Assessing the Long-term Outcomes of Ocrelizumab Treatment in Patients with Multiple Sclerosis in Germany – CONFIDENCE Baseline Characteristics

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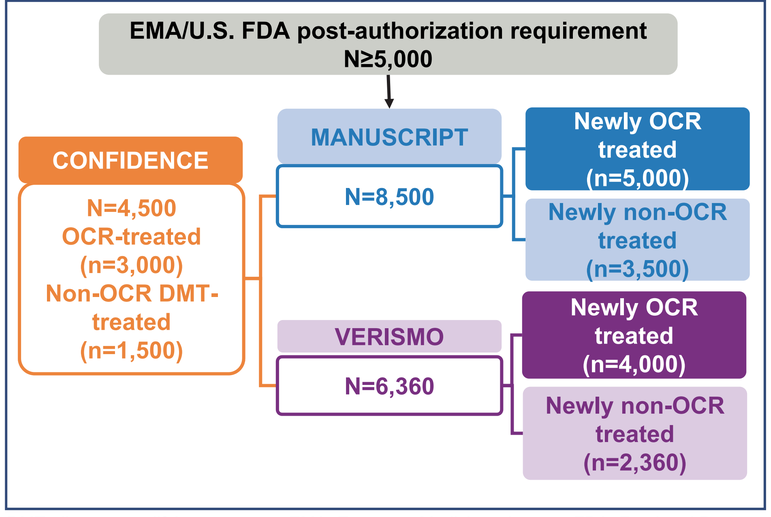
BACKGROUND

- Ocrelizumab (OCR, Ocrevus®) – a humanized monoclonal antibody that targets CD20+ B cells – has shown superior efficacy to interferon (IFN) β-1a with comparable safety for the treatment of relapsing MS (RMS) in phase III OPERA I and OPERA II clinical trials[1]
- Furthermore, OCR demonstrated superior efficacy with comparable safety to placebo for the treatment of primary progressive MS (PPMS) in the ORATORIO clinical trial[2]
- Pooled safety data collected in clinical trial patient populations suggested an imbalance of malignancies, driven by higher incidences of female breast cancer
  - Total incidences, however, remained within the range of placebo and epidemiological data[3]
- While the controlled-phases of the pivotal studies OPERA I & II and ORATORIO established the safety and efficacy of OCR in a selected patient population over a limited observational period, data are needed to describe the safety and effectiveness of OCR over a long treatment duration and, importantly, in a clinical practice setting
- CONFIDENCE (EUPAS22951) is a non-interventional study that will collect real-world safety and effectiveness data from MS patients newly exposed to OCR for up to 10 years
- Data from CONFIDENCE will be integrated into studies designed to fulfill FDA and EMA regulatory requirements, making it central to the OCR global post-authorization program (**Figure 1**)
- Here, we present baseline characteristics and safety of the first 500 MS patients newly treated with OCR, observed for up to 14.5 months

Figure 1. The ocrelizumab global post-authorization safety program



DMT, disease-modifying treatment; EMA, European Medicines Agency; FDA, Food and Drug Administration; MS, multiple sclerosis; OCR, ocrelizumab

OBJECTIVES

- CONFIDENCE assesses the long-term safety of OCR in the real-world MS populations with focus on uncommon adverse events (AEs) (incidence 0.1–1%) and to evaluate the long-term effectiveness of OCR in the real-world MS populations

METHODS

Study Design

- CONFIDENCE is a long-term, prospective, multicenter, non-interventional study
- Data will be collected from approximately 3,000 MS patients (~2000–2300 RMS, ~700–1000 PPMS) patients newly treated with OCR and 1,500 patients newly treated with other selected disease-modifying treatments (DMTs)* at approximately 300 centers in Germany
- Visits are to be documented approximately every 6 months up to 10 years regardless of discontinuation of study medication or the development of malignancy
- Enrollment began April 2018. The cutoff date for the present safety analysis was 15 July 2019

Study population

- Treatment decision must be made prior to and independent of enrollment in CONFIDENCE
- Treatment with OCR or other DMTs is to be according to the local label and at the discretion of the treating physician

Primary Outcome

- The primary outcome measure is the incidence of uncommon AEs (0.1–1%) and death with primary and underlying causes in patients newly exposed to OCR

Secondary Safety Outcomes

- The key secondary outcome measure is the incidence of uncommon AEs (0.1–1%) and death with primary and underlying causes in patients newly exposed to other DMTs
- Secondary safety outcomes include incidence of AEs, serious infections, and malignancy and mortality due to malignancy

*Other selected DMTs include: alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab and teriflunomide

Secondary Effectiveness Outcomes

- Effectiveness outcomes include treatment success (proportion of patients with no clinical disease activity measured by relapse and disease progression and no treatment discontinuation due to AE [excluding pregnancies] and lack of effectiveness), annualized relapse rate, proportions of patients with relapse, proportions of patients with confirmed disability progression (CDP), time to CDP onset, change in EDSS, time to confirmed disability improvement, and patient-reported outcomes

RESULTS

- Baseline characteristics of patients newly treated with OCR show that the average age is 43.4 years in patients with RMS and 53.2 in patients with PPMS
- Mean duration of disease is 10.34 years in patients with RMS and 6.90 years in patients with PPMS (**Table 1**)

Table 1. CONFIDENCE baseline characteristics

Characteristic	RMS	PPMS
Age at diagnosis, years		
Total patients	409	84
Mean (SD)	33.2 (10.5)	46.4 (10.7)
Median (Q1–Q3)	30.5 (24.5–40.5)	47.5 (38.5–54.0)
Range (min–max)	51.0 (14.5–65.5)	46.0 (20.5–66.5)
Age at OCR initiation, years		
Total patients	409	84
Mean (SD)	43.4 (11.5)	53.2 (8.7)
Median (Q1–Q3)	43.5 (33.5–52.5)	53.5 (48.0–58.0)
Range (min–max)	56.0 (18.5–74.5)	46.0 (30.5–76.5)
Sex		
Total patients	409	84
Female n (%)	285 (69.7)	51 (60.7)
Disease duration since onset of symptoms*, years		
Total patients	405	84
Mean (SD)	12.49 (9.45)	9.51 (8.63)
Median (Q1–Q3)	10.58 (4.62–18.44)	6.52 (3.41–11.45)
Range (min–max)	54.46 (0.08–54.54)	44.54 (0.19–44.73)
Disease duration since MS diagnosis*, years		
Total patients	406	84
Mean (SD)	10.34 (8.34)	6.90 (8.25)
Median (Q1–Q3)	8.68 (3.33–15.02)	4.19 (1.28–9.80)
Range (min–max)	38.53 (0.01–38.54)	38.41 (0.07–38.48)
Baseline EDSS (at OCR initiation)		
Total patients	339	64
Mean (SD)	3.4 (2.0)	4.7 (1.6)
Median (Q1–Q3)	3.0 (2.0–5.0)	4.5 (3.5–6.0)
Range (min–max)	8.0 (0.0–8.0)	6.0 (1.5–7.5)
MS relapses ≤12 months prior to OCR initiation		
Total patients	379	72
Mean (SD)	0.9 (0.9)	0.2 (0.5)
MS relapses ≤24 months prior to OCR initiation		
Total patients	346	70
Mean (SD)	1.4 (1.4)	0.2 (0.6)

*Prior to OCR initiation; EDSS, expanded disability status score; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive MS; RMS, relapsing MS; SD, standard deviation

- Nearly half (42%) of patients with RMS had ≥3 DMTs prior to OCR initiation
- The majority of patients with PPMS were treatment-naïve prior to OCR initiation (**Table 2**)

Table 2. Baseline therapy prior to OCR initiation in CONFIDENCE

Number of DMTs any time prior to OCR initiation, n (%)	RMS	PPMS
Total patients	409	84
Treatment-naïve	49 (11.98)	54 (64.29)
1	95 (23.23)	19 (22.62)
2	92 (22.49)	9 (10.71)
≥3	173 (42.30)	2 (2.38)
DMT ≤12 months prior to OCR initiation, n (%)		
Total patients	441	84
None	104 (23.58)	68 (80.95)
Fingolimod	85 (19.27)	1 (1.19)
Daclizumab	71 (16.10)	-
Natalizumab	67 (15.19)	-
Glatiramer acetate	26 (5.90)	1 (1.19)
Dimethyl fumarate	23 (5.22)	2 (2.38)
Teriflunomide	14 (3.17)	1 (1.19)
Interferon 1βa s.c.	11 (2.49)	1 (1.19)
Interferon 1β	9 (2.04)	1 (1.19)
Peginterferon	6 (1.36)	-
Rituximab	5 (1.13)	1 (1.19)
Azathioprine	1 (0.23)	-
Mitoxantrone	1 (0.23)	1 (1.19)
Other	18 (4.08)	7 (8.33)
Duration of most recent DMT prior to OCR initiation, years		
Total patients	348	26
Mean (SD)	2.72 (2.78)	3.16 (3.66)
Median (Q1–Q3)	1.66 (0.80–3.80)	1.95 (1.00–4.00)
Range (min–max)	14.41 (0.00–14.41)	17.00 (0.00–17.00)

MS, multiple sclerosis; DMT, disease-modifying treatment; PPMS, primary progressive MS; OCR, ocrelizumab; RMS, relapsing MS; SD, standard deviation

- Of the first 500 patients treated with OCR, 6 were excluded from the safety analysis for failure to fulfil the inclusion criteria
- In total, 55.1% of patients have thus far experienced at least one AE during OCR treatment, and 18.4% of patients experienced an AE that was considered related to treatment
- The most common AEs were infection and infestation, nervous system disorders, and general disorders and administration site conditions (**Table 3**)
- The most common serious AEs were nervous system disorders (**Table 3**)

Table 3. Adverse events in CONFIDENCE†

Event n (%)	Total AEs	Related‡ AE	Serious AE	Serious related AE
At least one	272 (55.1)	91 (18.4)	59 (11.9)	8 (1.6)
Infections and infestation	110 (22.3)	22 (4.5)	11 (2.2)	2 (0.4)[A]
Nervous system disorders	77 (15.6)	23 (4.7)	17 (3.4)	1 (0.2)[B]
General disorders and administration site conditions	46 (9.3)	15 (3.0)	3 (0.6)	-
Gastrointestinal disorders	34 (6.9)	7 (1.4)	3 (0.6)	1 (0.2)[C]
Skin and subcutaneous tissue disorders	35 (7.1)	8 (1.6)	2 (0.4)	-
Musculoskeletal and connective tissue disorders	35 (7.1)	5 (1.0)	2 (0.4)	1 (0.2)[D]
Investigations	25 (5.1)	11 (2.2)	2 (0.4)	-
Respiratory thoracic and mediastinal disorders	27 (5.5)	10 (2.0)	1 (0.2)	-
Injury, poisoning and procedural complications	21 (4.3)	2 (0.4)	4 (0.8)	-
Blood and lymphatic system disorders	12 (2.4)	6 (1.2)	3 (0.6)	1 (0.2)[E]
Psychiatric disorders	17 (3.4)	1 (0.2)	3 (0.6)	-
Metabolism and nutrition disorders	13 (2.6)	-	1 (0.2)	-
Renal and urinary disorders	9 (1.8)	1 (0.2)	2 (0.4)	-
Vascular disorders	7 (1.4)	1 (0.2)	1 (0.2)	-
Ear and labyrinth disorders	5 (1.0)	1 (0.2)	2 (0.4)	-
Eye disorders	6 (1.2)	1 (0.2)	1 (0.2)	-
Immune system disorders	5 (1.0)	2 (0.4)	1 (0.2)	-
Pregnancy, puerperium and perinatal conditions	3 (0.6)	1 (0.2)	2 (0.4)	1 (0.2)[F]
Reproductive system and breast disorders	6 (1.2)	-	1 (0.2)	-
Hepatobiliary disorders	3 (0.6)	-	3 (0.6)	-
Neoplasms, benign, malignant and unspecified	4 (0.8)[G]	-	2 (0.4)	-
Cardiac disorders	4 (0.8)	-	1 (0.2)	-
Congenital, familial and genetic disorders	1 (0.2)	-	-	-
Endocrine disorders	1 (0.2)	-	-	-
Not coded	15 (3.0)	7 (1.4)	4 (0.8)	1 (0.2)[H]

†cutoff date 15 July 2019; ‡causality determined by the treating physician; [A]urinary cystitis and recurrent endocarditis; [B]suspected brain stem attack; [C]Crohn's disease; [D]osteonecrosis (tibia); [E]agranulocytosis; [F]spontaneous abortion; [G]basal cell carcinoma in situ grade 1, fibroadenoma grade 2, uterine tumor grade 3, angiosarcoma fatal; [H]relapse; MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive MS; RMS, relapsing MS

CONCLUSIONS

- **Preliminary baseline characteristics show that patients enrolled in the non-interventional CONFIDENCE study represent the real-world population**
- **At baseline, patients with RMS are on average about 6 years older than patients in the OPERA clinical trials[1], while patients with PPMS are about 8.5 years older than those in the ORATORIO clinical trial[2]**
- **Patients with RMS have a slightly higher average EDSS than patients in clinical trials[1], while patients with PPMS have a comparable EDSS to those in clinical trials[2]**
- **No new or unexpected AEs were observed in CONFIDENCE. Incidences of infections and serious infections were within the expected ranges**

REFERENCES

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DISCLOSURES

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