Presented at the 28th annual meeting of the European Charcot Foundation, November 15–19, 2020

ID 21

Safety and tolerability in patients with multiple sclerosis receiving ocrelizumab in a real-world setting – CONFIDENCE one-year interim analysis

Buttmann M,[1] Meuth SG,[2] Weber MS,[3] Dirks P,[4] Eggebrecht JC,[5] Hieke-Schulz S,[5] Leemhuis J,[5] Ziemssen T,[6]

[1]Caritas Krankenhaus, Bad Mergentheim, Germany; [2]Neurology Clinic with Institute for Translational Neurology, University Clinic Munster, Germany; [3]Institute of Neuropathology, Department of Neurology, University Medicine Göttingen, Germany; [4]F. Hoffmann – La Roche AG, Basel, Switzerland, [5]Roche Pharma AG, Grenzach-Wyhlen, Germany; [6]Center of Clinical Neuroscience, Neurological Clinic, Carl Gustav Carus University Clinic, University of Technology, Dresden, Germany

BACKGROUND

- With more than 170,000 patients treated with ocrelizumab (OCR) worldwide as of July 2020[1], real-world effectiveness data are of relevance
- The safety and efficacy of OCR, a humanized monoclonal antibody selectively targeting CD20+ B-cells, in patients with relapsing forms of multiple sclerosis (RMS) or primary progressive MS (PPMS), have been characterised in Phase II and Phase III clinical trials[2–4]
- However, data on the safety and effectiveness of OCR in a real-world setting are currently limited
- CONFIDENCE (ML39632, EUPAS22951) is a non-interventional post-authorization safety study collecting real-world safety and effectiveness data for patients with MS newly treated with OCR for up to 10 years[5]

OBJECTIVES

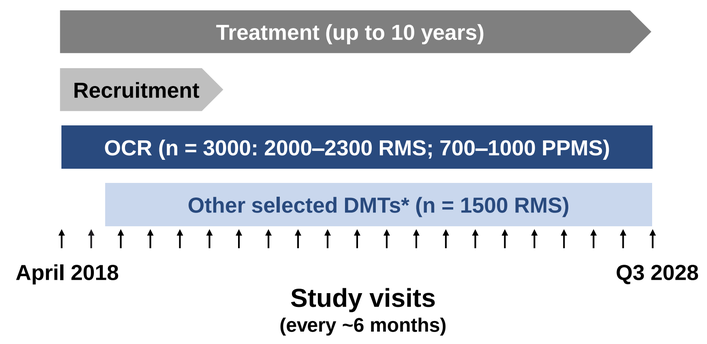
- Here, we present the results of the interim safety analysis from patients treated with OCR for approximately one year

METHODS

Study design

- CONFIDENCE aims to collect data for 3000 OCR-treated patients and 1500 patients treated with other disease-modifying treatments (DMTs) according to label at ~250 centers in Germany (**Figure 1**)
  - Study visits will be approximately every 6 months for up to 10 years regardless of discontinuation of study medication

Figure 1. CONFIDENCE study design



*Other DMTs include: alemtuzumab, cladribine, dimethyl fumarate, fingolimod, natalizumab and teriflunomide.
DMTs, disease-modifying treatments; MS, multiple sclerosis; PPMS, primary progressive MS; RMS, relapsing MS.

- The objectives of CONFIDENCE are to:
  - assess the long-term safety of OCR (primary objective)
  - estimate long-term effectiveness of OCR and the incidence of serious infections and malignancies (secondary objectives)

CONFIDENCE interim analysis

- This analysis included patients with one baseline visit and two follow-up visits (~1 year of treatment; data cutoff 1 April 2020)
- Statistical analyses are mainly descriptive and exploratory
- Error is reported as standard deviation unless stated otherwise
- Effectiveness outcomes are presented separately at this congress[6]

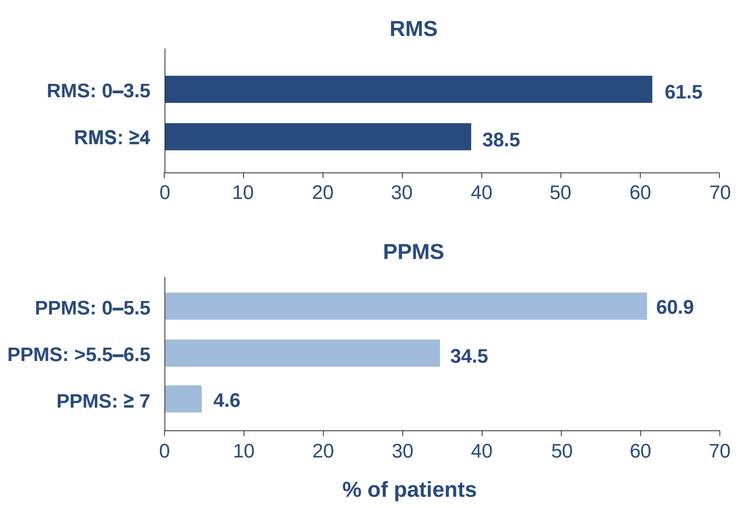
RESULTS

Population and baseline characteristics

- As of 17 August 2020, 2,277 patients have been recruited for OCR treatment in CONFIDENCE, of which 559 are included in this interim analysis (**Table 1**)
- Patients with RMS (456, 81.6%) were on average younger, and had a longer time since first MS symptoms and since MS diagnosis than patients with PPMS (103, 18.4%) (**Table 1**)
- Patients with PPMS had a higher baseline expanded disability status score (EDSS) than patients with RMS (4.5 vs 3.3) (**Figure 2**)
- Most patients with RMS (87.9%) had at least one prior MS DMT* (**Table 1**)
  - The most common DMTs were interferon β-1a, fingolimod and natalizumab
- Approximately 29% of patients with PPMS had at least one prior MS DMT, most commonly immune modulators such as interferon β-1a, interferon β-1b and glatiramer acetate (**Table 1**)

*includes all prior MS therapies over the course of a patient's disease prior to study entry.

Figure 2. EDSS scores at baseline by categories



RMS, n = 387; PPMS, n = 87
EDSS, expanded disability status scale, PPMS, primary progressive MS; RMS, relapsing MS.

Table 1. CONFIDENCE baseline characteristics

Characteristic	RMS (n = 456)	PPMS (n=103)	Total (n = 559)
Female, n (%)	303 (66.4)	57 (55.3)	360 (64.4)
Age, years			
Mean (SD)	43.9 (11.2)	52.8 (9.7)	45.5 (11.44)
Median (IQR)	44.0 (35.0; 53.0)	53.0 (47.0; 58.0)	47.0 (37.0; 54.0)
Time since first symptoms, years			
Mean (SD)	12.2 (9.3)	8.8 (8.1)	11.6 (9.2)
Median (IQR)	10.5 (4.31; 18.5)	5.8 (3.2; 11.8)	9.6 (3.7; 17.6)
Time since diagnosis, years			
Mean (SD)	10.2 (8.2)	6.1 (7.3)	9.5 (8.2)
Median (IQR)	8.4 (3.1; 15.7)	3.5 (1.1; 8.6)	7.5 (2.4; 14.3)
EDSS			
Mean (SD)	3.3 (1.9)	4.5 (1.7)	-
Median (IQR)	3.0 (2.0; 5.0)	4.5 (3.0; 6.0)	-
Patients with ≥1 comorbidity, n (%)‡			
Patients with ≥1	**320 (70.2)**	**83 (80.6)**	**403 (72.1)**
Metabolism and nutrition disorders	135 (29.6)	32 (31.1)	167 (29.9)
Psychiatric disorders	106 (23.2)	21 (20.4)	127 (22.7)
Nervous system disorders	101 (22.1)	27 (26.2)	128 (22.9)
Vascular disorders	75 (16.4)	27 (26.2)	102 (18.2)
Endocrine disorders	58 (12.7)	10 (9.7)	68 (12.2)
Musculoskeletal and connective tissue disorders	48 (10.5)	17 (16.5)	65 (11.6)
Patients with ≥1 prior MS therapy, n (%)†			
Patients with ≥1	**401 (87.9)**	**30 (29.1)**	**431 (77.1)**
Interferon β-1a	155 (34.0)	7 (6.8)	162 (29.0)
Fingolimod	145 (31.8)	4 (3.9)	149 (26.7)
Natalizumab	140 (30.7)	1 (1.0)	141 (25.2)
Glatiramer acetate	125 (27.4)	8 (7.8)	133 (23.8)
Interferon β-1b	96 (21.1)	8 (7.8)	104 (18.6)
Dimethyl fumarate	94 (20.6)	4 (3.9)	98 (17.5)
Daclizumab	68 (14.9)	-	68 (12.2)

‡Only system organ classes with >10% of total patients are listed; †Includes all prior MS therapies over the course of a patient's disease prior to study entry.

EDSS, expanded disability status scale; IQR, interquartile range; MS, multiple sclerosis; PPMS, primary progressive MS; RMS, relapsing MS; SD, standard deviation.

Adverse events

- 64.0% of patients with RMS had at least one adverse event (AE), most commonly from the categories infections and infestations, nervous system disorders and general disorders and administration site conditions (**Table 2**)
- 58.3% of patients with PPMS had at least one AE, most commonly from the categories infections and infestations, nervous system disorders, and musculoskeletal and connective tissue disorders (**Table 2**)

Serious adverse events

- Of the 14.5% of patients with RMS that experienced serious AEs (SAE), the most common were infections and infestations, nervous system disorders, and injury, poisoning and procedural complications (**Table 2**)
- Of the 11.7% of patients with PPMS that experienced a SAEs, the most common were nervous system disorders (**Table 2**)

Table 2. Adverse events, serious adverse events and malignancies in CONFIDENCE

Adverse event (AE)	RMS (n = 456)	PPMS (n = 103)	Total (n = 559)
Patients with ≥1 AE, n (%)§	**292 (64.0)**	**60 (58.3)**	**352 (63.0)**
Infections and infestations	149 (32.7)	27 (26.2)	176 (31.5)
Nervous system disorders‖	67 (14.7)	15 (14.6)	82 (14.7)
General disorders and administration site conditions	58 (12.7)	11 (1.7)	69 (12.3)
Injury, poisoning and procedural complications	53 (11.6)	9 (8.7)	62 (11.1)
Musculoskeletal and connective tissue disorders	50 (11.0)	11 (10.7)	61 (10.9)
Gastrointestinal disorders	44 (9.6)	5 (4.9)	49 (8.8)
Skin and subcutaneous disorders	41 (9.0)	4 (3.9)	45 (8.1)
Investigations	38 (8.3)	6 (5.8)	44 (7.9)
Respiratory, thoracic and mediastinal disorders	35 (7.7)	7 (6.8)	42 (7.5)
Psychiatric disorders	28 (6.1)	5 (4.9)	33 (5.9)
Patients with ≥1 related AEs, n (%)¶	**124 (27.2)**	**26 (25.2)**	**150 (26.8)**
Patients with ≥1 SAE, n (%)	**66 (14.5)**	**12 (11.7)**	**78 (14.0)**
Infections and infestations	18 (3.9)	2 (1.9)	20 (3.6)
Nervous system disorders	13 (2.9)	5 (4.9)	18 (3.2)
Injury, poisoning and procedural complications	10 (2.2)	2 (1.9)	12 (2.1)
Gastrointestinal disorders	5 (1.1)	-	5 (0.9)
Investigations	5 (1.1)	-	5 (0.9)
Musculoskeletal and connective tissue disorders	3 (0.7)	2 (1.9)	5 (0.9)
Renal and urinary disorders	5 (1.1)	-	5 (0.9)
General disorders and administration site conditions	4 (0.9)	2 (1.9)	6 (1.1)
Hepatobiliary disorders	4 (0.9)	-	4 (0.7)
Patients with ≥1 related SAEs, n (%)¶	**13 (2.9)**	**-**	**13 (2.3)**
Deaths, n (%)#	**1 (0.2)**	**-**	**1 (0.2)**
Patients with malignancies, n (%)	**3 (0.7)**	**-**	**3 (0.5)**
Basal cell carcinoma	1 (0.2)	-	1 (0.2)
Thyroid cancer	1 (0.2)	-	1 (0.2)
Breast cancer (invasive ductile)	1 (0.2)	-	1 (0.2)

A decrease of CD19+ cells is a therapeutic effect of ocrelizumab and was not considered an AE for this study. Medical occurrences or symptoms of deterioration that are anticipated as part of MS or which are expected in the patient population studied should be recorded as an AE only if judged by the physician to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. Infusion-related reactions are only recorded as an AE if judged by the physician as a serious or life-threatening event. §Only system organ classes with >5% incidence in total patients are listed; ‖nervous system disorders may include MS-related symptoms; ¶Causality determined by the treating physician. Related SAE were pneumonia and pyelonephritis (both n = 2), endocarditis, sinusitis, urinary tract infection, viral pharyngitis, aphthous ulcer, infusion related reaction, positive mycobacterium tuberculosis complex test, uterine leiomyoma and asthma (all n = 1); #unknown cause.

AE, adverse event; PPMS, primary progressive MS; RMS, relapsing MS; SAE, serious AE

.

Malignancies

- There were 3 cases of malignancies, all in patients with RMS (**Table 2**)

Deaths

- One patient died (unknown cause). There were no deaths reported due to infections or malignancies

Discontinuations

- Overall, 6 patients (0.3%) with RMS discontinued treatment, 2 of them were due to AEs (due to worsening of asthma and worsening of MS)
- The other reasons for discontinuation were lack of effectiveness, 'other', withdrawal by patient and death (unknown cause).
- One patient (1.0%) with PPMS discontinued treatment (withdrawal by patient)

Serious infections

- The most common serious infections in patients with RMS (n = 18; 3.9%) were urinary tract infections (1.3%), pneumonia (0.7%) and pyelonephritis (0.7%) (**Table 3**)
- In this PPMS cohort, the two serious infections were urinary tract infection and encephalitis (**Table 3**)

Table 3. Infections categorized as SAEs

Serious infections	RMS (n = 456)	PPMS (n = 103)	Total (n = 559)
Patients with ≥1, n (%)	18 (3.9)	2 (1.9)	20 (3.6)
Urinary tract infections	6 (1.3)	1 (1.0)	7 (1.3)
Pneumonia	3 (0.7)	-	3 (0.5)
Pyelonephritis	3 (0.7)	-	3 (0.5)
Urosepsis	2 (0.4)	-	2 (0.4)
Bronchitis	1 (0.2)	-	1 (0.2)
Cholecystitis infective	1 (0.2)	-	1 (0.2)
Encephalitis**	-	1 (1.0)	1 (0.2)
Endocarditis	1 (0.2)	-	1 (0.2)
Erysipelas	1 (0.2)	-	1 (0.2)
Febrile infection	1 (0.2)	-	1 (0.2)
Gingivitis	1 (0.2)	-	1 (0.2)
Progressive multifocal leukoencephalopathy	1 (0.2)	-	1 (0.2)
Sepsis	1 (0.2)	-	1 (0.2)
Sinusitis	1 (0.2)	-	1 (0.2)
Viral pharyngitis	1 (0.2)	-	1 (0.2)

**The encephalitis was not considered related to study medication by the treating physician; OCR treatment was continued after treatment for encephalitis.
OCR, ocrelizumab; PPMS, primary progressive MS; RMS, relapsing MS; SAE, serious adverse event.

CONCLUSIONS

- **CONFIDENCE represents a real-world cohort of MS patients**
  - **At baseline, patients with RMS and PPMS in CONFIDENCE were on average ~7 and ~8 years older, respectively, than those in the pivotal trials[3,4]**
  - **Patients with RMS had higher mean baseline EDSS and patients with PPMS had slightly lower mean baseline EDSS than patients in the pivotal trials**
  - **Most patients in CONFIDENCE had comorbidities**
- **Few patients experienced events such as serious infections (3.6%) or treatment-related SAEs (2.3%)**
- **Malignancies occurred in three patients with RMS (0.5%)**
- **No new or unexpected AEs were observed in this interim safety analysis of patients in CONFIDENCE**
  - **Effectiveness outcomes from CONFIDENCE are presented separately at this congress (ID 20)[6]**

ACKNOWLEDGEMENTS

We thank the patients all of the patients who are taking part in CONFIDENCE along with all of the study centers. CONFIDENCE is sponsored by Roche Pharma AG (Grenzach-Wyhlen, Germany). Physicians World Europe GmbH (Mannheim, Germany) provided medical writing support for this poster, funded by Roche Pharma AG. These data were originally presented at the 8th joint ACTRIMS-ECTRIMS meeting September 2020.

For more information on the CONFIDENCE study, please visit:

www.encepp.eu/encepp/viewResource.htm?id=23845

DISCLOSURES

The following authors hereby declare that since 1 Nov 2019 they have or have had business, personal or material relationships with the following companies, consulting firms or medical institutions and sponsors thereof: **MB:** Bayer, Biogen, Boehringer, Celgene, Coloplast, Daiichi-Sankyo, Das Fortbildungskolleg, Merck, Novartis, Roche, Sanofi and Teva // honoraria for lecturing, consulting and/or travel expenses for attending meetings; **JCE, PD, SHS, JL:** Roche Pharma AG // employee and shareholder; **SGM:** Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva // honoraria for lecturing, and travel expenses for attending meetings; German Ministry for Education and Research (BMBF), Bundesinstitut für Risikobewertung (BfR), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Gemeinsamer Bundesausschuss (G-BA), German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, German Foundation Neurology and Alexion, Almirall, Amicus Therapeutics Germany, Biogen, Diamed, Fresenius Medical Care, Genzyme, HERZ Burgdorf, Merck Serono, Novartis, ONO Pharma, Roche, and Teva // research funding; **TZ**: Biogen, Roche, Merck, TEVA, and Almirall // grants and personal fees from grants; Genzyme and Novartis; and personal fees from Bayer, BAT, Celgene and Gilead // personal fees and non-financial support.

MSW hereby declares that since 1 Nov 2019 he has had no business, personal or material relationships with companies, consulting firms or medical institutions and sponsors thereof, in regard to this study.

REFERENCES

1. https://www.ocrelizumabinfo.global/gb/en/homepage.html (accessed Oct 2020)
2. Kappos L, et al. Lancet 2011;378:1779-1787
3. Hauser SL, et al. N Engl J Med 2017;376:221–234
4. Montalban X, et al. N Engl J Med 2017;376:209–220
5. Dirks P, et al. BMC Neurol. 2020;20:95
6. Buttmann M, et al. ECF 2020; ID 20

Effectiveness

Safety