25 April 2024
EMA/CHMP/171408/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ocrevus

International non-proprietary name: Ocrelizumab

Procedure No. EMEA/H/C/004043/X/0039

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ARR	Annualized Relapse Rate
AUC	Area under the curve
CCOD	Clinical cutoff date
CI	Confidence interval
Cmax	Maximum serum concentration
CSR	Clinical Study Report
CTD	Common Technical Document
DMT	Disease-modifying treatment
ECLA	Electrochemiluminescent assay
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FPI	First patient in
GMR	Geometric mean ratio
HCPs	Healthcare professionals
HPQ	Healthcare Professional Questionnaire
IBD	International Birth Date
IR	Injection reaction
IRR	Infusion related reaction
IV	Intravenous
LIR	Local injection reaction
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	Pharmacodynamic
PK	Pharmacokinetic
PPK	Population PK
PPMS	Primary progressive multiple sclerosis
PPQ	Patient Preference Questionnaire
PRO	Patient-reported outcome
PY	Patient years
RMS	Relapsing forms of multiple sclerosis
SAE	Serious adverse event
SC	Subcutaneous

SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SFU	Safety follow-up
SIR	Systemic injection reaction
SOC	System Organ Class
T1Gd	T1 gadolinium-enhancing
TASQ-IV	Treatment Administration Satisfaction Questionnaire for ocrelizumab IV
TASQ-SC	Treatment Administration Satisfaction Questionnaire for ocrelizumab SC
USA	United States of America

1. Background information on the procedure

1.1 Submission of the dossier

Roche Registration GmbH submitted on 8 September 2023 extensions of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (solution for injection) associated with a new strength (920 mg) and a new route of administration (subcutaneous use). The RMP (version 9.1) is updated accordingly.

The Marketing Authorisation Holder (MAH) applied for an addition of a new strength, addition of a new pharmaceutical form and an addition of a new route of administration.

The MAH applied for the following indication for Ocrevus 920mg solution for injection:

Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features, and for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Furthermore, the PI is brought in line with the latest QRD template version.

1.2 Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, 2 point (c) - Extensions of marketing authorisations.

1.3 Information on Paediatric requirements

N/A

1.4 Information relating to orphan market exclusivity

1.4.1 Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5 Scientific advice

The MAH received Scientific advice from the CHMP on 22 April 2022 (EMA/SA/0000075948). The Scientific advice pertained to quality, non-clinical and clinical aspects.

1.6 Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: N/A

The application was received by the EMA on	8 September 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 December 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 January 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 March 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ocrevus on	25 April 2024

2. Scientific discussion

2.1 Problem statement

Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20-expressing B cells, while preserving the capacity of B cell reconstitution and preexisting humoral immunity. Ocrelizumab IV 600 mg (Ocrevus®) was first granted marketing approval in the Unites States of America (USA) on 28 March 2017. It was subsequently approved in the European Union (EU) on 8 January 2018 and is currently approved in over 100 countries worldwide.

Ocrelizumab is approved to be administered by IV infusion every 6 months. The initial 600 mg dose is administered as two separate IV infusions: first as a 300 mg infusion, followed by a second 300 mg infusion 2 weeks later. Subsequent doses of ocrelizumab are administered as a single 600 mg IV infusion that lasts from 2 to 3.5 hours every 6 months.

To provide an additional delivery option of ocrelizumab, the Applicant has developed a subcutaneous (SC) formulation of ocrelizumab. The SC formulation is a combination of ocrelizumab with rHuPH20, human recombinant hyaluronidase, which is approved to improve dispersion of large SC injection volumes (i.e., it functions as a permeation enhancer). The SC formulation of ocrelizumab is to be administered as a single 10-minute SC injection every 6 months.

2.1.1 Disease or condition

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterised by inflammation, demyelination, and oligodendrocyte and neuronal loss.

In the EU, ocrelizumab IV is indicated for:

- Treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.
- Treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

2.1.2 Epidemiology

MS is the most common progressive neurological disease of adults worldwide [Collaborators 2019]. The disease usually begins between the ages of 20 and 40 and is twice as common in women as in men. There is increasing incidence and prevalence of MS in both developed and developing countries.

2.1.3 Aetiology and pathogenesis

The cause of MS is unknown but the most striking pathogenic mechanism in MS is the immune system's attack and destruction of the body's own myelin sheath. Many cells and molecules of the immune system—likely unleashed by T-cell activation—participate in demyelination. The entire cascade of immune system events eventually culminates in myelin destruction. The key features of this cascade are not fully understood, including the precise ordering of events, the antigens targeted by T cells, and the contributions of B lymphocytes, or B cells, and other cells of the immune system.

2.1.4 Clinical presentation, diagnosis

The majority of MS patients (approximately 85%) present with subacute relapses or attacks, with symptoms and signs referable to the CNS. The relapse/attack is followed by a complete or partial remission/return to normal, only to be followed at a future date by another relapse usually in a different CNS location, thus presenting as RRMS. The first such attack is referred to as a clinically isolated syndrome. Some patients (approximately 15%) present with a gradually progressive course, without an initial well-defined attack. This is termed primary progressive MS. Most of these patients present with features of a spinal cord syndrome.

The diagnostic criteria for MS have been continuously evolved and include MRI with intravenous (IV) contrast agent containing gadolinium, lumbar puncture for cerebrospinal fluid examination, physical examinations, and electrophysiological tests.

2.1.5 Management

MS management includes treatment of acute relapses with high-dose steroids, DMTs, including injectables like interferons, glatiramer acetate, oral DMTs (teriflunomide, dimethyl fumarate, fingolimod, ozanimod, siponimod, cladribine), and infusions (e.g., natalizumab, alemtuzumab, ocrelizumab, mitoxantrone), as well as symptomatic treatments for managing MS symptoms (e.g., bladder problems, fatigue, spasticity).

2.2 About the product

Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20-expressing B cells, while preserving the capacity of B cell reconstitution and preexisting humoral immunity. Ocrelizumab IV 600 mg (Ocrevus®) was first granted marketing approval in the Unites States of America (USA) on 28 March 2017. It was subsequently approved in the European Union (EU) on 8 January 2018 and is currently approved in over 100 countries worldwide.

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2.3 Type of Application and aspects on development

The development programme/compliance with guidance/scientific advice

The purpose of this application is to seek marketing approval of the ocrelizumab SC formulation for the approved ocrelizumab IV indications based on data from the pivotal Phase III Study CN42097 (thereafter referred to as OCARINA II) and the supportive Phase Ib Study CN41144 (thereafter referred to as OCARINA I).

General comments on compliance with GMP, GLP, GCP

GMP

No issues have been identified during assessment of the Ocrevus dossier, which call for a pre-approval inspection.

GLP

No issues with GLP status for the submitted studies were identified during the assessment of the Ocrevus X-39 dossier.

GCP

The Applicant claims that OCARINA II and OCARINA I were conducted in accordance with the principles of Good Clinical Practice, the principles of the Declaration of Helsinki, and local laws and regulations of the countries in which the studies were conducted. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved each of the studies.

No audits were conducted in any of the two studies.

2.4 Quality aspects

2.4.1 Introduction

A new ocrelizumab formulation has been developed to enable subcutaneous administration (ocrelizumab SC), which offers a faster administration time and less invasive route of administration compared to intravenous (IV) infusions.

The ocrelizumab SC finished product is provided as a sterile, clear to slightly opalescent, and colourless to pale brown solution for subcutaneous injection with no preservatives. Each 50 mL single-dose vial contains 920 mg/23 mL (nominal) of ocrelizumab as active substance.

Other ingredients are sodium acetate (sodium acetate trihydrate and glacial acetic acid), methionine, trehalose, polysorbate 20, recombinant human hyaluronidase (rHuPH20) and water for injections.

The active substance used for production of ocrelizumab SC finished product is the same as that approved for ocrelizumab IV finished product. Therefore, where relevant, product and process knowledge from ocrelizumab IV are applied to the ocrelizumab SC Module 3.2 content.

2.4.2 Active Substance

2.4.2.1 *General Information*

Ocrelizumab is a recombinant, humanized, glycosylated, monoclonal IgG1 antibody with a H2L2 polypeptide structure that consists of two identical heavy chains of 452 amino acids and two identical light chains of 213 amino acids and targets CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Ocrelizumab selectively targets and depletes CD20-expressing B cells, while preserving the capacity of B-cell reconstitution and preexisting humoral immunity. The molecular mass is approximately 148 kDa.

2.4.2.2 Manufacture, process controls and characterisation

The active substance process supplying the ocrelizumab SC finished product is the approved ocrelizumab active substance process that also supplies the commercial ocrelizumab IV finished product; thus, the active substance process has been validated to deliver ocrelizumab consistently with the expected product quality as per prior approval.

Due to differences in patient dosing strategy, ocrelizumab SC-specific risk assessments were performed to demonstrate the relevance of the completed ocrelizumab process validation studies where dose-dependent criteria were applied.

Clearance of raw materials

The raw material clearance evaluation for the approved Ocrelizumab IV active substance process is considered applicable to Ocrelizumab SC.

Leachables

The original leachables testing performed for the approved ocrelizumab active substance process study supports ocrelizumab SC.

Use and Reuse of Purification Resins and Membranes

The data supporting reuse, regeneration, and sanitization of resins and membranes from the approved ocrelizumab active substance process is directly applicable to ocrelizumab SC.

Characterisation

Critical quality attributes (CQAs) for ocrelizumab have been previously identified as part of the initial marketing application for ocrelizumab IV. However, all ocrelizumab quality attribute (QA) classifications were reassessed to incorporate considerations specific to the subcutaneous route of administration. The reassessment concludes that the majority of the QA classifications remain unchanged The categories of potential impurities and control of impurities for ocrelizumab SC are the same as for ocrelizumab IV.

2.4.2.3 Specification, analytical procedures, reference standards, batch analysis, and container closure

The release and end-of-shelf life specification of active substance, the analytical procedures used to test active substance for release and/or stability, the validation of those analytical procedures, and the justification of specification for the active substance used to manufacture ocrelizumab SC are the same as for ocrelizumab IV.

Four ocrelizumab active substance batches manufactured were utilized for the ocrelizumab SC finished product process performance qualification (PPQ) campaign. General information and batch release data for these active substance batches have been provided.

The same reference standard, as previously approved for ocrelizumab IV, is used for active substance and finished product testing. Also, the active substance container closure system is the same as for ocrelizumab IV.

2.4.2.4 Stability

As the active substance is stored and assigned the same expiry period irrespective of whether it is used to produce ocrelizumab IV or ocrelizumab SC, all of the previously performed stability studies are directly applicable.

The post-approval active substance stability protocol and stability commitment remain unchanged.

2.4.3 Finished Medicinal Product

2.4.3.1 Description of the product and Pharmaceutical Development

Ocrelizumab SC finished product is presented in 50 mL vials as a sterile, single-dose, clear to slightly opalescent, and colorless to pale brown solution with no preservatives. Each single-dose vial contains 920 mg/23 mL (nominal) of ocrelizumab. rHuPH20 is the permeation enhancer to increase the dispersion and absorption of large drug volumes administered via the SC route.

The finished product is formulated as 40 mg/mL ocrelizumab SC with the following excipients: sodium acetate (sodium acetate trihydrate and glacial acetic acid), methionine, trehalose, polysorbate 20, recombinant human hyaluronidase (rHuPH20) and water for injections. The container closure system consists of a Type I borosilicate glass vial with a fluororesin-laminated rubber stopper and crimped with an aluminum seal fitted with a plastic flip-off cap.

Formulation development

A summary of the Ocrelizumab SC formulation development has been provided.

For physicochemical characteristics of ocrelizumab, reference to the already approved (ocrelizumab IV) sections S.1.3 and S.3.1 was made which is accepted as the active substance used in the approved IV finished product is the same as that used in ocrelizumab SC finished product.

The excipients used in ocrelizumab SC finished product are sodium acetate (sodium acetate trihydrate and glacial acetic acid), methionine, trehalose, polysorbate, rHuPH20 and water for injections. Compatibility with these excipients and ocrelizumab was demonstrated by long-term stability data for the finished product and formulation development studies. The IV and SC finished product stability is, overall, highly similar.

The finished product does not contain any overages.

The finished product is intended to be administered manually using a syringe attached to a subcutaneous infusion set (e.g., winged/butterfly) with or without a syringe pump. The finished product is stable when stored at the recommended storage temperature which is highly similar to the commercial ocrelizumab IV finished product. Potency data indicate that the finished product maintains biological activity throughout the recommended storage duration at the recommended temperature.

Manufacturing process development

The finished product manufacturing process development program was designed to ensure that robust and aseptic processes are in place across all steps, starting from the production of initial clinical batches to commercial manufacturing. Process design studies that support all acceptable manufacturing process parameters are described in Module 3.2, Section P.3.5 *Process Design Studies.* The differences in the manufacturing processes of the commercial product and clinical trial material are considered adequately explained and discussed.

Finished Product comparability

The comparability assessment included quantitative and qualitative comparisons of release and stability data of ocrelizumab SC finished product manufactured using the to-be-commercialized process, against the clinical finished product manufactured . Both quantitative and qualitative comparisons demonstrate that the product quality is highly similar between the clinical and commercial finished products.

The applicant intends to implement a Real-time release testing (RTRT) approach for finished product manufacturing. Real-time release testing is a component of the overall control strategy to confirm that the finished product is acceptable for release, and ensure suitable quality of the finished product based on information collected during manufacture. The Applicant’s applications of RTRT are intended to accelerate availability of patient supply by reducing the time between completion of manufacture and the release of the product.

In conclusion, the Applicant's understanding of the process and the product from process characterisation and validation, the parallel testing data, the RTRT risk assessment, and the pharmaceutical quality system altogether support the implementation of the proposed RTRT approach.

Container closure system

The initial clinical finished product container closure consists of a 20 mL vial and the subsequent clinical and commercial finished product container closure system consists of a 50 mL vial. Both are Type I borosilicate glass vials with the same glass composition and sourced from the same manufacturer, stoppered with a 20 mm fluororesin-laminated rubber stopper and crimped with a 20 mm aluminum seal with a plastic flip-off cap.

These components are considered suitable for packaging sterile liquid products and comply with relevant pharmacopeial requirements (USP/Ph. Eur./JP).

The results of the extractable studies performed with commercial stoppers and vials and the results of the leachable studies performed with the finished product demonstrate that the primary packaging components are suitable and safe for use with the finished product. The ocrelizumab SC finished product is compatible with the primary packaging components in the container closure system, as demonstrated by long-term stability data for the finished product.

In-use stability

The compatibility of the finished product with syringes and infusion sets has been demonstrated. Stability and compatibility studies are conducted to confirm the physicochemical stability of the solution for injection under the recommended in-use conditions.

Once transferred aseptically from the vial to the disposable syringe, the ocrelizumab SC finished product solution is physico-chemically stable for 30 days when stored at 2°C - 8°C and protected from light and for an additional 8 hours when stored at 9°C - 30°C in diffuse daylight. Ocrelizumab SC finished product does not contain any antimicrobial preservative; therefore, sterility of the solution must be ensured during in-use handling by maintaining appropriate aseptic conditions.

2.4.3.2 Manufacture of the product and process controls

The name, address, and responsibility of each manufacturer, production site or facility involved in the manufacturing and testing has been provided.

Process parameters for finished product manufacturing were evaluated for their criticality with respect to predetermined quality attributes. The evaluated parameters cover the manufacturing process from thawed active substance to final vial inspection. The acceptable ranges defined for the CPPs and non-CPPs in the finished product manufacturing process are considered adequate.

The manufacturing process consists of thawing of active substance, compounding, filtration and filling.

Testing is performed on samples collected at specified points of the manufacturing process to assess process consistency, verify microbial control, and to ensure the finished product is acceptable for release.

Process validation/verification

Three consecutive PPQ batches were included that represent the full range of batch sizes for commercial manufacturing. The data from the PPQ batches showed that all CQAs met their acceptance criteria, all IPCs and validation samples met their acceptance criteria or action limits, respectively, all CPPs and non-CPPs were maintained within their acceptable ranges, and process performance was consistent between the PPQ batches. Results from the process design studies in combination with the PPQ campaign demonstrate that the finished product manufacturing process is robust and consistently yields finished product that meets the acceptance criteria. The ranges and values selected for the PPs are acceptable to support commercial manufacturing.

Altogether, the development and validation of the ocrelizumab SC process are built upon a comprehensive science- and risk-based approach. This incorporates process and product understanding

developed from ocrelizumab SC finished product-specific studies, and applicable commercial ocrelizumab IV studies. Platform knowledge gained from similar molecules and processes and together, these elements are part of an overall quality by design approach taken for the development of ocrelizumab SC.

2.4.3.3 Product specification, analytical procedures, batch analysis

The finished product specifications used for the release/stability testing are considered appropriate, including adequate tests for appearance, particles, pH, osmolality, identity, content, polysorbate 20 content, purity, potency/activity, endotoxin, sterility and container closure integrity.

Ocrelizumab SC finished product release and shelf-life acceptance criteria for CQAs that are intrinsic to the molecule (e.g., size and charge variants) are aligned with the acceptance criteria for ocrelizumab IV finished product. Overall, the specifications and justifications for the specifications for ocrelizumab SC finished product are considered comprehensive and adequate.

Analytical procedures

The analytical procedure for each test used to analyze ocrelizumab SC finished product is adequately described. The compendial analytical procedures (tests performed according to pharmacopoeia) do not deviate from their respective monographs and were adequately verified to be suitable for their intended use. All non-compendial analytical procedures are fully validated in accordance with ICH Q2(R1). Many analytical procedures used to test ocrelizumab SC samples are already used for testing commercial ocrelizumab IV at the same testing site. In light of the formulation differences between the proposed ocrelizumab SC compared to the commercial ocrelizumab IV, the methods have been validated or confirmed to be suitable for their intended use.

Reference materials

The same primary and secondary reference standards approved for commercial ocrelizumab active substance and ocrelizumab IV will be used for ocrelizumab SC, which is considered acceptable.

Batch analysis

All batch analysis results meet the specifications that were in effect at the time of testing and release for each batch. In addition, all available release data from the finished product batches produced during the PPQ campaign meet the commercial release specification acceptance criteria.

2.4.3.4 Stability of the product

The proposed shelf-life for ocrelizumab SC finished product is 24 months at 2°C-8°C, protected from light. The proposed shelf-life is based on available stability data from primary and supportive ocrelizumab SC batches. The stability of the commercial 30 mg/mL ocrelizumab IV finished product further supports the shelf life for 40 mg/mL ocrelizumab SC, since ocrelizumab IV and ocrelizumab SC are derived from the same ocrelizumab active substance.

Stability protocols for long-term stability study at 5°C and for accelerated stability study (25°C) have been provided.

In conclusion, the results from stability studies of ocrelizumab SC finished product demonstrate consistent stability behavior across the primary and supportive batches.

The Applicant commits further that after approval, at least one commercial finished product batch will be added to the stability monitoring program annually if production occurs during the calendar year. Deterioration of the distributed finished product will be reported to the Agency if observed during stability studies at the recommended long-term storage condition. Appropriate actions will be proposed according to applicable regulations, and the Applicant's internal procedures and quality management system.

Based on the stability data provided, the proposed shelf life of 24 months at 2°C-8°C, protected from light for the ocrelizumab finished product is found acceptable.

2.4.3.5 Adventitious agents

There are no changes to the adventitious agents safety evaluation. This section as approved in the MAA for ocrelizumab IV is applicable also for ocrelizumab SC.

2.4.4 Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.5 Non-clinical aspects

2.5.1 Introduction

A type II variation for Ocrevus 920 mg solution for injection for all currently authorized Ocrevus intravenous (IV) indications was submitted in 2023, to apply for a line extension for an SC formulation.

The nonclinical strategy to support this Line Extension Application of the Marketing Authorization for Ocrevus→EMEA/H/C/004043 for SC administration of ocrelizumab leverages the available comprehensive nonclinical data packages (including pharmacology, pharmacokinetics/toxicokinetics, and toxicology) for IV administration of ocrelizumab (refer to MAA EMEA-H-C-4043) and Hylenex→ recombinant (hyaluronidase human injection) (BLA 021859; Halozyme Therapeutics, Inc. [San Diego, California; US]).

In monkeys, SC administration was tested in a formulation similar to the IV formulation without co-administration of rHuPH20. To support the proposed clinical SC formulation with recombinant human hyaluronidase enzyme (also known as ENHANZE→ drug product [EDP] and hereafter referred to as rHuPH20 [EDP], additional local tolerance studies were conducted with this formulation in rats and minipigs.

2.5.2 Pharmacology

The in vitro and in vivo pharmacology of ocrelizumab has already been extensively characterised in the assessment of the IV formulation (MAA EMEA-H-C-4043). No new studies were therefore submitted for the pharmacology of ocrelizumab. A study on the pharmacology, pharmacokinetics and local tolerance in cynomolgus monkeys was included in the original submission (Study 05-0025-1466), where it was shown that the degree of B cell depletion was similar between SC and IV administration routes. The SC formulation used in the study was the same as the IV formulation and did not include co-administration with recombinant human hyaluronidase enzyme (rHuPH20). However, it is assumed that the pharmacological results for the formulation without rHuPH20 is transferable to the Ocrevus SC formulation under review.

2.5.3 Pharmacokinetics

The pharmacokinetics of ocrelizumab has already been extensively characterised in the assessment of the IV formulation (MAA EMEA-H-C-4043). No new studies were therefore submitted for the

pharmacokinetics of ocrelizumab. A study on the pharmacology, pharmacokinetics and local tolerance in monkeys was included in the original submission (Study 05-0025-1466). The SC formulation used in the study was the same as the IV formulation and recombinant human hyaluronidase enzyme (rHuPH20) was not co-administered in the study. Extensive ADA formation was observed in Study 05-0025-1466, as 15/18 animals developed ADA during the study across dose groups, resulting in an increased clearance of ocrelizumab (5 of 6 for SC 1 dose, 6 of 6 for SC split dose, and 4 of 6 for IV). The ADA levels in some of the recovery animals appeared to have affected the serum concentrations of ocrelizumab at terminal timepoints and, therefore, PK parameters were calculated after excluding data from these animals. ADA formation was also observed in the original dossier for the IV formulation, especially for the lower doses of ocrelizumab. No PK data is available for the effect of rHuPH20 on ocrelizumab in non-clinical species and how this may affect the absorption of ocrelizumab after SC administration. Thus, no comparison of PK profiles between the proposed clinical SC formulation and the authorized IV formulation has been provided by the Applicant. However, it is considered acceptable that no further PK characterization is performed in non-clinical species also taking the ADA formation into account in the animals, which is not transferable to humans.

2.5.4 Toxicology

The toxicity of ocrelizumab has been thoroughly investigated in nonclinical studies following IV administration (refer to MAA EMEA-H-C-4043). No new studies on systemic toxicities after single or repeat dosing as well as genotoxicity, carcinogenicity and reproductive toxicities for ocrelizumab SC have been conducted. New local tolerance studies in rats and minipigs for ocrelizumab SC have been conducted to bridge between the existing data for ocrelizumab IV and ocrelizumab SC and the studies are assessed below. While the PD/PK study in monkeys were performed on the IV formulation without co-administration of rHuPH20, new local tolerance studies in rats and minipigs were conducted with the proposed clinical SC formulation of ocrelizumab with rHuPH20.

No new standalone studies on recombinant human hyaluronidase enzyme (rHuPH20) have been conducted. rHuPH20 has been extensively characterized in mice and cynomolgus monkeys in previous procedures (e.g. Herceptin (containing trastuzumab)) with no relevant toxicological findings in the general toxicity studies (e.g. Hylenex→ BLA 021859 (Halozyme Therapeutics, Inc.)). Though no new assessment of rHuPH20 is included in this procedure, the SmPC is aligned with previously authorised products specifically concerning information on rHuPH20.

2.5.4.1 Toxicokinetic data

Tolerance and toxicokinetic data

Several local tolerance studies have been conducted with ocrelizumab; a study in monkeys at 150 mg/mL without co-administration of rHuPH20, as well as studies in rats and minipigs with the clinical SC formulation with rHuPH20.

Swelling and redness were observed at the injection sites of monkeys administered ocrelizumab subcutaneously, when ocrelizumab was administered at high doses without co-administration of rHuPH20 (Study 05-0025-1466). The severity and duration of the injection site swelling increased as the SC dose volume was increased, and swelling only resolved by day 6 and day 8 for groups dosed with 0.5 mL and 1 mL, respectively. Redness and swelling were accompanied with clinical findings of local inflammation. According to the original assessment report for Ocrevus IV (MAA EMEA-H-C-4043), the SC formulation was discontinued at the time of assessment due to the severity of the local tolerance findings.

Based on tissue cross-reactivity and pharmacologic relevance, the cynomolgus monkey, a binding species, was determined to be the only appropriate species for use in the nonclinical toxicology program of ocrelizumab in the original procedure (MAA EMEA-H-C-4043). In the present procedure, rats have been used as an alternative relevant toxicological species for investigating local tolerance instead of monkeys. This is justified by the Applicant as an investigative study in rats (Study 06-0367) showed that the inflammation in the rat skin was more localized and severe than generally observed in the

cynomolgus monkeys (Study 05-0025-1466). Therefore, the rat was determined to be a sensitive and appropriate model to evaluate formulation optimization for ocrelizumab SC. Furthermore, local tolerance was investigated in minipigs to support the findings in rats, as the skin of minipigs are considered morphologically and functionally similar to human skin. Based on the justification from the Applicant and in light of the principles of 3R, it is accepted that no further local tolerance studies in monkeys were performed.

A dose-range finding study in rats was conducted to investigate the local effects at increasing doses of ocrelizumab (Study 06-0367). A clear dose-response correlation was observed when ocrelizumab was administered in rats without co-administration of rHuPH20, and at high dose levels of 150 mg/mL, a severe inflammatory response was observed while histological evidence of injection site inflammation was minimal at 30 mg/mL ocrelizumab. SC administration of ocrelizumab in rats with the proposed clinical SC formulation co-administered with 1000 U/mL rHuPH20 was in general well tolerated at lower doses. A dose dependent increase in inflammatory response as well as edema and fibrosis at the injection site was observed in Study 18-1377. However, the effects were minimal at 40 mg/mL in the GLP-compliant Study 18-1665, which is considered the NOAEL in rats. In minipigs, the proposed clinical SC formulation co-administered with 1000 U/mL rHuPH20 with a dose of 40 mg/mL and a dose volume of 6 mL was also well tolerated, and this is considered the NOAEL in minipigs (Study 18-1979).

In conclusion, the local tolerance studies in monkeys, rats and minipigs demonstrated that while ocrelizumab is not tolerated at high dose levels without the co-administration of rHuPH20, lower levels are well tolerated when co-administered with rHuPH20. Overall, dose levels of up to 40 mg/mL were well tolerated in non-clinical species, when co-administered with rHuPH20.

The Applicant provided exposure data from the local tolerance study in monkeys where TK measurements were included (Study 05-0025-1466), to compare with clinical exposure levels following IV and SC dosing in patients. However, severe local effects were observed in monkeys at the only dose level included of 150 mg/mL, and no safety margin could be determined. TK measurements were not included in the local tolerance studies in rats and minipigs so direct comparison with the exposure in patients is not possible. Instead, the Applicant provided body weight normalized doses for both rats and minipigs at the identified NOAEL values, corresponding to 80 mg/kg in rats (bw: 250 g) and 24 mg/kg in minipigs (bw: 10 kg), respectively. The body weight normalized dose in humans at the clinical dose concentration is 15.3 mg/kg by assuming a bodyweight of 60 kg. Thereby, a safety margin of 5.22 and 1.57 is calculated for rats and minipigs, respectively. It is generally considered that the non-clinical data supports that the treatment is well tolerated at clinically relevant dose levels.

2.5.5 Ecotoxicity/environmental risk assessment

As the drug substance is a monoclonal antibody no ERA is required according to EMA 2006 guidance and Q&A document. However, in spite of this, the Applicant performed several acute toxicity studies with ocrelizumab in the aquatic compartment, which all showed that the maximal tested concentration was tolerated by the test systems. Furthermore, ocrelizumab was biodegradable. No further data is considered necessary for the SC formulation as the new formulation is not considered to affect the fate of ocrelizumab in the environment. Further, rHuPH20 is a recombinant human enzyme and as per ERA guidance, no environmental assessment is considered warranted.

In conclusion, the active substance ocrelizumab and the excipient rHuPH20 are natural substances, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ocrelizumab and rHuPH20 are not expected to pose a risk to the environment.

2.5.6 Discussion on non-clinical aspects

No new pharmacological (PD), pharmacokinetic (PK) or repeat dose toxicity studies for systemic effects were submitted for the SC Ocrevus formulation. In order to bridge between the existing data for ocrelizumab IV and ocrelizumab SC, new local tolerance studies in rats and minipigs for ocrelizumab SC have been conducted by the Applicant, in addition to an existing PD/PK/local toxicity study performed in cynomolgus monkeys, which was submitted with the original IV formulation of Ocrevus.

In general, it is accepted that no further PD or PK studies are submitted to support the SC formulation of Ocrevus. The pharmacology of ocrelizumab after SC administration has been sufficiently demonstrated, although this was administered without prior treatment with rHuPH20. Extensive ADA formation was observed in monkeys after SC administration, which was shown to increase clearance of ocrelizumab during the study, however, ADA formation was also observed after IV injection, and increased with lower dose levels. No comparison of PK profiles was provided by the Applicant between the approved IV formulation and the proposed clinical SC formulation, as TK measurements were not included as part of the local tolerance tests in rats and minipigs. However, it is considered acceptable that no further PK characterization is performed in non-clinical species also taking the ADA formation into account in the animals, which is not transferable to humans.

In terms of local tolerance, the Applicant demonstrated that ocrelizumab was well tolerated at low doses in rats and minipigs when co-administered with rHuPH20. The Applicant sufficiently justified using rats and minipigs as an alternative non-clinical species for testing local tolerance, so that no further local tolerance tests in monkeys would be required. NOAEL levels were established in both rats and minipigs at 40 mg/mL. By converting the NOAEL values to body weight normalized doses, the Applicant demonstrated sufficient safety margins to clinical dose levels, supporting that the treatment should be locally well tolerated.

2.5.7 Conclusion on the non-clinical aspects

The submitted dossier for the SC formulation of ocrelizumab is in general considered sufficient to support approval of Ocrevus SC from a non-clinical perspective. Section 4.6 and 5.3 of the SmPC is generally considered to reflect the outcome of the studies on Ocrevus SC formulation.

Overall, the non-clinical study submitted with the present application is considered adequate and sufficient to support SC administration of ocrelizumab.

2.6 Clinical aspects

2.6.1 Introduction

Safety and tolerability, PK, PD, and immunogenicity are assessed in the initial OCARINA I study, a dose escalation study in 2 parts, in RMS and PPMS patients. The SC dose selected based on data obtained in OCARINA I was evaluated in the pivotal OCARINA II study. Both studies are summarized in Table 1.

- **Tabular overview of clinical studies**

Table 1 Studies contributing to PK and PD evaluation

Study Number	Study Design	Population	No. of Patients	Dose, Route, Regimen
CN41144 (OCARINA I)	Phase Ib, open-label, multicenter study to investigate the PK, safety and tolerability of SC ocrelizumab	Patients with RMS or PPMS, previously treated with ocrelizumab (A) or treatment-naïve (B)	134 A: 88 B: 46	40, 200, 600, 920 and 1200 mg SC; 600 mg IV
CN42097 (OCARINA II)	Phase III, randomized, open-label, parallel group, multicenter study to evaluate the PK, PD, safety, immunogenicity, radiological and clinical effects of SC ocrelizumab	Patients with RMS or PPMS (no anti-CD20 treatment in the last 2 years)	236 IV: 118 SC: 118	920 mg SC; 600 mg IV (2x 300 mg infusions 2 weeks apart)

IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PPMS = primary progressive multiple sclerosis; RMS = relapsing forms of multiple sclerosis; SC = subcutaneous.

A subcutaneous (SC) formulation has been developed for administration of 920 mg ocrelizumab as a single SC injection over approximately 10 minutes to be given every 6 months for the same indications as currently approved for ocrelizumab IV. The main objective of Study OCARINA II is to show non-inferiority of the SC formulation compared to the approved IV formulation of ocrelizumab.

2.6.2 Clinical pharmacology

2.6.2.1 Pharmacokinetics

Ocrelizumab concentration in human serum samples was measured with an enzyme linked immunosorbent assay (ELISA) using established and validated immunoassay procedures. A validated bridging ELISA was used to measure ADAs to ocrelizumab in human serum, and a validated bridging electro chemiluminescent assay (ECLA) was used to measure anti-rHuPH20 antibodies in human plasma. The ocrelizumab ADA assay had limited drug tolerance (500 ng/mL ADA could be detected in presence of 10 µg/mL ocrelizumab).

Two clinical studies in multiple sclerosis (MS) patients were conducted with the ocrelizumab SC formulation, Study CN41144 (OCARINA I) and Study CN42097 (OCARINA II). The PK of ocrelizumab after SC injection or IV infusion was assessed by Pop PK analysis using NONMEM and R.

All data from OCARINA II available at the cut-off March 10, 2023 were used for Pop PK analysis. The OCARINA I based IV SC model was fitted to the data of Study CN42097 (OCARINA II). All parameters were fixed (equal to the values of the original IV model), except for SC absorption parameters and Q which were re-estimated. Effects of age were re-evaluated and an effect of age on ka included. Table 2 shows parameter estimates of the IV model and Table 3 the re-estimated parameters of the final IV SC Model 500.

Table 2 Parameter estimates for Ocrelizumab IV population PK 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% multiplied by the square root of the variance, R: correlation coefficient.

Table 3 Estimated parameters for the final model 500

The NONMEM control stream and output files can be found in Appendix 2.

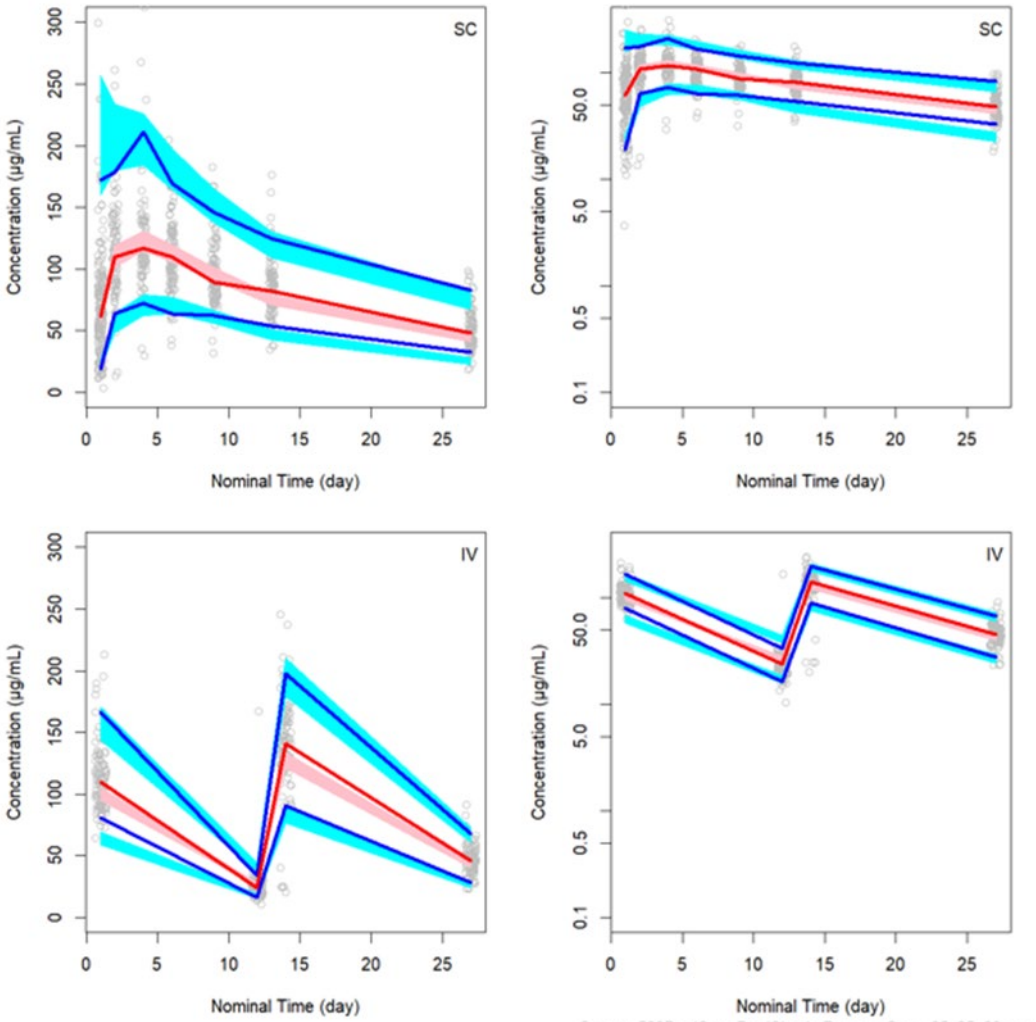
Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage (%)
Q (L/day)	θ_4	0.545	5.56	0.485 ; 0.604		
F_{SC}	θ_{15}	0.814	1.96	0.783 ; 0.845		
MTIME (day)	θ_{16}	0.0585	2.9	0.0552 ; 0.0619		
k_{a1} (1/day)	θ_{17}	0.0527	13.7	0.0385 ; 0.0669		
k_{a2} (1/day)	θ_{18}	0.418	6.63	0.363 ; 0.472		
$k_{a\text{-}age}$	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: 500ParEst.csv (DiagnosticPlots.R)

The final Model 500 was evaluated by diagnostic plots including Visual Predictive Checks (VPCs) and NPDE. Figure 1 and Figure 2 show VPCs for Cycle 1 of OCARINA II data stratified for route of administration.

Figure 1 Prediction corrected VPC for IV and SC administration

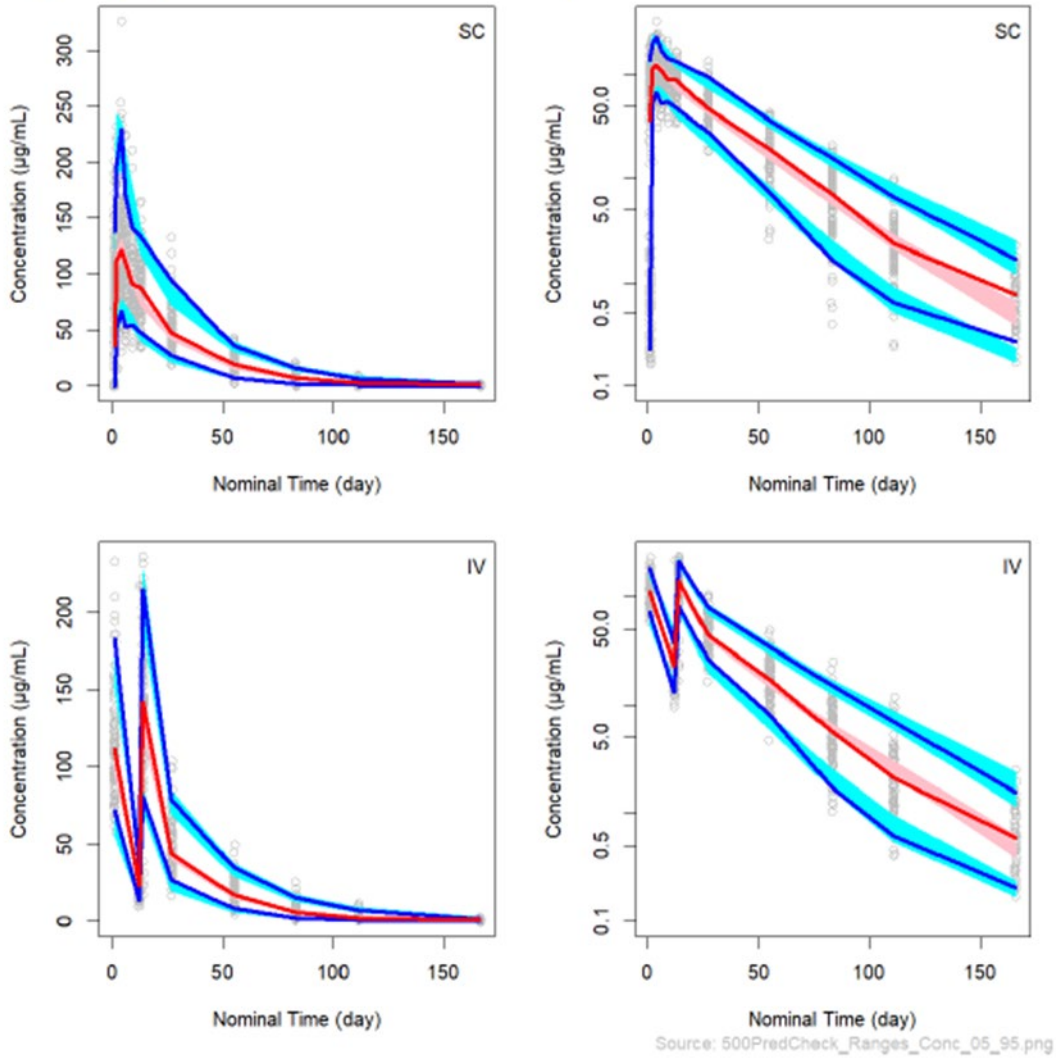


Source: 500PredCorr_PredCheck_Ranges_Conc_05_95_28.png

The lines show the median (red), and the 5th and 95th percentiles (blue) of the observed concentrations (circles). The shaded regions show the 90% confidence intervals on these quantities obtained by simulations. The left panels use normal scale and the right panels use semi-log scale.

Figure 2 Visual predictive 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: 500PredCheck_Ranges_Conc_05_95.png

Absorption

The applied sampling frequency enables exposure metrics to be calculated by NCA. Table 4 give a summary of exposure for the first two weeks and for Cycle 1 based on NCA of observations.

Table 4 Summary statistics of Ocrelizumab PK parameters following IV and SC administration

	C_{max} (ug/mL)	AUC_{w1-12} (ug/mL*day)	AUC_{w1-24} (ug/mL*day)	C_{trough} (ug/mL)
IV Formulation				
N	115	111	107	62
Mean	149	3250	3430	0.595
SD	37.8	923	1040	0.529
CV%	25.4	28.4	30.3	88.9
Min	68.5	1530	1650	0.00
Median	145	3020	3100	0.48
Max	236	5490	5840	2.53
Geometric Mean	144	3120	3280	
Geometric CV%	26.4	29.1	30.5	
SC Formulation				
N	117	117	117	59
Mean	147	3600	3830	0.771
SD	48.4	1010	1130	0.534
CV%	32.9	28.2	29.4	69.2
Min	39.6	1130	1160	0.00
Median	145	3630	3830	0.67
Max	326	6080	6730	2.29
Geometric Mean	138	3440	3650	
Geometric CV%	38.3	32.8	34.3	

IV=intravenous, PK=pharmacokinetic, SC=subcutaneous, SD=standard deviation

The PK data for non-inferiority analysis was derived by the population PK method. Exposure metrics were predicted for Cycle 1 of OCARINA II by Model 500 using individual Bayesian post-hoc parameter estimates. The model diagnostics indicated large eta-shrinkage on most disposition parameters and bioavailability. The bioavailability was estimated to 81.4%.

Following 920 mg SC ocrelizumab, the predicted mean Cmax was 132 µg/mL, tmax was reached after approximately 4 days (range 2-13 days) and the predicted AUCtau was 3730 µg/mL×day at Cycle 1 (Table 5).

Table 5 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)

Data from 4 patients, two of each subgroup, with major protocol violations or incomplete dose administration were excluded.

Figure 3 Box plots of predicted exposure by route, model 500

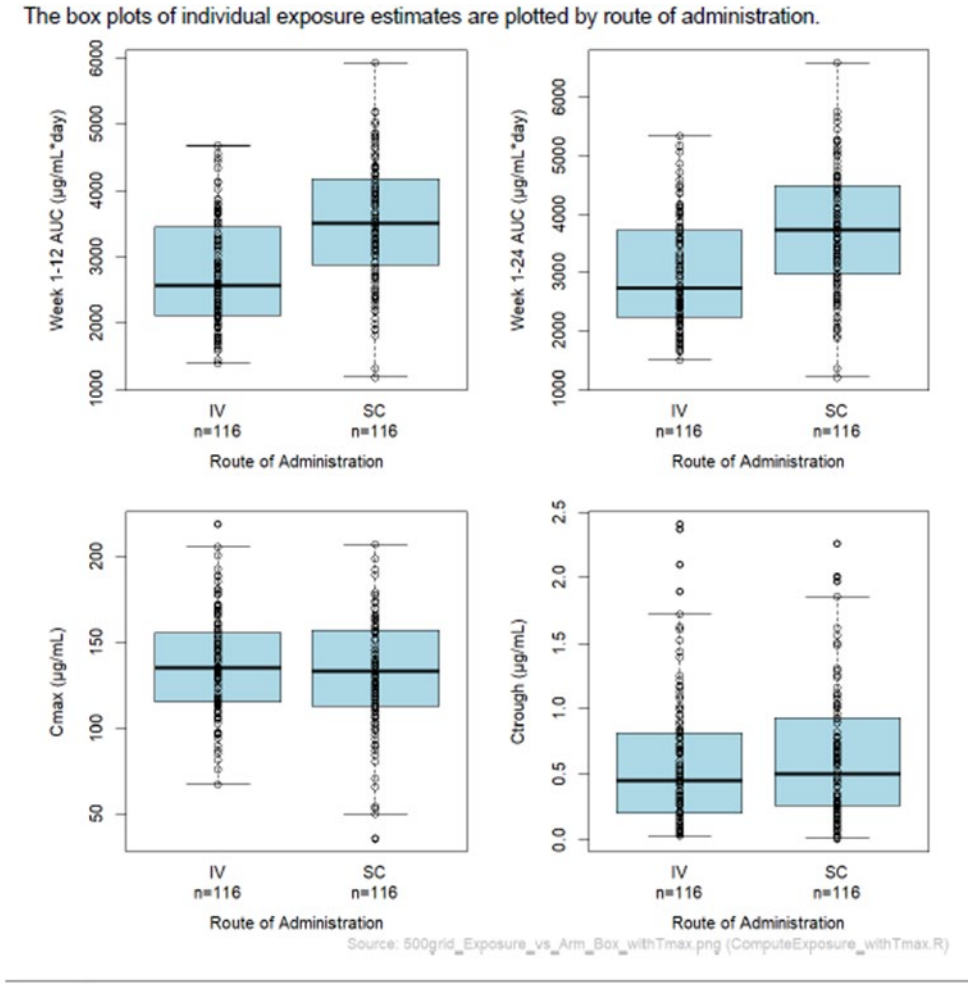


Figure 3 shows a comparable Cmax in Cycle 1 which is due to the split IV dose. The proposed 920 mg SC dose results in a higher exposure expressed as AUC compared to the approved IV dose.

AUC across Week 1 to Week 12 is the primary parameter for non-inferiority assessment and the time expected for complete absorption. AUCw1-12 constitute most (about 93%) of the AUC to Week 24 (tau). Non-inferiority was established based on the lower end of the two-sided 90% CI of the GMR of the AUCw1-12 which was > 0.8.

The GMR was calculated from a linear regression model of log model estimated AUCW1-12 for IV and SC, adjusted for stratification factors: baseline body weight [<70kg vs ≥70kg], disease subtype [relapsing forms of multiple sclerosis {RMS} vs primary progressive multiple sclerosis{PPMS}] and region [United States vs Rest of the World] (Table 6).

Table 6 OCARINA II: non-inferiority analysis AUC (week 1-12)

Estimated Ratios of Geometric Means and 90% Confidence Intervals for AUC from Week 1 to Week 12 of OCR SC in Comparison with OCR IV, PK-evaluable Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

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

OCR IV N=116 and OCR SC N=116
n represents the number of patients in the analysis model.
Estimates are from a linear regression model: log(PK parameter) = Treatment + baseline body weight (<70kg vs >=70kg) + disease subtype (RMS vs PPMS) + region (United States vs Rest of the world).
[1] Geometric Mean Ratio of test treatment group (SC arm) to reference treatment group (IV arm).
AUC = area under the concentration-time curve
CI = confidence interval

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_pk_est.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/
t_pk_est_AUCW12_PK_PKS.out
06JUL2023 22:16 Page 1 of 1

Distribution

N/A

Elimination

N/A

Dose proportionality and time dependencies

N/A

Special populations

A predominate part of the OCARINA II study population were White (89.8%); 84.3% of subjects had a CRCL >90 ml/min, while 15.7% had a CRCL of 50-90 ml/min; 62.1% of subjects were female and 37.9% were male. There was no clinically relevant influence of sex on any of the random effects of Model 500. Effects of body weight was included on ocrelizumab disposition parameters. Body weight ranged from 42-194 kg. An effect of age on ka was included in the Pop PK Model 500, with a decline in absorption rate with age. Age ranged from 17-65 years. The SC dose was not studied in subjects >65 years of age.

Pharmacokinetic interaction studies

N/A

Pharmacokinetics using human biomaterials

N/A

2.6.2.2 Pharmacodynamics

Mechanism of action

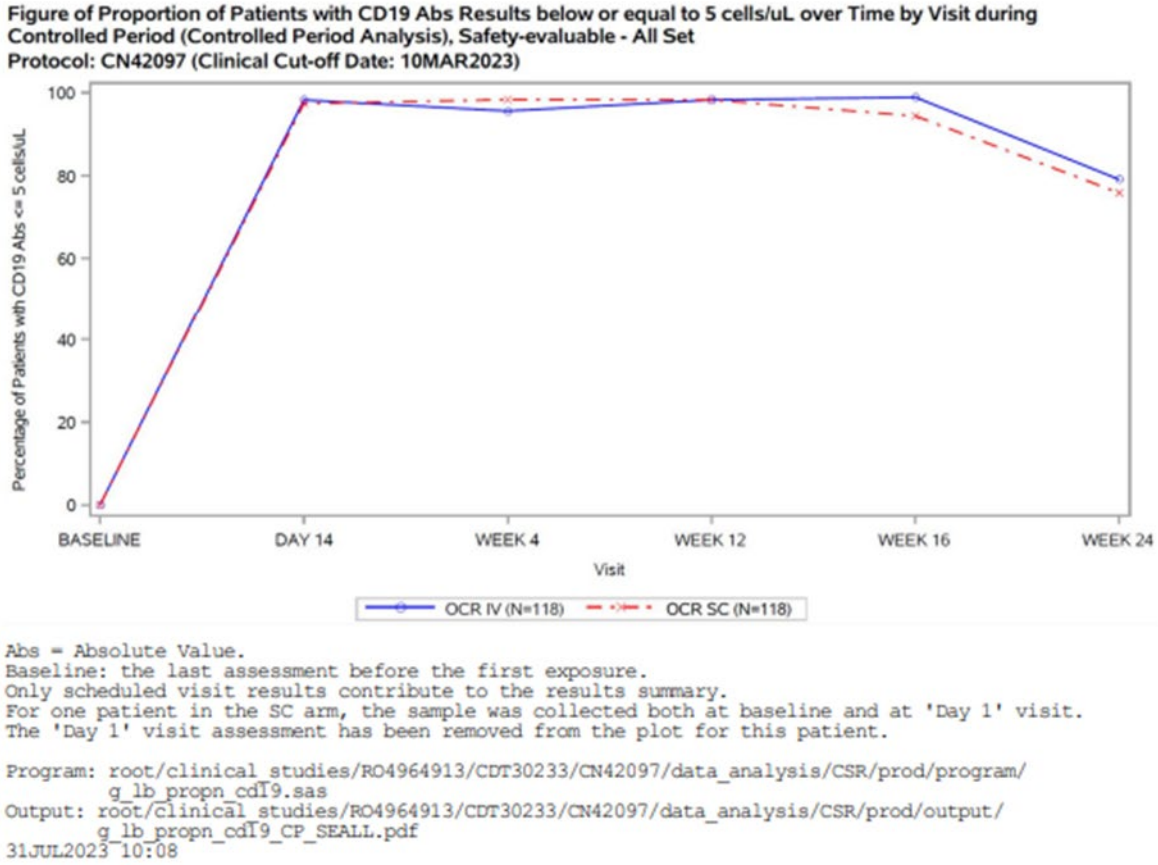
Ocrelizumab is a recombinant humanized monoclonal antibody directed against CD20-expressing B-cells. The precise mechanism by which ocrelizumab exerts its therapeutic effects in multiple sclerosis is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis and complement-mediated lysis of the B-cells.

Primary and Secondary pharmacology

Because ocrelizumab binds to CD20, its presence in blood interferes with the B-cell count based on the surface antigen CD20 itself. Thus, another cell-surface marker that largely mirrors CD20 expression during B-cell development is used: CD19. B-cell counts described in this document refer to flow cytometric counts of CD19+ cells in blood. An additional analysis was performed to evaluate the effect of ocrelizumab SC and IV on B-cell subsets (IgD transitional, memory, naive, double negative, and plasma cells).

Treatment with ocrelizumab SC and ocrelizumab IV led to a rapid and sustained depletion of CD19+ B cells in blood (Figure 4), as well as B-cell subsets.

Figure 4 Figure of proportion of patients with CD19 abs results below or equal to 5 cells/µL over time by visit during controlled period (controlled period analysis), safety-evaluable – all set



Immunogenicity

OCARINA I: Post-baseline, the incidence of treatment-emergent ADAs to ocrelizumab was 0 of 88 post-baseline evaluable patients (0%) in Group A, and 0 of 46 post-baseline evaluable patients (0%) in Group B.

Post-baseline, the incidence of treatment-emergent anti-rHuPH20 antibodies was 1 of 87 post-baseline evaluable patients (1.1%) in Group A.

Post-baseline, the incidence of treatment-emergent anti-rHuPH20 antibodies was 2 of 45 post-baseline evaluable patients (4.4%) in Group B.

OCARINA II:

No treatment-emergent ADAs to ocrelizumab or rHuPH20 were reported in either treatment arm based on, respectively, serum and plasma samples collected.

2.6.3 Discussion on clinical pharmacology

Validated methods were used for quantification of ocrelizumab and for immunogenicity testing of ADAs against ocrelizumab or the SC vehicle, rHuPH20. The first post-dose samples for test of ADAs against ocrelizumab were taken 4-, 12- and 24-weeks post-dose in OCARINA I and 24 weeks post-dose in OCARINA II. The late samples will allow for detection of persistent ADAs, however, there is potential to miss detection of immunogenicity at early onset due to limited drug tolerance of the ADA assay. The SmPC mentions that transient ADAs may not be detected between baseline and every 6-month post-treatment which has been accepted.

A Pop PK model for ocrelizumab IV and SC was used to describe the PK of OCARINA II data. The modelling and simulation were conducted using NONMEM and R. The final model built from a previous IV model was updated with data from OCARINA I across two data cut-offs in a sequential manner. Data from OCARINA II was fitted with re-estimation of absorption parameters and Q. The model diagnostics did not indicate any major misspecifications and could describe the observed data in Cycle 1. The bioavailability was estimated to 81.4%.

OCARINA II was described as a non-inferiority trial to compare 920 mg SC ocrelizumab to 600 mg (=2x300 mg) IV ocrelizumab. Data from 4 patients were excluded. One IV dosed subjects with extreme high body weight of 194 kg, did not impact the outcome of the non-inferiority test. Exposure metrics were predicted for Cycle 1 of OCARINA II. The applied sampling frequency enables exposure metrics to be calculated by NCA. AUCs derived by non-compartment analysis and observed Cmax and Ctrough values for Cycle 1 were provided upon request for comparison. Mean observed exposures were generally higher that the model predicted exposure measures. The NCA data confirms the SC dose results in a higher exposure based on AUC than the approved IV treatment. The mean ratio of the analysis of OCARINA II model predicted AUCs W1-12, is 1.2851 with a 90%CI of 1.2258 – 1.3473. The GMR is >0.8 and thus fulfilling the one-sided non-inferiority criteria outlined in the SAP. The results show a nominally significant difference between the two treatments and that ocrelizumab SC 920 mg exposure expressed as AUC is higher than the approved ocrelizumab IV 600 mg.

The pharmacodynamic objective in the studies was to evaluate the effect of SC ocrelizumab compared with IV ocrelizumab on the PD marker for the mechanism of action of ocrelizumab (B-cell depletion).

Ocrelizumab is a recombinant humanized monoclonal antibody directed against CD20-expressing B-cells. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis and complement-mediated lysis of the B-cells. Once absorbed to the systemic circulation, the mechanism of action is the same as with the approved IV administration.

Ocrelizumab selectively targets and depletes CD20-expressing B-cells. B-cell depletion is therefore the expected PD action of ocrelizumab; hence B-cell count in peripheral blood was used as the PD marker. The PD marker is considered adequate. B cell depletion was similar after administration of 920 mg ocrelizumab SC and 2 x 300 mg IV.

Overall, no treatment-emergent ADAs to ocrelizumab were observed. However, immunogenicity status following SC ocrelizumab is not considered adequately described, due to poor assay sensitivity and sparse sampling.

A total of 3 out of 132 patients (2.3%) had treatment-emergent anti-rHuPH20 antibodies in OCARINA I and no treatment-emergent anti-rHuPH20 antibodies was observed in OCARINA II. No safety concerns have been observed in patients with anti-rHuPH20 antibodies.

The Applicant provided an exposure-safety analysis considering the SC and IV data in different exposure ranges as requested. No meaningful difference was seen over the different exposure quartiles for SAEs, serious infections, infections, IRs and IRRs. The exposure-safety analysis confirms that the increased exposure that is seen for the SC formulation does not translate into a worse safety profile.

2.6.4 Conclusions on clinical pharmacology

Overall the clinical pharmacology is considered adequately described.

2.6.5 Clinical efficacy

Ocrelizumab SC is currently being investigated in two clinical trials: the pivotal Phase III Study CN42097 (hereinafter referred to as OCARINA II; Table 7) and the supportive Phase Ib Study CN41144 (hereinafter referred to as OCARINA I).

In this section, the supportive magnetic resonance imaging (MRI) data (secondary and exploratory radiological endpoints) and annualized relapse rate (ARR) data (exploratory clinical endpoint) collected in OCARINA II from the start of the study until the clinical cut off date (CCOD) are presented. There were no efficacy endpoints in OCARINA I.

Table 7 Summary of studies contributing to efficacy evaluation

Study Number, Phase	Study Design	Population	No. of Patients	Dose, Route, and Regimen	Data Clinical Cutoff Date
CN42097 (OCARINA II), Phase III	Non-inferiority, randomized, open-label, parallel group, multicenter	Adult patients (18-65 years) with RMS or PPMS [a]	236 patients randomized in 1:1 ratio to receive either ocrelizumab SC or IV as first dose	**Controlled Period:** Either 920 mg ocrelizumab administered as single SC injection, or 600 mg ocrelizumab administered as two 300 mg IV infusions **SC Ocrelizumab Treatment Period:** All patients: 920 mg ocrelizumab administered as single SC injection, every 24 weeks.	Primary analysis: 10 March 2023

IV = intravenous; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis; SC = subcutaneous.

[a] Patients who had previously received anti-CD20s (including ocrelizumab) were excluded from study if the last treatment was less than 2 years before screening, and/or if B-cell count was below lower limit of normal.

2.6.5.1 Dose response studies

N/A

2.6.5.2 Main study

CN42097 (OCARINA II) is a Phase III non-inferiority, randomized, open-label, parallel group, multicenter study to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of SC administration of ocrelizumab compared with the IV infusion of ocrelizumab in patients with either relapsing MS (RMS) or primary progressive MS (PPMS).

Methods

The study consists of the following study phases (Figure 5):

- Screening
- Treatment (controlled period and SC ocrelizumab treatment period)
- Safety follow-up (SFU)

Eligible patients were randomly assigned in a 1:1 ratio to one of two treatment arms: ocrelizumab SC arm (hereinafter referred to as OCR SC) or ocrelizumab IV arm (hereinafter referred to as OCR IV). The treatment phase of the study consisted of three ocrelizumab doses as follows:

- During the controlled period (i.e., until, but not including, the time of the second dose of ocrelizumab [Week 24 visit]):

– For patients assigned to OCR SC: Dose 1 of ocrelizumab administered as 920 mg single SC injection on Week 1/Day 1

– For patients assigned to OCR IV: Dose 1 of ocrelizumab administered as two 300 mg IV infusions separated by 2 weeks, i.e., on Week 1/Day 1 and Week 2/Day 14.

- During the SC ocrelizumab treatment period (i.e., Week 24 and Week 48 doses of ocrelizumab SC), patients in the OCR SC arm continued to receive 920 mg SC at Week 24 and Week 48, and patients in the OCR IV arm switched to 920 mg SC at Week 24 and continued to receive 920 mg SC at Week 48.

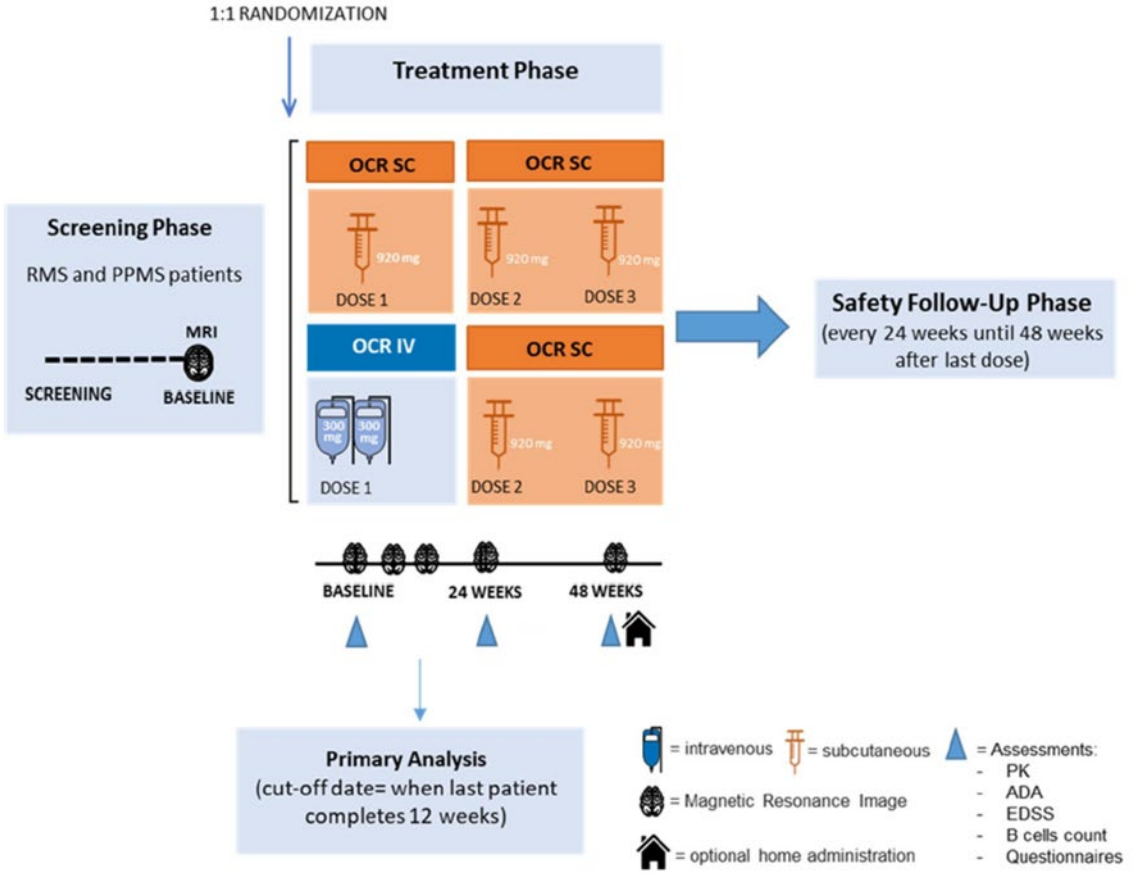
– For all patients:

– Dose 2 of ocrelizumab administered as 920 mg single SC injection at Week 24

– Dose 3 of ocrelizumab administered as 920 mg single SC injection at Week 48

Home administration of OCR SC is also permitted for eligible patients at Week 48, as described in the protocol.

Figure 5 Study design



ADA = anti-drug antibody; EDSS = expanded disability status scale; IV = intravenous; MRI = Magnetic Resonance Image; OCR = ocrelizumab; PK = pharmacokinetics; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis; SC = subcutaneous

Study Participants

Patients with RMS or PPMS were enrolled in Study CN42097.

The key inclusion criteria were as follows:

- Age 18-65 years
- Diagnosis of PPMS or relapsing forms of MS (RMS) according to the revised McDonald 2017 criteria (Thompson et al. 2018)
- EDSS score, 0-6.5, 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 expanded disability status scale (EDSS) score < 2.0 at screening

The key exclusion criteria were as follows:

- 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

- Immunocompromised state
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization (Influenza vaccination was permitted if the inactivated vaccine formulation was administered)
- Inability to complete an MRI or contraindication to gadolinium administration
- Contraindications to mandatory premedications (i.e., corticosteroids and 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
- Any concomitant disease that may require chronic treatment with systemic corticosteroids (e.g., mineralocorticoids and glucocorticoids) or immunosuppressants during the course of the study
- Systemic corticosteroid therapy within 4 weeks prior to screening

Treatments

Eligible patients were randomized once during the study to one of the two treatment arms: OCR SC or OCR IV (Table 8). Subsequently, all patients will receive two doses of ocrelizumab SC.

The ready-to-use SC ocrelizumab co-formulated with rHuPH20 does not require mixing with rHuPH20. Ocrelizumab SC will be provided as a sterile, single-dose liquid at a concentration of 40 mg/mL and contains no preservatives. The ocrelizumab in the ocrelizumab SC formulation is co-formulated with rHuPH20 at a concentration of 1000 U/mL.

During the controlled period, patients assigned to OCR IV received 600 mg of ocrelizumab IV administered as two 300-mg IV infusions on Study Week 1 and Week 2. Ocrelizumab IV was provided as a sterile, single-dose liquid at a concentration of 30 mg/mL and contains no preservatives.

Table 8 Ocrelizumab dosing regimen

Treatment Phase	Arm		Arm	
Controlled Period	**OCR IV**		**OCR SC**	
	Dose 1	600 mg IV dose (IV Infusion 1 [Study Week 1] + IV Infusion 2 [Study Week 2])	Dose 1	920 mg SC injection 1 (Study Week 1)
SC Ocrelizumab Treatment Period	**OCR IV/SC**		**OCR SC/SC**	
	Dose 2	920 mg SC injection 1 (Study Week 24)	Dose 2	920 mg SC injection 2 (Study Week 24)
	Dose 3	920 mg SC injection 2 (Study Week 48)	Dose 3	920 mg SC injection 3 (Study Week 48)

IV = intravenous; SC = subcutaneous; OCR IV = ocrelizumab intravenous; OCR IV/SC = patients who were randomized to OCR IV in the controlled period and received ocrelizumab SC as subsequent doses in the SC ocrelizumab treatment period; OCR SC = ocrelizumab subcutaneous; OCR SC/SC = patients who were randomized to OCR SC in the controlled period and received ocrelizumab SC as subsequent doses in the SC ocrelizumab treatment period.

Notes:

There should be a minimum of 22 weeks between all SC doses.

There should be a minimum of 20 weeks between the administration of the final ocrelizumab IV infusion (at Week 2) and the first ocrelizumab SC dose (at Week 24).

To minimize the risk of injection reactions (IRs), patients treated with ocrelizumab SC received mandatory premedications of 20 mg dexamethasone and 5 mg desloratadine given orally 1-2 hours before each ocrelizumab SC administration. After the CCOD, the protocol was amended so that premedication could be given shortly before SC injection.

To minimize the risk of infusion-related reactions (IRRs), all patients who received ocrelizumab IV treatment received mandatory prophylactic treatment with 100 mg methylprednisolone administered by slow IV infusion to be completed approximately 30 minutes before the start of each ocrelizumab infusion.

In the rare case when the use of dexamethasone or desloratadine was contraindicated for the patient or was not available, an equivalent dose of an alternative steroid or antihistaminic could have been used as premedication prior to the injection. Corticosteroids and antihistamine medications are considered as equivalent in terms of anti-inflammatory potency to the premedication given to patients treated with ocrelizumab IV. Oral analgesics (such as acetaminophen) were permitted.

Table 9 Premedications used prior to IV infusion or SC injection

Prior to Each IV Administration of Ocrelizumab	Prior to Each SC Administration of Ocrelizumab
Mandatory 100 mg methylprednisolone, given by slow IV infusion, 30 minutes before start of infusion [a]	Mandatory 20 mg dexamethasone, given orally, 1–2 hours before administration [a]
Mandatory 50 mg diphenhydramine, given orally or IV infusion, 30–60 minutes before start of infusion [a]	Mandatory 5 mg desloratadine, given orally, 1–2 hours before administration [a]
Oral analgesic as needed and as tolerated (if using acetaminophen, not to exceed 4 g/day, per label)	Recommended oral analgesic as needed and as tolerated (if using acetaminophen, not to exceed 4 g/day, per label)

IV = intravenous; SC = subcutaneous.

[a] After the CCOD, the protocol was amended so that premedication could be given shortly before SC injection (Section 3.1.2).

Hypotension, as a symptom of IRR, may occur during IV study drug infusions. Therefore, withholding antihypertensive treatments should be considered for 12 hours prior to and throughout each study drug infusion.

Objectives

This study evaluates the pharmacokinetics, pharmacodynamics, safety, immunogenicity, and radiological and clinical effects of SC administration of ocrelizumab compared with the IV infusion in patients with either relapsing multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS).

Outcomes/endpoints

Table 10 Overview of efficacy assessments

Endpoint	Definition	Assessment Time Points
Secondary Radiological Endpoints		
Total number of T1Gd+ lesions at Week 8 and Week 24	As detected by brain MRI scans analyzed by a blinded centralized reading center	Brain MRI at screening, baseline, Weeks 8, 12, 24, 48, unscheduled, and ET visits T1Gd+ lesions analysis performed for Week 8 and Week 24 visits, for all patients and separately for each MS subtype (RMS or PPMS)
Total number of new or enlarging T2 lesions at Week 12 and Week 24	As detected by brain MRI scans analyzed by a blinded centralized reading center	Brain MRI at screening, baseline, Weeks 8, 12, 24, 48, unscheduled, and ET visits New or enlarging T2 lesions analysis performed for Week 12 and Week 24, relative to the previous scan, for all patients and separately for each MS subtype (RMS or PPMS)
Exploratory Radiological Endpoints		
Total number of new or enlarging T2 lesions at Week 8	As detected by brain MRI scans analyzed by a blinded centralized reading center	Brain MRI at screening, baseline, Weeks 8, 12, 24, 48, unscheduled, and ET visits New or enlarging T2 lesions analysis performed for Week 8 (relative to the previous scan), for all patients and separately for each MS subtype (RMS or PPMS), per secondary radiological main estimand
Exploratory Clinical Endpoints		
Annualized relapse rate (in RMS patients)	Defined as number of relapses per patient-year The protocol definition of a relapse is described in CSR 1121154, Appendix 16.1.1, Protocol v2.0, Section 4.5.6	Neurologic examination at screening, baseline, Weeks 12, 24, 48, unscheduled, ET, and SFU visits Analysis of the annualized protocol-defined relapse rate performed by Week 24

ET = early termination; MS multiple sclerosis; IV = intravenous; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis; SFU = safety follow-up.

Sample size, Randomisation and blinding (masking)

236 patients. 1:1 randomisation.

This was an open-label study.

Statistical methods

Hypothesis testing was not performed for efficacy. All secondary and exploratory analyses were performed using descriptive statistics.

Results

Participant flow

A total of 236 patients were enrolled in the study: 118 were randomized to the OCR SC arm (patients only treated with ocrelizumab SC) and 118 were randomized to the OCR IV arm (patients first treated with ocrelizumab IV and then SC).

As of the CCOD, 236 patients had entered the controlled period (118 in OCR SC and 118 in OCR IV) and all received at least one dose of ocrelizumab. Of these 236 patients, 126 patients had completed the 24-week controlled period and entered the SC ocrelizumab treatment period (63 in OCR SC and 63 in OCR IV). Over the treatment phase (controlled period + SC ocrelizumab treatment period), 5 patients had discontinued treatment and were considered to have entered the SFU at the time of the last exposure. No patients had completed the study yet at the time of the CCOD.

Note: 2 patients (1 in OCR SC and 1 in OCR IV) withdrew consent and did not return for the Week 24 SFU visit.

Overall, the treatment withdrawal rate was low and similar between the OCR SC and OCR IV arms.

Of the 236 patients who had entered the controlled period, 2 patients in OCR IV discontinued treatment and entered the SFU, 1 due to pregnancy and 1 due to withdrawal by subject.

Of the 126 patients who had entered the SC ocrelizumab treatment period, 3 patients discontinued treatment and entered the SFU, 2 in OCR SC due to withdrawal by subject and lack of efficacy, and 1 in OCR IV due to withdrawal by subject.

Of the 5 patients who had entered the SFU, 1 in OCR IV discontinued from the study due to withdrawal by subject.

Recruitment

First Patient Enrolled: 3 May 2022

Data cut-off: 10 March 2023

Baseline data

Table 11 Baseline MS disease history, safety-evaluable – all set

MS Disease History, Safety-evaluable - All Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

	OCR IV (N=118)	OCR SC (N=118)	All Patients (N=236)
Current phenotype of MS			
n	118	118	236
RRMS	105 (89.0%)	105 (89.0%)	210 (89.0%)
PPMS	12 (10.2%)	11 (9.3%)	23 (9.7%)
aSPMS	1 (0.8%)	2 (1.7%)	3 (1.3%)
Duration since MS Symptoms Onset (years)			
n	117	117	234
Mean (SD)	6.84 (7.09)	7.67 (8.30)	7.26 (7.72)
Min - Max	0.2 - 38.7	0.3 - 41.8	0.2 - 41.8
Median	4.38	4.20	4.36
Duration since MS Symptoms Onset Category			
n	117	117	234
<=3 Years	47 (39.8%)	52 (44.1%)	99 (41.9%)
>3 to <=5 Years	16 (13.6%)	10 (8.5%)	26 (11.0%)
>5 to <=10 Years	24 (20.3%)	20 (16.9%)	44 (18.6%)
>10 Years	30 (25.4%)	35 (29.7%)	65 (27.5%)
Duration since MS Diagnosis (years)			
n	118	118	236
Mean (SD)	4.78 (5.81)	5.70 (6.81)	5.24 (6.34)
Min - Max	0.1 - 28.7	0.1 - 41.8	0.1 - 41.8
Median	2.35	3.10	2.73
Duration since Last Reported MS Relapse (years)			
n	89	85	174
Mean (SD)	1.81 (2.41)	2.26 (3.04)	2.03 (2.74)
Min - Max	0.1 - 10.6	0.1 - 11.2	0.1 - 11.2
Median	0.59	0.59	0.59
Prior Treatment with Any MS Disease Modifying Therapy Prior to Baseline			
n	118	118	236
Yes	59 (50.0%)	65 (55.1%)	124 (52.5%)
No	59 (50.0%)	53 (44.9%)	112 (47.5%)
Prior Treatment with Any Steroids as MS Therapy prior to baseline			
n	118	118	236
Yes	117 (99.2%)	118 (100%)	235 (99.6%)
No	1 (0.8%)	0	1 (0.4%)

Percentages are calculated based on the number of patients in the treatment arm (N).
n represents the number of patients contributing to summary statistics.

While the baseline counts for Gd-enhancing T1 lesions are influenced by a larger variability in OCR IV, in general, MRI characteristics were balanced across the arms. Of the 104 patients in OCR SC and 103 patients in OCR IV who had MRI assessments at baseline (OCR SC and OCR IV, respectively):

- The mean (SD) number of Gd-enhancing T1 lesions was: 0.54 (1.66) and 0.98 (2.52).
- The majority patients had 0 Gd-enhancing T1 lesions: 69.5% and 66.1%.

Numbers analysed

Table 12 Analysis sets, randomised population

Analysis Populations, Randomized Population
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

	OCR IV (N=118)	OCR SC (N=118)	All Patients (N=236)
PK-evaluable			
Included	116 (98.3%)	116 (98.3%)	232 (98.3%)
Excluded	2 (1.7%)	2 (1.7%)	4 (1.7%)
Safety-evaluable - all			
Included	118 (100%)	118 (100%)	236 (100%)
Safety-evaluable - SC			
Included	63 (53.4%)	118 (100%)	181 (76.7%)
Excluded	55 (46.6%)	0	55 (23.3%)
Efficacy-evaluable - MRI			
Included	118 (100%)	118 (100%)	236 (100%)
Full Analysis Set	118 (100%)	118 (100%)	236 (100%)
Immunogenicity-evaluable			
Included	116 (98.3%)	118 (100%)	234 (99.2%)
Excluded	2 (1.7%)	0	2 (0.8%)
Other endpoints-evaluable			
Included	118 (100%)	118 (100%)	236 (100%)

All percentages are based on N.

Outcomes and estimation

Secondary Efficacy Endpoints

Secondary Radiological Endpoints

The number of evaluable patients at each time point was (OCR SC and OCR IV, respectively):

- Week 8 (T1Gd+ lesions): n=112 and n=112
- Week 12 (T2 lesions): n=116 and n=116
- Week 24 (T1Gd+ lesions and T2 lesions): n=61 and n=65

T1Gd+ lesions (Table 13)

Over the treatment phase and SFU, no major differences in number of T1Gd+ lesions and lesion rates were observed between the two arms at Weeks 8 and 24, in both the RMS and PPMS populations. The numbers of T1Gd+ lesions and lesion rates were low in both arms and populations.

Treatment Phase or SFU – At Week 8: Of the patients who had a readable MRI assessment at the Week 8 visit, 17 and 24 T1Gd+ lesions were detected in OCR SC and OCR IV, respectively, all in the RMS population.

Treatment Phase or SFU – At Week 24: Of the patients who had a readable MRI assessment at the Week 24 visit, 2 T1Gd+ lesions were detected in OCR SC, all in the RMS population.

Table 13 Summary of number of T1Gd+ lesions by visit during treatment phase or SFU, efficacy-evaluable – MRI set

Summary of Number of T1Gd+ Lesions by Visit during Treatment Phase or SFU for RMS and PPMS Population, Efficacy-evaluable - MRI Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

Visit	OCR IV (N=118)	OCR SC (N=118)
Week 8		
Value at Visit		
n	112	112
Mean (SD)	0.21 (0.98)	0.15 (0.45)
Median	0.00	0.00
Min - Max	0.0 - 9.0	0.0 - 2.0
Number of Lesions		
n	112	112
0	102 (86.4%)	99 (83.9%)
1	5 (4.2%)	9 (7.6%)
2	2 (1.7%)	4 (3.4%)
3	2 (1.7%)	0
>3	1 (0.8%)	0
Week 24		
Value at Visit		
n	65	61
Mean (SD)	0.00 (0.00)	0.03 (0.18)
Median	0.00	0.00
Min - Max	0.0 - 0.0	0.0 - 1.0
Number of Lesions		
n	65	61
0	65 (55.1%)	59 (50.0%)
1	0	2 (1.7%)
2	0	0
3	0	0
>3	0	0
Week 48		
Value at Visit		
n	0	0
Mean (SD)	NE (NE)	NE (NE)
Median	NE	NE
Min - Max	NE - NE	NE - NE
Number of Lesions		
0	0	0
1	0	0
2	0	0
3	0	0
>3	0	0

n is the number of patients with a readable MRI assessment at the visit.

T2 lesions (Table 14, Table 15 and Table 16)

Over the treatment phase and SFU, no major differences in number of new or enlarging T2 lesions (with respect to the previous scheduled available visit) and lesion rates were observed between the two arms at Weeks 12 and 24, in both the RMS and PPMS populations. The numbers of new or enlarging T2 lesions and lesion rates were low in both arms and populations.

Note: One patient in OCR IV had an MS relapse 13 days after their first ocrelizumab IV dose. The relapse was reported at an unscheduled visit and lasted 7 days, with an initial NCI CTCAE Grade of 2 and a most extreme Grade of 3. The patient was administered methylprednisolone IV 1 g/day for 4 days as recommended therapy for treatment of relapses per Protocol, Section 4.4.2. At the Week 8 visit, 68 new or enlarging T2 lesions were observed on the patient's MRI scan, as well as 9 T1Gd+ lesions. At the Week 12 visit, the number of new or enlarging T2 lesions observed decreased to 3. This value is the main reason for the difference between mean (SD) numbers of new or enlarging T2 lesions at Week 8

between OCR SC (0.77 [1.81]) and OCR IV (1.41 [6.61]). The second largest number of new or enlarging T2 lesions at Week 8 in OCR IV was 13.

Treatment Phase or SFU – At Week 12: Of the patients who had a readable MRI assessment at the Week 12 visit and at a previous scheduled MRI visit, 6 and 7 new or enlarging T2 lesions were detected in OCR SC and OCR IV, respectively, all in the RMS population.

Treatment Phase or SFU – At Week 24: Of the patients who had a readable MRI assessment at the Week 24 visit and at a previous scheduled MRI visit, 2 new or enlarging T2 lesions were detected in OCR SC, all in the RMS population.

Table 14 Summary of number of new or enlarging T2 lesions by visit during treatment phase or SFU, efficacy-evaluable – MRI set

Summary of Number of New or Enlarging T2 Lesions by Visit during Treatment Phase or SFU for RMS and PPMS Population, Efficacy-evaluable - MRI Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

Visit	OCR IV (N=118)	OCR SC (N=118)
Week 8		
Value at Visit		
n	113	113
Mean (SD)	1.41 (6.61)	0.77 (1.81)
Median	0.00	0.00
Min - Max	0.0 - 68.0	0.0 - 11.0
Number of Lesions		
n	113	113
0	77 (65.3%)	78 (66.1%)
1	16 (13.6%)	18 (15.3%)
2	7 (5.9%)	7 (5.9%)
3	5 (4.2%)	3 (2.5%)
>3	8 (6.8%)	7 (5.9%)
Week 12		
Value at Visit		
n	116	116
Mean (SD)	0.06 (0.36)	0.05 (0.26)
Median	0.00	0.00
Min - Max	0.0 - 3.0	0.0 - 2.0
Number of Lesions		
n	116	116
0	112 (94.9%)	111 (94.1%)
1	2 (1.7%)	4 (3.4%)
2	1 (0.8%)	1 (0.8%)
3	1 (0.8%)	0
>3	0	0
Week 24		
Value at Visit		
n	65	61
Mean (SD)	0.00 (0.00)	0.03 (0.18)
Median	0.00	0.00
Min - Max	0.0 - 0.0	0.0 - 1.0
Number of Lesions		
n	65	61
0	65 (55.1%)	59 (50.0%)
1	0	2 (1.7%)
2	0	0
3	0	0
>3	0	0
Week 48		
Value at Visit		
n	0	0
Mean (SD)	NE (NE)	NE (NE)
Median	NE	NE
Min - Max	NE - NE	NE - NE
Number of Lesions		
0	0	0
1	0	0
2	0	0
3	0	0
>3	0	0

n is the number of patients with a readable MRI assessment at the visit and at a previous scheduled MRI visit
New or enlarging T2 lesion count measurement is performed with respect to the previous scheduled available visit.

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_mri_sum.sas
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Table 15 Rate of new or enlarging T2 lesions as detected by brain MRI during the treatment phase or SFU on week 12 for RMS, PPMS, and RMS+PPMS populations, efficacy-evaluable – MRI set

	RMS		PPMS		RMS + PPMS	
	OCR IV (N = 106)	OCR SC (N = 107)	OCR IV (N = 12)	OCR SC (N = 11)	OCR IV (N = 118)	OCR SC (N = 118)
Number of patients with a readable MRI assessment at the visit	104	105	12	11	116	116
Total number of lesions	7	6	0	0	7	6
Lesion rate, unadjusted	0.07	0.06	0.00	0.00	0.06	0.05
95% CI	(0.03, 0.14)	(0.02, 0.12)	(0.00, 0.31)	(0.00, 0.34)	(0.02, 0.12)	(0.02, 0.11)
n	104	105	NA	NA	116	116
Lesion rate, adjusted	0.05	0.05	NA	NA	0.05	0.04
95% CI	(0.01, 0.25)	(0.01, 0.20)	NA	NA	(0.01, 0.23)	(0.01, 0.18)

CI = confidence interval; IV = intravenous; MRI = magnetic resonance imaging; NA = not applicable; OCR = ocrelizumab; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis; SC = subcutaneous; SFU = safety follow-up.

The timepoint is based on the visit label reported by the site.

New or enlarging T2 lesion count measurement is performed with respect to the previous scheduled available visit.

The unadjusted lesion rate is the total number of lesions divided by the number of patients with a readable MRI assessment at the visit and its 95% CI is calculated using exact method based on the Poisson distribution.

n represents the number of patients in the analysis model.

The adjusted rate and two-sided 95% CI are from a Negative Binomial regression model, with log(lesion count) as the response variable, adjusted for geographical region (United States of America vs. Rest of the world).

Sources: t_newet2l_WK12_EMRI; t_newet2l_WK12_RMS_EMRI; t_newet2l_WK12_PPMS_EMRI.

Table 16 Rate of new or enlarging T2 lesions as detected by brain MRI during the treatment phase or SFU on week 24 for RMS, PPMS, and RMS+PPMS populations, efficacy-evaluable – MRI set

	RMS		PPMS		RMS + PPMS	
	OCR IV (N = 106)	OCR SC (N = 107)	OCR IV (N = 12)	OCR SC (N = 11)	OCR IV (N = 118)	OCR SC (N = 118)
Number of patients with a readable MRI assessment at the visit	59	56	6	5	65	61
Total number of lesions	0	2	0	0	0	2
Lesion rate, unadjusted	0.00	0.04	0.00	0.00	0.00	0.03
95% CI	(0.00, 0.06)	(0.00, 0.13)	(0.00, 0.61)	(0.00, 0.74)	(0.00, 0.06)	(0.00, 0.12)
n	56	56	NA	NA	65	61
Lesion rate, adjusted	0.00	0.00	NA	NA	0.00	0.00
95% CI	(0.00, 0.00)	(0.00, 0.00)	NA	NA	(0.00, 0.00)	(0.00, 0.00)

CI = confidence interval; IV = intravenous; MRI = magnetic resonance imaging; NA = not applicable; OCR = ocrelizumab; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis; SC = subcutaneous; SFU = safety follow-up.

The timepoint is based on the visit label reported by the site.

New or enlarging T2 lesion count measurement is performed with respect to the previous scheduled available visit.

The unadjusted lesion rate is the total number of lesions divided by the number of patients with a readable MRI assessment at the visit and its 95% CI is calculated using exact method based on the Poisson distribution.

n represents the number of patients in the analysis model.

The adjusted rate and two-sided 95% CI are from a Poisson regression model, with log(lesion count) as the response variable, adjusted for geographical region (United States of America vs. Rest of the world).

Sources: t_newet2l_WK24_EMRI; t_newet2l_WK24_RMS_EMRI; t_newet2l_WK24_PPMS_EMRI.

Exploratory Radiological and Clinical Endpoints

Table 17 Rate of new or enlarging T2 lesions as detected by brain MRI during the treatment phase or SFU on week 8 for RMS, PPMS and RMS+PPMS populations, efficacy-evaluable – MRI set

	RMS		PPMS		RMS + PPMS	
	OCR IV (N = 106)	OCR SC (N = 107)	OCR IV (N = 12)	OCR SC (N = 11)	OCR IV (N = 118)	OCR SC (N = 118)
Number of patients with a readable MRI assessment at the visit	101	102	12	11	113	113
Total number of lesions	158	86	1	1	159	87
Lesion rate, unadjusted	1.56	0.84	0.08	0.09	1.41	0.77
95% CI	(1.33, 1.83)	(0.67, 1.04)	(0.00, 0.46)	(0.00, 0.51)	(1.20, 1.64)	(0.62, 0.95)
n	101	102	12	11	113	113
Lesion rate, adjusted	1.14	0.63	0.00	0.00	1.04	0.58
95% CI	(0.62, 2.10)	(0.34, 1.16)	(0.00, 0.00)	(0.00, 0.00)	(0.56, 1.91)	(0.32, 1.07)

CI = confidence interval; IV = intravenous; MRI = magnetic resonance imaging; NA = not applicable; OCR = ocrelizumab; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis; SC = subcutaneous; SFU = safety follow-up.

The timepoint is based on the visit label reported by the site.

New or enlarging T2 lesion count measurement is performed with respect to the previous scheduled available visit.

The unadjusted lesion rate is the total number of lesions divided by the number of patients with a readable MRI assessment at the visit and its 95% CI is calculated using exact method based on the Poisson distribution.

n represents the number of patients in the analysis model.

The adjusted rate and two-sided 95% CI are from a Negative Binomial (RMS and RMS+PPMS) or Poisson (PPMS) regression model, with log(lesion count) as the response variable, adjusted for geographical region (United States of America vs. Rest of the world).

Sources: t_newet2l_WK8_EMRI; t_newet2l_WK8_RMS_EMRI; t_newet2l_WK8_PPMS_EMRI.

Treatment Phase or SFU – At Week 8: Of the patients who had a readable MRI assessment at the Week 8 visit and at a previous scheduled MRI visit, 87 and 159 new or enlarging T2 lesions were detected in OCR SC and OCR IV, respectively, most of them in the RMS population (86 and 158, respectively).

Exploratory Clinical Endpoints

Annualized Relapse Rate in RMS patients: In the RMS population, almost no patients experienced relapses during the controlled period up to Week 24 (99.1% [106 patients] in OCR SC and 99.1% [105 patients] in OCR IV). One patient (0.9%) in each arm had 1 relapse, yielding an unadjusted relapse rate (per year) of 0.02 in each arm, during a total follow-up time of 43.33 patient-years (PY) in OCR SC and 42.53 PY in OCR IV.

Summary of main efficacy results

Table 18 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18 Summary of efficacy for trial CN42097 (OCARINA II)

Title: A Phase III, non-inferiority, randomized, open-label, parallel group, multicenter study to investigate the pharmacokinetics, pharmacodynamics, safety and radiological and clinical effects of subcutaneous ocrelizumab versus intravenous ocrelizumab in patients with multiple sclerosis			
Study identifier	CN42097, OCARINA II, EUDRACT number: 2020-005448-48, NCT number: NCT05232825		
Design	CN42097 is a Phase III non-inferiority, randomized, open-label, parallel group, multicenter study to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of SC administration of ocrelizumab compared with the IV infusion of ocrelizumab in patients with either relapsing multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		approximately 24 weeks (controlled period) followed by approximately 24 weeks (SC treatment period) not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	OCR SC treatment arm		Single doses of 920 mg ocrelizumab SC (23 mL volume) at Day 1, Week 24, and Week 48; n=118
	OCR IV treatment arm		Patients received a 600 mg IV infusion of ocrelizumab as the first dose in this study as two 300 mg IV infusions 14 days apart (Day 1 and Day 14); n=118 Single doses of 920 mg ocrelizumab SC (23 mL volume) were administered at Week 24 and Week 48
Endpoints and definitions	Primary endpoint (the primary endpoint of this study is PK, not efficacy)	Serum ocrelizumab area under the concentration-time curve ($AUC_{W1–12}$) after SC administration compared to IV infusion from Day 1 to Week 12	Linear regression model to estimate the geometric mean ratio of OCR SC in comparison with OCR IV

	Secondary radiological endpoint	Total number of T1Gd+ lesions as detected by brain MRI at Weeks 8 and 24	Summarized using descriptive statistics at each visit. Negative binomial or Poisson regression used to estimate adjusted lesion rates. Unadjusted lesion rates also reported. No hypothesis testing was performed.
	Secondary radiological endpoint	Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 12 and 24 relative to the previous scan, respectively	Summarized using descriptive statistics at each visit. Negative binomial or Poisson regression used to estimate adjusted lesion rates. Unadjusted lesion rates also reported. No hypothesis testing was performed.
	Exploratory radiological endpoint	Total number of T1Gd+ lesions as detected by brain MRI at Week 48	Not presented, Week 48 data not available at the time of database lock.
	Exploratory radiological endpoint	Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 8 and 48 relative to the previous scan, respectively	Summarized using descriptive statistics at each visit. Negative binomial or Poisson regression used to estimate adjusted lesion rates. Unadjusted lesion rates also reported. No hypothesis testing was performed. Week 48 data not available at the time of database lock
	Exploratory clinical endpoint	Annualized protocol-defined relapse rate by Weeks 24 and 48 in RMS patients	Defined as number of relapses per patient-year. Week 48 data not available at the time of database lock.
	Exploratory clinical endpoint	Change from baseline in the EDSS at Week 48	Not presented, Week 48 data not available at the time of database lock.
Database lock	Clinical cutoff date (CCOD): 10 March 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis Set and time point description	other: PK-Evaluable Analysis Set All patients who have received the full assigned dose of ocrelizumab and have measurable serum concentrations of ocrelizumab unless major protocol deviations or unavailability of information (e.g., exact blood sampling time, exact dosing information or incomplete dose administration, missing concentration data) occurred, or if data are unavailable, not plausible, or incomplete, that may interfere with the PK evaluation. Patients were grouped according to the actual dose and actual route of administration. time point: From Day 1 to Week 12		
Descriptive statistics and estimate variability	Treatment group	OCR IV	OCR SC
	Number of subjects	116	116

	Serum ocrelizumab area under the concentration-time curve ($AUC_{W1–12}$) from Day 1 to Week 12 mean (SD) (µg/mL•day)	2750 (796)	3500 (914)
	median (µg/mL•day)	2570	3500
	min-max (µg/mL•day)	1390-4690	1180-5940
Effect estimate per comparison	Serum ocrelizumab area under the concentration-time curve ($AUC_{W1–12}$) after SC administration compared to IV infusion from Day 1 to Week 12	Comparison groups	OCR SC vs OCR IV
		Geometric mean ratio	1.2851
		90% confidence interval	1.2258-1.3473
Notes	The primary objective for OCARINA II is to establish the non-inferiority of ocrelizumab SC to ocrelizumab IV based on serum ocrelizumab AUC_{W1-12}. Non-inferior ocrelizumab exposure for the SC formulation versus the IV formulation is expected to translate into comparable efficacy outcomes, as per the principle of PK bridging. In line with this, OCARINA II was not specifically designed nor powered to formally test non-inferior efficacy of ocrelizumab SC to ocrelizumab IV. However, secondary and exploratory radiological and clinical endpoints were included to evaluate and explore the effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS and the results from these endpoints are presented below.		
Analysis description Analysis Set	**Secondary and exploratory analysis** These analyses were pre-specified. **MRI Analysis** - Analysis set: Efficacy-evaluable - MRI Analysis set - All randomized patients who received, during the controlled period (i.e., time until the Week 24 dose of ocrelizumab SC), at least one infusion (partial or complete) or injection (partial or complete) of study drug (ocrelizumab IV or ocrelizumab SC) and having at least one brain MRI scan with measurement taken. Patients were grouped according to the treatment they were assigned. **Annualized protocol-defined relapse rate analysis** - Analysis set: RMS patients among all randomized patients - Patients were grouped according to treatment they were assigned.		
Descriptive statistics and estimate variability	Treatment group	OCR IV	OCR SC
	Number of subjects	118	118
	Total number of T1Gd+ lesions as detected by brain MRI at Week 8 (Number of patients with a readable MRI assessment at the visit)	112	112
	Total number of lesions	24	17
	Lesion rate, unadjusted	0.21	0.15
	95% CI	(0.14, 0.32)	(0.09, 0.24)
	number of patients in the analysis model	98	98
	Lesion rate, adjusted	0.12	0.11

	95% CI	(0.04, 0.32)	(0.04, 0.33)
	Total number of T1Gd+ lesions as detected by brain MRI at Week 24 (Number of patients with a readable MRI assessment at the visit)	65	61
	Total number of lesions	0	2
	Lesion rate, unadjusted	0.00	0.03
	95% CI	(0.00, 0.06)	(0.00, 0.12)
	number of patients in the analysis model	52	49
	Lesion rate, adjusted	0.00	0.00
	95% CI	(0.00, 0.00)	(0.00, 0.00)
	Total number of new or enlarging T2 lesions as detected by brain MRI at Week 12 relative to the previous scan (Number of patients with a readable MRI assessment at the visit)	116	116
	Total number of lesions	7	6
	Lesion rate, unadjusted	0.06	0.05
	95% CI	(0.02, 0.12)	(0.02, 0.11)
	number of patients in the analysis model	116	116
	Lesion rate, adjusted	0.05	0.04
	95% CI	(0.01, 0.23)	(0.01, 0.18)
	Total number of new or enlarging T2 lesions as detected by brain MRI at Week 24 relative to the previous scan (Number of patients with a readable MRI assessment at the visit)	65	61
	Total number of lesions	0	2
	Lesion rate, unadjusted	0.00	0.03
	95% CI	(0.00, 0.06)	(0.00, 0.12)
	number of patients in the analysis model	65	61
	Lesion rate, adjusted	0.00	0.00
	95% CI	(0.00, 0.00)	(0.00, 0.00)

	Total number of new or enlarging T2 lesions as detected by brain MRI at Week 8 relative to the previous scan (Number of patients with a readable MRI assessment at the visit)	113	113
	Total number of lesions	159	87
	Lesion rate, unadjusted	1.41	0.77
	95% CI	(1.20, 1.64)	(0.62, 0.95)
	number of patients in the analysis model	113	113
	Lesion rate, adjusted	1.04	0.58
	95% CI	(0.56, 1.91)	(0.32, 1.07)
	Annualized protocol-defined relapse rate by Week 24 in RMS patients (Number of patients with an available assessment at the visit)	106	107
	Number of patients with 0 relapses 1 relapse 2 relapses >3 relapses	 105 (99.1%) 1 (0.9%) 0 0	 106 (99.1%) 1 (0.9%) 0 0
	Total number of relapses	1	1
	Total follow-up time (patient-years)	42.53	42.33
	Relapse rate (per year), unadjusted	0.02	0.02
Effect estimates per comparison	Not applicable, no hypothesis testing was performed for the secondary radiological and the exploratory radiological and clinical endpoints.		
Notes	The results presented above are based on the protocol-defined CCOD for the primary analysis (10 March 2023). An additional CCOD for study CN42097 is planned for early December 2023, which will include the complete data for the secondary radiological (MRI) endpoints at Week 24. Furthermore, data will also be available for the exploratory radiological (MRI) and clinical (ARR and EDSS) endpoints at Week 48.		

2.6.5.3 Clinical studies in special populations

N/A

2.6.5.4 In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5 Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.6.5.6 Supportive studies

N/A

2.6.6 Discussion on clinical efficacy

As an open label study with descriptive statistics, the efficacy data should be considered exploratory/supportive data only. The secondary and exploratory efficacy endpoints do not raise concerns on any imbalance between arms. Long-term efficacy data for ocrelizumab SC are not available in order to assess persistence of efficacy or tolerance.

2.6.7 Conclusions on the clinical efficacy

Clinical efficacy is not the primary focus of the main study submitted for approval. The submitted efficacy data do not raise immediate concerns.

2.6.8 Clinical safety

2.6.8.1 Patient exposure

Table 19 Summary of studies contributing to safety evaluation

Study Number, Phase	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cut-off Date
CN42097 (OCARINA II), Phase III	Non-inferiority, randomized, open-label, parallel group, multicenter	Adult patients with RMS or PPMS [a]	236 patients randomized 1:1 to receive either ocrelizumab SC or IV as first dose	**Controlled Period:** 920 mg ocrelizumab administered as single SC injection, or 600 mg ocrelizumab administered as two 300 mg IV infusions **SC Ocrelizumab Treatment Period:** 181 patients (as of the CCOD): 920 mg ocrelizumab administered as single SC injection, every 24 weeks.	Primary analysis: 10 Mar 2023
CN41144 (OCARINA I), Phase Ib	Open-label, multicenter	Adult patients with RMS or PPMS [b]	Cohort A1: 4 patients Cohort A2: 4 patients Cohort A3: 4 patients Cohort A4: 4 patients Cohort A5: 35 patients Cohort AA: 35 patients Cohort B1: 3 patients Cohort B2: 3 patients Cohort B3: 3 patients Cohort B4: 37 patients	**Dose Escalation Phase [c]:** Cohort A1/B1 [d]: single dose of 40 mg ocrelizumab SC Cohort A2/B2 [d]: single dose of 200 mg ocrelizumab SC Cohort A3/B3 [d]: single dose of 600 mg ocrelizumab SC Cohort A4/B4: single dose of 1200 mg ocrelizumab SC Cohort A5: single dose of 1200 mg (or 920 mg) [e] ocrelizumab SC Cohort AA: 600 mg ocrelizumab IV **Dose Continuation Phase:** 131 patients (as of the CCOD): candidate dose of 1200 mg ocrelizumab SC, and then 920 mg ocrelizumab SC once it had been selected as the final SC dose, every 24 weeks.	Interim analysis: 27 Jan 2023

Study Number, Phase	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cut-off Date

CCOD = clinical cut-off date; IV = intravenous; PPMS = primary progressive multiple sclerosis; RMS = relapsing forms of multiple sclerosis; SC = subcutaneous.

[a] Patients who had previously received anti-CD20s (including ocrelizumab) were excluded from study if the last treatment was less than 2 years before screening, and/or if B cell count was below lower limit of normal.

[b] In Group A, patients pre-treated with ocrelizumab were included if they had received treatment with IV ocrelizumab for at least 1 year prior to screening. In Group B, patients who had previously received treatment with any B cell-targeted therapies (e.g., ocrelizumab, rituximab, atacicept, belimumab, or ofatumumab) were excluded from study.

[c] Safety data after ocrelizumab doses other than 1200 mg and 920 mg are not presented in this Summary of Clinical Safety but are available in full in the OCARINA I Clinical Study Report 1118563, Section 5.2.

[d] Patients who received a low SC dose (≤ 600 mg ocrelizumab SC) in the dose escalation phase received 600 mg ocrelizumab IV 3 months after the initial SC injection in order to provide therapeutic benefit while selection of the SC dose for the dose continuation phase was pending. The 600 mg IV 'compensatory dose' was administered as a single infusion in Cohorts A1–A3 and as two 300 mg IV infusions 14 days apart in Cohorts B1–B3.

[e] Patients in Cohort A5 received a single dose of the candidate SC dose, i.e. 1200 mg ocrelizumab SC. Following the Safety Monitoring Committee review of preliminary pharmacokinetics data from the dose escalation phase, the dose for the last 6 patients randomized into Cohort A5 was changed to 920 mg ocrelizumab.

Ocarina II

During the controlled period, 118 patients received one injection of 920 mg ocrelizumab SC and 118 patients received one infusion of 600 mg ocrelizumab IV. The median treatment duration was 23.50 weeks (range: 12.3–27.7 weeks) in OCR SC and 23.43 weeks (range: 0.1–34.7 weeks) in OCR IV.

As of the clinical cut-off date, the total observation time per arm in the controlled period was 47 patient-years (PY; 47.17 PY in OCR IV and 47.52 PY in OCR SC).

Table 20 Exposure to OCR SC/IV during controlled period (controlled period analysis), safety-evaluable – all set

Exposure to SC/IV OCR during Controlled Period (Controlled Period Analysis), Safety-evaluable - All Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

	OCR IV (N=118)	OCR SC (N=118)
Treatment duration (a) (Weeks)		
n	118	118
>0 - <= 2	1 (0.8%)	0
>2 - <= 24	71 (60.2%)	72 (61.0%)
>24 - <= 48	46 (39.0%)	46 (39.0%)
n	118	118
Mean (SD)	20.86 (4.98)	21.01 (4.09)
Median	23.43	23.50
Min - Max	0.1 - 34.7	12.3 - 27.7
Number of Doses		
n	118	118
1	118 (100%)	118 (100%)
n	118	118
Mean (SD)	1.00 (0.00)	1.00 (0.00)
Median	1.00	1.00
Min - Max	1.0 - 1.0	1.0 - 1.0
Total Cumulative Dose (mg)		
n	118	118
Mean (SD)	595.29 (25.17)	919.66 (12.26)
Median	598.00	920.00
Min - Max	325.2 - 600.0	800.0 - 960.0

The first dose of intravenous Ocrelizumab (OCR IV group) is given in two infusions administered two weeks apart.
Total Cumulative Dose is capped at 100% for IV, so the actual dosage for IV infusion does not exceed 600 mg.
(a) Treatment duration is the end date minus the date of first study drug administration plus one day.
End date is defined as the earliest between
- Start of other Disease modifying therapies, or commercial ocrelizumab
- Start of 1st SC dose in the SC ocrelizumab treatment phase-1 second
- Withdrawal from study/death
- Withdrawal from treatment
- CCOD
Percentages are calculated based on the number of patients in the treatment arm (N).

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Ocarina I

In total, 131 patients received at least one dose of ocrelizumab 1200 mg SC or 920 mg SC. Across both these doses, starting from the first dose of ocrelizumab 1200 mg SC or 920 mg SC.

Table 21

Study Treatment Exposure, Safety-Evaluable Set, 920 or 1200 mg SC cohort (All Patients who Received at Least One Dose of Ocrelizumab 920 mg SC or 1200 mg SC)
Protocol: CN41144 (Clinical Cut-off Date: 27JAN2023)

	A-OCR SC 920/1200mg (N=86)	B-OCR SC 920/1200mg (N=45)	All Patients (N=131)
Overall SC Treatment Duration (weeks)			
n	86	45	131
Mean (SD)	87.23 (40.19)	107.86 (33.90)	94.32 (39.27)
Median	72.57	119.14	96.00
Min - Max	0.1 - 159.1	0.1 - 157.1	0.1 - 159.1
Overall SC Treatment Duration (weeks) (categorical)			
n	86	45	131
0 - < 24	2 (2.3%)	1 (2.2%)	3 (2.3%)
24- < 48	6 (7.0%)	1 (2.2%)	7 (5.3%)
48- < 72	19 (22.1%)	3 (6.7%)	22 (16.8%)
72- < 96	24 (27.9%)	8 (17.8%)	32 (24.4%)
96- < 120	15 (17.4%)	11 (24.4%)	26 (19.8%)
120- < 144	6 (7.0%)	14 (31.1%)	20 (15.3%)
144- < 168	14 (16.3%)	7 (15.6%)	21 (16.0%)
Number of Overall SC Doses			
n	86	45	131
1	2 (2.3%)	1 (2.2%)	3 (2.3%)
2	3 (3.5%)	1 (2.2%)	4 (3.1%)
3	17 (19.8%)	2 (4.4%)	19 (14.5%)
4	27 (31.4%)	6 (13.3%)	33 (25.2%)
5	17 (19.8%)	11 (24.4%)	28 (21.4%)
6	3 (3.5%)	17 (37.8%)	20 (15.3%)
7	16 (18.6%)	7 (15.6%)	23 (17.6%)
8	1 (1.2%)	0	1 (0.8%)
Overall SC Total Cumulative Dose (mg)			
n	86	45	131
Mean (SD)	4723.02 (1634.77)	5686.22 (1369.09)	5053.89 (1610.16)
Median	4240.00	6040.00	5160.00
Min - Max	1200.0 - 7840.0	1200.0 - 7840.0	1200.0 - 7840.0
Total number of patients with at least one SC dose modification	2 (2.3%)	0	2 (1.5%)
Reason for dose SC modification			
n	2	0	2
Adverse Event	0	0	0
Leakage	0	0	0
Equipment Malfunction	1 (50.0%)	0	1 (50.0%)
Medication Error	0	0	0
Other	1 (50.0%)	0	1 (50.0%)

The overall SC treatment duration is the date of the last dose of SC study medication minus the date of the first SC dose plus one day.
The percentages in Total number of patients with at least one SC dose modification are calculated based on the number of patients in the treatment arm (N).

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Analysis of adverse events

Ocarina II

Safety data reported during the treatment phase up to the clinical cut-off were summarized in the form of three different safety analyses. These comprised:

- Controlled period analysis, based on data collected during the controlled period. This analysis compared the OCR SC arm with the OCR IV arm.
- OCR SC all exposure analysis, based on data collected during the OCR SC all exposure period. This analysis presented data on the OCR SC All group (181 patients, 63 of which received two doses of ocrelizumab SC and 118 of which received exactly one dose of ocrelizumab SC).
- Switchers analysis, based on data collected during the OCR SC all exposure period. This analysis compared the OCR IV/SC group (63/118 patients initially assigned to the OCR IV arm that switched to receive one dose of ocrelizumab SC) with the OCR SC/SC group (118 patients initially assigned to the OCR SC arm, 63 of which proceeded to receive a second dose of ocrelizumab SC). As of the cut-off date, the extent of exposure among the switchers contributing to this analysis was considered sufficient to allow for a meaningful comparison only for the selected AE of IRs that occurred with the second ocrelizumab dose, in each group.

Ocarina I

- The Summary of clinical safety presents AEs observed during the dose escalation phase or the dose continuation phase in patients who received either ocrelizumab doses of 1200 mg SC or 920 mg SC. Safety data observed with the lower ocrelizumab doses other than 1200 mg and 920 mg are not presented in the Summary of clinical safety.

2.6.8.2 Adverse events

An overview of the key safety results of OCARINA II alongside key safety results of OCARINA I is presented in Table 22.

Table 22 Summary of adverse events across studies

	OCARINA II			OCARINA I
	Controlled Period Analysis		OCR SC All Exposure Analysis [a]	Ocrevus SC (at Least One Dose of 920 or 1200 mg)
	IV	SC		
Total number of infusions/injections	**118 infusions**	**118 injections**	**244 injections**	**608 injections**
Total safety observation time	**47.17 PY**	**47.52 PY**	**70.46 PY**	**258.63 PY**
Total number of patients	**118**	**118**	**181**	**131**
Total number of patients with at least one				
Adverse event	54 (45.8%)	87 (73.7%)	115 (63.5%)	127 (96.9%)
Adverse event of Grade ≥ 3	7 (5.9%)	4 (3.4%)	4 (2.2%)	31 (23.7%)
Serious adverse event	4 (3.4%)	3 (2.5%)	3 (1.7%)	16 (12.2%)
Adverse event with fatal outcome	0	0	0	1 (0.8%)
Adverse event leading to withdrawal from treatment	0	0	0	2 (1.5%)
IRR	20 (16.9%)	0	0	0
IR	0	57 (48.3%)	86 (47.5%)	107 (81.7%)
Local IRs	0	54 (45.8%)	81 (44.8%)	102 (77.9%)
Systemic IRs	0	13 (11.0%)	22 (12.2%)	31 (23.7%)
Infections [b]	33 (28.0%)	41 (34.7%)	47 (26.0%)	89 (67.9%)
Serious Infections	4 (3.4%)	0	0	13 (9.9%)
Medical concepts				
Malignancies [c]	0	0	0	2 (1.5%)
Anaphylactic reaction [d]	3 (2.5%)	5 (4.2%)	8 (4.4%)	18 (13.7%)
Hypersensitivity [e]	23 (19.5%)	58 (49.2%)	85 (47.0%)	44 (33.6%)

AE = adverse event; IR = injection reaction; IRR = infusion related reaction; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; SC = subcutaneous; SMQ = Standardised MedDRA Query; PY = patient-years.
Source: OCARINA II CSR 1121154, t_exp_cp_SEALL, t_ae_py_CP_SEALL, t_exp_ocr_tp_SW_SESC, t_ae_py_SC_SESC, t_ae_prfl_CP_SEALL, t_ae_ctc_AE35_CP_SEALL, t_ae_socpt_INFECT_CP_SEALL, t_ae_prfl_SC_SESC, t_ae_ctc_AE35_SC_SESC, t_ae_socpt_INFECT_SC_SESC. OCARINA I CSR 1118563, t_ex_ettrtrec_ALL.
t_exp_cdose_py_SE_SC, t_ae1_SE_SC, t_ae_ctc_AE35_SE_SC.
Notes: Investigator text for AEs encoded using MedDRA version 26.0 for OCARINA II and MedDRA 25.1 for OCARINA I.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Percentages are calculated based on the number of patients in the treatment arm (N).

[a] Per definition, patients who received ocrelizumab SC as their first dose are included in both controlled period analysis and the OCR SC all exposure analysis from the time they received their first dose. Patients who received ocrelizumab IV as their first dose are included in the controlled period analysis from the time they received their first dose; and they are included in the OCR SC all exposure analysis from the time they received their second dose (i.e., ocrelizumab SC).

[b] Identified by MedDRA System Organ Class "Infections and Infestations".
[c] Identified using the "Malignant tumours (SMQ)" narrow.
[d] Identified using the "Anaphylactic reactions (SMQ)".
[e] Identified using the "Hypersensitivity (SMQ)".

Ocarina I:

Table 23 and Table 24 presents a summary of safety events in patients who received 1200 mg ocrelizumab SC (Table 23) and 920 mg ocrelizumab SC (Table 24) respectively.

Table 23 Summary of adverse events in patients who received at least one dose of 1200mg Ocrelizumab SC (safety-evaluable set)

Adverse Events, Safety-Evaluable Set, 1200 mg SC cohort (All Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC)
Protocol: CN41144 (Clinical Cut-off Date: 27JAN2023)

	A-OCR SC 1200mg (N=80)	B-OCR SC 1200mg (N=45)	All Patients (N=125)
Total number of events	401	347	748
Total number of IR	106	95	201
Total number of local IR	83	84	167
Total number of systemic IR	23	11	34
Total number of IRR	0	0	0
Total number of patients with at least one			
Any AE	73 (91.3%)	44 (97.8%)	117 (93.6%)
AE suspected to be caused by IV Ocrelizumab	1 (1.3%)	1 (2.2%)	2 (1.6%)
AE suspected to be caused by SC Ocrelizumab	56 (70.0%)	41 (91.1%)	97 (77.6%)
AE with fatal outcome	1 (1.3%)	0	1 (0.8%)
Serious AE	10 (12.5%)	2 (4.4%)	12 (9.6%)
Infection*	44 (55.0%)	26 (57.8%)	70 (56.0%)
Serious Infection*	10 (12.5%)	1 (2.2%)	11 (8.8%)
Serious AE leading to withdrawal from treatment	0	1 (2.2%)	1 (0.8%)
Serious AE leading to dose modification/interruption	1 (1.3%)	0	1 (0.8%)
Adverse Events of Special Interest**	0	0	0
AE leading to withdrawal from treatment	0	1 (2.2%)	1 (0.8%)
AE leading to dose modification/interruption	2 (2.5%)	1 (2.2%)	3 (2.4%)
IR	54 (67.5%)	40 (88.9%)	94 (75.2%)
Local IR	50 (62.5%)	40 (88.9%)	90 (72.0%)
Systemic IR	16 (20.0%)	9 (20.0%)	25 (20.0%)
IRR	0	0	0
IRRs leading to withdrawal treatment	0	0	0
IRs leading to withdrawal treatment	0	0	0
Medical concepts: patients with			
Malignancies ***	0	1 (2.2%)	1 (0.8%)
Anaphylactic reactions ****	8 (10.0%)	5 (11.1%)	13 (10.4%)
Hypersensitivity *****	23 (28.8%)	14 (31.1%)	37 (29.6%)

Investigator text for AEs encoded using MedDRA version 25.1.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Percentages are calculated based on the number of patients in the treatment arm (N).
* Identified by MedDRA System Organ Class "Infections and Infestations".
** Adverse events of special interest include Hy's law cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice or cases of suspected transmission of an infectious agent by the study drug.
*** Identified using the "Malignant tumours (SMQ)" narrow.
**** Identified using the " Anaphylactic reactions (SMQ)".
***** Identified using the " Hypersensitivity (SMQ)".
Non-Serious Relapses are excluded.
IR = Injection Reaction; IRR = Infusion Related Reaction.
Program: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/program/t_ae1.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/output/t_ae1_SE_SC1200.out
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Table 24 Summary of adverse events in patients who received at least one dose of 920mg Ocrelizumab SC (safety-evaluable set)

Adverse Events, Safety-Evaluable Set, 920 mg SC cohort (All Patients who Received at Least One Dose of Ocrelizumab 920 mg SC)
Protocol: CN41144 (Clinical Cut-off Date: 27JAN2023)

	A-OCR SC 920mg (N=79)	B-OCR SC 920mg (N=39)	All Patients (N=118)
Total number of events	181	129	310
Total number of IR	67	45	112
Total number of local IR	54	44	98
Total number of systemic IR	13	1	14
Total number of IRR	0	0	0
Total number of patients with at least one			
Any AE	62 (78.5%)	32 (82.1%)	94 (79.7%)
AE suspected to be caused by IV Ocrelizumab	0	0	0
AE suspected to be caused by SC Ocrelizumab	42 (53.2%)	26 (66.7%)	68 (57.6%)
AE with fatal outcome	0	0	0
Serious AE	2 (2.5%)	2 (5.1%)	4 (3.4%)
Infection*	34 (43.0%)	13 (33.3%)	47 (39.8%)
Serious Infection*	2 (2.5%)	0	2 (1.7%)
Serious AE leading to withdrawal from treatment	0	0	0
Serious AE leading to dose modification/interruption	0	1 (2.6%)	1 (0.8%)
Adverse Events of Special Interest**	0	0	0
AE leading to withdrawal from treatment	0	1 (2.6%)	1 (0.8%)
AE leading to dose modification/interruption	0	4 (10.3%)	4 (3.4%)
IR	42 (53.2%)	26 (66.7%)	68 (57.6%)
Local IR	36 (45.6%)	26 (66.7%)	62 (52.5%)
Systemic IR	12 (15.2%)	1 (2.6%)	13 (11.0%)
IRR	0	0	0
IRRs leading to withdrawal treatment	0	0	0
IRs leading to withdrawal treatment	0	0	0
Medical concepts: patients with			
Malignancies ***	0	1 (2.6%)	1 (0.8%)
Anaphylactic reactions ****	4 (5.1%)	3 (7.7%)	7 (5.9%)
Hypersensitivity *****	13 (16.5%)	3 (7.7%)	16 (13.6%)

Investigator text for AEs encoded using MedDRA version 25.1.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.
Percentages are calculated based on the number of patients in the treatment arm (N).
* Identified by MedDRA System Organ Class "Infections and Infestations".
** Adverse events of special interest include Hy's law cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice or cases of suspected transmission of an infectious agent by the study drug.
*** Identified using the "Malignant tumours (SMQ)" narrow.
**** Identified using the " Anaphylactic reactions (SMQ)".
***** Identified using the " Hypersensitivity (SMQ)".
Non-Serious Relapses are excluded.
IR = Injection Reaction; IRR = Infusion Related Reaction.
Program: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/program/t_ae1.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/output/t_ae1_SE_SC920.out
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Common Adverse Events

OCARINA II

Controlled Period Analysis

The most frequent AEs by PT (≥ 3% of patients in either arm) are presented in Table 25.

Table 25 Adverse events with an incidence rate of at least 3% by preferred term during controlled period

Adverse Events with an Incidence Rate of at least 3% by Preferred Term during Controlled Period (Controlled Period Analysis), Safety-evaluable - All Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

MedDRA Preferred Term	OCR IV (N=118)	OCR SC (N=118)
Injection related reaction	0	55 (46.6%)
Infusion related reaction	20 (16.9%)	0
Upper respiratory tract infection	9 (7.6%)	8 (6.8%)
Headache	3 (2.5%)	12 (10.2%)
COVID-19	5 (4.2%)	8 (6.8%)
Bronchitis	6 (5.1%)	2 (1.7%)
Urinary tract infection	5 (4.2%)	3 (2.5%)
Arthralgia	5 (4.2%)	2 (1.7%)
Nasopharyngitis	2 (1.7%)	5 (4.2%)
Dizziness	4 (3.4%)	2 (1.7%)
Fall	4 (3.4%)	2 (1.7%)
Oral herpes	1 (0.8%)	4 (3.4%)

Investigator text for AEs encoded using MedDRA version 26.0.
Only treatment emergent adverse events (TEAE) are included in the outputs.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Medical occurrences or symptoms of deterioration anticipated as part of MS are not recorded as adverse events.
Percentages are calculated based on the number of patients in the treatment arm (N).

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_ae_pt_3p.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/t_ae_pt_3p_CP_SEALL.out
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OCR SC All Exposure Analysis

The most frequent AEs by PT (≥3% of patients) are presented in Table 26.

Table 26 Adverse events with an incidence rate of at least 3% by preferred term during OCR SC all exposure period (OCR SC all exposure analysis)

Adverse Events with an Incidence Rate of at least 3% by Preferred Term during OCR SC All Exposure Period (OCR SC All Exposure Analysis), Safety-evaluable - SC Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

MedDRA Preferred Term	OCR SC All (N=181)
Injection related reaction	81 (44.8%)
Headache	12 (6.6%)
COVID-19	9 (5.0%)
Upper respiratory tract infection	9 (5.0%)
Nasopharyngitis	6 (3.3%)

Investigator text for AEs encoded using MedDRA version 26.0.
Only treatment emergent adverse events (TEAE) are included in the outputs.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Medical occurrences or symptoms of deterioration anticipated as part of MS are not recorded as adverse events.
Percentages are calculated based on the number of patients in the treatment arm (N).

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_ae_pt_3p.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/t_ae_pt_3p_SC_SESC.out
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OCARINA I: Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC or 920 mg SC

Among patients who received at least one dose of ocrelizumab 1200 mg SC:

- The most frequent AEs by SOC (≥30% of patients) were:
  - General disorders and administration site conditions: 75.2% (94 patients)
  - Infections and infestations: 56.0% (70 patients)
  - Injury, poisoning and procedural complications: 35.2% (44 patients)
  - Musculoskeletal and connective tissue disorders: 32.8% (41 patients)
- The most frequent AEs by PT (≥10% of patients) were:
  - Injection site reaction: 72.0% (90 patients)
  - COVID-19: 33.6% (42 patients)
  - Injection related reaction: 20.8% (26 patients)
  - Fatigue: 16.0% (20 patients)
  - Headache: 13.6% (17 patients)
  - Urinary tract infection: 11.2% (14 patients)

Among patients who received at least one dose of ocrelizumab 920 mg SC:

- The most frequent AEs by SOC (≥15% of patients) were:
  - General disorders and administration site conditions: 55.9% (66 patients)
  - Infections and infestations: 39.8% (47 patients)
  - Injury, poisoning and procedural complications: 16.9% (20 patients)
  - Nervous system disorders: 15.3% (18 patients)

- The most frequent AEs by PT (≥10% of patients) were:
    - Injection site reaction: 52.5% (62 patients)
    - COVID-19: 21.2% (25 patients)
    - Injection related reaction: 11.0% (13 patients)

2.6.8.3 Serious adverse events, deaths, and other significant events

Serious adverse events

Ocarina II

Controlled Period Analysis

The proportions of patients with at least one SAE were comparable between the two treatment arms (2.5 % in the OCR SC arm vs. 3.4% in the OCR IV arm).

In the OCR SC arm, the SAEs were Multiple sclerosis pseudo relapse, Multiple sclerosis relapse, Eye pain, and Anxiety, reported at least once in one patient (0.8 %). All SAEs resolved as of the cut-off date, and none led to dose schedule modification or treatment discontinuation. All were considered by the investigator to not be related to study treatment.

In the OCR IV arm, the SAEs were Appendicitis, Cellulitis staphylococcal, Pneumonia, Subcutaneous abscess, Upper respiratory tract infections, and Diabetes mellitus, each reported at least once (0.8 %). All SAEs resolved as of the cut-off date, except for the SAE of Diabetes mellitus. None of the SAEs led to infusion modification, dose schedule modification or treatment discontinuation, except for the AE of Diabetes mellitus which led to a 3-month delay of the next ocrelizumab dose. All SAEs were considered by the investigator to not be related to study treatment, except for the AE of Upper respiratory tract infection.

OCR SC All Exposure Analysis

The proportions of patients with at least one SAE in the OCR SC All group was 1.7%. The SAEs were Multiple sclerosis pseudo relapse, Multiple sclerosis relapse, Eye pain, and Anxiety, each reported at least once in one patient (0.6 %). All SAEs were reported during the controlled period, and are as such, discussed above.

Ocarina I: Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC or 920 mg SC

Among patients who received at least one dose of ocrelizumab 1200 mg SC:

- The proportion of patients with at least one SAE was 9.6% (12 patients).
- The SAEs were: COVID-19 (3.2% [4 patients]); COVID-19 pneumonia (3.2% [4 patients]); pneumonia (2.4% [3 patients]); multiple sclerosis relapse (1.6% [2 patients]); and encephalitis, asthenia, muscular weakness, and pulmonary embolism (0.8% [1 patient] each).

Among patients who received at least one dose of ocrelizumab 920 mg SC:

- The proportion of patients with at least one SAE was 3.4% (4 patients).
- The SAEs were (0.8% [1 patient] each): COVID-19, COVID-19 pneumonia, pneumonia, papillary thyroid cancer, and nephrolithiasis.

Deaths

As of the clinical cut-off date, no deaths were reported in Ocarina II.

One patient died due to an SAE of COVID-19 pneumonia in Ocarina I.

Adverse events of special interest

Ocarina II Controlled Period and OCR SC All Exposure Analyses

As of the clinical cut-off date, no AESIs (cases of potential drug-induced liver injury, cases of suspected transmission of an infectious agent by the study drug, or cases of Grade 3 or higher injection site reactions) were reported.

Ocarina I Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC or 920 mg SC

As of the clinical cut-off date, no AESIs (cases of potential drug-induced liver injury or cases of suspected transmission of an infectious agent by the study drug) were reported.

Selected adverse events

Injection Reactions

Ocarina II

Controlled Period Analysis

The proportion of patients in OCR SC (i.e., ocrelizumab-naïve) who experienced at least one IR with the first injection was 48.3% (57/118 patients; see Table 4). Overall, 57 IRs were reported in OCR SC. None were serious.

Of the 57 patients in OCR SC who experienced at least one IR with the first injection, 41 had IRs of Grade 1 maximum severity (71.9%) and 16 had IRs of Grade 2 maximum severity (28.1%). No patients had an IR of Grade 3 or higher. No actions were taken with ocrelizumab SC in response to an IR (including LIRs and SIRs).

Of these IRs, most (26/30 reactions [86.7%]) occurred within 6 hours of the injection. The median time from the end of injection administration to IR onset was 0.265 hours (range: -0.15 to 14.85). Overall, among patients in OCR SC who experienced at least one IR, most (82.5%) had it within 24 hours after the end of injection as opposed to during the injection. Among patients in OCR SC who experienced at least one IR with the first injection, treatment was provided to 16/57 patients (28.1%). Treatment for IRs was standard of care treatments, including mostly analgesics (e.g., ibuprofen, paracetamol), and oral or topical antihistamines (e.g., diphenhydramine, cetirizine).

Local Injection Reactions

The proportion of patients in OCR SC (i.e., ocrelizumab-naïve) who experienced at least one LIR with the first injection was 45.8% (54/118 patients; see Table 4). Overall, 54 LIRs were reported in OCR SC. None were serious.

Among patients in OCR SC, the most common symptoms of LIRs (reported in ≥3% of patients) were:

- Erythema: 29.7% (35/118 patients)

- Pain: 14.4% (17/118 patients)

- Swelling: 8.5% (10/118 patients)

- Pruritus: 6.8 % (8/118 patients)

Systemic Injection Reactions

The proportion of patients in OCR SC (i.e., ocrelizumab-naïve) who experienced at least one SIR with the first injection was 11.0% (13/118 patients; see Table 4). Overall, 13 SIRs were reported in OCR SC. None were serious.

Among patients in OCR SC, symptoms of SIRs reported in ≥1 patients were:

- Headache: 2.5% (3/118 patients)

- Nausea: 1.7 % (2/118 patients)

Switchers Analysis

The proportion of patients who experienced at least one IR was comparable between OCR IV patients at their first SC injection and OCR SC patients at their second SC injection (i.e., both groups having been previously exposed to one dose of ocrelizumab):

- 36.5% (23/63 patients) in OCR IV/SC

- 41.3% (26/63 patients) in OCR SC/SC

Local Injection Reactions

The proportion of patients who experienced at least one LIR was comparable between OCR IV patients at their first SC injection and OCR SC patients at their second SC injection (i.e., both groups having been previously exposed to one dose of ocrelizumab):

- 34.9% (22/63 patients) in OCR IV/SC

- 36.5% (23/63 patients) in OCR SC/SC

Systemic Injection Reactions

The proportion of patients who experienced at least one SIR was comparable between OCR IV patients at their first SC injection and OCR SC patients at their second SC injection (i.e., both groups having been previously exposed to one dose of ocrelizumab):

- 9.5% (6/63 patients) in OCR IV/SC

- 6.3% (4/63 patients) in OCR SC/SC

OCR SC All Exposure Analysis

The proportion of patients in OCR SC All who experienced at least one IR with any injection was 47.5% (86/181 patients; see Table 4). Overall, 106 IRs were reported in OCR SC All. None were serious.

With repeated injections, in OCR SC All (i.e., including both first injections in ocrelizumab-naïve patients and second injections in pre-treated patients), the incidence of IRs decreased from 44.2% (80/181 patients) at the first injection to 41.3% (26/63 patients) at the second injection.

Of the 86 patients in OCR SC All who experienced at least one IR with any injection, 66 had IRs of Grade 1 maximum severity (76.7%) and 20 had IRs of Grade 2 maximum severity (23.3%). No patients had an IR of Grade 3 or higher.

With repeated injections, the intensity of IRs decreased:

- Of the 80 patients that experienced at least one IR at the first injection, 61 had IRs of Grade 1 maximum severity (76.3%) and 19 had IRs of Grade 2 maximum severity (23.8%).

- Of the 26 patients that experienced at least one IR at the second injection, 23 had IRs of Grade 1 maximum severity (88.5%) and 3 had IRs of Grade 2 maximum severity (11.5%).

Overall, among patients in OCR SC All who experienced at least one IR, most (75.6%) had it within 24 hours after the end of injection as opposed to during the injection.

Among patients in OCR SC All who experienced at least one IR at any injection, treatment was provided to 18/86 patients (20.9%).

With repeated injections, fewer patients required treatment. Among patients in OCR SC All who experienced at least one IR, treatment was provided to 18/80 patients (22.5%) after the first injection and 3/26 patients (11.5%) after the second injection.

Local Injection Reactions

The proportion of patients in OCR SC All who experienced at least one LIR with any injection was 44.8% (81/181 patients; see Table 4). Overall, 99 LIRs were reported in OCR SC All. None were serious.

Among patients in OCR SC All, the most common symptoms of LIRs (reported in ≥3% of patients) were:

- Erythema: 32.6% (59/181 patients)

- Pain: 14.9% (27/181 patients)

- Swelling: 8.3% (15/181 patients)

- Pruritus: 5.0 % (9/181 patients)

Systemic Injection Reactions

The proportion of patients in OCR SC All who experienced at least one SIR with any injection was 12.2% (22/181 patients; see Table 4). Overall, 23 SIRs were reported in OCR SC All. None were serious.

Among patients in OCR SC All, symptoms of SIRs reported in >1 patients were:

- Headache: 1.7 % (3/181 patients)

- Fever: 1.1 % (2/181 patients)

- Flushing: 1.1 % (2/181 patients)

- Nausea: 1.1 % (2/181 patients)

- Pain: 1.1% (2/181 patients)

Ocarina I: Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC or 920 mg SC

Among patients who received at least one dose of ocrelizumab 1200 mg SC, 75.2% (94 patients) experienced IRs (Table 5).

Among patients who received at least one dose of ocrelizumab 920 mg SC, 57.6% (68 patients) experienced IRs (Table 6).

Among patients who received at least one dose of ocrelizumab 1200 mg SC:

- The majority of IRs were Grade 1 or 2.

- 1 patient had a Grade 3 systemic IR (previously treated with ocrelizumab IV prior to study, after first injection of ocrelizumab 1200 mg SC, the patient experienced symptoms of dyspnea and wheezing, 4 hours following completion of ocrelizumab 1200 mg SC, which resolved with anti-allergy treatment after another hour). Further details on this case are included in the patient narratives.

Among patients who received at least one dose of ocrelizumab 920 mg SC, all IRs were Grade 1 or 2. No patients had IRs of Grade 3 or higher.

Local Injection Reactions

Among patients who received at least one dose of ocrelizumab 1200 mg SC, 72.0% (90 patients) experienced LIRs (Table 5).

Among patients who received at least one dose of ocrelizumab 920 mg SC, 52.5% (62 patients) experienced LIRs (Table 6).

Systemic Injection Reactions

Among patients who received at least one dose of ocrelizumab 1200 mg SC, 20.0% (25 patients) experienced SIRs (Table 5).

Among patients who received at least one dose of ocrelizumab 920 mg SC, 11.0% (13 patients) experienced SIRs (Table 6).

Infusion Related Reactions

Ocarina II Controlled Period Analysis

The proportion of patients in OCR IV who experienced at least one IRR was 16.9% (20/118 patients; see Table 4). Overall, 27 IRRs were reported in OCR IV. None were serious.

Split by infusion, the incidence of IRRs decreased from 16.1% (19/118 patients) at the Day 1 infusion to 6.0% (7/117 patients) at the Day 14 infusion. Among patients in OCR IV, the most common symptom of IRRs (reported in >3% of patients) was Pruritus: 3.4% (4/118 patients). In addition, the symptoms reported in >1 patient were:

- Headache: 2.5% (3/118 patients

- Erythema: 1.7% (2/118 patients)

- Tachycardia: 1.7% (2/118 patients)

- Throat irritation: 1.7% (2/118 patients)

Of the 20 patients in OCR IV who experienced at least one IRR, 9 had IRRs of Grade 1 maximum severity (45.0%) and 11 had IRRs of Grade 2 maximum severity (55.0%). No patients had an IRR of Grade 3 or higher.

Among patients in OCR IV who experienced at least one IRR with any infusion, treatment was provided to 9/20 patients (45.0%).

Treatment for IRRs was standard of care treatments, including mostly IV corticosteroids (e.g., hydrocortisone), analgesics (e.g., paracetamol), and oral or IV antihistamines (e.g., loratadine, chlorphenamine, promethazine).

The median duration of IRRs was 1 day (range: 1 to 10 days). Most IRRs (23/27 reactions [85.2%]) resolved within 3 days of onset.

Infections

Ocarina II

Controlled Period Analysis

The proportion of patients with an infection was 34.7% in the OCR SC arm and 28.0% in the OCR IV arm. The most frequent infections by PT (≥5% of patients in either arm) were (OCR SC arm vs. OCR IV arm, respectively):

- Upper respiratory tract infection (6.8% vs. 7.6%)

- COVID-19 (6.8% vs. 4.2%)

- Bronchitis (1.7% vs. 5.1%)

No patients in the OCR SC arm had a serious infection (see Table 4). In the OCR IV arm, 4 patients (3.4%) had a serious infection (see Table 4). The serious infections were Appendicitis, Cellulitis staphylococcal, Pneumonia, Subcutaneous abscess, Upper respiratory tract infection.

No infections of Grade 3 were reported in the OCR SC arm. All serious infections in the OCR IV arm were of Grade 3.

OCR SC All Exposure Analysis

The proportions of patients with an infection in the OCR SC All group was 26.0%. The most frequent infections by PT (≥5% of patients) were:

- Upper respiratory tract infection (5.0%)

- COVID-19 (5.0%)

No patients in the OCR SC All group had a serious infection (see Table 4). No infections of Grade ≥3 in severity were reported. No patients had a serious infection lasting more than 4 weeks (>28 days).

Ocarina I: Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC or 920 mg SC

Among patients who received at least one dose of ocrelizumab 1200 mg SC:

- The proportion of patients who experienced infections and serious infections, respectively was 56.0% (70 patients) and 8.8% (11 patients; Table 5).

- 11 patients (8.8%) had Grade 3 infection AEs and 1 patient (0.8%) had a Grade 5 infection AE. All other infections were Grade 1 or 2.

– The Grade 3 infections were: COVID-19 (5 patients [4.0%]), pneumonia (3 patients [2.4%]), COVID-19 pneumonia (1 patient [0.8%]), encephalitis (1 patient [0.8%]), SARS-CoV-2 sepsis (1 patient [0.8%]), and tooth abscess (1 patient [0.8%]).

– The Grade 5 infection AE was COVID-19 pneumonia.

- The most frequent infections by PT (≥3% of patients) were:

– COVID-19: 33.6% (42 patients)

– Urinary tract infection: 11.2% (14 patients)

– Nasopharyngitis: 7.2% (9 patients)

– Sinusitis: 4.8% (6 patients)

– Pneumonia: 4.0% (5 patients)

– COVID-19 pneumonia: 3.2% (4 patients)

- The serious infections were:

– COVID-19: 3.2% (4 patients)

– COVID-19 pneumonia: 3.2% (4 patients)

– Pneumonia: 2.4% (3 patients)

– Encephalitis: 0.8% (1 patient)

Among patients who received at least one dose of ocrelizumab 920 mg SC:

- The proportion of patients who experienced infections and serious infections, respectively was 39.8% (47 patients) and 1.7% (2 patients; Table 6).

- 4 patients (3.4%) had Grade 3 infections. All other infections were Grade 1 or 2. The Grade 3 infections were: COVID-19 (2 patients [1.7%]), pneumonia (1 patient [0.8%]), COVID-19 pneumonia (1 patient [0.8%]), and Clostridium difficile infection (1patient [0.8%]).

- The most frequent infection AEs by PT (≥3% of patients) were:

– COVID-19: 21.2% (25 patients)

– Urinary tract infection: 6.8% (8 patients)

– Bronchitis: 5.1% (6 patients)

– Nasopharyngitis: 4.2% (5 patients)

– Upper respiratory tract infection: 4.2% (5 patients)

- The serious infections were:

– COVID-19: 0.8% (1 patient)

– COVID-19 pneumonia: 0.8% (1 patient)

– Pneumonia: 0.8% (1 patient)

Hypersensitivity and Anaphylactic Reaction Events

In both studies, AEs potentially representing hypersensitivity and anaphylactic reactions were retrieved using the MedDRA Anaphylactic reactions SMQ [Broad] and the Hypersensitivity SMQ [Broad]. All AEs

were subsequently medically reviewed for identification of an event representing a hypersensitivity or anaphylactic reaction related to ocrelizumab.

None of the AEs were confirmed to be hypersensitivity or anaphylactic reactions but rather IRs, IRRs or respective symptoms of the LIRs, SIRs and IRRs.

Malignancies

Ocarina II Controlled Period and OCR SC All Analyses

As of the clinical cut-off date, no malignancies were reported.

Ocarina I: Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC or 920 mg SC

A total of 2 patients in the Safety-Evaluable Set (i.e., all patients who received at least one dose of study drug) experienced AEs retrieved by the Malignant Tumours SMQ:

One patient experienced a Grade 2 AE of basal cell carcinoma and one patient experienced a Grade 3 AE of papillary thyroid cancer.

2.6.8.4 Laboratory findings

Hematology and Chemistry

Ocarina II Controlled Period Analysis

The marked laboratory abnormalities reported in >1 patient in either arm were (OCR SC arm vs. OCR IV arm, respectively):

- Low neutrophils, total, absolute: 3.4% (4/118 patients) vs. 3.4% (4/118 patients)

- High neutrophils, total, absolute: 0 vs. 1.7 % (2/118 patients)

- Low lymphocytes, absolute: 1.7 % (2/118 patients) vs. 1.7 % (2/118 patients)

Shifts to NCI CTCAE Grade 3 or 4 post-baseline abnormalities are presented in Table 27.

Table 27

Laboratory Test Shifts to NCI-CTCAE Grade 3-4 Post-Baseline during Controlled Period (Controlled Period Analysis), Safety-evaluable - All Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

Laboratory Test	Direction of Abnormality	OCR IV (N=118)	OCR SC (N=118)
Chemistry			
Alkaline Phosphatase	High	0/115	0/115
ALT	High	0/112	0/114
Amylase	High	0/116	0/116
AST	High	0/116	0/117
Creatinine	High	0/115	0/115
Gamma Glutamyl Transferase	High	0/115	0/115
Potassium	Low	0/115	0/115
	High	0/115	0/115
Sodium	Low	0/115	0/115
	High	0/115	0/115
Bilirubin	High	0/115	0/116
Hematology			
Hemoglobin	Low	0/111	0/114
	High	0/111	0/114
Lymphocytes Abs	Low	1/110 (0.9%)	1/114 (0.9%)
	High	0/111	0/114
Neutrophils, Total, Abs	Low	2/112 (1.8%)	0/114
Platelet	Low	0/110	0/114
Total Leukocyte Count	Low	1/111 (0.9%)	0/114
	High	0/111	0/114

Baseline: the last assessment before the first exposure. For each laboratory test, patients with at least 1 post-baseline assessment are included in the analysis. For each cell, the denominator is the number of patients with baseline NCI-CTCAE Grade 0-2 in the specified direction of abnormality, or Grade 1-4 in the opposite direction of abnormality. Patients with missing baseline values are included in the denominator.

Program: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_lb_shift.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/t_lb_shift_CP_SEALL.out
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Liver Tests

No clinically meaningful difference was observed between the OCR SC and OCR IV arms with respect to liver tests.

All reported liver enzyme elevations were of Grade 1 maximum severity. In the majority of cases, the observed elevation in liver enzymes were single occurrences or sustained baseline elevations.

No cases of potential drug-induced liver injury were reported.

Ocarina I Patients who Received at Least One Dose of Ocrelizumab SC

The most common marked laboratory abnormalities were:

- High neutrophils, total, absolute: 40.5% (51/126 patients)

- High neutrophils, total, percentage: 16.7% (5/30 patients)

- Low lymphocytes, absolute: 15.9% (20/126 patients)

- Low lymphocytes, percentage: 40.0% (12/30 patients)

- High total leukocyte count: 13.7% (18/131 patients)

For the majority of patients (≥85% of patients with abnormalities), the marked laboratory abnormalities were single occurrences and were not sustained or replicated.

Elevated Liver Enzymes

Post-baseline elevations in liver enzymes were as follows (N=131):

- High ALT: 20.6% (27 patients)

- High AST: 11.5% (15 patients)

- High bilirubin: 3.8% (5 patients)

All post-baseline liver enzyme elevations were Grade 1, except for one Grade 2 bilirubin elevation. In the majority of cases, the observed elevation in liver enzymes were single occurrences and were not sustained or replicated and not requiring symptomatic treatment or treatment interruption.

There were no reported cases of potential drug-induced liver injury.

Shifts to NCI CTCAE Grade 3 or 4 post-baseline abnormalities are presented in Table 28.

Table 28

Laboratory Test Shifts to NCI-CTCAE Grade 3-4 Post-Baseline, Safety-Evaluable Set, 920 or 1200 mg SC cohort (All Patients who Received at Least One Dose of Ocrelizumab 920 mg SC or 1200 mg SC)
Protocol: CN41144 (Clinical Cut-off Date: 27JAN2023)

Laboratory Test	Direction of Abnormality	A-OCR SC 920/1200mg (N=86)	B-OCR SC 920/1200mg (N=45)	All Patients (N=131)
Chemistry				
Amylase	High	1/86 (1.2%)	0/45	1/131 (0.8%)
Creatinine	High	1/86 (1.2%)	0/45	1/131 (0.8%)
Potassium	Low	3/86 (3.5%)	0/45	3/131 (2.3%)
	High	0/86	0/45	0/131
Sodium	Low	1/86 (1.2%)	0/45	1/131 (0.8%)
	High	0/86	0/45	0/131
Hematology				
Hemoglobin	Low	1/86 (1.2%)	0/45	1/131 (0.8%)
	High	0/86	0/45	0/131
Lymphocytes Abs	Low	3/80 (3.8%)	5/45 (11.1%)	8/125 (6.4%)
	High	0/80	0/45	0/125
Neutrophils, Total, Abs	Low	0/80	0/45	0/125
Platelet	Low	0/86	0/45	0/131
Total Leukocyte Count	Low	0/86	0/45	0/131
	High	0/86	0/45	0/131

Baseline is defined as the latest assessment prior to the first exposure of any dose of 920 or 1200mg SC OCR.
For each laboratory test, patients with at least 1 post-baseline assessment are included in the analysis.
For each cell, the denominator is the number of patients with baseline NCI-CTCAE Grade 0-2 in the specified direction of abnormality, or Grade 1-4 in the opposite direction of abnormality.
Patients with missing baseline values are included in the denominator.

Program: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/program/t_lbt.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN41144/data_analysis/CSR/prod/output/t_lbt_SE_SC.out
10MAY2023 11:46 Page 1 of 1

Vital signs

OCARINA II

Overall, the proportions of patients with vital signs abnormalities, regardless of abnormality at baseline, were comparable between the two treatment arms (Table 29).

Table 29 Vital sign parameters outside normal limits regardless of abnormality at baseline during controlled period

Vital Sign Parameters outside Normal Limits Regardless of Abnormality at Baseline during Controlled Period Controlled Period Analysis), Safety-evaluable - All Set
Protocol: CN42097 (Clinical Cut-off Date: 10MAR2023)

Assessment	Direction of Abnormality	OCR IV (N=118)	OCR SC (N=118)
Oxygen Saturation	Low	6/105 (5.7%)	3/103 (2.9%)
	High	0/105	0/103
Diastolic Blood Pressure, Sitting	Low	12/117 (10.3%)	2/118 (1.7%)
	High	70/117 (59.8%)	64/118 (54.2%)
Systolic Blood Pressure, Sitting	Low	3/117 (2.6%)	3/118 (2.5%)
	High	54/117 (46.2%)	46/118 (39.0%)
Pulse Rate, Sitting	Low	21/117 (17.9%)	11/118 (9.3%)
	High	5/117 (4.3%)	0/118

Table entries provide the number of patients with an abnormality assessed during the treatment phase in the direction specified, regardless of abnormality at baseline.
Abnormalities reported in patients with missing baseline values are included.
Baseline: the assessment taken "within 45 minutes prior to premedication" of Week 1 on IV arm and "before premedication prior to the ocrelizumab injection" of Week 1 on SC arm; if not available the screening assessment will be used.

Program:
root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/program/t_vs_abn.sas
Output: root/clinical_studies/RO4964913/CDT30233/CN42097/data_analysis/CSR/prod/output/
t_vs_abn_CP_SEALL.out
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OCARINA I

Vital signs were measured at dosing visits prior to study drug administration. Vital signs were also measured 1, 4, and 24 hours after the end of the infusion/injection.

4 patients (2 treated with ocrelizumab 1200 mg SC and 2 treated with ocrelizumab 600 mg IV) experienced blood pressure abnormalities reported as AEs (2 AEs of hypertension, 1 AE of blood pressure increased, and 1 AE of hypotension). All 4 events were non-serious, Grade 2, and were resolved or resolving at the time of clinical cut-off date. None of them were symptoms of IRs or IRRs.

When comparing patients in Dose Escalation Group A who received ocrelizumab SC (920 mg or 1200 mg) vs. ocrelizumab 600 mg IV, there were no clinically relevant differences between the OCR SC arm and the OCR IV arm with respect to vital sign parameters. The incidence of vital signs abnormalities was generally higher in the OCR SC arm compared with the OCR IV arm; however, the majority of the vital signs abnormalities were not considered clinically significant and were not reported as AEs.

Electrocardiography

No clinically meaningful trends and no safety concerns had been observed from the analysis of ECG data collected in OCARINA I, up to the clinical cut-off date of 9 November 2021 used to select the ocrelizumab dose to be evaluated in OCARINA II. ECG assessments were not conducted in OCARINA II.

No patients had absolute QTcF values >500 msec. One patient had a change from baseline in QTcF of >60 msec that occurred 60 minutes after their fifth injection of ocrelizumab 1200 mg SC at Week 96.

Clinical significance of ECG results was determined by the investigator's medical judgment and reported on the eCRF. Two patients had clinically significant ECG abnormalities, both of which were reported as AEs. One patient had a Grade 2 sinus tachycardia event after receiving their fifth dose of ocrelizumab 1200 mg SC at Week 96 (and experienced the >60 msec change from baseline in QTcF described above). One patient had a Grade 1 atrioventricular block first degree approximately 5 months after receiving their first dose of ocrelizumab 920 mg SC at Week 48 that led to interruption of ocrelizumab SC treatment. Treatment was resumed with a delay of approximately 6 weeks. Both AEs were ongoing at the time of clinical cut-off date.

2.6.8.5 In vitro biomarker test for patient selection for safety

Not applicable. There are no *in vitro* biomarker tests relevant for patient selection for safety.

2.6.8.6 Safety in special populations

Intrinsic factors

No AE analyses were performed by any intrinsic factors.

Extrinsic factors

No AE analyses were performed by any extrinsic factors.

2.6.8.7 Immunological events

Prevalence of ADAs at baseline was defined as the proportion of the evaluable patient population in a study that is ADA positive at the baseline timepoint. The incidence of ADAs (at post-baseline timepoints) was defined as the proportion of the study population found to have seroconverted (i.e., developed treatment-induced ADAs).

In both studies, no patients developed treatment-emerged anti-drug antibodies (ADAs) to ocrelizumab SC, as of the clinical cut-off date.

Ocarina II: Controlled Period Analysis

At baseline, among the baseline-evaluable patients of the immunogenicity-evaluable – all set, the prevalence of anti-ocrelizumab antibodies was 0.9% (1/117 patients) in OCR SC and 0.9% (1/116 patients) in OCR IV.

At baseline, among the baseline-evaluable patients of the immunogenicity-evaluable all set, the prevalence of anti-rHuPH20 antibodies was 5.8% (3/52 patients) in OCR SC and 6.5% (4/62 patients) in OCR IV.

No treatment-emergent ADAs to ocrelizumab or anti-rHuPH20 were reported in either treatment arm based on, respectively, serum and plasma samples collected up to the clinical cut-off date.

Ocarina I

At baseline, 85/88 patients in Group A and 45/46 patients in Group B were evaluable for anti-ocrelizumab antibodies, and the baseline prevalence of ADAs was 0% in both groups. Post-baseline, the incidence of treatment-emergent ADAs to ocrelizumab was 0 of 88 post-baseline evaluable patients (0%) in Group A, and 0 of 46 post-baseline evaluable patients (0%) in Group B.

In Group A, 82/88 patients were evaluable for anti-rHuPH20 antibody assessment at baseline. The baseline prevalence of anti-rHuPH20 antibodies was 11.0% (9/82 patients). Post-baseline, the incidence of treatment-emergent anti-rHuPH20 antibodies was 1 of 87 post-baseline evaluable patients (1.1%) in Group A.

In Group B, 44/46 patients were evaluable for anti-rHuPH20 antibody assessment at baseline. The baseline prevalence of anti-rHuPH20 antibodies was 9.1% (4/44 patients).

Post-baseline, the incidence of treatment-emergent anti-rHuPH20 antibodies was 2 of 45 post-baseline evaluable patients (4.4%) in Group B.

No safety concerns have been observed in patients with anti-rHuPH20 antibodies.

2.6.8.8 Safety related to drug-drug interactions and other interactions

No formal drug-drug or drug-food interaction assessments were conducted.

2.6.8.9 Discontinuation due to adverse events

Ocarina II Controlled Period and OCR SC All Exposure Analyses

As of the clinical cut-off date, no AEs led to discontinuation of treatment.

Ocarina I Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC or 920 mg SC

One patient (0.8%) who received ocrelizumab 1200 mg SC experienced an SAE of Grade 3 multiple sclerosis relapse that led to study drug discontinuation.

One patient (0.8%) who received ocrelizumab 920 mg SC experienced a Grade 2 AE of multiple sclerosis (verbatim term recorded by investigator: "worsening multiple sclerosis") that led to study drug discontinuation.

2.6.8.10 Post marketing experience

Post-marketing data summarized in this section originates from the experience with ocrelizumab IV, the only formulation of ocrelizumab marketed to date.

Ocrelizumab was first granted marketing authorization on 28 March 2017, in the United States. In the European Union (EU), ocrelizumab was approved on 8 January 2018, and as of 27 March 2023, it is approved in over 100 countries worldwide.

Since the Developmental International Birth Date on 23 December 2003 and until 31 March 2023, the estimated cumulative exposure to ocrelizumab (both IV and SC formulations) in clinical trials is 13,087 patients, of which 5,790 patients with RMS, 3,378patients with PPMS; and the rest in other no longer pursued indications or different categories (e.g., studies in both RMS and PPMS patients, or high ocrelizumab dose studies).

Since the International Birth Date (IBD) on 28 March 2017 and until 31 March 2023, the estimated cumulative market exposure to ocrelizumab is 302,199 patients. This corresponds to an estimated 721,879 PYs of exposure since IBD. The safety data from post-marketing experience and from the ongoing clinical trials overall remained consistent with that observed in the controlled periods of the pivotal clinical trials, with longer treatment duration, as well as with exposure of broader and more heterogeneous population.

2.6.9 Discussion on clinical safety

Safety data

The clinical safety database for the SC formulation of ocrelizumab is based on a phase 1b and a phase 3 study (OCARINA I and OCARINA II) in the targeted population. The safety database was summarised in three different safety analyses for OCARINA II (Controlled period analysis, OCR SC all exposure analysis and Switchers analysis) and one for OCARINA I (Patients who Received at Least One Dose of Ocrelizumab 1200 mg SC or 920 mg SC).

In the following assessment the controlled period analysis will be used as main safety analysis, since the main aim is to compare the IV formulation with the SC formulation. The OCR SC all exposure analysis, switchers analysis and OCARINA I analysis will be used as supportive safety analysis.

Ocarina II: During the controlled period, 118 patients received one injection of 920 mg ocrelizumab SC and 118 patients received one infusion of 600 mg ocrelizumab IV. The median treatment duration was 23.50 weeks (range: 12.3-27.7 weeks) in OCR SC and 23.43 weeks (range: 0.1-34.7 weeks) in OCR IV.

63 patients (53.4%) in ocrelizumab SC received a second ocrelizumab SC injection (Dose 2) at Week 24 and 63 patients (53.4%) in ocrelizumab IV received their first ocrelizumab SC injection (Dose 2) at Week 24. As of the clinical cut-off date, no patients in either arm had reached Week 48 of the study and therefore none received Dose 3.

Throughout the treatment phase, 181 patients received at least one injection of ocrelizumab SC with a median treatment duration of 17.71 weeks (range 0.1 – 44.6 weeks) and a total observation time on ocrelizumab SC of 70.46 PY. A total of 244 ocrelizumab SC injections were administered throughout the study.

Ocarina I: In total, 125 patients received at least one injection of ocrelizumab 1200 mg SC, and a maximum of 5 consecutive injections of this dose have been administered. Overall, 346 injections of 1200 mg ocrelizumab SC were administered in OCARINA I.

In total, 118 patients received at least one injection of ocrelizumab 920 mg SC. A maximum of 4 consecutive injections of 920 mg SC have been administered as of the cut-off date. Overall, 262 injections of 920 mg ocrelizumab SC have been administered in OCARINA I, as of the cut-off date.

In total, 131 patients received at least one dose of ocrelizumab 1200 mg SC or 920 mg SC. The median overall SC ocrelizumab treatment duration was 96.0 weeks (range: 0.1-159.1). 92.4% of patients were treated with SC ocrelizumab for ≥48 weeks and 94.7% of patients received 3 or more doses of SC ocrelizumab.

Overall, the safety database consisted of a total of 312 patients treated with at least one injection of ocrelizumab SC. A total of 246 patients were treated with ocrelizumab SC for at least 24 weeks and 121 patients were treated with ocrelizumab SC beyond 48 weeks and 99 were treated with ocrelizumab SC beyond 96 weeks. The SC safety database is limited with regard to the total exposure. However, since the safety profile is well-known from the ocrelizumab IV, the total exposure is considered acceptable since the patient population and active substance is the same. Furthermore, long-term safety of ocrelizumab treatment is missing information in the safety specification in the RMP and two PASS studies are ongoing for the IV formulation. The MAH states that the safety data from the OCARINA I and OCARINA II studies will be presented in the final CSRs, which will be submitted when they are available.

Adverse events

OCARINA II: Controlled Period Analysis: AEs were reported more frequent in the OCR SC arm (73.7%) compared to the OCR IV arm (45.8%).

The difference in AEs is primarily due to the difference reported in Injection reactions (IRs) in the OCR SC arm and infusion related reactions (IRRs) in the OCR IV arm; 48.3% patients experienced at least one IR in the OCR SC arm and 16.9% patients experienced at least one IRR in the OCR IV arm.

With regard to the IRs in the OCR SC arm, 45.8% patients experienced at least one local injection reaction (LIR) and 11.0% patients experienced at least one systemic injection reaction (SIR).

Anaphylactic reactions and hypersensitivity (identified using the" Anaphylactic reaction" and "hypersensitivity" (SMQ)) were reported more often in the OCR SC arm compared to the OCR IV arm (4.2% and 49.2% vs. 2.5% and 19.5%). The SmPC have been updated to reflect the risk of hypersensitivity and appropriate risk minimisation measures.

Infections were also reported more frequent in the OCR SC arm (34.7%) compared to the OCR IV arm (28.0%). However, serious infections were only observed in the OCR IV arm (3.4%).

AEs of grade ≥ 3 and serious were reported slightly more frequent in the OCR IV arm (5.9% and 3.4%) compared to the OCR SC arm (3.4% and 2.5%). No deaths were reported, and no AEs led to discontinuation of treatment.

OCARINA II: OCR SC All Exposure Analysis: AEs were reported in 63.5% of patients in the OCR SC All group. 47.5% patients in the OCR SC All group experienced at least one IR; 44.8% patients experienced at least one LIR and 12.2% patients experienced at least one SIR. No deaths were reported, and no AEs led to discontinuation of treatment.

OCARINA I: Ocrevus SC (at Least One Dose of 920 or 1200 mg): AEs were reported in 96.9% in patients receiving OCR SC 920 or 1200 mg. 23.7% had AEs of grade 3 and 12.2% has serious adverse events. One adverse event with fatal outcome were reported and 2 (1.5%) AEs leading to withdrawal from treatment. The AE leading to death were in the ocrelizumab 1200 mg dose. IRs were reported more

frequent in the ocrelizumab 1200 mg group compared to 900 mg (75.2% vs. 57.6%) and the same pattern was seen with anaphylactic reactions and hypersensitivity (10.4% 29.6% vs. 5.9% and 13.6%).

Overall, AEs were reported more frequent in OCR SC compared to OCR IV. The difference in AEs is primarily due to the difference reported in Injection reactions (IRs) in the OCR SC arm and infusion related reactions (IRRs) in the OCR IV arm. Anaphylactic reactions and hypersensitivity were reported more often in the OCR SC compared to OCR IV. Appropriate risk minimisation measures have been added to the SmPC section 4.2 to minimise this risk for the SC formulation.

Common adverse events

OCARINA II: Controlled Period Analysis: In the Controlled Period Analysis, the most common reported AEs were Injection related reaction (46.6% in OCR SC), Headache (10.2% in OCR SC vs. 2.5% in OCR IV), Infusion related reactions (16.9% in OCR IV), Upper respiratory tract infection (6.8% in OCR SC vs. 7.6% in OCR IV) Covid-19 (6.8% in OCR SC vs. 4.2% in OCR IV) and Bronchitis (1.7% in OCR SC vs. 5.1% in OCR IV). Headache is not in the Adverse reaction table in the SmPC section 4.8. The MAH states that, among the 12 patients in the OCR SC arm that experienced an AE of Headache, 5 had a medical history of headache, and 3 reported the headache more than 4 months after the last ocrelizumab dose. Three AEs of Headache occurred 1-4 days after ocrelizumab SC and were considered by the investigator to be related to study treatment. The imbalance for headache observed in the OCARINA II study (10.2% in the SC arm versus 2.5% in the IV arm), were mainly driven by events assessed as not related to ocrelizumab SC by the investigator and caused by other causes (other/concomitant medications). None of the 3 events of headache in the IV group were assessed by the investigator as related to ocrelizumab IV and none had a history of headache reported. Most of the reported AEs of headache were causally not associated with ocrelizumab treatment as assed by the investigator. The remaining AEs, assessed as to be causally associated with ocrelizumab, had an onset time indicative of them being a symptom of systemic IR (1-4 days).

Overall, the Applicant has justified not including headache as a separate ADR for ocrelizumab SC. Since headache is characterized as a common symptom associated with systemic injection reactions in Section 4.4 and Section 4.8, it is considered acceptable not to include headache as a separate ADR in section 4.8.

Overall, the proportions of patients with AEs of Grade 3 were comparable between the two treatment arms (3.4% in the OCR SC arm vs. 5.9% in the OCR IV arm).

OCARINA II: OCR SC All Exposure Analysis: In the OCR SC All Exposure Analysis, the most common reported AEs were Injection related reaction (44.8%) and Headache (6.6%), COVID-19 (5.0%), Upper respiratory tract infection (5.0%) and Nasopharyngitis (3.3%). All AEs of Headache were reported during the controlled period.

The proportion of patients with AEs of Grade 3 was 2.2%. The Grade 3 AEs by PT were: Eye pain, Lymphocyte count decreased, Back pain and Multiple sclerosis relapse, each reported at least once (0.6%).

OCARINA I: Ocrevus SC (at Least One Dose of 920 or 1200 mg): In OCARINA I, the most common reported AES were similar to OCARINA II; Injection site reaction (52.5%), COVID-19: (21.2%) and Injection related reaction (11.0%) in the 920 mg dose group and Injection site reaction (72.0%), COVID-19 (33.6%), Injection related reaction (20.8%), Fatigue (16.0%), Headache (13.6%) and Urinary tract infection (11.2%).

The majority of patients who experienced AEs had AEs of Grade 1 or 2 (89.4% in 920mg dose and 80.3% in 1200 mg dose).

Overall, the most comment reported adverse events were generally mild in severity and manageable. The most common AEs are represented in the ADR table in the SmPC section 4.8, except for Headache and Covid-19. Due to the Covid-19 pandemic and the lack of a placebo arm, causal relationship between Covid-19 and ocrelizumab cannot be concluded.

Serious adverse events and Deaths, other significant events

Serious adverse events

OCARINA II: Controlled Period Analysis: The proportions of patients with at least one SAE were comparable between the two treatment arms (2.5 % in the OCR SC arm vs. 3.4% in the OCR IV arm).

In the OCR SC arm, the SAEs were Multiple sclerosis pseudo relapse, Multiple sclerosis relapse, Eye pain, and Anxiety, reported at least once in one patient (0.8 %). All were considered by the investigator to not be related to study treatment.

In the OCR IV arm, the SAEs were Appendicitis, Cellulitis staphylococcal, Pneumonia, Subcutaneous abscess, Upper respiratory tract infections, and Diabetes mellitus, each reported at least once (0.8 %). All SAEs were considered by the investigator to not be related to study treatment, except for the AE of Upper respiratory tract infection.

OCARINA II: OCR SC All Exposure Analysis. The proportions of patients with at least one SAE in the OCR SC All group was 1.7%. All SAEs were reported during the controlled period and are described above.

OCARINA I: Ocrevus SC (at Least One Dose of 920 or 1200 mg): Among patients who received at least one dose of ocrelizumab 1200 mg SC, the proportion of patients with at least one SAE was 9.6% (12 patients). The SAEs were: COVID-19 (3.2%); COVID-19 pneumonia (3.2%); pneumonia (2.4%); multiple sclerosis relapse (1.6%); and encephalitis, asthenia, muscular weakness, and pulmonary embolism (0.8% each).

Among patients who received at least one dose of ocrelizumab 920 mg SC, the proportion of patients with at least one SAE was 3.4%. The SAEs were (0.8% each): COVID-19, COVID-19 pneumonia, pneumonia, papillary thyroid cancer, and nephrolithiasis.

Overall, no SAEs in the OCR SC 920 mg group were reported in more than one patient each.

Deaths

One death was reported in a patient who received OCR SC 1200 mg. The patient died due to an SAE of COVID-19 pneumonia. It was reported that pneumothorax and renal failure were complications of COVID-19. The investigator assessed the event of COVID-19 pneumonia as unrelated to ocrelizumab SC. Comorbidities have probably contributed to the outcome of death. However, ocrelizumab are associated with a higher risk of infections, infections are an important identified risk in the safety specification in the RMP, and serious infections were especially reported in the SC 1200 mg dose group. Any sound conclusion on the risk cannot be made, but it is reassuring that the MAH has chosen the 920 mg dose and nor the 1200 mg dose.

Adverse events of special interest

None of the predefined adverse events of special interest (cases of potential drug-induced liver injury, cases of suspected transmission of an infectious agent by the study drug, or cases of Grade 3 or higher injection site reactions) were reported in OCARINA II or OCARINA I. Dedicated analysis was performed for IRRs, IRs, infections, hypersensitivity, anaphylactic reactions and malignancies. These are assessed below.

Selected adverse events

Injection Reactions

OCARINA II: Controlled Period Analysis: Injection reactions were reported in 48.3% patients with the first injection. None were serious. 71.9% were of Grade 1 severity and 28.1% were of grade 2 severity. No patients had an IR of Grade 3 or higher. Most (86.7%) occurred within 6 hours of the injection. The median time from the end of injection administration to IR onset was 0.265 hours (range: -0.15 to 14.85). Treatment was provided to 28.1% of patients. Treatment for IRs was standard of care treatments, including mostly analgesics (e.g., ibuprofen, paracetamol), and oral or topical antihistamines (e.g., diphenhydramine, cetirizine).

Local Injection Reactions were reported in 45.8% of the patients with the first injection. The most common symptoms were Erythema (29.7%), Pain (14.4%), Swelling (8.5%) and Pruritus (6.8 %).

64.3% occurred within 1 hours of the injection. The median time from the end of injection administration to LIR onset was 0.265 hours (range: -0.15 to 14.85).

Systemic Injection Reactions were reported in 11.0% of the patients with the first injection. The most common symptoms were Headache (2.5%) and Nausea (1.7 %). 46.2% were of Grade 1 maximum severity and 53.8% were Grade 2 maximum severity. Treatment was provided to 38.5% of the patients with SIRs. The median duration of SIRs was 3 days (range: 1 to 16 days). The majority of SIRs (53.8%) resolved within 3 days of onset.

OCARINA II: Switchers Analysis: The proportion of patients who experienced at least one IR was comparable between OCR IV patients at their first SC injection and OCR SC patients at their second SC injection (36.5% in OCR IV/SC vs. 41.3% in OCR SC/SC). The intensity of IRs was comparable between OCR IV patients at their first SC injection and OCR SC patients at their second SC injection (87.0% Grade 1 and 13.0% Grade 2 in OCR IV/SC vs. 88.5% Grade 1 and 11.5% Grade 2 in OCR SC/SC). Treatment for IRs was provided in 8.7% in OCR IV/SC and 11.5% in OCR SC/SC.

Local Injection Reactions were reported in 34.9% in OCR IV/SC and 36.5% in OCR SC/SC.

Systemic Injection Reactions were reported in 9.5% in OCR IV/SC and 6.3% (4/63 patients) in OCR SC/SC.

OCARINA II: OCR SC All Exposure Analysis: Injection reactions were reported in 47.5% of patients with any injection. None were serious. 76.7% were of Grade 1 severity and 23.3% were of grade 2 severity. No patients had an IR of Grade 3 or higher. With repeated injections, the incidence of IRs decreased from 44.2% at the first injection to 41.3% at the second injection and the intensity of IRs decreased (76.3% Grade 1 and 23.8% Grade 2 at the first injection vs. 88.5% Grade 1 and 11.5% Grade 2 at the second injection). Treatment was provided to 20.9% of patients and fewer patients required treatment with repeated injections (22.5% after first injection and 11.5% after second injection).

Local Injection Reactions were reported in 44.8%. The incidence of LIRs decreased from 42.0% at the first injection to 36.5% at the second injection. The most common symptoms of LIRs were Erythema (32.6%), Pain (14.9%), Swelling (8.3%) and Pruritus (5.0 %).

Systemic Injection Reactions were reported in 12.2%. The incidence of SIRs decreased from 10.5% at the first injection to 6.3% at the second injection. The most common symptoms of SIRs were Headache (1.7 %), Fever (1.1 %), Flushing (1.1 %), Nausea (1.1 %) and Pain (1.1%).

OCARINA I: Ocrevus SC (at Least One Dose of 920 or 1200 mg): Injection reactions were reported in 75.2% of patients receiving ocrelizumab 1200 mg SC and 57.6% receiving ocrelizumab 920 mg SC.

In the 1200 mg group, 1 patient had a Grade 3 systemic IR (previously treated with ocrelizumab IV prior to study, after first injection of ocrelizumab 1200 mg SC, the patient experienced symptoms of dyspnea and wheezing, 4 hours following completion of ocrelizumab 1200 mg SC, which resolved with anti-allergy treatment after another hour. No other patients had Grade 3 or higher IRs. Treatment was provided to 24.5% of patients who experienced IRs in the 1200 mg dos group and 10.3% in the 920 mg dose group. Concomitant medications received for injection reaction symptoms were standard treatments, mostly analgesics (e.g., paracetamol, ibuprofen), antihistamines (e.g., diphenhydramine, loratadine), and corticosteroids (e.g., hydrocortisone, prednisone).

Local Injection Reactions were reported in 72.0% of patients receiving 1200 mg SC and 52.5% receiving 920 mg SC. The most common LIR symptoms were: Injection site erythema (46.4%), Injection site pain: (46.4%), Injection site swelling (27.2%) and Injection site bruising (15.2%) in the 1200 mg dose group and Injection site pain (33.9%), Injection site erythema (23.7%) and Injection site swelling (22.0%) in the 920 mg dose group.

Systemic Injection Reactions were reported in 20.0% of patients receiving ocrelizumab 1200 mg SC and 11.0% of patients receiving ocrelizumab 920 mg SC. The most common SIR symptoms were Headache (8.8%), Flushing (3.2%) and Tachycardia (1.6%) in the 1200 mg dose group and headache (2.5%) in the 920 mg dose group. All other SIR symptoms occurred in only 1 patient each. One patient had a

Grade 3 SIR in the 1200 mg dose group, as described above. In the 920 mg dose group, all SIRs were Grade 1 or 2.

Overall, the frequency of IRs was high throughout the studies. The reported injection reactions were mild or moderate in intensity and none were severe. Only one IR in a patient receiving 1200 gm SC were a grade 3 SIR. Local reactions were reported more frequent than systemic reactions. Even though IRs were mostly mild and moderate in intensity, the risk for more severe injection reactions is not completely ruled out and a signal has been seen in the 1200 mg dose for a severe systemic injection reaction. Appropriate risk minimisation measures have been added to the SmPC section 4.2 to minimise the risk for injection reactions, hypersensitivity reactions and anaphylactic reactions for the SC formulation.

Infusion Related Reactions

Infusion related reactions were reported in 16.9% of patients receiving ocrelizumab IV in OCARINA II. None IRRs were serious. The incidence of IRRs decreased from 16.1% at the Day 1 infusion to 6.0% at the Day 14 infusion. Among patients in OCR IV, the most common symptom of IRRs was Pruritus (3.4%), Headache (2.5%), Erythema (1.7%), Tachycardia (1.7%) and Throat irritation (1.7%). All the IRRs were Grade 1 (45.0%) or Grade 2 (55.0%) severity. Treatment was provided to 45.0% of the patients with IRRs. Treatment for IRRs was standard of care treatments, including mostly IV corticosteroids (e.g., hydrocortisone), analgesics (e.g., paracetamol), and oral or IV antihistamines (e.g., loratadine, chlorphenamine, promethazine).

Overall, the IRRs observed in OCARINA II support the known safety profile with regard to IRRs in ocrelizumab IV.

Infections

OCARINA II: Controlled Period Analysis: Infections were reported in 34.7% in the OCR SC arm and 28.0% in the OCR IV arm. The most frequent infections by PT were Upper respiratory tract infection (6.8% vs. 7.6%), COVID-19 (6.8% vs. 4.2%) and Bronchitis (1.7% vs. 5.1%). No patients in the OCR SC arm had a serious infection. In the OCR IV arm, 4 patients (3.4%) had a serious infection. The serious infections were Appendicitis, Cellulitis staphylococcal, Pneumonia, Subcutaneous abscess and Upper respiratory tract infection. No infections of Grade 3 were reported in the OCR SC arm. All serious infections in the OCR IV arm were of Grade 3.

OCARINA II: OCR SC All Exposure Analysis: Infections were reported in 26.0% in the OCR SC All group. The most frequent infections by PT were Upper respiratory tract infection (5.0%) and COVID-19 (5.0%). No patients in the OCR SC All group had a serious infection. No infections of Grade 3 or more in severity were reported.

OCARINA I: Ocrevus SC (at Least One Dose of 920 or 1200 mg): In the ocrelizumab 1200 mg SC group, infections were reported in 56.0% and 8.8% had a serious infection. 8.8% was a Grade 3 infection and 1 patient (0.8%) had a Grade 5 infection. All other infections were Grade 1 or 2. The Grade 3 infections were: COVID-19 (4.0%), pneumonia (2.4%), COVID-19 pneumonia (0.8%), encephalitis (0.8%), SARS-CoV-2 sepsis (0.8%), and tooth abscess (0.8%). The Grade 5 infection AE was COVID-19 pneumonia. The most frequent infections by PT were COVID-19 (33.6%), Urinary tract infection (11.2%), Nasopharyngitis (7.2%), Sinusitis (4.8%), Pneumonia (4.0%), COVID-19 pneumonia (3.2%).

In the ocrelizumab 920 mg SC group, infections were reported in 39.8% and 1.7% had a serious infection. 3.4% had Grade 3 infections. All other infections were Grade 1 or 2. The Grade 3 infections were COVID-19 (1.7%), pneumonia (0.8%), COVID-19 pneumonia (0.8%), and Clostridium difficile infection (0.8%). The most frequent infections by PT were COVID-19 (21.2%), Urinary tract infection (6.8%), Bronchitis (5.1%), Nasopharyngitis: 4.2% and Upper respiratory tract infection (4.2%). The serious infections were COVID-19 (0.8%), COVID-19 pneumonia (0.8%) and Pneumonia (0.8%).

Overall, infections were reported more frequent in OCR SC compared to OCR IV in OCARINA II. However, the infections in OCR SC were less severe and none were serious compared to OCR IV.

In OCARINA I, infections were reported more frequent and the infections were more frequent severe and serious in the 1200 mg dose group compared to the 920 mg dose group, which support the chosen dose

of 920 mg. The most common infections reported are all included in the ADR table in the SmPC section 4.8, except for Covid-19. Due to the Covid-19 pandemic and the lack of a placebo arm, causal relationship between Covid-19 and ocrelizumab cannot be concluded.

Hypersensitivity and Anaphylactic Reaction Events

Anaphylactic reactions and hypersensitivity (identified using the" Anaphylactic reaction" and "hypersensitivity" (SMQ)) were reported more often in the OCR SC arm compared to the OCR IV arm (4.2% and 49.2% vs. 2.5% and 19.5%). In OCARINA I 13.7% had Anaphylactic reactions and 33.6% Hypersensitivity.

The MAH states that none of the AEs were confirmed to be hypersensitivity or anaphylactic reactions but rather IRs, IRRs or respective symptoms of the LIRs, SIRs and IRRs. The MAH described how hypersensitivity and anaphylactic reactions were distinguish from IRs or IRRs. Different criteria were set up for infusion related reactions, injection reactions, hypersensitivity and anaphylactic reactions in OCARINA I and II. Hypersensitivity can be difficult to distinguish from IR and IRR in terms of symptoms. This is reflected in the SmPC section 4.4.

The MAH discussed the Grade 3 IR with symptoms of dyspnoea and wheezing in Study OCARINA I. The adverse event occurred in a patient who was treated with ocrelizumab IV prior to entering the study, and reported repeated mild hypersensitivity reactions upon prior IV administration. This was not known when enrolling the patient. This patient should not have been included in the clinical study, as hypersensitivity to the studied drugs was an exclusion criterion.

The symptoms of dyspnoea and wheezing were assessed by the Applicant as a Grade 3 IR, that was clinically difficult to distinguish from a hypersensitivity reaction. In the SmPC section 4.4, hypersensitivity reactions are described as a potential risk with ocrelizumab, and the difficulties in distinguishing it from IRs/IRRs is described. This is considered acceptable.

Malignancies

In OCARINA II, no malignancies were reported.

In OCARINA I, two malignancies were reported. One patient experienced a Grade 2 AE of basal cell carcinoma and one patient experienced a Grade 3 AE of papillary thyroid cancer. Both were assessed as unrelated to ocrelizumab SC by the investigator.

Malignancies including breast cancer, is included in the safety specification in the RMP as an important potential risk. No sound conclusion can be made on the risk at this point. A PASS is ongoing for the IV formulation. This is considered to also inform on the SC formulation.

Laboratory findings

Hematology and Chemistry

Ocarina II: Controlled Period Analysis: No clinically relevant changes from baseline were observed for mean or median values of any laboratory parameter, in either arm (Data not shown her, but available in the OCARINA II study report).

The proportions of patients with marked laboratory abnormalities were low and comparable between the two treatment arms (Low neutrophils: 3.4% in both arms, High neutrophils: 0 in OCR SC vs. 1.7% in OCR IV, and Low lymphocytes: 1.7% in both arms).

Shifts to NCI CTCAE Grade 3 or 4 post-baseline abnormalities were observed in few patients in both arms (Low lymphocytes: 0.9% in both arms, Low neutrophils: 0 in OCR SC vs. 1.8% in OCR IV and Low leukocyte count: 0 in OCR SC vs. 0.9% in OCR IV).

No clinically meaningful difference was observed between the OCR SC and OCR IV arms with respect to liver tests. All reported liver enzyme elevations were of Grade 1 maximum severity and no cases of potential drug-induced liver injury were reported.

Ocarina I: Patients who Received at Least One Dose of Ocrelizumab SC: No clinically relevant changes from baseline were observed for mean or median values of any laboratory parameter, in either arm (Data not shown her, but available in the OCARINA I study report).

The most common marked laboratory abnormalities were High neutrophils (40.5%), Low lymphocytes (15.9%), and High total leukocyte count (13.7%). High ALT was observed in 20.6%, High AST in 11.5% and High bilirubin in 3.8%.

All post-baseline liver enzyme elevations were Grade 1, except for one Grade 2 bilirubin elevation. In the majority of cases, the observed elevation in liver enzymes were single occurrences and were not sustained or replicated and not requiring symptomatic treatment or treatment interruption. There were no reported cases of potential drug-induced liver injury.

Shifts to NCI CTCAE Grade 3 or 4 post-baseline abnormalities were observed in a small number of patients for the following laboratory parameters: Low lymphocytes (6.4%), Low potassium (2.3%), High amylase (0.8%), High creatinine (0.8%), Low sodium (0.8%) and Low haemoglobin (0.8%).

Overall, no clinically relevant changes from baseline were observed for mean or median values of any laboratory parameter. The proportions of patients with marked laboratory abnormalities were low and comparable between the two treatment arms in OCARANA II. In OCARINA I, marked laboratory abnormalities were observed more frequent. Shifts to NCI CTCAE Grade 3 or 4 post-baseline abnormalities were observed in few patients in both studies. No new safety concerns were identified from the laboratory findings.

Vital signs and ECG

No relevant differences were observed between ocrelizumab SC and ocrelizumab IV with respect to changes in vital signs in OCARINA II or OCRARINA I (Data not shown here for OCARINA I, but available in OCRARINA I study report).

4 patients (2 treated with ocrelizumab 1200 mg SC and 2 treated with ocrelizumab 600 mg IV) experienced blood pressure abnormalities reported as AEs (2 AEs of hypertension, 1 AE of blood pressure increased, and 1 AE of hypotension). All 4 events were non-serious, Grade 2, and were resolved or resolving at the time of clinical cut-off date.

No patients had absolute QTcF values > 500 msec. One patient had a change from baseline in QTcF of > 60 msec that occurred 60 minutes after their fifth injection of ocrelizumab 1200 mg SC at Week 96. One patient had a Grade 1 atrioventricular block first degree approximately 5 months after receiving their first dose of ocrelizumab 920 mg SC at Week 48 that led to interruption of ocrelizumab SC treatment.

Overall, blood pressure abnormalities and severe ECG abnormalities were in general low in both studies.

Safety in special populations

The MAH has not provided any analysis for special populations. The MAH have justified not to include an analyses of safety data by special populations, because no issues were identified in subgroup analyses performed for the IV clinical trial population with a longer exposure time. The ocrelizumab SC development program followed the principle of PK bridging. The PK results from studies OCARINA II and OCARINA I support a comparable benefit-risk profile for ocrelizumab SC relative to ocrelizumab IV for sex, body weight and age.

In the SmPC it is stated that safety and efficacy of ocrelizumab for patients with hepatic and renal impairment has not been formally studied. Ocrelizumab is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a dose adjustment is not expected to be required for patients with hepatic or renal impairment. This is considered acceptable.

Immunological events

Overall, no treatment-emergent ADAs to ocrelizumab were observed. As stated in the evaluation of pharmacokinetics methods (2.1.2), immunogenicity status following SC ocrelizumab is not considered

adequately described, due to poor assay sensitivity and sparse sampling. An OC have been raised due to this concern.

A total of 3 out of 132 patients (2.3%) had treatment-emergent anti-rHuPH20 antibodies in OCARINA I and no treatment-emergent anti-rHuPH20 antibodies was observed in OCARINA II. No safety concerns have been observed in patients with anti-rHuPH20 antibodies.

Drug-drug interactions

No formal (PK or PD) drug-drug interaction studies were performed in the initial application for ocrelizumab IV, which is acceptable for a mAb. Due to the effective and long-lasting PD effect by depleting CD20-expressing B-cells, the efficacy of vaccinations and the safety if giving live attenuated vaccines was questioned by the initial assessment for ocrelizumab IV. This is not expected to be different in SC use. This is adequately reflected in the SmPC section 4.5.

In the SmPC section 4.5 it is stated that it is not recommended to use other immunosuppressive therapies concomitantly with ocrelizumab except corticosteroids for symptomatic treatment of relapses. Since only one relapse was reported in the studies, an analysis cannot be made on concomitant use of corticosteroids with OCR SC for symptomatic treatment of relapses at this point.

Discontinuations due to adverse events

No AEs led to discontinuation of treatment in OCARINA II and two AEs led to study drug discontinuation in OCARINA I; SAE of Grade 3 multiple sclerosis relapse in the 1200 mg dose group and a Grade 2 AE of multiple sclerosis (worsening multiple sclerosis) in the 920 mg dose group.

Overall, AEs leading to discontinuations were low. The discontinuation data does not raise any new safety concerns.

Post marketing experience

The MAH states that the safety data from post-marketing experience and from the ongoing clinical trials remained consistent with that observed in the controlled periods of the pivotal clinical trials. No new concerns are raised for ocrelizumab IV.

2.6.10 Conclusions on the clinical safety

Overall, the safety database consisted of a total of 312 patients treated with at least one injection of ocrelizumab SC. A total of 246 patients were treated with ocrelizumab SC for at least 24 weeks and 121 patients were treated with ocrelizumab SC beyond 48 weeks and 99 were treated with ocrelizumab SC beyond 96 weeks. The SC safety database is limited with regard to the total exposure. Since the application relies on safety data from the ocrelizumab SC, with well-known safety data from the ocrelizumab IV, the total exposure is considered acceptable since the patient population and active substance is the same.

Overall, available safety data from the clinical development program show that ocrelizumab SC were generally well tolerated and comparable to ocrelizumab IV. More AEs were reported in the SC arm compared to the IV arm in OCARINA II. Injection reactions contributed to the higher frequency in the SC arm. No treatment-emergent ADAs to ocrelizumab were observed. However, immunogenicity status following SC ocrelizumab is not considered adequately described.

2.7 Risk Management Plan

The applicant submitted an updated RMP version 9.1 addressing the requests regarding RMP core document and annexes. Further the applicant confirmed that patients with SC administration of ocrelizumab can be included in the ongoing Category 3 studies BA39730 and BA39732 without the need to make additional updates.

2.7.1 Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation) Infections
Important potential risks	Malignancies including breast cancer Progressive multifocal leukoencephalopathy
Missing information	Safety in pregnancy and lactation Long-term safety of ocrelizumab treatment Safety in pediatric population

IV = intravenous; SC = subcutaneous

Discussion on safety specification

The MAH has updated the important identified risk of infusion related reactions to infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation). The other identified risks and missing information was kept from the IV RMP. This is considered appropriate.

Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are appropriate.

2.7.2 Pharmacovigilance plan

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
BA39730- A Long-Term Surveillance of Ocrelizumab-Treated Patients with	The primary objective is: ● To estimate (overall and by MS type) the event rates of SAEs, including malignancy and serious infections, following ocrelizumab treatment in patients with MS. The secondary objective is:	Malignancies including breast cancer Progressive multi focal leukoencephalopathy	Start date of study End of study Semi-annual	2019 2028 Cumulative reports submitted with

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Multiple Sclerosis Ongoing	● To compare the incidence of each serious safety event between ocrelizumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs: overall, and by individual DMTs if possible), within the same data source. If sufficient data are available, an exploratory objective of this study is to compare the safety profile of patients with PPMS exposed to ocrelizumab to the safety profile of patients with PPMS not exposed to any DMTs.	Long-term safety of ocrelizumab treatment Infections	safety reports Interim report 1 Interim report 2 Interim report 3 Final report of study results	PBRER 2022 2024 2026 2029
BA39732- A multi-source surveillance study of pregnancy and infant outcomes in ocrelizumab-exposed women with multiple sclerosis (MS) Ongoing	● To estimate the frequency of selected adverse pregnancy outcomes in women with MS exposed to ocrelizumab during the defined exposure window (i.e., spontaneous abortions, fetal death/stillbirths, elective abortions, preterm births, C-sections, and urinary and other infections in pregnancy) ● To estimate the frequency of selected adverse fetal/neonatal/infant outcomes at birth and up to the first year of life of infants from pregnancies in women with MS exposed to ocrelizumab—i.e., major congenital malformations, small for gestational age, adverse effects on immune system development (e.g., severe infectious disease in the first year of life) ● To compare the frequency of each safety event of interest between ocrelizumab-exposed pregnant women with MS and two comparison cohorts: (1) primary comparison cohort —pregnancies in women with MS who have not been exposed to ocrelizumab (overall and in two strata—pregnancies exposed to any non-ocrelizumab DMTs approved for the treatment of MS or any new DMT approved during the study period [subcohort 1a], and pregnancies not exposed to these	Safety in pregnancy and lactation	Protocol Submission : Start of study dataset creation: Study finish Final report	November 2019 2018 March 2029 March 2030

Study/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
	DMTs [subcohort 1b]) and (2) secondary comparison cohort — pregnancies in women without MS who have not been exposed to ocrelizumab.			
Study WA40404- A Phase IIIb Multicenter, Randomised, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults with Primary Progressive Multiple Sclerosis Ongoing	To evaluate the safety and efficacy of ocrelizumab (Ocrevus™) compared with placebo in patients EDSS 3 to 8 using 9HPT as the primary efficacy outcome, and 12 week confirmed disability progression as a key secondary endpoint. Baseline assessment of features characteristic of imaging inflammatory activity (T1 Gd enhancing MRI lesions and/or new/enlarging T2 lesions) will be undertaken to explore treatment effect in subgroups with different inflammatory profiles	Infection Malignancies including breast cancer Long-term safety of ocrelizumab treatment	Final report	June 2024

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product. The applicant confirmed that patients with SC administration of ocrelizumab can be included and evaluated in the ongoing category 3 studies BA39730 and BA39732. Also, routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3 Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion-related reactions (observed with the IV formulation) and injection reactions (observed with the SC formulation)	**Routine risk communication:** Section 4.2 of the EU SmPC-Posology and method of administration Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.8 of the EU SmPC-Undesirable effects Sections 2, 3, and 4 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Injection reactions (observed with SC formulation) ● Physicians should alert patients that injection reactions can within 24 hours of injection. ● Patients should be observed for at least one hour after the initial dose of the medicinal product for any symptom of severe injection reactions. ● Appropriate resources for the management of severe reactions of severe injection reactions, hypersensitivity reactions and/or anaphylactic reactions should be available for the initial dose of the medicinal product. ● Shortly before injection, patients should receive premedication to reduce the potential for occurrence of injection reactions. Refer to Section 4.2 of the EU SmPC for ocrelizumab SC-(Posology and method of administration) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Infusion-related reactions (observed with the IV formulation)** ● Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion. ● Premedication for infusion-related reactions is required. ● Appropriate resources for the management of severe reactions such as serious IRR, hypersensitivity reactions and/or anaphylactic reactions should be available. ● Patients should be observed for at least one hour after the completion of the ocrelizumab infusion for any symptom of IRR. Physicians should alert patients that an IRR can occur within 24 hours of infusion. Refer to Section 4.2 of the EU SmPC-Posology and method of administration) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription: Section 4.2 of the EU SmPC states: **SC formulation**: Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions.	

Safety concern	Risk minimization measures	Pharmacovigilance activities
	IV formulations: Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion related reactions (IRRs). **Additional risk minimization measures:** None	
Infections	**Routine risk communication:** Section 4.3 of the EU SmPC- Contraindications Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.8 of the EU SmPC-Undesirable effects Section 2 and 4 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** ● An active infection must be excluded prior to ocrelizumab administration, because the infusion must be delayed in patients with an active infection until the infection is resolved. ● It is recommended to verify the patient's immune status before dosing since severely immunocompromised patients should not be treated. ● Physicians should take prompt action for patients presenting with pneumonia because there may be an increased risk of aspiration pneumonia and severe pneumonia in patients treated with ocrelizumab. ● HBV screening should be performed before initiation of treatment with ocrelizumab as per local guidelines because patients with active HBV infection should not be treated with ocrelizumab. Patients with positive serology; carriers of HBV should be referred to a liver disease expert before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. ● For PML, see under respective risk. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study BA39730 Study WA40404

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	
Malignancies including breast cancer	**Routine risk communication:** Section 4.3 of the EU SmPC- Contraindications Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 5.3 of the EU SmPC- Preclinical safety data Section 2 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** ● Patients should be asked whether they have an active malignancy, are actively being monitored for a malignancy, or have known risk factor for malignancy, because patients with a known active malignancy should not be treated with ocrelizumab, and individual benefit risk should be considered in patients with known risk factors for malignancies and in patients who are being actively monitored for recurrence of malignancy. Patients should be instructed to follow standard breast cancer screening per local guidelines. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study BA39730 Study WA40404
Progressive multifocal leukoencephalopathy	**Routine risk communication:** Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 2 of the EU Package Leaflet **Routine risk minimization activities recommending specific clinical measures to address the risk:** ● Physicians should be vigilant for the early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire **Additional pharmacovigilance activities:** Study BA39730

Safety concern	Risk minimization measures	Pharmacovigilance activities
	symptoms. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation including MRI scan preferably with contrast (compared with pre-treatment MRI), confirmatory CSF testing for JCViral Deoxyribonucleic acid and repeat neurological assessments, should be considered. If PML is confirmed treatment must be discontinued permanently. As for any other active infection, current PML is a contraindication for treatment with ocrelizumab. Refer to Section 4.3 of the EU SmPC- (Contraindications) and to Section 4.4 (Special warnings and precautions for use) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	
Safety in pregnancy and lactation	**Routine risk communication:** Section 4.4 of the EU SmPC- Special warnings and precautions for use Section 4.6 of the EU SmPC- Section 4.6 Fertility, pregnancy and lactation Section 5.3 of the EU SmPC-Preclinical safety data Section 2 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** ● Women of childbearing potential should be instructed that they should use contraception while receiving ocrelizumab and for 12 months after the last infusion of ocrelizumab. ● For activities required in case that an infant is exposed in utero to ocrelizumab, please refer to the risk of impaired immunisation response. ● Women should be advised to discontinue breast-feeding during ocrelizumab therapy. Refer to Section 4.4 (Special warnings and precautions for use) and Section 4.6 (Fertility, pregnancy and lactation) for detailed information. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire **Additional pharmacovigilance activities:** Study BA39732

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	
Long-term safety of ocrelizumab treatment	**Routine risk communication:** Section 3 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study BA39730 Study WA40404
Safety in pediatric population	**Routine risk communication:** Section 4.2 of the EU SmPC "Posology and method of administration" Section 2 of the EU Package Leaflet. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Ocrelizumab is a medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

The PRAC Rapporteur agrees that routine risk minimisation activities are considered sufficient to manage the safety concerns of the medicinal products.

2.7.4 Conclusion

The CHMP and PRAC considered that the risk management plan version 9.1 is acceptable.

2.8 Pharmacovigilance

2.8.1 Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2 Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9 Non-Conformity of paediatric studies

N/A

2.10 Product information

2.10.1 User consultation

N/A

2.10.2 Labelling exemptions

The request to omit certain particulars from the immediate labelling of the vial as per Art.63.3 and display the minimum particulars has been found acceptable by the QRD Group due to the space constraints and the fact that Ocrevus 920 mg solution for injection is to be administered under the supervision of a healthcare professional.

2.10.3 Quick Response (QR) code

N/A

2.10.4 Additional monitoring

N/A

3. Benefit-Risk Balance

3.1 Therapeutic Context

3.1.1 Disease or condition

MS is a chronic autoimmune and neurodegenerative disorder of the CNS that is characterised by inflammation, demyelination, and oligodendrocyte and neuronal loss.

3.1.2 Available therapies and unmet medical need

Patients with MS are offered a number of biologic therapies that are provided by different administration routes and in a variety of different settings, ranging from in-office neurology practices and hospital-affiliated settings, to free-standing infusion centers.

An alternative method of administration with a shorter procedure duration, while keeping the 6 monthly administration regimen, could improve treatment access for patients with MS.

The marketed formulation of ocrelizumab is given by IV infusion over 2 to 3.5 hours and patients are observed for at least one hour after the completion of the infusion. Patients go through the procedure of transit to and from the institution, lead time for IV premedication, the infusion itself and the 1-hour post-infusion observation.

An alternative SC dosing form with a shorter administration time (approximately 10 minutes) could be preferred by some patients and healthcare providers. However, the lead time for premedication and the observation time are still considered necessary.

3.1.3 Main clinical studies

The ocrelizumab SC clinical development program consists of two studies:

- Safety and tolerability, PK, pharmacodynamics (PD), and immunogenicity were assessed in the initial study OCARINA I, a dose escalation study in RMS and PPMS patients.
- PK, PD, safety, immunogenicity, radiological and clinical effects of the dose selected based on data obtained in OCARINA I was assessed in the pivotal study OCARINA II.

Studies OCARINA II and OCARINA I are both ongoing in their treatment continuation periods.

3.2 Favourable effects

The pivotal OCARINA II was a non-inferiority trial to compare 920 mg SC ocrelizumab to 600 mg (=2x300 mg) IV ocrelizumab. The primary endpoint, AUC_{W1-12} after SC injection of 920 mg ocrelizumab, was shown to be non-inferior to the 600 mg IV administration (2 x 300 mg infusions given 2 weeks apart). The GMR for $AUCW_{1-12}$ was 1.2851 (90% CI: 1.2258;1.3473). Non-inferiority was also shown based on the estimated AUC up to Week 24. Ocrelizumab Cmax values were comparable between the 920 mg SC and the 2 x 300 mg IV arm.

Treatment with ocrelizumab SC and ocrelizumab IV led to a rapid and overall sustained depletion of CD19+ B cells in blood. The mean proportion of patients achieving CD19+ B cell ≤ 5 cells/µL and < 10 cells/µL following a single dose up to Week 24 were comparable between ocrelizumab SC and IV.

Detectable MRI lesions were also evaluated as secondary endpoints and did not show any difference between the two administration methods.

3.3 Uncertainties and limitations about favourable effects

The mean ratio of the analysis of OCARINA II AUCs W1-12, is 1.29 with a 90%CI of 1.23 – 1.35. The GMR is >0.8 and thus fulfilling the one-sided non-inferiority criteria as outlined in the SAP. The result shows a nominally significant difference between the two treatments and that ocrelizumab SC 920 mg exposure expressed as AUC is higher than ocrelizumab IV 600 mg. The Applicant provided an exposure-safety analysis considering the SC and IV data in different exposure ranges. No meaningful difference was seen over the different exposure quartiles for SAEs, serious infections, infections, IRs and IRRs. The exposure-safety analysis confirms that the increased exposure that is seen for the SC formulation does not translate into a worse safety profile.

Regarding the efficacy, OCARINA II was an open label study with descriptive statistics and the efficacy data should be considered exploratory/supportive only. The secondary and exploratory efficacy endpoints do not raise concerns on any imbalance between arms. Long-term efficacy data for ocrelizumab SC are not available in order to assess persistence of efficacy or tolerance.

In relation to the immunogenicity, validated methods were used for quantification of ocrelizumab and for immunogenicity testing of ADAs against ocrelizumab or the SC vehicle, rHuPH20. The ocrelizumab ADA assay had limited drug tolerance. Samples taken every 24 weeks will allow for detection of persistent ADAs, however, there is potential to miss detection of immunogenicity at early onset.

3.4 Unfavourable effects

In OCARINA II, AEs were reported more frequent in the OCR SC arm (73.7%) compared to the OCR IV arm (45.8%). The difference in AEs is primarily due to the difference reported in Injection reactions (IRs)

in the OCR SC arm and infusion related reactions (IRRs) in the OCR IV arm; 48.3% patients experienced at least one IR in the OCR SC arm and 16.9% patients experienced at least one IRR in the OCR IV arm.

In OCARINA I, AEs were reported in 96.9% in patients receiving OCR SC 920 or 1200 mg. 23.7% had AEs of grade 3 and 12.2% has serious adverse events. One adverse event with fatal outcome were reported and 2 (1.5%) AEs leading to withdrawal from treatment. The AE leading to death were in the ocrelizumab 1200 mg dose. IRs were reported more frequent in the ocrelizumab 1200 mg group compared to 900 mg (75.2% vs. 57.6%).

With regard to the IRs in the OCR SC arm in OCARINA II, 45.8% patients experienced at least one local injection reaction (LIR) and 11.0% patients experienced at least one systemic injection reaction (SIR). None were serious. 71.9% were of Grade 1 severity and 28.1% were of grade 2 severity. No patients had an IR of Grade 3 or higher. Local Injection Reactions were reported in 45.8% of the patients with the first injection. The most common symptoms were Erythema (29.7%), Pain (14.4%), Swelling (8.5%) and Pruritus (6.8 %). Systemic Injection Reactions were reported in 11.0% of the patients with the first injection. The most common symptoms were Headache (2.5%) and Nausea (1.7 %). 46.2% were of Grade 1 maximum severity and 53.8% were Grade 2 maximum severity. Treatment was provided to 38.5% of the patients with SIRs.

Infections were also reported more frequent in the OCR SC arm (34.7%) compared to the OCR IV arm (28.0%). However, serious infections were only observed in the OCR IV arm (3.4%). The most frequent infections by PT were Upper respiratory tract infection (6.8% vs. 7.6%), COVID-19 (6.8% vs. 4.2%) and Bronchitis (1.7% vs. 5.1%). No patients in the OCR SC arm had a serious infection. In the OCR IV arm, 4 patients (3.4%) had a serious infection.

Overall, AEs of grade ≥ 3 and serious were reported slightly more frequent in the OCR IV arm (5.9% and 3.4%) compared to the OCR SC arm (3.4% and 2.5%). No deaths were reported, and no AEs led to discontinuation of treatment.

In the Controlled Period Analysis, the most common reported AEs were Injection related reaction (46.6% in OCR SC), Headache (10.2% in OCR SC vs. 2.5% in OCR IV), Infusion related reactions (16.9% in OCR IV), Upper respiratory tract infection (6.8% in OCR SC vs. 7.6% in OCR IV) Covid-19 (6.8% in OCR SC vs. 4.2% in OCR IV) and Bronchitis (1.7% in OCR SC vs. 5.1% in OCR IV).

In OCARINA I, the most common reported AES were similar to OCARINA II.

Overall, the most common reported adverse events were generally mild in severity and manageable for the 920 mg dose.

3.5 Uncertainties and limitations about unfavourable effects

Overall, the safety database consisted of a total of 312 patients treated with at least one injection of ocrelizumab SC. A total of 246 patients were treated with ocrelizumab SC for at least 24 weeks and 121 patients were treated with ocrelizumab SC beyond 48 weeks and 99 were treated with ocrelizumab SC beyond 96 weeks. The SC safety database is limited with regard to the total exposure. Since the application relies on safety data from the ocrelizumab SC, with well-known safety data from the ocrelizumab IV, the total exposure is considered acceptable since the patient population and active substance is the same. However, as ocrelizumab is intended to be used as a chronic therapy, long-term safety of ocrelizumab treatment is missing information in the safety specification in the RMP and two PASS studies are ongoing for the IV formulation.

Anaphylactic reactions and hypersensitivity (identified using the" Anaphylactic reaction" and "hypersensitivity" (SMQ)) were reported more often in the OCR SC arm compared to the OCR IV arm (4.2% and 49.2% vs. 2.5% and 19.5%). In OCARINA I 13.7% had Anaphylactic reactions and 33.6% Hypersensitivity. The MAH states that none of the AEs were confirmed to be hypersensitivity or anaphylactic reactions but rather IRs, IRRs or respective symptoms of the LIRs, SIRs and IRRs. The MAH described how hypersensitivity and anaphylactic reactions were distinguish from IRs or IRRs. Different criteria were set up for infusion related reactions, injection reactions, hypersensitivity and anaphylactic

reactions in OCARINA I and II. Hypersensitivity can be difficult to distinguish from IR and IRR in terms of symptoms. This is reflected in the SmPC section 4.4.

With regard to injection reactions, even though IRs were mostly mild and moderate in intensity, the risk for more severe injection reactions is not completely ruled out and a signal has been seen in the 1200 mg dose for a severe systemic injection reaction.

In total, two malignancies were reported in the studies. One patient experienced a Grade 2 AE of basal cell carcinoma and one patient experienced a Grade 3 AE of papillary thyroid cancer. Both were assessed as unrelated to ocrelizumab SC by the investigator. Malignancies including breast cancer, is included in the safety specification in the RMP as an important potential risk. No sound conclusion can be made on the risk at this point. A PASS is ongoing for the IV formulation. This is considered to also inform on the SC formulation.

Overall, no treatment-emergent ADAs to ocrelizumab were observed. However, immunogenicity status following SC ocrelizumab is not considered adequately described, due to poor assay sensitivity and sparse sampling.

3.6 Effects Table

Table 30 Effects Table for Ocrevus (RMS and PPMS)

Effect	Short Description	Unit	Ocrevus IV	Ocrevus SC	Uncertainties/ Strength of evidence	References
Favourable Effects						
			N=116	N=116		
Primary PK endpoint	Serum ocrelizumab area under the concentration-time curve ($AUC_{W1–12}$) after SC administration compared to IV infusion from Day 1 to Week 12	AUC $_{W1–12}$ mean (SD) (µg/mL•day)	2750 (796)	3500 (914)	**Unc**: Exposure 29% higher (GMR) after SC administration compared to IV administration. This gives uncertainty related to the safety	CN42097 (OCARINA II)
Effect estimate		GMR (90% CI)	1.29 (1.23-1.35)			
Secondary radiological endpoint	Total number of T1Gd+ lesions at week 8 and 24 detected by brain MRI	Total number of lesions	N=112 24	N=112 17	**Unc**: exploratory analyses (predefined)	
	Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 12 and 24 relative to the previous scan, respectively	Total number of lesions	N=65 N=0	N=61 N=2	**Unc**: exploratory analyses (predefined)	

Effect	Short Description	Unit	Ocrevus IV	Ocrevus SC	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
			N=118	N=118		
Adverse events	Incidence	%	45.8	73.7		CN42097 (OCARINA II)
IRR	Incidence	%	16.9	0		
IR	Incidence	%	0	48.3		
Local IRs	Incidence	%	0	45.8		
Systemic IRs	Incidence	%	0	11.0		
Infections	Incidence	%	28.0	34.7		
Headache	Incidence	%	2.5	10.2		

Abbreviations: IRR: Infusion related reaction, IR: Injection reaction
Notes:

3.7 Benefit-risk assessment and discussion

3.7.1 Importance of favourable and unfavourable effects

Non-inferior exposure $AUC_{1\text{-}12w}$ was shown for ocrelizumab SC compared with the IV formulation and even a significantly higher exposure was seen for the SC version. However, the SC version carries the advantage that the administration time is considerably shorter (10 minutes SC compared to 2-2.5 hours for the IV administration) which may be beneficial for the patients and the caregivers. The exposure-safety analysis confirms that the increased exposure that is seen for the SC formulation does not translate into a worse safety profile.

Overall, available safety data from the clinical development program show that ocrelizumab SC were generally well tolerated and comparable to ocrelizumab IV. More AEs were reported in the SC arm compared to the IV arm in OCARINA II. Injection reactions contributed to the higher frequency in the SC arm. Even though injection reactions were mostly mild and moderate in intensity, the risk for more severe injection reactions is not completely ruled out. No treatment-emergent ADAs to ocrelizumab were observed. However, immunogenicity status following SC ocrelizumab is not considered adequately described.

3.7.2 Balance of benefits and risks

Since the increased exposure of the SC version of ocrelizumab compared to the IV version does not impact the safety profile, the benefit-risk is positive.

3.7.3 Additional considerations on the benefit-risk balance

N/A

3.8 Conclusions

The overall B/R of Ocrevus 920 mg solution for injection as SC administration is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Ocrevus 920 mg, solution for injection, subcutaneous use is favourable in the following indication:

Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features, and for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Ocrevus subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.