High-Efficacy Therapies for Treatment-Naïve Individuals with Relapsing-Remitting Multiple Sclerosis

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Supplementary Table 1. Efficacy and safety data in pivotal Phase 3 trials for high-efficacy therapies with active comparators of lower efficacy.

	ASCLEPIOS I & II		OPERA I & II		CARE-MS I		CARE MS-II	
	Ofatumumab ASCLEPIOS I: N=465 ASCLEPIOS II: N=481	**Teriflunomide (RG)** N=462 N=474	**Ocrelizumab** OPERA I: N=410 OPERA II: N=417	**IFNβ-1a (RG)** N=411 N=418	**Alemtuzumab** N=376	**IFNβ-1a (RG)** N=187	**Alemtuzumab 12 mg** N=426	**IFNβ-1a (RG)** N=202
Baseline characteristics								
MS phenotype	RMS		RMS		Treatment-naïve RRMS		RRMS patients with ≥1 relapse on IFNβ-1a or glatiramer	
Treatment duration	Up to 30 months		96 weeks		2 years		2 years	
Relapses in year prior to study entry, mean (SD)	1.2-1.3 (0.6-0.7)	1.3 (0.7)	1.31-1.32 (0.65-0.69)	1.33-1.34 (0.64-0.73)	1.8 (0.8)	1.8 (0.8)	1.7 (0.86)	1.5 (0.75)
Age, years, mean (SD)	38.0-38.9 (8.8-9.3)	37.8-38.2 (9.0-9.5)	37.1-37.2 (9.1-9.3)	36.9-37.4 (9.0-9.3)	33.0 (8.0)	33.2 (8.5)	35.1 (8.40)	35.8 (8.77)
Disease duration, years, mean (SD)	8.20-8.36 (6.84-7.40)*	8.18-8.19 (7.21-7.38)*	6.72-6.74 (6.10-6.37)*	6.25-6.68 (5.98-6.13)*	2.1 (1.4)†	2.0 (1.3)†	1.7 (0.86)‡	1.5 (0.75)
EDSS, mean (SD)	2.90-2.97 (1.34-1.36)	2.86-2.94 (1.36-1.37)	2.78-2.86 (1.24-1.30)	2.75-2.84 (1.29-1.38)	2.0 (0.8)	2.0 (0.8)	2.7 (1.26)	2.7 (1.21)
Efficacy results								
ARR (95% CI)	0.10-0.11 (0.08-0.09 to 0.13-0.14)	0.22-0.25 (0.18-0.21 to 0.26-0.30)	0.16 (0.12 to 0.20)	0.29 (0.23-0.24 to 0.36)	0.18 (0.13 to 0.23)	0.39 (0.29 to 0.53)	0.26 (0.21 to 0.33)	0.52 (0.41 to 0.66)

	ASCLEPIOS I & II		OPERA I & II		CARE-MS I		CARE MS-II	
	Ofatumumab ASCLEPIOS I: N=465 ASCLEPIOS II: N=481	Teriflunomide (RG) N=462 N=474	Ocrelizumab OPERA I: N=410 OPERA II: N=417	IFNβ-1a (RG) N=411 N=418	Alemtuzumab N=376	IFNβ-1a (RG) N=187	Alemtuzumab 12 mg N=426	IFNβ-1a (RG) N=202
	Rate ratio (95% CI), p-value: 0.42-0.49 (0.31-0.37 to 0.56-0.65), p<0.001		Rate ratio (95% CI), p-value: 0.53-0.54 (0.40 to 0.71-0.72), p<0.001		Rate ratio (95% CI), p-value: 0.45 (0.32 to 0.63), p<0.0001		Rate ratio (95% CI), p-value: 0.51 (0.39 to 0.65), p<0.0001	
Disability progression/ worsening confirmed	At 3 month, K-M estimate at 24 months: 10.9% At 6 month: 8.1%	15.0% 12.0%	At 12 weeks, % pts with event: 9.1% At 24 weeks: 6.9%	13.6% 10.5%	Sustained disability accumulation confirmed over 6 months: 8.0%	11.1%	Sustained disability accumulation confirmed over 6 months: 12.7%	21.1%
	HR (95% CI), p-value: 0.66-0.68 (0.50 to 0.86-0.92), p≤0.01		HR (95% CI), p-value: 0.60 (0.43-0.45 to 0.81-0.84), p≤0.003		HR (95% CI), p-value: 0.70 (0.40 to 1.23), p=0.22		HR (95% CI), p-value: 0.58 (0.38 to 0.87), p=0.008	
Disability improvement confirmed	At 6 month, K-M estimate at 24 months: 11.0%	8.1%	At 12 weeks, % pts with event: 20.7%	15.6%	NA	NA	Sustained reduction for 6 months (95% CI): 28.82% (24.18 to 34.13)	12.93% (8.34 to 19.77)
	HR (95% CI), p-value: 1.35 (0.95 to 1.92), p=0.09		Difference, p-value: 33%, p=0.02		NA		HR (95% CI), p-value: 2.57 (1.57 to 4.20), p=0.0002	
% pts achieving NEDA	1 year: 47.0 2 years: 87.8	24.5 48.2	By 96 weeks: 47.5-47.9	25.1-29.2	NA	NA	NA	NA
	OR (95% CI), p-value 1 year: 3.36 (2.67 to 4.21), p<0.001 2 years: 8.09 (6.26 to 10.45), p<0.001		Difference (95% CI), p-value: 64-89% (36-54 to 98-132), p<0.001		NA		NA	

	ASCLEPIOS I & II		OPERA I & II		CARE-MS I		CARE MS-II	
	Ofatumumab ASCLEPIOS I: N=465 ASCLEPIOS II: N=481	**Teriflunomide (RG)** N=462 N=474	**Ocrelizumab** OPERA I: N=410 OPERA II: N=417	**IFNβ-1a (RG)** N=411 N=418	**Alemtuzumab** N=376	**IFNβ-1a (RG)** N=187	**Alemtuzumab 12 mg** N=426	**IFNβ-1a (RG)** N=202
# new or enlarged T2 lesions, mean (95% CI)	0.64-0.72 (0.55-0.61 to 0.75-0.85)	4.00-4.15 (3.47-3.64 to 4.61-4.74)	0.32-0.33 (0.26 to 0.41)	1.41-1.90 (1.12-1.54 to 1.78-2.36)	% pts new or enlarged T2 lesions: 48%	58%	% pts new or enlarged T2 lesions: 46%	68%
	Rate ratio (95% CI), p-value: 0.15-0.18 (0.13-0.15 to 0.19-0.22), p<0.001		Rate ratio (95% CI), p-value: 0.17-0.23 (0.13-0.17 to 0.23-0.30), p<0.001		Rate ratio (95% CI), p-value: NA (NA), p=0.04		Rate ratio (95% CI), p-value: NA (NA), p<0.0001	
% brain volume reduction	Annual rate of change (95% CI): −0.29 to −0.28 (−0.35-−0.34 to −0.23-−0.22)	−0.35 (−0.42-−0.41 to −0.29)	Mean % change (95% CI) from Week 24-96: −0.64 to −0.57 (−0.73-−0.66 to −0.54-−0.49)	−0.75-−0.74 (−0.85-−0.83 to −0.65)	Median change in brain parenchymal fraction (IQR), p-value: −0.867% (−1.470 to −0.254)	−1.488% (−2.355 to −0.567)	Median change in brain parenchymal fraction (IQR), p-value: −0.615% (−1.299 to 0.006)	−0.810% (−1.539 to 0.203)
	% points, (95% CI), p-value: 0.07 (−0.02 to 0.15), p=0.12-0.13		OPERA I: 22.8%, p=0.004 OPERA II: 14.9%, p=0.09		p<0.0001		p=0.010	
Safety results, n (%)								
Patients with ≥1 AE	382-409 (82.2-85.0)	380-408 (82.3-86.1)	327-360 (80.1-86.3)	331-357 (80.9-85.6)	361 (96)	172 (92)	428 (98)	191 (95)
Discontinuation due to AE	27 (5.6-5.8)	24-25 (5.2-5.3)	13-16 (3.2-3.8)	25-26 (6.0-6.4)	5 (1)	11 (6)	14 (3)	15 (7)
Serious AEs	38-48 (7.9-10.3)	36-38 (7.6-8.2)	28-29 (6.9-7.0)	32-40 (7.8-9.6)	69 (18)	27 (14)	85 (20)	44 (22)

	ASCLEPIOS I & II		OPERA I & II		CARE-MS I		CARE MS-II	
	Ofatumumab ASCLEPIOS I: N=465 ASCLEPIOS II: N=481	Teriflunomide (RG) N=462 N=474	Ocrelizumab OPERA I: N=410 OPERA II: N=417	IFNβ-1a (RG) N=411 N=418	Alemtuzumab N=376	IFNβ-1a (RG) N=187	Alemtuzumab 12 mg N=426	IFNβ-1a (RG) N=202
Reference(s)	[1, 2]		[3, 4]		[5]		[6, 7]	

Not intended to compare across trials. Data presented as presented in reference(s). Numbers shown in ranges indicate data from two trials for ASCLEPIOS and

OPERA; data of pooled analysis of two trials (I/II for each) are shown where available.

*Time since symptom onset.

ARR, annualized relapse rate; BPF, brain parenchymal fraction; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFNβ-1a,

interferon β-1a; K-M, Kaplan–Meier; NA, not available; NEDA-3, No Evidence of Disease Activity-3; OR, odds ratio; RMS, relapsing multiple sclerosis; RG,

Reference Group, SD, standard deviation.

Supplementary Table 2. Efficacy and safety data in placebo-controlled pivotal Phase 3 trials of high-efficacy therapies.

	AFFIRM		CLARITY		ORACLE MS	
	Natalizumab N=627	**Placebo (RG)** N=315	**Cladribine 3.5 mg/kg** N=433	**Placebo (RG)** N=437	**Cladribine 3.5 mg/kg** N=206	**Placebo (RG)** N=206
Baseline characteristics						
MS phenotype	RMS		RRMS		Clinically definite MS patients with a first clinical demyelinating event	
Treatment duration	Up to 116 weeks		96 weeks		96 weeks	
Relapses in year prior to study entry, mean (SD)	1.53 (0.91)	1.50 (0.77)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
Age, years, mean (SD)	35.6 (8.5)	36.7 (7.8)	37.9 (10.3)	38.7 (9.9)	31.7 (9.1)	32.2 (8.2)
Disease duration, years, mean (SD) except where indicated	Median (range): 5.0 (0 to 34)	Median (range): 6.0 (0 to 33)	7.9 (7.2)	8.9 (7.4)	NA	NA
EDSS, mean (SD) except where indicated	2.3 (1.2)	2.3 (1.2)	2.8 (1.2)	2.9 (1.3)	Median (IQR) 1.5 (1.0–2.0)	Median (IQR): 1.5 (1.0–2.0)
Efficacy results						
ARR (95% CI)	1 year: 0.27 (0.21 to 0.33) 2 years: 0.23 (0.19 to 0.28)	0.78 (0.64 to 0.94) 0.73 (0.62 to 0.87)	0.14 (0.12 to 0.17)	0.33 (0.29 to 0.38)	NA (NA)	NA (NA)
	Rate ratio (95% CI), p-value: NA (NA), p<0.001		Rate ratio (95% CI), p-value: NA (NA), p<0.001		Rate ratio (95% CI), p-value: NA (NA), p<0.001	
Disability progression/ worsening confirmed	Cumulative probability of sustained disability progression at 2 years:		Relative reduction in the risk of 3-month sustained disability progression:		NA	NA

	AFFIRM		CLARITY		ORACLE MS	
	Natalizumab N=627	**Placebo (RG)** N=315	**Cladribine 3.5 mg/kg** N=433	**Placebo (RG)** N=437	**Cladribine 3.5 mg/kg** N=206	**Placebo (RG)** N=206
	17%	29%	33%			
	HR (95% CI), p-value: 0.58 (0.43 to 0.77), p<0.001		HR (95% CI), p-value: 0.67 (0.48 to 0.93), p=0.02		NA	
Disability improvement confirmed	NA	NA	NA	NA	NA	NA
	NA		NA		NA	
% pts achieving NEDA	Over 2 years: 41	8	44.3*	15.8*	NA	NA
	Absolute difference (95% CI), p-value: 32.4% (27.4–37.4%), p<0.0001		OR (95% CI), p-value 4.28 (3.05 to 6.02), p<0.0001		NA	
# new or enlarged T2 lesions, mean (95% CI)	1 year: 1.2 (4.7) 2 years: 1.9 (9.2)	6.1 (9.0) 11.0 (15.7)	Mean (95% CI): 0.38 (NA)	1.43 (NA)	Median cumulative number of lesions (IQR): 0.0 (0.0 to 2.0)	2.0 (0.0 to 8.0)
	Rate ratio (95% CI), p-value: NA (NA), p<0.001		Rate ratio (95% CI), p-value: NA (NA), p<0.001		Rate ratio (95% CI), p-value: 0.212 (0.152 to 0.295), p<0.0001	
% brain volume reduction	Mean % reduction in BPF Over 1 year: -0.56 Over 2 years: -0.80	-0.40 -0.82	Annual PBVC, mean (SD): −0.56 (0.68)	−0.70 (0.79)	NA	NA
	Over 1 year: p=0.002 Over 2 years: p=0.822		p=0.010		NA	
Safety results, n (%)						

	AFFIRM		CLARITY		ORACLE MS	
	Natalizumab N=627	Placebo (RG) N=315	Cladribine 3.5 mg/kg N=433	Placebo (RG) N=437	Cladribine 3.5 mg/kg N=206	Placebo (RG) N=206
Patients with ≥1 AE	596 (95)	300 (96)	347 (80.7)	319 (73.3)	168 (82)	162 (79)
Discontinuation due to AE	37 (6)	12 (4)	15 (3.5)	9 (2.1)	10 (5)	4 (2)
Serious AEs	119 (19)	75 (24)	36 (8.4)	28 (6.4)	23 (11)	21 (10)
Reference(s)	[8-11]		[12-14]		[15]	

Not intended to compare across trials. Data presented as presented in reference(s). Numbers shown in ranges indicate data from two trials for ASCLEPIOS and OPERA; data of pooled analysis of two trials (I/II for each) are shown where available.

*Time since symptom onset.

ARR, annualized relapse rate; BPF, brain parenchymal fraction; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFNβ-1a, interferon β-1a; K-M, Kaplan–Meier; NA, not available; NEDA-3, No Evidence of Disease Activity-3; OR, odds ratio; RMS, relapsing multiple sclerosis; RG, Reference Group, SD, standard deviation.

Supplementary Table 3. Long-term open-label extension (OLE) studies for high-efficacy therapies with active comparators of lower efficacy.

	Ofatumumab	Ocrelizumab	Alemtuzumab
OLE study name (NCT identifier)	ALITHIOS (NCT03650114)	OPERA OLE	TOPAZ (NCT02255656)
Included core trial(s)	ASCLEPIOS (phase 3), 2.5 years APLIOS (phase 2), 12 weeks	OPERA (phase 3), 2 years	CARE-MS (phase 3), 2 years CAMMS03409, 4 years
Comparator in core trial(s), duration	Teriflunomide (in ASCLEPIOS)	IFNβ-1a	IFNβ-1a (in CARE-MS)
Duration of OLE	up to 5 years	up to 6 years	up to 5.6 years
n	2010 (estimated)	1325	1062
Study completion	October 2028 (estimated)	December 2020	July 2020
Reference(s)	NCT03650114	Interim results: [16]	[17]

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