CT Application(s) Summary Report

- **Protocol title:** An open Label, Single-arm, 4-year study to evaluate effectiveness and safety of Ocrelizumab treatment in patients with progressive multiple sclerosis
- **Protocol code number:** MN39159 "Consonance study"
- **Public Registry Number:** 2017-001313-93
- **Version: 6.0**
- **Date: 26-July-2023**

- **Investigational Medicinal Product being tested:**

Biological ■ **Pharmaceutical** ☐ **Innovative** ☐

Herbal medicine ☐ **Medical device** ☐

- **Sponsor:** Hoffmann-La Roche Ltd
- **Indication:** progressive multiple sclerosis
- **Investigator's brochure (IB)**

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- **Name of all Sites:**
  1. CRC, MASRI, Ain Shams University
  2. CRC, Faculty of Medicine, Alexandria University
- **Name of PI(s):**
  1. Dr. Magd Zakria
  2. Dr. Farouk Talaat

- **EDA approval date:**
  1. Initial (Protocol V 4.0 and IB edition 19): 20/09/2022
  2. Protocol V5.0 Amendment : 10/10/2022
  3. IB edition 21 Amendment: 20/08/2023
  4. Protocol V6.0 and IB edition 22 Amendment: 29/05/2024

- **Summary of pre-clinical studies:**

▪ **Non-clinical Pharmacology:**

- Ocrelizumab was evaluated in multiple in vitro studies, demonstrating high-affinity binding to CD20 on human B cells, comparable to rituximab. It showed similar binding to complement C1q and most Fcγ receptors, with stronger binding to FcγRIIIa. Functionally, ocrelizumab mediated ADCP, ADCC, CDC, and apoptosis, with enhanced ADCC and reduced CDC compared to rituximab.

In Vivo studies in cynomolgus monkeys showed dose-dependent depletion of circulating B cells. Lower doses caused short-term depletion, while higher or repeated doses led to prolonged and near-complete depletion in blood and significant reduction in peripheral tissues, with less effect on bone marrow.

1- Primary Pharmacodynamics:

- Selectivity, Binding, and Activity In Vitro:

- Ocrelizumab showed similar high-affinity binding to CD20, C1q, and most Fcγ receptors compared to rituximab, with notably stronger binding (2–3×) to FcγRIIIa. Functionally, ocrelizumab demonstrated higher ADCC activity (2–5×) but lower CDC activity (3–4×) than rituximab, while also effectively mediating ADCP. Both antibodies similarly induced apoptosis in B cells, with ocrelizumab showing comparable Annexin V staining levels to rituximab.

- **In Vivo B-Cell Depletion in Cynomolgus Monkeys:**

- Ocrelizumab demonstrated dose-dependent depletion of peripheral blood B cells in cynomolgus monkeys, with higher doses leading to rapid (within 24 hours) and near-complete depletion and longer recovery times. Lower doses caused only short-term depletion, while higher doses (≥10 mg/kg) resulted in prolonged depletion lasting weeks to months.

Retreatment after recovery did not increase toxicity and led to greater B-cell depletion in most tissues (except bone marrow), with full recovery observed afterward. Tissue depletion was most pronounced in blood and spleen, less in lymph nodes, and minimal in bone marrow due to CD20-low precursor cells. No consistent effects were observed on CD4+, CD8+ T cells, or NK cells.

2- Secondary Pharmacodynamics:

- No secondary PD studies have been conducted.

3- Safety Pharmacology:

- No dedicated safety pharmacology studies have been conducted for ocrelizumab; **safety pharmacology endpoints were incorporated into the general toxicity studies**. There were **no changes** reported in **blood pressure**, **rectal temperature**, **heart rate**, **respiratory rate**, or **ECGs** following administration of ocrelizumab to **cynomolgus monkeys** in the 4-week IV study with once weekly injections of 0, 50, or 100 mg/kg **or** the Q3W×8 study with injections of 0, 50, or 100 mg/kg

4- Pharmacodynamic Drug Interactions

- No nonclinical PD drug interaction studies have been conducted.

▪ **Pharmacokinetics and Drug metabolism in animals:**

- Ocrelizumab pharmacokinetics were evaluated after single IV doses in mice, rats, and cynomolgus monkeys, and after multiple doses in monkey toxicity studies. No formal distribution or biotransformation studies were conducted, as monoclonal antibodies like ocrelizumab are known to be degraded into peptides and amino acids.

- Methods of Analysis:

- The **serum concentrations of ocrelizumab** were quantified by **ELISA**.
- **Anti-ocrelizumab antibodies** (ADA) were detected by **immunoassays**.

1- Absorption/Pharmacokinetic/Toxicokinetic Parameters:

- <u>Mice and Rats:</u>

- The **CD20 on mouse and rat B cells do not bind ocrelizumab**. Therefore, the **pharmacokinetics** in these species are **expected to be reflective of non-specific binding and to show little dependence on dose**.
- **Studies of single IV bolus doses in these species confirmed this expectation**. The **clearance** of ocrelizumab in **mice** across a 100-fold range of doses (0.5, 5, and 50 mg/kg) **indicated relatively weak dose-dependence** (5.38, 5.67, and 8.42 mL/day/kg, respectively). In **rats**, **clearance was comparable across this dose range** (8.15, 8.11, and 7.53 mL/day/kg). Similarly, **V_{ss} and $t_{1/2}$ demonstrated little dose dependence**.

- <u>Cynomolgus Monkeys:</u>

- Ocrelizumab showed dose-dependent pharmacokinetics after IV administration, likely due to saturation of CD20 binding. Clearance decreased and half-life increased with higher doses and more frequent dosing, indicating nonlinear kinetics. The volume of distribution was low, suggesting the drug remains mainly within the vasculature with limited extravascular distribution.

Anti-drug antibodies were frequently detected, particularly at lower doses, potentially affecting PK parameters, while no gender differences were observed. Fetal exposure in monkeys was variable, with low transfer into amniotic fluid. Overall, high safety margins were demonstrated, with up to ~23-fold (dose) and ~7-fold (AUC) margins in general studies, and higher margins in reproductive toxicity studies.

2- Distribution:

- Tissue distribution studies in mice engineered to express human CD20 (huCD20 transgenic mice) demonstrated that there was **clear binding** of **ocrelizumab with B-cells in huCD20 transgenic mice**. Moreover, huCD20 transgenic mice **cleared ocrelizumab significantly faster** and in a **dose-dependent manner** than **wild-type mice**, **consistent with** what was observed in species such as **cynomolgus monkeys and humans** where ocrelizumab recognizes and binds CD20+ B-cells.
- Tissue distribution studies by **positron emission tomography (PET) imaging** in **cynomolgus monkeys** indicated the **presence of the labeled antibody within blood pool and distribution to organs having high levels of B-cells** (e.g., **spleen** and **lymphoid tissues**). These data support the assertion that CD20 expression on B cells is involved in the in vivo distribution and clearance of ocrelizumab.

3- Metabolism:

- The expected products of ocrelizumab are **small peptides** and **individual amino acids**. Free-circulating ocrelizumab enters the **metabolic pathway of endogenous soluble IgG**, whereas ocrelizumab bound to CD20+ lymphocytes can be phagocytized together with destroyed B-cells by infiltrating macrophages and granulocytes.

4- Immune Response to Ocrelizumab in Cynomolgus Monkeys:

- Anti-drug antibodies (ADAs) to ocrelizumab were frequently observed in cynomolgus monkeys (≈30%), as expected for a heterologous protein, but animal immunogenicity is not predictive of human response.

ADA incidence was dose-dependent, occurring more often at lower doses due to incomplete B-cell depletion.

-The presence of ADAs was associated with increased drug clearance, while higher doses showed fewer detectable ADAs, slower clearance, and longer half-life. However, ADA detection at higher doses may have been underestimated due to assay interference from circulating drug levels. Overall, the findings are consistent with target-mediated drug disposition.

5- Excretion:

- **No formal studies on excretion have been performed**. Like other monoclonal antibody therapeutics, the elimination of ocrelizumab occurs through both antigen-specific and non-specific processes common to the IgG1 antibody isotype.

6- Pharmacokinetic Drug Interactions:

- No drug interaction studies have been performed.

▪ **Toxicology and Safety Pharmacology:**

- Toxicology studies have been conducted **in vitro** (tissue cross-reactivity and hemolysis/blood compatibility) and **in vivo**. As expected, ocrelizumab cross-reacts only with human and non-human primate tissues in a manner consistent with CD20 expression (cells of lymphoid origin); therefore, the **toxicology program was conducted in cynomolgus monkeys as this was identified as a relevant toxicology species for ocrelizumab.**

- **Repeat-dose toxicology studies** of ocrelizumab at **doses of up to 100 mg/kg**, administered as **two bi-weekly doses** (Days 1 and 15), **four weekly doses** (Days 1, 8, 15, and 22), or **8 doses Q3W** (Days 1, 22, 43, 64, 85, 106, 127, and 148), have been conducted. An **embryo-fetal development study**, a **pre- and post-natal development study** and **male and female fertility studies** in cynomolgus monkeys have also been completed.

1- Repeat-Dose Toxicity

- Repeated IV bolus injections of up to 100 mg/kg were **well tolerated** by cynomolgus monkeys, with **no evidence of overt toxicity**. An IV injection administered once every 3weeks (Q3W) for 24 weeks (8 total administrations) at doses of 50 and 100 mg/kg achieved continuous exposure to ocrelizumab during the treatment period.

- Immune System-Related Effects:

- **Statistically significant reductions** in the mean absolute lymphocyte counts with a **dose-dependent trend** at multiple time points were observed at doses of 50 mg/kg and 100 mg/kg during the treatment period; these reductions were considered to be **ocrelizumab-related**. The **mean absolute lymphocyte count**s at the end of the **recovery period approximately 23 weeks after last treatment in** the two male and two female monkeys previously receiving 100 mg/kg were **similar to the mean pre-study value**.

- Effects on the Red Blood Cell System:

- There was a slight to mild reduction (5% to 10%) in the circulating erythrocyte mass at the end of study (1-2 occasions) in individually affected ocrelizumab-treated animals of both sexes at 50 and 100 mg/kg.

- This was accompanied by **erythropoiesis,** characterized by a **slight to mild increase in the absolute reticulocyte counts**, and **bone marrow erythroid hypercellularity** observed microscopically. **Recovery** of the hemoglobin concentration together with normal erythroid cellularity was observed in the **1 affected animal at 100 mg/kg** that was included in the recovery group. The reduction in circulating erythrocyte mass was considered to be **ocrelizumab-related**, but the **cause was not evident**.

- Anti-Ocrelizumab Antibodies:

- ADAs were detected in all of the ocrelizumab-treated groups in these studies. Regardless, the presence of ADA was associated with lower systemic exposure in animals in lower dose groups (<10 mg/kg). **There was no safety sequelae attributed to the presence of ADAs**, and ADA response in cynomolgus monkeys is not necessarily a predictor for immune responses in humans.

2- Genotoxicity:

- Per current ICH S6 (R1) Guidance on the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6; ICH S6 (R1)), **no genotoxicity studies were conducted**. It is not expected that ocrelizumab would interact directly with DNA or other chromosomal material.

3- Fertility and Early Embryonic Development to Implantation:

- In **male and female** fertility studies in cynomolgus monkeys, there were **no effects of ocrelizumab on male or female reproductive endpoints**. **In males** dosed up to 100 mg/kg/week for eight weeks, the only observed effect was the **anticipated pharmacologic reduction of B cells**. **In females**, dosed up to 100 mg/kg/week for three menstrual cycles, the only observed effects were the pharmacologic **diminishing of CD40+B cells and microscopic hypocellularity of lymphoid follicles** in the spleen and lymph nodes.

4- Carcinogenicity:

- **No carcinogenicity studies have been conducted with ocrelizumab**. Per current ICH guidance (ICH S6; ICH S6 (R1), **standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals**. In addition, as non-human primates are the only relevant nonclinical species; **carcinogenicity studies in rodents** with a homologous product (rodent surrogate antibody) are generally of **limited value** in the assessment of **carcinogenic potential of the clinical candidate**.
- As ocrelizumab functions by depleting B-cells, the risk of **virally mediated malignancies** may be impacted.

5- Reproductive and Developmental Toxicity:

- Ocrelizumab showed no maternal toxicity, teratogenicity, or embryotoxicity in cynomolgus monkeys; however, as an IgG antibody, it crosses the placenta and caused fetal B-cell depletion, indicating potential risk to human fetuses and supporting avoidance during pregnancy.

Pre- and postnatal studies revealed adverse effects in offspring, including kidney pathology, immune-related changes, reduced testicular weight, and increased susceptibility to infections, likely linked to B-cell depletion. Increased rates of abortion or fetal death were also observed. Ocrelizumab was detected in milk at low levels, and exposed newborns showed postnatal B-cell depletion.

6- Local Tolerance:

- Local tolerance for IV administration was assessed by **macroscopic** and **microscopic examination** of the injection sites as part of **repeat-dose toxicity studies in cynomolgus monkeys**. In general, **chronic SC inflammation**, **very slight to marked SC hemorrhage**, and **very slight to slight muscle fiber degeneration and regeneration** were observed at cephalic and saphenous injection sites. These findings were **similar** in nature and severity to those anticipated from **venipuncture** and were **not considered related to ocrelizumab** administration.

7- Other Toxicity Studies:

- Ex vivo, ocrelizumab demonstrated immunohistochemical **cross-reactivity** to lymphoid follicles of organized lymphoid tissues (i.e., lymph nodes, spleen, and tonsil) and to lymphoid-associated tissue of other organs (i.e., gastrointestinal tract and pancreas) in both human and cynomolgus monkey tissues. **The distribution of positive lymphoid follicle cells was similar in both human and cynomolgus monkey tissues.** This comparable tissue cross-reactivity supports the use of cynomolgus monkey as an appropriate species for toxicological studies.
- Ocrelizumab at concentrations up to 10 mg/mL **did not cause hemolysis**, **precipitation**, or **coagulation** of either human or cynomolgus monkey **whole blood**, **serum**, or **plasma**.

➢ **Summary of previous clinical studies:**

Protocol	Study Design	Population	Evaluation Criteria	Dose / Duration	Number of patients	Status	Results
WA21493	Placebo-controlled, double-blind, multicenter, dose-finding Phase II study	Patients with RRMS with evidence of recent activity	Effect on gadolinium-enhancing T1 brain lesions; relapse rate; safety and tolerability; pharmacokinetics and pharmacodynamics	OCR 1000 mg or 300 mg IV; doses separated by 24 weeks	220 patients enrolled	Completed	Efficacy: ↓ MRI lesions, ↓ ARR; no major difference With acceptable safety Conclusion: Supported Phase III dose
MN30035 (CHORDS)	Open-label study to evaluate the effectiveness and safety of ocrelizumab in patients with	Patients with RRMS who have had a suboptimal response to an adequate course of a disease modifying treatment	Effectiveness of ocrelizumab 600 mg IV every 24 weeks over 96 weeks.	First dose of ocrelizumab 600 mg given as dual IV infusions of 300 mg x 2 separated by 14 days followed by	608 patients	Completed	Efficacy: Sustained low relapse activity With Consistent safety

	RRMS who have had a suboptimal response to an adequate course of disease modifying treatment, Phase IIIb study		Safety and tolerability. Patient-reported outcomes related to quality of life and treatment satisfaction.	one 600 mg infusion every 24 weeks for the study duration of 96 weeks (last dose administered at Week 72).			Conclusion: Confirms effectiveness
MA30005 (CASTING)	Open-label study to evaluate the efficacy and safety of ocrelizumab, Phase IIIb study	Patients with RRMS who have a suboptimal response to an adequate course of a disease modifying treatment	Effect on annualized relapse rate; time to onset of sustained disability progression; number of T1 lesions and change in T2 lesion; change in EDSS; brain volume, and cognitive performance safety and tolerability.	First dose of ocrelizumab 600 mg given as dual IV infusions of 300 mg x 2 separated by 14 days followed by one 600 mg infusion every	681 patients	Completed	Efficacy: Improved disease control in switch patients With Consistent safety Conclusion: Effective DMT failure
MA30143 (ENSEMBLE)	Phase IIIb prospective multicenter open-label single-arm study	Patients with definite diagnosis of RRMS	Annualized relapse rate; sustained disability progression; MRI lesions; safety and tolerability	OCR IV infusion approximately 300 mg then 600 mg	1225 patients	Completed	Efficacy: No efficacy change Safety: Short infusion → similar IRRs Conclusion: Supports flexible administration
WA21092 (OPERA I)	Double-blind, double-dummy Phase III study	Patients with RRMS with evidence of recent activity	Annualized relapse rate; sustained disability	OCR 600 mg IV every 24 weeks	821 patients	Completed	Efficacy: ↓ ARR ~46%, ↓ CDP ~40%,

			progression; MRI lesions; safety				↓ MRI lesions (up to 94%) Safety: Higher IRRs, mild ↑ infections Conclusion: Superior to IFN; strong efficacy
WA21093 (OPERA II)	Double-blind, double-dummy Phase III study	Patients with RRMS with evidence of recent activity	Annualized relapse rate; sustained disability progression; MRI lesions; safety	OCR 600 mg IV every 24 weeks	835 patients	Completed	Similar efficacy and safety profile as OPERA I
BN42082	Controlled, double-blind Phase III study	Patients with RMS	Difference in time to confirmed disability progression	OCR IV infusion every 24 weeks	865 patients	Ongoing	
BN29739 (VELOCE)	Phase IIIb randomized study	Patients with RRMS	Characterize humoral immune response to vaccines	OCR 300 mg ×2 then 600 mg every 24 weeks	102 patients	Completed	Efficacy: Reduced humoral response Safety: Expected immunosuppression Conclusion: Important risk consideration
WA39085	Phase II open-label study	Children and adolescents with RRMS	Characterize pharmacokinetics and pharmacodynamics	OCR 300 mg or 600 mg depending on cohort	23 patients	Ongoing	
WN42086 2	Phase III randomized study	Children and adolescents with RRMS	To evaluate the safety and efficacy of	OCR IV infusion every 24 weeks	187 patients	Ongoing	

			ocrelizumab compared with fingolimod until the last randomized patient has completed 24 weeks.				
ML42071 (CHIMES)	Phase IV, openlabel, multicenter study	Self-identified Black and Hispanic patients age 18−65 years with a diagnosis of RMS in accordance with the revised 2017 McDonald Criteria, EDSS 0−5.5 inclusive at enrollment.	To assess disease activity and biomarkers of neuronal damage	Ocrelizumab 600mg IV six-monthly over 48-week (optional 168 weeks extension)	182 patients enrolled	Ongoing	
ML29966 (OBOE)	Phase IIIb, open-label, multicenter, biomarker study	Patients with relapsing multiple sclerosis and primary progressive multiple sclerosis	To assess neurofilament light on neuronal damage in CSF, CD19+ B cells in CSF, CD3+ T cells in CSF	For RMS: OCR 300 mg IV infusions Day 1 and Day 15 For PPMS: OCR 600 mg will be administered as two 300 mg IV infusions separated by 14 days at a scheduled	132 patients randomized	Completed	Efficacy: Disease stabilization Safety: No new signals Conclusion: Supports effectiveness

				interval of every 24 weeks			
MN39158	Single-arm study	Patients with multiple sclerosis	Tolerability and safety	OCR 600 mg IV	Not formally defined	Ongoing	
BA45841	Phase II open-label, single-arm, multicenter study to evaluate the PK, safety, tolerability, immunogenicity and PD effects of ocrelizumab SC administration	Patients with RRMS	Children and adolescents aged 10 to < 18 years with RRMS	Participants 10 years of age and older weighing < 35 kg: 480 mg ocrelizumab SC every 6 months. Participants 10 years of age and older weighing ≥ 35 kg: 920 mg ocrelizumab SC every 6 months. Treatment periods: Screening, 48-week treatment period, Optional Ocrelizumab Extension (OOE) period of at least 48 weeks (i.e., starting at Week 48 visit), Safety follow-up for 104 weeks (starting after the last ocrelizumab SC dose)	The study will enroll approximately 25 participants, including at least 3 participants with a body weight less than 50 kg	Planned	

WA25046 (ORATORIO)	Placebo-controlled Phase III study	Patients with primary progressive MS	Time to onset of confirmed disability progression	OCR 600 mg IV every 24 weeks	732 patients	Completed	Efficacy: ↓ CDP ~24–25%, ↓ brain atrophy, ↓ disability progression Safety: Comparable SAEs; ↑ IRRs Conclusion: First effective therapy in PPMS
WA40404	Placebo-controlled study	Patients with primary progressive MS	Time to onset of composite 12-week confirmed disability progression (9-HPT or EDSS), annual rate of percent change of T2 lesions in the brain; and safety	OCR IV infusion	~1000 patients	Ongoing	
BN42083	Controlled double-blind study	Patients with primary progressive MS	Difference in time to disability progression	OCR higher dose vs standard dose	699 patients	Ongoing	
MN39159 (CONSONANCE)	Prospective open-label study	Patients with progressive MS	Evaluate effectiveness and safety	OCR 600 mg IV every 24 weeks	927 patients	Ongoing	
CN41144 (OCARINA I)	Phase Ib open-label study	Patients with RMS or PPMS	Investigate pharmacokinetics and safety of SC formulation	SC dose escalation then maintenance	135 patients	Ongoing	

CN42097 (OCARINA II)	Phase III randomized study	Patients with RMS or PPMS	To evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of SC administration of ocrelizumab	OCR SC administration	236 patients	Ongoing
WN45319 (OCARINA III)	Phase Ib study	Patients with PPMS	To investigate the safety, tolerability, pharmacokinetics, immunogenicity, and pharmacodynamics of single ascending doses of a new SC formulation of ocrelizumab	Treatment of 3 cohorts of 25 patients each with escalating doses of ocrelizumab SC test formulation	75 patients planned	Ongoing
MN43964 (OLERO)	Phase IIIb open-label extension	Patients previously enrolled in OPERA or ORATORIO studies	To evaluate the longer-term safety and efficacy of ocrelizumab in participants diagnosed with MS who were previously enrolled in	OCR 600 mg IV every 24 weeks	1105 patients	Ongoing

			Roche sponsored Phase III pivotal studies				
MN42988 (MINORE)	Phase IV, multicenter, open-label	Pregnant women with clinically isolated syndrome or multiple sclerosis receiving commercial ocrelizumab up to 6 months before the LMP or during the first trimester of pregnancy (up to gestational Week 13)	To evaluate the potential placental transfer of ocrelizumab in pregnant women and pharmacodynamic effects (B cells) in infants	Ocrelizumab must not be administered post-baseline and until the infant's birth.	35 patients enrolled	Ongoing Primary CSR available	Efficacy: Limited added value Safety: Acceptable safety Conclusion: Supportive data
MN42989 (SOPRANINO)	Phase IV, open-label, international, single group, non-controlled	Infants of lactating women receiving ocrelizumab postpartum with clinically isolated syndrome or multiple sclerosis	To evaluate pharmacokinetics of ocrelizumab in the breastmilk of lactating women receiving ocrelizumab, ocrelizumab and B-cell levels in infants	Ocrelizumab 600 mg, IV, 2x300-mg infusions 2 weeks apart; subsequent doses as single 600mg infusions every 6 months	13 mothers and 13 infants enrolled	Completed	Low levels of ocrelizumab were detected in breast milk, with no significant safety concerns identified in infants. No new safety signals were observed in either mothers or infants during the study period. Findings are consistent with known safety profile, including minimal transfer into milk and expected B-cell effects.

BA39730	PASS observational cohort study	Patients with MS receiving OCR or other DMTs	To characterize the long-term safety data from the use of ocrelizumab in patients with MS including serious infections and malignancies	Follow-up of patients on ocrelizumab or other DMT as per standard of care for up to 10 years.	10801 OCR exposed	Ongoing
ML39632 (CONFIDENCE)	prospective, multicenter, noninterventional, longterm study (primary data collection in Germany)	RMS and PPMS patients newly treated with ocrelizumab, or other selected MS DMTs in routine clinical practice	Long-term safety and effectiveness data of ocrelizumab in the real-world setting	Observational study, all treatments received as per standard of care; Up to 10 years, once the initial dose of ocrelizumab (dosing as per label), or other selected MS DMTs, has been administered to the patient	2632 ocrelizumabexposed patients, and 624 exposed to other DMT, of a total of 3767 MS patients planned	Ongoing
BA39731 (VERISMO)	Prospective, noninterventional, longitudinal, observational study (primary data collection)	MS patients who have newly initiated treatment with ocrelizumab or other DMTs according to the local routine clinical practice	Incidence and mortality rates of all malignancies including breast cancer, and the long-term safety regarding SAEs	Observational study: all treatment received as per standard of care. Follow-up of a minimum of 6.5 years or until death (whichever comes first)	4,083 patients in the ocrelizumab exposed cohort, and 1,263 patients in the Other DMT comparator cohort enrolled	Ongoing

CN45320 (PORTAMENTO)	Phase II randomized, open label, multicenter, parallel-group study to demonstrate bioequivalence of the ocrelizumab SC test formulation compared with the ocrelizumab SC reference formulation	Patients with either RMS or PPMS and an EDSS of 0 to 6.5	Bioequivalence of the ocrelizumab SC test formulation compared with the ocrelizumab SC reference formulation, and evaluation of safety, tolerability, pharmacodynamics, and immunogenicity of the two SC formulations	SC test formulation. Total duration is expected to be approximately 168 weeks (treatment phase for up to 144 weeks, safety follow-up phase for up to 24 weeks after the last ocrelizumab administration).	Approximately 182 individuals will be enrolled	Planned	
WA40063 (Pregnancy Registry)	Prospective noninterventional observational registry (primary data collection).	Pregnant women with MS who have been exposed to ocrelizumab (during the 6 months prior to their last menstrual period) or who have not been exposed to ocrelizumab.	To assess and characterize frequency of maternal, fetal, and infant outcomes among women with MS exposed to ocrelizumab during the 6 months before the estimated date of conception or at any time during pregnancy.	Observational study with total duration of participation up to 21 months, and the expected total duration of the study is approximately 10 years	Approximately 462 enrolled out of a planned total of 580 pregnant women with MS.	Completed	Efficacy: Limited data; ongoing Safety: No clear signal yet Conclusion: Requires monitoring
BA39732	Observational cohort study, (secondary	Ocrelizumab exposed pregnancies in	To assess and characterize pregnancy and	Observational study, monitored	1,005 ocrelizumab exposed		

(MELODIC)	data use from US and Danish data sources).	women with MS, pregnancies not exposed to ocrelizumab in women with MS, and pregnancies not exposed to ocrelizumab in women without MS.	infant outcomes of women with MS exposed to ocrelizumab during the 6 months before the estimated date of conception or at any time during pregnancy.	annually for a maximum of 11 years	pregnancies and 3,015 unexposed pregnancies planned	Ongoing

➢ **Clinical Pharmacokinetics**

- **Pharmacokinetics in Patients with Multiple Sclerosis**

- Population pharmacokinetics of ocrelizumab in RMS and PPMS patients were well described by a two-compartment model with time-dependent clearance, consistent with IgG1 monoclonal antibodies. The drug has low clearance and limited distribution volume.

-Ocrelizumab showed minimal penetration into cerebrospinal fluid (~0.2% of serum levels). Subcutaneous administration demonstrated high bioavailability (~81%), with peak levels reached in about 4 days, and exposure (AUC) was non-inferior to the standard IV dosing regimen.

- **Pharmacokinetics in Special Patient Populations**

Ocrelizumab pharmacokinetics have been evaluated in pediatric MS patients, infants with in utero exposure, and lactating women:

-Children and adolescents (≥10 to <18 years; OPERETTA 1 & 2): IV dosing of 300 mg (<35 kg) or 600 mg (≥35 kg) as two infusions 14 days apart resulted in median AUC and Cmax values (3130 µg·day/mL and 147 µg/mL) within the adult MS exposure range.

-Infants within utero exposure (MINORE): Minimal placental transfer was observed; ocrelizumab was undetectable at birth in 94.3% of cord blood samples and in 97% of infant serum at 6 weeks. Detected levels were near the assay's limit and well below therapeutic levels.

-Breastfeeding women (SOPRANINO): Low concentrations of ocrelizumab were detected in breastmilk (median relative infant dose 0.27%, range 0–1.8%), with no measurable drug in infant serum 30 days after maternal infusion, indicating minimal transfer via lactation.

➢ **Clinical Pharmacodynamics**

- **B-Cell Depletion in Multiple Sclerosis**

-In the RRMS Study WA21493, treatment with both 300 mg × 2 and 1000 mg × 2 ocrelizumab led to rapid and complete depletion of CD19+ B cells in blood through the 24 weeks DB treatment period.

-In the two Phase III studies in RMS (WA21092 [OPERA I] and WA21093 [OPERA II]), treatment with ocrelizumab 600 mg led to a sustained depletion of CD19+ B-cells in blood, while in the IFN group, CD19+ B-cells appeared stable over the 96-week treatment period.

- **Pharmacodynamics in Special Patient Populations**

Ocrelizumab pharmacodynamics have been studied in pediatric MS patients, infants with in utero exposure, and breastfed infants:

-Children and adolescents (OPERETTA 1 & 2): IV ocrelizumab induced rapid and sustained near-complete B-cell depletion in blood.

-Breastfed infants (SOPRANINO): No B-cell depletion was observed 30 days after maternal postpartum infusion; all infants maintained age-appropriate B-cell levels. Extended follow-up up to 13 months indicated B-cell counts remained above the lower limit of normal.

➢ **Clinical Efficacy**

- **Efficacy in Multiple Sclerosis**

Studies WA21092 (OPERA I) and WA21093 (OPERA II)

-Ocrelizumab (600 mg IV every 6 months) demonstrated superior efficacy compared with active comparators in patients with RMS across multiple studies:

Phase III RMS studies (WA21493): Ocrelizumab showed significant reductions in annualized relapse rate (ARR) and maintained low counts of Gd-enhancing T1 lesions through Week 144, including in patients who switched from placebo or IFN β-1a at Week 24. Approximately 75% of patients completed Week 144 visits.

Pediatric RMS studies (OPERETTA 1 & 2): Ocrelizumab markedly reduced T1 Gd-enhancing lesions compared with fingolimod, with an 87.2% reduction (rate ratio 0.128, 95% CI: 0.034–0.414, p = 0.001). Only 5 lesions were observed in 4 patients on ocrelizumab versus 33 lesions in 14 patients on fingolimod. No T1 Gd-enhancing lesions were observed at Week 12 after the first ocrelizumab dose.

Overview of Efficacy from Study MA30143 (ENSEMBLE)

-The majority of patients in Cohort 1 intent-to-treat (ITT) population did not show disability progression over the 4 years of ocrelizumab treatment

Overview of Efficacy from Study MA30005 (CASTING)

-A total of 74.8% of the patients in the mITT population had NEDA and were free from a protocol-defined event during the 96-week study period (the primary endpoint). In addition, 89.8% had no relapses; 97.7% had no T1 Gd-enhanced lesions after Week 8; 91.5% had no new/enlarging T2 lesions after Week 8; 87.5%

had no CDP sustained for at least 24 weeks; 91.5% had no MRI activity (T1 or T2 lesions) after Week 8; and 80.4% had no clinical activity (24-week CDP or protocol-defined relapse)

- **Overview of Efficacy in PPMS**

Study WA25046 (ORATORIO)

- Ocrelizumab demonstrated efficacy in slowing disability progression and MRI disease activity in RMS patients:

Clinical endpoint: Reduced the progression rate of the 25-foot timed walk (T25-FW) by 29% versus placebo at Week 120 (p = 0.0404), with consistent effects observed during the open-label extension (OLE).

MRI endpoints: Ocrelizumab decreased total T2 lesion volume by 3.4% versus a 7.4% increase on placebo (p < 0.0001) and reduced the rate of brain volume loss by 17.5% (p = 0.0206) from Week 24 to Week 120. OLE MRI data (Weeks 48–336) confirmed sustained reductions in new or enlarging T2 lesions, with particularly low lesion activity from OLE Week 144 onward.

Overview of Efficacy in High-Dose Studies BN42082 (MUSETTE) and BN42083 (GAVOTTE)

-Both BN42082 (MUSETTE) and BN42083 (**GAVOTTE**) studies did not demonstrate additional benefit of the higher dose compared to the approved dose of 600 mg. Further development of the high dose has been discontinued; the safety follow-up is ongoing.

- **Clinical Safety**

Ocrelizumab demonstrated a favorable safety profile across multiple studies and populations:

-Open-Label Extension (OLE): No new safety concerns observed for infusion-related reactions (IRRs), infections, or malignancies.

-High-Dose Studies (MUSETTE & GAVOTTE): Safety of higher doses was consistent with the approved 600 mg regimen.

-Pediatric Studies (OPERETTA 1 & 2): Well-tolerated in children and adolescents; no new safety concerns, and overall profile aligned with adults.

-Pregnancy Exposure Study (MINORE): No serious infections leading to treatment withdrawal; common maternal AEs included COVID-19, iron deficiency, nasopharyngitis, and cough. Infant AEs were typical for healthy infants.

-Lactation Study (SOPRANINO): No serious adverse events, deaths, or withdrawals; no Grade ≥3 maternal AEs or infusion-related modifications, and infant safety was maintained during the first year of life.

- **Deaths**

- As of the November 2023 cutoff date, 110 deaths were reported in the MS All Exposure Population. The fatality rate (0.362 per 100 patient-years; 95% CI: 0.297–0.436) was consistent with prior analyses and

comparable to rates observed in real-world MS cohorts (1.21–1.36 per 100 PY). Of these deaths, 50 were COVID-19 related. No new pooled safety analyses were conducted after November 2023, and post-cutoff death reviews did not identify any new safety concerns.

- **Serious Adverse Events**

Studies WA21092 (OPERA I) and WA21093 (OPERA II)

-The proportion of patients reporting SAEs in the OLE period remained low and analysis of individual cases did not reveal any safety pattern.

Study WA25046 (ORATORIO)

-The overall safety profile remained consistent in the OLE period. The most frequently reported SAEs were in the Infections and infestations SOC and remained balanced across the placebo and ocrelizumab groups.

Study WA21493

-The proportion of patients who experienced SAEs during the OLE period was 27.2% (28 patients), excluding COVID-19 terms (19.4% [20 patients]). Considering that the COVID-19 pandemic coincided with the OLE period, the most commonly reported SAE was COVID-19 pneumonia (5.8% [6 patients]); all other SAEs were reported in < 5% of patients. Four patients (3.9%) experienced SAEs reported by the investigator as related to study treatment. The most common SAE related to study treatment (reported in 2 patients) was pneumonia.

- **MS All Exposure Population**

-Overall, there were no meaningful changes in type, rate, or severity of SAEs and no new safety concerns were identified.

Adverse Events Leading to Treatment Discontinuation

Studies WA21092 (OPERA I) and WA21093 (OPERA II)

-Ocrelizumab was well tolerated over the 10-year treatment period with a total of 8% of patients having discontinued due to non-fatal AEs by the end of the study compared with 3.5% during the controlled treatment period as described above. The most common AEs leading to withdrawal by PT, including and excluding COVID-19 terms, were IRRs.

Study WA25046 (ORATORIO)

-The percentage of patients with AEs or SAEs leading to discontinuation from treatment was similar in both ocrelizumab and placebo groups

Study WA21493

-Four patients experienced an AE leading to withdrawal from treatment during the placebo-controlled 24-week period: 2 patients in the ocrelizumab 600 mg group (SAE of hypersensitivity occurring within 24 hours of infusion but not identified by investigator as an IRR and non-serious AE of IRR), 1 patient in the ocrelizumab 1000 mg group (SAE of anxiety), and 1 patient in the Avonex group who experienced a non-serious AE of vomiting.

➢ **MS All Exposure Population**

-The rate of SAEs leading to withdrawal from treatment was 0.53 (95% CI: 0.45, 0.62).

- **Immunogenicity – Anti-Drug Antibodies (ADAs):**

- RMS and PPMS Studies:

- **OPERA I & II (WA21092/WA21093):** 14 of 1,415 patients (1%) developed treatment-emergent ADAs; 4 had neutralizing antibodies (NAbs).
- **ORATORIO (WA25046):** 11 of 639 patients (1.7%) developed ADAs; 1 patient had NAbs. Low incidence precluded determination of impact on efficacy or safety.
- **WA21493:** No ADAs during the 96-week treatment; 3.9% incidence in the OLE (4/102).
- **OBOE (ML29966):** No treatment-emergent ADAs (0/126).
- **OPERETTA 1 & 2 (WA39085/WN42086):** OPERETTA 1: 0% incidence; OPERETTA 2: 2 of 90 patients (2.2%) developed ADAs.
- **OCARINA I & II (CN41144/CN42097):** No treatment-emergent ADAs; 3 of 132 patients (2.3%) had anti-rHuPH20 antibodies in OCARINA I; none in OCARINA II.

- **Rheumatoid Arthritis and Lupus:** ADA positivity showed no apparent association with adverse events, including infusion-related reactions.

Overall, treatment-emergent ADAs to ocrelizumab were rare across studies, with minimal observed impact on safety or efficacy.

➢ **Marketing Experience**

-Since approval in the US in March 2017 until 31 March 2025, and not accounting for the patients participating in clinical trials, 408,744 patients are estimated to have received ocrelizumab in the post-marketing setting for the MS indication, corresponding to 1,274,195 PYs of exposure. Overall, the case reports received and reviewed during the post-marketing period (up to 27 March 2025) were consistent with the known safety profile of ocrelizumab seen in the clinical trial setting.

- **Protocol:** An open Label, Single-arm, 4-year study to evaluate effectiveness and safety of Ocrelizumab treatment in patients with progressive multiple sclerosis

  Phase: IIIb

Objective(s):

This study will evaluate the effectiveness and safety of ocrelizumab in PMS patients. Specific objectives and corresponding endpoints for the study are outlined below:

Objectives	Corresponding Endpoints
Primary Effectiveness Objective:	
• To evaluate the effectiveness of ocrelizumab treatment in patients with PMS disease course	• Proportion of patients with no evidence of progression (NEP) defined as no progression sustained for at least 24 weeks on all of the following three components (CDP a; ≥20% increase in T25FWT; ≥20% increase in 9HPT) from baseline to Week 96, Week 96 to Week 192 and baseline to Week 192 • Proportion of patients with no evidence of progression and no active disease (NEPAD) defined as no progression sustained for at least 24 weeks on all of the three components of NEP (CDP, T25FWT, 9HPT), no protocol-defined relapse, no enlarging or new T2 lesion from Week 24, and no T1 gadolinium (Gd+)- enhancing lesion from baseline to Week 96, Week 96 to Week 192 and baseline to Week 192
Secondary Effectiveness Objectives:	
• To evaluate the effectiveness of ocrelizumab treatment in patients with PMS disease course	• Change from baseline in cognitive function as measured by the symbol digit modalities test (SDMT) and the Brief Visuospatial Memory Test – Revised (BVMT-R) • Mean change from baseline in the EDSS score over the course of the study • Time to onset of first CDP sustained for at least 24 and 48 weeks • Time to onset of first ≥20% increase in T25FWT sustained for at least 24 weeks • Time to onset of first ≥20% increase in 9HPT sustained for at least 24 weeks

		• Proportion of patients with NEP defined above from Week 24 to Week 96, Week 24 to Week 192 and Week 48 to Week 192 • Proportion of patients with NEPAD defined above from Week 24 to Week 96, Week 24 to Week 192 and Week 48 to Week 192 • Proportion of patients with confirmed disability improvement (CDI) defined as improvement sustained for at least 24 weeks on at least one of the following three components (EDSS c; ≥ 20% decrease in T25FWT; ≥ 20% decrease in 9HPT) from baseline to Week 96, Week 96 to Week 192 and baseline to Week 192
	• To evaluate the effectiveness of ocrelizumab treatment in PMS patients using a range of patient-relevant measures	• Change from baseline in the following patient-reported outcomes (PROs): – Multiple Sclerosis Impact Scale (MSIS-29) – Multiple Sclerosis Walking scale (MSWS-12) – ABILHAND-56 Questionnaire – Fatigue scale for Motor and cognitive function (FSMC) – SymptoMScreen – 88-item Multiple Sclerosis Spasticity Scale (MSSS-88) – Numerical Pain Rating Scale (NPRS) – Patient Global Impression of Severity (PGIS) for upper limb, lower limb and cognitive functions • Change in the number of falls and near-falls
	• To evaluate the effectiveness of ocrelizumab treatment in PMS patients using imaging outcomes	Change in the following MRI volumetric measures: • Whole brain volume • Cerebral white matter volume • Cortical grey matter volume • Deep grey matter volume • Thalamic volumes • Whole and regional cerebellar volume Change in the following lesion and tissue integrity parameters:

	• Number of new/enlarging T2 lesions and total T2 lesion volume • Number of T1 Gd+ lesions and total volume • Number of T1 lesions and total volume • Gd-enhancing late- fluid-attenuated inversion-recovery (FLAIR) meningeal lesions
Secondary Safety Objectives:	
To evaluate the safety and tolerability of ocrelizumab in PMS patients	• Rate and nature of adverse events • Changes in clinical laboratory results • Rates of study treatment discontinuation due to adverse events
Exploratory Objectives:	
To evaluate the effectiveness of ocrelizumab treatment in PMS patients using advanced imaging (MRI) outcomes	Change in the following brain MRI measures: • Basal ganglia (putamen, caudate, globus pallidus) volumes • Hippocampal volumes • Measure of the relative spectroscopic signal amplitude of N acetyl aspartate (NAA), myo-inositol to creatine (mIn/Cr), choline to creatine (Cho/Cr) and glutathione to creatine (Glx/Cr) ratios, using spectroscopic MR in centres with 1.5-Tesla MRI) • Measure of cortical and periventricular magnetization transfer ratio (MTR) gradients • SWI measurements in normal appearing cortical grey matter (NACGM) and periventricular white matter bands • Measure of MTR intensity in SELs and phase-rim lesions and mean MTR in normal-appearing white and grey matter (NAWM and NAGM) • Measure of MTR and SWI in the lesion edge of SELs and phase-rim lesions

		• MRI-driven subtypes and stages using the SuStaIn model (Subtyping and Staging Inference) using conventional and advanced MRI sequences • Network-based measures for cortical and subcortical networks of grey matter regions • Brain predicted age difference (brain-progression or active disease [PAD]) • Slowly evolving lesions (SEL) • Normalised T1 intensity/T1 Gd+ enhancement in new focal T2 lesions, SELs, persistent areas of non-SEL T2 lesions, and normal-appearing brain tissue • Measure of phase rim lesions (using a Susceptibility-Weighted Imaging [SWI]/T2 sequence in centres with 3-Tesla MRI) Change in the following brainstem MRI measures • Total brainstem volume and volume of midbrain, pons and medulla oblongata • Quantitative MTR changes in the brainstem Change in the following spinal cord MRI measures • Total cervical cord area at C1 using brain sequences • Total cross-sectional cord area (C2, C3, C4) phase-sensitive inversion recovery (PSIR) or Magnetization Prepared – Rapid Gradient Echo (MPRAGE) • Total grey matter areas (C2, C3, C4) using PSIR • Left-right width (LRW) and anterior-posterior width (APW) at C1 in the cervical cord area using brain sequences • PSIR intensity (C2, C3, C4) • Cervical cord cross-sectional area • Cervical cord grey and white matter area

	To evaluate the effectiveness of ocrelizumab treatment in PMS patients using retinal imaging and motor electrophysiological outcomes	Change in latency and amplitude of motor evoked potentials (MEP) in upper limbs • Change in the following optical coherence tomography (OCT) outcomes: o Thickness of peripapillary retinal nerve fibre layer (pRNFL): average and in the following sectors (temporal, superior, nasal and inferior [TSNI], and papillomacular bundle [PMB]) o Thickness/volume of the combined macula complete measurements from the Early Treatment Diabetic Retinopathy Screening (ETDRS) grid o Thickness/volume of macular ganglion-cell layer/inner plexiform layer (mGCL/IPL), o Thickness/volume of macular inner nuclear layer (INL) and outer nuclear layer (ONL) o Thickness/volume of macular IPL and outer plexiform layer (OPL) o Reflectivity of the photoreceptor layers and the retinal pigment epithelium (RPE) • Change in high-contrast (100%) and low-contrast (2.5% and 1.25%) visual acuity using the Sloan high- and low-contrast letter acuity (LCLA) charts
	To evaluate fluid (blood and CSF) biomarkers to better understand the pathogenesis of PMS and response to treatment with ocrelizumab	• Change in serum and CSF neurofilament light chain (NfL) levels and its association with disability progression and brain MRI outcomes • Change in levels of soluble neurodegeneration markers, and/or inflammatory markers in the peripheral blood serum or plasma • Change in compartment-specific cell type composition identified by single-cell RNA sequencing (scRNA-seq) in the CSF and matched blood samples

• To explore whether technology-enabled high-yield functional measures (Floodlight RPM Test Battery application) may detect progressive change prior to conventional clinical outcomes in PMS patients	• Change in Floodlight RPM Test Battery: – Cognitive test: Information processing speed (IPS) test – Hand motor function tests (HMFT): Draw a Shape and Pinching Tomatoes – 2-Minute Walk test (2MWT) – U-Turn test (UTT) – Static balance test (SBT) – Continuous sensor-based passive analysis of mobility and gait-related motion (CAG) – Daily Mood Questions (DMQ) – Smartphone version of MSIS-29 – MS Symptom Tracker (MSST) – T25FWT • Change in above mentioned primary and secondary clinical endpoints in Group 1 versus Group 2, to measure the impact that Floodlight RPM with data playback may have on the PMS disease course.
• To measure patient adherence to and satisfaction with the Floodlight RPM Test Battery application	• Adherence to smartphone assessments quantified as compliance level (%), which will be measured in terms of number of tests performed or number of days of completed testing • Feedback by the patients on the smartphone schedule of assessments and impact on their daily activities using a satisfaction questionnaire and semi-structured interviews in a subset of patients.
• To evaluate the association between clinical outcomes, PROs and subclinical disease activity as measured by advanced MRI metrics and technology-enabled high-yield functional measures in PMS patients over 4 years	• Association between NEP/NEPAD and all above mentioned PROs • Association between SDMT and BVMT-R and all above mentioned PROs • Association between time to onset of first 24-week CDP and all above mentioned PROs • Association between time to onset of first 24-week sustained progression ≥20% on T25FWT and all above mentioned PROs • Association between time to onset of first 24-week sustained progression ≥20% on 9HPT and ABILHAND

	• Association between change in clinical and brain MRI outcomes • Association between change in clinical and OCT outcomes • Association between change in upper-limb MEP latency and 9 HPT, ABILHAND and Floodlight hand motor function tests • Association between change in RPM Test Battery and brain MRI • Association between change in RPM Test Battery and PROs • Proportion of patients with a clinically meaningful deterioration in above mentioned PROs
• To investigate the effect of ocrelizumab on antibody and T cell responses in patients administered an approved severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) vaccine	• Analysis of immune response (SARS-CoV-2 antibody titres and SARS-CoV-2 T cell responses) to SARS-CoV-2 vaccine

Rationale:

The primary objective of this study is to assess the effectiveness and safety of ocrelizumab in patients with progressive forms of multiple sclerosis, i.e., primary progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS). The efficacy of ocrelizumab in PPMS patients was demonstrated in Phase III ORATORIO study (NCT01194570). This study will further elaborate the clinical and safety profile of ocrelizumab in progressive multiple sclerosis patients (including both SPMS and PPMS) as well as provide a comprehensive evaluation of clinical, paraclinical, patient-reported and advanced neuroimaging outcomes in patients over 4 years.

Benefit-risk Analysis:

1. Therapeutic Context and Unmet Medical Need

Multiple sclerosis (MS) is a chronic, immune-mediated neurodegenerative disorder characterized by progressive neurological impairment, accumulation of disability, and a substantial impact on patients' quality of life.

- In relapsing multiple sclerosis (RMS), disease activity is primarily driven by inflammatory relapses and the accumulation of lesions detectable by magnetic resonance imaging (MRI).
- In primary progressive multiple sclerosis (PPMS), disease progression occurs independently of relapses, and historically, there has been a lack of highly effective therapeutic options, representing a significant unmet medical need.

Prior to the introduction of ocrelizumab, treatment options for PPMS were limited. Additionally, a proportion of patients with RMS demonstrated suboptimal response or intolerance to available disease-modifying therapies (DMTs), further highlighting the need for more effective and better-tolerated treatments.

2. Clinical Benefit Assessment

2.1 Efficacy in Relapsing MS (RMS)

Robust evidence from pivotal Phase III trials demonstrates that ocrelizumab provides clinically meaningful and statistically significant benefits compared with the active comparator (interferon β-1a), including:

- A significant reduction in annualized relapse rate (~46–47%)
- Reduction in confirmed disability progression (~40%)
- Marked reductions in MRI disease activity:
  - T1 gadolinium-enhancing lesions (up to ~95% reduction)
  - T2 lesions (up to ~83% reduction)
- Increased proportion of patients achieving no evidence of disease activity (NEDA)
- Favorable trends in functional outcomes and reduced brain volume loss

These findings are consistent across studies and supported by Phase II trials and long-term extension data.

2.2 Efficacy in Primary Progressive MS (PPMS)

In the pivotal PPMS study, ocrelizumab demonstrated:

- A 24–25% reduction in confirmed disability progression
- Slowing of ambulatory decline, as measured by timed walk assessments
- Reduction in brain atrophy and lesion accumulation

These results represent a clinically meaningful benefit in a population with limited treatment options and support a favorable efficacy profile in PPMS.

2.3 Long-Term and Real-World Effectiveness

Data from extension phases and real-world studies indicate:

- Sustained suppression of relapse activity
- Maintenance of disability stabilization

- Durable reduction in MRI activity

Furthermore, patients switching from prior DMTs due to suboptimal response have shown maintained or improved disease control following initiation of ocrelizumab.

2.4 Special Populations and Administration Flexibility

- **Pediatric population:** Pharmacokinetic and pharmacodynamic data support extrapolation from adults, with comparable exposure and no new safety signals identified.
- **Subcutaneous (SC) formulation:** Demonstrates non-inferior exposure and comparable pharmacodynamic effects relative to intravenous (IV) administration, offering enhanced convenience and potential adherence benefits.
- **Infusion optimization:** Shorter infusion durations do not adversely impact safety outcomes.

3. Safety Assessment

3.1 Overall Safety Profile

The safety profile of ocrelizumab is well characterized and consistent with its mechanism of action (B-cell depletion):

- Overall incidence of adverse events is comparable to control groups
- Low rates of treatment discontinuation due to adverse events

3.2 Identified Risks

3.2.1 Infusion- and Injection-Related Reactions

- Common, particularly during initial administrations
- Generally mild to moderate in severity
- Effectively managed with premedication and monitoring

3.2.2 Infections

- Increased incidence, primarily:
  - Upper respiratory tract infections
  - Mostly mild to moderate in severity
- Serious infections occur at low frequency and are comparable to or slightly higher than control groups
- Consistent with the immunomodulatory mechanism of action

3.3 Important Potential Risks

3.3.1 Malignancies

- Slight numerical imbalance observed in clinical trials
- No confirmed causal association

- Requires continued long-term surveillance

3.3.2 Progressive Multifocal Leukoencephalopathy (PML)

- Rare cases reported post-marketing
- Overall risk considered low but clinically significant

3.3.3 Immunological Effects

- Gradual reduction in immunoglobulin levels over time
- Attenuated vaccine responses
- Potential implications for infection susceptibility

3.4 Safety in Special Situations

- **Pregnancy:** Limited data; ongoing registry studies required
- **Pediatric use:** No new safety concerns identified to date
- **Long-term exposure:** No emerging or unexpected safety signals observed

4. Benefit–Risk Evaluation

4.1 Favorable Aspects

- Demonstrated high efficacy across multiple clinically relevant endpoints
- Unique and meaningful benefit in PPMS, addressing a critical unmet need
- Sustained long-term effectiveness
- Flexible administration options (IV and SC)
- Predictable and manageable safety profile

4.2 Uncertainties and Limitations

- Long-term malignancy risk remains to be fully characterized
- Limited data in pregnancy and certain special populations
- Long-term effects of sustained immunosuppression require continued monitoring

4.3 Overall Conclusion on Benefit–Risk Balance

Considering:

- The magnitude and consistency of clinical benefit
- The serious and progressive nature of multiple sclerosis
- The well-characterized and manageable safety profile

The benefit–risk balance of ocrelizumab is considered **favorable** for the treatment of both RMS and PPMS.

5. Risk Management and Pharmacovigilance Recommendations

To ensure continued safe use, the following measures are recommended:

- **Routine monitoring of:**

- Infections, including serious infections
- Immunoglobulin levels

- **Clinical vigilance for:**
  - Malignancies
  - Signs and symptoms of PML
- **Vaccination considerations:**
  - Assessment and completion of required vaccinations prior to treatment initiation
- **Ongoing data collection through:**
  - Post-marketing surveillance programs
  - Pregnancy registries
  - Long-term extension studies

Design:

This study is a prospective, multicentre, open-label, single-arm effectiveness and safety study in patients with PMS. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride separated by 14 days (i.e., Days 1 and 15); followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the remainder of the study duration. This study will enroll approximately 900 patients. The ratio between PMS patients with relapsing onset as per Lublin et al. 2014 criteria and PPMS patients as per revised McDonald 2010 criteria (Polman et al. 2011) will be 1.25:1 (approximately 500 PMS with relapsing onset and approximately 400 PPMS patients). Patients will be assessed for effectiveness and safety every 24 weeks as described in the schedule of assessments presented in Appendix 1. The study will consist of the following periods:

- Screening period: up to 4 weeks.
- Treatment period: open-label treatment period of 192 weeks (i.e., 24 weeks after the last dose of ocrelizumab, which will be administered at Week 168).
- A follow-up period of 48 weeks after the last infusion of the study drug.

- ***Recommendation &/ or*** **Questions & Answers:**

SN	EDA Comment	Applicant Reply
1	A Clarification is required regarding the status of the mean absolute lymphocyte counts in the rest of monkeys during the recovery period in the study (04-0192-0134) as the recovery to the mean pre-study value of only monkeys (2	only 2 male and 2 female monkeys from the control and 100 mg/kg dose group were monitored for recovery as already reported. Please note that extensive B cell level monitoring has been undertaken during

	male/2 female) receiving 100 mg/Kg was mentioned .	clinical trials on human subjects and the data is fully available in CSRs that shared.
2	It was mentioned in page 83, an ICF taken before SARS-COV-2 Vaccine and collection blood samples for immunological assessment but as an optional procedure. A Clarification is required regarding if this will be conduction at Egypt sites.	Egypt's sites are not participating in this step.

- **Abbreviation:**

9HPT	Nine-Hole Peg Test
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
AE	Adverse Event
ARR	Annualized Relapse Rate
AUC	Area Under the Curve
BVMT-R	Brief Visuospatial Memory Test – Revised
CDC	Complement-Dependent Cytotoxicity
CDI	Confirmed Disability Improvement
CDP	Confirmed Disability Progression
CI	Confidence Interval
CSF	Cerebrospinal Fluid
CT	Clinical Trial
DB	Double Blind
DNA	Deoxyribonucleic Acid
EC50	Half Maximal Effective Concentration
EDA	Egyptian Drug Authority
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-Linked Immunosorbent Assay
Fc	Fragment crystallizable region of antibody
FLAIR	Fluid-Attenuated Inversion Recovery
FSMC	Fatigue Scale for Motor and Cognitive Function
Gd	Gadolinium
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN	Interferon
IRR	Infusion-Related Reaction
ITT	Intention To Treat
IV	Intravenous
LLN	Lower Limit of Normal
LMP	Last Menstrual Period
mITT	Modified Intention To Treat
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale
MSSS-88	Multiple Sclerosis Spasticity Scale
MSWS-12	Multiple Sclerosis Walking Scale
MTX	Methotrexate
NAbs	Neutralizing Antibodies
NEDA	No Evidence of Disease Activity
NEP	No Evidence of Progression
NEPAD	No Evidence of Progression or Active Disease
NHL	Non-Hodgkin Lymphoma
NK	Natural Killer Cells
NPRS	Numerical Pain Rating Scale
OBDS	On-Body Delivery System
OCR	Ocrelizumab
OLE	Open-Label Extension
PD	Pharmacodynamics
PK	Pharmacokinetics
PMS	Progressive Multiple Sclerosis
PPK	Population Pharmacokinetics
PPMS	Primary Progressive Multiple Sclerosis
PRO	Patient-Reported Outcome
RA	Rheumatoid Arthritis
RMS	Relapsing Multiple Sclerosis

RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SC	Subcutaneous
SDMT	Symbol Digit Modalities Test
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
T1	T1-weighted MRI lesion
T2	T2-weighted MRI lesion
T25FWT	Timed 25-Foot Walk Test