Ocrelizumab in Patients with Early-Stage RRMS: Results from the Phase IIIb ENSEMBLE Trial and the Matched Real-World NTD MS Registry Cohort

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BACKGROUND

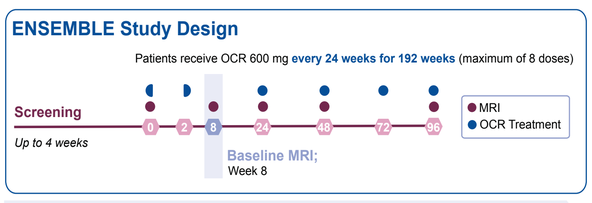
- Early treatment of multiple sclerosis (MS) with high-efficacy disease-modifying therapies (DMTs) can provide long-term benefits in terms of disease outcomes compared with escalation from low-efficacy therapies, which can involve frequent treatment switching[1]
- Ocrelizumab (OCR) was the first anti-CD20 monoclonal antibody approved at a dose of 600 mg intravenous twice yearly, for the treatment of relapsing MS and primary progressive MS (PPMS); it remains the only approved treatment for PPMS[2,3]
- Our understanding of OCR effectiveness in early-stage MS is still limited
- ENSEMBLE (NCT03085810) is a multicentre, open-label, single-arm, Phase IIIb study, evaluating the effectiveness and safety of OCR in treatment-naive patients with early-stage relapsing-remitting MS (RRMS)
- The NeuroTransData (NTD) network is a Germany-wide physicians network founded and run by physicians in 2008 in the fields of neurology and psychiatry, and captures patient demographics, clinical histories, patient-related outcomes, socioeconomic outcomes and clinical variables in real-time during clinical visits[4,5]

To assess treatment effectiveness of OCR in patients with early-stage RRMS from ENSEMBLE (NCT03085810) compared with commonly used, first-line DMTs in a real-world setting, using the German NTD MS registry as an external control arm

METHODS

ENSEMBLE Study Design and Matched NTD Population

ENSEMBLE Study Design



ENSEMBLE patients (18–55 years) have a diagnosis of RRMS (McDonald 2010)[6]

- Disease duration from first symptom ≤3 years **(early-stage MS)**
- EDSS score at screening of 0.0–3.5
- Treatment naive
- At least one relapse or T1w-CEL in the prior 12 months

NTD Population

- The NTD registry database includes ~25,000 people with MS[5]
- The data included in these analyses are from 2009–January 2022
- The ENSEMBLE inclusion criteria were applied to the NTD population. The NTD and ENSEMBLE populations were then matched[a]
- NTD registry patients were initiating their first treatment with one of the following DMTs:[b]
  - IFN β-1a and 1b subcutaneous
  - Glatiramer acetate
  - Dimethyl fumarate
  - Teriflunomide

[a]Details on matching can be found in the Supplemental Material; [b]For all cohorts (NTD and ENSEMBLE), the index date is the start of the relevant therapy.

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; NTD, NeuroTransData; OCR, ocrelizumab; RRMS, relapsing remitting MS; T1w-CEL, T1-weighted contrast-enhancing lesion.

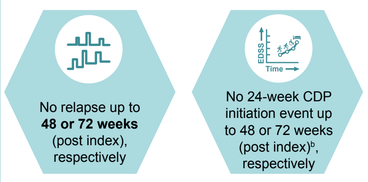
Cohort Matching

- A propensity score matching (PSM) algorithm was used to derive a matched sample of comparable patients between the OCR cohort in the ENSEMBLE study and a cohort using IFN β-1a and 1b subcutaneous, glatiramer acetate, dimethyl fumarate or teriflunomide from the NTD registry
- This PSM strategy was used to balance baseline characteristics between the cohorts before comparing the study outcome measurements
- A 2:1 PSM strategy was applied in R (R Core Team, 2020) using a standard greedy matching algorithm provided by the MatchIt package, giving rise to up to two ENSEMBLE patients per NTD patient
- The propensity score (PS) was estimated using logistic regression with the treatment cohort as the dependent variable and covariates at index therapy initiation as independent variables; the covariates selected were considered important potential confounders[7]
- The following baseline covariates were included in the PS: age, sex, baseline Expanded Disability Status Scale (EDSS) score, prior relapses, presence of contrast enhancing lesions (CELs) and time since first MS symptom onset

Primary and Secondary Endpoints

Primary endpoint: NEDA-2

- **NEDA-2** assessed at Week 48 or Week 72 is defined as having:



Secondary endpoint: NEDA-3

- **NEDA-3** assessed at Week 48[a] is defined as having:

Based on the endpoints, the NTD registry-matched population was split into the following cohorts:

Cohort A
Sufficient on-therapy data to define **NEDA-2**

Cohort B
Sufficient on-therapy data to define **NEDA-3**

[a]NEDA-3 was assessed at Week 48 only, as ENSEMBLE has no MRI measurement at 72 weeks; [b]For the NTD population, an increment of 12 is needed either side of week number because EDSS time windows ([48–12, 48+12] or [72–12, 72+12]) need to be defined due to the heterogeneity of the NTD visit pattern.

CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; NEDA, no evidence of disease activity; NTD, NeuroTransData.

Exploratory Analyses

Sensitivity analyses were carried out:

- With or without the inclusion of time since MS symptom onset
- With presence of CELs
- In subgroups of NTD patients (data not shown):
  - Restricted to patients who initiated therapy after April 2017 to align with ENSEMBLE
  - In patients diagnosed following McDonald 2010 to align with ENSEMBLE

T1 Gd+

RESULTS

Matched Baseline Characteristics and Endpoints

	NTD Cohort A[a] (N=601)	NTD Cohort B[a] (N=162)	ENSEMBLE (N=1,050)[b]
Median age, years (SD)	34.0 (9.4)	33.6 (8.7)	32.0 (9.2)
Female, n (%)	401 (66.7)	105 (64.8)	666 (63.4)
Baseline EDSS score	1.1 (1.0)	1.2 (1.0)	1.8 (1.0)
Relapses in previous year, n	1.0 (0.6)	1.0 (0.6)	1.2 (0.7)
Median time since diagnosis, years (SD)	0.2 (0.6)	0.1 (0.5)	0.2 (0.4)
Median time since manifestation, years (SD)	0.4 (0.7)	0.3 (0.6)	0.8 (1.0)
Treatment, n (%)			
Dimethyl fumarate	120 (20.0)	33 (20.4)	0 (0.0)
Glatiramer acetate	136 (22.6)	38 (23.5)	0 (0.0)
IFN β-1a	285 (47.4)	76 (46.9)	0 (0.0)
Teriflunomide	60 (10.0)	15 (9.3)	0 (0.0)
CELs	159 (50.0)[c]	84 (51.9)	486 (46.3)
Diagnosis criteria, n (%)			
McDonald version 2005	29 (5.1)	1 (0.6)	0 (0.0)
McDonald version 2010	395 (68.8)	107 (68.2)	1,050 (100.0)
McDonald version 2017	54 (9.4)	19 (12.1)	0 (0.0)
Not specified	123 (21.2)	35 (22.2)	0 (0.0)
NEDA-3 at Week 48, n (%)	**–**	**75 (46.3)**	**639 (60.9)**
NEDA-2 at Week 72, n (%)	**464 (77.2)**	**–**	**911 (86.8)**

Baseline characteristics for ENSEMBLE and NTD cohorts were similar; ENSEMBLE patients were diagnosed according to the McDonald criteria 2010, whilst in NTD, patients were diagnosed according to McDonald criteria 2005, 2010 or 2017

[a]Cohort A had sufficient on-therapy data to define NEDA-2; Cohort B had sufficient on-therapy data to define NEDA-3; [b]Some ENSEMBLE patients were removed, either due to missing baseline data or because patients did not have a time point from Week 72 onwards; [c]For Cohort A CELs, 159 is recorded as 50% of the cohort, due to missing data for CELs.

CELs, contrast enhancing lesions; EDSS, Expanded Disability Status Scale; NEDA, no evidence of disease activity; NTD, NeuroTransData; SD, standard deviation.

NEDA-2 Comparison Between ENSEMBLE and NTD Cohorts

NEDA-2 at Week 48
OR: 1.68
(95% CI 1.04, 2.72)
p=0.047
Patients: 462 vs 278
Events: 40 vs 40

NEDA-2 at Week 72
OR: 1.99
(95% CI 1.29, 3.07)
p=0.00184
Patients: 462 vs 278
Events: 55 vs 59

Treatment with OCR in patients with early RRMS was associated with significantly lower risk of disease activity according to NEDA-2, compared with first-line treatment with other DMTs in the real world

CI, confidence intervals; NEDA, no evidence of disease activity; OR, odds ratio.

NEDA-3 Comparison Between ENSEMBLE and NTD Cohorts

NEDA-3 at Week 48
OR: 1.65
(95% CI 1.10, 2.46)
p=0.00167
Patients: 280 vs 148
Events: 114 vs 79

Treatment with OCR in patients with early RRMS was associated with significantly lower risk of disease activity according to NEDA-3, compared with first-line treatment with other DMTs in the real world

CI, confidence intervals; NEDA, no evidence of disease activity; OR, odds ratio.

Sensitivity Analysis of NEDA-2

	ENSEMBLE all vs NTD Cohort A Time since manifestation not part of matching	ENSEMBLE all vs NTD Cohort A Main analysis	ENSEMBLE all vs NTD Cohort A CELs not part of matching
NEDA-2 at Week 72	491 vs 288 patients (62 vs 59 events)	462 vs 278 patients (55 vs 59 events)	717 vs 468 patients (90 vs 108 events)
OR (95% CI)	**1.69 (1.1, 2.5); p=0.00784**	**1.99 (1.3, 3.1); p=0.00184**	**2.18 (1.6, 3.0); p<0.001**

Week 72 NEDA-2 did not change substantially when duration since first MS symptom or T1-weighted contrast-enhancing lesions were excluded from matching

CELs, contrast enhancing lesions; CI, confidence interval; NEDA, no evidence of disease activity; NTD, NeuroTransData; OR, odds ratio.

Sensitivity Analysis of NEDA-3

	ENSEMBLE all vs NTD Cohort B Time since manifestation not part of matching	ENSEMBLE all vs NTD Cohort B Main analysis	ENSEMBLE all vs NTD Cohort B CELs not part of matching
NEDA-3 at Week 48	298 vs 157 patients (117 vs 83 events)	280 vs 148 patients (114 vs 79 events)	279 vs 149 patients (107 vs 81 events)
OR (95% CI)	**1.70 (1.15, 2.52); p=0.00966**	**1.65 (1.10, 2.46); p=0.0167**	**1.92 (1.29, 2.88); p=0.00172**
NEDA-2 at Week 48	298 vs 157 patients (28 vs 38 events)	280 vs 148 patients (27 vs 37 events)	279 vs 149 patients (27 vs 38 events)
OR (95% CI)	**3.27 (1.84, 5.79); p<0.001**	**3.22 (1.81, 5.74); p<0.001**	**3.02 (1.73, 5.28); p<0.001**

NEDA-3 and NEDA-2 at Week 48 did not change substantially when duration since first MS symptom or T1-weighted contrast-enhancing lesions were excluded from matching

CELs, contrast enhancing lesions; CI, confidence interval; NEDA, no evidence of disease activity; NTD, NeuroTransData; OR, odds ratio.

LIMITATIONS

- Real-world patients from the NTD registry were not as closely monitored in terms of clinical visits and MRI assessments as ENSEMBLE patients, which could have led to more heterogenous data in terms of both quality and quantity
  - Clinical visit structuring/frequency was more flexible in the NTD registry compared with ENSEMBLE, which may have resulted in an underestimation of OCR effectiveness in early RRMS
  - MRI data collection varied in the NTD real-world setting compared with MRI analyses during the ENSEMBLE trial, which occurred at fixed time points
  - Furthermore, CEL injections are only recommended under specific circumstances, which may have introduced bias within the results. However, these recommendations are a recent change and do not impact the majority of patients included in the NTD analysis cohorts
- Relapses or disease worsening in the real-world setting could lead to loss of patients due to treatment discontinuation or switching
- The validity of PSM relies on the inclusion of covariates that influence the compared outcomes; as such, it is important to acknowledge that the exclusion of potentially relevant covariates (such as body mass index due to lack of data availability) may reduce the reliability of these analyses, though sensitivity analyses dropping certain matching factors suggest stability of results

CONCLUSIONS

- Treatment with ocrelizumab in patients with early RRMS was associated with significantly lower risk of disease activity (according to NEDA-2 and NEDA-3) compared with first-line treatment with other DMTs in the real world
  - Sensitivity analyses of NEDA-2 and NEDA-3 support robustness of results
- To robustly analyse subcomponents of NEDA (i.e. relapses, MRI activity and CDP), to achieve sufficient statistical power, a larger study cohort and/or a longer follow-up time to increase the number of events is needed
- PSM enables a robust comparison of real-world data vs clinical trial data, supporting individual daily therapy decisions beyond results from randomised-controlled trials

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DISCLOSURES

HP Hartung has received honoraria for consulting, serving on steering committees and speaking at scientific symposia with approval by the Rector of Heinrich-Heine University Düsseldorf from Bayer, Biogen, BMS Celgene, F. Hoffmann-La Roche Ltd, GeNeuro SA, Genzyme, MedImmune, Merck-Serono, Novartis, Octapharma, Sanofi-Genzyme, Teva, TG Therapeutics and Viela Bio. **T Holmøy** has received honoraria/consultation fees from Biogen Idec., Merck, F. Hoffmann-La Roche Ltd, Bristol Myers Squibb, Santen and Sanofi-Genzyme. **J Wuerfel** is an employee of MIAC AG and of F. Hoffmann-La Roche Ltd. He has received grants from EU (Horizon2020), Else Kröner-Fresenius Foundation and Novartis Foundation; and his institution has received consulting fees from Actelion, Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genzyme/Sanofi, Idorsia, INmuneBio, Novartis and Teva. **Y Heer** is an employee of PricewaterhouseCoopers AG. **S Braune** receives honoraria for patient care from public and private health insurances in Germany; for clinical studies from Biogen, Bristol Myers Squibb, Novartis and F. Hoffmann-La Roche Ltd; for lectures from Biogen, CSL Behring and Novartis; for consultancy from Celgene, NTD, F. Hoffmann-La Roche Ltd, Teva and TG Therapeutics; and as a board member of NTD. **A Bergmann** has received consulting fees from advisory board, speaker and other activities for NeuroTransData; project management and clinical studies for and travel expenses from Novartis and Servier. **M Zuercher** is an employee of PricewaterhouseCoopers AG. **C Liu** is an employee of F. Hoffmann-La Roche Ltd. **T Kuenzel** is an employee of F. Hoffmann-La Roche Ltd. **S Moore** is an employee of F. Hoffmann-La Roche Ltd. **T Vollmer** has received compensation for activities such as advisory boards, lectures and consultancy from the following companies and organisations: Biogen, Genentech/F. Hoffmann-La Roche Ltd and Novartis; and has received research support from Rocky Mountain Multiple Sclerosis Center, Celgene, Biogen, Anokion, Genentech, F. Hoffmann-La Roche Ltd, GW Pharma and TG Therapeutics, Inc.

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