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Safety of Ocrelizumab in Multiple Sclerosis: Updated Analysis in Patients with Relapsing and Primary Progressive Multiple Sclerosis

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Ongoing safety reporting is crucial to understanding the long-term benefit–risk profile of ocrelizumab (OCR) in patients with multiple sclerosis (MS). The safety and efficacy of OCR have been characterised in one Phase II study in relapsing-remitting MS (NCT00676715), two identical Phase III trials in relapsing MS (RMS; OPERA I/II [NCT01247324]/[NCT01412333]) and the Phase III trial in primary progressive MS (PPMS; ORATORIO [NCT01194570]).

Safety outcomes were reported for all patients who received OCR during the controlled treatment and associated OLE periods of the Phase II and Phase III clinical trials, plus the ongoing Phase IIIb trials VELOCE, CHORDS/CASTING, OBOE, ENSEMBLE and associated substudies (OCR all-exposure population). The number of post-marketing patients exposed to OCR is based on estimated total number of vials sold, as well as US claims data. To account for the different exposure lengths, the incidence rate per 100 patient years (PY) is presented. Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities.

As of July 2018, 4,501 patients with MS received OCR in clinical trials resulting in 12,559 PY of exposure. Reported rates per 100 PY in the OCR all-exposure population (95% confidence interval) were as follows: AEs, 255 (252–258); serious AEs, 7.52 (7.05–8.02); infections, 77.1 (75.5–78.6); serious infections, 2.01 (1.77–2.27); malignancies, 0.47 (0.36–0.61); and AEs leading to treatment discontinuation, 1.15 (0.97–1.35). As of April 2019, approximately 96,000 patients with MS have initiated OCR globally in the post-marketing setting and the data remain generally consistent with that observed in clinical trials. Updated OCR all-exposure population data using a January 2019 cut-off and selected post-marketing data will be presented.

The reported rates of events per 100 PY in the ocrelizumab all-exposure clinical trial population and post-marketing settings continue to be generally consistent with those seen during the controlled treatment period in the RMS and PPMS populations. The rate of AEs leading to treatment discontinuation also remained stable with additional patient exposure. Long-term safety data will continue to be reported on a regular basis.

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Preliminary Clinical Experience with Ocrelizumab, a New Recombinant Humanized Monoclonal Antibody for Multiple Sclerosis

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Multiple Sclerosis (MS) is a disease affecting the central nervous system with disabling consequences. Several treatments have been identified for reducing the frequency of relapses, modifying disease course and even delaying disability progression. Ocrelizumab (Ocrevus, Roche) is a recently approved Disease Modifying Drug (DMD) for MS. We report our initial experience on patient profile and safety of consecutive patients with MS who have received ocrelizumab.

A retrospective study on patients with MS in a private healthcare setting, between September 2017 and 2019. Participants received an initial dose of two ocrelizumab 300mg IV infusion, followed by one 600mg every 6 months. Data was extracted from the electronic medical records and variables assessed included gender, age, disease onset, disease course, previous medications, ocrelizumab treatment duration, adherence and adverse effects. Analysis was done using the Statistical Package for Social Sciences (SPSS).

The study identified 26 patients diagnosed with MS for an average duration of 4.8 years (over 0 to 12 years) (figure 1). More than half were female patients (61.5%), with overall average age of 40 years. It was identified that 22 patients (77%) had RRMS, while five (19.2%) had PPMS (figure 2). Only two patients were lost to follow up (7.7%), with the remainder being adherent to ocrelizumab treatment for an average of 9.6 months (over 6 to 18 months) (figure 3). One hospital admission was reported from symptomatic urinary tract infection (3.8%). Furthermore, six patients (23%) were naive to treatment before the initiation of ocrelizumab, 10 (38.5%) were switched from fingolimod, with 10 (38.5%) on various other disease modifying treatments.

This study provides preliminary insight into the demographics of patients with MS in Dubai. Our results demonstrate good adherence to ocrelizumab with low complication rates.

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No Effect on Infant Birth Weight and Head Circumference After Exposure to Interferon Beta Prior to Or During Pregnancy: A Register-Based Cohort Study in Finland and Sweden Among Women with Multiple Sclerosis

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Women with multiple sclerosis (MS) are in most cases diagnosed and treated at childbearing age. Some studies with limited sample size suggested that MS and interferon-beta (IFNβ) exposure might affect birth weight and head circumference. Prevalence of these two measures at birth was determined in IFNβ-exposed and unexposed pregnant women with MS from health registers in Finland and Sweden.

Health register data from Finland (1996-2014) and Sweden (2005-2014) were used to study women with MS: 1)dispensed only IFNβ within 6-months prior to date of last menstrual period or during pregnancy (IFNβ-exposed) and 2)without any dispensed MS disease modifying drugs (unexposed). Prevalence (95% confidence interval

[CI]) of the following birth outcomes was described for IFNβ-exposed and unexposed women: low birth weight for live births (<2500g), low head circumference for infants with full-term live birth (≥37 gestational weeks) and small or large for gestational age (SGA and LGA respectively). For SGA, LGA, and head circumference, national gestational age and sex-specific national references were used. No adjustments for potential confounding factors were performed.

Among 666 IFNβ-exposed and 1330 unexposed live births, the prevalence of birth outcomes was similar between IFNβ-exposed vs unexposed. Prevalence of low birth weight (95%CI) was 3.9%(2.6-5.7) among IFNβ-exposed and 4.8%(3.7-6.1) among unexposed live births. Among 619 IFNβ-exposed and 1219 unexposed full-term live births, prevalence of low head circumference (95%CI) was 1.9%(1.0-3.4) vs 1.1%(0.6-1.8) respectively. Comparing the IFNβ-exposed vs unexposed, SGA (95%CI) was 2.1%(1.2-3.5) vs 2.0%(1.3-2.9), and LGA (95%CI) was 0.8%(0.2-1.7) vs 0.8%(0.4-1.5).

Data from Finnish and Swedish health registers showed no evidence that IFNβ exposure before and during pregnancy affected infant birth weight and head circumference.

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Efficacy and Safety of Satralizumab for Relapse Prevention in Neuromyelitis Optica Spectrum Disorder: A Pooled Analysis from Two Phase 3 Clinical Trials

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Satralizumab is a humanised recycling monoclonal antibody that binds to the interleukin-6 (IL-6) receptor; IL-6 has been implicated in the pathophysiology of neuromyelitis optica spectrum disorder (NMOSD). Satralizumab significantly reduced the risk of NMOSD relapse in two Phase 3 studies: SAkuraSky (SA-307JG; NCT02028884) and SAkuraStar (SA-309JG; NCT02073279). Hazard ratios (HR) for the risk reduction were 0.38 (95% confidence interval [CI] 0.16–0.88) in SA-307JG and 0.45 (95% CI 0.23–0.89) in SA-309JG (both p=0.018). Satralizumab was particularly effective in AQP4-IgG-seropositive patients (HR 0.21 [95% CI 0.06–0.75] in SA-307JG and HR 0.26 [95% CI 0.11–0.63] in SA-309JG).

Patients were randomized 1:1 (SA-307JG) or 2:1 (SA-309JG) to satralizumab (120 mg) or placebo, with treatment at Weeks 0, 2, 4, and Q4W thereafter. Satralizumab or placebo were administered as monotherapy (SA-309JG) or add-on to baseline immunosuppressants (SA-307JG). The primary endpoint of both studies and the pooled analysis was time to first protocol-defined relapse (PDR). Efficacy analyses were performed on the pooled intention-to-treat population. Between-group HRs for time to PDR were calculated based on Cox proportional hazards models, stratified by study. To assess the validity of pooling data across the two studies, individual study treatment effects within the pooled analysis and study by treatment interaction effect were calculated.

The pooled analysis included 104 patients who received satralizumab and 74 who received placebo. HR for time to first PDR was 0.42 (95% CI 0.25–0.71; 58% risk reduction vs placebo). For AQP4-IgG seropositive patients, the HR was 0.25 (95% CI 0.12–0.50; 75% risk reduction); in the seronegative group, the HR was 0.97 (95% CI 0.41–2.23). The validity of pooling the data was confirmed, as no interaction between study and treatment effect was observed. Incidence of adverse events was similar in satralizumab and placebo groups; there were no deaths or anaphylactic reactions.

This pooled analysis of data from two Phase 3 studies demonstrated the efficacy of satralizumab in reducing relapse risk in patients with NMOSD. Satralizumab had a favourable safety profile as monotherapy or alongside immunosuppressants.

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Long-Term Reduction of Relapse Rate and Confirmed Disability Progression After 6 Years of Ocrelizumab Treatment in Patients with Relapsing Multiple Sclerosis

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The efficacy and safety of ocrelizumab (OCR) in relapsing multiple sclerosis (RMS) were demonstrated in the 96-week controlled double-blind period (DBP) of the Phase III trials OPERA I and OPERA II (NCT01247324; NCT01412333). Results for the 3-year follow-up of the pooled OPERA open-label extension (OLE) period have previously been reported (Hauser SL, et al. ECTRIMS 2018;Abstract P590).

At the start of the OLE period, patients who completed the DBP either continued OCR (OCR-OCR) or were switched from interferon (IFN) β-1a to OCR (IFN-OCR). Adjusted annualised relapse rate (ARR), time to onset of 24-week confirmed disability progression (CDP24) and change in adjusted mean Expanded Disability Status Scale (EDSS) score from the DBP baseline were analysed.

Overall, 82.3% of patients who entered the OLE completed OLE study Year 4. Among IFN-OCR patients, ARR decreased from 0.20 in the year pre-switch to 0.10, 0.08, 0.07 and 0.04 at Years 1, 2, 3 and 4 post-switch (Year 1 vs pre-switch, p<0.001; Year 1 vs Year 2, p=0.31; Year 2 vs Year 3, p=0.56; Year 3 vs Year 4, p=0.05). OCR-OCR continuers maintained the low ARR through the year pre-OLE and the 4 years of the OLE period (0.13, 0.10, 0.08, 0.07 and 0.05). OCR-OCR continuers vs IFN-OCR switchers had lower proportions of patients with CDP24 in the year pre-switch (7.7% vs 12.0%), and at OLE Year 1 (10.1% vs 15.6%), OLE Year 2 (13.9% vs 18.1%), OLE Year 3 (16.2% vs 21.3%), and OLE Year 4 (19.2% vs 23.7%); p<0.05, all difference comparisons. The safety profile observed in the OLE was generally consistent with that observed during the DBP.

After 6 years of follow-up, the proportion of patients with CDP24 remained lower in patients who initiated ocrelizumab treatment earlier (OCR-OCR), compared with patients who received initial IFN treatment (IFN-OCR), demonstrating that the benefits of earlier initiation of ocrelizumab were maintained compared with patients switching from IFN. Switching from IFN to ocrelizumab after 2 years at the start of the OLE period was associated with a reduction in ARR. Both OCR-OCR