Baseline Demographics and Disease Characteristics From OPERA Phase III Trials Evaluating Ocrelizumab in Patients With Relapsing Multiple Sclerosis

Poster 3791

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on behalf of the OPERA I and II clinical investigators

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INTRODUCTION

- Multiple sclerosis (MS) is a heterogeneous disease with an unpredictable disease course and no cure[1–4]
- Approximately 85% of patients present with relapsing forms of MS (RMS)
- B cells are believed to contribute to the pathogenesis of MS[5,6]
- Ocrelizumab is a recombinant humanized monoclonal antibody that selectively depletes CD20-expressing B cells,[7,8] while preserving the capacity for B-cell reconstitution and pre-existing humoral immunity[9,10]
- In a Phase II, randomized, placebo-controlled trial in patients with relapsing-remitting multiple sclerosis, ocrelizumab significantly reduced the number of gadolinium (Gd)-enhancing lesions and annualized relapse rate at Week 24 compared with placebo[11]
- Based on the Phase II results, two Phase III, multicenter, randomized, double-blind, double-dummy, parallel-group trials were undertaken (OPERA I/NCT01247324 and OPERA II/NCT01412333) to further investigate the efficacy and safety of ocrelizumab in RMS. The baseline characteristics from both studies are described here

ENDPOINTS

Primary endpoint

- Annualized protocol-defined relapse rate in patients with RMS at 2 years (96 weeks)

Key secondary endpoints

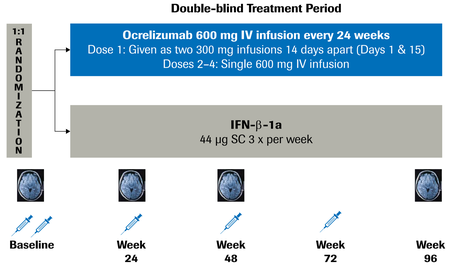
- Time to onset of 12-week confirmed disability progression during the 96 weeks
- Total number of T1 Gd-enhancing lesions at Weeks 24, 48, and 96
- Total number of new and/or enlarging T2 hyperintense lesions at Weeks 24, 48, and 96
- Proportion of patients who have 12-week confirmed disability improvement during the 96 weeks
- Time to onset of 24-week confirmed disability progression during the 96 weeks
- Safety and tolerability of ocrelizumab
- Pharmacokinetics, immunogenicity, and pharmacodynamics of ocrelizumab

METHODS

Study design

- Patients were randomized to receive either 600 mg ocrelizumab by intravenous (IV) infusion or 44 µg IFN-β-1a subcutaneous for 96 weeks (**Figure 1**)
- Eligible patients were stratified by region (USA vs rest of world [ROW]) and baseline Expanded Disability Status Scale (EDSS) score (< 4.0 vs ≥ 4.0)
- Magnetic resonance imaging (MRI) was performed at baseline and Weeks 24, 48, and 96

Figure 1. Study design



SC, subcutaneous; IFN, interferon; IV, intravenous

Key eligibility criteria

- Age 18–55 years with a diagnosis of RMS, in accordance with the 2010 revised McDonald criteria[12]
- EDSS score of 0–5.5 at screening
- At least two documented clinical attacks within the previous 2 years or one clinical attack occurring within the year prior to screening (but not within 30 days prior to screening)
- Documented MRI of brain with abnormalities consistent with MS
- Neurological stability for ≥ 30 days prior to both screening and baseline
- Patients with a disease duration of ≥ 10 years and an EDSS score ≤ 2.0 at screening were excluded

RESULTS (intention-to-treat [ITT] population)

Patient demographics

- Overall, 821 and 835 patients were randomized in the OPERA I and II studies, respectively
  - —Mean age was 37.0 years in OPERA I and 37.3 years in OPERA II
  - —66.0% of patients were female in both trials
  - —91.4% and 89.8% of patients were white in OPERA I and II, respectively
- In OPERA I, 210 (25.6%) and 611 (74.4%) enrolled patients were from the USA and ROW, respectively; similarly, in OPERA II, 226 (27.1%) and 609 (72.9%) enrolled patients were from the USA and ROW, respectively (**Table 1**)

Table 1. Regions enrolling patients into the OPERA studies

	OPERA I (N = 821)	OPERA II (N = 835)
EU[a]	438	391
USA	210	226
Eastern Europe[b]	97	89
Canada	0	84
Latin America[c]	61	45
Africa[d]	12	0
Australia	3	0

[a]Includes EU countries + Bosnia & Herzegovina + Israel + Norway + Serbia + Switzerland + Turkey; [b]Includes Belarus + Russian Federation + Ukraine; [c]Includes Argentina + Brazil + Chile + Mexico + Peru; [d]Includes South Africa + Tunisia

Disease history

- Mean (SD) baseline EDSS scores were 2.77 (1.26) in OPERA I and 2.75 (1.34) in OPERA II
  - —Overall, 633 (77.2%) and 621 (74.7%) patients had baseline EDSS scores < 4 in OPERA I and II, respectively

Table 2. Duration since MS symptom onset and MS diagnosis

	OPERA I (N = 821)	OPERA II (N = 835)
Duration since MS symptom onset, years		
n	821	835
Mean (SD)	6.48 (6.16)	6.70 (6.11)
Median (min–max)	4.75 (0.2–34.9)	5.09 (0.2–33.9)
25th, 75th percentiles	1.65, 9.35	1.71, 9.83
Duration since MS diagnosis, years		
n	821	835
Mean (SD)	3.77 (4.72)	4.14 (5.01)
Median (min–max)	1.57 (0.0–28.9)	1.91 (0.1–28.5)
25th, 75th percentiles	0.48, 5.62	0.44, 6.37

MS, multiple sclerosis; SD, standard deviation

Relapse history

Table 3. Relapse history prior to randomization

	OPERA I (N = 821)	OPERA II (N = 835)
n	820	833
Time since last onset of MS relapse prior to randomization, years		
Mean (SD)	0.48 (0.29)	0.51 (0.31)
Median (min–max)	0.41 (0.1–1.8)	0.41 (0.1–2.0)
Number of relapses in the past year, n		
Mean (SD)	1.32 (0.65)	1.33 (0.71)
Median (min–max)	1 (0–5)	1 (0–6)
Number of relapses in the past 2 years, n		
Mean (SD)	1.77 (0.89)	1.78 (0.94)
Median (min–max)	2 (1–7)	2 (1–8)

MS, multiple sclerosis; SD, standard deviation

Treatment history

Table 4. MS treatments in the 2 years prior to study entry[a]

	OPERA I (N = 821)	OPERA II (N = 835)
Number of patients treated with any MS medication, n (%)	226 (27.5)	219 (26.2)
IFNs[b]	167 (20.3)	158 (18.9)
Glatiramer acetate	75 (9.1)	84 (10.1)
Natalizumab	1 (0.1)	1 (0.1)
Fingolimod	1 (0.1)	4 (0.5)
Dimethyl fumarate	1 (0.1)	0 (0.0)
Normal immunoglobulin	4 (0.5)	0 (0.0)
Mycophenolate mofetil	1 (0.1)	1 (0.1)
Azathioprine	0 (0.0)	1 (0.1)

IFN, interferon; MS, multiple sclerosis
[a]Patients can be counted in more than one category; [b]Includes IFN-β-1a intramuscular (IM), IFN-β-1a subcutaneous (SC), IFN-β-1b SC, IFN-β not otherwise specified (NOS)/IFN NOS/IFN blinded, IFN-β-1a intravenous, IFN-β-1b IM, IFN-β1b transdermal, and IFN-β-1b unknown. Patients may have received different types of IFN and be counted multiple times

MRI assessments

Table 5. Baseline MRI characteristics

	OPERA I (N = 821)	OPERA II (N = 835)
Number of Gd+ T1 lesions		
n	812	826
Mean (SD)	1.78 (4.69)	1.87 (4.88)
Categorical number of Gd+ T1 lesions, n (%)		
n	812	826
0	485 (59.7)	494 (59.8)
≥ 1	327 (40.3)	332 (40.2)
Volume of T2 lesions, cm³		
n	816	828
Median (min–max)	5.88 (0.0–83.2)	5.65 (0.0–96.0)
Normalized brain volume, cm³		
n	810	828
Mean (SD)	1500.06 (85.86)	1502.72 (91.55)
Median (min–max)	1501.25 (1251.8–1736.5)	1507.92 (1202.7–1761.3)

Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; SD, standard deviation

CONCLUSIONS

- Data presented here indicate that the populations enrolled in the OPERA I and II studies are consistent with an RMS population[13–15]
- The results of the OPERA studies will provide information on the efficacy and safety of ocrelizumab compared with IFN-β-1a in patients with RMS

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