Effect of Ocrelizumab on Clinical Disability in Two Identical Phase III, Double-Blind, Double-Dummy, Interferon β-1a–Controlled Studies

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BACKGROUND

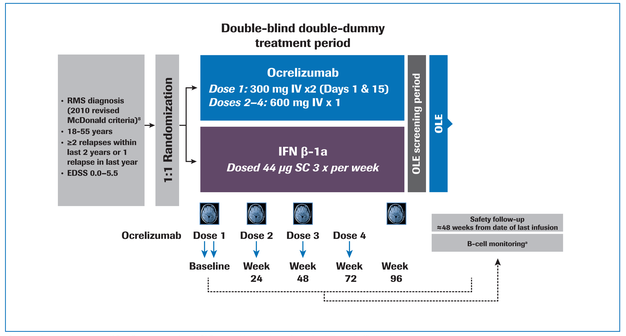
- Accrual of neurological disability is a manifestation of disease progression in multiple sclerosis (MS)[1]
- Patients may experience disease activity despite the availability of disease-modifying treatments for relapsing multiple sclerosis (RMS)[2-4]
- Safety concerns have emerged with certain higher-efficacy treatments[2,5,6]
- Preventing disability progression is an important treatment goal for patients with MS;[1] the choice of MS therapy is currently a compromise between treatment benefits and potential safety risks[7]
- Ocrelizumab (OCR) is a humanized monoclonal antibody that selectively depletes CD20+ B cells, while preserving the capacity for B-cell reconstitution and preexisting humoral immunity
- This pooled analysis evaluated the effect of OCR on clinical disability in RMS compared with interferon (IFN) β-1a in two Phase III, randomized, double-blind, double-dummy trials (OPERA I and OPERA II)

METHODS

Study Design

- Patients were randomized (1:1) to receive OCR 600 mg via intravenous infusion every 24 weeks or subcutaneous IFN β-1a 44 µg three-times weekly through a 96-week treatment period (**Figure 1**)
- Patients in both groups received corresponding subcutaneous or intravenous placebo treatments
- All patients received intravenous methylprednisolone 100 mg (and optional analgesics/antipyretics and antihistamines) prior to infusion
- Eligible patients were stratified by region (USA vs rest of world) and baseline Expanded Disability Status Scale (EDSS) score (<4.0 vs ≥4.0)

Figure 1. OPERA study design



*Continued monitoring occurs if B cells are not repleted. OLE to provide ongoing safety, tolerability and efficacy data.
EDSS, Expanded Disability Status Scale; IFN, interferon; IV, intravenous; OLE, open-label extension; RMS, relapsing multiple sclerosis; SC, subcutaneous.

Study Endpoints

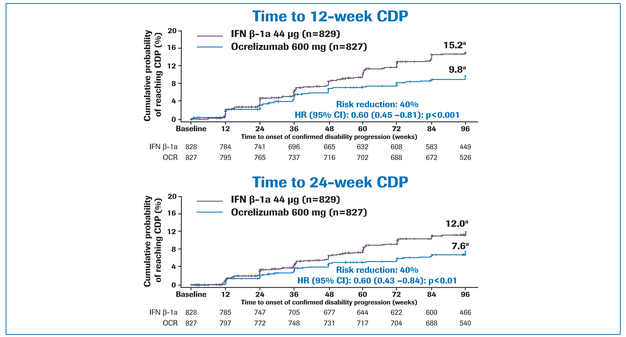
- Primary endpoint
  - — Protocol-defined annualized relapse rate by 96 weeks during the double-blind, double-dummy treatment period
- Key disability endpoints
  - — Time to onset of 12- and 24-week confirmed disability progression (CDP) through Week 96 (secondary [prespecified pooled analyses])
  - — The proportion of patients who achieved 12- and 24-week confirmed disability improvement (CDI) through Week 96 (secondary [prespecified pooled analysis] and exploratory, respectively)
    - For patients with a baseline EDSS score of ≥2.0 and ≤5.5, disability improvement was defined as a reduction in EDSS score ≥1.0 point compared with baseline EDSS score
  - — The proportion of patients with improved, stable or worsened disability at Week 96 compared to baseline (exploratory)
    - Improved disability: a reduction in EDSS score of >0.5
    - Stable disability: a difference in EDSS score of no greater than ±0.5
    - Worsened disability: an increase in EDSS score of >0.5

RESULTS

Confirmed Disability Progression

- In prespecified pooled analysis of OPERA I and OPERA II, compared with IFN β-1a, OCR reduced the risk of 12-week CDP by 40% (p<0.001) and 24-week CDP by 40% (p<0.01) (**Figure 2**)

Figure 2. Pooled analysis of time to onset of disability progression confirmed after ≥12 weeks and ≥24 weeks

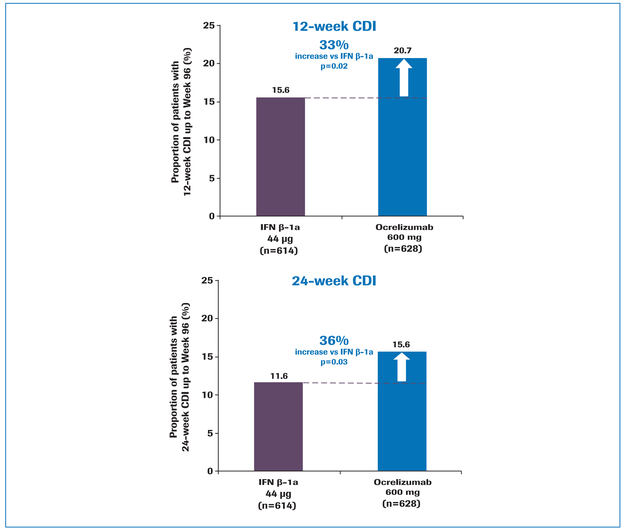


ITT; secondary endpoints
Prespecified analysis, pooled OPERA I and OPERA II. CDP defined as an increase in EDSS score of ≥1.0 point from baseline EDSS score when baseline score was ≤5.5, or ≥0.5 point when baseline score was >5.5.
[a]Proportion of patients having CDP through Week 96.
CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFN, interferon; ITT, intent-to-treat.

Confirmed Disability Improvement

- In a prespecified pooled analysis of OPERA I and OPERA II, compared with IFN β-1a, OCR increased the proportion of patients who achieved 12-week CDI by 33% (relative risk [95% CI]: 1.33 [1.05–1.68], p=0.02; **Figure 3**)
- In a pooled analysis of OPERA I and OPERA II, compared with IFN β-1a, OCR increased the proportion of patients who achieved 24-week CDI by 36% (relative risk [95% CI]: 1.36 [1.02–1.80], p=0.03)

Figure 3. Pooled analysis of the proportion of patients who achieved disability improvement confirmed after ≥12 weeks and ≥24 weeks

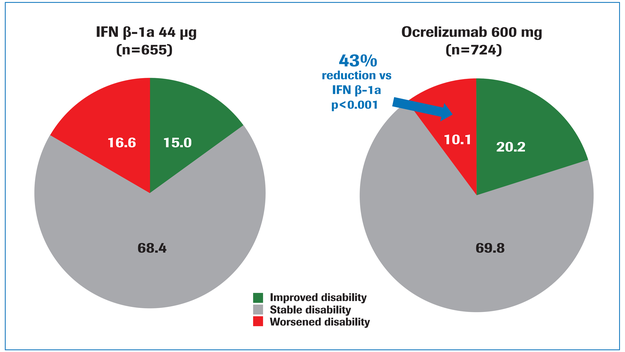


ITT; secondary and exploratory endpoints12-week CDI prespecified analysis, 24-week CDI prespecified analysis; both in patients with baseline EDSS ≥2.0, pooled OPERA I and OPERA II.
Compared with IFN β-1a , OCR increased the proportion of patients who achieved 12-week CDI in OPERA I by 61% (relative risk [95% CI]: 1.61 [1.11–2.33], p=0.01), with no difference in OPERA II (p=0.40).
For patients with a baseline EDSS score of ≥2.0 and ≤5.5, disability improvement was defined as a reduction in EDSS score ≥1.0 point compared with baseline EDSS score.
For patients with a baseline EDSS score of >5.5, disability improvement was defined as a reduction in EDSS score of ≥0.5 point. P value for relative improvement is from the Cochran-Mantel-Haenszel chi-squared test, stratified by study, baseline EDSS score (<4.0 vs ≥4.0), and geographic region (USA vs rest of the world), and includes stratification factors.
Patients with missing EDSS or no confirmation after onset of disability improvement are counted as not having CDI.
CDI, confirmed disability improvement; EDSS, Expanded Disability Status Scale; IFN, interferon; ITT, intent-to-treat.

Improved, Stable, Worsened Disability

- The majority of patients in the pooled population had stable disability at Week 96 compared with baseline independent of treatment group (**Figure 4**)
- Pooled analysis of OPERA I and OPERA II showed that compared with IFN β-1a, OCR reduced the proportion of patients with worsened disability status by 43% (adjusted odds ratio [95% CI]: 0.575 [0.414–0.797], p<0.001)
- The proportion of patients with improved disability was 15% and 20.2% in the IFN β-1a and OCR group, respectively (adjusted odds ratio [95% CI]: 1.288 [0.964, 1.72], p=0.09)

Figure 4. Pooled analysis of the proportion of patients with improved, stable or worsened disability at Week 96 compared with baseline



ITT; exploratory endpoint
Disability definitions (EDSS score at Week 96 compared with baseline): stable, a difference of no greater than ±0.5; worsened, an increase of >0.5; improved, a reduction of >0.5.
P value for relative decrease in worsening is from multinomial logistic regression, adjusted for baseline EDSS score (<4.0 vs ≥4.0) and geographic region (USA vs rest of world).
Patients with missing EDSS data at baseline or Week 96 are excluded from this analysis.
EDSS, Expanded Disability Status Scale; IFN, interferon; ITT, intent-to-treat.

CONCLUSIONS

- **Ocrelizumab was consistently effective on disability outcomes in patients with RMS in a pooled analysis of the OPERA I and OPERA II studies**
- **Ocrelizumab significantly reduced disability progression and increased the proportion of patients experiencing disability improvement compared with IFN β-1a**
- **The consistent and robust effect of ocrelizumab on disability suggests ocrelizumab may have the potential to address an important unmet need in MS**

DISCLOSURES

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