B-cell Depletion and Efficacy Outcomes with Ofatumumab: Subgroup Analysis from the Pooled Phase 3 ASCLEPIOS I and II Trials

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Background

Methods

Results

Conclusions

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Disclosures

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Background

- Ofatumumab is the first fully human anti-CD20 monoclonal antibody, binds to two distinct non-continuous regions on a unique conformational epitope,[1,2] giving rise to a low off-rate,[3] and delivers potent and sustained effector activity[1]
- In the Phase 3 ASCLEPIOS I and II trials, ofatumumab 20 mg s.c. monthly demonstrated superior efficacy versus oral teriflunomide 14 mg once daily, and a favorable safety profile in patients with RMS[4]
  - Relative reduction in 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 CDW: 34.4% (p=0.002) and 32.5% (p=0.012) in the pre-specified pooled analysis

Objective

To evaluate the effect of ofatumumab 20 mg s.c. on B-cell depletion and efficacy outcomes in subgroups of patients defined by baseline demographic and disease characteristics from ASCLEPIOS I and II trials

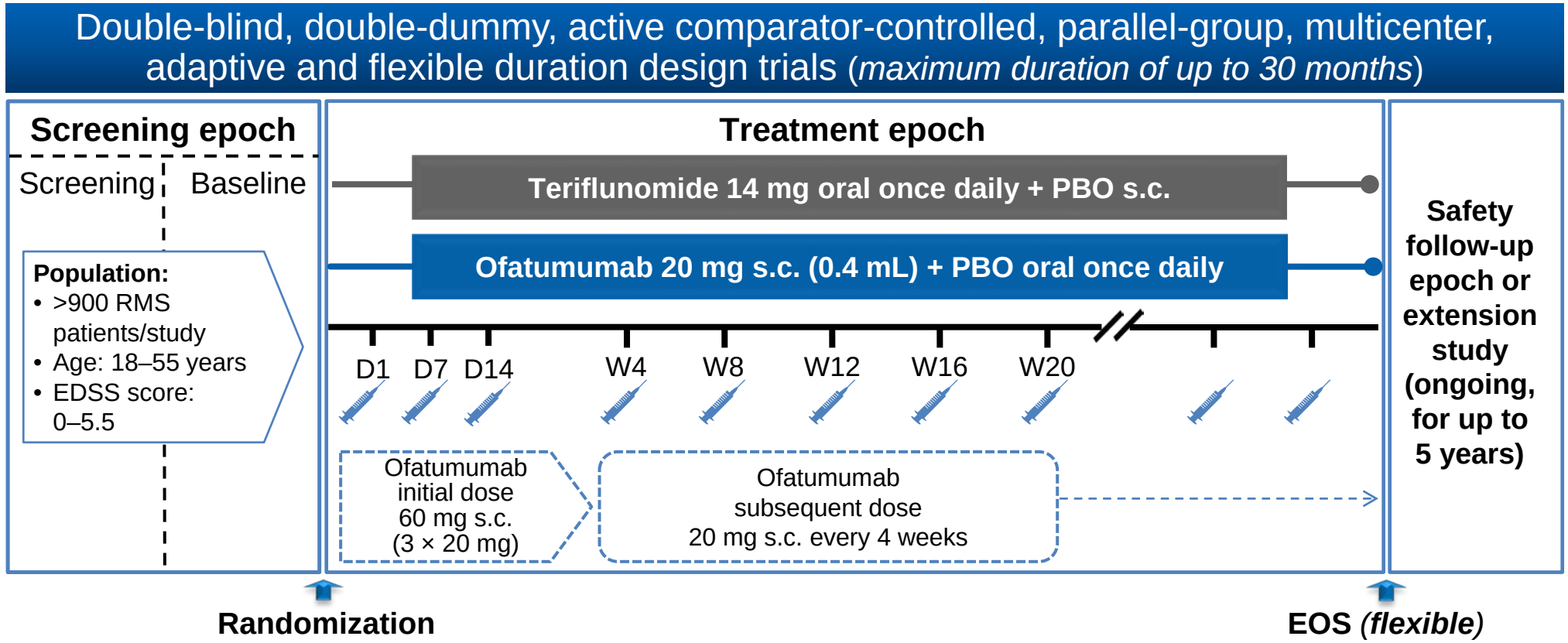
ARR, annualized relapse rate; CDW, confirmed disability worsening; RMS, relapsing multiple sclerosis; s.c., subcutaneous

1. Smith P, et al. Presented at ECTRIMS 2016; P1143; 2. Klein C, et al. MAbs. 2013;5:22–33; 3. Pacheco-Fernandez T, et al. AAN 2018;S52.003; 4. Hauser SL et al, Presented at ECTRIMS 2019; OP336

Methods

ASCLEPIOS I and II: Study design

Identical study designs, conducted in parallel



Patients received **ofatumumab 20 mg (0.4 mL) s.c.** injections on **Days 1, 7, and 14** (*initial dose*) and **every 4 weeks from Week 4** onwards (*subsequent dose*) or **teriflunomide 14 mg oral** once daily

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

Hauser SL et al, Presented at ECTRIMS 2019; OP336.

Methods

Study outcomes and statistical analysis

ASCLEPIOS I and II (pooled analysis)

Outcomes	Assessments	Statistical method
B-cell levels (over 96 weeks) • Median B-cell counts* • Proportion of patients with B-cell counts ≤10 cells/µL	• **By total population** • **By quartiles of baseline body weight (kg)** – Q1 (<60.1) – Q2 (≥60.1–<70.8) – Q3 (≥70.8–<84.4) – Q4 (≥84.4)	• Descriptive statistics
Efficacy outcomes (up to end of the study) • ARR • 3mCDW • 6mCDW	• **By demographic subgroups** – Age – Gender – Body weight • **By baseline disease characteristics** – EDSS score – Number of relapses in the previous 2 years – Gd+ T1 lesions – Prior DMTs	• Negative binomial regression model (ARR) • Cox regression model (3mCDW and 6mCDW)

*B-cell counts were measured categorically in the categories of 0–4, 5–14, 15–24 up to 250 cells/µL.
3mCDW, 3-month confirmed disability worsening; 6mCDW, 6-month confirmed disability worsening; ARR, annualized relapse rate; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; Gd+, Gadolinium-enhancing; Q, quartile

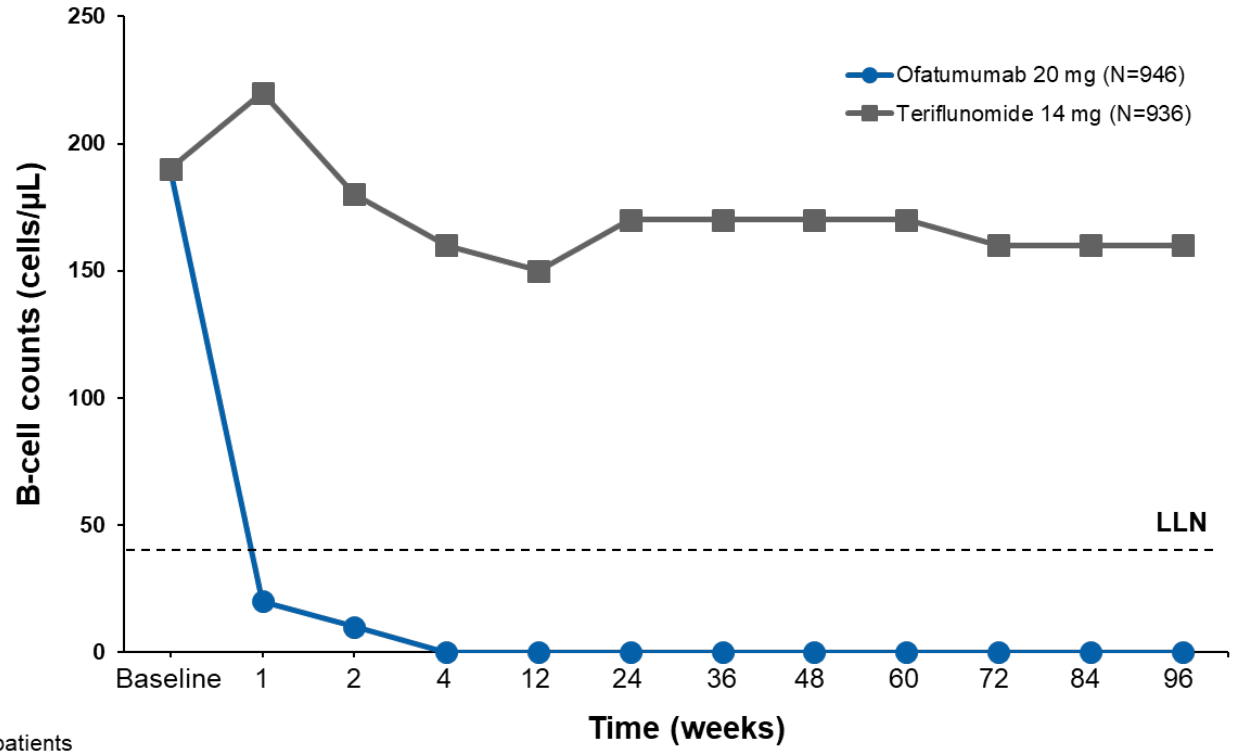
Results

Effect on B-cell counts in the total population

ASCLEPIOS I and II (pooled analysis)

- Ofatumumab dosing regimen led to rapid B-cell depletion, from median B-cell counts of 190 cells/µL at baseline to ≤10 cells/µL by Week 2, and sustained at 0 cells/µL up to Week 96
- In the teriflunomide group, the median B-cell counts were in the range of 150−220 cells/µL throughout the observation period

Median B-cell counts over 96 weeks in the total study population



No. of patients	Baseline	1	2	4	12	24	36	48	60	72	84	96
Ofatumumab	944	890	897	902	884	863	839	798	785	745	505	316
Teriflunomide	936	889	890	893	884	848	812	781	763	604	379	

LLN, lower limit of normal; s.c., subcutaneous

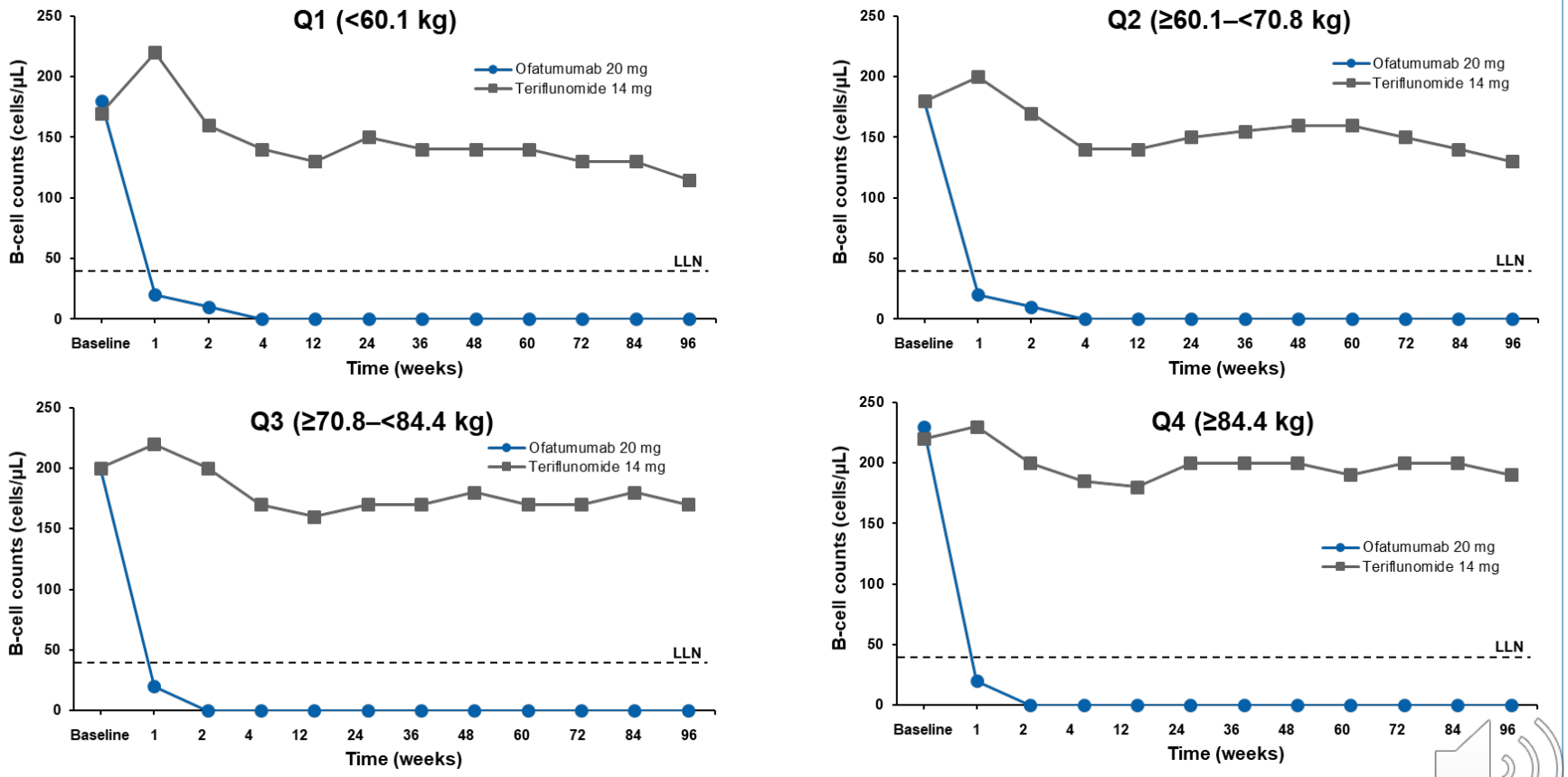
Results

Effect on B-cell counts by body weight

ASCLEPIOS I and II (pooled analysis)

- Across all body weight subgroups, the median B-cell counts in ofatumumab-treated patients were 10 cells/µL by Week 2 and sustained at 0 cells/µL up to Week 96
- In the teriflunomide subgroups, B-cell counts were in the range of 115−230 cells/µL throughout the entire observation period

Median B-cell counts over 96 weeks in subgroups by quartiles of baseline body weight



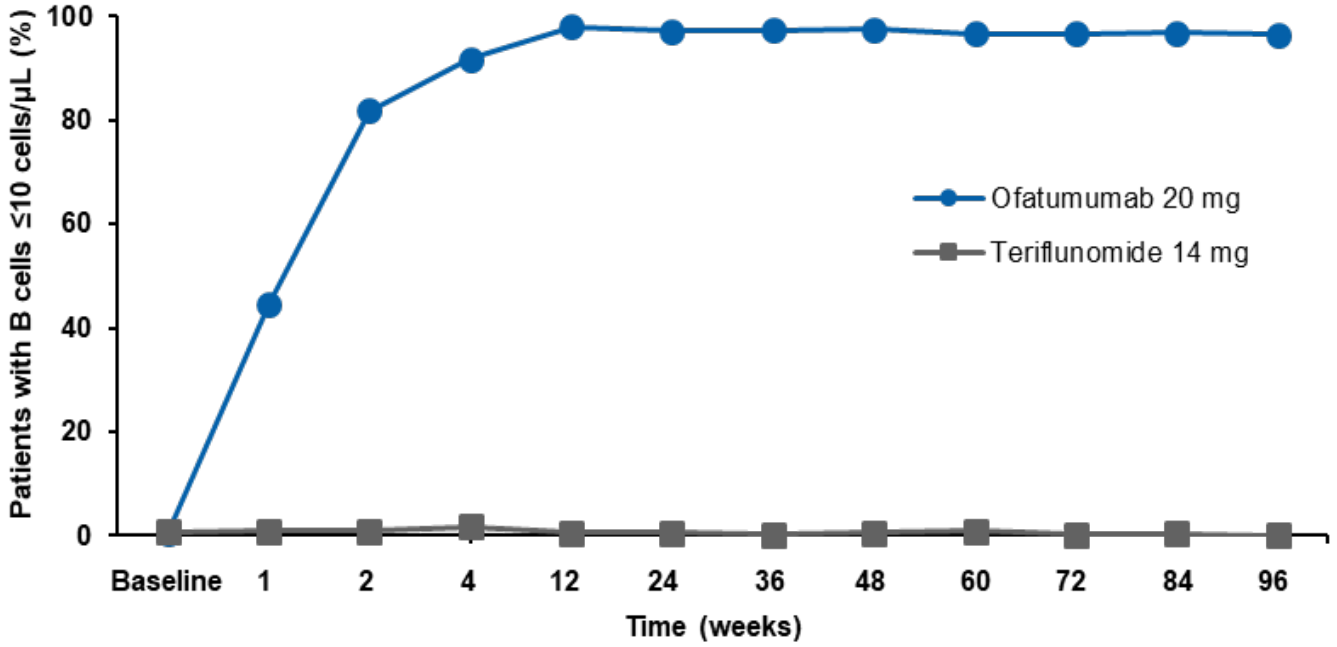
LLN, lower limit of normal; Q, quartile

Results

Proportion of patients with B-cell counts ≤10 cells/µL in the total population

- 82% of ofatumumab-treated patients achieved B-cell counts ≤10 cells/µL by Week 2 and 98% achieved this by Week 12, which was maintained at 96.5% up to Week 96. In the teriflunomide group, this was achieved in <2% of patients at any give time point

Proportion of patients with B-cell counts ≤10 cells/µL over 96 weeks

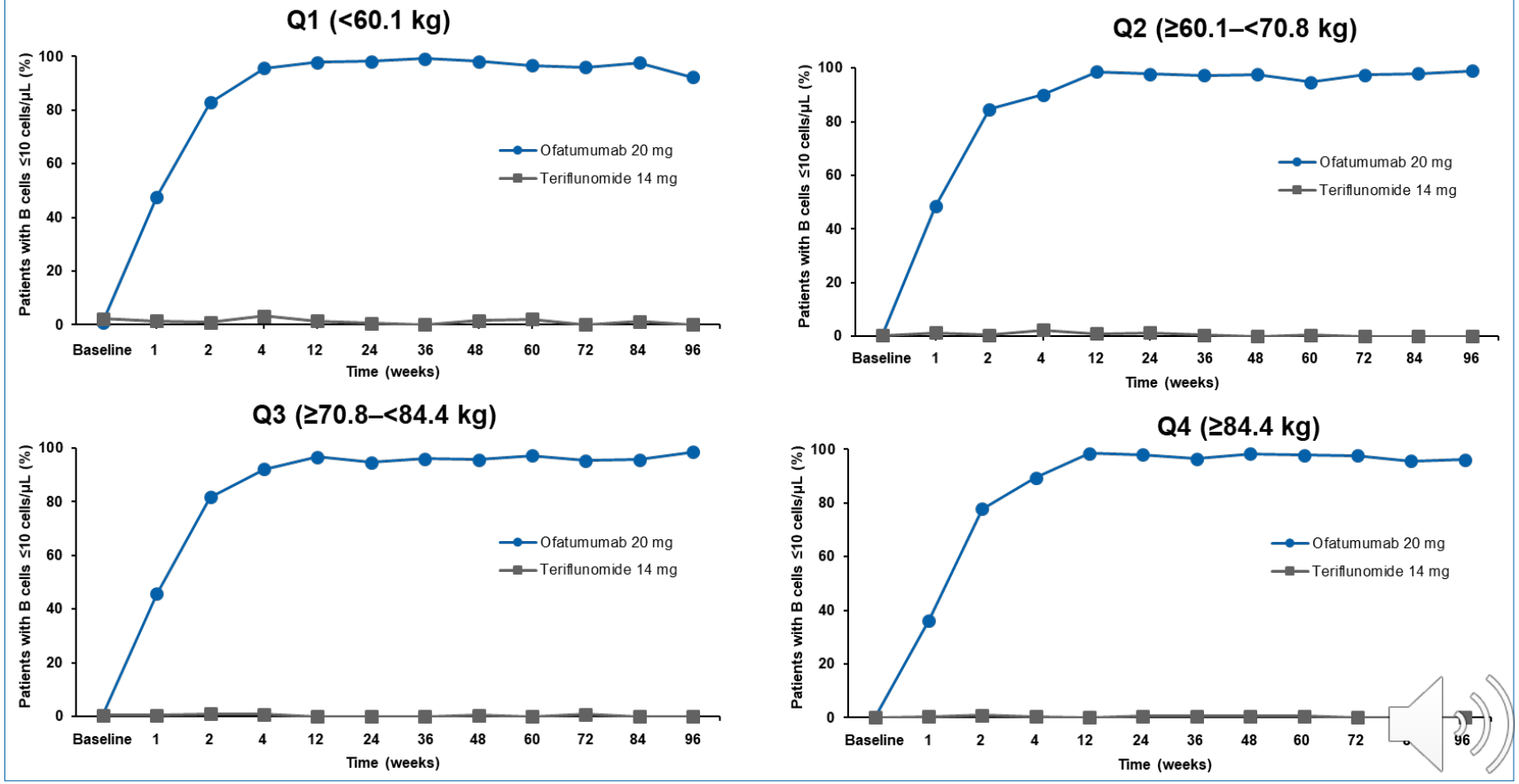


Results

Proportion of patients with B-cell counts ≤10 cells/μL by body weight subgroups

- Irrespective of the body weight, >92% of ofatumumab-treated patients achieved B-cell counts ≤10 cells/μL by Week 96. In the teriflunomide group, across all body weight subgroups, this was achieved in <4% of patients at any give time point

Proportion of patients with B-cell counts ≤10 cells/μL over 96 weeks in subgroups by quartiles of baseline body weight



Q, quartile

Results

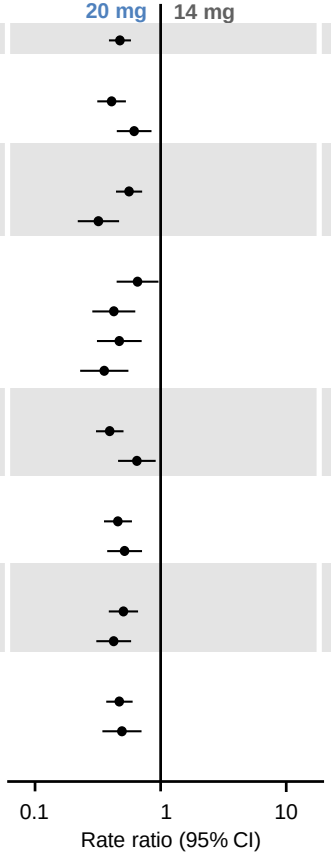
Effect on ARR across subgroups

ASCLEPIOS I and II (pooled analysis)

- Ofatumumab demonstrated higher efficacy versus teriflunomide for ARR across all subgroups

ARR by subgroups

	Ofatumumab 20 mg N/Adj. rate (95% CI)	Teriflunomide 14 mg N/Adj. rate (95% CI)	Interact. P-value[a]
Overall	946/0.12 (0.10, 0.14)	936/0.26 (0.23, 0.29)	
Age (years)			**0.049**
≤40	529/0.12 (0.10, 0.15)	564/0.29 (0.25, 0.34)	
>40	417/0.12 (0.10, 0.16)	372/0.20 (0.16, 0.25)	
Gender			**0.013**
Female	637/0.13 (0.11, 0.16)	636/0.24 (0.21, 0.28)	
Male	309/0.09 (0.07, 0.13)	300/0.29 (0.23, 0.36)	
Body weight (kg)			**0.198**
Q1 (<60.1)	240/0.16 (0.12, 0.21)	227/0.24 (0.19, 0.31)	
Q2 (≥60.1–<70.8)	249/0.12 (0.09, 0.16)	224/0.28 (0.22, 0.35)	
Q3 (≥70.8–<84.4)	226/0.12 (0.09, 0.16)	244/0.25 (0.20, 0.32)	
Q4 (≥84.4)	231/0.09 (0.06, 0.13)	241/0.25 (0.20, 0.32)	
Baseline EDSS			**0.023**
≤3.5	670/0.10 (0.08, 0.12)	679/0.25 (0.21, 0.29)	
>3.5	276/0.18 (0.14, 0.23)	257/0.28 (0.22, 0.35)	
Number of relapses in the previous 2 years			**0.560**
≤2	695/0.10 (0.08, 0.12)	666/0.21 (0.18, 0.24)	
>2	251/0.19 (0.15, 0.25)	270/0.37 (0.30, 0.45)	
Gd+ T1 lesions at baseline			**0.398**
0	561/0.11 (0.09, 0.14)	584/0.23 (0.19, 0.27)	
>0	362/0.13 (0.10, 0.17)	338/0.31 (0.25, 0.37)	
Prior MS disease-modifying drug			**0.829**
Previously treated	560/0.14 (0.12, 0.17)	573/0.30 (0.26, 0.35)	
Treatment naïve	386/0.09 (0.07, 0.12)	363/0.18 (0.15, 0.23)	



[a]P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant). Model was adjusted for study, treatment for the overall analysis, with additional co-factors of subgroup, treatment by subgroup interaction for subgroup analysis. Natural log of the time-in-study was used as offset to annualize the relapse rate.

Adj,, adjusted; ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; N, total number of patients included in the analysis

Results

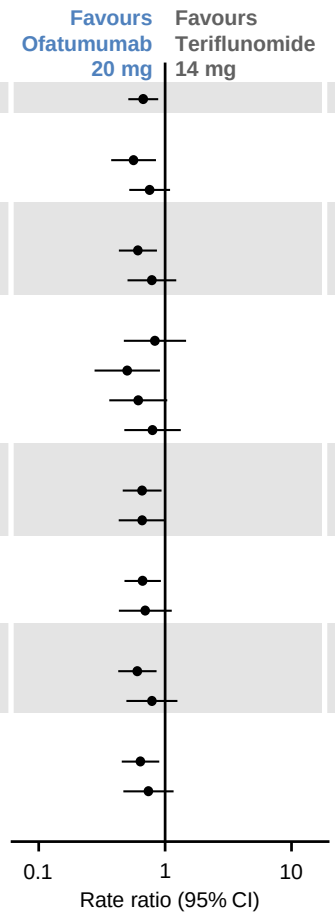
Effect on 3mCDW across subgroups

ASCLEPIOS I and II (pooled analysis)

- Reductions in 3mCDW favored ofatumumab versus teriflunomide across all subgroups and the treatment effect of ofatumumab was consistent among all subgroups

3mCDW by subgroups

	Ofatumumab 20 mg n/N (%)	Teriflunomide 14 mg n/N (%)	Interact. P-value[a]
Overall	88/944 (9.3)	125/932 (13.4)	
Age (years)			**0.300**
≤40	36/527 (6.8)	65/560 (11.6)	
>40	52/417 (12.5)	60/372 (16.1)	
Gender			**0.375**
Female	52/636 (8.2)	82/635 (12.9)	
Male	36/308 (11.7)	43/297 (14.5)	
Body weight (kg)			**0.577**
Q1 (<60.1)	23/240 (9.6)	25/226 (11.1)	
Q2 (≥60.1–<70.8)	17/249 (6.8)	30/223 (13.5)	
Q3 (≥70.8–<84.4)	22/225 (9.8)	37/243 (15.2)	
Q4 (≥84.4)	26/230 (11.3)	33/240 (13.8)	
Baseline EDSS			**0.993**
≤3.5	51/668 (7.6)	77/676 (11.4)	
>3.5	37/276 (13.4)	48/256 (18.8)	
Number of relapses in the previous 2 years			**0.873**
≤2	60/694 (8.6)	84/663 (12.7)	
>2	28/250 (11.2)	41/269 (15.2)	
Gd+ T1 lesions at baseline			**0.369**
0	51/560 (9.1)	83/582 (14.3)	
>0	33/361 (9.1)	39/337 (11.6)	
Prior MS disease-modifying drug			**0.616**
Previously treated	55/560 (9.8)	83/570 (14.6)	
Treatment naïve	33/384 (8.6)	42/362 (11.6)	



[a]*P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).*

Model was adjusted for the study as stratum, treatment for the overall analysis, with additional co-factors of subgroup, treatment by subgroup interaction for subgroup analysis

3mCDW, 3-month confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; n: total number of events included in the analysis; N, total number of patients included in the analysis

Results

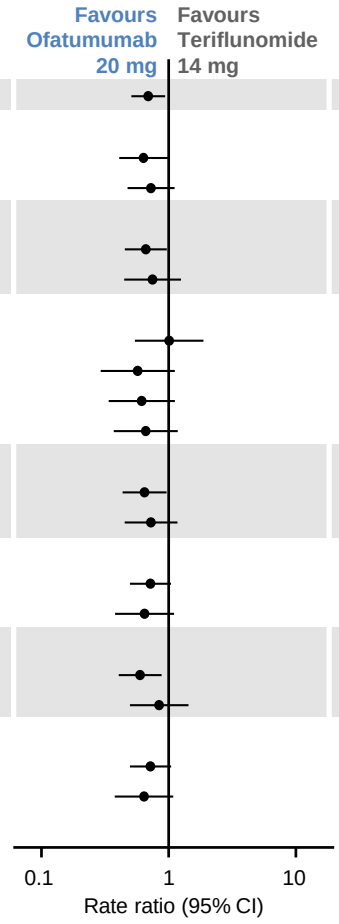
Effect on 6mCDW across subgroups

ASCLEPIOS I and II (pooled analysis)

- Reductions in 6mCDW favored ofatumumab versus teriflunomide across all subgroups and the treatment effect of ofatumumab was consistent among all subgroups

6mCDW by subgroups

	Ofatumumab 20 mg n/N (%)	Teriflunomide 14 mg n/N (%)	Interact. P-value[a]
Overall	71/944 (7.5)	99/932 (10.6)	
Age (years)			**0.664**
≤40	32/527 (6.1)	52/560 (9.3)	
>40	39/417 (9.4)	47/372 (12.6)	
Gender			**0.709**
Female	45/636 (7.1)	66/635 (10.4)	
Male	26 / 308 (8.4)	33/297 (11.1)	
Body weight (kg)			**0.593**
Q1 (<60.1)	21/240 (8.8)	19/226 (8.4)	
Q2 (≥60.1–<70.8)	14/249 (5.6)	22/223 (9.9)	
Q3 (≥70.8–<84.4)	17/225 (7.6)	29/243 (11.9)	
Q4 (≥84.4)	19/230 (8.3)	29/240 (12.1)	
Baseline EDSS			**0.711**
≤3.5	40/668 (6.0)	62/676 (9.2)	
>3.5	31/276 (11.2)	37/256 (14.5)	
Number of relapses in the previous 2 years			**0.749**
≤2	49/694 (7.1)	64/663 (9.7)	
>2	22/250 (8.8)	35/269 (13.0)	
Gd+ T1 lesions at baseline			**0.304**
0	41/560 (7.3)	68/582 (11.7)	
>0	26/361 (7.2)	29/337 (8.6)	
Prior MS disease-modifying drug			**0.722**
Previously treated	48/560 (8.6)	65/570 (11.4)	
Treatment naïve	23/384 (6.0)	34/362 (9.4)	



[a]*P-value for the type-3 test of the treatment by subgroup interaction is a heterogeneity test (the treatment effect is similar between subgroups if the test is non-significant).*

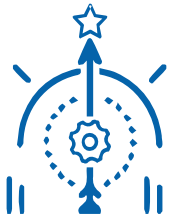
Model was adjusted for the study as stratum, treatment for the overall analysis, with additional co-factors of subgroup, treatment by subgroup interaction for subgroup analysis

6mCDW, 6-month confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; n: total number of events included in the analysis; N, total number of patients included in the analysis

Conclusions

Ofatumumab 20 mg with a monthly s.c. dosing regimen over 96 weeks versus teriflunomide:

Resulted in rapid B-cell depletion in all patients, demonstrating that the ofatumumab dosage regimen achieves and maintains low levels of B cells in patients independent of body weight



Demonstrated consistent treatment benefits on clinical (ARR) and disability (3mCDW and 6mCDW) outcomes across subgroups defined by baseline characteristics, similar to the effects observed in the overall pooled Phase 3 ASCLEPIOS I and II patient population[1]

3mCDW, 3-month confirmed disability worsening; 6mCDW, 6-month confirmed disability worsening; ARR, annualized relapse rate; s.c. subcutaneous

1. Hauser SL et al, Presented at ECTRIMS 2019; OP336

Thank you