Ofatumumab vs Teriflunomide in Relapsing Multiple Sclerosis: Analysis of No Evidence of Disease Activity (NEDA-3) from ASCLEPIOS I and II Trials

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Background

- Ofatumumab, the first fully human anti-CD20 monoclonal antibody,[1] depletes CD20+ B cells and CD20+ T cells in the blood and lymphoid tissues through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity[2,3]
- In the Phase 3 ASCLEPIOS I and II trials, ofatumumab 20 mg monthly subcutaneous (s.c.) (0.4 mL) demonstrated superior efficacy versus oral teriflunomide 14 mg once daily, and a favourable safety profile in patients with relapsing multiple sclerosis (RMS)[4]
  - Relative reduction in annualised relapse rate (ARR): 50.5% (p<0.001) in ASCLEPIOS I and 58.5% (p<0.001) in ASCLEPIOS II
  - Risk reduction in 3- and 6-month confirmed disability worsening (CDW): 34.4% (p=0.002) and 32.5% (p=0.012) in the pre-specified pooled analysis
  - Risk reduction in gadolinium-enhancing (Gd+) T1 lesions and new/enlarging T2 lesions: 97.5% (p<0.001) and 82% (p<0.001) in ASCLEPIOS I; 93.8% (p<0.001) and 84.5% (p<0.001) in ASCLEPIOS II, respectively

Objective

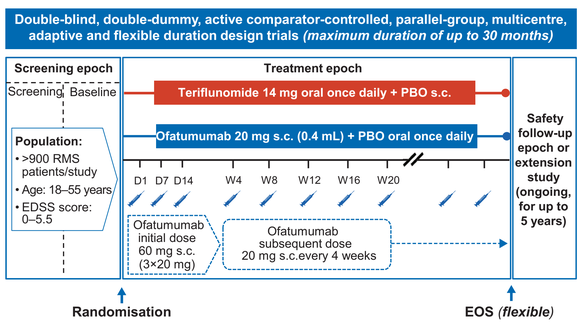
- To investigate the effect of s.c. ofatumumab 20 mg versus oral teriflunomide 14 mg in achieving no evidence of disease activity (NEDA-3), and to separately assess the ARR in the pooled ASCLEPIOS I and II trials

Methods

Study design and treatment pattern

- Data were pooled from the randomised, double-blind, double-dummy, active comparator-controlled, parallel-group, multicentre, adaptive and flexible duration design Phase 3 ASCLEPIOS I and II trials (maximum duration of up to 30 months)[4]
- Both trials had an identical study design and were conducted in parallel, enrolling 1882 RMS patients (ASCLEPIOS I [N=927], ASCLEPIOS II [N=955]) from 385 sites across 37 countries (**Figure 1**)
- Patients received ofatumumab 20 mg (0.4 mL) s.c. injections on Days 1, 7 and 14 (*initial doses*) and every 4 weeks from Week 4 onwards (*subsequent doses*) or teriflunomide 14 mg oral once daily

Figure 1. Study design of ASCLEPIOS I and II[4]



D, day; EDSS, Expanded Disability Status Scale; EOS, end of study; RMS, relapsing multiple sclerosis; PBO, placebo; s.c., subcutaneous; W, week

Study assessments and statistical analysis

- NEDA-3* and its components in Year 1 and 2 were analysed via logistic regression model[5] in modified full analysis set (mFAS)
  - The mFAS used for NEDA calculations consisted of all patients in the FAS, except those who discontinued from study drug prematurely for reasons other than 'lack of efficacy' or 'death' and had NEDA before early discontinuation. Patients who discontinued from study drug prematurely for reasons 'lack of efficacy' or 'death' were considered as having evidence of disease activity in the analysis (even if no evidence of disease activity was reported)
- ARR by time intervals were analysed via negative binomial model in FAS

**Defined as no 6-month confirmed disability worsening [6mCDW], no confirmed multiple sclerosis [MS] relapse, no new/enlarging T2 lesions, and no gadolinium-enhancing [Gd+] T1 lesions*

Results

- Patient demographics and baseline disease characteristics of pooled ASCLEPIOS I and II trials were consistent across treatment groups and representative of a typical RMS population **(Table 1)**

Table 1. Patient demographics and baseline characteristics (pooled ASCLEPIOS I and II trials)

Characteristics Mean±SD or n (%)	Teriflunomide 14 mg (N'=936)	Ofatumumab 20 mg (N'=946)	All patients (N'=1882)
Age (years)	38.0±9.22	38.4±9.04	38.2±9.13
Female, n (%)	636 (67.9)	637 (67.3)	1273 (67.6)
Duration of MS since first symptoms (years)	8.19±7.3	8.27±7.1	8.23±7.2
Previously treated with DMTs, n (%)	573 (61.2)	560 (59.2)	1133 (60.2)
Number of relapses in last 12 months	1.3±0.71	1.2±0.69	1.3±0.70
EDSS score	2.90±1.4	2.93±1.4	2.92±1.4
T2 lesion volume (cm^3)	12.5±13.8	13.7±13.8	13.1±13.8
Patients free of Gd+ T1 lesions, n (%)	584 (62.4)	561 (59.3)	1145 (60.8)
Number of Gd+ T1 lesions	1.3±3.4	1.7±4.5	1.5±4.0

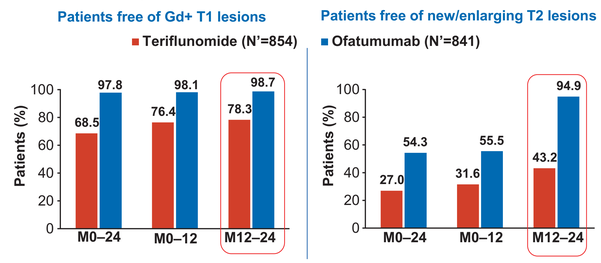
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; FAS, full analysis set; Gd+, gadolinium-enhancing; MS, multiple sclerosis; RMS, relapsing multiple sclerosis; SD, standard deviation

Effect of ofatumumab on individual NEDA-3 components

- Over 2 years, more ofatumumab-treated patients were free of Gd+ T1 lesions and new/enlarging T2 lesions, compared with teriflunomide (**Figure 2A**)
- Over the entire ASCLEPIOS I and II trials, ofatumumab-treated patients (n=871) had a total of 52 Gd+ T1 lesions in 1678 magnetic resonance imaging (MRI) scans, versus 1016 Gd+ T1 lesions in 1608 MRI scans in teriflunomide-treated patients (n=856)
  - The adjusted number of Gd+ T1 lesions per scan was reduced with ofatumumab versus teriflunomide by 96%, rate ratio (95% confidence interval [CI]): 0.04 (0.03; 0.06)
- Over 2 years, more ofatumumab-treated patients were free of confirmed relapse (**Figure 2B**) and 6mCDW (**Figure 2C**), compared with teriflunomide

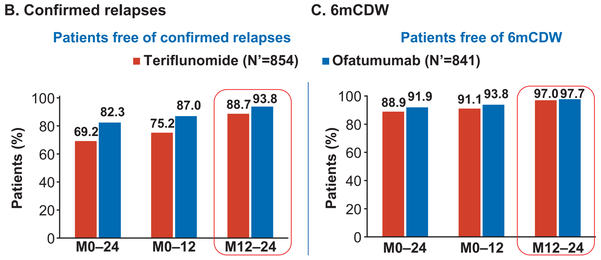
Figure 2. Effect of ofatumumab on individual NEDA-3 components

A. MRI focal activity



B. Confirmed relapses

C. 6mCDW

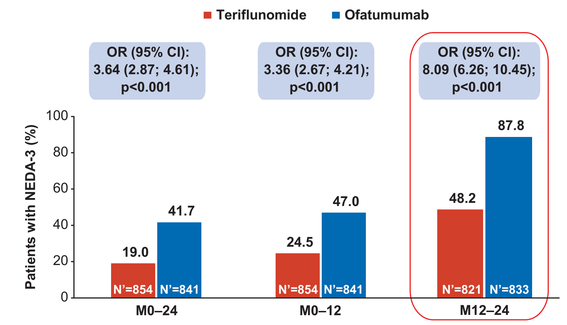


6mCDW, 6-month confirmed disability worsening; CI, confidence interval; Gd+, gadolinium-enhancing; M, month; MRI, magnetic resonance imaging; N', number of patients in each group; NEDA, no evidence of disease activity

Effect of ofatumumab on NEDA-3 in Years 1, 2 and Years 0–2

- The odds of achieving NEDA-3 with ofatumumab versus teriflunomide was >3-fold higher in the first year and 8-fold higher in the second year of treatment (**Figure 3**)

Figure 3. Effect of ofatumumab on NEDA-3

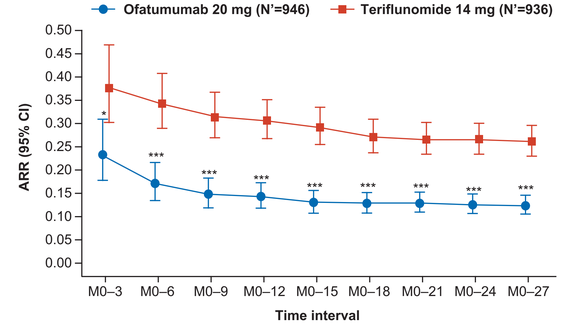


CI, confidence interval; M, Month; N', number of patients in each group; NEDA, no evidence of disease activity; OR, odds ratio

ARR by time interval

- Ofatumumab significantly reduced ARR versus teriflunomide within the first 3 months of treatment (M0–3: p=0.011), and in all subsequent time intervals (p<0.001) (**Figure 4**)

Figure 4. Effect of ofatumumab on ARR by time interval



*p<0.05 and ***p<0.001 vs teriflunomide
ARR, annualised relapse rate; CI, confidence interval; M, Month; N', total number of patients included in the analysis

Summary and Conclusions

- Ofatumumab significantly increased the chances of patients achieving NEDA-3 both in the first and second year of treatment, versus teriflunomide
  - In the first year of treatment, nearly 5 out of 10 patients achieved NEDA-3 with ofatumumab
  - In the second year of treatment, nearly 9 out of 10 patients achieved NEDA-3 with ofatumumab
- Treatment with ofatumumab led to nearly complete abrogation of MS disease activity and worsening in the second year of treatment:
  - 93.8% free of relapses
  - 97.7% free of 6mCDW
  - 98.7% free of Gd+ T1 lesions
  - 94.9% free of new/enlarging T2 lesions
- Significant reduction in ARR in the first three months and in all subsequent time-intervals for over 2 years with ofatumumab treatment versus teriflunomide, suggests sustained efficacy of ofatumumab in RMS patients

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