Real-World Response and Super-Response to Eptinezumab over 48 Weeks in Migraine: The Prospective Multicenter EMBRACE III Study

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Supplementary table 1: Baseline demographic and clinical characteristics of 261 patients with migraine who received at least 1 dose of erenumab (safety population) stratified by diagnosis.

Variables	Number (%) or mean ± SD			
	All	HFEM	CM	*p*-value
Patients	261	63	198	
Age, *yrs*	48.8±12.0	48.7±12.1	48.0±11.6	0.890
Females	204 (78.2%)	55 (87.3%)	149 (75.3%)	0.066
BMI, kg/m^2	23.7±4	23.1±3.2	23.9±4.2	0.124
Age at onset, *yrs*	18.2±9.7	18.5±10.9	18.1±9.3	0.806
MMD	-	11.0±2.2	-	-
MHD	-	-	24.3±5.4	-
NRS score	8.1±1.1	8.0±1.1	8.1±1.1	0.301
Medication overuse	-	-	140 (53.6%)	-
Medication overuse duration*, yrs*	-	-	8.5±9.11	-
MAI	22.7±22.6	11.8±6.2	26.3±24.8	<0.001
Unilateral pain	147 (56.3%)	102 (51.8%)	45 (70.3%)	0.023
UAS	98 (37.5%)	72 (36.4%)	26 (41.3%)	0.582
CAPS score	0.9±1.6	0.9±1.6	1.0±1.4	0.762
Ictal allodynia	70 (26.8%)	0	70 (35.4%)	<0.001
Interictal allodynia	16 (6.1%)	5 (7.9%)	11 (5.6%)	0.547
ASC-12 score	2.6±4.2	2.3±4.7	2.7±4.1	0.534
Dopaminergic symptoms	110 (42.1%)	24 (38.1%)	86 (43.4%)	0.548
Concomitant prophylaxis, *pts*	68 (26.1%)	10 (15.9%)	58 (29.3%)	0.355
Prior treatment failures	4.6±1.8	4.6±1.9	4.3±1.4	0.413
Prior anti-CGRP mAb failures*, *pts*	140 (53.6%)	31 (49.2%)	109 (55.1%)	0.506

Prior BONT-A failure[¶], *pts*	115 (44.1%)	16 (23.4%)	99 (50.0%)	0.003
≥1 comorbidity, *pts*	155 (59.4%)	37 (58.7%)	118 (59.6%)	1.000
Psychiatric comorbidities, *pts*	71 (27.2%)	9 (14.3%)	62 (31.3%)	0.013
HIT-6 score	66.4±5.6	64.6±5.9	66.9±5.4	0.008
MIDAS score	90.2±59.3	69.5±42.1	96.8±62.5	<0.001
MIBS-4 score	5.7 (3.2%)	5.0 (3.0%)	5.9 (3.3%)	0.033
None (0)	8 (3.1%)	2 (3.2%)	6 (3.0%)	0.016
Mild (1-2)	20 (7.7%)	8 (12.7%)	12 (6.1%)	
Moderate (3-4)	75 (28.7%)	25 (39.7%)	50 (25.3%)	
Severe (>4)	158 (60.5%)	28 (44.4%)	130 (65.7%)	

Abbreviations: *All*, overall migraine population; *HFEM*, high-frequency episodic migraine; *CM*, chronic migraine; *BMI*, Body Mass Index; *MHD*, monthly headache days; *MMD*, monthly migraine days; *NRS*, Numeric Rating Scale; *UAS*, unilateral cranial autonomic symptoms; *CAPS*, Cranial Autonomic Parasympathetic Symptom Scale; *ASC-12*, Allodynia Symptom Checklist; *Dopaminergic symptoms*, presence during prodromes, headache stage or postdromes of have at least one of the following symptoms: yawning, somnolence, nausea, vomiting, mood changes, fatigue or diuresis; *MAI*, analgesic doses taken per month; BoNT-A, OnabotulinumtoxinA; *HIT-6*, Headache Impact Test-6, *MIDAS*, Migraine Disability Assessment Scale; *MIBS-4*, Migraine Interictal Burden Scale-4.

[*]Of the 261 patients, 137 had failed treatment with a single anti-CGRP mAb (erenumab, n= 135; galcanezumab, n= 2), while 3 patients had failed two agents (erenumab and galcanezumab, n=3).

[¶] Proportion calculated based on the total number of subjects treated with OnabotulinumtoxinA.

Supplementary table 2: Comparison of baseline demographic and clinical characteristics in patients with migraine who completed 48 weeks of follow-up stratified by anti-CGRP mAb use (mAb-naïve vs prior mAb failures).

Variables	Anti-CGRP mAb-naïve	Prior anti-CGRP mAb failures*	p-value
Patients	n=60	n=64	
HFEM	8 (13.3%)	13 (20.3%)	0.426
CM	52 (86.7%)	51 (79.7%)	
Age, *yrs*	47.6±11.2	50.0±13.1	0.273
Females	43 (71.7%)	51 (79.7)	0.405
BMI, kg/m^2	24.2±4.8	23.1±3.4	0.143
Age at onset, *yrs*	20.3±10.6	15.3±8.2	0.004
MMD	18.0±6.1	20.5±6.8	0.038
MHD	22.4±6.4	22.6±7.2	0.832
NRS score	8±1.2	8.4±1	0.053
Medication overuse	41 (68.3)	41 (64.1)	0.755
Medication overuse duration, *yrs*	7.1±9.3	10.3±8.6	0.119
MAI	22.8±11.5	29.8±36.3	0.148
Unilateral pain	40 (66.7)	34 (53.1)	0.299
UAS	29 (48.3)	21 (32.8)	0.115
CAPS score	1.2±1.7	1±1.6	0.552
Ictal allodynia	15 (25.0%)	21 (32.8%)	0.447
Interictal allodynia	2 (3.3%)	3 (4.7%)	1.000
ASC-12 score	2±3.6	2.7±4.7	0.325

Dopaminergic symptoms	35 (58.3)	27 (42.2)	0.106
Concomitant prophylaxis, *pts*	21 (48.7)	16 (25)	0.308
Prior treatment failures	4.2±1.9	4.9±1.7	0.041
Prior BONT-A failure¶, *pts*	13 (22.0)	39 (60.9)	<0.001
≥1 comorbidity, *pts*	32 (53.3)	38 (59.4)	0.619
Psychiatric comorbidities, *pts*	12 (20.0)	23 (35.9)	0.077
HIT-6 score	66.4±4.8	68.2±5.6	0.057
MIDAS score	79.6±40.9	113±66	0.001
MIBS-4 score	5.8±3.5	6.4±3.4	0.331
None (0)	1 (1.67)	2 (3.12)	0.855
Mild (1-2)	5 (8.33)	3 (4.69)	
Moderate (3-4)	15 (25.0)	16 (25.0)	
Severe (>4)	39 (65.0)	43 (67.2)	

Abbreviations: *All*, overall migraine population; *HFEM*, high-frequency episodic migraine; *CM*, chronic migraine; *BMI*, Body Mass Index; *MHD*, monthly headache days; *MMD*, monthly migraine days; *NRS*, Numeric Rating Scale; *UAS*, unilateral cranial autonomic symptoms; *CAPS*, Cranial Autonomic Parasympathetic Symptom Scale; *ASC-12*, Allodynia Symptom Checklist; *Dopaminergic symptoms*, presence during prodromes, headache stage or postdromes of have at least one of the following symptoms: yawning, somnolence, nausea, vomiting, mood changes, fatigue or diuresis; *MAI*, analgesic doses taken per month; BoNT-A, OnabotulinumtoxinA; *HIT-6*, Headache Impact Test-6, *MIDAS*, Migraine Disability Assessment Scale; *MIBS-4*, Migraine Interictal Burden Scale-4.

*Of the 64 patients, 63 had failed treatment with a single anti-CGRP mAb (erenumab, n= 62; galcanezumab, n=1), while 1 had failed two agents (erenumab and galcanezumab, n= 1).

¶ Proportion calculated based on the total number of subjects treated with OnabotulinumtoxinA.

Supplementary table 3: Baseline characteristics of patients who escalated from eptinezumab 100 mg to 300 mg and patients consistently treated with eptinezumab 100 mg and completed at least 48 weeks of follow-up.

Variables	Number (%) or mean±SD		
	Patients consistently treated with eptinezumab 100 mg	Patients with ≥1 dose escalation to eptinezumab 300 mg	*p-value*
Patients	38	86	
Age, *yrs*	48±13.3	49.2±11.8	0.655
Females	30 (78.9)	64 (74.4)	0.752
BMI, kg/m^2	24.1±4	23.4±4.2	0.343
Age at onset, *yrs*	21.2±12.5	16.2±7.8	0.027
MMD	21.3±7	23.0±6.6	0.196
MHD	17.3±6.5	20.2±6.4	0.026
NRS score	8.4±1.1	7.9±1.1	0.039
Medication overuse	23 (60.5)	59 (68.6)	0.503
Medication overuse duration, *yrs*	7.4±7.5	9.2±9.6	0.382
MAI	18.4±11.3	29.9±31.5	0.003
Unilateral pain	10 (62.5)	21 (24.4)	0.963
UAS	18 (47.4)	32 (37.2)	0.387
CAPS score	1.6±2.3	0.9±1.3	0.085
Allodynia	11 (28.9)	25 (29.1)	1000
ASC-12 score	2.7±4.2	2.3±4.2	0.626
Dopaminergic symptoms	20 (52.6)	42 (48.8)	0.846
Concomitant prophylaxis, *pts*	10 (26.3)	27 (31.4)	0.721

Prior treatment failures	3.9±1.6	4.8±1.8	0.007
Prior anti-CGRP mAb failures*, *pts*	12 (31.6)	52 (60.5)	0.006
Prior BONT-A failure¶, *pts*	10 (21.3)	42 (37.2)	0.090
≥1 comorbidity, *pts*	19 (50.0)	51 (59.3)	0.443
Psychiatric comorbidities, *pts*	7 (18.4)	28 (32.6)	0.163
HIT-6 score	67.1±4.4	67.4±5.7	0.800
MIDAS score	87.7±55.9	101±58.2	0.245
MIBS-4 score	5.9±3.2	6.2±3.3	0.606
None (0)	0 (0.0)	3 (3.5)	0.479
Mild (1-2)	4 (10.5)	4 (4.6)	
Moderate (3-4)	6 (26.3)	21 (24.4)	
Severe (>4)	24 (63.2)	58 (67.4)	

Abbreviations: *BMI*, Body Mass Index; *MHD*, monthly headache days; *MMD*, monthly migraine days; *NRS*, Numeric Rating Scale; *UAS*, unilateral cranial autonomic symptoms; *CAPS*, Cranial Autonomic Parasympathetic Symptom Scale; *ASC-12*, Allodynia Symptom Checklist; *Dopaminergic symptoms*, presence during prodromes, headache stage or postdromes of have at least one of the following symptoms: yawning, somnolence, nausea, vomiting, mood changes, fatigue or diuresis; *MAI*, analgesic doses taken per month; BoNT-A, OnabotulinumtoxinA; *HIT-6*, Headache Impact Test-6, *MIDAS*, Migraine Disability Assessment Scale; *MIBS-4*, Migraine Interictal Burden Scale-4.

*Of the 64 patients, 63 had failed treatment with a single anti-CGRP mAb (erenumab, n= 62; galcanezumab, n=1), while 1 had failed two agents (erenumab and galcanezumab, n= 1).

¶ Proportion calculated based on the total number of subjects treated with OnabotulinumtoxinA.

Supplementary table 4: Response rates at week 12 in patients treated with eptinezumab who completed ≥48 weeks of treatment, compared with those who had received ≤12 weeks, ≤24 weeks, ≤36 weeks of treatment and had not yet reached week 48. Values are reported as counts and percentages (%). P-values refer to between-group comparisons computed with the Chi-square test, or with Fisher's exact test when expected cell counts were less than 5.

Response rate	Patients treated for ≥12 weeks who had not yet reached week 48 (n=134)	Patients treated for ≥48 weeks (n=124)	p-value	Patients treated for ≥24 weeks who had not yet reached week 48 (n=83)	Patients treated for ≥48 weeks (n=124)	p-value	Patients treated for ≥36 weeks who had not yet reached week 48 (n=50)	Patients treated for ≥48 weeks (n=124)	p-value
≥50%	54 (40.3%)	52 (41.9%)	0.789	46 (55.4%)	77 (62.1%)	0.387	34 (68.0%)	85 (68.5%)	0.955
≥75%	15 (11.2%)	16 (12.9%)	0.853	11 (13.3%)	43 (34.7%)	0.001	12 (24.0%)	51 (41.1%)	0.047
100%	2 (1.5%)	1 (0.8%)	1.000	4 (4.8%)	6 (4.8%)	1.000	5 (10.0%)	5 (4.0%)	0.172

Supplementary table 5. Mean ± SD of clinical outcomes measured at baseline and during weeks 9–12, 21–24, 33–36, and 45–48 in the overall patient population, high-frequency episodic migraine (HFEM), and chronic migraine (CM) subgroups among patients who completed the 48-week follow-up.

Variable	Timepoint	All (N=124)	HFEM (n=21)	CM (n=103)
MMD/MHD	B	22.5±6.8	11.9±2.0	24.6±5.2
	9-12 w	14.5±8.8	10.6±6.0	15.3±9.1
	21-24 w	10.7±8.8	9.6±7.5	10.9±9.0
	33-36 w	9.0±7.5	7.2±6.1	9.3±7.7
	45-48 w	7.0±6.6	5.4±6.3	7.3±6.6
MAI	B	21.7±19.8	18.0±11.1	22.4±21.1
	9-12 w	15.1±12.8	10.4±5.2	16.0±13.7
	21-24 w	10.4±10.5	8.5±8.6	10.8±10.8
	33-36 w	8.6±8.5	5.3±3.5	9.2±9.0
	45-48 w	6.8±7.4	4.1±3.7	7.3±7.8
NRS	B	8.2±1.1	8.2±0.8	8.2±1.2
	9-12 w	7.1±2.2	7.1±2.0	7.1±2.3
	21-24 w	5.8±2.8	6.3±2.7	5.7±2.8
	33-36 w	5.8±2.5	5.8±2.4	5.8±2.5
	45-48 w	5.0±2.6	4.7±2.8	5.0±2.6
HIT-6	B	67.3±5.3	64.9±4.9	67.8±5.3
	9-12 w	62.9±9.4	62.8±7.2	62.9±9.8
	21-24 w	56.6±13.0	60.3±8.1	55.9±13.7
	33-36 w	54.2±12.7	54.4±12.5	54.2±12.8
	45-48 w	46.6±11.2	45.7±10.2	46.8±11.4
MIDAS	B	96.7±57.5	75.5±36.6	101.0±60.2
	9-12 w	69.7±64.6	46.8±44.5	74.3±67.2
	21-24 w	44.4±48.2	37.9±34.5	45.7±50.6
	33-36 w	34.8±34.9	23.8±26.9	37.0±36.0
	45-48 w	22.7±26.2	15.3±23.0	24.2±26.7

MIBS-4	B	6.1±3.3	5.4±2.8	6.2±3.4
	9-12 w	3.1±2.7	2.1±1.3	3.3±2.8
	21-24 w	2.1±2.1	1.4±1.4	2.2±2.2
	33-36 w	1.8±1.9	1.3±1.3	1.9±2.0
	45-48 w	1.7±1.9	1.3±1.3	1.8±1.9

Abbreviations: *B*, baseline; *W*, week; *MMD*, monthly migraine days; *MHD*, monthly headache days; *MAI*, analgesic doses taken per month; *NRS*, Numeric Rating Scale; *HIT-6*, Headache Impact Test-6, *MIDAS*, Migraine Disability Assessment Scale; *MIBS-4*, Migraine Interictal Burden Scale-4.

Supplementary table 6: Mean difference of clinical outcomes at baseline and weeks 9–12, 21–24, 33–36, and 45–48 across all time points in the overall patient population (n = 124), HFEM (n = 21), and CM (n = 103) who completed the 48-week follow-up.

	Comparison	MMD/MHD	MAI	NRS	HIT-6	MIDAS	MIBS-4
ALL	B vs 9-12 w	-8.0*	-6.6*	-1.2*	-4.4*	-27.0*	-3.0*
	B vs 21-24 w	-11.8*	-11.2*	-2.4*	-10.7*	-52.2*	-4.0*
	B vs 33-36 w	-13.5*	-13.1*	-2.4*	-13.1*	-61.9*	-4.3*
	B vs 45-48 w	-15.5*	-14.9*	-3.3*	-20.6*	-74.0*	-4.3*
	9-12 w vs 21-24 w	-3.8*	-4.6*	-1.3*	-6.2*	-25.2*	-1.0*
	9-12 w vs 33-36 w	-5.5*	-6.5*	-1.2*	-8.6*	-34.9*	-1.3*
	9-12 w vs 45-48 w	-7.5*	-8.3*	-2.1*	-16.2*	-47.0*	-1.3*
	21-24 w vs 33-36 w	-1.7*	-1.9*	0.1	-2.4*	-9.6*	-0.3*
	21-24 w vs 45-48 w	-3.7*	-3.7*	-0.8*	-10.0*	-21.8*	-0.3*
	33-36 w vs 45-48 w	-2.0*	-1.8*	-0.9*	-7.6*	-12.1*	-0.0
	Comparison	**MMD**	**MAI**	**NRS**	**HIT-6**	**MIDAS**	**MIBS-4**
HFEM	B vs 9-12 w	-1.3	-7.6***	-1.1**	-2.0	-28.7**	-3.3*
	B vs 21-24 w	-2.3	-9.6**	-1.9**	-4.6***	-37.5*	-4.0*
	B vs 33-36 w	-4.7**	-12.8*	-2.4*	-10.5**	-51.7*	-4.0*
	B vs 45-48 w	-6.5*	-13.9*	-3.5*	-19.1*	-60.1*	-4.0*
	9-12 w vs 21-24 w	-1.0***	-2.0**	-0.8	-2.5	-8.9	-0.7**
	9-12 w vs 33-36 w	-3.4*	-5.1*	-1.3	-8.4**	-23.0***	-0.8**
	9-12 w vs 45-48 w	-5.2*	-6.3*	-2.4***	-17.1*	-31.5**	-0.8**
	21-24 w vs 33-36 w	-2.3***	-3.2***	-0.5	-5.9**	-14.1***	-0.1
	21-24 w vs 45-48 w	-4.2**	-4.3***	-1.6***	-14.6*	-22.6*	-0.1
	33-36 w vs 45-48 w	-1.9**	-1.1	-1.1	-8.7*	-8.5**	0.0
	Comparison	**MHD**	**MAI**	**NRS**	**HIT-6**	**MIDAS**	**MIBS-4**
CM	B vs 9-12 w	-9.4*	-6.4**	-1.2*	-4.9*	-26.7*	-3.0*
	B vs 21-24 w	-13.7*	-11.6*	-2.6*	-11.9*	-55.3*	-4.0*

	B vs 33-36 w	-15.3*	-13.2*	-2.4*	-13.6*	-64.0*	-4.4*
	B vs 45-48 w	-17.4*	-15.1*	-3.2*	-21.0*	-76.8*	-4.4*
	9-12 w vs 21-24 w	-4.4*	-5.2*	-1.4*	-7.0*	-28.6*	-1.1*
	9-12 w vs 33-36 w	-5.9*	-6.8*	-1.2*	-8.7*	-37.3*	-1.4*
	9-12 w vs 45-48 w	-8.0*	-8.7*	-2.1*	-16.1*	-50.2*	-1.4*
	21-24 w vs 33-36 w	-1.6**	-1.6***	0.2	-1.7***	-8.7***	-0.3*
	21-24 w vs 45-48 w	-3.6*	-3.5*	-0.7**	-9.0*	-21.6*	-0.4*
	33-36 w vs 45-48 w	-2.1*	-1.9**	-0.9*	-7.4*	-12.9*	-0.0

Abbreviations: *B*, baseline; *W*, week; *MMD*, monthly migraine days; *MHD*, monthly headache days; *MAI*, analgesic doses taken per month; *NRS*, Numeric Rating Scale; *HIT-6*, Headache Impact Test-6, *MIDAS*, Migraine Disability Assessment Scale; *MIBS-4*, Migraine Interictal Burden Scale-4.

Statistical significance levels: $p<0.05$=***; $p<0.01$=**; $p<0.001$=*.