequency and severity of infusion reactions." Therefore, these protocol amendments were not considered acceptable by the Agency.

Based on Agency's feedback provided on June 1, 2023, protocols CN41144 (version 7) and CN42097 (version 4) were submitted on July 10, 2023, proposing a revised premedication administration window of 30 to 60 minutes and reintroducing the mandatory 1-hour postinjection monitoring period, in alignment with Ocrevus labeling. Of note, the amendments proposing a premedication administration window of "shortly before initiating the ocrelizumab SC injection" and removing the one-hour postinjection monitoring period were implemented at non-US sites.

Assessment

Coding of Adverse Events of Injection- or Infusion-Related Reactions and Adverse Event Datasets

Upon review of this safety issue, the Division found that most TEAEs of injection-related reactions were coded to the MedDRA PT injection related reaction. The coding of most TEAEs of injection-related reaction to this MedDRA PT, rather than to more granular PTs that indicated the signs or symptoms observed by investigators for each injection-related reaction (e.g., injection site erythema, injection site pain) did not allow for the Division to comprehensively characterize the spectrum of local and systemic injection-related reactions that occurred with SC OCR.

Several Information Requests were sent to the Applicant to ensure all available information regarding verbatim terms for AEs was submitted to the BLA, to clarify the methods for collection of injection reaction-related AEs, to clarify the source of the information provided in the submitted datasets (i.e., subjects versus investigators), to ensure that all potential injection reactions were captured, to clarify the nature and timing of injection reactions, to clarify noted discrepancies in AE datasets, and to request additional datasets and analyses from the Applicant. As a result of these Information Requests, three additional AEs were considered to be injection reactions for purposes of the Agency's analysis.

Following clarification of the issues discussed above, the Agency's analyses of injection-related reactions and infusion-related reactions presented in this section of the review were performed based on the updated ADAE2 dataset, received on June 21, 2024.

FDA Analyses of Treatment-Emergent Adverse Events of Injection- and Infusion-Related Reactions

All Injection-Related Reactions (Local and Systemic)

Table 45 presents the frequency of AEs of local and systemic injection-related reactions, as defined in the study protocol (i.e., those that occurred within the first 24 hours following a SC OCR injection and that were considered by the investigator to be related to the study drug) that occurred in the Safety Population. There were no reported life-threatening or severe injection-

related reactions. Specifically, of the subjects who experienced injection-related reactions within 24 hours following SC OCR injection (n=58), 72.4% (42/58) experienced mild and 27.6% (16/58) experienced moderate events. Additionally, no events of injection-related reactions resulted in study treatment discontinuation. The duration of the reported injection-related reactions ranged from 1 to 16 days, with a median duration of 3 days.

Table 45. Adverse Events of Injection-Related Reactions (Custom Query) That Occurred Within 24 Hours After SC OCR Injection, Safety Population, Study CN42097, Controlled Period

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Injection related reactions (GQ)	58 (49.2)	0 (0.0)	49.2 (40.3, 58.1)*
Injection related reaction	55 (46.6)	0 (0.0)	46.6 (37.8, 55.6)*
Injection site erythema	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Injection site reaction	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Injection site warmth	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Moderate	16 (13.6)	0 (0.0)	13.6 (8.5, 20.9)*
Mild	42 (35.6)	0 (0.0)	35.6 (27.5, 44.6)*
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	58 (49.2)	0 (0.0)	49.2 (40.3, 58.1)*
Number of subjects with adverse events with end dates on or before treatment end dates	58/58 (100)	0/0 (NA)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	4.1 (3.2)	NA	NA
Median (Q1, Q3)	3 (2, 5)	NA	NA
Min, max	1, 16	NA, NA	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/58 (0.0)	0/0 (NA)	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/58 (0.0)	0/0 (NA)	NA

Source: adae2.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab, Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Table 46 presents the frequency of injection-related reactions (local and systemic) that occurred in the Safety Population at any time following SC OCR injection. Again, no events of life-threatening or severe injection-related reactions were reported. Specifically, of the 59 subjects who experienced an injection-related reaction at any time following SC OCR injection, 72.9% (43/59) experienced mild and 27.1% (16/59) experienced moderate events. Additionally, no events of injection-related reactions resulting in study treatment discontinuation occurred. The

duration of the reported injection-related reactions ranged from 1 to 16 days, with a median duration of 3 days. All events were considered resolved by the data cutoff date.

Table 46. Adverse Events of Injection-Related Reactions (Custom Query) That Occurred at Any Time After SC OCR Injection, Safety Population, Study CN42097, Controlled Period

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Injection related reactions (GQ)	59 (50.0)	0 (0.0)	50.0 (41.1, 58.9)*
Injection related reaction	55 (46.6)	0 (0.0)	46.6 (37.8, 55.6)*
Injection site erythema	3 (2.5)	0 (0.0)	2.5 (-0.7, 7.2)
Injection site reaction	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Injection site warmth	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Moderate	16 (13.6)	0 (0.0)	13.6 (8.5, 20.9)*
Mild	43 (36.4)	0 (0.0)	36.4 (28.3, 45.4)*
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	59 (50.0)	0 (0.0)	50.0 (41.1, 58.9)*
Number of subjects with adverse events with end dates on or before treatment end dates	59/59 (100)	0/0 (NA)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	4.1 (3.2)	NA	NA
Median (Q1, Q3)	3 (2, 5)	NA	NA
Min, max	1, 16	NA, NA	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/59 (0.0)	0/0 (NA)	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/59 (0.0)	0/0 (NA)	NA

Source: adae2.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab, Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Local Injection-Related Reactions

Table 47 presents the frequency of protocol-defined local injection-related reactions that occurred in the safety population within 24 hours following SC OCR injection and that were considered by the investigator to be related to the study drug (Controlled Period). No life-threatening or severe local injection-related reactions occurred. Specifically, of the 55 subjects who experienced local injection-related reactions within 24 hours following SC OCR injection, 72.7% (40/55) experienced mild and 27.3% (15/55) experienced moderate events of local injection-related reactions. Additionally, no events of local injection-related reactions resulted in

study treatment discontinuation. The duration of the reported injection-related reactions ranged from 1 to 16 days, with a median duration of 3.5 days.

Table 47. Adverse Events of Local Injection-Related Reactions (Custom Query) That Occurred Within 24 Hours After SC OCR Injection, Safety Population, Study CN42097, Controlled Period

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Injection related reactions, local (GQ)	55 (46.6)	0 (0.0)	46.6 (37.8, 55.6)*
Injection related reaction	52 (44.1)	0 (0.0)	44.1 (35.4, 53.1) *
Injection site reaction	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Injection site erythema	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Injection site reaction	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Moderate	15 (12.7)	0 (0.0)	12.7 (7.8, 19.9)*
Mild	40 (33.9)	0 (0.0)	33.9 (26.0, 42.8)*
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	55 (46.6)	0 (0.0)	46.6 (37.8, 55.6)*
Number of subjects with adverse events with end dates on or before treatment end dates	55/55 (100)	0/0 (NA)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	4.3 (3.2)	NA	NA
Median (Q1, Q3)	3.5 (2, 5.5)	NA	NA
Min, max	1, 16	NA, NA	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/55 (0.0)	0/0 (NA)	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/55 (0.0)	0/0 (NA)	NA

Source: adae2.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Reactions were determined to be local, systemic, or local/systemic by the Applicant, per protocol.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab, Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Table 48 presents the frequency of events of local injection-related reactions that occurred at any time following a SC OCR injection. No events were life-threatening or severe. Specifically, of the 56 subjects who experienced TEAEs of local injection-related reactions following SC OCR injection, 73.2% (41/56) experienced mild and 26.8% (15/56) experienced moderate events. Additionally, no events of local injection-related reactions resulted in study treatment discontinuation. The duration of the reported injection-related reactions ranged from 1 to 16 days, with a median of 3.5 days.

Table 48. Adverse Events of Local Injection-Related Reactions (Custom Query) That Occurred at Any Time After SC OCR Injection, Safety Population, Study CN42097, Controlled Period

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Injection related reactions, local (GQ)	56 (47.5)	0 (0.0)	47.5 (38.7, 56.4)*
Injection related reaction	52 (44.1)	0 (0.0)	44.1 (35.4, 53.1)*
Injection site erythema	3 (2.5)	0 (0.0)	2.5 (-0.7, 7.2)
Injection site reaction	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Injection site warmth	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Moderate	15 (12.7)	0 (0.0)	12.7 (7.8, 19.9)*
Mild	41 (34.7)	0 (0.0)	34.7 (26.7, 43.7)*
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	56 (47.5)	0 (0.0)	47.5 (38.7, 56.4)*
Number of subjects with adverse events with end dates on or before treatment end dates	56/56 (100)	0/0 (NA)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	4.2 (3.2)	NA	NA
Median (Q1, Q3)	3.5 (2, 5.2)	NA	NA
Min, max	1, 16	NA, NA	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/56 (0.0)	0/0 (NA)	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/56 (0.0)	0/0 (NA)	NA

Source: adae2.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Reactions were determined to be local, systemic, or local/systemic by the Applicant, per protocol.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab, Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Systemic Injection-Related Reactions

Table 49 summarizes events of protocol-defined systemic injection-related reactions that occurred in the Safety Population within the first 24 hours following a SC OCR injection and that were considered by the investigator to be related to the study drug. Of note, only systemic injection-related reactions that occurred within 24 hours following SC OCR injection were recorded as injection reactions by the Applicant. There were no life-threatening or severe systemic injection-related reactions. Specifically, of the 13 subjects who experienced systemic injection-related reactions, 46.2% (6/13) experienced mild and 53.8% (7/13) experienced moderate events. Additionally, there were no events resulting in study treatment discontinuation. The duration of the reported systemic injection-related reactions ranged from 1 to 16 days, with a median of 3 days.

Table 49. Adverse Events of Systemic Injection-Related Reactions (Custom Query), Safety Population, Study CN42097, Controlled Period

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Injection related reactions, systemic (GQ)	13 (11.0)	0 (0.0)	11.0 (6.5, 18.0)*
Injection related reaction	12 (10.2)	0 (0.0)	10.2 (5.9, 17.0)*
Injection site reaction	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Moderate	7 (5.9)	0 (0.0)	5.9 (2.7, 11.8)*
Mild	6 (5.1)	0 (0.0)	5.1 (1.8, 10.7)*
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	13 (11.0)	0 (0.0)	11.0 (6.5, 18.0)*
Number of subjects with adverse events with end dates on or before treatment end dates	13/13 (100)	0/0 (NA)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	5.6 (4.8)	NA	NA
Median (Q1, Q3)	3 (2, 8)	NA	NA
Min, max	1, 16	NA, NA	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/13 (0.0)	0/0 (NA)	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/13 (0.0)	0/0 (NA)	NA

Source: adae2.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Reactions were determined to be local, systemic, or local/systemic by the Applicant, per protocol.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab, Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Infusion-Related Reactions

Table 50 summarizes events of protocol-defined infusion-related reactions in the Safety Population that occurred within the first 24 hours following an IV OCR infusion and that were considered by the investigator to be related to treatment with IV OCR. There were no life-threatening or severe infusion-related reactions. Specifically, of the 21 subjects who experienced infusion-related reactions, 42.9% (9/21) experienced mild and 57.1% (12/21) experienced moderate events. Additionally, there were no events resulting in study treatment discontinuation. The duration of the reported infusion-related reactions ranged from 1 to 15 days, with a median of 1 day.

Table 50. Adverse Events of Infusion-Related Reactions (Custom Query) That Occurred Within 24 Hours of IV OCR Infusion, Safety Population, Study CN42097, Controlled Period

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Infusion reactions (GQ)	0 (0.0)	21 (17.8)	-17.8 (-25.7, -11.9)*
Infusion-related reaction	0 (0.0)	20 (16.9)	-16.9 (-24.8, -11.2)*
Nausea	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Moderate	0 (0.0)	12 (10.2)	-10.2 (-17.0, -5.9)*
Mild	0 (0.0)	9 (7.6)	-7.6 (-13.9, -4.1)*
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	0 (0.0)	20 (16.9)	-16.9 (-24.8, -11.2)*
Number of subjects with adverse events with end dates on or before treatment end dates	0/0 (NA)	21/21 (100)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	NA	3.1 (3.5)	NA
Median (Q1, Q3)	NA	1 (1, 4)	NA
Min, max	NA, NA	1, 15	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/0 (NA)	0/21 (0.0)	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/0 (NA)	0/21 (0.0)	NA

Source: adae2.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab, Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Table 51 summarizes the frequency of events of infusion-related reactions in the Safety Population that occurred within 2 days of an IV OCR infusion. No events of life-threatening or severe infusion-related reactions occurred. Specifically, of the 22 subjects who experienced infusion-related reactions within 2 days from infusion, 36.4% (8/22) experienced mild and 63.6% (14/22) experienced moderate events. Additionally, no events resulted in study treatment discontinuation. The duration of the reported infusion-related reactions ranged from 1 to 15 days, with a median of 1 day.

Table 51. Adverse Events of Infusion-Related Reactions (Custom Query) That Occurred Within 2 Days From IV OCR Infusion, Safety Population, Study CN42097, Controlled Period

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Infusion reactions (GQ)	0 (0.0)	22 (18.6)	-18.6 (-26.6, -12.6)*
Infusion-related reaction	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Fatigue	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Headache	0 (0.0)	20 (16.9)	-16.9 (-24.8, -11.2)*
Nausea	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Moderate	0 (0.0)	14 (11.9)	-11.9 (-19.0, -7.2)*
Mild	0 (0.0)	8 (6.8)	-6.8 (-12.8, -3.5)*
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	0 (0.0)	20 (16.9)	-16.9 (-24.8, -11.2)*
Number of subjects with adverse events with end dates on or before treatment end dates	0/0 (NA)	22/22 (100)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	NA	3.5 (4)	NA
Median (Q1, Q3)	NA	1 (1, 4)	NA
Min, max	NA, NA	1, 15	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/0 (NA)	0/22 (0.0)	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/0 (NA)	0/22 (0.0)	NA

Source: adae2.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab, Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

Premedication Administration Window

Section 2 ((b) (4) Recommended Premedication) of the proposed labeling for SC OCR indicated that patients should be premedicated "orally with 20 mg of dexamethasone (or an equivalent corticosteroid) and an antihistamine (e.g., desloratadine) administered (b) (4) each OCREVUS ZUNOVO administration to reduce the risk of local and systemic injection reactions." However, in Study CN42097, premedication was initially administered 1 to 2 hours prior to each study treatment administration (see Background section above) and per Ocrevus labeling, patients should be premedicated "with 100 mg of methylprednisolone (or an equivalent corticosteroid) administered IV approximately 30 minutes prior" and with "an antihistamine (e.g., diphenhydramine) approximately 30-60 minutes prior to each OCREVUS infusion to further reduce the frequency and severity of infusion reactions."

An Information Request was sent to the Applicant to obtain additional data to support the premedication regimen and timing [redacted], which conflicted with that in the protocols for Studies CN41144 and CN42097 and were subject to interpretation.

To support their proposal, the Applicant indicated that, following the protocol amendment to implement a premedication administration window of "shortly before" SC OCR administration for non-US sites, 53.2% (n=124 [OCR SC All analysis set, n=233]) of subjects had at least one SC OCR injection with premedication administered ≤30 minutes from the start of the injection and that 39.5% (n=92) of subjects had at least one SC OCR injection with premedication administered ≥20 and ≤40 minutes from the start of the injection. Per the Applicant, both premedication administration windows (≤30 minutes and ≥20 to ≤40 minutes) were considered in their proposal to specify a premedication administration window of [redacted] 30 minutes" in labeling for SC OCR. Refer to Table 52 for additional details regarding timing of premedication administration window prior to SC OCR in Study CN42097.

Table 52. Median Premedication Administration Timing for Subcutaneously Administered OCR, SC OCR All Analysis Set, Study CN42097

	SC OCR Premedication Administration Timing (Prior to Dosing, Minutes)	
Injection Number	**Median**	**Range**
1	65.02	2.0 to 140.0
2	60.02	3.0 to 144.0
3	35.02	0.0 to 499.0
4	31.02	5.0 to 80.0

Source: Applicant's Response to Information Request, dated 6/14/2024.
Data cutoff date: 120-Day Safety Update (12/4/2023)
Abbreviations: OCR, ocrelizumab; SC, subcutaneous

Per the Applicant, there were no additional safety concerns identified for subjects who received SC OCR with the shorter premedication administration window of [redacted] 30 minutes." However, an analysis of AEs by premedication timing was not presented. Refer to the Conclusion section below for additional details.

Postinjection Monitoring

Section 5.1 (Warnings and Precautions, Injection Reactions) of proposed labeling indicated that "[redacted]" and that "[redacted]." [redacted] Protocols CN41144 and CN42097 and current approved labeling for Ocrevus specify a one-hour postinjection monitoring period after each dose (refer to Background section above). An Information Request was sent to the Applicant to obtain a justification for this proposal, which was based on safety data collected from Study CN42097, as of the 120-Day Safety Update cutoff date and is summarized below.

Injection-Related Reactions (Overall)

The Applicant indicated that injection-related reactions reported with SC OCR were mostly local injection-related reactions (e.g., erythema, pain, and swelling) and mild systemic injection-related reactions (i.e., headache, flushing, and nausea) that were nonserious, mild, or moderate, did not result in treatment discontinuation, and resolved without treatment in most cases. Additionally, the Applicant stated that the type of symptoms experienced by subjects did not

depend on time-to-event onset (except for bruising, which typically occurred more than an hour after SC OCR injection).

Per the Applicant, the proportion of subjects who required treatment for injection-related reactions decreased with subsequent injections (21.9% following the first injection and 7.1% following the fourth injection). Treatments included analgesics and topical or systemic antihistamines. The Applicant concluded that the one-hour postinjection monitoring period for subsequent injections was not warranted based on the overall profile of injection-related reactions observed during Study CN42097.

Local Injection-Related Reactions

Regarding local injection reactions, the Applicant stated that the most common symptoms reported by subjects were injection site erythema, injection site pain, injection site swelling, and injection site pruritus. Per the Applicant, all local injection-related reactions were mild or moderate in severity, their incidence was highest with the first injection and decreased with subsequent injections, and the majority occurred within the first hour from the end of the injection. The Applicant concluded that the one-hour postinjection monitoring period was not warranted based on the profile of local injection-related reactions observed during Study CN42097.

The Applicant's claim that the risk of local injection-related reactions decreased with subsequent injections does not appear to be supported by data presented in the 120-Day Safety Update. Refer to Figure 6 below for additional details regarding the frequency of local injection-related reactions observed with subsequent SC OCR injections.

Systemic Injection-Related Reactions

In terms of systemic injection-related reactions, per the Applicant, there were a total of 17 events that occurred within 24 hours from the end of the injection, of which 9 (52.9%) occurred within 1 hour from the end of the injection. The most common symptoms were headache (2.1%), flushing (1.3%), and nausea (1.3%). The type of systemic injection-related reaction experienced by subjects, according to the Applicant, did not depend on time-to-event onset (except for flushing and fatigue, which typically occurred more than one hour after the end of the injection). Per the Applicant, all systemic injection-related reactions were mild or moderate in severity and their incidence was highest with the first injection and decreased with subsequent injections.

The Applicant's claim that the risk of systemic injection-related reactions decreased with subsequent injections does not appear to be supported by data presented in the 120-Day Safety Update. Refer to Figure 7 below for additional details regarding the frequency of systemic injection-related reactions observed with subsequent SC OCR injections.

When considering the proposed one-hour postinjection observation period, the Division also considered the need for and timing of treatment for both local and systemic injection reactions, by dose number. This information is summarized in Table 53.

Table 53. Characterization of Systemic Injection-Related Reactions That Required Symptomatic Treatment Stratified by Dose Number and by Time-to-Event Onset, SC OCR All Set, Study CN42097, Treatment Period

Injection Number	N	Subjects With Any IRR n (%)	Subjects With at Least One Local IRR n (%)	Subjects With at Least One Systemic IRR n (%)	Subjects With Systemic IRRs Requiring Symptomatic Treatment n (%)	Subjects With Systemic IRRs Requiring Symptomatic Treatment – Time to Onset			
						During Injection n (%)	≤1 hr After Injection Completion n (%)	>1 hr to ≤24 hrs After Injection Completion n (%)	>24 hrs After Injection Completion* n (%)
1	118	58 (49.2)	55 (46.6)	13 (11.0)	4 (3.4)	0 (0.0)	2 (1.7)	2 (1.7)	NC
2	118	39 (33.1)	37 (31.4)	4 (3.4)	2 (1.7)	1 (0.8)	0 (0.0)	1 (0.8)	NC
3	114	37 (32.4)	37 (32.5)	4 (3.5)	2 (1.8)	0 (0.0)	1 (0.9)	1 (0.9)	NC
4	30	14 (46.6)	13 (43.3)	2 (6.7)	1 (3.3)	0 (0.0)	0 (0.0)	1 (3.3)	NC

Source: Adapted from Applicant's Response to Information Request, dated 7/24/2024.
Data cutoff date: 120-Day Safety Update (12/4/2023)
*Systemic IRRs that occurred >24 hrs after injection completion did not meet the protocol definition of IRR. Therefore, this information was not collected by the Applicant.
Abbreviations: IRR, injection-related reaction; N, number of subjects who remained on SC OCR throughout the duration of the study; n, number of subjects who experienced each event; NC, not collected.

The proportion of subjects who experienced each type of injection-related reaction for injections 3 and 4, as presented by the Applicant, was based on the total number of subjects enrolled in the SC OCR/SC OCR group (n=118), rather than on the number of subjects who received each injection, which is not appropriate. Therefore, the proportion of subjects presented in Table 53 for injections 3 and 4 represents the Agency's revisions. The number and proportion of subjects who experienced any injection-related reaction or a local injection-related reaction during the first injection were also revised based on updates made by the Applicant to the ADAE2 dataset (see above).

Of note, Subject # (b) (6) experienced a Grade 2 event of systemic injection-related reaction characterized by "feeling of dry mouth accompanied by feeling of tongue swelling" that occurred 4 minutes after completion of the third SC OCR injection. The event resolved after the subject received treatment with oral bisulepin hydrochloride. This event could potentially be consistent with a hypersensitivity reaction.

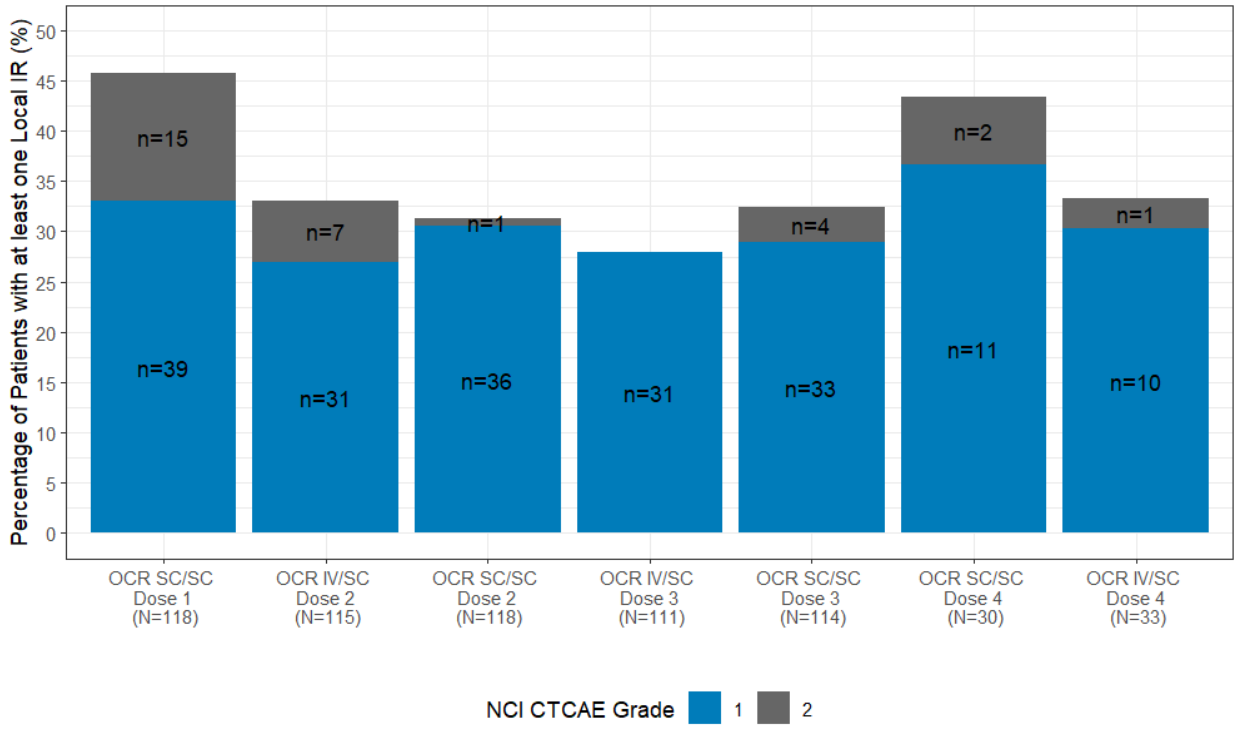
The Applicant indicated that three of the events of systemic injection-related reaction that required symptomatic treatment reported in Table 53 only required symptomatic treatment due to a concomitant local or systemic symptom that was not considered part of the systemic injection-related reaction. Such events included one event of lightheadedness and one event of headache that occurred within one hour after completion of injection #1 and one event of chills that occurred >1 hour to ≤24 hours after the completion of injection #1. Per the Applicant, overall, the benign nature of the symptoms experienced by subjects with systemic injection-related reactions that required symptomatic treatment and the low frequency of these events do not warrant a mandatory one-hour postinjection monitoring period with subsequent SC OCR injections.

Per the Applicant, with subsequent injections, the risk of developing an injection-related reaction decreased and injection-related reactions occurred at a lower frequency and severity and required symptomatic treatment less often, compared to the first injection. This trend appeared to be most apparent when comparing the first and the second injections, but was not apparent when comparing the third or fourth injections with the first injection (refer to Figure 6 and Figure 7 for local and systemic injection reactions, respectively).

The group that remained on SC OCR throughout the Treatment Period (SC OCR/SC OCR) and the group that switched from IV OCR to SC OCR (IV OCR/SC OCR group) after Week 24 are not comparable in terms of exposure to hyaluronidase, which affects the risk of experiencing an injection-related reaction. Dose #2 was the second hyaluronidase and second ocrelizumab exposure for the SC OCR/SC OCR group, but was the first hyaluronidase and second ocrelizumab exposure for the IV OCR/SC OCR group. Therefore, the Agency's evaluation of risk of injection-related reactions with subsequent injections was performed based on data from the SC OCR/SC OCR group only (n=118).

The Applicant's analyses of frequency of TEAEs of local and systemic injection-related reactions reported with subsequent SC OCR injections are presented in Figure 6 and Figure 7, respectively. The Clinical review team was able to replicate the Applicant's analyses upon submission of updated datasets.

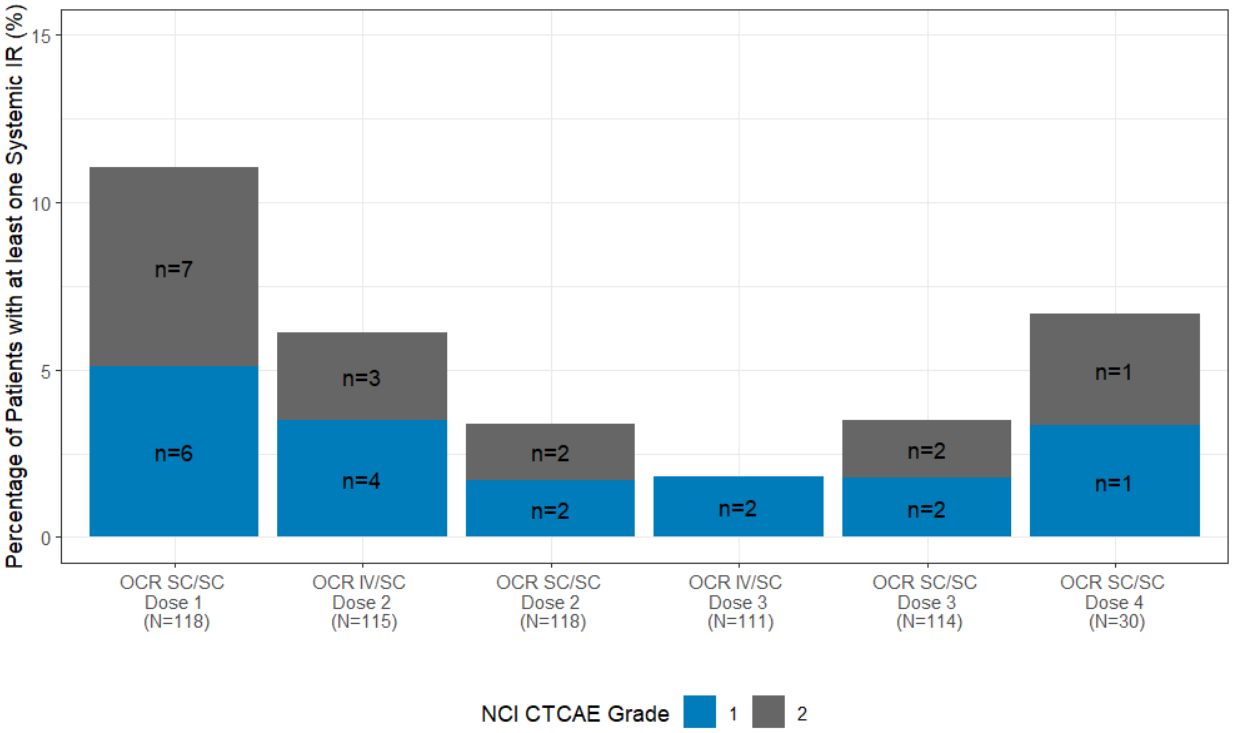
Figure 6. Frequency of Treatment-Emergent Adverse Events of Local Injection-Related Reactions During the Controlled Period and the SC Treatment Period, SC OCR All Set, Study CN42097



Source: adae2.xpt, adex.xpt; adsl.xpt; Software: R.
Percentage of subjects with at least one IR for each injection is calculated as number of subjects with IRs at this injection (n) divided by the number of subjects who received the injection per treatment arm (N).
Reactions were determined to be local, systemic, or local/systemic by the Applicant, per protocol.
Abbreviations: IR; injection reaction; OCR, ocrelizumab; SC, subcutaneous; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event

Per the data presented in the 120-Day Safety Update, the proportion of subjects who remained on SC OCR throughout the Controlled and SC OCR Treatment Periods that experienced local injection-related reactions appeared to decrease between the first (54/118, 45.8%) and the second injections (37/118, 31.4%), but this reduction was not apparent between the second and third injections (37/114, 32.5%). Data for the fourth injection were only available for a few subjects (13/30, 43.3%) and are therefore difficult to interpret.

Figure 7. Frequency of Treatment-Emergent Adverse Events of Systemic Injection-Related Reactions During the Controlled Period and the SC Treatment Period, SC OCR All Set, Study CN42097



Source: adae2.xpt, adex.xpt; adsl.xpt; Software: R.
Percentage of subjects with at least one IR for each injection is calculated as number of subjects with IRs at this injection (n) divided by the number of subjects who received the injection per treatment arm (N).
Reactions were determined to be local, systemic, or local/systemic by the Applicant, per protocol.
Abbreviations: IR; injection reaction; IV, intravenous; OCR, ocrelizumab; SC, subcutaneous; N, number of subjects in treatment arm; n, number of subjects with adverse event

Per the data presented in the 120-Day Safety update, the proportion of subjects who remained on SC OCR throughout the Controlled and SC OCR Treatment Periods who experienced systemic injection-related reactions appeared to decrease between the first (15/118, 12.7%) and the second injection (4/118, 3.4%), but this reduction was not apparent between the second and third injections (4/114, 3.5%). Data for the fourth injection were only available for a few subjects (2/30, 6.7%) and are therefore difficult to interpret.

Regarding timing of these events, 52% of overall injection-related reactions (9/17 events) occurred within the first hour following completion of the injection. The Applicant also provided details regarding time to systemic injection-related reaction by injection number.

- Of the subjects who experienced a systemic injection-related reaction with any injection, 81.5% had a reaction within 24 hours following the end of the injection.
- Of the subjects who experienced a systemic injection-related reaction following the first injection, 85% experienced the reaction within 24 hours after the end of the injection.
- Of the subjects who experienced a systemic injection reaction with the second injection, 50% of subjects experienced the reaction during the injection and 50% of subjects experienced the reaction within 24 hours following the end of the injection.
- Of the subjects who experienced systemic injection-related reactions after the third or the fourth injections, 100% experienced the reaction within 24 hours from the end of the injection.

As noted above, the proportion of subjects who required treatment for injection-related reactions decreased with subsequent injections (21.9% following the first injection and 7.1% following the fourth injection) and the event duration became shorter with each subsequent injection.

Refer to Table 53 for an analysis of the frequency of systemic injection-related reactions requiring treatment stratified by dose number and time-to-event onset. The proportion of subjects who experienced any injection-related reaction (local and systemic) and systemic injection-related reactions requiring treatment decreased between injections 1 and 2 and remained relatively stable between injections 2 and 3. Although these frequencies appear higher for injection 4, the data are difficult to interpret due to the relatively small number of subjects who had received injection 4 as of the cutoff date (December 4, 2023).

The Applicant also provided data from 80 subjects from Study CN42097 who did not undergo the one-hour postinjection monitoring period (34.3% of the OCR SC All population). Refer to Section 15 (Study/Trial Design) and to the background section above for details regarding protocol amendments that resulted in the Applicant removing and then reimplementing (at the Agency's request) the one-hour postinjection monitoring period. Per the Applicant, the safety data from these subjects were consistent with that of the overall study population. Specifically, 8 (10%) subjects who did not undergo postinjection monitoring reported an injection-related reaction following the second and third injections and 5 (6.2%) subjects reported an injection-related reaction following the fourth injection. There were no Grade 3 or higher injection-related reactions reported among these subjects. Of note, the 120-Day Safety Update indicated that data from subjects who did not undergo the one-hour postinjection monitoring period were available for 75 subjects and therefore the information included in this Response to Information Request for 80 subjects was a correction.

Based on the submitted information, it is unclear whether the injection-related reactions reported by subjects who did not undergo the one-hour post-injection monitoring period were local or systemic, or whether these injection-related reactions required symptomatic treatment.

The Applicant concluded that, based on the available safety data, the one-hour postinjection monitoring period could be optional starting with the second injection. See above for a discussion regarding issues with local and systemic injection-related reaction AE

characterization and for additional details regarding the frequency and severity of local and systemic injection-related reactions that occurred during Study CN42097.

Conclusion

Injection-related reactions, both local and systemic, were common in subjects treated with SC OCR in Studies CN41144 and CN42097. No serious or severe injection-related reactions were reported in either study. The risk of injection-related reactions is expected given the known safety profile of IV OCR and hyaluronidase, and the SC route of administration. However, the ascertainment and characterization of injection-related reactions specified in the protocol for Study CN42097 resulted in uncertainties pertaining to this risk:

- The coding of all investigator-determined injection-related reactions (both local and systemic) under the PT of injection related reaction did not capture the level of detail regarding the nature of these reactions generally required by the Division. As discussed earlier in this section, several Information Requests were required to clarify injection-related reaction reporting procedures per the protocol, obtain all available information regarding these AEs, and obtain updated datasets with more informative flag variables. The Applicant was not able to provide the detailed data regarding investigator-reported symptoms of injection-related reactions requested by the Division.
- The potential consolidation of several TEAEs of injection-related reactions that were temporally associated with one SC OCR administration under a single AE may have resulted in underestimation of the number of TEAEs of injection-related reactions that occurred in Study CN42097.

These uncertainties and limitations of the submitted data did not allow for comprehensive characterization of the risk profile (i.e., signs and symptoms) of injection-related reactions that occurred with SC OCR administration during Study CN42097. Though this issue would not preclude approval, as the seriousness and severity of events appears to have been reliably captured, the Division determined that a postmarketing requirement (PMR) for the comprehensive characterization of local and systemic injection-related reactions with SC OCR would be issued, should approval be granted.

Current approved labeling for Ocrevus specifies a 30- to 60-minute premedication administration window for mitigation of infusion reactions; however, the Applicant proposed a premedication administration window of (b) (4) 30 minutes" for SC OCR, which is supported by data. The data presented by the Applicant from Study CN42097 indicated a median premedication administration window of 31 to 65 minutes for injections 1 through 4 and current approved labeling for IV OCR (Ocrevus) indicates a premedication administration window of 30 to 60 minutes (Genentech 2024). Therefore, a premedication administration window for SC OCR of at least 30 minutes will be specified in labeling, should approval be granted.

Current approved labeling for Ocrevus specifies a one-hour postinfusion monitoring period following each dosing, but the Applicant proposed to make the one-hour postinjection monitoring optional for subsequent SC OCR injections following the first injection. The risk of injection-related reactions appeared to decrease with subsequent injections. However, an event potentially consistent with oral angioedema occurring within one hour after completion of the third SC OCR injection and requiring treatment was reported as a TEAE of systemic injection-related reaction. This event could also be consistent with a hypersensitivity reaction, either of

which would require treatment. As noted above, the characterization of injection-related reaction TEAEs in the protocol for Study CN42097 was not sufficiently detailed to allow for comprehensive characterization of the risk profile (i.e., signs and symptoms) of injection-related reactions with SC OCR. Though this issue would not preclude approval, as the seriousness of injection-related reactions was captured and the risk-benefit profile was found to be acceptable, the uncertainties regarding this risk necessitate mitigation in labeling and warrant a PMR. Therefore, a mandatory one-hour postinjection monitoring period following the first dose and a 15-minute monitoring period following subsequent doses will be recommended in labeling, should approval be granted.

7.7.2. Hypersensitivity

Issue

Hypersensitivity is a potential risk with monoclonal antibody administration, and according to current approved labeling, allergic and anaphylactic-like reactions have been reported with postmarket use of recombinant hyaluronidase. Additionally, Hylenex recombinant is contraindicated in patients with known hypersensitivity to hyaluronidase or any of the excipients (Halozyme 2024).

Background

Section 5.1 (Warnings and Precautions [Infusion Reactions] of current approved labeling for IV OCR (Ocrevus) discusses anaphylaxis in the context of infusion reactions (Genentech 2024). Section 6 (Adverse Reactions) of current approved labeling for recombinant hyaluronidase (Hylenex recombinant) discusses allergic and anaphylactic-like reactions as adverse reactions with recombinant hyaluronidase identified during postmarketing experience (Halozyme 2024).

Assessment

The Applicant flagged TEAEs with PTs contained within the MedDRA Standard Medical Dictionary for Regulatory Activities Query (SMQ) Hypersensitivity via the variable *SMQ02NAM*. See Table 54. None of these were considered SAEs and all were mild or moderate in severity. Overall, the majority of these events were related to injection-related reactions and infusion-related reactions. Additionally, per the CSR of Study CN42097, there were no confirmed events of hypersensitivity, and all were considered events of injection-related reactions and infusion-related reactions.

Table 54. Treatment-Emergent Adverse Events With Preferred Terms Within the MedDRA SMQ Hypersensitivity, Safety Population, Study CN42097, Controlled Period

Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)
Injection-related reaction	55 (46.6)	0 (0.0)
Rash	2 (1.7)	1 (0.8)
Erythema	1 (0.8)	1 (0.8)
Rhinitis allergic	1 (0.8)	0 (0.0)
Stomatitis	1 (0.8)	0 (0.0)
Urticaria	1 (0.8)	0 (0.0)
Infusion-related reaction	0 (0.0)	20 (16.9)
Bronchial hyperreactivity	0 (0.0)	1 (0.8)
Conjunctivitis	0 (0.0)	1 (0.8)
Drug hypersensitivity	0 (0.0)	1 (0.8)

Source: ADAE, SAFFL = Y, APERIODC = Controlled Period, TRTEMFL = Y, SMQ02NAM = Hypersensitivity (SMQ), by TRT01A.
Abbreviations: IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous; SMQ, Standard Medical Dictionary for Regulatory Activities Query

Refer to Section 7.7.1 (Injection-Related Reaction, Postinjection Monitoring) for a description of an event of injection related reaction with reported symptoms of “feeling of dry mouth accompanied by feeling of tongue swelling” (subject # (b) (6)) that occurred four minutes after the completion of the third SC OCR injection, required symptomatic treatment, and could be consistent with a hypersensitivity reaction.

Additionally, TEAEs with PTs within the MedDRA SMQ anaphylactic reactions were flagged with the variable *SMQ03NAM*. See Table 55. None of these were considered SAEs and all were mild or moderate in severity. Per the CSR of Study CN42097, there were no confirmed events of anaphylactic reaction, and all were considered events of injection-related reactions and infusion-related reactions.

Table 55. Treatment-Emergent Adverse Events With Preferred Terms Within the MedDRA SMQ Anaphylactic Reactions, Safety Population, Study CN42097, Controlled Period

Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)
Rash	2 (1.7)	1 (0.8)
Cough	2 (1.7)	1 (0.8)
Erythema	1 (0.8)	1 (0.8)
Urticaria	1 (0.8)	0 (0.0)
Swelling	0 (0.0)	1 (0.8)

Source: ADAE, SAFFL = Y, APERIODC = Controlled Period, TRTEMFL = Y, SMQ03NAM = Anaphylactic reaction (SMQ), by TRT01A.
Abbreviations: IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous; SMQ, Standard Medical Dictionary for Regulatory Activities Query

Events of rash and urticaria occurring in the SC OCR group were further reviewed.

- Subject (b) (6) experienced an event of rash ("rash on the face") in (b) (6) (exact event start date missing); however, the last dose of study drug had been received on Study Day 169 ((b) (6)). This event was ongoing as of the data cutoff date.
- Subject (b) (6) experienced urticaria ("rash on left thigh/ urticaria") and rash ("rash on right thigh") on Study Days 24 ((b) (6)) and 45, respectively; however, the last dose of study drug had been received on Study Day 1. The events of urticaria and rash resolved after 22 days and 3 days, respectively.
- Subject (b) (6) experienced rash ("rash") on Study Day 9; however, the last dose of study drug had been received on Study Day 1. This event resolved after 6 days.

Conclusion

The events of rash and urticaria that occurred in subjects receiving SC OCR in Study CN42097 cannot be definitively attributed to SC OCR given the lack of close temporal association with study drug administration and the event resolution despite ongoing exposure to study drug in most cases. There was one event reported as an injection-related reaction with "feeling of dry mouth accompanied by feeling of tongue swelling" that could be consistent with hypersensitivity.

The Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus. Current approved labeling for Ocrevus discusses the risks of rash, urticaria, bronchospasm, angioedema, hypotension, and anaphylaxis within the context of infusion-related reactions in Section 5.1 (Warnings and Precautions, Infusion Reactions). Therefore, these risks will also be included as a warning in labeling for SC OCR within the context of injection-related reactions, should approval be granted.

7.7.3. Headache

Issue

Headache, which was the most common TEAE reported in Study CN42097 after injection rection, is a known clinical manifestation of injection- and infusion-related reactions. Therefore, TEAEs of headache were reviewed in further detail and analyzed in that context.

Background

Section 5.1 (Warnings and Precautions [Infusion Reactions]) of current approved labeling for IV OCR (Ocrevus) discusses headache in the context of infusion reactions (Genentech 2024).

Assessment

Table 56 presents the results of FDA analyses of TEAEs of headache contained within the headache FMQ (narrow) that occurred at any time in the Safety Population during the Controlled Period of Study CN42097.

Table 56. Treatment-Emergent Adverse Events With Preferred Terms Contained Within the Headache FDA Medical Query (Narrow), Safety Population, Study CN42097, Controlled Period

FMQ (Narrow) Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Headache (FMQ)	13 (11.0)	5 (4.2)	6.8 (-0.0, 14.3)
Headache	12 (10.2)	3 (2.5)	7.6 (1.6, 14.7)*
Migraine	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Occipital neuralgia	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Moderate	6 (5.1)	3 (2.5)	2.5 (-2.8, 8.5)
Mild	7 (5.9)	1 (0.8)	5.1 (0.6, 11.0) *
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	3 (2.5)	0 (0.0)	2.5 (-0.7, 7.2)
Number of subjects with adverse events with end dates on or before treatment end dates	9/13 (69.2)	4/5 (80.0)	-10.8 (-46.3, 38.9)
Duration, days (from AE start date to AE end date)			
Mean (SD)	17.8 (45.5)	2.5 (0.6)	NA
Median (Q1, Q3)	1 (1, 5)	2.5 (2, 3)	NA
Min, max	1, 139	2, 3	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	4/13 (30.8)	1/5 (20.0)	10.8 (-38.9, 46.3)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/13 (0.0)	0/5 (0.0)	0.0 (-44.9, 23.8)

Source: adae.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

TEAEs with PTs contained within the headache FMQ (narrow) were more common in the SC OCR group (11% [n =13]) when compared to the IV OCR group (4.2% [n =5]). There were no life-threatening or severe events of headache in the SC OCR group. One subject (n=0.8%) in the IV OCR group experienced a severe TEAE of occipital neuralgia. A total of 5.1% (n=6) of subjects in the SC OCR group and 2.5% (n=3) of subjects in the IV OCR group experienced moderate events. Mild events of headache were reported in 5.9% (n=7) of subjects in the SC OCR group and in 0.8% (n=1) of subjects in the IV OCR group. There were no events resulting in study treatment discontinuation in either treatment group. The difference in median event duration between the groups did not appear to be clinically significant. As of the clinical cutoff date, 4 out of 13 and 1 out of 5 events of headache were ongoing in the SC OCR and IV OCR groups, respectively.

TEAEs of headache were evaluated in further detail via Information Request. The Applicant indicated that, in Study CN42097, there were 23 TEAEs of headache that occurred in 10.2% (n=12) of subjects receiving SC OCR compared to 2.5% (n=3) of subjects receiving IV OCR and that headache appeared to be the most common symptom of systemic injection-related reaction. Per the Applicant, most TEAEs of headache occurred more than 24 hours after SC OCR administration and therefore were not classified as systemic injection-related reactions. Additionally, most events were considered by the investigator to be unrelated to study treatment administration. Therefore, the Applicant concluded that the imbalance in the incidence of TEAEs of headache between the groups was driven by events in the SC OCR group that occurred more than 24 hours after study treatment administration.

The Applicant submitted updated ADAE dataset containing TEAEs with PTs under the HLTs Headaches NEC and Migraine Headaches that occurred up to the 120-Day Update cutoff date (December 4, 2023). Clinical review of this information found that several headache TEAEs had a prolonged time to onset following the most recent study drug administration, and that several subjects had a known diagnosis of a headache disorder, which confounded assessment of a causal association with SC OCR.

Conclusion

The Applicant's assessment that most events with PTs contained within the HLT Headaches NEC and Migraine headaches cannot be definitively attributed to treatment with SC OCR appears accurate, due to the long latency between last exposure to SC OCR and event onset in most cases. Additionally, several subjects had a prior medical history of headache or migraine. However, headaches did occur in a few subjects and are a known clinical manifestation of infusion-related reactions with IV OCR, a risk discussed in Section 5.1 (Warnings and Precautions [Infusion Reactions]) of current approved labeling for Ocrevus. Therefore, the risk of headache should be discussed in the context of systemic injection reactions in Section 5 (Warnings and Precautions) of the SC OCR Prescribing Information, should approval be granted. Refer to Section 7.7.1 (Injection-Related Reactions) for details regarding the planned PMR for characterization of injection-related reactions with SC OCR.

7.7.4. Infections

Issue

Both ocrelizumab and hyaluronidase carry a risk of serious (including life-threatening or fatal) infections and spreading of localized infections, as described in current approved labeling for Ocrevus (IV OCR) and Hylenex recombinant (recombinant hyaluronidase), respectively (Genentech 2024; Halozyme 2024).

Background

Section 5.2 (Warnings and Precautions, Infections) of current approved labeling for IV OCR (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 (Genentech 2024). Clinical trials of IV OCR 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 fulminant hepatitis, hepatic failure, and death caused by HBV 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. Lastly, Section 5.1 (Warnings and Precautions, Spread of Localized Infection) of current approved labeling for Hylenex recombinant discusses the risk of spreading a localized infection if hyaluronidase is injected into or around an infected or acutely inflamed area (Halozyme 2024).

Assessment

Table 57 presents the results of FDA analyses of TEAEs of infection (PTs contained within the MedDRA SOC Infections and Infestations) that occurred in the safety population of Study CN42097 during the Controlled Period.

Table 57. Treatment-Emergent Adverse Events With Preferred Terms Within the System Organ Class Infections and Infestations, Safety Population, Study CN42097, Controlled Period

System Organ Class Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference (%) (95% CI)
Infections (SOC)	41 (34.7)	33 (28.0)	6.8 (-5.1, 18.5)
Upper respiratory tract infection	8 (6.8)	9 (7.6)	-0.8 (-8.0, 6.2)
COVID-19	8 (6.8)	5 (4.2)	2.5 (-3.7, 9.1)
Nasopharyngitis	5 (4.2)	2 (1.7)	2.5 (-2.3, 8.1)
Oral herpes	4 (3.4)	1 (0.8)	2.5 (-1.6, 7.7)
Urinary tract infection	3 (2.5)	5 (4.2)	-1.7 (-7.3, 3.5)
Pharyngitis	3 (2.5)	3 (2.5)	-0.0 (-5.0, 5.0)
Influenza	3 (2.5)	1 (0.8)	1.7 (-2.4, 6.5)
Rhinitis	3 (2.5)	1 (0.8)	1.7 (-2.4, 6.5)
Bronchitis	2 (1.7)	6 (5.1)	-3.4 (-9.2, 1.5)
Sinusitis	1 (0.8)	3 (2.5)	-1.7 (-6.5, 2.4)
Viral infection	1 (0.8)	2 (1.7)	-0.8 (-5.2, 3.1)
Cystitis	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Gastroenteritis	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Herpes virus infection	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Vulvovaginal mycotic infection	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Borrelia infection	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Ear infection	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Laryngopharyngitis	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Nasal herpes	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Otitis externa	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Tooth abscess	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Tooth infection	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Viral upper respiratory tract infection	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Appendicitis	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Cellulitis staphylococcal	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Conjunctivitis	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Laryngitis	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Lower respiratory tract infection	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Otitis media	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Pneumonia	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Respiratory tract infection	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Respiratory tract infection viral	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Subcutaneous abscess	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Tonsillitis	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	4 (3.4)	-3.4 (-8.4, -0.2)*
Moderate	24 (20.3)	20 (16.9)	3.4 (-6.7, 13.5)
Mild	17 (14.4)	9 (7.6)	6.8 (-1.3, 15.2)
Serious	0 (0.0)	4 (3.4)	-3.4 (-8.4, -0.2)*
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in study drug discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in hospitalization	0 (0.0)	4 (3.4)	-3.4 (-8.4, -0.2)*
Relatedness	6 (5.1)	11 (9.3)	-4.2 (-11.5, 2.6)

System Organ Class Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference (%) (95% CI)
Number of subjects with adverse events with end dates on or before treatment end dates	41/41 (100)	32/33 (97.0)	3.0 (-5.8, 15.4)
Duration, days (from treatment end date to AE end date)			
Mean (SD)	14.2 (11.7)	20.8 (13.1)	NA
Median (Q1, Q3)	10 (7, 16)	17.5 (11, 26.2)	NA
Min, max	3, 62	2, 55	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/41 (0)	1/33 (3.0)	-3.0 (-15.4, 5.8)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/41 (0)	0/33 (0)	0.0 (-10.6, 8.7)

Source: adae.xpt; Software: R.
* Indicates that 95% confidence interval excludes zero.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; CI, confidence interval; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation; SOC, system organ class

There were no life-threatening or severe events of infection in the SC OCR group. Specifically, 14.4% of subjects experienced mild and 20.3% of subjects experienced moderate events of infection. There were no events of life-threatening events of infection in the IV OCR group, but four subjects in the IV OCR group experienced TEAEs of severe infection. Additionally, there were no events of infection resulting in study treatment discontinuation in either treatment group. However, in the IV OCR group, four subjects experienced TEAEs of infection leading to hospitalization and four subjects experienced SAEs of infection. The median event duration was shorter in the SC OCR group (10 days, range 3 to 62 days), as compared to the IV OCR group (17.5 days, range 11 to 26.2 days), and one event was ongoing in the IV OCR group by the data cutoff date.

Of note, the eligibility criteria for Study CN42097 indicated that subjects previously treated with other anti-CD20 therapies, including ocrelizumab, who discontinued treatment at least two years prior to Screening were eligible for study participation. Per the Applicant's CSR, except for two subjects (one in each treatment group), all subjects were naive to ocrelizumab. Additionally, one subject in the IV OCR group was previously treated with rituximab. Therefore, the number of subjects previously exposed to anti-CD20 monoclonal antibodies in both treatment groups appeared to be balanced.

Table 58 presents the results of FDA analyses of TEAEs of infection (PTs contained within the MedDRA SOC Infections and Infestations) that occurred in the safety population of Study CN41144.

Table 58. Treatment-Emergent Adverse Events With Preferred Terms Within the System Organ Class Infections and Infestations, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
System Organ Class Preferred Term	**Group A N=79 n (%)**	**Group B N=39 n (%)**	**Group A N=80 n (%)**	**Group B N=45 n (%)**
Infections and infestations (SOC)	34 (43.0)	13 (33.3)	44 (55.0)	26 (57.8)
Acute sinusitis	3 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Bronchitis	4 (5.1)	2 (5.1)	1 (1.2)	0 (0.0)
Candida infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Cellulitis orbital	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Clostridium difficile infection	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Conjunctivitis	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
COVID-19	17 (21.5)	8 (20.5)	24 (30.0)	18 (40.0)
COVID-19 pneumonia	1 (1.3)	0 (0.0)	3 (3.8)	1 (2.2)
Ear infection	1 (1.3)	0 (0.0)	1 (1.2)	0 (0.0)
Encephalitis	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Folliculitis	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Fungal infection	1 (1.3)	0 (0.0)	1 (1.2)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Gingivitis	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Hand-foot-and-mouth disease	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Herpes zoster	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Hordeolum	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza	1 (1.3)	0 (0.0)	1 (1.2)	0 (0.0)
Nail infection	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Nasopharyngitis	3 (3.8)	2 (5.1)	6 (7.5)	3 (6.7)
Oral herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Pharyngitis	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Pharyngitis streptococcal	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Pneumonia	2 (2.5)	0 (0.0)	5 (6.2)	0 (0.0)
Rhinovirus infection	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
SARS-CoV-2 sepsis	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	6 (7.5)	0 (0.0)
Tinea infection	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Tooth abscess	2 (2.5)	0 (0.0)	0 (0.0)	1 (2.2)
Tooth infection	0 (0.0)	0 (0.0)	2 (2.5)	1 (2.2)
Upper respiratory tract infection	3 (3.8)	2 (5.1)	2 (2.5)	0 (0.0)
Urinary tract infection	6 (7.6)	2 (5.1)	9 (11.2)	5 (11.1)
Urinary tract infection bacterial	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Viral infection	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Viral upper respiratory tract infection	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Wound infection	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Maximum severity				
Death	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Life threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	4 (5.1)	0 (0.0)	8 (10.0)	3 (6.7)
Moderate	22 (27.8)	6 (15.4)	23 (28.8)	11 (24.4)
Mild	8 (10.1)	7 (17.9)	12 (15.0)	12 (26.7)
Serious	2 (2.5)	0 (0.0)	10 (12.5)	1 (2.2)
Deaths	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)

	SC OCR 920 mg		SC OCR 1200 mg	
System Organ Class Preferred Term	**Group A N=79 n (%)**	**Group B N=39 n (%)**	**Group A N=80 n (%)**	**Group B N=45 n (%)**
Resulting in discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Resulting in hospitalization	2 (2.5)	0 (0.0)	10 (12.5)	1 (2.2)
Relatedness	3 (3.8)	0 (0.0)	6 (7.5)	2 (4.4)
Number of subjects with adverse events with end dates on or before treatment end dates	26/34 (76.5)	9/13 (69.2)	42/44 (95.5)	24/26 (92.3)
Duration, days (from AE start date to AE end date)				
Mean (SD)	19.9 (14.8)	16.3 (14.8)	27.4 (21.5)	17.9 (8.3)
Median (Q1, Q3)	15.5 (9, 26)	9 (8, 13)	21 (13.2, 34.8)	17.5 (13.8, 21)
Min, max	3, 56	5, 43	2, 90	6, 40
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	1/34 (2.9)	0/13 (0.0)	0/44 (0.0)	0/26 (0.0)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/34 (0.0)	0/13 (0.0)	0/44 (0.0)	0/26 (0.0)

Source: adae.xpt; Software: R.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
SC OCR 920 mg refers to any subject who received at least one dose of OCR SC 920 mg during OCARINA I.
SC OCR 1200 mg refers to any subject who received at least one dose of OCR SC 1200 mg during OCARINA I, either in dose escalation phase or in dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Treatment-emergent adverse events defined as any adverse event that occurs after initiation of study drug up until 48 weeks after the final dose of study drug.
Duration is up to 3 years.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; Q1, first quartile; Q3, third quartile; SARS, severe acute respiratory syndrome; SC, subcutaneous; SD, standard deviation; SOC, system organ class

A higher proportion of subjects who received at least one dose of SC OCR 1200 mg experienced TEAEs with PTs within the SOC Infections and Infestations, when compared to subjects who received at least one dose of SC OCR 920 mg. Among subjects who received at least one dose of SC OCR 920 mg, subjects treated with IV OCR prior to study enrollment (43.0%) were more likely to experience TEAEs with PTs within the SOC Infections and Infestations, as compared to OCR-naive subjects (33.3%). Among subjects who received at least one dose of SC OCR 1200 mg, the difference in the proportion of subjects previously treated with IV OCR (55.0%) and OCR-naive subjects (57.8%) who experienced TEAEs with PTs within the SOC Infections and Infestations did not appear to be clinically significant. However, among subjects who received at least one dose of SC OCR 1200 mg, subjects previously treated with IV OCR (Group A) were more likely to experience SAEs related to infections, including SAEs of COVID-19 infection, COVID-19 pneumonia, and pneumonia, compared to ocrelizumab-naive subjects (Group B). Refer to Section 7.6.1.3 for additional details.

These differences between subjects previously treated with IV OCR prior to study enrollment and ocrelizumab-naive subjects were further investigated. The Clinical review team considered

possibilities related to individual subject characteristics (i.e., age, EDSS scores, MS phenotype, medical history), duration of prior exposure to anti-CD20 therapies (including ocrelizumab, if applicable), prior exposure to other MS therapies, laboratory parameters (white blood cell counts, $CD19^+$ B-cell counts, absolute lymphocyte counts, ANCs, and serum immunoglobulin [Ig] levels [IgG, IgM, IgA]), the impact of the COVID-19 pandemic, and the availability of vaccines for COVID-19.

In a Response to Information Request, the Applicant indicated that Study CN41144 was not designed or powered for direct comparison of safety outcomes between Groups A and B, and that the number of subjects enrolled in Group A (n=88) was larger than in Group B (n=47), which could have contributed to the difference in the number of serious infections seen between the groups. Most infections and serious infections reported in Study CN41144 were COVID-19-related events, and given the timing of the study in relation to the COVID-19 pandemic, the frequency of COVID-19 infection was the main driver of differential serious infection risk between the groups.

The period in which Study CN41144 was conducted overlapped significantly with COVID-19 public health emergency. Per the Applicant, the first study subject was vaccinated against COVID-19 in (b) (6). Of the subjects who developed SAEs of COVID-19-related infections, none had been vaccinated at baseline, four experienced COVID-19-related infections prior to being vaccinated, four experienced COVID-19-related infections after vaccination, and two experienced COVID-19-related infections over six months after last vaccine administration.

The Applicant also noted differences between Groups A and B that could have contributed to the observed differenced in the rate of serious COVID-19-related infections (n=9 [Group A] versus n=1 [Group B]). Compared to Group B, subjects in Group A had a higher mean age (46.0 years [Group A] versus 39.5 years [Group B]), weight (92.0 kg [Group A] versus 84.0 kg [Group B]), MS symptom duration (9.62 years [Group A] versus 6.43 years [Group B]), and EDSS score (3.0 [Group A] versus 2.5 [Group B]). Additionally, most of the subjects who experienced serious infection in Study CN41144 had normal IgG and IgA levels, but IgM levels below the lower limit of normal (LLN) (<LLN at baseline in most cases) throughout the study. There were no other laboratory abnormalities identified by the Applicant that could have contributed to these observed differences. Per the Applicant, another potential contributing factor was that study sites that enrolled a larger number of subjects in Group A compared to Group B tended to be located in states more severely affected by the COVID-19 public health emergency, such as Florida, Ohio, Tennessee, and South Carolina.

Herpes Virus Infections

A higher frequency of TEAEs with the PTs oral herpes and nasal herpes occurred in the SC OCR group (3.4% and 0.8%, respectively), as compared to the IV OCR group (0.8% and 0.0%, respectively). Therefore, TEAEs of herpes virus infections through the 120-Day Safety Update cutoff date were evaluated in further detail via Information Requests. Refer to Table 59 for a summary of these TEAEs. Of note, none of these subjects had a known history of herpes virus infections. None of the reported herpes virus infection-related TEAEs were serious.

Table 59. Treatment-Emergent Adverse Events With Preferred Terms Under the High-Level Term Herpes Viral Infections, Study CN42097

Characteristic	OCR SC (N=118) n (%)	OCR IV (N=118) n (%)
Any herpes viral infection TEAE (per HLT)	6 (5.1)	2 (1.7)
Serious herpes viral infection TEAE	0 (0.0)	0 (0.0)
Preferred term		
Oral herpes	5 (4.2)	1 (0.8)
Herpes virus infection	1 (0.8)	1 (0.8)
Nasal herpes	1 (0.8)	0 (0.0)
Herpes zoster	1 (0.8)	0 (0.0)
Severity		
Mild	5 (4.2)	1 (0.8)
Moderate	1 (0.8)	1 (0.8)
Severe	0 (0.0)	0 (0.0)
Treatment received		
Acyclovir	4 (3.4)	1 (0.8)
None or unknown	1 (0.8)	1 (0.8)
Considered related to study treatment	3 (2.5)	0 (0.0)
Outcome		
Recovered/resolved	6 (5.1)	2 (1.7)
Not resolved	0 (0.0)	0 (0.0)

Source: Applicant's Response to Information Request dated 6/14/2024, and ADAE2.xpt dataset (received on 6/21/2024).
Data cutoff date: 120-Day Safety Update (12/4/2023)
Abbreviations: HLT, high-level term; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event

Overall, given the limitations of the comparison due to small sample size, it does not appear that the risk of serious herpes viral infections differed between the SC OCR and IV OCR groups.

Other Infections

One TEAE with the PT borrelia infection occurred in the SC OCR group. There were no reported events of tick-borne infection in the IV OCR group. There were no TEAEs of hepatitis B reactivation or PML reported in either treatment group.

Conclusion

The Applicant is partially relying on confirmatory safety and efficacy evidence from BLA 761053 for Ocrevus. 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. Though the small sample size of Study CN42097 limited comparison of the frequency of these events, there did not appear to be an increased risk of serious infection with OCR SC compared to OCR IV. Therefore, the risk of serious, including life-threatening or fatal, bacterial, viral, parasitic, and fungal infections, is expected with SC OCR and will also be included as a warning in labeling for SC OCR, should approval be granted.

7.7.5. Reduction in Immunoglobulins

Issue

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

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 (RMS [Studies WA21092 and WA21093] and PPMS [Study WA25046]) and their open-label extensions (up to approximately seven 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 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 OCR-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 subjects at baseline reporting IgG, IgA, and IgM below the LLN in OCR-treated subjects was 0.0%, 0.2%, and 0.2%, respectively. Following treatment, the proportion of OCR-treated subjects reporting IgG, IgA, and IgM below the LLN at 120 weeks was 1.1%, 0.5%, and 15.5%, respectively.

Therefore, current 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

There were no TEAEs of hypogammaglobulinemia reported in Study CN42097. Table 60 summarizes the frequency of subjects in each treatment group with immunoglobulin values meeting clinically relevant thresholds by Week 22 during the Controlled Period of Study CN42097. Of note, none of these laboratory abnormalities occurred in close temporal association with TEAEs of serious or opportunistic infections.

Although a higher proportion of subjects in the SC OCR group experienced IgA levels below the LLN, as indicated in Section 17 (Clinical Safety), there did not appear to be a clinically meaningful difference in mean or median IgM, IgG, or IgA levels over time between the groups. Additionally, a trend for declining IgM in both groups was observed during the Controlled Period. Lastly, there were no subjects in either treatment group who experienced IgG levels below the LLN.

Table 60. Subjects With Decreased Immunoglobulin Laboratory Values by Week 22, Safety Population, Study CN42097, Controlled Period

Immunoglobin Type	Criteria	SC OCR N=118	IV OCR N=118
Immunoglobulin A	<0.8 g/L	5 (4.2)	1 (0.8)
Immunoglobulin G	<5.5 g/L	0 (0.0)	0 (0.0)
Immunoglobulin M	<0.4 g/L	4 (3.4)	7 (5.9)

Source: ADLB dataset.
Values reported as n (%).
Duration of controlled period is 24 weeks.
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous.

Conclusion

The proportion of subjects in both treatment groups who experienced immunoglobulin levels meeting clinically relevant thresholds was lower in Study CN42097, as compared to that observed in clinical trials of Ocrevus. However, this observation was expected based on the short exposure to SC OCR and IV OCR during Study CN42097. A trend for declining IgM in OCR-treated subjects (both SC OCR and IV OCR) was observed during the double-blind treatment period.

Based upon regulatory experience with other anti-CD20 therapies, the likelihood of observing consistent hypogammaglobulinemia and other immunoglobulin reductions in a 22-week study period is low. Decreases in IgG associated with Ocrevus required years of exposure to identify, so the lack of a finding in the Controlled Period of Study CN42097 was expected and does not preclude labeling for what appears to be an effect that requires prolonged exposure to any anti-CD20 therapy.

The Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus. Current 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 will also be included as a warning in labeling for SC OCR, should approval be granted.

7.7.6. Cytopenias

Issue

Ocrelizumab carries a known risk of decreased neutrophil levels, as discussed in current approved labeling for Ocrevus (IV OCR). Additionally, decreases in lymphocyte counts are expected based on the mechanism of action of ocrelizumab and other anti-CD20 monoclonal antibodies.

Background

Section 6.1 (Adverse Reactions - Clinical Trials Experience) of current approved labeling for Ocrevus discusses the risk of decreased neutrophil levels. In the PPMS clinical trial (Study WA25046), decreased neutrophil counts occurred in 13% of OCR-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 Ocrevus and were between the LLN and

1.0×10^9/L. Overall, 1% of subjects in the Ocrevus-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 61 summarizes the frequency of TEAEs related to cytopenias that occurred in the safety population during the Controlled Period of Study CN42097. TEAEs with PTs pertaining to cytopenias were manually selected. Laboratory results for Study CN2097 are reviewed in Section 7.6.1.6 (Laboratory Findings, Study CN42097) and Section 17 (Clinical Safety).

Table 61. Cytopenia-Related Treatment-Emergent Adverse Events, Safety Population, Study CN42097, Controlled Period

White Blood Cell Type	SC OCR N=118 n (%)	IV OCR N=118 n (%)
Lymphocytes		
Lymphocyte count decreased	1 (0.8)	0 (0.0)
CD4 lymphocytes decreased	0 (0.0)	1 (0.8)
Neutrophils		
Neutrophil count decreased	0 (0.0)	1 (0.8)
Neutropenia	0 (0.0)	2 (1.7)

Source: ADAE, SAFFL = Y, APERIODC = Controlled Period, TRTEMFL = Y, by TRT01A.
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous

The number of TEAEs related to lymphopenia appeared comparable between the groups. There were no subjects in the SC OCR group who experienced TEAEs related to neutropenia; however, three subjects receiving IV OCR experienced neutropenia-related TEAEs. There were no subjects in either treatment group who experienced TEAEs related to decreased white blood cells, platelets, or hemoglobin.

Conclusion

Although there were no subjects in the SC OCR group who experienced TEAEs related to neutropenia or neutropenia meeting clinically relevant thresholds, the lack of a finding in the SC OCR group does not preclude labeling for what appears to be an effect with exposure to any anti-CD20 therapy. Additionally, the Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus. Current approved labeling for Ocrevus discusses the risk of neutropenia in Section 6.1 (Adverse Events - Clinical Trials Experience). Therefore, the risk of neutropenia will also be included in Section 6.1 of the labeling for SC OCR, should approval be granted.

7.7.7. Malignancy

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 for Ocrevus (IV OCR), ocrelizumab may increase the risk of malignancies.

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, 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 Rebif or placebo. Labeling recommends that OCR-treated patients follow standard breast cancer screening guidelines.

Assessment

There were no TEAEs with PTs contained within the SMQ Malignant tumors in Study CN42097. There were two TEAEs with PTs contained within the SMQ Malignant tumors reported during Study CN41144 (PTs basal cell carcinoma [n=1, moderate] and papillary thyroid cancer [n =1, severe]), for which the Applicant submitted narratives (discussed below). Per the 120-Day Safety Update, no malignancies have been reported for Study CN42097 and no additional events of malignancy were reported for Study CN41144.

Subject (b) (6)

Subject (b) (6), a 55-year-old OCR-naive woman who received at least one dose of SC OCR 920 mg, experienced the SAE papillary thyroid cancer (severe) on Study Day 676. She had previously received SC OCR 1200 mg on Study Days 1 and 168, and SC OCR 920 mg on Study Days 345 and 501. The subject's presenting symptoms were not reported. She underwent a thyroid ultrasound with biopsy on Study Day 673. Laboratory evaluations performed on Study Day 676 included TSH (0.07), free T4 (2.0), thyroglobulin (0.5), thyroglobulin antibody (<1.0), cancer antigen (9.0), albumin (4.0), intact parathyroid hormone (21), follicle stimulating hormone (77), and estradiol (<15); units and reference range were not provided. She was diagnosed with papillary thyroid cancer ("tumor: PT2, lymph nodes: PN1A") based on biopsy results. Reportedly, there was no metastatic disease detected. The subject underwent total thyroidectomy and central neck dissection on Study Day 695. The study treatment was temporarily interrupted due to this AE, which was ongoing as of the data cutoff date. The investigator assessed the event as unrelated to study treatment.

Discussion: The subject had been exposed to SC OCR for approximately 1.9 years by the time of malignancy diagnosis, so a contributory role of ocrelizumab in this AE cannot be ruled out.

Subject (b) (6)

Subject (b) (6) a 41-year-old OCR-naive woman who received at least one dose of SC OCR 1200 mg, experienced the TEAE basal cell carcinoma (moderate) on Study Day 55. She had previously received one dose of SC OCR 1200 mg. The subject reportedly received treatment

with a “topical antiseptic.” There were no additional details provided regarding location of basal cell carcinoma, physical examination findings, diagnostic evaluations performed, or treatment received. The event was considered resolved on Study Day 74. This event did not result in study treatment discontinuation. The investigator assessed the event as unrelated to study treatment.

Discussion: This event is likely unrelated to treatment with SC OCR due to the short exposure to SC OCR treatment by the time of event occurrence. Additionally, basal cell carcinoma is not infrequent in the general population.

Table 62 shows a tabulation of TEAEs related to malignancy, using manually selected PTs, that occurred in the SC OCR development program.

Table 62. Malignancy-Related Treatment-Emergent Adverse Events in the SC Administered OCR Development Program

	Study CN42097		Study CN41144			
			SC OCR 920 mg		SC OCR 1200 mg	
Malignancy Type	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Group A N=79 n (%)	Group B N=39 n (%)	Group A N=80 n (%)	Group B N=45 n (%)
Any Malignancy	0 (0.0)	0 (0.0)	1 (1.3)	1 (2.6)	4 (5.0)	1 (2.2)
Renal cyst	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Mammogram abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.3)	0 (0.0)
Papillary thyroid cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Benign breast neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)
Thyroid neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Bladder cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Basal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)

Source: ADAE for CN42097, SAFFL = Y, TRTEMFL = Y, by TRT01A and ADAE for CN41144, SAFFL = Y, TRTEMFL = Y, by TRT01A.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during Study CN41144.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during Study CN41144, either in the dose escalation phase or in the dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCR, ocrelizumab; SC, subcutaneous.

There were no TEAEs with PTs related to malignancy in Study CN42097, which is not unexpected due to the short duration of treatment exposure and overall follow-up as of the data cutoff date. In Study CN41144, there was an overall higher frequency of events with PTs related to malignancy in subjects exposed to Ocrevus prior to study enrollment, which could be related to the longer exposure to anti-CD20 monoclonal antibody treatment.

Conclusion

Overall, the incidence of malignant neoplasms was low in the SC OCR development program and no single type of malignancy appeared prominent. Additionally, the duration of exposure was short (particularly in Study CN42097) and may limit the interpretation of these data regarding this safety signal.

The Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus. Current approved labeling for Ocrevus discusses the risk of malignancies, including breast cancer, in Section 5.5 (Warnings and Precautions, Malignancies). Therefore, the risk of malignancies will also be included as a warning in labeling for SC OCR, should approval be granted.

Upon review of BLA 761053 for Ocrevus, a higher frequency of malignancies (breast cancer in particular) was observed among IV OCR-treated subjects, as compared to subjects treated with placebo or interferon-beta in the Phase 3 trials. As a result, PMR 3194-2 was issued to determine the incidence and mortality rates of breast cancer and all malignancies in patients exposed to Ocrevus, which is ongoing. Because PMR 3194-2 is outstanding with an ongoing study, the same PMR related to malignancy will also be issued for SC OCR, should approval be granted.

7.7.8. Immune-Mediated Colitis

Issue

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

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 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

Table 63 shows the results of FDA analyses of TEAEs with PTs related to abdominal discomfort/pain, diarrhea, and constipation, which could be suggestive of colitis, that occurred in the safety population of Study CN42097 during the Controlled Period. There were no TEAEs with PTs contained within the MedDRA High Level Term Colitis (excluding infective) in Study CN42097.

Table 63. Treatment-Emergent Adverse Events With Preferred Terms Related to Immune-Mediated Colitis (Custom Query), Safety Population, Study CN42097, Controlled Period

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Immune-mediated colitis (CQ)	4 (3.4)	1 (0.8)	2.5 (-1.6, 7.7)
Constipation	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Diarrhea	1 (0.8)	1 (0.8)	-0.0 (-3.9, 3.9)
Abdominal discomfort	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Abdominal pain lower	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Abdominal pain upper	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Abdominal pain	0 (0.0)	1 (0.8)	-0.8 (-4.7, 2.3)

Grouped Query Preferred Term	SC OCR N=118 n (%)	IV OCR N=118 n (%)	Risk Difference % (95% CI)
Maximum severity			
Death	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Life-threatening	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Severe	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Moderate	3 (2.5)	1 (0.8)	1.7 (-2.4, 6.5)
Mild	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Serious	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Deaths	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Resulting in discontinuation	0 (0.0)	0 (0.0)	0.0 (-3.2, 3.2)
Relatedness	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Number of subjects with adverse events with end dates on or before treatment end dates	4/4 (100)	1/1 (100)	0.0 (-54.6, 82.8)
Duration, days (from AE start date to AE end date)			
Mean (SD)	71.5 (82.2)	45 (NA)	NA
Median (Q1, Q3)	64.5 (1, 135)	45 (45, 45)	NA
Min, max	1, 156	45, 45	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/4 (0.0)	0/1 (0.0)	0.0 (-82.8, 54.6)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/4 (0.0)	0/1 (0.0)	0.0 (-82.8, 54.6)

Source: adae.xpt; Software: R.
All data in the SC OCR and IV OCR columns are presented as n (%) except for the rows listing Mean (SD); Median (Q1, Q3); and Min, max.
Duration of controlled period is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; CQ, custom query; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCR, ocrelizumab, Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation

TEAEs with PTs potentially related to immune-mediated colitis were slightly more common in the SC OCR group (3.4% [n=4]) when compared to the IV OCR group (0.8% [n=1]). There were no life-threatening or severe events with PTs related to immune-mediated colitis in either treatment group. Specifically, 2.5% (n=3) of subjects in the SC OCR group and 0.8% (n=1) of subjects in the IV OCR group experienced moderate events and 0.8% (n=1) of subjects in the SC OCR group experienced mild events. There were no events resulting in study treatment discontinuation in either treatment group. The median event duration was longer in the SC OCR group (64.5 days, range 1 to 135 days), as compared to the IV OCR group (45 days). There were no ongoing events in either treatment group as of the data cutoff date.

Due to the TEAEs discussed above and the known risk of immune-mediated colitis, these cases were further evaluated via Information Requests. Based on the additional information provided by the Applicant, none of these cases in Study CN42097 appeared to be consistent clinically with immune-mediated colitis as described in current approved labeling for Ocrevus. Additionally, several TEAEs were reported to resolve despite ongoing treatment with ocrelizumab, suggesting that the events were unrelated to ocrelizumab treatment.

In Study CN41144, there were two TEAEs reported with PTs contained within the HLT Colitis (excluding infective):

Subject (b) (6)

Subject (b) (6), a 35-year-old woman previously exposed to Ocrevus who received at least one dose of SC OCR 1200 mg, experienced the TEAE colitis (Moderate) on Study Day 717. She had previously received SC OCR 600 mg on Study Day 1, IV OCR 600 mg on Study Day 87, and SC OCR 1200 mg on Study Days 247, 415, and 603. No additional details were provided regarding presenting symptoms, diagnostic evaluations, or treatment received. The event resolved by Study Day 728 and did not result in study treatment discontinuation.

Discussion: This event is unlikely to represent a case of immune-mediated colitis due to prompt event resolution (duration was 12 days) despite ongoing treatment with SC OCR.

Subject (b) (6)

Subject (b) (6), a 59-year-old woman previously exposed to Ocrevus who received at least one dose of SC OCR 920 mg, experienced the TEAE colitis collagenous (mild) on Study Day 1001. She had previously received SC OCR 1200 mg on Study Days 1, 171, and 330 and SC OCR 920 mg on Study Days 499, 679, and 843. Of note, this subject experienced a TEAE of folliculitis ("folliculitis on scalp," severe) on Study Day 970, which resulted in treatment with mupirocin and steroids. It is unclear if the subject was also treated with oral antibiotics. As of the 120-Day cutoff date, the event outcome was "resolving." On Study Day 1001, the subject was diagnosed with colitis collagenous ("collagenous colitis," Mild) due to ongoing diarrhea. Additional details regarding diagnostic evaluations were not provided; however, treatment with SC OCR was permanently discontinued on Study Day 1001 due to the TEAEs of folliculitis and colitis. The event of colitis collagenous was reported as part of the 120-Day Safety update. The PT for this event was initially reported as colitis microscopic but was subsequently updated to collagenous colitis.

Discussion: Collagenous colitis is a type of inflammatory bowel disease. There were not enough details provided regarding this case to facilitate an assessment of causality with SC OCR. However, this subject had been exposed to Ocrevus prior to study enrollment, which has a known risk of immune-mediated colitis.

Conclusion

There was one TEAE of collagenous colitis in Study CN41144, which can be drug-related. However, there were no events clearly consistent with serious immune-mediated colitis cases described in Ocrevus labeling identified in Studies CN41144 or CN42097.

The Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus. Current approved labeling for Ocrevus discusses the risk of immune-mediated colitis in Section 5.6 (Warnings and Precautions, Immune-Mediated Colitis). Therefore, the risk of immune-mediated colitis will also be included as a warning in labeling for SC OCR, should approval be granted.

7.7.9. Comparability of Safety Profile to IV OCR

Issue

The Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus, pending demonstration of PK comparability of SC OCR to IV OCR in Study CN42097.

Background

A secondary objective of Study CN42097 was to compare the safety profile of SC OCR to that of IV OCR. In response to an Information Request, the Applicant compared the safety profiles using data from the SC OCR and IV OCR development programs. This comparison was limited by differences in the number of subjects exposed and duration of exposure and follow-up between the 2 development programs.

Assessment

IV OCR Development Program

The Applicant discussed pooled safety data from the Phase 3 Studies WA21092 (RMS), WA21093 (RMS), and WA25046 (PPMS), which were the basis for the primary safety analyses of BLA 761053 for IV OCR. Additionally, the Phase 2 Study WA21493 (RRMS) provided supportive safety data. All four studies included an Open-Label-Extension Period, where eligible subjects continued treatment with IV OCR.

The IV OCR development program included safety data from 2147 OCR-treated subjects (4485 PY of exposure) with MS. Most subjects experienced at least one TEAE, most of which were Grade 1 or 2 in severity. The rates of Grade 3 or 4 TEAEs and of SAEs were comparable between OCR-treated subjects and comparator groups. Infections and infusion-related reactions were the most frequently reported TEAEs. The majority of infusion-related reactions were Grade 1 or 2 in severity and incidence was highest with the initial infusion and decreased with subsequent infusions.

Grade 1 and 2 upper respiratory tract infections and urinary tract infections were the most commonly reported infections. Serious infections occurred at a rate of 2.97 per 100 PY in subjects treated with IV OCR and of 2.88 per 100 PY (95% CI 1.73, 4.50) in those treated with placebo. There were no reports of opportunistic infections. The incidence rate of malignancy was higher in subjects treated with IV OCR relative to that of comparator groups; however, the Applicant indicated the rate of malignancy in OCR-treated subjects was within the range of incidence rates of malignancy reported in placebo groups of clinical trials of MS.

The Applicant also reviewed controlled and open-label long-term (>10 years) safety data from Studies WA21092 (RMS), WA21093 (RMS), WA25046 (PPMS), and WA21493 (RRMS) collected after the approval of BLA 761053. The review also evaluated data from 12 additional Phase 2, 3, 3b, and 4 IV OCR Studies, WA21092, WA21093, WA25046, WA21493, BN29739, MA30005, ML29966, MN30035, MN39158, MN39159, MA30143, and ML42071, with a cutoff date of November 2022. Overall, the review included 28,269 PY of exposure data from 6,155 subjects treated with IV OCR. Per the Applicant, the safety results from these additional analyses were consistent with those included in BLA 761053.

SC Ocrelizumab Development Program

The Applicant indicated that, as the data cutoff date of the CSRs for Studies CN41144 and CN42097 (January 27, 2023, and March 10, 2023, respectively), SC OCR had been evaluated in 312 subjects and appeared to be well tolerated. Refer to other subsections of Section 7 (Safety Risk and Risk Management) for a detailed review of the safety profile of SC OCR, as compared to that of IV OCR, based on data from the Controlled Period of Study CN42097.

Applicant's Assessment of the Safety Profile of SC Ocrelizumab, Compared to IV Ocrelizumab

Based on safety data from trials of IV OCR in subjects with RMS and PPMS, the Applicant indicated that the most common TEAEs were infusion-related reactions and Grade 1 and 2 infections, and that the safety profile remained comparable upon evaluation of the 10-year pooled safety data. Additionally, the Applicant indicated that the safety profile of SC OCR was comparable to that of IV OCR, based on data from Studies CN41144 and CN42097, where the most frequently reported TEAEs were injection site reactions. However, the Applicant indicated that a direct comparison of safety data from the SC OCR and IV OCR development programs was not feasible due to differences in exposure duration, sample size, and data collection strategies between the programs.

Conclusion

Refer to Section 7.6 of this review for a direct comparison of the safety profiles of SC OCR and IV OCR based on data obtained from the Controlled Period of Study CN42097. Overall, the safety profile of both products appears comparable; however, this assessment is limited by the short duration of the Controlled Period (24 weeks). The Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus; therefore, labeling for SC OCR will be aligned with that of IV OCR, should approval be granted.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Subjects with hepatic or renal impairment were not included in the relative bioavailability study CN42097 (OCARINA II). As noted in current approved labeling for ocrelizumab IV, mild renal or hepatic impairment did not affect ocrelizumab PK following IV administration, and no dose adjustment is recommended based on those factors. Administration of ocrelizumab SC is not expected to affect ocrelizumab PK in patients with mild renal or hepatic impairment, and therefore no dose adjustment is needed based on those factors. Population PK analysis of IV OCR identified bodyweight as a covariate, but no dose adjustment is recommended. Refer to Section 14.5 for details.

8.2. Extrinsic Factors

Clinical drug interaction studies have not been performed with ocrelizumab and hyaluronidase-ocsq. Ocrelizumab is not expected to be an object/precipitant of major CYP450 enzymes or major transporter systems.

8.3. Plans for Pediatric Drug Development

The safety and efficacy of IV OCR (Ocrevus, BLA 761053) is currently being evaluated for the treatment of relapsing forms of MS in pediatric subjects age ≥10 to <18 years old, via a study intended to fulfill Pediatric Research Equity Act PMR 3194-14. No pediatric subjects were enrolled in Studies CN41144 or CN42097.

An Agreed Initial Pediatric Study Plan (iPSP) for SC OCR was issued on January 12, 2023. Consistent with the Agreed iPSP, the Applicant is requesting a partial waiver of the requirement for studies in pediatric subjects under the age of 10 years, and a full waiver of the requirement for studies in pediatric subjects with primary or secondary progressive MS.

The Applicant is requesting a deferral of pediatric studies for subcutaneous ocrelizumab for pediatric subjects with RRMS aged 10 years to <18 years. The pediatric study intended to evaluate the safety and effectiveness of ocrelizumab IV in pediatric subjects 10 to <18 years of age is ongoing. The Applicant proposed to conduct an open-label, single-arm, PK, safety, and tolerability study to determine the appropriate dose of SC OCR that would result in exposures comparable to the IV formulation in subjects ≤40 kg, then extrapolate the potential findings of safety and effectiveness in pediatric subjects 10 to <18 years of age from the ongoing IV OCR Pediatric Research Equity Act PMR study to the SC formulation.

The Pediatric Research Committee met on August 6, 2024, and agreed with the Division's approach to pediatric deferrals and waivers, as well as with the proposed PMRs.

The review team therefore recommends that 2 Pediatric Research Equity Act PMRs be issued, should this BLA be approved. Refer to Section 24 (Postmarketing Requirements and Commitments) for further details.

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

8.4.1. Human Data

No adequate and well-controlled studies of SC OCR have been conducted in the pregnant population. Therefore, there are no adequate human data available to establish if SC OCR poses a risk to pregnancy outcomes. Pregnancy registry and outcomes studies are ongoing to fulfill PMRs for Ocrevus (BLA 761053), and the results of these studies are anticipated to inform labeling determinations regarding the risks of SC OCR in pregnant patients and fetuses.

There were two pregnancies reported in Study CN42097. The first pregnancy occurred in Subject (b) (6), a 31-year-old woman with RRMS receiving IV OCR. The subject received IV OCR on

Study Days 1 and 23. The subject's last menstrual period was on Study Day 76 and the reported contraception method was condom. The subject was subsequently found to be pregnant on an unknown date. The type of pregnancy test and collection date were not reported. Per the CSR, the estimated date of conception was Study Day 71. The study treatment was permanently discontinued on Study Day 122 due to pregnancy. The pregnancy was ongoing as of the BLA submission cutoff date.

The second pregnancy in Study CN42097 was reported in the 120-Day Safety update for Subject (b) (6), a 25-year-old woman with RRMS receiving SC OCR. The subject received SC OCR on Study Days 1 and 175. The subject's last menstrual period was on Study Day 190 and the reported contraception method was condom. Per the 120-Day Safety Update, the date of conception was Study Day 220. On Study Day 253, "beta hCG (human chorionic gonadotropins) test showed result in greater than 10000 (exact value not provided)." A serum pregnancy test was positive on Study Day 282 and study treatment was discontinued on the same day. The outcome of the pregnancy was not provided.

There was one pregnancy reported in Study CN41144, which occurred in Subject (b) (6), a 21-year-old woman with relapsing MS who had been exposed to IV OCR prior to study enrollment. She received SC OCR 920 mg on Study Days 1, 169, 333, 508, and 676. The subject's last menstrual period was on Study Day 693 and the reported contraception method was "horm comb." The date of conception was reported as Study Day 734. Study drug was permanently discontinued on Study Day 812. The pregnancy was ongoing as of the cutoff date.

9. Product Quality

The Office of Pharmaceutical Quality review team has assessed BLA 761371 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 Office of Pharmaceutical Quality recommends approval of this BLA from a quality perspective. The chemistry, manufacturing, and controls postmarketing commitment listed below should be included in the action letter.

> Perform real-time ocrelizumab SC drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-volatile organic compounds, non-volatile organic compounds, and trace metals at regular intervals through the end of shelf-life. The final results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

9.1. Device or Combination Product Considerations

Not applicable.

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

Human Subjects Protections

The Applicant indicated that Studies CN42097 and CN41144 were conducted in accordance with the principles of Good Clinical Practice, the principles of the Declaration of Helsinki, and local laws and regulations. The Applicant also indicated that the appropriate Ethics Committees and Institutional Review Boards reviewed and approved these studies.

Clinical Site Inspections

No clinical site inspections were conducted by the Office of Scientific Investigations for the studies reviewed with this BLA, as the primary endpoint was PK-based rather than clinical.

The Office of Study Integrity and Surveillance was consulted for analytical site inspections. The Office of Study Integrity and Surveillance determined that an on-site inspection was not needed for the analytical site due to the Remote Regulatory Assessment conducted in July 2023 (DARRTS ID: 5349828). Therefore, the review team considers the bioanalytical data submitted under this BLA to be reliable. See Section 22.

Financial Disclosures

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry, *Financial Disclosure by Clinical Investigators* (November 2013), and by 21 CFR 54.4. Refer to Section 25.

The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoint of Study CN42097 is based on objective laboratory measurements that are assessed centrally and not vulnerable to investigator bias.

In conclusion, the likelihood that trial results were biased on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

An advisory committee was not held during this marketing application review, as this drug is not the first in its class, the clinical trial design was acceptable, and evaluation of the safety data did not raise significant safety or efficacy issues that were unexpected for a drug of this class or in the intended populations.

III. Additional Analyses and Information

12. Summary of Regulatory History

Ocrevus (ocrelizumab, RO4964913) injection for intravenous (IV) use was developed by Genentech, Inc. under investigational new drug (IND) 100593 and approved under biologics license application (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 (MS).

Genentech, Inc. developed a subcutaneous (SC) formulation of ocrelizumab which contains recombinant human hyaluronidase (rHuPH20). The SC formulation was developed as a solution for injection in a single dose vial to be administered subcutaneously in the abdomen over approximately ten minutes every six months. Ocrelizumab with RHuPH20 is a fixed-combination product per 21 CFR 300.50 because both ocrelizumab and hyaluronidase are considered active ingredients. Hyaluronidase is a permeation-enhancing enzyme that facilitates the rapid SC delivery of large volumes of drug.

Genentech, Inc. submitted Protocol CN41144/OCARINA I, entitled "A Phase Ib, open-label, multicenter study to investigate the pharmacokinetic (PK), safety and tolerability of subcutaneous ocrelizumab administration in patients with multiple sclerosis" on March 12, 2019, under IND 100593. The objective of Protocol CN41144/OCARINA I was to evaluate the PKs, safety, tolerability, and immunogenicity of ocrelizumab administered by SC injection compared with 600 mg ocrelizumab administered IV to subjects with MS. The Division of Neurology 2 (DN2) had chemistry, manufacturing, and controls-related concerns regarding the ocrelizumab drug product (b) (4) and issued an information request on August 9, 2019, for more details. The Division found the response submitted on October 18, 2019, acceptable.

Genentech, Inc. requested a Type C meeting on June 29, 2020, to discuss further development of a SC route of administration of ocrelizumab, including the adequacy of completed nonclinical studies, the proposed Phase 3 study design, (b) (4) and the filing plan for a future BLA. Written responses were provided on September 11, 2020, stating that, in addition to the completed acute-dose local tolerance studies, a subcutaneous toxicity study would need to be conducted in one species to provide PK data, and additional nonclinical studies might be needed depending on whether a bridge could be established to the completed nonclinical studies using the IV studies. Agreement was reached regarding key features (dose selection strategy, endpoints, timepoint for primary analysis, selected study population, methods of treatment and assignment, and statistical considerations) of the Phase 3 study (Protocol CN42097) and the Division agreed that the proposed safety database seemed reasonable in the context of available Ocrevus safety data. The safety of (b) (4) was agreed to be a matter of review.

Genentech, Inc. submitted Protocol CN42097/OCARINA II, entitled "A Phase III, noninferiority, randomized, open-label, parallel group, multicenter study to investigate the PK, pharmacodynamics (PD), the safety, and the radiological and clinical effects of subcutaneous

ocrelizumab in patients with multiple sclerosis" on January 22, 2021. The objective of Protocol CN42097/OCARINA II was to demonstrate noninferiority and to evaluate the PK, PD, safety, immunogenicity, and radiological and clinical effects of SC administration of ocrelizumab compared with the IV infusion of ocrelizumab in subjects with either relapsing forms of multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS). The Applicant requested additional information on the most appropriate regulatory submission pathway for a planned marketing application for subcutaneously administered ocrelizumab (SC OCR). The protocol was found to be acceptable by the Division, and no comments were conveyed to the Applicant.

Genentech, Inc. requested a Type C meeting on January 6, 2022, to discuss use of Real Time Release Testing (RTRT) as an alternative approach to conventional end-product testing. Genentech, Inc. also requested feedback on method development and validation plans for Modeling Approaches to Reimagine Stability (MARS) for both ocrelizumab SC and another SC drug non-responsive, identity testing with Raman spectroscopy, and recombinant factor C (rFC) endotoxin tests. At the chemistry, manufacturing, and controls-only meeting on March 30, 2022, Genentech, Inc. was advised to involve the Agency (including the Emerging Technology Team) in future product discussions with RTRT approaches. The Division provided points for clarification and additional description of testing procedures to be incorporated in future submissions, and informed Genentech, Inc. that differences in quality attributes would be assessed based on the totality of data and information provided to support implementation of RTRT. The Division agreed that the MARS method validation strategy seemed reasonable but recommended broader ranges for validation studies and establishment of model suitability criteria as part of model validation.

Feedback was relayed regarding the submission of MARS procedure information and guidance was given on determining what types of changes to the MARS models would necessitate postapproval regulatory reporting. The Division agreed that the alternative endotoxin rFC method seemed reasonable and gave recommendations regarding validation and using rFC reagents from different suppliers. While the Division agreed that the general approach for validating Raman spectroscopy for identity testing appeared reasonable, the Division requested additional information to determine the adequacy of method validation and provided considerations for additional model lifecycle management. Despite use of RTRT, the Division informed Genentech, Inc. that a Certificate of Analysis (CoA) needed to include reported results, acceptance criteria related to the method used, and method references, and not just results aligning with external-facing information. Genentech, Inc. was advised that alternative approaches to CoAs was beyond the scope of this meeting and should be addressed in a future meeting. Meeting minutes were issued to the Applicant on April 29, 2022.

Genentech, Inc. submitted version 2 of Protocol CN42097/OCARINA II on March 4, 2022, to include the finalized SC dose (920 mg) based on data from the ongoing Phase 1b study CN41144. This dose selection strategy was deemed reasonable by the Division in the Type C written responses sent September 11, 2020. The Statistical Analysis Plan (version 1) for Protocol CN42097 was submitted on March 11, 2022. The Division had an issue with data collection performed at mobile nursing visits rather than at the study site, which was resolved by the Applicant through submission of additional information on March 21, 2022. The Division had concerns regarding SC dose and related PK parameters and issued an information request on May 10, 2022. The response received on May 12, 2022, confirmed that the maximum plasma concentration (C_{max}) from the SC route of administration did not exceed the C_{max} from the IV

infusion based on individual PK parameters from Study CN41144. The Division had no additional comments.

On May 16, 2022, Genentech, Inc. submitted their rationale for why nonclinical studies were not necessary at this stage of development of SC OCR and requested feedback from the Agency. The Division informed the Applicant on July 19, 2022, that the available nonclinical and clinical data did not support a change in the route of administration from IV to SC. The Division reiterated that a subcutaneous toxicity study would need to be done in one species, as originally stated in the meeting minutes issued on September 11, 2020. In response, Genentech, Inc. submitted a revised protocol on September 9, 2022, for a 4-week SC toxicity and toxicokinetics study in rats. The Division informed the Applicant on November 28, 2022, that the study would need to be performed in monkey because rat is not a pharmacologically relevant species. However, because there was now clinical experience with the SC formulation and the SC route was not anticipated to result in higher exposures in humans, the Division concluded that a nonclinical study would not be needed to support the change in route from IV to SC.

An initial Pediatric Study Plan (iPSP) with a Request for Waiver of Pediatric Studies was initially submitted on June 28, 2022, under IND 100593. Additional information regarding infusion time for SC OCR was requested to evaluate the proposed infusion parameters in children and was submitted by the Applicant on September 12, 2022. A written response from the Division was issued on September 26, 2022. The Applicant submitted a revised iPSP on November 16, 2022, and submitted an agreed iPSP on December 14, 2022. The Division issued an Agreed iPSP on January 12, 2023, with a partial waiver for children under 10 years of age with pediatric relapsing-remitting multiple sclerosis, a deferral for children between 10 and less than 18 years of age with pediatric relapsing-remitting multiple sclerosis, and a full waiver for children with secondary progressive MS and PPMS.

The Applicant submitted a request for proprietary name review for "Ocrevus Zunovo" to the IND on February 2, 2023, and again to BLA 761371 on November 17, 2023. The Division of Medication Error Prevention and Analysis determined the name request was conditionally acceptable on February 7, 2024. Genentech, Inc. submitted a request for review of proposed nonproprietary name suffixes to the IND on April 12, 2023, and again to BLA 761371 on November 10, 2023. The nonproprietary name, ocrelizumab and hyaluronidase-ocsq, was found conditionally acceptable on July 19, 2024.

Genentech, Inc. submitted version 6 of Protocol CN41144/OCARINA I on February 20, 2023, and submitted version 3 of Protocol CN42097/OCARINA II and version 2 of the related Statistical Analysis Plans on March 4, 2022. The Division issued comments to the Applicant for all submissions on June 1, 2023. The Division disagreed with the revised (b) (4)

for both protocols. For Protocol CN42097/OCARINA II, the Division had concerns about secondary efficacy endpoint analysis. Genentech, Inc. responded to the Division's comments on June 21, 2023, and submitted revised protocols (version 7 of Protocol CN41144/OCARINA I and version 4 of Protocol CN42097/OCARINA II) on July 10, 2023, to address the Division's concerns. The revisions were found to be acceptable, and no additional comments were sent to the Applicant.

No formal pre-BLA meeting was held under IND 100593. The original BLA 761371 was submitted on November 10, 2023, and received on November 13, 2023, with the proposed indication of treatment of RMS, to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults, and treatment of PPMS, in adults. The BLA contained the Phase 1b clinical study CN41144/OCARINA I and Phase 3 clinical study CN42097/OCARINA II. This original BLA was not reviewed under "The Program" as it is not a new molecular entity. This BLA was filed on January 12, 2024, and no filing issues were identified.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Ocrevus Zunovo is a fixed-dose combination of ocrelizumab and hyaluronidase formulated for subcutaneous administration. The maximum recommended human dose is a single injection of 920 mg ocrelizumab with 230,000 U hyaluronidase (1,000 U/mL) every 6 months. In pre-BLA feedback, the Division indicated that local tolerance studies would be sufficient to support a BLA for this new formulation and route of administration.

To support clinical development, local tolerance studies assessing a single subcutaneous injections of the clinical formulation were conducted in Sprague-Dawley rat and Göttingen minipig. There were no dermal observations in either rat or minipig in the 7-day post-dosing period. Drug-related microscopic effects at the injection site were assessed at 3 and 7 days post-injection in rat and 7-days post-injection in minipig; findings consisted of non-adverse inflammation characterized by minimal to mild perivascular infiltrate, fibroplasia, and edema. In the rat study in which two time points were assessed, recovery was not observed from Day 3 to Day 7 post-injection.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. PD, PK, and Local Tolerance Study of rhuMAb 2H7 (PRO70769)

Table 64. RhuMAb 2H7 Administered by SC Injection to Cynomolgus Monkeys as a Single or Divided Dose

Study No:	**NC 05-0025-1466**
Study report location	EDR
Conducting laboratory and location	(b) (4)
Date of study initiation	March 14, 2005
GLP compliance	Yes
QA statement	Yes
Drug, lot #, and % purity	rhuMAb 2H7 (ocrelizumab), M3-TOX102, purity: 99%
Methods	
Doses	0, 155.3 mg/animal
Frequency of dosing	Once
Route of administration	SC and IV
Dose volume	Single injection: 1 mL; divided injection: 0.5 mL per injection (2)
Formulation/vehicle	(b) (4) mM sodium acetate, (b) (4) % trehalose dihydrate, and (b) (4) % polysorbate 20, pH (b) (4)
Species/strain	Cynomolgus monkey
Number/sex/group	3 to 7 s/g
Age	3.0 to 4.7 years old
Weight	2.5 to 3.4 kg
Satellite groups	NA
Unique study design	NA
Deviation from study protocol	There were no major deviations from study protocol.

Source: Reviewer-created table derived from Study Report NC 05-0025-1466.
Abbreviations: GLP, good laboratory practice; IV, intravenous; QA, quality assurance; NA, not available; rhuMAb 2H7, ocrelizumab; SC, subcutaneous; s/g, sex per group

Table 65. Group Assignments and Dose Levels of OCR (rhuMAb 2H7) for Study NC 05-0025-1466

Group	No. of M/F	Route of Admin	No. of Injections	Total Dose (mg)	Released on Day 8 (M/F)	Released on Day 15 (M/F)	Released on Week 19 (M/F)
1	7/7	SC	2	0	4/0	0/4	3/3
2	7/7	SC	1	155.3	2/2	2/2	3/3
3	3/3	SC	2	155.3	-	-	3/3
4	3/3	IV	1	155.3	-	-	3/3

Source: Reviewer-created table derived from Study Report NC 05-0025-1466.
A subset of monkeys in groups 1 and 2 were released from the study on Day 8 and 15 for local tolerance assessments (i.e., injection site biopsies).
Abbreviations: F, female; IV, intravenous; M, male; SC, subcutaneous

Mortality and Clinical Signs

Monkeys were assessed cageside twice daily. Injection site observations were conducted 3 times post-dose on Day 1 and once daily through Day 14. There were no drug-related effects on mortality. In both subcutaneously dosed groups, swelling and redness at the injection site were observed that resolved by Day 8. Severity of swelling/redness was higher in the single SC injection group compared to the group in which the dose was divided between two SC injections.

Body Weights and Food Consumption

Body weights were recorded weekly, and food consumption was recorded as a part of the cageside observation. There were no drug-related effects on body weight and food consumption.

Electrocardiogram

Not evaluated.

Hematology, Chemistry, Urinalysis

Blood for hematology and clinical chemistry was collected by venipuncture from a peripheral vein. There were no drug-related changes in clinical chemistry parameters. Lymphocytes were decreased in all drug-dosed groups and recovered to baseline levels by Day 57.

Gross Pathology

Not evaluated.

Organ Weights

Not Evaluated

Histopathology

Adequate Battery: Histopathology was limited to assessment of the injection site

Signed and Dated Pathology Report: Yes

Peer Review: In-house peer review conducted by laboratory facility

Histological Findings: Skin biopsies from the injection site were taken on Days 8 and 15. At both timepoints, hemorrhage, fibroplasia, and macrophage infiltrate were observed in deep subcutaneous layers in the group receiving a single 1-mL injection of rhuMAb 2H7. The macrophage infiltrate reduced in severity from Day 8 to 15 indicating ongoing recovery.

ADA Evaluation

Blood samples for antidrug antibody (ADA) evaluation were collected by venipuncture on Days 15 and 29. Sixty-two percent of all monkeys treated with rhuMAb 2H7 developed ADA. Of monkeys that were observed through Week 19, 83% had ADA by Day 29.

Toxicokinetics

Toxicokinetics of rhuMAb 2H7 was conducted following SC and IV administration on Day 1. Single and divided SC dosing resulted in similar C_{max} and area under the concentration-time curve (AUC). Bioavailability after SC administration was 28-30%.

Table 66. Toxicokinetics of rhuMAb 2H7 After 1 Dose

Dose Route*	C_{max} (µg/mL)	T_{max} (day)	AUC_{last} (µg·day/mL)	$t_{1/2}$ (h)	F (%)
Single SC dose	274	2.39	2640	7.82	28.0
Divided SC dose	241	2.33	2870	5.23	30.4
Single IV dose	1520	NA	8350	10.6	-

Source: Reviewer-created table derived from Study Report NC 05-0025-1466.
*All doses were 155.3 mg/animal.
Abbreviations: AUC_{last}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; F, fraction absorbed; h, hour; IV, intravenous; rhuMAb 2H7, ocrelizumab; SC, subcutaneous; T_{max}, time to maximum concentration; $t_{1/2}$, half-life

Flow Cytometry Analysis

Blood samples collected by venipuncture were used for quantification of leukocytes (T cells, B cells, NK cells). $CD3^-$ B-cells were reduced to 1.5% of baseline in all three drug-dosed groups by Day 3. $CD3^+$ B cells were reduced to 25 to 50% of baseline in all drug-dosed groups. In recovery animals, total peripheral B cells increased to greater than 25% of baseline by the end of the recovery in all dose groups but ranged greatly.

Dosing Solution Analysis

Formulations were supplied ready-to-use by the Applicant.

13.2.2. Single Dose Toxicity (Non-Good Laboratory Practice)

Study 06-0367: 72-Hour Postdose Toxicity Study of rhuMAb 2H7 in Male Sprague Dawley Rats Following a Single Subcutaneous Injection

Male Sprague Dawley rats (5/group) were administered single SC injections of the vehicle (b) (4) mM sodium acetate, (b) (4)% trehalose, and (b) (4)% polysorbate 20, pH (b) (4) or rhuMAb 2H7 (150 mg/mL) and vehicle. Clinical observations, body weights, and morbidity were assessed over a 72-h post-dose period. Redness and/or swelling was present in the drug group (3 of 5) from Day 2 through 4, but not in vehicle-only group. There were no drug-related effects on body weight. At necropsy, examination of the injection site indicated swelling with severe subcutaneous inflammation characterized by neutrophils, eosinophilic granular material, macrophages, lymphocytes, and proliferative fibrous tissue in all animals in the drug group.

Study 06-0367 A: 72-Hour Postdose Toxicity Study of rhuMAb 2H7 in Male Sprague Dawley Rats Following a Single Subcutaneous Injection

Eight groups of male Sprague Dawley rats (3/group) were dosed with either one of 3 vehicle solutions (b) (4) 15% HP-beta cyclodextrin, or 10% HP-gamma cyclodextrin) or rhuMAb 2H7 in one of those three vehicles, or the vehicle for the approved IV

formulation (see Table 67). Efalizumab (Raptiva) was used as a control comparator. Body weight and clinical observations were assessed over the study period. At the end of the 72-hour post-dose observation period, rats were euthanized, and histopathological examination of the injection sites were conducted. There were no drug-related effects on body weight. At the injection site, gross and histopathological findings were most prominent in Group 9 (rhuMAb 2H7 in (b) (4) mM sodium acetate) and consisted of severe inflammation and necrosis (see Table 67, Table 68, and Table 69). Drug-related findings of cutaneous inflammation in Groups 7 and 8 in which the rhuMAb 2H7 dose was 25 mg and 31.25mg, respectively, were dose-dependent (i.e., increased in severity in Group 8 versus Group 7). Rats dosed with vehicle alone (Groups 2,4, and 6) showed little to no inflammation indicating that majority of injection site changes were due to the drug. Of all drug-dosed groups, Group 5 (25 mg rhuMAb 2H7 in 15% HP-beta cyclodextrin) had the least amount of inflammation.

Table 67. Dose Groups for Study 06-0367 A

Group No.	Drug	Vehicle	Drug Concentration (mg/mL)	Dose Volume (mL)	Total Dose (mg)
1	Raptiva (efalizumab)	(b) (4) mM histidine, (b) (4) mM sucrose, (b) (4) % polysorbate 20, pH 6.2	100	0.25	25
2	NA	(b) (4)	0	0.25	0
3	rhuMAb 2H7	(b) (4)	100	0.25	25
4	NA	15% HP-beta cyclodextrin	0	0.25	0
5	rhuMAb 2H7	15% HP-beta cyclodextrin	100	0.25	25
6	NA	10% HP-gamma cyclodextrin	0	0.25	0
7	rhuMAb 2H7	10% HP-gamma cyclodextrin	100	0.25	25
8	rhuMAb 2H7	10% HP-gamma cyclodextrin	125	0.25	31.25
9	rhuMAb 2H7	(b) (4) mM sodium acetate (approved intravenous formulation)	150	0.25	37.5

Source: Reviewer-created table derived from Study Report 06-0367 A.
Abbreviations: HP, hydroxypropyl; NA, not applicable; rhuMAb 2H7, ocrelizumab

Table 68. Selected Injection Site Clinical Observations on Study Day 4

	Group								
Finding	1 (C)	2 (V)	3 (D)	4 (V)	5 (D)	6 (V)	7 (D)	8 (D)	9 (D)
Tissue examined (N)	3	3	3	3	3	3	3	3	3
Swelling									
Slight	-	-	2	-	-	-	2	3	2
Mild	-	-	-	-	-	-	-	-	-
Moderate	-	-	-	-	-	-	-	-	1
Severe	-	-	-	-	-	-	-	-	-
Thickened skin	-	-	2	-	-	-	2	3	3
Definite raised area	-	-	-	-	-	-	-	-	2

Source: Reviewer-created table derived from Study Report 06-0367 A.
Abbreviations: C, control/efalizumab; D, drug/rhuMAb 2H7; N, number of animals in treatment group; rhuMAb 2H7, ocrelizumab; V, vehicle only

Table 69. Selected Injection Site Histopathological Findings

	Group								
Finding	**1 (C)**	**2 (V)**	**3 (D)**	**4 (V)**	**5 (D)**	**6 (V)**	**7 (D)**	**8 (D)**	**9 (D)**
Tissue examined (N)	3	3	3	3	3	3	3	3	3
Inflammation									
Slight	3	2	-	3	1	1	1	-	-
Mild	-	-	-	-	2	-	-	-	-
Moderate	-	-	3	-	-	-	2	3	-
Severe	-	-	-	-	-	-	-	-	3

Source: Reviewer-created table derived from Study Report 06-0367 A.
Abbreviations: C, control/efalizumab, D, drug/rhuMAb 2H7; N, number of animals in treatment group; rhuMAb 2H7, ocrelizumab; V, vehicle only

Study 06-0367 B: 72-Hour Postdose Toxicity and Toxicokinetics Study of rhuMAb 2H7 in Male Sprague Dawley Rats Following a Single Subcutaneous Injection

Eight groups of male Sprague Dawley rats (3/group) were injected SC with either a vehicle formulation or rhuMAb 2H7 (see Table 70). None of the vehicles used in this experiment was the vehicle in the intended clinical product. Efalizumab (Raptiva) was used as a control comparator. Rats were observed for 72 hours after dose administration; the injection site was examined upon necropsy. Across all dose groups, rhuMAb 2H7 was associated with swelling as well as histopathological findings of inflammation (mild to severe; see Table 71 and Table 73). These findings were least severe when rhuMAb 2H7 was delivered in 10% HP-gamma cyclodextrin and most severe when rhuMAb 2H7 was delivered in the original vehicle for the IV formulation ([(b) (4)]mM sodium acetate, [(b) (4)]% trehalose, [(b) (4)]% polysorbate 20). In Group 9, in which the findings were most severe, necrosis and cavitation at the injection site was observed in all three animals. Abbreviated TK analyses (i.e., only 3 timepoints assessed) indicated that serum concentrations were highest when delivered in 10% HP-gamma cyclodextrin and [(b) (4)] [(b) (4)]/10% HP-gamma cyclodextrin vehicles (Groups 4 and 7).

Table 70. Dose Groups for Study 06-0367 B

Group No.	Drug	Vehicle	Drug Concentration (mg/mL)	Dose Volume (mL)	Total Dose (mg)
1	Raptiva (efalizumab)	(b) (4) mM histidine, (b) (4) mM sucrose, (b) (4) % polysorbate 20, pH 6.2	100	0.25	25
2	NA	10% HP-gamma cyclodextrin (vehicle 1)	0	0.25	0
3	rhuMAb 2H7	10% HP-gamma cyclodextrin (vehicle 1)	100	0.25	25
4	rhuMAb 2H7	10% HP-gamma cyclodextrin (vehicle 1)	150	0.25	37.5
5	rhuMAb 2H7	(b) (4)	150	0.25	37.5
6	NA	(b) (4) 10% HP-gamma cyclodextrin (vehicle 2)	0	0.25	0
7	rhuMAb 2H7	(b) (4), 10% HP-gamma cyclodextrin (vehicle 2)	150	0.25	37.5
8	rhuMAb 2H7	(b) (4) mM sodium acetate, (b) (4) % trehalose, (b) (4) % polysorbate 20 (original IV formulation)	100	0.25	25
9	rhuMAb 2H7	(b) (4) mM sodium acetate, (b) (4) % trehalose, (b) (4) % polysorbate 20 (original IV formulation)	150	0.25	37.5

Source: Reviewer-created table derived from Study Report 06-0367 B.
Abbreviations: HP, hydroxypropyl; IV, intravenous; rhuMAb 2H7, ocrelizumab

Table 71. Selected Injection Site Clinical Observations on Study Day 4

	Group								
Finding	1 (C)	2 (V)	3 (D)	4 (D)	5 (D)	6 (V)	7 (D)	8 (D)	9 (D)
Tissue examined (N)	3	3	3	3	3	3	3	3	3
Swelling									
Slight	-	-	-	-	-	-	-	-	-
Mild	-	-	-	-	-	-	-	-	-
Moderate	-	-	-	-	-	-	-	-	-
Severe									
Thickened skin	-	-	-	-	-	-	-	-	
Definite raising	-	-	-	-	-	-	-	-	3

Source: Reviewer-created table derived from Study Report 06-0367 B.
Abbreviations: C, control/efalizumab; D, drug/rhuMAb 2H7; N, number of animals in treatment group; rhuMAb 2H7, ocrelizumab; V, vehicle only

Table 72. Serum Drug (rhuMAb 2H7 or Raptiva) Concentration (µg/mL)

	Group								
Time (h)	1 (C)	2 (V)	3 (D)	4 (D)	5 (D)	6 (V)	7 (D)	8 (D)	9 (D)
0.25	55.8	-	30.0	45.9	21.1	-	46.8	32.0	35.9
1	438	-	245	415	300	0.0266	376	275	333
1.25	452	-	258	427	341	0.0274	400	292	328

Source: Reviewer-created table derived from Study Report 06-0367 B.
Abbreviations: C, control/efalizumab, D, drug/rhuMAb 2H7; h, hour; rhuMAb 2H7, ocrelizumab; V, vehicle

Table 73. Selected Injection Site Histopathological Findings

	Group								
Finding	**1 (C)**	**2 (V)**	**3 (D)**	**4 (D)**	**5 (D)**	**6 (V)**	**7 (D)**	**8 (D)**	**9 (D)**
Tissue examined (N)	3	3	3	3	3	3	3	3	3
Inflammation									
Slight	1	2	-	-	-	-	-	-	-
Mild	2	1	2	-	-	-	-	1	-
Moderate	-	-	1	3	-	-	3	2	-
Severe					3				3

Source: Reviewer-created table derived from Study Report 06-0367 B.
Abbreviations: C, control/efalizumab; D, drug/rhuMAb 2H7; N, number of animals in treatment group; rhuMAb 2H7, ocrelizumab; V, vehicle

Study 06-0367 C: 72-Hour Postdose Toxicity Study of rhuMAb 2H7 in Male Sprague Dawley Rats Following a Single Subcutaneous Injection

Seven groups of male Sprague Dawley rats (3/group) were injected SC once with rhuMAb 2H7 or vehicle solution and observed for 72 h post-dose (see Table 74). Efalizumab (Raptiva) was used as a control comparator. There were no effects on body weight. Clinical observations consisted of swelling and redness and microscopic inflammation across rhuMAb 2H7 dosed groups (see Table 75 and Table 76). Severity of these findings was decreased in groups in which the concentration of rhuMAb 2H7 was lower (i.e., Group 7); however, the total drug dose was also lower because the injection volume was the same at 0.25 mL.

Table 74. Dose Groups for Study 06-0367 C

Group No.	**Drug**	**Vehicle**	**Drug Concentration (mg/mL)**	**Dose Volume (mL)**	**Total Dose (mg)**
1	Raptiva (efalizumab)	(b)(4) mM histidine, (b)(4) mM sucrose, (b)(4) % polysorbate 20, pH 6.2	100	0.25	25
2	NA	30% HP-gamma cyclodextrin, (b)(4) % polysorbate 20	0	0.25	0
3	rhuMAb 2H7	5% HP-gamma cyclodextrin, (b)(4) % trehalose, (b)(4) % polysorbate 20	150	0.25	37.5
4	rhuMAb 2H7	15% HP-gamma cyclodextrin, (b)(4) % trehalose, (b)(4) % polysorbate 20	150	0.25	37.5
5	rhuMAb 2H7	30% HP-gamma cyclodextrin, (b)(4) % polysorbate 20	100	0.25	25
6	rhuMAb 2H7	30% HP-gamma cyclodextrin, (b)(4) % polysorbate 20	150	0.25	37.5
7	rhuMAb 2H7	(b)(4) mM sodium acetate, (b)(4) % trehalose, (b)(4) % polysorbate 20, pH (b)(4)	30	0.25	8
8	rhuMAb 2H7	(b)(4) mM sodium acetate, (b)(4) % trehalose, (b)(4) % polysorbate 20, pH (b)(4)	150	0.25	37.5

Source Reviewer-created table derived from Study Report 06-0367 C.
Abbreviations: HP, hydroxypropyl; rhuMAb 2H7, ocrelizumab

Table 75. Selected Injection Site Clinical Observations on Study Day 4

	Group							
Finding	**1 (C)**	**2 (V)**	**3 (D)**	**4 (D)**	**5 (D)**	**6 (D)**	**7 (D)**	**8 (D)**
Tissue examined (N)	3	3	3	3	3	3	3	3
Swelling								
Slight	-	-	-	-	1	2	-	-
Mild	-	-	-	3	-	1	-	-
Moderate	-	-	3	-	-	-	-	1
Severe	-	-	-	-	-	-	-	2
Thickened skin	-	-	-	-	-	-	-	-
Definite raising	-	-	-	-	-	-	-	-

Source: Reviewer-created table derived from Study Report 06-0367 C.
Abbreviations: C, control/efalizumab; D, drug/rhuMAb 2H7; N, number of animals in treatment group; rhuMAb 2H7, ocrelizumab; V, vehicle only

Table 76. Selected Injection Site Histopathological Findings

	Group							
Finding	**1 (C)**	**2 (V)**	**3 (D)**	**4 (D)**	**5 (D)**	**6 (D)**	**7 (D)**	**8 (D)**
Tissue examined (N)	3	3	3	3	3	3	3	3
Inflammation								
Slight	2	1	-	-	-	-	2	-
Mild	1	1	-	-	3	3	1	-
Moderate	-	1	-	2	-	-	-	-
Severe	-	-	3	1	-	-	-	3

Source: Reviewer-created table derived from Study Report 06-0367 C.
Abbreviations: C, control/efalizumab; D, drug/rhuMAb 2H7; N, number of animals in treatment group; rhuMAb 2H7, ocrelizumab; V, vehicle only

Study 06-0367 D: 72-Hour Postdose Toxicity Study of rhuMAb 2H7 in Male Sprague Dawley Rats Following a Single Subcutaneous Injection

Eight groups of male Sprague Dawley rats (3/group) were dosed SC with rhuMAb 2H7 (in one of several vehicles) or vehicle solution once and observed for 72 hours after dosing (see Table 77). None of the formulations was the intended clinical formulation. Efalizumab (Raptiva) was used as a control comparator. Clinical signs of swelling and redness as well as histopathological inflammation were observed across all rhuMAb 2H7-dosed groups (see Table 78 and Table 79). However, groups with formulations with higher concentrations of polyvinylpyrrolidone (10% and 20%) had decreased severity of redness/swelling and inflammation compared to concentrations with little or no polyvinylpyrrolidone. Extensive inflammation with necrosis was observed in Group 3 (100 mg/mL rhuMAb 2H7 in 5% polyvinylpyrrolidone) and Group 9 (150 mg/mL rhuMAb 2H7 in original formulation for IV administration). Severity of irritation and inflammation were also dose-dependent; however, it is unclear if this is due to concentration or total dose because the dose volumes were constant across all concentrations.

Table 77. Dose Groups for Study 06-0367 D

Group No.	Drug	Vehicle	Drug Concentration (mg/mL)	Dose Volume (mL)	Total Dose (mg)
1	Raptiva (efalizumab)	(b)(4) mM histidine, (b)(4) mM sucrose, (b)(4) % polysorbate 20, pH 6.2	100	0.25	25
2	NA	20% 17K polyvinylpyrrolidone, (b)(4) % polysorbate 20	0	0.25	0
3	rhuMAb 2H7	(b)(4) % 17K polyvinylpyrrolidone	100	0.25	25
4	rhuMAb 2H7	(b)(4) % 17K polyvinylpyrrolidone	100	0.25	25
5	rhuMAb 2H7	(b)(4) % 17K polyvinylpyrrolidone, (b)(4) % polysorbate 20	100	0.25	25
6	rhuMAb 2H7	(b)(4) % 17K polyvinylpyrrolidone	150	0.25	37.5
7	rhuMAb 2H7	Vehicle	150	0.25	37.5
8	rhuMAb 2H7	(b)(4) mM sodium acetate, (b)(4) % trehalose, (b)(4) % polysorbate 20, pH (b)(4)	75	0.25	18.8
9	rhuMAb 2H7	(b)(4) mM sodium acetate, (b)(4) % trehalose, (b)(4) % polysorbate 20, pH (b)(4)	150	0.25	37.5

Source: Reviewer-created table derived from Study Report 06-0367 D.
Abbreviations: rhuMAb 2H7, ocrelizumab

Table 78. Selected Injection Site Clinical Observations on Study Day 4

	Group								
Finding	1 (C)	2 (V)	3 (D)	4 (D)	5 (D)	6 (D)	7 (V)	8 (D)	9 (D)
Tissue examined (N)	3	3	3	3	3	3	3	3	3
Swelling									
Slight	-	2	1	3	3	1	3	1	-
Mild	-	-	-	-	-	2	-	1	-
Moderate	-	-	2	-	-	-	-	1	3
Severe	-	-	-	-	-	-	-	-	-
Thickened skin	-	-	-	-	-	-	-	-	-
Definite raising	-	-	-	-	-	-	-	2	3

Source: Reviewer-created table derived from Study Report 06-0367 D.
Abbreviations: C, control/efalizumab; D, drug/rhuMAb 2H7; N, number of animals in treatment group; rhuMAb 2H7, ocrelizumab; V, vehicle only

Table 79. Selected Injection Site Histopathological Findings

	Group								
Finding	1 (C)	2 (V)	3 (D)	4 (D)	5 (D)	6 (D)	7 (V)	8 (D)	9 (D)
Tissue examined (N)	3	3	3	3	3	3	3	3	3
Inflammation									-
Slight	3	3	-	3	-	1	-	-	-
Mild	-	-	-	-	3	2	3	-	-
Moderate	-	-	-	-	-	-	-	3	-
Severe	-	-	3	-	-	-	-	-	3

Source: Reviewer-created table derived from Study Report 06-0367 D.
Abbreviations: C, control/efalizumab; D, drug/rhuMAb 2H7; N, number of animals in treatment group; rhuMAb 2H7, ocrelizumab; V, vehicle only

14. Clinical Pharmacology

14.1. In Vitro Studies

No *in vitro* studies were conducted.

14.2. In Vivo Studies

The clinical development program of Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) includes two studies CN41144 (OCARINA I) and CN42097 (OCARINA II). Both are ongoing studies, with clinical cutoff dates of January 27, 2023, and March 10, 2023, respectively.

CN41144 (OCARINA I)

Study CN41144 is a Phase 1b, open-label, multicenter study to investigate the PK, safety, and tolerability of SC OCR administration in subjects with MS. Refer to Section 15.2 for a detailed discussion of the study design. Principles of population pharmacokinetics (PopPK) were used to analyze PK data, and the data are presented in Section 14.5 (Pharmacometrics).

CN42097 (OCARINA II)

Study CN42097 is a Phase 3 noninferiority, randomized, open-label, parallel group, multicenter study to evaluate the PK, PD, safety, immunogenicity, radiological, and clinical effects of SC administration of ocrelizumab compared with the IV infusion of ocrelizumab in subjects with either RMS or PPMS. Refer to Section 15.1 for a detailed discussion of the study design. Principles of PopPK were used to analyze PK data, and the data are presented in Section 14.5 (Pharmacometrics).

14.3. Bioanalytical Method Validation and Performance

Ocrelizumab concentrations in human serum were determined using a validated sandwich enzyme-linked immunosorbent assay. Microtiter plates were coated with an affinity purified goat polyclonal antibody against ocrelizumab complementarity determining region at 1.0 µg/mL to capture ocrelizumab. Diluted samples, standards, and controls were added to the plate and incubated. Subsequently, goat F(ab')2 antihuman IgG (Fc gamma fragment specific) horseradish peroxidase conjugate was added for detection and incubated. A peroxidase substrate (tetramethyl benzidine) was added to develop color, and the reaction was stopped by adding 1 M phosphoric acid. The plates were read at 450 nm for detection absorbance and at 630 nm for reference absorbance.

The Assay validation parameters (Method validation Report: ICD 723) are summarized in Table 80. All samples were analyzed within the 2095 days of demonstrated long-term storage stability in human serum at -80°C. The results of the incurred sample repeats met the acceptance criteria, with 182 of the 210 incurred samples ≤±30% RPD, for an overall pass rate of 86.7%.

Table 80. Validation Summary for OCR PK Assay

(b) (4) **Project Code**	RJQH2				
Method ID	ICD 723				
Analyte	Ocrelizumab (rhuMAb 2H7)				
MRD	1/100 in sample diluent				
Matrix	Human serum from patients with MS				
Method Description	ELISA				
Sample Volume	20.0 µL aliquot				
Sample Storage Temperature	-80 °C[a]				
LLOQ	156 ng/mL (neat serum concentration, prior to assay MRD)				
ULOQ	5000 ng/mL (neat serum concentration, prior to assay MRD)				
Regression, Weighting	Four-parameter logistic, unweighted				
Standard Curve Concentration Limits	1.56 to 50.0 ng/mL (in-well concentrations)				
QC Concentrations	156, 250, 1500, 3500, and 5000 ng/mL				
QC Inter-Assay Statistics (%)[b]	Level (in Neat Serum)	Conc. (ng/mL)	Precision (%CV)	Accuracy (%DFT)	Total Error (%)
	LLOQ	156	6.39	-8.20	14.6
	Low	250	4.68	-8.68	13.4
	Mid	1500	7.92	-2.23	10.2
	High	3500	11.5	-5.45	17.0
	ULOQ	5000	8.41	-5.84	14.2
Hook Effect, Accuracy, and Linearity of Dilution	• 1.48 mg/mL diluted to five dilutions on the curve plus additional dilutions above and below the curve. • No apparent hook effect observed at concentrations up to 1.48 mg/mL. • Dilutional linearity is acceptable with a maximum allowable sample dilution of 1/640,000 (dilution includes the 1/100 MRD).				
Recovery/Specificity and Linearity	• Specificity is acceptable, as 10 out of 10 unfortified human serum samples from individuals with MS and the NHS pool quantitating below the LLOQ. • Low-level recovery is acceptable, as 10 out of 10 human serum samples from individuals with MS and the NHS pool fortified at the LLOQ level (156 ng/mL) recovered within ± 25% of theoretical. • High-level recovery is acceptable, as 10 out of 10 human serum samples from individuals with MS and the NHS pool fortified at the high QC level (3500 ng/mL) recovered within ± 20% of theoretical and had acceptable linearity %CV within ± 20%.				

Stability	Reagent: • Diluted matrix stability for 7 days at 2-8 °C • Blocked plate stability for 35 days at -80 °C Analyte: • Up to 72.17 consecutive hours at room temperature • 6 freeze/thaw cycles thawed at room temperature (for a combined total of 25.4 hours) and frozen at -80 °C
Ruggedness/Robustness	The minimum and maximum incubation times for the coat, block, sample, and HRP conjugate incubations were evaluated; the low, mid, and high-level QCs met the acceptance criteria.

CV = coefficient of variation; DFT = difference from theoretical; ELISA = enzyme-linked immunosorbent assay; ID = identification; LLOQ = lower limit of quantification; MRD = minimum required dilution; MS = multiple sclerosis; QC = quality control; ULOQ = upper limit of quantification.

[a] -80 °C freezer setpoint with a range of -90 °C to -60 °C.
[b] Statistics obtained from runs 1RJQH2 through 6RJQH2.

Source: ICD 723 Validation Report, Page 6 to 7.
Abbreviations: OCR, ocrelizumab; PK, pharmacokinetic

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

A bridging enzyme-linked immunosorbent assay was developed and validated to detect, confirm, and titer antibodies to ocrelizumab in human serum. An electrochemiluminescent bridging immunoassay using the MSD platform was developed and validated for detection of antibodies to rHuPH20 in human plasma. Refer to both method validation reviews by Dr. Dokmanovic and Dr. George of the Office of Product Quality III (DARRTS ID: 5432001 2024). In Study CN42097, no treatment-emergent ADAs to ocrelizumab or rHuPH20 were observed.

14.5. Pharmacometrics Assessment

Applicant's Population PK Analysis for Study CN41144

Two PopPK study reports were submitted for Study CN41144: 1) Abbreviated Population PK Analysis Report (RDR 1114115 dated February 7, 2021) with a data cutoff of November 9, 2021, and 2) Population PK Analysis of SC and IV administered ocrelizumab (IV OCR) in Patients with Multiple Sclerosis (RDR 1124537 dated August 16, 2023) with a data cutoff of January 27, 2023.

Abbreviated Population PK Analysis Report: RDR 1114115

This abbreviated PopPK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, Version 7.4.3 (ICON Development Solutions). The analysis dataset contained 1427 quantifiable serum samples from 134 subjects. Of these samples, 1216 were obtained following SC administration.

The objectives of the PopPK analysis were:

- Based on the earlier population PK model of IV OCR in subjects with MS, to develop a predictive population PK model that describes ocrelizumab PK following IV and subcutaneous (SC) administration in Study CN41144.
- Based on the developed model, to determine individual predicted exposures (AUC) following the first single dose over 168 days (Cycle 1 AUC) of Study CN41144.
- To support the selection of the SC dose for the future Phase 3 trial based on comparison of individual predicted IV and SC exposures in Study CN41144 and previous Phase 3 studies.

Population PK Model Development Approach

The earlier population PK model of ocrelizumab IV in subjects with MS (henceforth referred to as the original/initial model) was used. Briefly, the PK of ocrelizumab IV in serum was described by a two-compartment disposition model with clearance that was the sum of constant clearance (CL_{inf}) and time-dependent clearance (CL_t) that decreased exponentially with time to on treatment ($CL = CL_{inf}+CLT_0 \cdot \exp(-kdes \cdot t)$). The half-life of the time-dependent part of clearance was 0.63 years (230 days); the other parameters were typical for monoclonal antibodies. The covariates retained in the final model were body weight on CL_{inf}, CLT_0, central (V1) and peripheral (V2) volumes and intercompartment clearance (Q); B-cell count at baseline on CL_{inf}; and sex on V1. The model was appended with an absorption model for SC doses.

Two additional changes to the original model were made. First, the subjects in Group A were previously treated with ocrelizumab. Clearance in the original model was described as a sum of time-independent and time-dependent terms, where the time-dependent part of clearance decreased with time on treatment (exponentially with the decay coefficient of kdes). Therefore, for previously treated subjects, initial time-dependent clearance (CLT_0) was defined as:

$$CLT_0 = CL_{T0}*\exp(-kdes*TRTDUR)$$

in which CLT_0 is initial time-dependent clearance at the start of previous treatment (when the subject is treatment-naive), a parameter in the original model, and TRTDUR is time on treatment at the start of dosing in the current study.

Second, some of the previously treated subjects had quantifiable ocrelizumab concentrations at the time of the first dose in the study. To account for these subjects, initial concentrations in the central and peripheral compartments were set to be equal to predose values.

Initially, all population parameters of the original model were fixed to their original values. Several models of SC absorption were tried: first-order absorption with or without lag time, two sequential first-order absorption processes, and zero-order absorption followed by the first-order absorption. After the absorption model was selected, it was observed that the distribution of the random effect on the intercompartment clearance was biased. To correct for the bias, the model with estimated intercompartment clearance and absorption model parameters was tested.

Table 81. Estimated Parameters of the Original Model

Parameter		Estimate	RSE (%)	95%CI		
CL_{inf} (L/day)	θ1	0.17	1.26	0.166 - 0.174		
V_1 (L)	θ2	2.78	1.35	2.71 - 2.85		
V_2 (L)	θ3	2.68	2.76	2.53 - 2.82		
Q (L/day)	θ4	0.294	7.46	0.251 - 0.337		
k_{des} ($year^{-1}$)	θ5	1.11	5.95	0.979 - 1.24		
CL_{T0} (L/day)	θ6	0.0489	2.62	0.0464 - 0.0514		
CL_{T02} (L/day)	θ7	0.0199	8.16	0.0167 - 0.0231		
$CL_{inf,WT}$ [a]	θ8	0.684	5.19	0.615 - 0.754		
$V_{1,WT}$ [a]	θ9	0.397	8.4	0.331 - 0.462		
$V_{2,WT}$ [a]	θ10	0.853	6.46	0.745 - 0.961		
$Q_{,WT}$ [a]	θ11	0.75 Fix	NA	NA		
$CL_{T0,WT}$ [a]	θ12	0.981	7.82	0.831 - 1.13		
$V_{1,Male}$ [b]	θ13	1.12	2.08	1.07 - 1.16		
$CL_{inf,BCD19}$ [c]	θ14	0.0403	13.6	0.0295 - 0.051		
					Variability	Shrinkage
ω^2_{CLinf}	Ω(1,1)	0.0535	5.07	0.0482 - 0.0588	CV=23.1%	7.1%
$\omega_{CLinf}\,\omega_{V1}$	Ω(1,2)	0.026	11.3	0.0202 - 0.0318	R=0.528	NA
ω^2_{V1}	Ω(2,2)	0.0453	8.23	0.038 - 0.0526	CV=21.3%	31.30%
ω^2_{Q}	Ω(3,3)	0.239	8.91	0.197 - 0.281	CV=48.9%	53.30%
ω^2_{CLT0}	Ω(4,4)	0.125	12.3	0.095 - 0.156	CV=35.4%	47.20%
$\sigma^2_{TAD\leq1}$	Σ(1,1)	0.0346	9.01	0.0285 - 0.0407	CV=18.6%	28.7%
$\sigma^2_{TAD>1}$	Σ(2,2)	0.0487	1.31	0.0474 - 0.0499	CV=22.1%	17.9 %

a. Power coefficient of the power function with the reference value of 75 kg.
b. Multiplicative factor for the respective subpopulation compared to the rest of patients.
c. Power coefficient of the power function with the reference value of $0.225*10^9$/L.
SE: Standard Error: %RSE: Relative Standard Error, RSE=100·SE/PE, where PE is parameter estimate. 95% CI: 95% confidence interval. CV: coefficient of variation computes as 100%

Source: Abbreviated Population PK: Study CN41144 (RDR 1114115). Page 22, Table 1.
Abbreviations: CL_{inf}, constant clearance; CL_{T0}, initial time dependent clearance; k_{des}, rate constant of decay of CL_t with time t; PK, pharmacokinetic; Q, inter-compartmental clearance; NA, not applicable; V_1, central volume ; V_2, peripheral volume ; WT, body weight; σ^2 sigma^2, residual variance; ω^2, omega^2, inter-individual variance; θ, NONMEM fixed effect parameter.

The Applicant-developed model has sequential first-order absorption, slow absorption until MTIME and fast absorption after it, which described the PK data following SC administration well. The parameter estimates of the final model are presented in Table 82. The SC bioavailability was estimated to be 71.7% (95% CI: 66.8 to 76.6%). Intercompartment clearance was estimated to be 0.616 L/day (95% CI: 0.503 to 0.728 L/day).

Table 82. Estimated Parameters for the Final Model 093

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage (%)
Q (L/day)	θ_4	0.616	9.32	0.503 - 0.728		
F_{SC}	θ_{15}	0.717	3.48	0.668 - 0.766		
MTIME (day)	θ_{16}	0.136	2.69	0.129 - 0.143		
Ka1 (1/day)	θ_{17}	0.042	17.8	0.0273 - 0.0567		
Ka2 (1/day)	θ_{18}	0.439	8.22	0.368 - 0.509		
ω^2_{Fsc}	Ω(5,5)	0.0507	17.7	0.0332 - 0.0683	CV=22.5%	17.2%
ω^2_{Ka1}	Ω(6,6)	0.94	22.7	0.522 - 1.36	CV=96.9%	26.4%
ω^2_{Ka2}	Ω(7,7)	0.347	17.7	0.227 - 0.468	CV=58.9%	7.1%

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100·SE/PE; 95% CI: 95% confidence interval; CV: coefficient of variation.

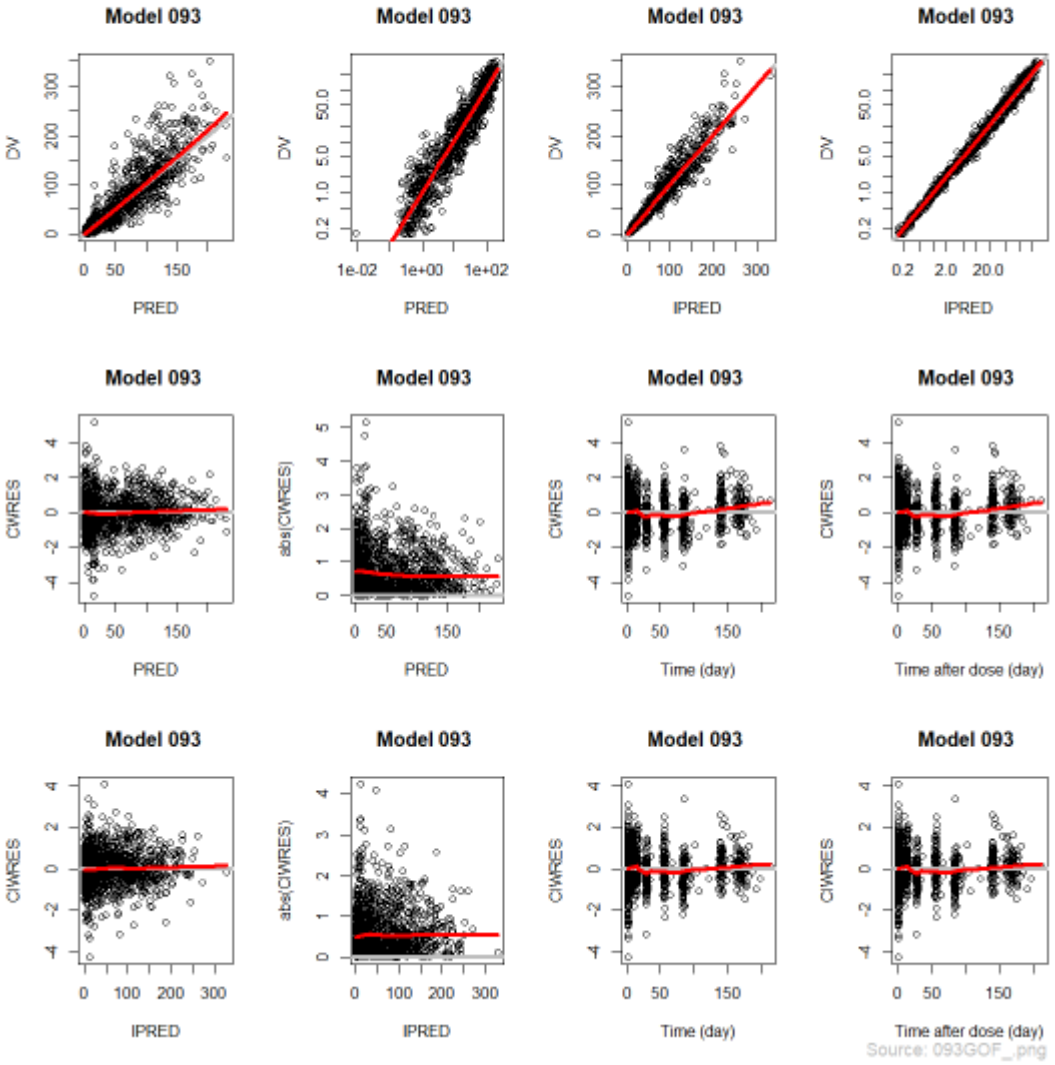
Source: Abbreviated Population PK: Study CN41144 (RDR 1114115). Page 25, Table 4.
Abbreviations: F_{SC}, SC bioavailability; k_{a1}, initial (before MTIME) absorption constant; k_{a2}, later (after MTIME) absorption constant; MTIME, model event time; PK, pharmacokinetic; Q, inter-compartmental clearance; V_1, central volume; V_2, peripheral volume; WT, body weight; ω^2, omega^2, inter-individual variance.

Final Model Evaluation

The diagnostic plots shown in Figure 8 demonstrated a good fit of the data. The developed model was used to predict individual exposures (Cycle 1 AUC) for all subjects. The predicted exposures were summarized to aid selection of the SC dose for a Phase 3 study.

Figure 8. Goodness-of-Fit, Model 093, Cohort All Data

DV: Observed concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES and CIWRES: conditional weighted residuals and conditional individual weighted residuals; TIME: time after the first dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.



Source: Abbreviated Population PK: Study CN41144 (RDR 1114115). Page 41, Table 14.

The summary of predicted PK exposures for the subjects previously treated with ocrelizumab in Study CN41144 and for Cycle 4 for subjects in the Phase 3 Studies WA21092/WA21093 is shown in Table 83. The exposures in SC cohorts are scaled to 800-, 900-, 1000-, or 1200-mg doses. For ocrelizumab (OCR)-naive subjects, the exposures are summarized in Table 84. The exposures in the SC cohort (B4 cohort) are scaled to 800-, 900-, 1000-, or 1200-mg doses and compared to Cycle 1 of Studies WA21092/WA21093.

Table 83. Summary of Predicted Exposures, OCR Pretreated Subjects, Model 093

Study	Cohorts	Dose[a]	N	Weight (kg)	AUC (µg/mL*day)						
				Mean	Mean	SD	Median	Min	Max	Q25	Q75
41144	AA	600 mg IV	35	94.2	2960	997	2850	1230	6080	2350	3400
21092/21093	-	600 mg IV[b]	782	74.9	3510	962	3450	1420	11300	2820	4070
41144	A4-A5	800 mg SC	41	92.9	3320	1040	3300	1620	5720	2570	3860
41144	A4-A5	900 mg SC	41	92.9	3730	1170	3720	1830	6430	2890	4340
41144	A4-A5	1000 mg SC	41	92.9	4150	1310	4130	2030	7150	3210	4820
41144	A4-A5	1200 mg SC	41	92.9	4970	1570	4960	2440	8580	3860	5790
41144	A3-A4-A5	800 mg SC	45	92.6	3280	1080	3300	1350	5720	2520	3860
41144	A3-A4-A5	900 mg SC	45	92.6	3690	1210	3720	1520	6430	2840	4340
41144	A3-A4-A5	1000 mg SC	45	92.6	4100	1340	4130	1690	7150	3160	4820
41144	A3-A4-A5	1200 mg SC	45	92.6	4920	1610	4960	2020	8580	3790	5790

a. Exposures in the SC cohorts are scaled to the shown dose
b. Cycle 4

Source: Abbreviated Population PK: Study CN41144 (RDR 1114115). Page 26, Table 5.
Abbreviations: AUC, area under the concentration-time curve; IV, intravenous; N, number of subjects in treatment arm; OCR, ocrelizumab; Q25, first quartile; Q75, third quartile; SC, subcutaneous

Table 84. Summary of Predicted Exposures, OCR-Naive Subjects, Model 093

Study	Cohorts	Dose[a]	N	Weight (kg)	AUC						
				Mean	Mean	SD	Median	Min	Max	Q25	Q75
21092/ 21093	-	600 mg IV[b]	782	74.9	2900	754	2840	1260	8850	2370	3350
41144	B4	800 mg SC	37	88.5	2810	1130	2540	909	5530	1940	3620
41144	B4	900 mg SC	37	88.5	3160	1280	2860	1020	6220	2190	4070
41144	B4	1000 mg SC	37	88.5	3510	1420	3170	1140	6910	2430	4520
41144	B4	1200 mg SC	37	88.5	4210	1700	3810	1360	8290	2910	5420

a. Exposures in the SC cohort are scaled to the shown dose
b. Cycle 1

Source: Abbreviated Population PK: Study CN41144 (RDR 1114115). Page 27, Table 6.
Abbreviations: AUC, area under the concentration time curve; IV, intravenous; OCR, ocrelizumab; PK, pharmacokinetic; Q25, first quartile; Q75, third quartile; SC, subcutaneous

Dose Selection for Phase 3 Study

The Applicant noted that, since higher exposure variability is observed after SC dosing, the SC dose was selected with a slightly higher mean exposure compared to the mean exposure after 600 mg IV dosing, to ensure that patients on the lower range of the exposure distribution have adequate exposure to ocrelizumab for therapeutic benefit. Based on the AUC values reported in Table 83 and Table 84, a dose of 900 mg is likely to achieve this. (b) (4)

In conclusion, a dose of 920 mg SC is expected to provide comparable exposure versus the approved 600 mg IV dose and has therefore been selected for the subsequent Phase 3 study.

This interim population PK model was updated by the Applicant in the Population PK Report (RDR 1124537) for Study CN41144 with a cutoff date of January 27, 2023. The analysis dataset contained 1882 quantifiable serum samples from 134 subjects. Of them, 300 samples were obtained from subjects from IV cohort, and 1582 samples were obtained from the subjects of SC cohorts. Model-predicted exposures following IV and SC administrations are presented in Table

85. The predicted median (range) of AUC from Week 1 to Week 12 (AUC_{W1-12}) and AUC over the first 24 weeks following 920 mg SC administration are 2720 µg/mL·day (574 to 5520 µg/mL·day) and 2870 µg/mL·day (581 to 6380 µg/mL·day). The predicted median (range) of AUC_{W1-12} and AUC over the first 24 weeks following 600 mg IV administration are 2290 µg/mL·day (1050 to 4200 µg/mL·day) and 2420 µg/mL·day (1070 to 4800 µg/mL·day). Overall, the full report supported the findings of the interim report, including the dose selection for the subsequent Phase 3 study.

Table 85. Summary of Predicted AUC and C_{max} by Cycle, Model 194

Exposure	mean	sd	median	min	max	Q25	Q75
All SC subjects assumed to be OCR-naive, 920 mg SC Q24W (N=99)							
Weeks 1-12 AUC (µg/mL·day)	2810	995	2720	574	5520	2070	3380
Weeks 1-24 AUC(µg/mL·day)	3020	1120	2870	581	6380	2170	3620
Weeks 25-48 AUC (µg/mL·day)	3330	1220	3170	633	7160	2380	4010
Weeks 49-72 AUC (µg/mL·day)	3540	1290	3370	669	7650	2490	4280
Weeks 73-96 AUC (µg/mL·day)	3680	1330	3480	693	7980	2600	4460
Weeks 1-24 C_{max} (µg/mL)	112	42.6	106	16.9	257	85.1	138
Weeks 25-48 C_{max} (µg/mL)	115	43	108	18	262	86.7	139
Weeks 49-72 C_{max} (µg/mL)	116	43.2	109	18.6	264	87.8	140
Weeks 73-96 C_{max} (µg/mL)	117	43.3	110	19	266	88.4	141
All IV subjects assumed to be OCR-naive, 600 mg IV Q24W, first dose is given as two 300 mg infusions (N=35)							
Weeks 1-12 AUC (µg/mL·day)	2300	675	2290	1050	4200	1900	2570
Weeks 1-24 AUC (µg/mL·day)	2470	800	2420	1070	4800	1980	2800
Weeks 25-48 AUC(µg/mL·day)	2720	911	2660	1160	5440	2140	3080
Weeks 49-72 AUC(µg/mL·day)	2890	982	2820	1230	5850	2260	3280
Weeks 73-96 AUC(µg/mL·day)	3010	1030	2930	1270	6150	2350	3410
Weeks 1-24 C_{max} (µg/mL)	122	20.3	124	83.6	168	110	135
Weeks 25-48 C_{max} (µg/mL)	200	31.3	203	134	258	181	220
Weeks 49-72 C_{max} (µg/mL)	200	31.4	203	134	259	181	220
Weeks 73-96 C_{max} (µg/mL)	200	31.4	203	135	259	181	220

Source: 194cond2_Summary_AUC.csv (StudySimulations_Cond_Ocrelizumab_Cond2.R)

Source: Population PK Analysis Report (RDR 1124537), page 40, Table 19.
Abbreviations: AUC, area under the concentration time curve; C_{max}, maximum plasma concentration; IV, intravenous; OCR, ocrelizumab; PK, pharmacokinetic; Q24W, every 24 weeks; Q25, first quartile; Q75, third quartile; SC, subcutaneous

The review team independently verified the Applicant's PK models and agrees with the dose selection for Phase 3 study.

Applicant's Population PK Analysis for Study CN42097 (RDR No 1125240)

Refer to Section 15.1 for a detailed discussion of the study design.

The objectives of the population PK analysis were:

- To describe the concentration-time course of ocrelizumab in serum on the population and individual level, i.e., including interindividual variability.
- To evaluate the effect of ADAs on ocrelizumab IV and SC exposure.
- To compute individual measures of exposure, including AUC over the first 12 weeks, AUC over the first 24 weeks, and maximum concentration after the first dose.
- To perform model-based simulations in order to visualize and quantify the impact of route of administration on ocrelizumab exposure.

PopPK modeling was conducted via nonlinear mixed-effects modeling using NONMEM, version 7.5.1 (Icon Development Solutions). The analysis dataset contained 2050 quantifiable serum samples from 235 subjects; 1223 samples were obtained from subjects in the SC arm, and 827 samples were obtained from subjects in the IV arm.

The initial model was fitted to the data of Study CN42097. Systemic parameters, except Q, were fixed at the values shown in Table 81, while SC absorption parameters and Q were estimated.

The parameter estimates of the final model are presented in Table 86. SC bioavailability was estimated as 81.4% (95%CI: 78.3 to 84.5%). Intercompartment clearance was estimated as 0.545 L/day (95%CI: 0.485 to 0.604 L/day). There were no differences between individual systemic parameters of SC and IV arms (Table 86 and Table 87).

As no major deficiencies were found, this model was accepted as the final model of the analysis. The effect of ADAs on ocrelizumab PK was not evaluated because no ADAs were reported.

Table 86. Estimated Parameters for the Final PK Model 500 of OCR

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage (%)
Q (L/day)	θ_4	0.545	5.56	0.485 ; 0.604		
F_{SC}	θ_{15}	0.814	1.96	0.783 ; 0.845		
MTIME (day)	θ_{16}	0.0585	2.9	0.0552 ; 0.0619		
k_{a1} (1/day)	θ_{17}	0.0527	13.7	0.0385 ; 0.0669		
k_{a2} (1/day)	θ_{18}	0.418	6.63	0.363 ; 0.472		
$k_{a\text{-}age}$	θ_{19}	-0.353	44.5	-0.66 ; -0.0452		
ω^2_{Fsc}	$\Omega(5,5)$	0.0154	34.1	0.00509 ; 0.0257	CV=12.4%	36.4%
ω^2_{ka1}	$\Omega(6,6)$	0.875	11.2	0.683 ; 1.07	CV=93.5%	14.9%
ω^2_{ka2}	$\Omega(7,7)$	0.194	18.9	0.122 ; 0.266	CV=44.0%	18.9%

PE: Parameter Estimate; SE: Standard Error; RSE: Relative Standard Error, RSE=100·SE/PE; 95% CI: 95% confidence interval; CV: coefficient of variation.

Source: Population PK Analysis CN42907 (RDR 1125240), page 28, Table 7.
Abbreviations: F_{SC}, SC bioavailability; k_{a1}, initial (before MTIME) absorption constant; k_{a2}, later (after MTIME) absorption constant; MTIME, model event time; PK, pharmacokinetic; Q, apparent inter-compartmental clearance; ω^2, omega^2, inter-individual variance.

Table 87. Summary of Individual PK Parameters

Covariate	Description (Units)	Mean (Standard Deviation)		Median [Range]	
		SC (N=117)	IV (N=118)	SC (N=117)	IV (N=118)
CL_{inf}	Clearance at steady-state (L/day)	0.171 (0.0531)	0.173 (0.0519)	0.161 [0.0955-0.421]	0.172 [0.0862-0.317]
CL_T	Time-dependent part of clearance at baseline (L/day)	0.0498 (0.015)	0.0521 (0.0181)	0.0468 [0.028 - 0.114]	0.0497 [0.0267-0.115]
V_{SS}	Volume of steady-state (L)	5.61 (0.946)	5.52 (1.22)	5.54 [4.16 - 9.38]	5.24 [3.6 - 10.7]
t_β	Terminal half-life at baseline (day)	20 (3.08)	20 (3.42)	20.1 [12.2 – 26.3]	20.1 [13.7 – 35.3]
t_{eff}	Effective half-life at baseline (day)	18.3 (3.08)	17.7 (3.14)	18.7 [11.1 - 24.7]	17.7 [10.1 - 25.8]

Source file: 500_ParametersTableMean.csv, 500_Parameters TableMedian.csv (DiagnisticPlots.R)

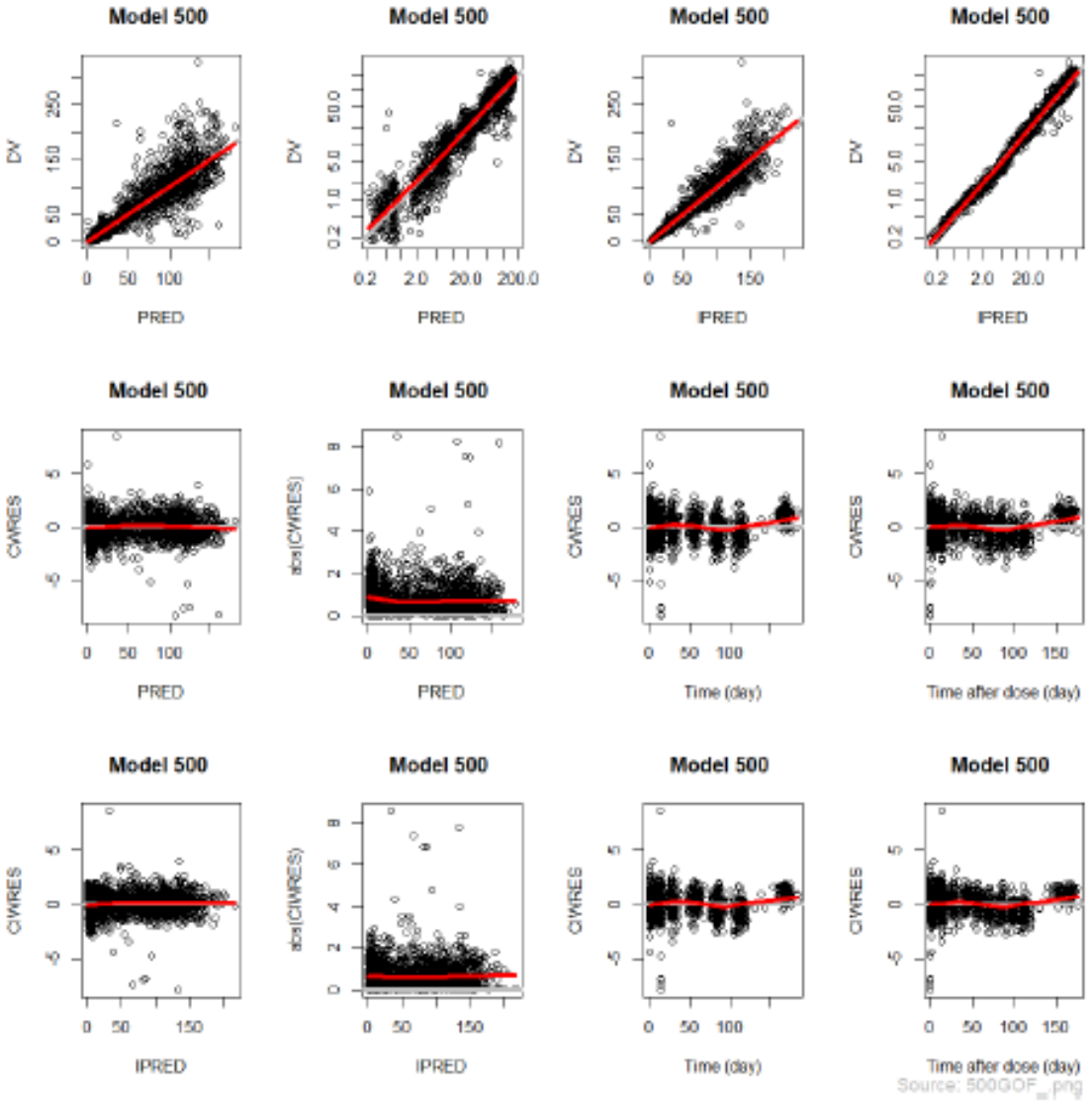
Source: Population PK Analysis CN42907 (RDR 1125240), page 29, Table 8.
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; PK, pharmacokinetic; SC, subcutaneous

Final Model Evaluation

The diagnostic plots shown in Figure 9 demonstrated a good fit of the data. The results of the predictive check presented in Figure 10 indicated a good agreement between the simulated and observed data and absence of covariate trends. Thus, the results of model evaluation indicated that the final model provided a good description of all observed data, and it could be used to predict individual ocrelizumab exposures for comparison of exposures for IV and SC administration.

Figure 9. Goodness-of-Fit, Model 500, All Data

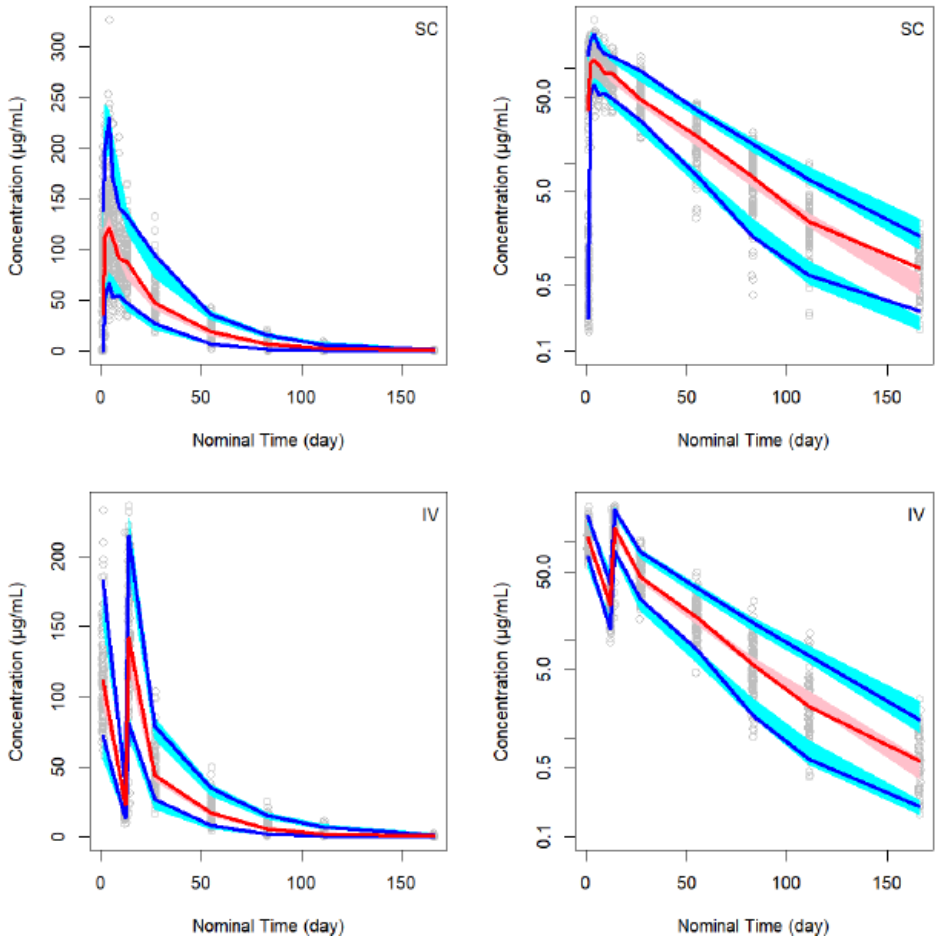
DV: Observed concentrations; PRED: population predictions of the model; IPRED: individual predictions of the model; CWRES and CIWRES: conditional weighted residuals and conditional individual weighted residuals; TIME: time after the first dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.



Source: Population PK Analysis CN42907 (RDR 1125240), page 34, Figure 3.

Figure 10. Visual Predicative Check, Model 500

The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations. The shaded regions show the 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.



Source: Population PK Analysis CN42907 (RDR 1125240), page 50, Figure 19.
Abbreviation: PK, pharmacokinetic

Table 88 shows summaries of computed exposure measures by treatment group using actual dosing history. Table 89 shows the summary of exposures for four 24-week cycles for IV subjects administered 600 mg IV every 24 weeks (with the first dose given as two 300-mg infusions two weeks apart), and SC subjects administered 920-mg SC doses every 24 weeks. The simulated profiles are shown in Figure 11.

Table 88. Summary of Predicted Exposure Measures, Model 500 (Actual Dosing History)

Exposure	Arm	N	mean	sd	median	min	max	Q25	Q75
Week 1-12 AUC (µg/mL·day)	SC	116	3500	914	3500	1180	5940	2910	4170
	IV	116	2750	796	2570	1390	4690	2120	3450
Cycle 1 AUC (µg/mL·day)	SC	116	3730	1030	3720	1200	6590	2990	4470
	IV	116	2970	921	2730	1490	5340	2240	3720
Cycle 1 C_{max} (µg/mL)	SC	116	132	31.9	133	35.6	207	113	157
	IV	116	137	29.5	135	67.3	219	115	155
Cycle 1 T_{max} (day)	SC	116	3.83	1.5	3.75	1.75	13.2	3.00	4.00
	IV	116	End of infusion						
Cycle 1 C_{trough} (µg/mL)	SC	116	0.626	0.492	0.503	0.0112	2.26	0.269	0.926
	IV	116	0.575	0.504	0.451	0.0319	2.41	0.204	0.819

Source: 500grid_Table7_with_Tmax.csv (ComputeExposure_with_Tmax.R)

Source: Population PK Analysis CN42907 (RDR 1125240), page 30, Table 9.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{trough}, lowest plasma concentration at steady-state; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous; Q25, first quartile; Q75, third quartile; T_{max}, time to maximum concentration

Table 89. Summary of Predicted Exposure Measures by Cycle, Model 500 (Nominal Dosing History)

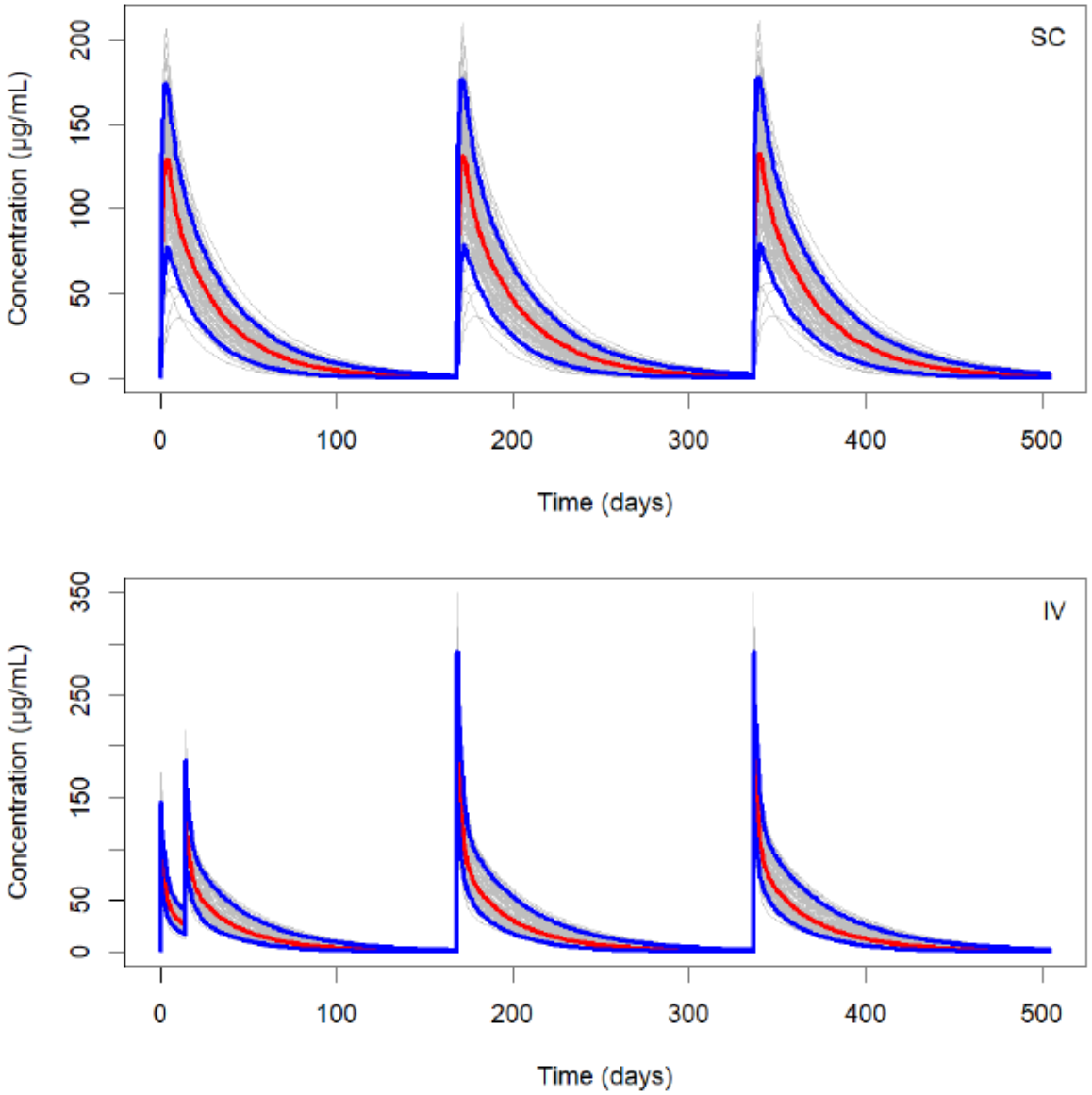
Exposure	mean	sd	median	min	max	Q25	Q75
920 mg SC Q24W							
Weeks 1-12 AUC (µg/mL·day)	3510	920	3520	1180	5940	2920	4190
Cycle 1 AUC (µg/mL·day)	3740	1040	3720	1200	6590	3000	4520
Cycle 2 AUC (µg/mL·day)	4110	1140	4070	1310	7260	3300	4940
Cycle 3 AUC (µg/mL·day)	4350	1210	4300	1380	7690	3510	5250
Cycle 4 AUC (µg/mL·day)	4510	1250	4450	1430	7970	3640	5420
Cycle 1 C_{max} (µg/mL)	133	31.9	133	35.6	207	113	157
Cycle 2 C_{max} (µg/mL)	135	32.3	136	36.4	210	115	159
Cycle 3 C_{max} (µg/mL)	136	32.5	137	36.9	212	116	161
Cycle 4 C_{max} (µg/mL)	137	32.6	138	37.2	214	117	162
Cycle 1 T_{max} (day)	3.81	1.48	3.75	1.75	13.2	3	4
Cycle 2 T_{max} (day)	3.87	1.57	3.75	1.75	13.8	3	4
Cycle 3 T_{max} (day)	3.91	1.61	3.75	1.75	14	3	4.25
Cycle 4 T_{max} (day)	3.94	1.61	3.75	1.75	14	3	4.25
Cycle 1 C_{trough} (µg/mL)	0.624	0.489	0.5	0.0112	2.26	0.272	0.925
Cycle 2 C_{trough} (µg/mL)	0.9	0.678	0.765	0.0187	3.12	0.404	1.31
Cycle 3 C_{trough} (µg/mL)	1.12	0.825	0.984	0.0254	3.79	0.506	1.62
Cycle 4 C_{trough} (µg/mL)	1.29	0.929	1.15	0.0306	4.26	0.578	1.85
600 mg IV Q24W, first dose is given as two 300 mg infusions							
Weeks 1-12 AUC (µg/mL·day)	2760	795	2580	1390	4700	2130	3430
Cycle 1 AUC (µg/mL·day)	2970	919	2740	1500	5360	2250	3740
Cycle 2 AUC (µg/mL·day)	3260	1020	2980	1630	5940	2460	4060
Cycle 3 AUC (µg/mL·day)	3450	1070	3150	1730	6300	2610	4260
Cycle 4 AUC (µg/mL·day)	3590	1110	3260	1790	6550	2710	4430
Cycle 1 C_{max} (µg/mL)	137	29.2	135	67.2	217	116	155
Cycle 2 C_{max} (µg/mL)	219	46	219	98.6	349	188	246
Cycle 3 C_{max} (µg/mL)	219	46	219	98.7	350	188	246
Cycle 4 C_{max} (µg/mL)	219	46.1	219	98.8	350	188	247
Cycle 1 C_{trough} (µg/mL)	0.569	0.5	0.451	0.0327	2.41	0.208	0.806
Cycle 2 C_{trough} (µg/mL)	0.649	0.576	0.488	0.0399	2.77	0.239	0.909
Cycle 3 C_{trough} (µg/mL)	0.813	0.704	0.611	0.0575	3.36	0.315	1.14
Cycle 4 C_{trough} (µg/mL)	0.934	0.797	0.705	0.0704	3.78	0.373	1.3

Source: 500cond1_Table9.csv (StudySimulations_Cond_Ocrelizumab_Cond1.R)

Source: Population PK Analysis CN42907 (RDR 1125240), page 31, Table 10.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{trough}, lowest plasma concentration at steady-state; PK, pharmacokinetic; SC, subcutaneous; Q24W, every 24 weeks; Q25, first quartile; Q75, third quartile; T_{max}, time to maximum concentration

Figure 11. Individual PK Predictions Following IV and SC Doses, Final Model

The bold lines show median (red), and the 5th and 95th percentiles (blue) of the simulated concentrations. The thin lines show individual predictions for all patients. The simulated values were computed using the first dose, the covariate values, and the individual PK parameters of patients of the analysis dataset.



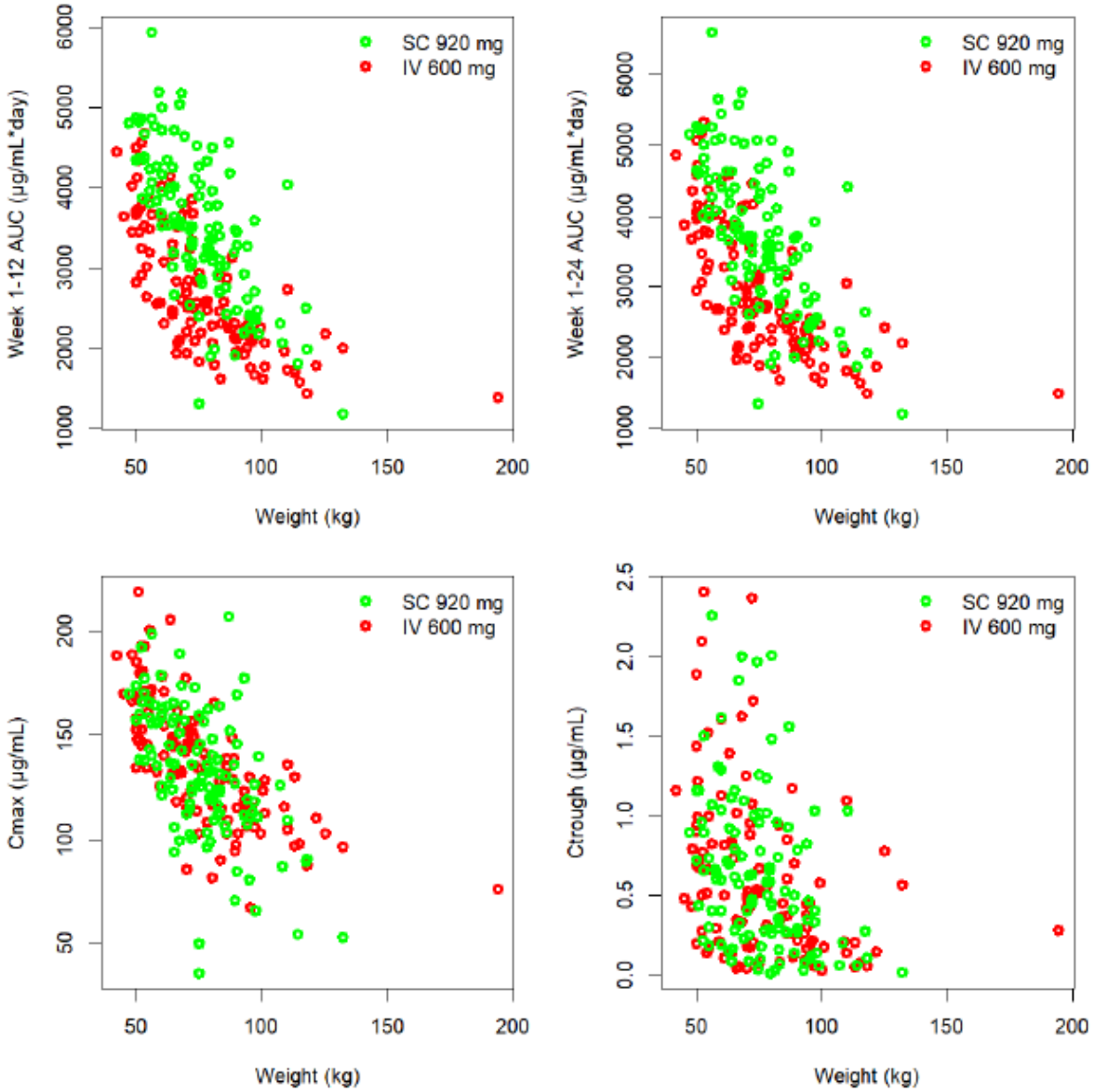
Source: Population PK Analysis CN42907 (RDR 1125240), page 57, Figure 26.
Abbreviations: IV, intravenous; PK, pharmacokinetic; SC, subcutaneous

Effect of Body Weight on the PK of Ocrelizumab

Figure 12 shows the relationship between different PK exposure metrics and body weight following SC OCR or IV OCR. The effect of body weight on exposures following IV OCR was evaluated previously in the Ocrevus BLA (DARRTS ID: 3986651), which concluded that although body weight was identified as a significant covariate in the PopPK analysis, the effect of body weight on ocrelizumab PK was relatively small. Specifically, C_{max} values were estimated

to be 19% higher for RMS subjects weighing <60 kg and 13% lower for subjects weighing >90 kg compared with the 60 to 90 kg weight group. $AUC_{\tau,ss}$ values were 26% higher for subjects weighing <60 kg and 21% lower for subjects weighing >90 kg compared with the 60 to 90 kg weight group. Therefore, no dose adjustment is recommended based on body weight.

Figure 12. Predicted PK Exposures vs. Weight by Route, Model 500



Source: Population PK Analysis CN42907 (RDR 1125240), page 57, Figure 25.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{trough}, lowest plasma concentration at steady-state; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous

The review team independently verified the Applicant's population PK models and agrees with the findings.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Study CN42097

15.1.1. Study Design

Overview and Objective

Study CN42097 is an ongoing study intended to demonstrate PK noninferiority of SC OCR compared to IV OCR. The study also assessed the safety, tolerability, PD, and immunogenicity of SC OCR, as compared to IV OCR. At the time of the BLA data cutoff (March 10, 2023), Protocol CN42097 version 2 was in effect and is therefore the protocol version discussed in this BLA review. Wherever applicable, revisions implemented in the most recent version of Protocol CN42097 (version 4, dated July 13, 2023) will be discussed.

The primary objective of the study was to demonstrate PK noninferiority of ocrelizumab 920 mg SC injection, compared to ocrelizumab at a 600-mg IV infusion, based on AUC_{W1-12}.

Secondary objectives were to examine the effects of SC OCR, as compared to IV OCR, on the following:

- Additional PK parameters
- MRI parameters
- Annualized relapse rate
- Expanded disability status scale (EDSS) scores
- Subject study drug administration satisfaction and experience scores
- Safety of SC OCR compared to IV OCR, as determined by adverse events (AEs), vital signs, and safety laboratory assessments
- Immunogenicity of SC OCR, as compared to IV OCR
- PD effects of SC OCR compared to IV OCR, as determined by the proportion of subjects achieving $CD19^+$ B-cell counts ≤5 cells/µL

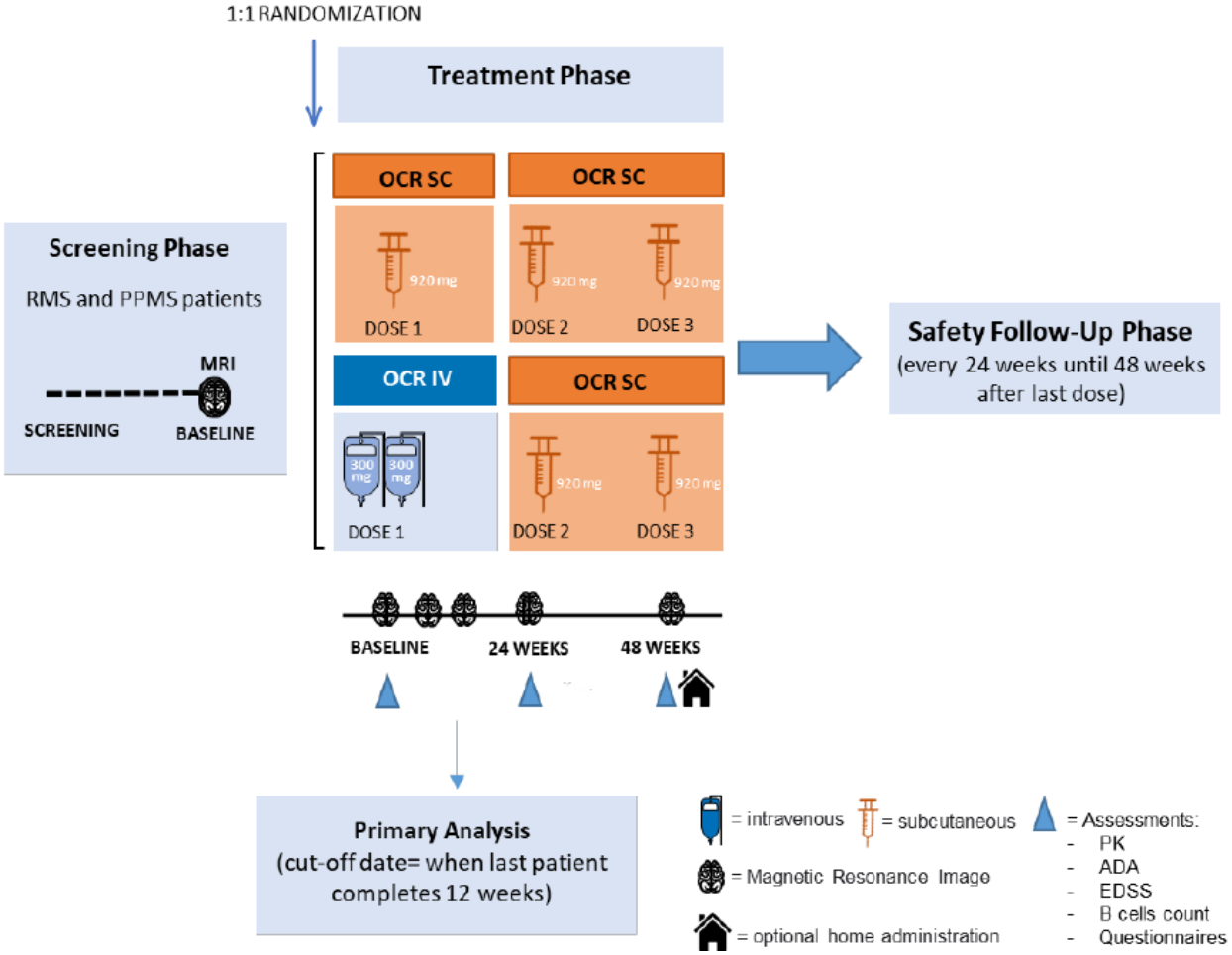
Trial Design

Study CN42097 is an ongoing 96-week, Phase 3, randomized, noninferiority, open-label, parallel-group, multicenter study designed to evaluate the PK noninferiority of SC OCR as compared to IV OCR in subjects with RMS and PPMS, as per the revised McDonald 2017 Criteria. Subjects were required to have an EDSS score of 0.0 to 6.5 at screening and a disease duration (from MS symptom onset) of <15 years for subjects with EDSS score <2.0 at screening. Subjects were randomized 1:1 to receive treatment with either SC OCR or IV OCR for 72 weeks

(last SC OCR injection at Week 48) and subsequently entered the 48-week Safety Follow-Up Period.

The study schematic for Study CN42097 (Protocol version 2) is presented in Figure 13. The study consisted of a Screening Period of up to 6 weeks, a 48-week Treatment Period (including a 24-week Controlled Period and a 24-week SC Ocrelizumab Treatment Period), and a 48-week Safety Follow-Up Period. Of note, in Protocol CN42097 version 4, the Treatment Period duration was increased to 96 weeks (last SC OCR injection at Week 96 [total treatment duration: 120 weeks]) and the Safety Follow-Up Period was reduced to 24 weeks.

Figure 13. Study Schematic, Study CN42097 (Protocol Version 2)



Source: Applicant's Clinical Study Report, Study CN42097.
Abbreviations: ADA, antidrug antibody; EDSS, expanded disability status scale; IV, intravenous; MRI, magnetic resonance imaging; OCR, ocrelizumab; PK, pharmacokinetics; PPMS, primary progressive multiple sclerosis; RMS, relapsing forms of multiple sclerosis; SC, subcutaneous

Blinding

Not applicable. Study CN42097 was an open-label study and did not include an Independent Relapse Adjudication Committee, which is acceptable since the primary endpoint was PK-based and did not involve relapse assessment.

Eligibility Criteria

Inclusion Criteria

- Diagnosis of PPMS or relapsing forms of MS (RMS) according to the revised McDonald 2017 criteria (Thompson et al. 2018)
- Signed Informed Consent Form
- Age 18 to 65 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the study protocol and schedule of protocol assessments, in the investigator's judgment
- EDSS score 0 to 6.5, inclusive, at screening
- Neurological stability for ≥30 days prior to both screening and baseline
- Disease duration from onset of MS symptoms of less than 15 years for patients with EDSS score <2.0 at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 6 or 12 months (as applicable by the ocrelizumab IV [Ocrevus] local label) after the final dose of ocrelizumab
- For female patients without reproductive potential: women may be enrolled if postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle-stimulating hormone level [>40 IU/mL]) unless the patient is receiving a hormonal therapy for menopause or surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

Exclusion Criteria

- Any known or suspected active infection at screening or baseline (except nailbed infections), or any major episode of infection requiring hospitalization or treatment with IV antimicrobials within 8 weeks prior to and during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening.
- History of confirmed or suspected progressive multifocal leukoencephalopathy.
- History of cancer, including hematologic malignancy and solid tumors, within 10 years of screening. Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy >1 year prior to screening is not exclusionary.

- Immunocompromised state, defined as one or more of the following:
  - CD4 count <250/µL
  - Absolute neutrophil count (ANC) $<1.5\times10^3$/µL
  - Serum IgG <4.6 g/L
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization. Influenza vaccination is permitted if the inactivated vaccine formulation is administered.
- Inability to complete an MRI (contraindications for MRI, e.g., pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to gadolinium administration.
- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines), including closed-angle glaucoma for antihistamines.
- Known presence of other neurologic disorders that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study, including, but not limited to, the following:
  - History of hemorrhagic or ischemic cerebral or spinal stroke.
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma).
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency).
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, HTLV-1, herpes zoster myelopathy).
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke syndrome).
  - Neuromyelitis optica.
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, antiphospholipid antibody syndrome, Sjögren syndrome, Behçet disease).
  - History or known presence of sarcoidosis.
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression).
- Any concomitant disease that may require chronic treatment with systemic corticosteroids (e.g., mineralocorticoids and glucocorticoids) or immunosuppressants during the course of the study.
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine or gastrointestinal, or any other significant disease that may preclude patient from participating in the study.
- History of or currently active primary or secondary (non-drug-related) immunodeficiency.

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 6 or 12 months (as applicable by the ocrelizumab [Ocrevus] local label) after last administration of the study drug. Females of childbearing potential must have a negative serum and urine pregnancy test result prior to initiation of study drug (negative serum β-CG measured at screening and negative urine β-CG at baseline).
- Lack of peripheral venous access.
- History of alcohol or other drug abuse within 12 months prior to screening.
- Treatment with any investigational agent within 24 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency).
- Patients who have previously received anti-CD20s (including ocrelizumab) if the last treatment was less than 2 years before screening, and/or if B-cell count is below lower limit of normal, and/or the discontinuation of the treatment was due to safety reasons or lack of efficacy.
- Previous treatment with cladribine, atacicept, and alemtuzumab.
- Previous treatment with fingolimod, siponimod, ponesimod, or ozanimod within 6 weeks of baseline.
- Previous treatment with interferons beta (1a or 1b), or glatiramer acetate within 2 weeks of baseline.
- Previous treatment with natalizumab within 4.5 months of baseline.
- Treatment with mitoxantrone within 2 years prior to baseline visit or evidence of cardiotoxicity following mitoxantrone use or a cumulative lifetime dose of more than 60 mg/m^2.
- Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label. If the washout requirements are not described in the applicable local label (washout to be completed prior to baseline), then the washout period must be 5 times the half-life of the medication. The PD effects of the previous medication must also be considered when determining the required time for washout.
- Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation.
- Any previous history of transplantation or antirejection therapy.
- Treatment with IVIg or plasmapheresis within 12 weeks prior to randomization.

- Systemic corticosteroid therapy within 4 weeks prior to screening. The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.
- Positive screening tests for active, latent, or inadequately treated hepatitis B (as evidenced by either of the following):
  - Positive hepatitis B surface antigen.
  - Positive hepatitis B core antibody (total HBcAb) and detectable hepatitis B virus DNA.
- Sensitivity or intolerance to any ingredient (including excipients) of ocrelizumab.
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus) local label, if more stringent than the above.

Study Treatment

Dose Regimen

Subjects were randomized to receive either SC OCR 920 mg or IV OCR 600 mg for a total treatment duration of 72 weeks (last dose administered at Week 48). Subjects in the SC OCR group received ocrelizumab 920 mg SC every 24 weeks for a total of 3 doses (Weeks 1, 24, and 48). For subjects randomized to the IV OCR group, Dose 1 of ocrelizumab was administered as two separate 300 mg IV infusions (600 mg total) given 2 weeks apart (Weeks 1 and 2). Subsequently, subjects randomized to IV OCR transitioned to SC OCR, which was administered at Weeks 24 (Dose 2) and 48 (Dose 3). After receiving each injection or infusion, subjects remained on-site for at least one hour for observation. At certain sites, subjects had the option of having study treatment Dose 3 (SC OCR) administered at home by study staff. After SC OCR home administration, subjects were monitored by a healthcare provider for at least one hour postinjection. See details above regarding revisions to treatment duration and safety follow-up implemented in Protocol CN42097 version 4.

Management of Injection and Infusion-Related Reactions

Due to the known risk of infusion-related reactions with ocrelizumab, subjects received premedication prior to each study treatment administration (see Figure 14), as follows:

- Premedication for SC OCR: Subjects received an orally administered corticosteroid (dexamethasone 20 mg) and an orally administered antihistamine (desloratadine 5 mg PO) 1 to 2 hours prior to each SC OCR administration. Subjects could also receive an oral analgesic, such as acetaminophen. Protocol CN42097 version 4 was revised to indicate that subjects should receive premedication 30 to 60 minutes prior to each SC OCR administration.
- Premedication for IV OCR: Subjects received an IV corticosteroid (methylprednisolone 100 mg) infusion to be completed approximately 30 minutes prior to study treatment administration. Additionally, subjects received and IV antihistamine (diphenhydramine 50 mg) approximately 30 to 60 minutes prior to study treatment administration, which could also be substituted by an equivalent oral alternative. Subjects could also receive an oral analgesic, such as acetaminophen. Due to the potential for infusion-related hypotension, the

protocol instructed investigators to consider withholding antihypertensive medications for 12 hours prior to study infusion.

Table 90. Premedication Regimen for SC and IV OCR, Study CN42097

Prior to IV Administration of Ocrelizumab	Prior to SC Administration of Ocrelizumab
Mandatory methylprednisolone, given by slow IV infusion	Mandatory dexamethasone, given orally
Mandatory diphenhydramine, given orally or IV infusion	Mandatory desloratadine, given orally
Oral analgesic as needed and as tolerated (if using acetaminophen not to exceed 4g/daily per label).	Recommended oral analgesic/as needed/and as tolerated (if using acetaminophen, not to exceed 4g/day, per label)

Source: Protocol CN42097, version 2.
Abbreviations: SC, subcutaneous; IV, intravenous; OCR, ocrelizumab

Retreatment Criteria

Subjects had to fulfill retreatment criteria prior to receiving additional treatment with ocrelizumab, as follows:

- No history of severe hypersensitivity reaction to ocrelizumab.
- No significant or uncontrolled medical condition or clinically significant laboratory abnormality.
- No current active infection.
- ANC $\geq 1.5 \times 10^3/\mu L$
- $CD4^+$ lymphocyte count $\geq 250/\mu L$.
- IgG ≥ 3.3 g/L.
- Negative pregnancy test.
- For SC OCR home administration only: No history of local or systemic injection-related reaction Grade ≥ 3 with previous SC OCR injections.

Relapse Assessment and Treatment

Subjects who experienced new or worsening neurologic symptoms that could be consistent with clinical relapse were instructed to contact the treating investigator. Subsequently, within 7 days of reporting of the suspected relapse, subjects were scheduled for a study visit and assessed by the treating investigator. Relapse assessments included EDSS and Functional Systems Scores.

At each study visit (including unscheduled visits), subjects were evaluated for potential relapse by the treating investigator. Subjects with suspected relapses were not evaluated separately by an examining investigator. Per the Applicant, independent EDSS evaluation by treating and examining investigators was not implemented because annualized relapse rate was an exploratory endpoint of Study CN42097. The Applicant also indicated that subjects with a suspected relapse were evaluated by the treating investigator, who then determined whether the

clinical relapse was consistent with a protocol-defined relapse. Additionally, the Applicant stated that MRI evaluation was not required for relapse confirmation. If a subject received treatment with systemic corticosteroids for treatment of MS relapse, an attempt was made to obtain the next scheduled MRI prior to the first systemic corticosteroid dose administration. The Applicant did not provide details regarding timeline and procedures for study staff notification for subjects who developed new symptoms potentially consistent with MS relapse.

Relapses were considered protocol-defined by the treating investigator if the subject experienced new or worsening neurological symptoms attributable to MS in the absence of fever, infection, or other condition that could result in MS symptom worsening, that persisted for at least 24 hours, and that were preceded by ≥30 days of neurologic symptom stability. The new or worsening neurological symptoms had to be accompanied by an objective change in neurological exam (0.5-point increase in EDSS, 2-point increase in any functional system, or 1-point increase in 2 or more functional systems [except bladder/bowel and cerebral/mental functional system]) from the previous assessment.

After a relapse was identified by the treating investigator, relapse treatment was initiated with IV methylprednisolone 1 g daily for up to 5 days (or oral equivalent dose of prednisolone or methylprednisolone), with or without oral corticosteroid taper for up to 10 days. All clinical relapses (i.e., suspected and protocol-defined), were recorded in the case report form.

Study Assessments

The schedule of assessments is summarized in Table 91.

Table 91. Schedule of Assessments, Study CN42097

Assessment	Screening	Baseline	Controlled Period							SC OCR Period		Delayed Dosing Visit	Unscheduled Visit	EOT Visit	Follow-Up Period
	Week														
	-6 to 0	1	2	4	8	12	16	22	24	46	48				
SC OCR injection		X[1]							X		X				
IV OCR infusion[2]		X[3]	X[3]												
EDSS	X	X				X			X		X		X	X	
Neurological examination	X	X				X			X		X		X	X	X
MRI	X	X			X	X			X		X		X	X	
$CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ flow cytometry	X	X	X	X		X	X		X		X	X	X	X	X
$CD4^+$ flow cytometry								X		X					
IgG, IgA, IgM	X	X						X		X			X	X	X
ADA (OCR)		X							X		X	X	X	X	X
ADA (rHuPH20)									X		X	X	X	X	X
CBC, CMP, UA	X	X				X		X		X			X	X	X
Adverse events		X	X	X	X	X	X		X		X	X	X	X	X
PK sample (serum)		X	X	X	X	X	X		X		X	X	X	X	X
Biomarkers (serum)		X				X			X		X			X	X

Source: Study CN42097 protocol, version xxx.
X indicates the assessment is carried out at the specified week.
[1] Only subjects in the SC ocrelizumab group
[2] Only subjects in the IV ocrelizumab group
[3] Half-dose (300 mg IV infusion)
Abbreviations: ADA, antidrug antibody; CBC, complete blood count; CMP, complete metabolic panel; EDSS, Expanded Disability Status Scale; EOT, end-of-treatment; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; IV, intravenous; MRI, magnetic resonance imaging; OCR, ocrelizumab; PK, pharmacokinetic; rHuPH20, recombinant human hyaluronidase; SC, subcutaneous; UA, urinalysis

PK Sample Collection

- IV arm, Controlled Period (time until dose at Week 24): On IV infusion days (Days 1 and 14), two serum samples (one prior to infusion and one 30 minutes after completion of infusion) were collected. In addition, PK samples were collected at Days 28, 56, 84, 112 and 168.
- SC arm, Controlled Period: On the first SC injection day (Day 1), two serum samples (one prior to injection and one 1 hour after completion of injection) were collected. In addition, PK samples were collected at Days 2, 3, 5, 7, 10, 14, 28, 56, 84, 112 and 168.
- IV and SC arms, SC Treatment Period: On SC injection days (Days 168 and 336), one serum sample (prior to injection) was collected. In addition, PK samples were collected at delayed dosing visits, unscheduled visits, end-of-treatment (discontinuation of the treatment) visit, and safety follow-up visits.

Brain MRI

Brain MRIs were obtained with and without gadolinium contrast in all subjects at Screening, Baseline, Weeks 8, 12, 24, and 48, at Unscheduled Visits, and at the End-of-Treatment Visit. MRIs were evaluated locally for safety reasons, and were formally read by a centralized, blinded reading center for secondary efficacy and exploratory radiological endpoints. MRI reports were provided to the treating investigator, who could also access MRI scans.

EDSS Scores

Annualized protocol-defined relapse rate by Weeks 24 and 48 in subjects with RMS and change from baseline in EDSS by Week 48 were exploratory clinical endpoints of Study CN42097. These exploratory clinical endpoints were evaluated using EDSS assessments performed by the examining investigator at Screening, Weeks 1, 12, 24, and 48, at Unscheduled Visits, at the End-of-Treatment Visit, and during the Safety Follow-Up Period.

Study Endpoints

Primary PK Endpoint

The primary endpoint for Study CN42097 was the serum ocrelizumab AUC_{W1-12} after administration of SC OCR, as compared to IV OCR.

Secondary Endpoints

Secondary PK Endpoint

- SC Ocrelizumab C_{max}

Secondary MRI Endpoints

- Total number of T1 gadolinium-enhancing brain MRI lesions at Weeks 8 and 24
- Total number of new or enlarging T2 brain MRI lesions at Weeks 12 and 24, compared to the previous scan

Safety Endpoints

- Incidence and Severity of AEs
- Change from baseline in targeted vital signs
- Change from baseline in targeted safety laboratory evaluations

Immunogenicity Endpoints

- Incidence of treatment-emergent ADAs to SC or IV OCR, as compared to baseline
- Relationship between ADA status and PK, PD, and safety
- Incidence of treatment-emergent ADAs to rHuPH20 after SC OCR administration compared to baseline and relationships between ADAs to rHuPH20 and safety

Pharmacodynamic Endpoints

- Proportion of subjects with $CD19^+$ B-cell levels $\leq$5 cells/µL at Weeks 12 and 24.

Statistical Analysis Plan

Analysis Populations

The Full Analysis population included all randomized subjects.

The PK-evaluable population was defined as all subjects who received a full dose of assigned study treatment and had a measurable serum concentration of ocrelizumab. The PK-evaluable population was utilized for PK-related analyses, including analyses of the primary endpoint.

The Safety-Evaluable population included all randomized subjects who received at least one dose (partial or complete) of study medication. The Safety-Evaluable-SC population included all randomized subjects who received at least one injection (partial or complete) of SC OCR. All safety analyses were conducted in the Safety-Evaluable populations.

The Efficacy-Evaluable-MRI population included all randomized subjects who received at least one dose (partial or complete) of study medication and had a brain MRI during the Controlled Treatment Period. Analyses of all radiological endpoints were conducted in the Efficacy-Evaluable-MRI population.

The Immunogenicity-Evaluable population included all randomized subjects with at least one postbaseline ADA assessment. The Immunogenicity-Evaluable-SC population included all randomized subjects with at least one postbaseline ADA assessment who received at least one injection (partial or complete) of SC OCR. All immunogenicity analyses were conducted in the Immunogenicity-Evaluable populations.

The Pharmacodynamics-Evaluable population included all randomized subjects who received at least one dose (partial or complete) of study medication. All PD-endpoint-related analyses were conducted in the Pharmacodynamics-Evaluable population.

The Other Endpoints-Evaluable population included all RMS, PPMS, or overall study population subjects (as applicable, based on each specific endpoint) who received at least one dose (partial or complete) of study medication. All analyses of exploratory radiological, clinical, and subject-reported endpoints were conducted in the Other Endpoints-Evaluable population.

Primary Endpoint

Refer to Section 6.2.1.3 (Statistical Analysis Plan, Study CN42097) for statistical considerations regarding the primary endpoint (AUC_{W1-12}).

Secondary Radiological Endpoints

The secondary radiological endpoints listed above were analyzed separately based on MS phenotype (RMS and PPMS). Again, the Efficacy-Evaluable-MRI population was utilized for each analysis.

The total number of T1 gadolinium-enhancing brain MRI lesions was analyzed at Weeks 8 and 24. The total number of new or enlarging T2 brain MRI lesions was analyzed at Week 12 (compared to Week 8) and Week 24 (compared to Week 12). These count data were analyzed using negative binomial regression, accounting for treatment assignment group. Covariates for analyses of total number of T1 gadolinium-enhancing brain MRI lesions included presence or absence of T1 gadolinium-enhancing lesions at baseline and geographical region. Covariates for analyses of total number of new or enlarging T2 brain MRI lesions included baseline T2 lesion count and geographical region.

Protocol Amendments

There were three protocol amendments to the original Protocol CN42097 from January 21, 2021, which are summarized in Table 92.

Table 92. Protocol Amendments, Study CN42097

Protocol Version	Date	Changes	Subjects Randomized
1.0	1/21/2021	Not applicable	8 (3.4%)
2.0* (Version in effect as of the COD)	2/24/2022	• Provided the selected SC OCR dose to be studied in Study CN42097 (920 mg), based on Phase 1b data from Study CN41144 • Updated safety findings based on results from Study CN41144 • Updated washout periods for previously used MS treatments	228 (96.6%); enrollment completed 12/2022
3.0	3/13/2023	• Revised timing of premedication administration to be given shortly before SC OCR injection • Removed postinjection monitoring requirement • Extended Treatment Period from 48 to 96 weeks • Allowed home administration of SC OCR after the 3rd dose • Shortened Safety Follow-Up Period from 48 to 24 weeks	0
4.0	7/10/2023	• Revised timing of premedication administration to be given 30 to 60 minutes before SC OCR injection • Reintroduced postinjection monitoring requirement	0

Source: Applicant's Response to Information Request, received 2/6/2024.
* Protocol version discussed in this review
Abbreviations: COD, cutoff date; MS, multiple sclerosis; OCR, ocrelizumab; SC, subcutaneous

Overall Assessment of Phase 3 Study Design

Overall, Study CN42097 was appropriately designed to meet its stated objectives. As the primary endpoint of Study CN42097 was PK-based, an open-label design was acceptable. The Applicant and the Agency reached agreement on the primary endpoint and on the size of the safety database prior to submission of the BLA, as indicated in the Type C Written Responses dated September 11, 2020 (see Section 12).

The eligibility criteria were appropriate to select a representative patient population and to mitigate the potential risks to subjects in the studies. MS diagnosis in clinical practice is based on application of the most current revised McDonald criteria, which were also used in Study CN42097. Though the inclusion criteria did not require documented evidence of recent clinical relapses or MRI lesions for subjects with RMS, and did not specify additional considerations for subjects with PPMS and history of clinical relapses, the PK-based primary endpoint was not likely to be affected by MS phenotype or disease activity.

The protocol required reporting of injection site reactions and drug-induced liver injury (DILI) (as defined by Hy's Law) as adverse events of special interest, which was appropriate. The protocol also included appropriate prospective monitoring for potential safety signals of interest in this population, including infusion and injection-related reactions, serious or opportunistic infections (including progressive multifocal leukoencephalopathy), and hypogammaglobulinemia.

15.2. Study CN41144

15.2.1. Study Design

Overview and Objective

Study CN41144 was a Phase 1b, multicenter, open-label, dose-ranging study that evaluated the PK, safety, tolerability, and immunogenicity of SC OCR, compared to ocrelizumab 600 mg IV infusion, in subjects with RMS or PPMS.

The primary objective of the study was to determine the bioavailability of SC OCR in order to select an appropriate dose to be evaluated in the Phase 3 Study CN42097 (see Section 15.1), based on the AUC of SC OCR, compared to IV OCR. The secondary objectives were to assess the safety, tolerability, and immunogenicity 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 and electrocardiogram parameters, incidence and severity of clinical laboratory abnormalities, incidence of injection site pain and injection site reactions, and incidence of treatment-emergent ADAs.

Trial Design

Subjects previously treated with ocrelizumab and ocrelizumab-naive subjects were enrolled in Groups A (Figure 14) and B (Figure 15), respectively, to receive SC OCR 40 mg, 200 mg, 600 mg, or 1200 mg injection. The Dose-Escalation Period was initially nonrandomized. Subjects who received a SC OCR dose ≤600 mg subsequently received a "compensatory" IV OCR dose (600 mg) 3 months following the initial SC OCR injection. After a candidate dose

was selected, additional subjects in Group A were randomized 1:1 to receive the selected SC OCR dose or ocrelizumab 600 mg IV infusion. Subsequently, during the Dose-Continuation Period, all subjects were transitioned to the selected SC OCR dose for a total treatment duration of up to 3 years.

Eligibility Criteria

Inclusion Criteria

Key inclusion criteria were age 18 to 65 years, diagnosis of PPMS or RMS according to the 2017 Revised McDonald Criteria, EDSS score 0 to 6.5, and neurologic stability for ≥30 days. Additionally, subjects previously treated with ocrelizumab (Group A) needed to have received treatment with ocrelizumab for at least one year prior to screening.

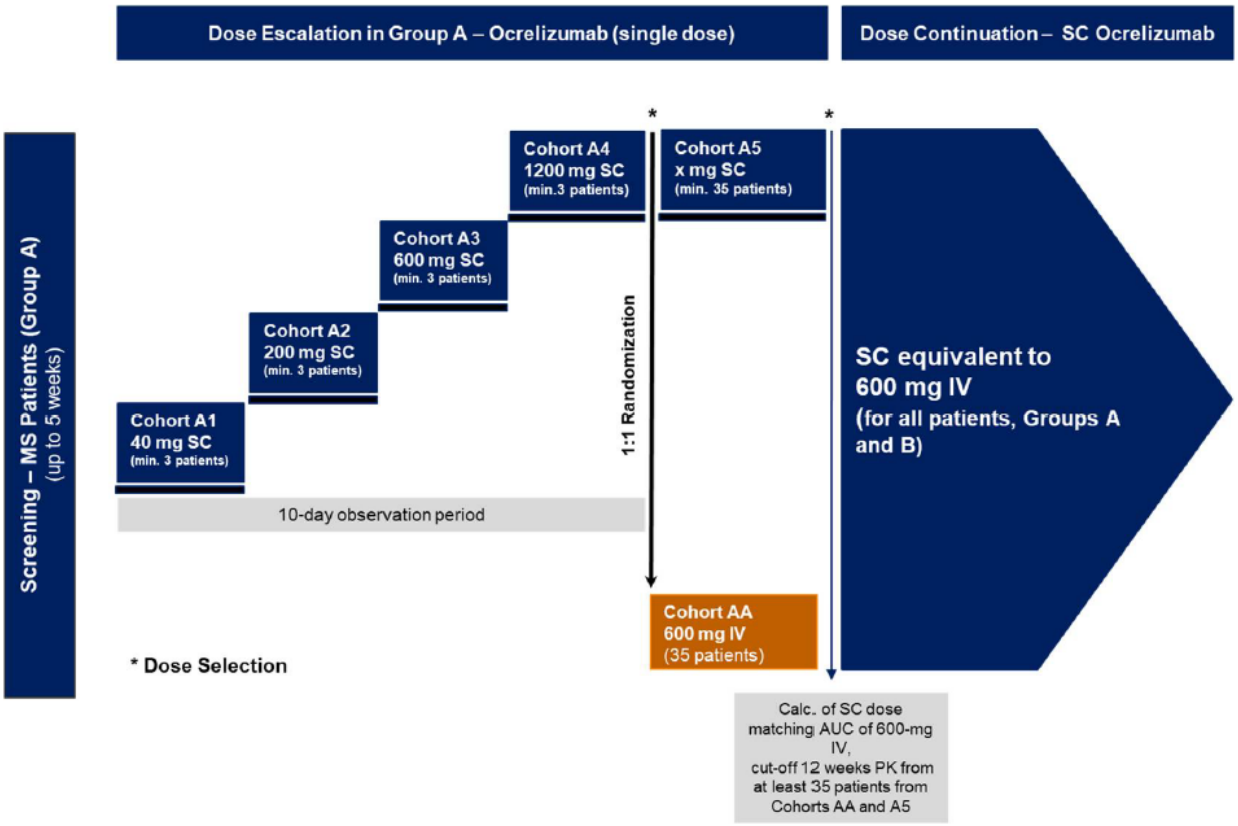
Exclusion Criteria

Key exclusion criteria were MS disease duration ≥15 years for subjects with EDSS score <2.0 and history of severe hypersensitivity reactions to humanized or murine monoclonal antibodies. Subjects who had previously received treatment with any B-cell-depleting therapies were not eligible for Group B (ocrelizumab-naive).

Pharmacokinetic Sampling

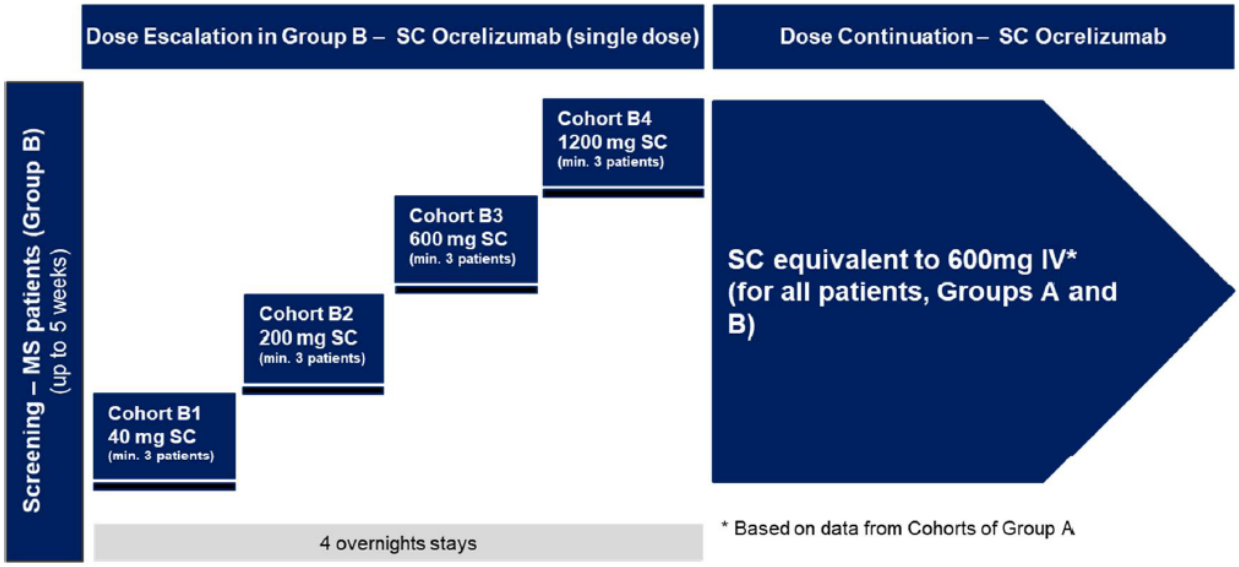
In the SC cohorts, samples were drawn at baseline (before administration of premedication prior to ocrelizumab administration), 0.5 hours, 6 hours, and 12 hours postdose, and on Days 2, 3, 4, 7, 10, 14, 28, 56, 84, 140, and 168 (before administration of premedication prior to ocrelizumab administration). In the IV cohort (cohort AA), samples were drawn at baseline (before administration of premedication prior to ocrelizumab administration), 0.5 hours after end of ocrelizumab infusion, and on Days 14, 28, 56, 84, 140, and 168 (before administration of premedication prior to ocrelizumab administration). For all cohorts, a sample was also drawn at Early Termination.

Figure 14. Study Schematic – Group A (OCR-Pretreated Subjects), Study CN41144



Source: Applicant's protocol, version 5, Study CN41144.
Abbreviations: AUC, area under the concentration-time curve; IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab; PK, pharmacokinetics; SC, subcutaneous

Figure 15. Applicant's Study Schematic (OCR-Naive Subjects), Study CN41144



Source: Applicant's protocol, version 5, Study CN41144.
Abbreviations: IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab; SC, subcutaneous

Overall Assessment of Phase 1b Study Design

Study CN41144 was appropriately designed to meet its stated dose-finding objective. Similar to the Phase 3 Study CN42097, the inclusion criteria did not require documented evidence of recent clinical relapses or MRI lesions for subjects with RMS and did not specify additional considerations for subjects with PPMS and history of clinical relapses. However, this finding is not expected to impact the interpretability of the PK-based results.

The study was not designed to allow the identification of dose-dependent or route-of-administration-dependent safety signals due to the following reasons. First, subjects in Group A (previously treated with ocrelizumab) who received an initial ocrelizumab SC injection of <600 mg subsequently received a "compensatory dose" of ocrelizumab 600 mg IV infusion. Therefore, over the course of the study, those subjects were exposed to both SC OCR and IV OCR. Second, the initially selected SC OCR candidate dose was 1200 mg. However, upon further review by the Safety Monitoring Committee, it was determined that ocrelizumab 920 mg SC injection resulted in a PK exposure that was more comparable to the approved ocrelizumab 600 mg IV infusion. Consequently, over the course of the study, a number of subjects were exposed to both SC OCR 920 mg and 1200 mg injections. Therefore, Study CN41144 can only provide limited data to inform the safety of SC OCR in subjects with RMS and PPMS.

16. Efficacy

Refer to Section 6 (Efficacy – Evaluation of Benefit). As the primary endpoint for Study CN42097 was PK-based, the discussion of the clinical and MRI-based efficacy data is limited to that described in Section 6. Note that "efficacy" in the context of this review refers to demonstration of comparable/noninferior PK of SC OCR to that of IV OCR, which is anticipated to result in the same efficacy as the approved IV OCR, for which safety and effectiveness in RMS and PPMS are established.

17. Clinical Safety

Laboratory Assessments – Additional Information

Laboratory data from the ADLB dataset were analyzed for Study CN42097. This analysis will focus on laboratory parameters of interest that were identified based on prior knowledge of the safety profile of ocrelizumab and other anti-CD20 therapies, as well as the AEs from the SC OCR development program.

Laboratory values were evaluated at each scheduled timepoint during the Controlled Period (designated by Applicant's ANL02FL = Y in ADLB dataset), and descriptive analyses (including analyses of change from baseline) are presented for Baseline, Week 12, and Week 22 for Study CN42097. Laboratory data collected via local laboratories or outside of scheduled study visits are discussed in the context of AEs.

Study CN42097

Hematology

Leukocytes

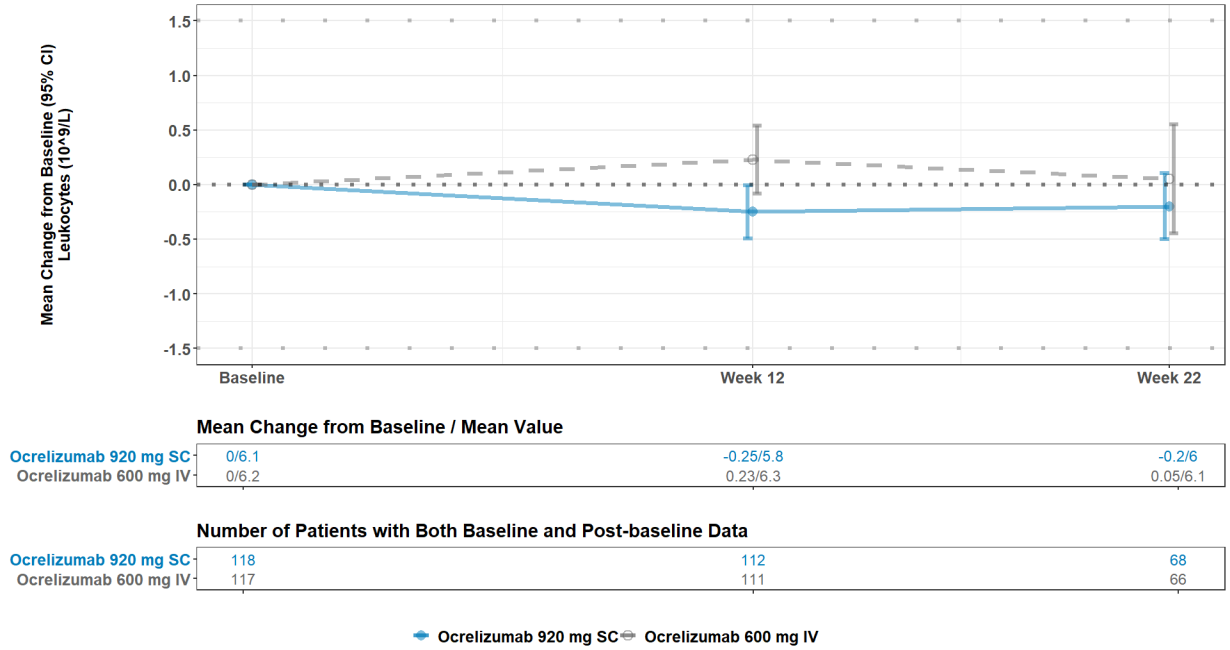
Overall leukocyte count (white blood cell count [WBC], # cells $\times 10^9$/L) were evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 93 and mean WBC change over time in Figure 16.

Table 93. White Blood Cell Count ($\times 10^9$/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR N=118	IV OCR N=118
Baseline	n	118	117
	Mean (SD)	6.1 (1.6)	6.2 (1.8)
	Median	5.9	6.0
	Min, max	3.2, 10.4	2.4, 13.7
Week 12	n	112	110
	Mean (SD)	5.8 (1.7)	6.3 (1.8)
	Median	5.5	6.3
	Min, max	3.0, 10.3	2.0, 12.5
	Mean (SD) change from baseline	-0.2 (1.3)	0.2 (1.7)
	Median change from baseline	-0.1	0.5
	Min, max change from baseline	-4.9, 3.6	-9.0, 4.1
Week 22	n	67	66
	Mean (SD)	5.9 (1.7)	6.1 (2.0)
	Median	5.8	5.7
	Min, max	2.7, 10.7	2.7, 12.2
	Mean (SD) change from baseline	-0.2 (1.3)	0.0, 2.1
	Median change from baseline	-0.2	-0.3
	Min, max change from baseline	-3.8, 3.1	-8.2, 5.9

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = WBCSI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 16. Mean White Blood Cell Count (×10⁹/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = WBCSI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for leukocytes. There was one subject (0.8%) in the SC OCR group and three subjects (2.5%) in the IV OCR group with leukocyte counts <3.0×10^9/L at any timepoint after Baseline. There were no subjects in either treatment group with leukocyte counts ≥13.0×10^9/L at any timepoint after Baseline. One subject in the IV OCR group experienced leukopenia <3.0×10^9/L that was temporally associated with the treatment-emergent adverse events (TEAEs) neutropenia and upper respiratory tract infection. One subject in the IV OCR group experienced leukopenia <3.0×10^9/L associated with TEAEs of neutropenia on two separate occasions (Baseline and Week 12). However, this subject's WBC count increased by Week 22.

The number of subjects with leukopenia <3.0×10^9/L at any point after baseline appeared to be similar between the groups, and the number of subjects with leukopenia <3.0×10^9/L or leukocytosis ≥13.0×10^9/L in either treatment group appeared to be low. Overall, these results do not raise concern for risk of leukopenia or leukocytosis specifically associated with SC OCR.

Neutrophils

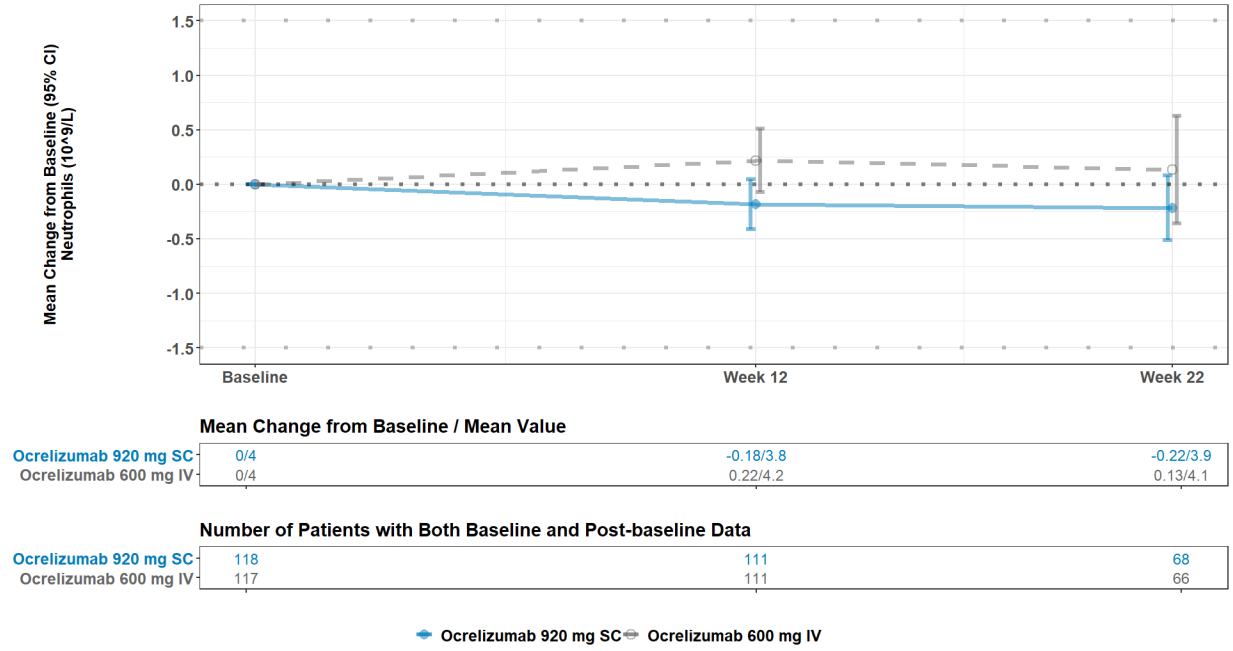
ANC (# cells×10^9/L) was evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 94 and mean ANC change over time in Figure 17.

Table 94. Absolute Neutrophil Count (×10⁹/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR N=118	IV OCR N=118
Baseline	n	118	117
	Mean (SD)	4.0 (1.5)	4.0 (1.6)
	Median	3.9	3.7
	Min, max	1.7, 9.4	1.4, 12.9
Week 12	n	112	110
	Mean (SD)	3.8 (1.5)	4.2 (1.4)
	Median	3.5	4.2
	Min, max	1.3, 7.7	0.8, 9.8
	Mean (SD) change from baseline	-0.2	0.2 (1.6)
	Median change from baseline	0.0	0.3
	Min, max change from baseline	-3.8, 3.0	-10.1, 4.0
Week 22	n	67	66
	Mean (SD)	3.9 (1.5)	4.1 (1.7)
	Median	3.8	3.6
	Min, max	1.1, 7.5	0.6, 9.3
	Mean (SD) change from baseline	-0.2 (1.3)	0.1 (2.0)
	Median change from baseline	-0.2	0.0
	Min, max change from baseline	-3.9, 3.5	-9.8, 6.6

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = NEUTRSI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 17. Mean Absolute Neutrophil Count (×10⁹/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = NEUTRSI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for ANC. There were no subjects in the SC OCR group and two subjects (1.7%) in the IV OCR group with ANC $<1.0\times10^9$/L at any point after Baseline. There were no subjects in either treatment group with ANC $<0.5\times10^9$/L at any point after Baseline. One subject in the IV OCR group experienced neutropenia $<1.0\times10^9$/L that was temporally associated with the TEAEs upper respiratory tract infection and neutropenia. One subject (b) (6)) in the IV OCR group experienced neutropenia with ANC $<1.0\times10^9$/L at Week 12 that was temporally associated with the TEAE neutropenia. Of note, Subject (b) (6) also had decreased neutrophils at 1.4×10^9/L at Baseline.

Subjects in the SC OCR group appeared to have a slightly lower mean ANC and a slightly greater decrease from baseline in mean ANC at Weeks 12 and 22, as compared to the IV OCR group; however, these differences between the SC OCR and IV OCR groups were not thought to be clinically significant. Neutropenia is discussed in Section 6.1 (Adverse Reactions - Clinical Trials Experience) of current approved labeling for Ocrevus (IV OCR), and is therefore not unexpected with SC OCR and is likely related to the study drug. Of note, the Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus. Additionally, the exclusion criteria for Study CN42097 indicated that subjects with "immunocompromised state," as defined by CD4 count <250/µL, ANC $<1.5\times10^3$/µL, or serum IgG <4.6 g/L would be excluded. Therefore, the enrollment of Subject (b) (6) represents a protocol violation.

Lymphocytes

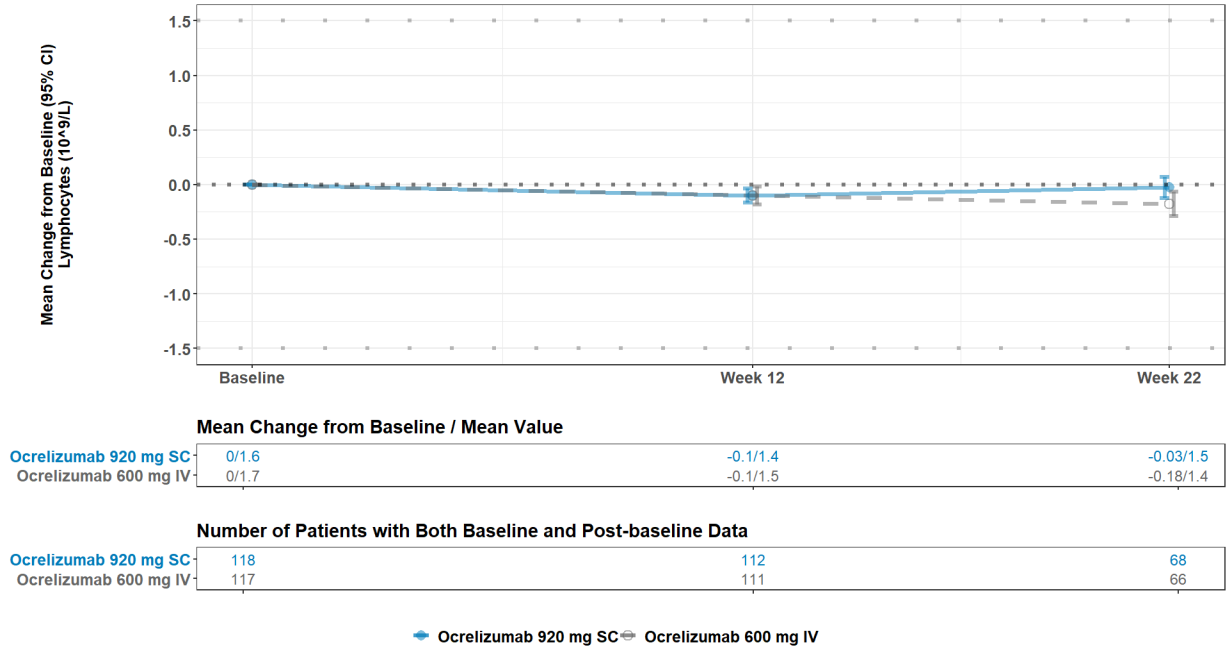
ANC (# cells $\times10^9$/L) was evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 95 and mean WBC change over time in Figure 18.

Table 95. Absolute Lymphocyte Count ($\times10^9$/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR N=118	IV OCR N=118
Baseline	n	118	117
	Mean (SD)	1.6 (0.5)	1.7 (0.6)
	Median	1.5	1.6
	Min, max	0.5, 2.9	0.4, 3.1
Week 12	n	112	110
	Mean (SD)	1.4 (0.4)	1.5 (0.6)
	Median	1.4	1.5
	Min, max	0.4, 2.8	0.4, 4.1
	Mean (SD) change from baseline	-0.1 (0.4)	-0.1, (0.4)
	Median change from baseline	-0.1	-0.1
	Min, max change from baseline	-0.9, 1.1	-1.3, 1.2
Week 22	n	67	66
	Mean (SD)	1.5 (0.4)	1.4 (0.4)
	Median	1.4	1.4
	Min, max	0.6, 2.4	0.6, 2.4
	Mean (SD) change from baseline	0.0 (0.4)	-0.2 (0.5)
	Median change from baseline	0.0	-0.2
	Min, max change from baseline	-0.9, 1.2	-2.1, 1.4

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = LYMPHSI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 18. Mean Absolute Lymphocyte Count (×10^9/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = LYMPHSI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for ALC. There were 15 subjects (12.7%) in the SC OCR group and 20 subjects (16.9%) in the IV OCR group with ALC <1.0×10^9/L at any point after Baseline. There was one subject (0.8%) in the SC OCR group and one subject (0.8%) in the IV OCR group with ALC <0.5×10^9/L at any point after Baseline.

TEAEs that occurred in close temporal association with postbaseline ALC <1.0×10^9/L in subjects in the SC OCR group (n=1 each) included COVID-19 infection, lymphocyte count decreased, helicobacter test positive, blood alkaline phosphatase (ALP) increased, foot fracture, and nasopharyngitis. TEAEs that occurred in close temporal association with postbaseline ALC <1.0×10^9/L in subjects in the IV OCR group (n=1 each, unless otherwise specified) included skin rash, asthenia, gait disturbance, herpes virus infection, headache, disturbance in attention, otitis media, CD4 lymphocytes decreased, urinary tract infection (n=2), upper respiratory tract infection, concussion, fall, and neutropenia. Additionally, one subject in the SC OCR group experienced the TEAEs lymphocyte count decreased, and helicobacter pylori test positive, in association with ALC <0.5×10^9/L at Week 12.

The proportion of subjects who experienced ALC <1.0×10^9/L at any timepoint after baseline was higher in the IV OCR group, as compared to the SC OCR group. Comparison of summary statistics (e.g., mean/median ALC and change in ALC from baseline) did not indicate a clinically meaningful difference in ALC over time between the groups. In both treatment groups, events of viral and bacterial infections occurred in association with lymphopenia. Lymphopenia is expected with both IV and SC OCR, given the mechanism of action of the drug. Additionally, the risk of infections (including serious and life-threatening infections) is discussed in Section 5.2 (Warnings and Precautions [Infections]) of current approved labeling for Ocrevus (IV OCR),

and is therefore not unexpected with SC OCR. Of note, the Applicant is partially relying on safety and efficacy evidence from BLA 761053 for Ocrevus.

Hemoglobin, Hematocrit, and Erythrocytes

There did not appear to be a clinically significant difference or trend in hemoglobin, hematocrit, or erythrocyte count values or change between the treatment groups. There were 12 subjects (10.2%) in the SC OCR group and 14 subjects (11.9%) in the IV OCR group with hemoglobin <120 g/L and 10 subjects (8.9%) in the SC OCR group and 6 subjects (5.1%) in the IV OCR group with hemoglobin >160 g/L at any timepoint after baseline. In terms of erythrocytes, there were 10 subjects (8.9%) in SC OCR group and 18 subjects (15.3%) in the IV OCR group with erythrocytes <4.1 $\times 10^{12}$/L and 14 subjects (11.9%) in the SC OCR group and 20 subjects (16.9%) in the IV OCR group with erythrocytes >5.2 $\times 10^{12}$/L at any timepoint after baseline. For hematocrit, there were 11 subjects (9.3%) in the SC OCR group and 11 subjects (9.3%) in the IV OCR group with hematocrit <0.36 L/L. There were no subjects in either treatment group with hematocrit >0.50 L/L at any timepoint after baseline.

Overall, the frequency of subjects experiencing abnormal hemoglobin (either <120 g/L or >160 g/L) or hematocrit (either <0.36 L/L or >0.50 L/L) was similar between the treatment groups. However, a higher proportion of subjects in the IV OCR group experienced erythrocytes <4.1$\times 10^{12}$/L (15.3% versus 8.9%) and >5.2$\times 10^{12}$/L (11.9% versus 16.9%) at any timepoint after baseline, as compared to those in the SC OCR group. The etiology and clinical significance of these cases are not clear.

Platelets

Platelet count was evaluated ($\times 10^9$/L) at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 96 and mean platelet change over time in Figure 19.

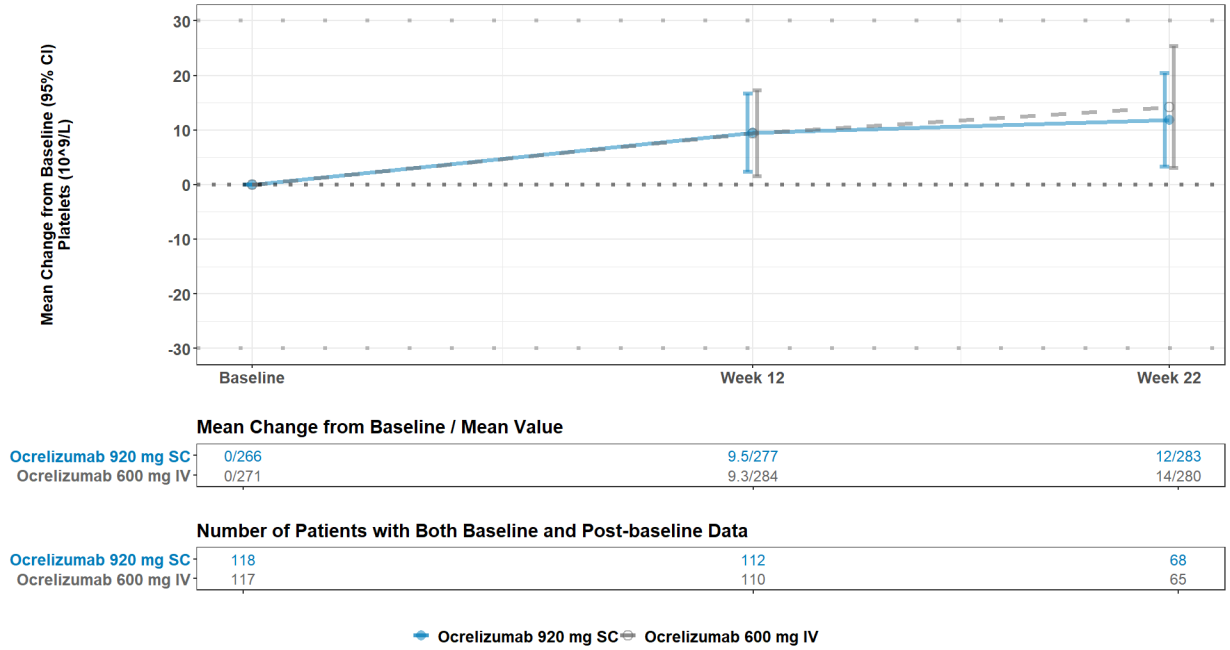
Table 96. Platelet Count ($\times 10^9$/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR N=118	IV OCR N=118
Baseline	n	118	117
	Mean (SD)	266.0 (55.3)	271.1 (61.9)
	Median	260	269
	Min, max	113, 417	112, 508
Week 12	n	112	109
	Mean (SD)	275.2 (56.3)	283.9 (57.3)
	Median	271.5	285
	Min, max	166, 442	148, 421
	Mean (SD) change from baseline	8.9 (38.7)	8.9 (42.0)
	Median change from baseline	9	6
	Min, max change from baseline	-152, 98	-148, 109

Time	Parameter	SC OCR N=118	IV OCR N=118
Week 22	n	67	65
	Mean (SD)	282.6 (49.8)	280.1 (65.3)
	Median	290	272
	Min, max	191, 418	133, 421
	Mean (SD) change from baseline	11.3 (36.7)	14.1 (45.7)
	Median change from baseline	12	8
	Min, max change from baseline	-79, 88	-118, 208

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = PLATESI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 19. Mean Platelet Count (×10^9/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = PLATESI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for platelets. There were zero subjects (0.0%) in the SC OCR group and one subject (0.8%) in the IV OCR group with platelets <140 ×10^9/L at any timepoint after baseline. There were no subjects in either treatment group with platelets <100 ×10^9/L or <50 ×10^9/L at any timepoint after baseline. There were four subjects (3.4%) in the SC OCR group and five subjects (4.2%) in the IV OCR group with platelets >400×10^9/L at any timepoint after baseline. TEAEs were reviewed for subjects with platelets <100×10^9/L and >400×10^9/L at any timepoint after baseline. No TEAEs were identified in association with platelets <100×10^9/L at any timepoint after baseline. One subject in the OCR SC group experienced platelets >400×10^9/L in close temporal association with oral sores. Additionally, one subject in the IV OCR group had platelets >400×10^9/L in close temporal association with the serious adverse event subcutaneous abscess (“multiple recurrent

subcutaneous abscess on abdominal wall") and subcutaneous abscess ("right axillary abscess") and with the TEAEs erythema and swelling ("right axillary swelling and erythema").

The mean and median platelet count at baseline was higher in the IV OCR group ($271.1\pm61.9\times10^9$/L and 269×10^9/L, respectively), as compared to the SC OCR group ($266.0\pm55.3\times10^9$/L and 260×10^9/L, respectively). However, the median change from baseline at Weeks 12 and 22 was greater in the SC OCR group, as compared to the IV OCR group. As a result, although the mean platelet count at Week 22 was comparable between the groups, the median platelet count at Week 22 was higher in the SC OCR group, as compared to the IV OCR group (290×10^9/L versus 272×10^9/L, respectively); this difference does not appear to be clinically significant. The etiology of these cases is not clear; however, the frequency of clinically significant abnormalities in platelets appeared similar between the groups.

Chemistry

AST

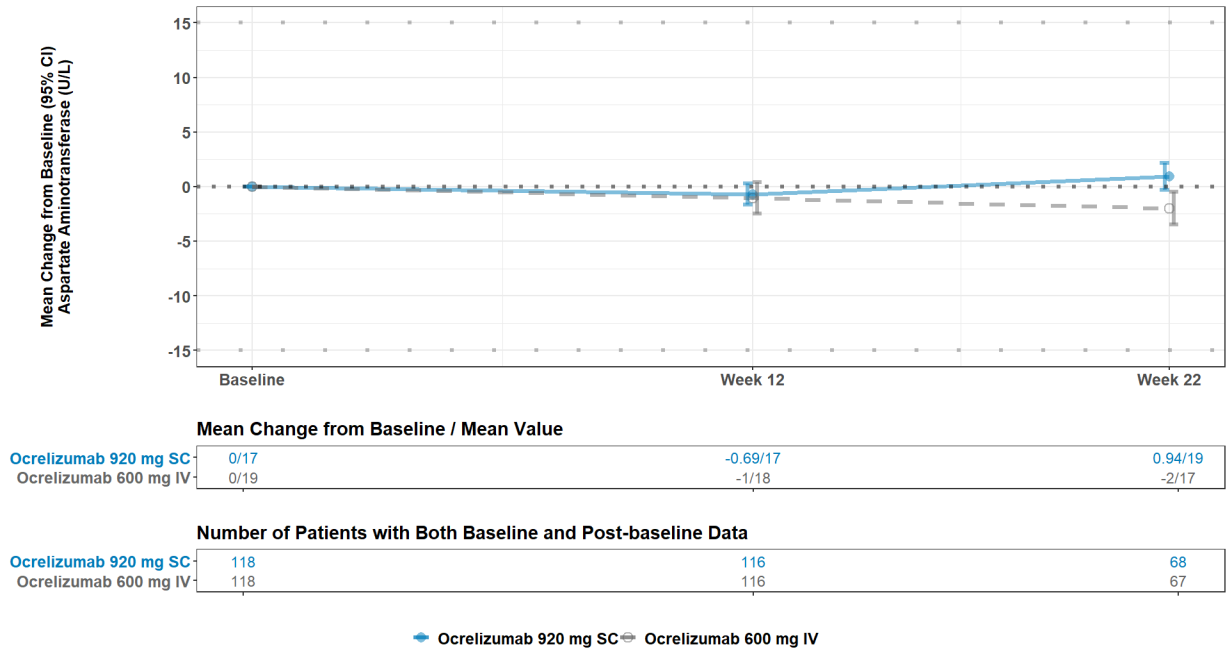
Aspartate aminotransferase (AST) was evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 97 and mean AST change over time in Figure 20.

Table 97. AST (IU/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR N=118	IV OCR N=118
Baseline	n	118	118
	Mean (SD)	18.6 (7.5)	20.1 (9.1)
	Median	16.0	17.5
	Min, max	10, 64	11, 80
Week 12	n	117	117
	Mean (SD)	18 (5.15)	19.2 (7.4)
	Median	17.0	18.0
	Min, max	10, 38	11, 59
	Mean (SD) change from baseline	-0.6 (5.7)	-1.0 (8.6)
	Median change from baseline	0.0	0.0
	Min, max change from baseline	-44, 15	-62, 20
Week 22	n	*67*	*67*
	Mean (SD)	*19.6 (8.9)*	*18.5 (6.2)*
	Median	17.0	17.0
	Min, max	10, 54	10, 54
	Mean (SD) change from baseline	1.0 (5.5)	-2.1 (6.7)
	Median change from baseline	0.0	-1.0
	Min, max change from baseline	-14, 18	-36, 15

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = ASTSI, by TRT01A.
Abbreviations: AST, aspartate aminotransferase; IU/L, international units per liter; IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 20. Mean AST (IU/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = ASTSI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; AST, aspartate aminotransferase; IU/L, international units per liter; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for AST. Shift analyses indicated that there were no subjects in either treatment group who experienced increased AST to ≥3× upper limit of normal (ULN) from normal baseline values (8 to 40 U/L).

Refer to Section 7.6.1.7 for assessment of DILI risk in Study CN42097.

Comparison of summary statistics (e.g., mean/median AST values and change from baseline) did not indicate a clinically meaningful difference in AST over time between the groups. Additionally, no clinically significant abnormalities in AST were identified in either treatment group. These results do not raise concern for risk of transaminitis associated with SC OCR.

ALT

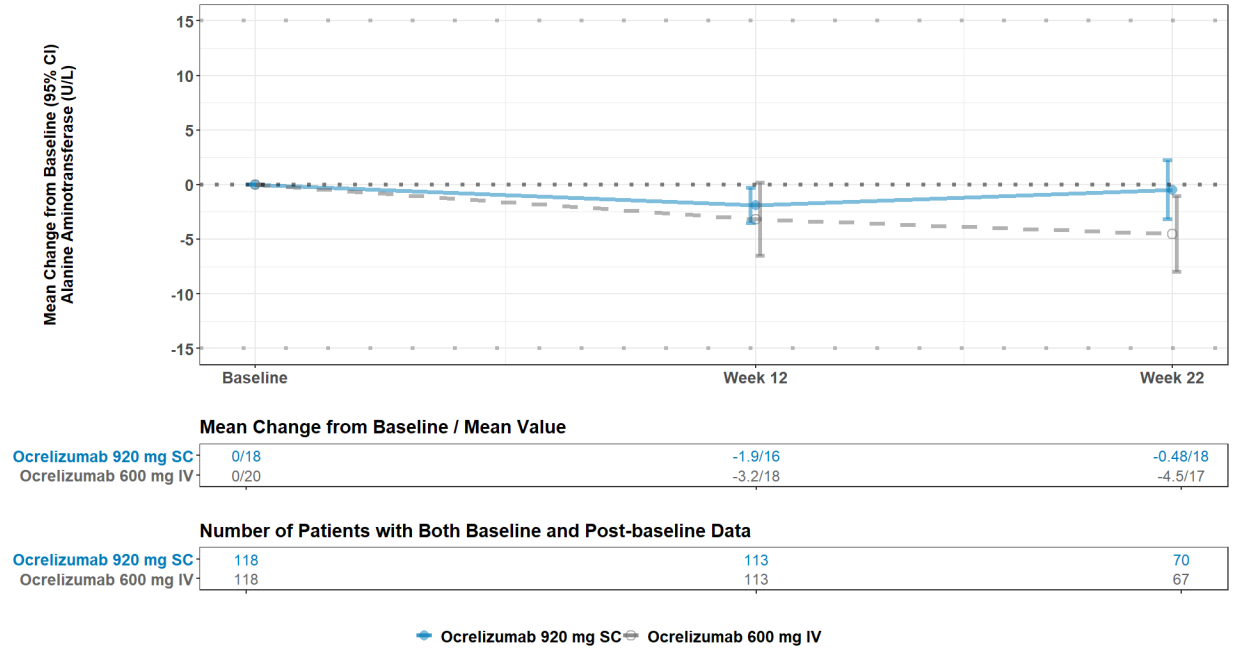
Alanine aminotransferase (ALT) was evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 98 and mean ALT change over time in Figure 21.

Table 98. ALT (IU/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	118	118
	Mean (SD)	20.6 (15.0)	23.0 (21.1)
	Median	16.0	17.0
	Min, max	6, 95	6, 158
Week 12	n	114	111
	Mean (SD)	18.9 (13.1)	20.0 (11.4)
	Median	15.0	17.0
	Min, max	7, 102	5, 72
	Mean (SD) change from baseline	-1.9 (10.2)	-3.6 (20.7)
	Median change from baseline	0.0	0.0
	Min, max change from baseline	-78, 31	-140, 33
Week 22	n	69	67
	Mean (SD)	20.7 (15.3)	19.6 (10.5)
	Median	15.0	17
	Min, max	6, 77	5, 62
	Mean (SD) change from baseline	-0.4 (13.0)	-5.1 (16.6)
	Median change from baseline	0.0	-1.0
	Min, max change from baseline	-81, 31	-106, 14

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = ALTSI, by TRT01A
Abbreviations: AST, aspartate aminotransferase; IU/L, international units per liter; IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 21. Mean ALT (IU/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = ALTSI, by TRT01A.
Error bars represent 95% confidence intervals.
The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ALT, alanine aminotransferase; IU/L, international units per liter; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for ALT. Shift analyses indicated that there were no subjects in either treatment group who experienced increased ALT to ≥3×ULN from normal baseline values (4 to 43 U/L or 5 to 48 U/L).

Refer to Section 7.6.1.7 for assessment of DILI risk in Study CN42097.

Comparison of summary statistics (e.g., mean/median ALT values and change from baseline) did not indicate a clinically meaningful difference in ALT over time between the groups. Additionally, no clinically significant abnormalities in ALT were identified in either treatment group. These results do not raise concern for risk of transaminitis associated with SC OCR.

Bilirubin

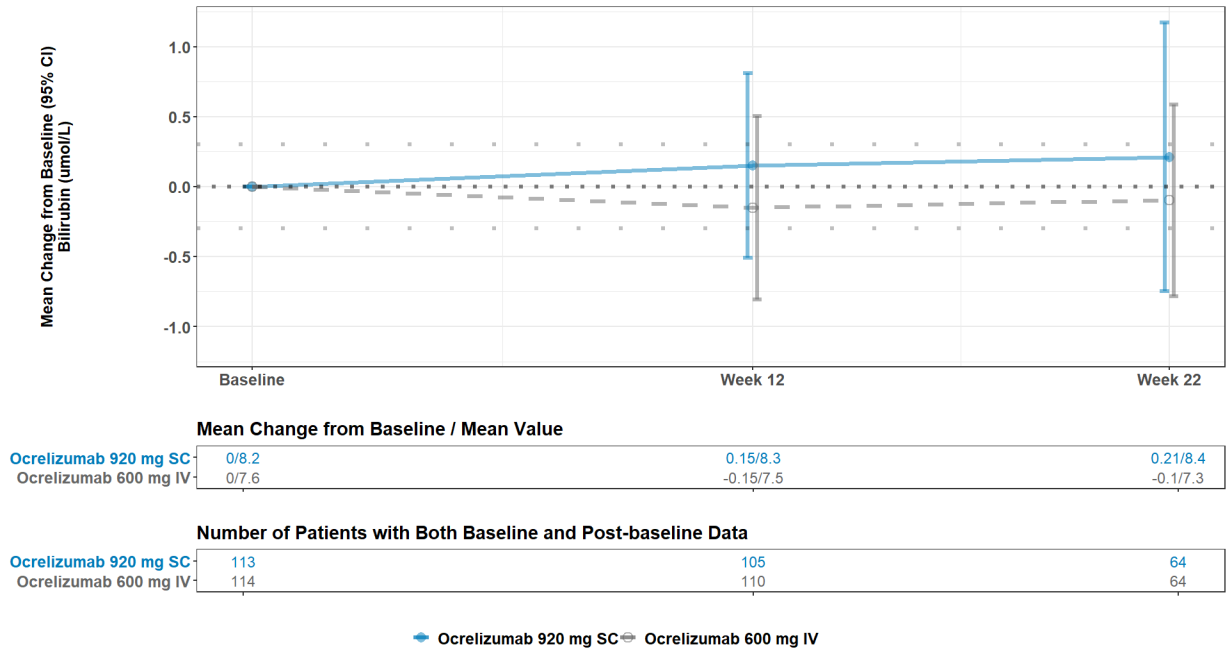
Total bilirubin was evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 99 and mean total bilirubin change over time in Figure 22.

Table 99. Total Bilirubin (µmol/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	113	114
	Mean (SD)	9.1 (6.3)	8.4 (5.4)
	Median	8.0	7.0
	Min, max	3, 50	3, 37
Week 12	n	110	109
	Mean (SD)	9.2 (5.9)	8.3 (4.8)
	Median	7.5	7.0
	Min, max	3, 38	3, 34
	Mean (SD) change from baseline	0.2 (3.8)	-0.2 (3.9)
	Median change from baseline	0.0	0.0
	Min, max change from baseline	-17, 11	-12, 11
Week 22	n	66	64
	Mean (SD)	9.3 (6.6)	8.1 (4.4)
	Median	7.0	8.0
	Min, max	3, 39	3, 26
	Mean (SD) change from baseline	0.2 (3.8)	-0.1 (3.1)
	Median change from baseline	0.0	0.0
	Min, max change from baseline	-17, 11	-11, 5

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = TBILISI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 22. Mean Total Bilirubin (µmol/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = TBILISI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for total bilirubin. Shift analyses indicated that there were no subjects in either treatment group who experienced increased total bilirubin to ≥1.5×ULN at any point after baseline from normal baseline values (3 to 21 µmol/L). There were two subjects (1.7%) in the SC OCR group and one subject (0.8%) in the IV OCR group who experienced increased total bilirubin to ≥1.5×ULN from baseline values above the ULN. There were no subjects in either treatment group who experienced increased total bilirubin to ≥2× or ≥3×ULN at any point after baseline.

Comparison of summary statistics (e.g., mean/median total bilirubin values and change from baseline) did not indicate a clinically meaningful difference in total bilirubin over time between the groups. Additionally, no clinically significant abnormalities in total bilirubin were identified in either treatment group. These results do not raise concern for risk of increased bilirubin associated with SC OCR.

Alkaline Phosphatase

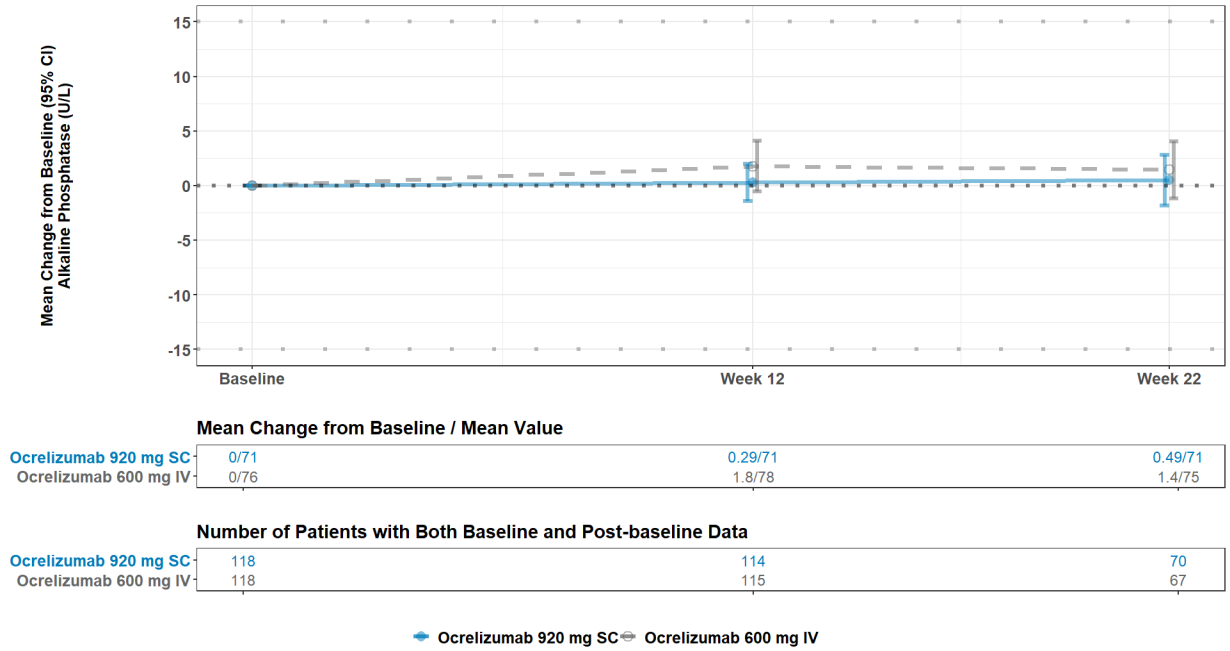
ALP was evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 100 and mean ALP change over time in Figure 23.

Table 100. ALP (U/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	118	118
	Mean (SD)	68.3 (19.7)	74.1 (19.1)
	Median	65.0	75.0
	Min, max	39, 163	30-138
Week 12	n	115	114
	Mean (SD)	68.6 (22.0)	75.7 (21.5)
	Median	65.0	75.0
	Min, max	38, 170	27, 148
	Mean (SD) change from baseline	0.6 (9.3)	1.6 (12.3)
	Median change from baseline	0.0	1.0
	Min, max change from baseline	-29, 32	-45, 52
Week 22	n	69	67
	Mean (SD)	69.1 (21.5)	72.7 (19.1)
	Median	65.0	73.0
	Min, max	38, 164	35, 132
	Mean (SD) change from baseline	0.6 (9.8)	1.4 (10.6)
	Median change from baseline	1.0	1.0
	Min, max change from baseline	-40, 29	-50, 35

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = ALKPHSI, by TRT01A.
Abbreviations: ALP, alkaline phosphatase; IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 23. Mean ALP (U/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = ALKPHSI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; ALP, alkaline phosphatase; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for ALP. Shift analyses indicated that there were no subjects in either treatment group that experienced increased ALP to ≥2×ULN from normal baseline values (35 to 104 U/L, 40 to 129 U/L, or 55 to 149 U/L).

Comparison of summary statistics (e.g., mean/median ALP values and change from baseline) revealed higher mean and median ALP at Baseline, Week 12, and Week 22 in the IV OCR group, as compared to the SC OCR group. However, no clinically significant abnormalities in ALP were identified in either treatment group. These results do not raise concern for risk of increased ALP associated with SC OCR.

Creatinine

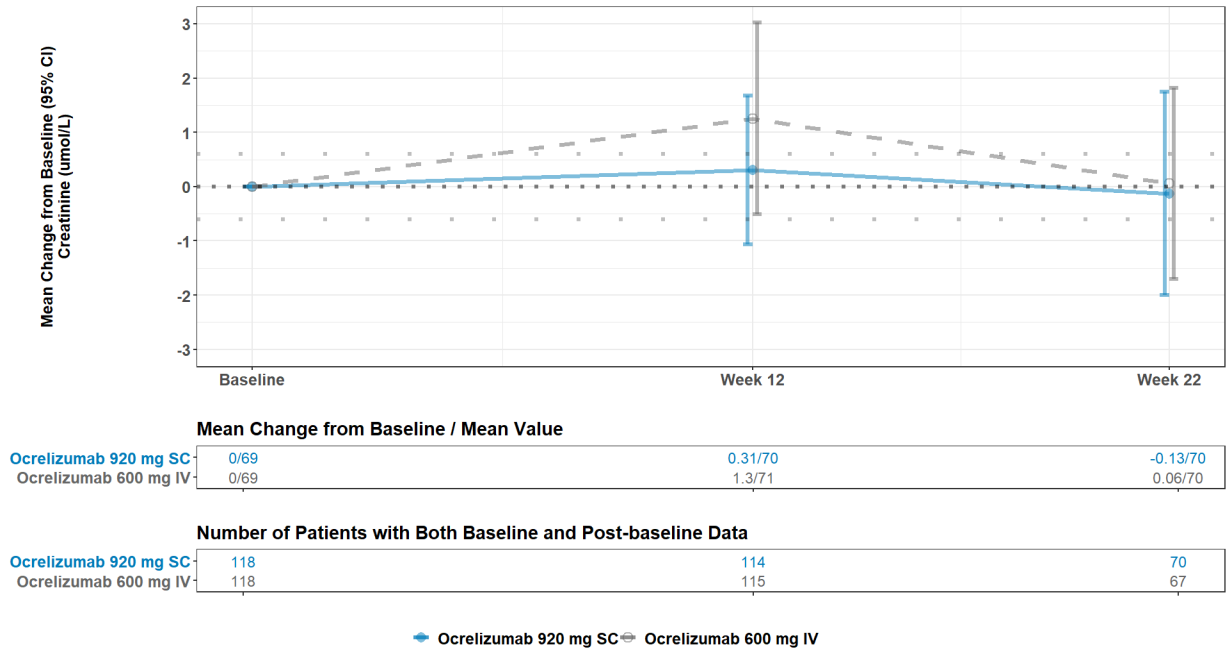
Creatinine was evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 101 and mean creatinine change over time in Figure 24.

Table 101. Creatinine (µmol/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	118	118
	Mean (SD)	69.1 (11.9)	69.5 (13.0)
	Median	69.0	68.0
	Min, max	44-98	42-112
Week 12	n	115	114
	Mean (SD)	69.6 (12.2)	70.8 (14.1)
	Median	69.0	69.5
	Min, max	48, 114	40, 120
	Mean (SD) change from baseline	0.2 (7.5)	1.2 (9.7)
	Median change from baseline	1.0	0.0
	Min, max change from baseline	-20, 33	-23, 41
Week 22	n	69	67
	Mean (SD)	70.1 (11.2)	69.8 (11.9)
	Median	70.0	71.0
	Min, max	47, 98	42, 97
	Mean (SD) change from baseline	-0.3 (8.0)	0.1 (7.4)
	Median change from baseline	-1.0	0.0
	Min, max change from baseline	-14, 26	-19, 18

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = CREATNSI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 24. Mean Creatinine (µmol/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = CREATNSI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for creatinine. There were no subjects in either treatment group with creatinine ≥120 µmol/L at any timepoint after baseline. Additionally, shift analyses indicated that there were two subjects in the IV OCR group that experienced increased creatinine to 1.5× from baseline values (Subjects (b) (6) had creatinine values of 71 µmol/L and 118 µmol/L, respectively, at Week 12). No TEAEs occurred in close temporal association with these outlier values.

Comparison of summary statistics (e.g., mean/median creatinine values and change from baseline) did not indicate a clinically meaningful difference in creatinine over time between the groups. Additionally, no clinically significant abnormalities in creatinine were identified in either treatment group. These results do not raise concern for risk of impaired renal function with SC OCR.

Amylase

Amylase was evaluated at Baseline and at Weeks 12 and 22 during the Controlled Period, with representative timepoints shown in Table 102.

Table 102. Amylase (U/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	118	118
	Mean (SD)	61.6 (27.7)	64.2 (26.6)
	Median	53.5	60.5
	Min, max	25, 249	15, 170
Week 12	n	117	115
	Mean (SD)	63.0 (25.0)	65.9 (26.2)
	Median	57.0	64.0
	Min, max	21, 184	16, 164
	Mean (SD) change from baseline	1.4 (17.2)	1.5 (17.3)
	Median change from baseline	1.0	1.0
	Min, max change from baseline	-93, 110	-106, 63
Week 22	n	69	67
	Mean (SD)	59.7 (20.6)	62.2 (22.1)
	Median	58.0	59.0
	Min, max	23, 126	30, 127
	Mean (SD) change from baseline	0.3 (18.5)	0.4 (15.8)
	Median change from baseline	2.0	2.0
	Min, max change from baseline	-129, 27	-99, 36

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = AMYLASSI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for amylase. Shift analyses indicated that there were no subjects in either treatment group that experienced increased amylase to ≥2 × or 3 × ULN from normal baseline values (28 to 150 U/L). Additionally, there were six subjects (n=5.1%) in the SC OCR group and seven subjects (n=5.9%) in the IV OCR group who experienced increased amylase to ≥1.1 ×ULN at any point after baseline. Of these, four subjects in the SC OCR group and two subjects in the IV OCR group had baseline amylase levels above the ULN. Therefore, there were two subjects (n=1.7%) in the SC OCR group and five subjects (n=4.3%) in the IV OCR group who experienced increased amylase to ≥1.1 ×ULN at any point after baseline. The clinical significance of these outlier values is not clear. Subject [redacted] (b) (6) (IV OCR group) experienced the TEAEs nasopharyngitis, headache, asthenia, gait disturbance, herpesvirus infection, disturbance in attention, hyperesthesia, limb injury, dizziness, arthralgia, and fall in close temporal association with increased amylase to ≥1.1 × ULN. No AEs of pancreatitis were reported.

Comparison of summary statistics (e.g., mean/median amylase values and change from baseline) did not indicate a clinically meaningful difference in amylase over time between the groups. Additionally, no clinically significant abnormalities in amylase were identified in either treatment group. Pancreatic toxicity does not appear to be a concern with SC OCR. Of note, the Applicant is partially relying on safety and efficacy evidence from BLA 761053 for Ocrevus. A concern for pancreatic toxicity was raised during the review of Ocrevus (IV OCR), and enhanced pharmacovigilance was recommended. Enhanced pharmacovigilance was discontinued on March 8, 2023, at the Applicant's request and because the Applicant had passed the agreed upon 5-year expedited reporting period. [redacted] (b) (4)

(b) (4) Therefore, enhanced pharmacovigilance for cases of pancreatitis with SC OCR does not appear to be warranted.

Other Chemistry

There were no apparent clinically significant trends for sodium or potassium in either treatment group over time, as mean/median values and changes from baseline were similar between the treatment groups.

Urinalysis

There were no apparent clinically significant trends for urine pH or urine specific gravity in either treatment group over time, as mean/median values and changes from baseline were similar between the treatment groups. A higher proportion of subjects (4.2%, n=5) in the IV OCR group had trace (+1) protein in urine, as compared to the SC OCR group (0.8%, n=1) at Baseline and Week 12. The clinical significance of this difference and etiology of these values are unclear. There was no clinically significant difference in the proportion of subjects between the groups who experienced qualitative abnormalities pertaining to glucose, ketones, or blood in urine at each visit and over time.

Immunoglobulins

IgG

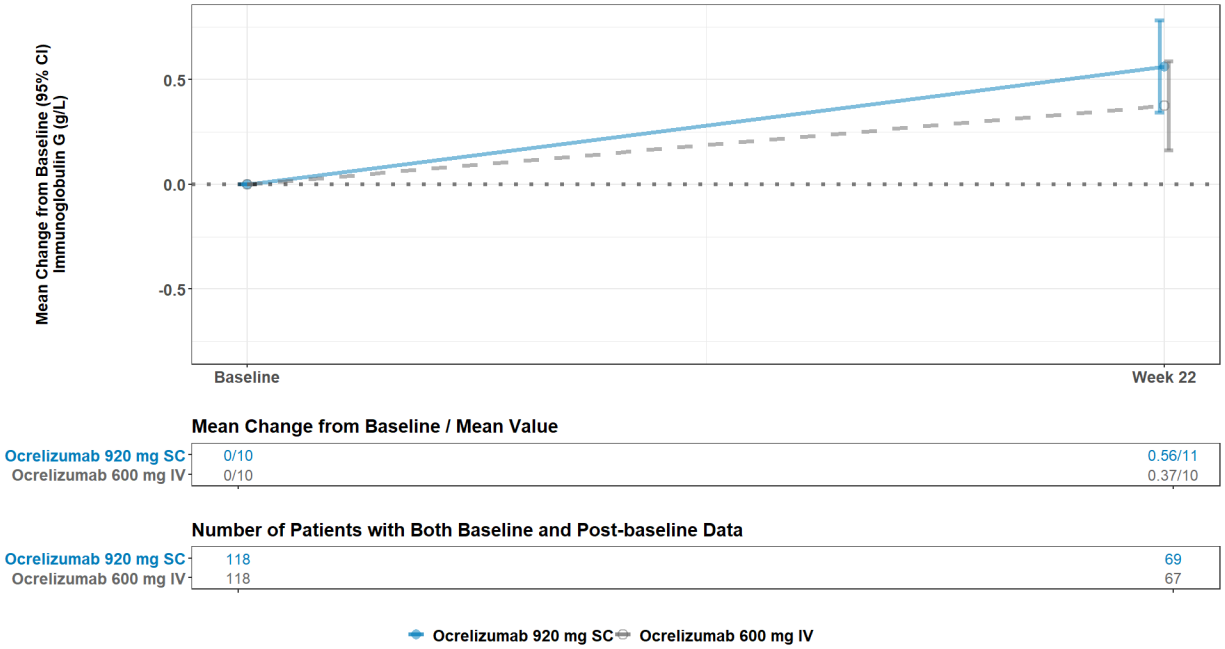
Immunoglobulin G (IgG) was evaluated at Baseline and at Week 22 during the Controlled Period, with representative timepoints shown in Table 103 and mean IgG change over time in Figure 25.

Table 103. Immunoglobulin G (g/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	118	118
	Mean (SD)	10.3 (2.5)	10.0 (2.5)
	Median	10.2	9.9
	Min, max	5.0, 16.3	4.7, 18.1
Week 22	n	69	67
	Mean (SD)	10.8 (2.5)	10.3 (2.5)
	Median	10.3	10.6
	Min, max	5.7, 17.2	5.6, 18.3
	Mean (SD) change from baseline	0.6 (0.9)	0.4 (0.9)
	Median change from baseline	0.5	0.4
	Min, max change from baseline	-1.7, 3.8	-2.5, 3.4

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = IM0113SI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 25. Mean Immunoglobulin G (g/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = IM0113SI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for IgG. There were no subjects in either treatment group who experienced IgG <5.5 g/L at Week 22.

Comparison of summary statistics (e.g., mean/median IgG values and change from baseline) did not indicate a clinically meaningful difference in IgG over time between the groups. Changes in IgG noted for Ocrevus (IV OCR) required years of exposure to identify, so the lack of a finding in the Controlled Period is expected and does not preclude labeling for what appears to be an effect that requires prolonged exposure to any anti-CD20 therapy. Additionally, the Applicant is partially relying on supportive safety and efficacy evidence from BLA 761053 for Ocrevus. Section 5.4 (Warnings and Precautions [Reduction in Immunoglobulins]) of current approved labeling for Ocrevus discusses the risk of decreased immunoglobulin levels with any B-cell-depleting therapies, including with OCR.

IgM

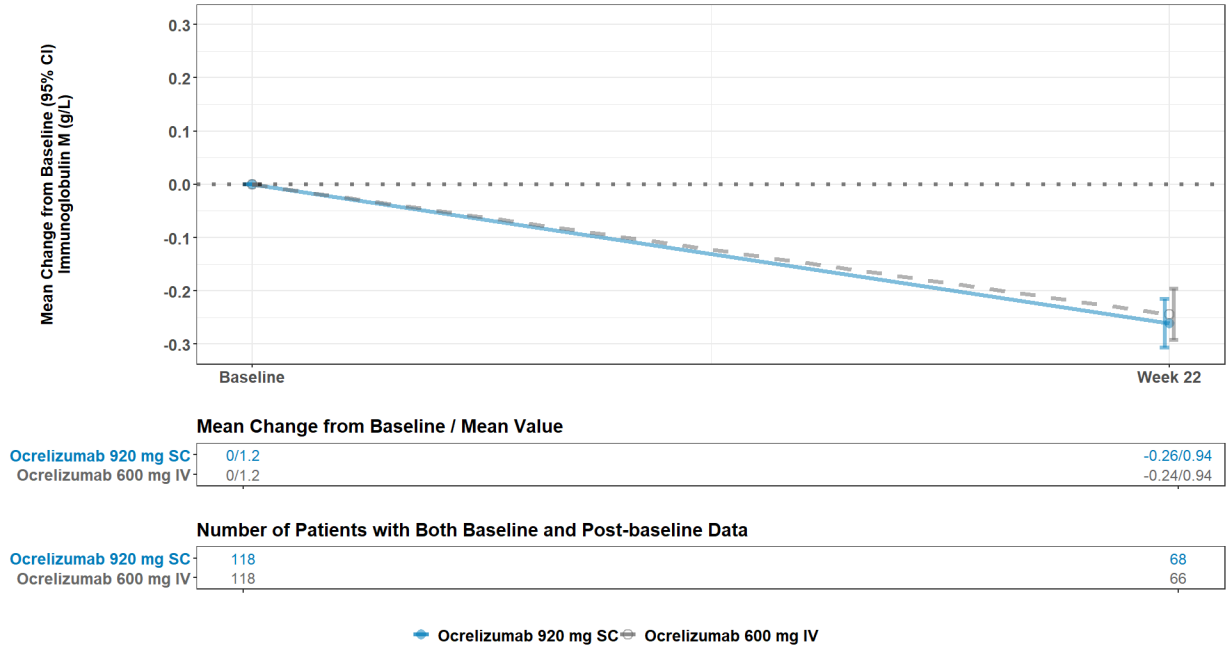
Immunoglobulin M (IgM) was evaluated at Baseline and at Week 22 during the Controlled Period, with representative timepoints shown in Table 104 and mean IgM change over time in Figure 26.

Table 104. Immunoglobulin M (g/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	118	118
	Mean (SD)	1.2 (0.6)	1.2 (0.6)
	Median	1.0	1.1
	Min, max	0.3, 3.2	0.2, 3.0
Week 22	n	68	66
	Mean (SD)	0.9 (0.5)	0.9 (0.5)
	Median	0.8	0.8
	Min, max	0.2, 2.8	0.2, 2.3
	Mean (SD) change from baseline	-0.3 (0.2)	-0.2 (0.2)
	Median change from baseline	-0.2	-0.2
	Min, max change from baseline	-0.8, 0.0	-0.9, 0.3

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = IM0120SI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 26. Mean Immunoglobulin M (g/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = IM0120SI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for IgM. There were four subjects (n=3.4%) in the SC OCR group and seven subjects (n=5.9%) in the IV OCR group who experienced IgM <0.4 g/L at Week 22. One subject in the IV OCR group had IgM of 0.32 g/L at Week 22 in close temporal association with the TEAEs bronchitis and micturition urgency.

Comparison of summary statistics (e.g., mean/median IgM values and change from baseline) did not indicate a clinically meaningful difference in IgM over time between the groups. Clinically

significant reduction in IgM values at Week 22 occurred at a slightly higher frequency in the IV OCR group. However, reduction in immunoglobulins is expected long-term given the mechanism of action of OCR administered via any route, SC or IV.

IgA

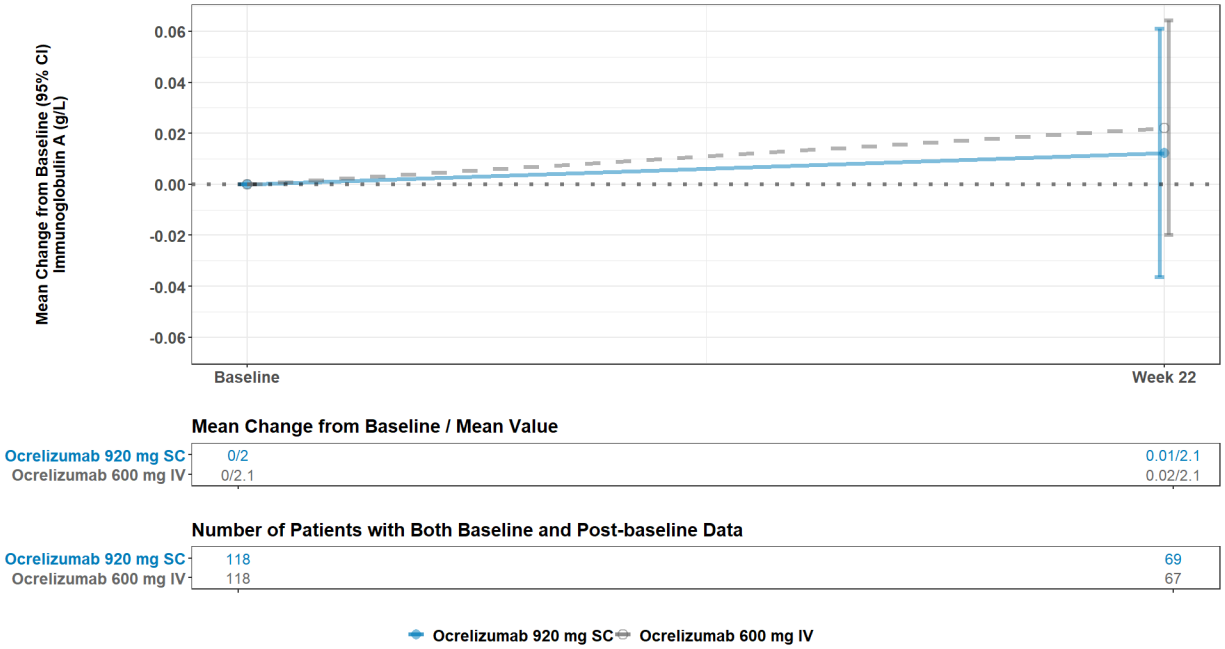
Immunoglobulin A (IgA) was evaluated at Baseline and at Week 22 during the Controlled Period, with representative timepoints shown in Table 105 and mean IgA change over time in Figure 27.

Table 105. Immunoglobulin A (g/L) Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	118	118
	Mean (SD)	2.0 (0.9)	2.1 (0.9)
	Median	1.8	1.8
	Min, max	0.5, 4.5	0.6, 5.8
Week 22	n	69	67
	Mean (SD)	2.1 (0.8)	2.1 (0.8)
	Median	1.9	1.9
	Min, max	0.7, 4.8	0.6, 4.4
	Mean (SD) change from baseline	0.0 (0.2)	0.0 (0.2)
	Median change from baseline	0.0	0.0
	Min, max change from baseline	-0.8, 0.5	-0.4, 0.6

Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = IM0107SI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

Figure 27. Mean Immunoglobulin A (g/L) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period



Source: ADLB, SAFFL = Y, ANL02FL = Y, PARAMCD = IM0107SI, by TRT01A.
Error bars represent 95% confidence intervals.
Visit number as per ADY. The timeframe (e.g., by day, week, month) that corresponds best with the prespecified visit number is used as the study visit (±7 days, as defined in Protocol CN42097).
Abbreviations: ADY, analysis day; IV, intravenous; SC, subcutaneous

Outliers based on clinically meaningful thresholds were reviewed for IgA. There were five subjects (n=4.2%) in the SC OCR group and one subject (n=0.8%) in the IV OCR group who experienced IgA <0.8 g/L at Week 22. No TEAEs were identified in close temporal association with these outliers.

Comparison of summary statistics (e.g., mean/median IgA values and change from baseline) did not indicate a clinically meaningful difference in IgA over time between the groups. However, reduction in immunoglobulins is expected long-term given the mechanism of action of OCR administered via any route, SC or IV.

CD19^{+} B-cells

The primary PD effect of SC OCR and IV OCR is depletion of CD19^{+} B-cells. Absolute CD19^{+} B-cell count was evaluated at Baseline and at Weeks 2, 4, 12, 16, and 24 during the Controlled Period, with representative timepoints shown in Table 106.

Table 106. Mean Absolute CD19+ B-Cell Count (cells/µL) Change From Baseline Over Time, Safety Population, Study CN42097, Controlled Period

Time	Parameter	SC OCR (N=118)	IV OCR (N=118)
Baseline	n	118	118
	Mean (SD)	205.5 (114.6)	214.9 (124.3)
	Median	185.0	189.0
	Min, max	14, 646	26, 591
Week 2	n	115	114
	Mean (SD)	1.0 (4.4)	2.2 (17.5)
	Median	0.0	0.0
	Min, max	0, 46	0, 187
	Mean (SD) change from baseline	-205.2 (115.0)	-213.1 (127.3)
	Median change from baseline	-186.0	-184.0
	Min, max change from baseline	-646, -14	-585, -10
Week 4	n	118	113
	Mean (SD)	0.6 (1.5)	1.3 (8.8)
	Median	0.0	0.0
	Min, max	0, 12	0, 93
	Mean (SD) change from baseline	-205.0 (114.8)	-212.9 (126.9)
	Median change from baseline	-182.5	-184.0
	Min, max change from baseline	-646, -14	-589, -26
Week 12	n	115	115
	Mean (SD)	1.7 (13.7)	0.6 (1.6)
	Median	0.0	0.0
	Min, max	0, 147	0, 14
	Mean (SD) change from baseline	-203.1 (114.4)	-213.4 (124.9)
	Median change from baseline	-180.0	-183.0
	Min, max change from baseline	-643, -13	-591, -26
Week 16	n	89	90
	Mean (SD)	1.4 (3.5)	0.9 (1.1)
	Median	0.0	1.0
	Min, max	0, 22	0, 6
	Mean (SD) change from baseline	-204.3 (117.5)	-205.9 (120.0)
	Median change from baseline	-179.0	-177.5
	Min, max change from baseline	-645, -20	-576, -26
Week 24	n	62	62
	Mean (SD)	13.2 (33.1)	8.4 (20.3)
	Median	2.0	2.0
	Min, max	0, 173	0, 127
	Mean (SD) change from baseline	-198.2 (102.3)	-201.0 (126.4)
	Median change from baseline	-190.0	-176.0
	Min, max change from baseline	-462, -18	-576, -11

Source: ADZF, SAFFL = Y, ANL02FL = Y, PARAMCD = FC0083SI, by TRT01A.
Abbreviations: IV, intravenous; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with available measurement; OCR, ocrelizumab; SC, subcutaneous

There were three subjects (n=2.5%) who received SC OCR and two subjects (n=1.7%) who received IV OCR who had postbaseline CD19+ B-cell counts >100 cells/µL. These values were most common at Week 24 (n=3), prior to dosing. Of these five subjects, none experienced a relapse (protocol-defined or other relapse).

It appears that SC OCR depleted CD19+ B-cells in a majority of subjects, and the effect appeared to be comparable to that of IV OCR. Of note, the Applicant is partially relying on safety and efficacy evidence from BLA 761053 for Ocrevus (IV OCR).

Study CN41144

Results of the analysis of laboratory value abnormalities for subjects enrolled in Study CN41144 are summarized in this section. Table 107 presents the results of blood chemistry outlier analyses for Study CN41144. Overall, it appears that a higher proportion of subjects who received at least one dose of SC OCR 1200 mg experienced hypokalemia, as compared to subjects who received at least one dose of SC OCR 920 mg. These results should be interpreted with caution, as the sample size was relatively small, several subjects (n=112) were exposed to both dose levels, and several subjects were also exposed to IV OCR prior to and during Study CN41144.

Table 107. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Study CN411144

	SC OCR 920 mg		SC OCR 1200 mg	
Laboratory Parameter	Group A N=79 n/N_w (%)	Group B N=39 n/N_w (%)	Group A N=80 n/N_w (%)	Group B N=45 n/N_w (%)
Sodium, low (mEq/L)				
Level 1 (<132)	0/77 (0)	0/39 (0)	2/80 (2.5)	0/45 (0)
Level 2 (<130)	0/77 (0)	0/39 (0)	1/80 (1.2)	0/45 (0)
Level 3 (<125)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Sodium, high (mEq/L)				
Level 1 (>150)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 2 (>155)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 3 (>160)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Potassium, low (mEq/L)				
Level 1 (<3.6)	3/76 (3.9)	3/39 (7.7)	16/80 (20.0)	12/45 (26.7)
Level 2 (<3.4)	1/76 (1.3)	1/39 (2.6)	8/80 (10.0)	6/45 (13.3)
Level 3 (<3)	0/76 (0)	0/39 (0)	3/80 (3.8)	0/45 (0)
Potassium, high (mEq/L)				
Level 1 (>5.5)	1/76 (1.3)	0/39 (0)	3/80 (3.8)	0/45 (0)
Level 2 (>6)	0/76 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 3 (>6.5)	0/76 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Amylase, high (U/L)				
Level 1 (>1.1× ULN)	3/77 (3.9)	1/38 (2.6)	3/80 (3.8)	2/45 (4.4)
Level 2 (>1.5× ULN)	0/77 (0)	0/38 (0)	1/80 (1.2)	0/45 (0)
Level 3 (>3× ULN)	0/77 (0)	0/38 (0)	0/80 (0)	0/45 (0)

Source: adlb.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during Study CN41144.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during Study CN41144, either in dose escalation phase or in dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Threshold levels 1, 2, and 3, as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is up to 3 years.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous; ULN, upper limit of normal

Table 108 presents the results of kidney function analyte outlier analyses for Study CN41144. Overall, it appears that a higher proportion of subjects who received at least one dose of SC OCR 1200 mg experienced creatinine elevation and decreased estimated glomerular filtration rate (eGFR) meeting prespecified thresholds, as compared to subjects who received at least one dose

of SC OCR 920 mg. Decreases in eGFR also appeared to be more common in subjects exposed to ocrelizumab prior to study enrollment (Group A). These results should be interpreted with caution, as the sample size was relatively small, several subjects (n=112) were exposed to both dose levels, and several subjects were also exposed to IV OCR prior to and during Study CN41144.

Table 108. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Study CN41144

	SC OCR 920 mg		Ocrelizumab SC 1200 mg	
Laboratory Parameter	**Group A N=79 n/N_w (%)**	**Group B N=39 n/N_w (%)**	**Group A N=80 n/N_w (%)**	**Group B N=45 n/N_w (%)**
Creatinine, high (mg/dL)				
Level 1 (≥1.5× baseline)	0/77 (0)	0/39 (0)	1/80 (1.2)	1/45 (2.2)
Level 2 (≥2× baseline)	0/77 (0)	0/39 (0)	1/80 (1.2)	0/45 (0)
Level 3 (≥3× baseline)	0/77 (0)	0/39 (0)	1/80 (1.2)	0/45 (0)
eGFR, low (mL/min/1.73 m^2)				
Level 1 (≥25% decrease)	3/76 (3.9)	0/39 (0)	10/79 (12.7)	3/45 (6.7)
Level 2 (≥50% decrease)	0/76 (0)	0/39 (0)	1/79 (1.3)	0/45 (0)
Level 3 (≥75% decrease)	0/76 (0)	0/39 (0)	1/79 (1.3)	0/45 (0)

Source: adlb.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during OCARINA I.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during OCARINA I, either in dose escalation phase or in dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Threshold levels 1, 2, and 3, as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is up to 3 years.
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 the chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IV, intravenous; min., minimum; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous

Table 109 presents the results of hematology analyte outlier analyses for Study CN41144. Overall, it appears that a higher proportion of subjects who received at least one dose of SC OCR 1200 mg experienced leukopenia, leukocytosis, lymphopenia, and reductions or increases in hemoglobin meeting prespecified thresholds, as compared to subjects who received at least one dose of SC OCR 920 mg. Leukopenia, leukocytosis, and lymphopenia also appeared to be more common in OCR-naive subjects (Group B). These results should be interpreted with caution, as the sample size was relatively small, several subjects (n=112) were exposed to both dose levels, and several subjects were also exposed to IV OCR prior to and during Study CN41144.

Table 109. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
Laboratory Parameter	**Group A N=79 n/N_w (%)**	**Group B N=39 n/N_w (%)**	**Group A N=80 n/N_w (%)**	**Group B N=45 n/N_w (%)**
Complete blood count				
WBC, low (10^3 cells/µL)				
Level 1 (<3.5)	2/77 (2.6)	0/39 (0)	4/80 (5.0)	6/45 (13.3)
Level 2 (<3)	2/77 (2.6)	0/39 (0)	2/80 (2.5)	2/45 (4.4)
Level 3 (<1)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
WBC, high (10^3 cells/µL)				
Level 1 (>10.8)	14/77 (18.2)	2/39 (5.1)	33/80 (41.2)	22/45 (48.9)
Level 2 (>13)	7/77 (9.1)	2/39 (5.1)	26/80 (32.5)	17/45 (37.8)
Level 3 (>15)	6/77 (7.8)	0/39 (0)	24/80 (30.0)	10/45 (22.2)
Hemoglobin, low (g/dL)				
Level 2 (>1.5 g/dL dec. from baseline)	1/77 (1.3)	1/39 (2.6)	6/80 (7.5)	2/45 (4.4)
Level 3 (>2 g/dL dec. from baseline)	1/77 (1.3)	0/39 (0)	3/80 (3.8)	0/45 (0)
Hemoglobin, high (g/dL)				
Level 2 (>2 g/dL inc. from baseline)	2/77 (2.6)	3/39 (7.7)	6/80 (7.5)	4/45 (8.9)
Level 3 (>3 g/dL inc. from baseline)	0/77 (0)	1/39 (2.6)	1/80 (1.2)	1/45 (2.2)
Platelets, low (10^3 cells/µL)				
Level 1 (<140)	0/77 (0)	0/39 (0)	1/80 (1.2)	0/45 (0)
Level 2 (<125)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 3 (<100)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
WBC differential				
Lymphocytes, low (10^3 cells/µL)				
Level 1 (<1)	12/69 (17.4)	6/37 (16.2)	21/74 (28.4)	22/44 (50.0)
Level 2 (<0.75)	2/69 (2.9)	1/37 (2.7)	9/74 (12.2)	18/44 (40.9)
Level 3 (<0.5)	1/69 (1.4)	1/37 (2.7)	2/74 (2.7)	4/44 (9.1)
Lymphocytes, high (10^3 cells/µL)				
Level 1 (>4)	0/69 (0)	1/37 (2.7)	2/74 (2.7)	2/44 (4.5)
Level 2 (>10)	0/69 (0)	0/37 (0)	0/74 (0)	1/44 (2.3)
Level 3 (>20)	0/69 (0)	0/37 (0)	0/74 (0)	0/44 (0)
Neutrophils, low (10^3 cells/µL)				
Level 1 (<2)	5/68 (7.4)	3/37 (8.1)	6/74 (8.1)	4/44 (9.1)
Level 2 (<1)	0/68 (0)	0/37 (0)	0/74 (0)	0/44 (0)
Level 3 (<0.5)	0/68 (0)	0/37 (0)	0/74 (0)	0/44 (0)
Eosinophils, high (10^3 cells/µL)				
Level 1 (>0.65)	1/69 (1.4)	1/37 (2.7)	4/74 (5.4)	1/44 (2.3)
Level 2 (>1.5)	1/69 (1.4)	0/37 (0)	1/74 (1.4)	0/44 (0)
Level 3 (>5)	0/69 (0)	0/37 (0)	0/74 (0)	0/44 (0)

Source: adlb.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during OCARINA I.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during OCARINA I, either in dose escalation phase or in dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Threshold levels 1, 2, and 3, as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is up to 3 years.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: dec., decrease; inc., increase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous; WBC, white blood cells

Table 110 presents the results of liver biochemistry analyte outlier analyses for Study CN41144. Among subjects who received at least one dose of SC OCR 920 mg, none experienced hyperbilirubinemia, transaminitis, or ALP elevations meeting prespecified thresholds. A few OCR-naive subjects who received at least one dose of SC OCR 1200 mg experienced ALT elevation >3 ×ULN (n=1; Subject (b) (6)) and total bilirubin elevation >1.5 ×ULN (n=2; Subjects (b) (6)) and >2 ×ULN (n=1; Subject (b) (6)). Additionally, Subject (b) (6) experienced ALT elevation 3 ×ULN and is discussed below in the context of Table 111. These results should be interpreted with caution, as the sample size was small, several subjects (n=112) were exposed to both dose levels, and several subjects were also exposed to IV OCR prior to and during Study CN41144.

Table 110. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 1200 mg	
	Group A N=79	Group B N=39	Group A N=80	Group B N=45
Laboratory Parameter	**n/N_w (%)**	**n/N_w (%)**	**n/N_w (%)**	**n/N_w (%)**
Alkaline phosphatase, high (U/L)				
Level 1 (>1.5× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 2 (>2× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 3 (>3× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Alanine aminotransferase, high (U/L)				
Level 1 (>3× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	1/45 (2.2)
Level 2 (>5× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 3 (>10× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Aspartate aminotransferase, high (U/L)				
Level 1 (>3× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 2 (>5× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Level 3 (>10× ULN)	0/77 (0)	0/39 (0)	0/80 (0)	0/45 (0)
Bilirubin, total, high (mg/dL)				
Level 1 (>1.5× ULN)	0/77 (0)	0/38 (0)	0/80 (0)	2/45 (4.4)
Level 2 (>2× ULN)	0/77 (0)	0/38 (0)	0/80 (0)	1/45 (2.2)
Level 3 (>3× ULN)	0/77 (0)	0/38 (0)	0/80 (0)	0/45 (0)

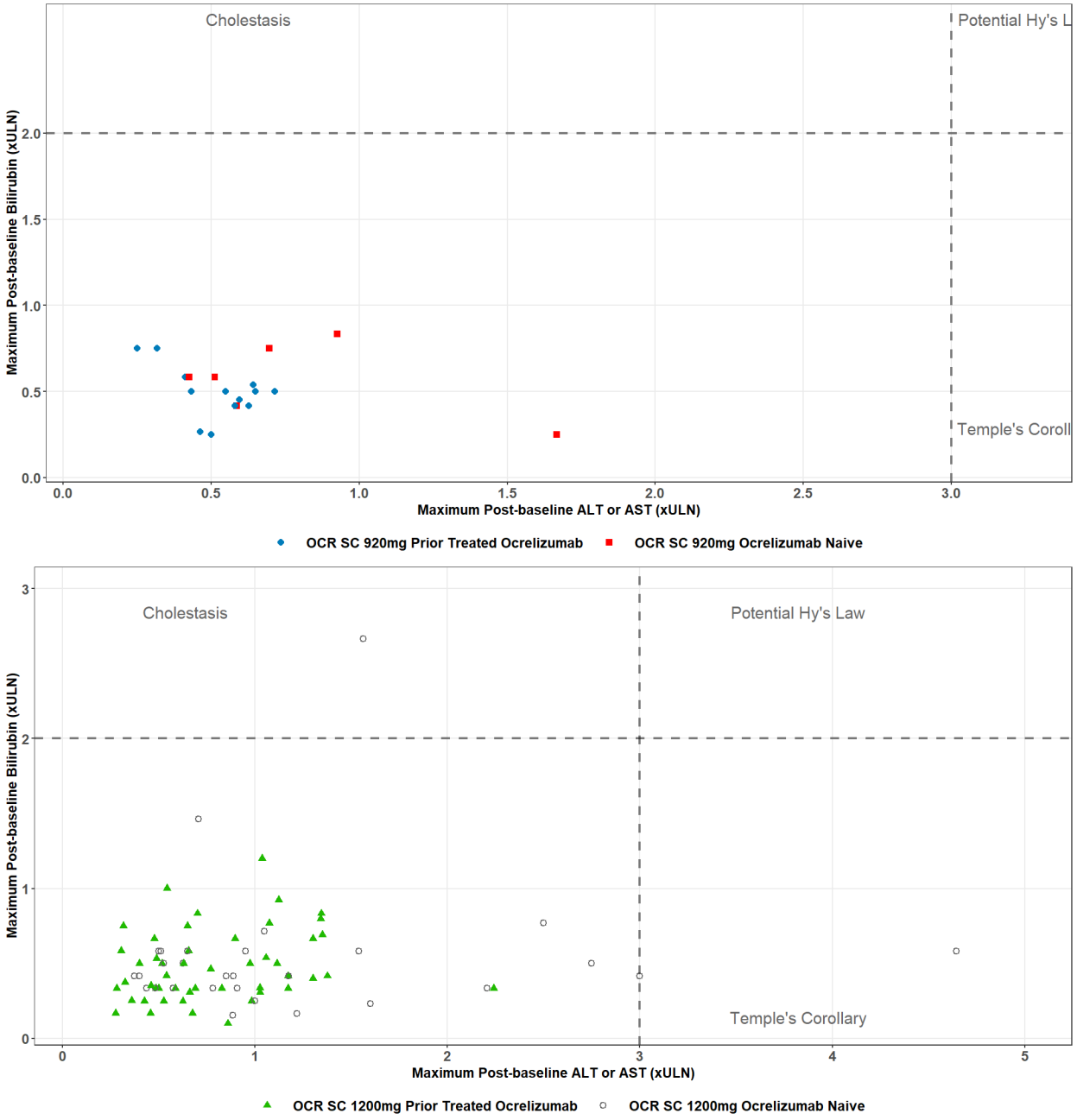
Source: adlb.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during OCARINA I.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during OCARINA I, either in dose escalation phase or in dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
Threshold levels 1, 2, and 3, as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is up to 3 years.
For specific evaluation of drug-induced liver injury (DILI), see Figure 28 "Cholestatic Drug-Induced Liver Injury Screening Plot..." and Table 111 "Subjects in Each Quadrant for Cholestatic DILI Screening Plot..."
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: DILI, drug-induced liver injury; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous; ULN, upper limit of normal

Figure 28 shows a screening assessment for potential cases of serious DILI. There were no potential Hy's Law cases. However, as shown in Table 111, there were one potential case of cholestatic DILI (total bilirubin elevation >2× ULN) and two potential cases meeting Temple's corollary (AST or ALT elevation >3×ULN) among OCR-naive subjects who received at least one dose of SC OCR 1200 mg.

- Subject (b) (6), an OCR-naive 31-year-old woman who received at least one dose of SC OCR 1200 mg, experienced ALT elevation to 4.6×ULN on Study Day 326 with slight AST elevation to 84 U/L (reference range 0 to 31.9 U/L), and normal total bilirubin and ALP levels. Of note, this subject's baseline ALT levels were above the ULN at 52 U/L (reference range 0 to 31 U/L). A TEAE of ALT increase was reported for this subject with a start date of (b) (6) (Study Day 3). This TEAE was ongoing at the time of data cutoff.
- Subject (b) (6), an OCR-naive 43-year-old woman who received at least one dose of SC OCR 1200 mg, experienced ALT elevation to 3×ULN on Study Day 7 with slight AST elevation to 49 U/L (reference range 0 to 40 U/L), and normal total bilirubin and ALP levels. Of note, this subject's baseline ALT levels were above the ULN at 84 U/L (reference range 0 to 32 U/L). A TEAE of fatigue was reported on Study Day 4 ((b) (6)), which resolved on Study Day 28 ((b) (6)).
- Subject (b) (6), an OCR-naive 38-year-old woman who received at least one dose of SC OCR 1200 mg, experienced total bilirubin elevation to 2.0×ULN on Study Day 8, to 1.6x ULN on Study Day 11, to 2.7×ULN on Study Day 15, and to 2.1×ULN on Study Day 29. ALT, AST, and ALP levels remained within normal limits. Of note, this subject's baseline total bilirubin levels were above the ULN at 22.2 µmol/L (reference range 1.71 to 20.52 µmol/L). A TEAE of fatigue was reported on Study Day 5 ((b) (6)), which resolved on Study Day 22 ((b) (6)). A TEAE of headache was reported on Study Day 7 ((b) (6)), which resolved on the same day.

  These transaminase and total bilirubin elevations occurred in isolation without elevation in other liver biochemistry analytes. Although these outliers only occurred in OCR-naive subjects who received at least one dose of SC OCR 1200 mg, the subjects who experienced these abnormalities had baseline abnormal values for the respective analyte and in all cases the laboratory abnormality resolved or improved despite ongoing treatment with study drug.

Figure 28. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study CN41144



Source: adlb.xpt; Software: R.
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 (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3× ULN, and ALP less than 2× ULN (note ALP values are not circled).
All subjects with at least one postbaseline ALT or AST and bilirubin are plotted. The within-30 days analysis window rule does not apply to cholestatic DILI and Temple's Corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; OCR, ocrelizumab; SC, subcutaneous; ULN, upper limit of normal

Table 111. Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study CN41144

	SC OCR 920 mg		SC OCR 200 mg	
Quadrant	Group A N=79 n/N_w (%)	Group B N=39 n/N_w (%)	Group A N=80 n/N_w (%)	Group B N=45 n/N_w (%)
Potential Hy's Law (right upper)	0/77 (0)	0/38 (0)	0/80 (0)	0/45 (0)
Cholestasis (left upper)	0/77 (0)	0/38 (0)	0/80 (0)	1/45 (2.2)
Temple's Corollary (right lower)	0/77 (0)	0/38 (0)	0/80 (0)	2/45 (4.4)
Total	0/77 (0)	0/38 (0)	0/80 (0)	3/45 (6.7)

Source: adlb.xpt; Software: R.
SC OCR 920 mg refers to any subject who received at least one dose of 920 mg subcutaneously during OCARINA I.
SC OCR 1200 mg refers to any subject who received at least one dose of 1200 mg subcutaneously during OCARINA I, either in dose escalation phase or in dose continuation phase prior to the decision to use 920 mg as the equivalent subcutaneous dose.
Group A refers to subjects who had been treated with Ocrevus (IV OCR) for at least one year prior to study enrollment.
Group B refers to OCR-naive subjects.
A total of 112 subjects received both ocrelizumab SC 920 mg and ocrelizumab SC 1200 mg over the course of Study CN41144 and are represented in both the SC OCR 920 mg and the SC OCR 1200 mg groups.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3× ULN, and ALP less than 2× ULN. The within-30 days analysis window rule does not apply to cholestatic DILI and Temple's Corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: DILI, drug-induced liver injury; IV, intravenous; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OCR, ocrelizumab; SC, subcutaneous

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Refer to Section 5.

21. Other Drug Development Considerations

Not applicable.

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

No clinical site inspections were conducted by the Office of Scientific Investigations for the studies reviewed with this BLA, as the primary endpoint was PK-based rather than clinical.

The Office of Study Integrity and Surveillance was consulted for analytical site inspections. The Office of Study Integrity and Surveillance determined that an on-site inspection was not needed for the analytical site due to the Remote Regulatory Assessment conducted in (b) (4). Refer to the Bioequivalence Establishment Inspection Report Review by Folaremi Adeyemo, dated March 20, 2024 (DARRTS ID: 5349828).

Therefore, the review team considers the bioanalytical data submitted under this BLA to be reliable.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (Table 112). 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 112. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	Not applicable.
1 INDICATIONS AND USAGE	No changes from Applicant's Draft PI.
2 DOSAGE AND ADMINISTRATION	In the *Important Administration Information* subsection (2.1): • Information that was proposed under the (b) (4) subsection was relocated to this new subsection to highlight the importance of the information. • The administration instructions were revised from stating that Ocrevus Zunovo should be administered (b) (4) to "by a healthcare professional" to clarify that the drug is not intended for patient administration. In the *Assessments Prior to First Dose of Ocrevus Zunovo* subsection (2.2): • The recommendation to consult immunology experts before initiating treatment was revised from stating '(b) (4) to "with ocrelizumab" to account for patients who may be switching from ocrelizumab administered intravenously to Ocrevus Zunovo who have already received consultations from immunology experts. In the *Assessments and Premedication Prior to Every Dose* subsection (2.3): • The subsection title was revised to better reflect the content of the subsection. • The timing of the recommended premedication before administration of Ocrevus Zunovo was revised from (b) (4) to "at least 30 minutes prior to" to be more specific and to align with the study protocols.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	In the *Recommended Dosage* subsection (2.4): • The proposed [(b) (4)] " was deleted to mitigate medication errors. The following administration statement was relocated [(b) (4)] • The proposed statement that [(b) (4)] was deleted as this instruction is not necessary for Ocrevus Zunovo. • The proposed post-injection monitoring was revised [(b) (4)] because of 1) the case of Grade 2 systemic injection reaction after the patient's third injection, 2) concerns related to comprehensive characterization of injection reactions with Ocrevus Zunovo, and 3) the inadequacy of the safety database for Ocrevus Zunovo to support conclusions that monitoring subsequent injections is not needed. The duration of recommended monitoring after the initial dose (i.e., for at least one hour) was not revised; the duration of the monitoring after subsequent injections was added as "at least 15 minutes." In the *Delayed or Missed Doses* subsection (2.5), there were no major changes from the Applicant's Draft PI. In the *Preparation and Administration* subsection (2.6): • In the sentence regarding inspecting the vial, the clause "whenever solution and container permit" was added per 21 CFR 201.57(c)(3)(iv). • The term [(b) (4)]" was deleted as the subsection already includes a statement that the product should not be diluted. In addition, [(b) (4)], which the labeling must not be per 21 CFR 201.56(a)(2). • For clarity, the phrase "at or below 25°C (77°F)" was added to the instructions to allow the drug to acclimate to room temperature before administration. • Additional organizational and editorial revisions were made.
4 CONTRAINDICATIONS	No major changes from Applicant's Draft PI.
5 WARNINGS AND PRECAUTIONS	In the *Injection Reactions* subsection (5.1): • The incidence of injection reactions that occurred with the first injection (i.e., 49%) was included. This incidence [(b) (4)] includes the preferred terms injection site erythema and injection site warmth in addition to injection related reaction and injection site reaction. • Information as added from the Ocrevus PI regarding infusion reactions seen in the clinical trials. • The premedication and post-injection monitoring recommendations were revised; see comments above under Dosage and Administration.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
6 ADVERSE REACTIONS	In the *Infections* subsection (5.2): • Information was added from the Ocrevus PI regarding serious, including life-threatening or fatal, bacterial, viral, parasitic, and fungal infections reported in patients receiving ocrelizumab and other anti-CD20 B-cell depleting therapies. In subsections 5.3 through 5.6 there were no major changes from the Applicant's Draft PI. In the *Clinical Trials Experience* subsection (6.1): • Because the controlled efficacy data and main support for the treatment of multiple sclerosis is from the ocrelizumab intravenous (IV) studies, the presentation of the safety data in this subsection was revised to present the active-controlled and placebo-controlled ocrelizumab safety data first, followed by the open-label Ocrevus Zunovo safety information. • The information regarding (b) (4) was removed. (b) (4) (b) (4) • Information regarding frequency and severity of local and systemic injection reactions for subsequent injections (i.e., after the first injection) was added based on the 120-Day Safety Update. In the *Postmarketing Experience* subsection (6.2): • The adverse reaction "babesiosis" was added to align with the approved labeling for IV ocrelizumab (Ocrevus).
7 DRUG INTERACTIONS	No major changes from Applicant's Draft PI.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	In the *Pregnancy* subsection (8.1): • The hyaluronidase safety margin for the doses given to animals compared to the human dose of Ocrevus Zunovo was revised (b) (4) • The standard statement regarding a lack of data was revised to not only include Ocrevus Zunovo, as proposed, but also ocrelizumab-containing products. In the *Lactation* subsection (8.2): • The standard statement regarding a lack of data was revised to not only include ocrelizumab, as proposed, but also hyaluronidase.
9 DRUG ABUSE AND DEPENDENCE	Not applicable.
10 OVERDOSAGE	Not applicable.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
12 CLINICAL PHARMACOLOGY	In the *Mechanism of Action* (12.1) and *Pharmacodynamics* (12.2) subsections there were no major changes from the Applicant's Draft PI. In the *Pharmacokinetics* subsection (12.3): • The (b) (4) was replaced with a qualitative summary. Per the guidance for industry, Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format (December 2016), (b) (4) are generally not included in labeling. In addition, noting that there are not clinically significant differences in pharmacokinetic exposures following administration of Ocrevus Zunovo compared to IV ocrelizumab is more useful to the healthcare provider. • The inter-compartment clearance was revised (b) (4) to that of the subcutaneous route of administration from Ocrevus Zunovo (0.55 L/day). • The terminal elimination half-life was revised (b) (4) to that of the subcutaneous route of administration from Ocrevus Zunovo (20 days). In the *Immunogenicity* subsection (12.6): • The information pertaining to (b) (4) was removed (b) (4)
13 NONCLINICAL TOXICOLOGY	The safety margins for hyaluronidase were revised (b) (4) .
14 CLINICAL STUDIES	(b) (4) the full text and graphics from the approved Ocrevus PI were included as the primary information pertaining to the efficacy for the treatment of multiple sclerosis. Information regarding the (b) (4) were removed (b) (4)
17 PATIENT COUNSELING INFORMATION	Revisions were made to align the section with the approved Ocrevus PI.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	• The acceptable nonproprietary name suffix, ocsq, was added in the appropriate locations. • The parenthetical after the mention of the hyaluronidase ingredient [i.e., (b) (4) was revised to "human recombinant" to align with the USAN adopted name. • The inactive ingredient list was revised using established names per the USP/NF monographs titles for trehalose, methionine, and sodium acetate. The inactive ingredient amounts were calculated per the USP monograph definition for trehalose and sodium acetate. • The inactive ingredients were revised to be presented in alphabetical order per USP recommendations *(see USP General Chapters <1091>Labeling of Inactive Ingredients*). • The (b) (4) was removed to avoid potential misinterpretation (b) (4) • The statement regarding storage without refrigeration was revised for readability and clarity.

Source: Applicant proposed Prescribing Information, submitted 11/10/2023, and amended 6/7/2024.
[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 finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): AUC, area under the concentration-time curve; AUC_{w1-12},area under the concentration-time curve over the first 12 weeks; IV, intravenous; NF, National Formulary; PI, Prescribing Information; USAN, United States Adopted Names; USP, United States Pharmacopeia

23.1. Approved Labeling Types

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

- PI
- Medication Guide
- Container
- Carton

24. Postmarketing Requirements and Commitments

Required Pediatric Assessments

This BLA for SC OCR involves a new active ingredient, a new dosage form, a new dosing regimen, and a new route of administration, which triggers the Pediatric Research Equity Act. As discussed in Section 8.3, the Applicant will be granted a deferral for pediatric studies in patients 10 to <18 years of age with relapsing-remitting multiple sclerosis. To fulfill Pediatric Research

Equity Act requirements, the following Pediatric Research Equity Act postmarketing requirements (PMRs) will be issued:

- Conduct an open-label study of the safety, tolerability, PK, and PD of ocrelizumab and hyaluronidase in pediatric patients with relapsing multiple sclerosis (RMS) at least 10 years and less than 17 years of age, weighing 40 kg or less. The objective of this study is to determine a dose of ocrelizumab and hyaluronidase that will result in PK and PD effects that are comparable to those of the dose administered to adult patients with RMS. Safety assessments will continue for at least two years after the last dose of ocrelizumab and hyaluronidase.
  - Draft Protocol Submission: 06/2027
  - Final Protocol Submission: 12/2027
  - Study Completion: 10/2031
  - Final Report Submission: 04/2032
- Conduct a pediatric assessment, with extrapolation to ocrelizumab and hyaluronidase, of the findings from Studies WN42086 (a randomized, double-blind, parallel-group study in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of Ocrevus [IV OCR] compared to an appropriate control for the treatment of RMS) and WA39085 (an open-label study of the safety, tolerability, PK, and PD of ocrelizumab in pediatric patients), which are studies intended to fulfill PMR 3194-14 for Ocrevus (ocrelizumab).
  - Draft Protocol Submission: 06/2027
  - Final Protocol Submission: 12/2027
  - Study Completion: 10/2031
  - Final Report Submission: 04/2032

Injection-Related Reactions

As discussed in Section 7.7.1, the characterization of TEAEs of injection-related reactions in Study CN42097 was not sufficiently detailed to allow for comprehensive characterization of the risk profile (i.e., signs and symptoms) of injection-related reactions that occurred with SC OCR. Though this issue did not preclude approval, it was determined that, should approval be granted, a PMR would be issued under section 505(o)(3) to evaluate the incidence, clinical features, and severity of injection-related reactions to enable a detailed characterization of local and systemic injection-related reactions that can occur with SC OCR. Refer to Section 7.7.1 (Injection-Related Reactions) for additional details. The following PMR will be issued:

- Conduct an observational, single-arm safety study to assess the risk of injection-related reactions in patients treated with subcutaneously-administered ocrelizumab. The study should evaluate the incidence, clinical features, and severity of injection-related reactions to enable a detailed characterization of local and systemic injection-related reactions that can occur with subcutaneously-administered ocrelizumab. The study should involve monitoring subjects for at least two years following subcutaneously-administered ocrelizumab treatment initiation.
  - Draft Protocol Submission: 02/2025
  - Final Protocol Submission: 02/2026
  - Study Completion: 02/2030
  - Final Report Submission: 02/2031

Malignancy

Upon review of BLA 761053 for Ocrevus, a higher frequency of malignancies (breast cancer in particular) was observed among IV OCR-treated subjects, as compared to subjects treated with placebo or interferon-beta in the Phase 3 trials. As a result, PMR 3194-2 was issued to determine the incidence and mortality rates of breast cancer and all malignancies in patients exposed to Ocrevus; the study intended to fulfill this PMR is ongoing. Because the study intended to fulfill PMR 3194-2 is ongoing and the target follow-up time for exposed patients has not been met, the following malignancy PMR will also be issued under section 505(o)(3) for SC OCR, should approval be granted. Refer to Section 7.7.7 (Malignancy) for additional details regarding TEAEs of malignancy that occurred during the SC OCR development program.

- Conduct a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study should be followed for a minimum of five years or until death following their first exposure to ocrelizumab. The protocol must specify two appropriate populations to which the observed incidence and mortality rates will be compared.
  - Draft Protocol Submission: 01/2025
  - Final Protocol Submission: 01/2026
  - Study Completion: 11/2029
  - Final Report Submission: 11/2030

Pregnancy

Upon approval of BLA 761053 for Ocrevus, PMRs 3194-3 and 3194-4 were issued for a prospective pregnancy exposure registry and a pregnancy outcomes study of a different study design, respectively. The target sample size of pregnancy outcomes was reached, and the information pertaining to the pregnancy registry was removed from Sections 8.1 (Pregnancy) and 17 (Patient Counseling Information) of the PI, and from the Medication Guide for Ocrevus on June 21, 2024. Given the completion of the studies intended to fulfill PMRs 3194-3 and 3194-4, and because it would not be possible to independently evaluate the effects of ocrelizumab and hyaluronidase as part of a pregnancy outcomes study of SC OCR, it was determined that a PMR to evaluate pregnancy outcomes would not be issued for SC OCR.

Chemistry, Manufacturing, and Controls Postmarketing Commitment

The chemistry, manufacturing, and controls review team determined that the following Postmarketing Commitment would be issued for container closure system leachate studies.

- Perform real-time Ocrevus Zunovo drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC and trace metals at regular intervals through the end of shelf-life. The final results of this study and the toxicology risk evaluation for the levels of leachate detected in the drug product will be provided in the final study report to the BLA.
  - Final Report Submission: 03/2025

25. Financial Disclosure

Table 113. Covered Clinical Studies: CN42097, CN41144

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Study CN42097: 240; Study CN41144: 166		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
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: 3 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:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Guidance Documents

Guidance document *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995)

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

Guidance for industry *Financial Disclosure by Clinical Investigators* (November 2013)

Published Literature

Thompson, AJ, BL Banwell, F Barkhof, WM Carroll, T Coetzee, G Comi, J Correale, F Fazekas, M Filippi, MS Freedman, K Fujihara, SL Galetta, HP Hartung, L Kappos, FD Lublin, RA Marrie, AE Miller, DH Miller, X Montalban, EM Mowry, PS Sorensen, M Tintore, AL Traboulsee, M Trojano, BMJ Uitdehaag, S Vukusic, E Waubant, BG Weinshenker, SC Reingold, and JA Cohen, 2018, Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria, Lancet Neurol, 17(2):162-173.

DARRTS References

DARRTS ID: 5349828, 2024, Bioequivalence Establishment Inspection Report Review.

DARRTS ID: 3986651, 2016, OCREVUS Clinical Pharmacology Review (BLA 761053).

DARRTS ID: 5432001, 2024, BLA 761371 Executive Summary. Office of Biotechnology Products.

Approved Drug Labeling

Prescribing Information: OCREVUS - ocrelizumab injection. Genentech. 2024. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9da42362-3bb5-4b83-b4bb-b59fd4e55f0d.

Prescribing Information: HYLENEX RECOMBINANT - hyaluronidase injection, solution. Halozyme. 2024. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3023cc56-ed4b-4e87-b3a1-81b20943f658.

27. Review Team

Table 114. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Elaine Gettelman, PharmD, PhD
Nonclinical reviewer	Elizabeth Khoury, PhD
Nonclinical team leader	David Carbone, PhD
OCP reviewer(s)	Ramakrishna Samala, PhD
OCP team leader(s)	Gopichand Gottipati, PhD, Vishnu Sharma, PhD
Clinical reviewer	Daniela Pimentel Maldonado, MD, MSCR
Clinical team leader	Laura Baldassari, MD, MHS
Biometrics reviewer	Not applicable
Biometrics team leader	Not applicable
Associate director for labeling	Tracy Peters, PharmD
Cross-disciplinary team leader	Laura Baldassari, MD, MHS
Division director (pharm/tox)	Lois Freed, PhD
Division director (OCP)	Mehul Mehta, PhD
Division director (OB)	Not applicable
Division director (clinical)	Paul R. Lee, MD, PhD, MA
Designated signatory authority	Paul R. Lee, MD, PhD, MA

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

Table 115. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Andrea George, PhD (Acting Team Leader) Riley Myers, PhD (Acting Team Leader) Milos Dokmanovic, PhD Zhong Li, PhD, SPQA Liming Lu, PharmD
Microbiology	Maxwell Van Tassell, PhD Jeanne Fringer, PhD Esther Broner, PhD
Emerging Technology Team	Scott Krull, PhD Daniel Willett, PhD
DMPP	Marcia Williams, PhD (Team Leader) Nyedra Booker, PharmD, MPH
OPDP	Samuel Fasanmi, PharmD
OSI	Not applicable
OSE/DEPI	Catherine Callahan, PhD, MA (Team Leader) Danielle Abraham, PhD, MPH
OSE/DMEPA	Stephanie DeGraw, PharmD (Team Leader) Rina Patel, PharmD, BCPS
OSE/DPV	Allen Brinker, MD (Team Leader) Tiffany Kim, PharmD, BCPS
OSE/DRISK	Jacqueline Sheppard, PharmD (Team Leader) May Chan-Liston, PharmD, MPH
Other	Alice Hughes, MD Christine Phipps, PharmD
Clinical Data Scientists	Ling Cao, PhD (Team Leader) Elizabeth Booth, PharmD
Medical Editors	Katherine Brophy Allison Cruz Shira Klapper

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

26.1. Reviewer Signatures

Table 27-116 Signatures of Reviewers

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	Gopichand Gottipati OCP DNP	Sections: Clinical Pharmacology	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Gopichand Gottipati**			**Digitally signed by Gopichand Gottipati** **Date: 9/10/2024 5:05 PM EDT** **GUID: 202491021546**	

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 for Labeling Discipline Primary Reviewer	Tracy Peters ON DNI	Sections: 23	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: 9/10/2024 5:34 PM EDT** **GUID: 2024910213452**	

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 for Labeling Discipline Secondary Reviewer	Tracy Peters ON DNI	Sections: 23	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: 9/10/2024 5:35 PM EDT
GUID: 2024910213558

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: 9, 24.2	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: 9/10/2024 6:02 PM EDT
GUID: 20249102228

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: 9, 24.2	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: 9/10/2024 9:39 PM EDT** **GUID: 202491113921**	

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, 13.1, 13.2	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: 9/11/2024 7:23 AM EDT** **GUID: 2024911112322**	

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	Kristen Haslam ORO DRON	Sections: 12. Summary of Regulatory History	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Kristen Haslam**			**Digitally signed by Kristen Haslam** **Sign on behalf of Elaine Gettelman** **Date: 9/11/2024 7:41 AM EDT** **GUID: 2024911114135**	

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	Vishnu Sharma OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Vishnu Sharma**			**Digitally signed by Vishnu Sharma** **Date: 9/11/2024 8:38 AM EDT** **GUID: 2024911112387**	

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, 13.1, 13.2	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: 9/11/2024 9:39 AM EDT** **GUID: 2024911133912**	

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	Sandra Folkendt ORO DRON	Sections: 12. Summary of Regulatory History	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sandra Folkendt			**Digitally signed by Sandra Folkendt** **Date: 9/11/2024 10:10 AM EDT** **GUID: 2024911141032**	

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, 6.1, 6.3.1, 8.1, 8.2, and 14	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: 9/11/2024 11:21 AM EDT** **GUID: 2024911152154**	

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, 2.1, 3, 3.1, 3,2, 3.3, 4, 6.2, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 8.3, 8.4, 10, 15, 16, 17, 24, 25	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: 9/11/2024 12:17 PM EDT** **GUID: 202491116172**	

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	Lois Freed ON DPTN	Sections: 5.1, 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lois Freed			**Digitally signed by Lois Freed** **Date: 9/11/2024 3:42 PM EDT** **GUID: 2024911194237**	

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 DN2	Sections: 1-4, 6-12, 15-21, 23-26	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: 9/11/2024 3:56 PM EDT** **GUID: 2024911195641**	

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
09/13/2024 09:19:09 AM

PAUL R LEE
09/13/2024 09:27:11 AM