# Supplementary data

*CNS drugs*

# Long term treatment over 52 weeks with monthly fremanezumab in drug resistant migraine: a prospective, multicenter study

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**Table S1.** Concomitant and prior preventive treatments.

| | Overall population (n =83) | HFEM (n=16) | CM (n=67) |
|---|---|---|---|
| Patients with concomitant preventive treatment, n (%) | 27 (32.5) | 4 (25.0) | 23 (34.3) |
| Concomitant preventive treatment, mean ± SD | 1.3±0.6 | 1.5±0.5 | 1.2±0.6 |
| Prior preventive classes failures, mean ± SD | 4.0±1.4 | 3.5±1.1 | 4.1±1.5 |
| Prior preventive classes non-tolerated, mean ± SD | 0.3±0.6 | 0.3±0.7 | 0.2±0.5 |
| **Prior preventive class failures** | | | |
| <3 classes | 12 (14.4) | 3 (18.8) | 9 (13.5) |
| ≥3 classes | 71 (85.6) | 13 (81.5) | 58 (86.5) |
| ≥4 classes | 54 (69.6) | 8 (50.0) | 41 (61.1) |
| ≥5 classes | 32 (38.6) | 3 (18.7) | 29 (43.2) |
| ≥6 classes | 13 (15.7) | 1 (6.2) | 12 (17.9) |
| ≥7 classes | 2 (2.4) | 0 | 2 (2.9) |
| **Drug Classes** | | | |
| Beta-blockers | 64 (78.1) | 11 (68.8) | 53 (80.3) |
| Tricyclic antidepressant | 74 (89.2) | 15 (93.8) | 59 (88.1) |
| Calcium channel blockers | 53 (63.9) | 13 (81.3) | 40 (59.7) |
| Antiseizure medications | 65 (78.3) | 11 (68.8) | 54 (80.6) |
| SSRIs/SNRIs | 15 (18.1)/ 8 (9.6) | 3 (18.8)/ 1 (6.3) | 12 (17.9)/ 7 (10.4) |
| OnabotulinumtoxinA | 35 (42.2) | 2 (12.5) | 33 (49.3) |
| Angiotensin receptor antagonists | 18 (21.7) | 1 (6.3) | 17 (25.4) |

*Abbreviations: CM, chronic migraine; HFEM, high frequency episodic migraine; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitor. Percentages are expressed on column total.*

**Table S2.** Adverse events reported though 12 months of follow-up.

| | Overall population (n =83) | HFEM (n=16) | CM (n=67) |
|---|---|---|---|
| Patients reporting at least one AE, n (%) | 8 (9.6) | 2 (12.5) | 6 (8.9) |
| Overall AEs rate, n (%) | 10 (12.0) | 3 (18.7) | 7 (10.4) |
| AEs leading to drug discontinuation, n (%) | 1 (1.2) | 1 (6.2) | - |
| **AEs reported** | | | |
| Constipation, n (%) | 6 (7.2) | 2 (12.5) | 4 (5.9) |
| Injection site reaction, n (%) | 3 (3.6) | 1 (6.2) [a] | 2 (2.9) |
| Effluvium, n (%) | 1 (1.2) | - | 1 (1.4) |

*Abbreviations: AE, adverse event; CM, chronic migraine; HFEM, high frequency episodic migraine. Percentages are expressed on column total. HFEM and CM are part of the overall population. [a]leading to discontinuation.*

**Table S3.** Changes in migraine-related variables during fremanezumab treatment in the overall, HFEM and CM populations (LOCF).

| | Median (IQR) | Median difference (IQR) | | |
| --- | --- | --- | --- | --- |
| | **Baseline** | **3 months** | **6 months** | **12 months** |
| **Overall population (n=83)** | | | | |
| **Monthly headache days** | 20.0 (15.0) | -9.2 (12.0) | -9.0 (14.0) | -9.0 (16.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| **Analgesic medication days** | 15.0 (18.0) | -9.0 (11.0) | -9.0 (12.0) | -9.0 (13.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| **Analgesic medication number** | 20.0 (20.0) | -10.0 (18.0) | -11.0 (12.0) | -12.0 (17.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| **MIDAS score** | 64.0 (60.0) | -35.0 (49.0) | -35.0 (54.0) | -35.0 (54.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| **HIT-6 score** | 67.0 (7.0) | -10.0 (15.0) | -12.0 (16.0) | -12.0 (17.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| *HFEM (n=16)* | | | | |
| **Monthly headache days** | 10.0 (2.0) | -5.0 (5.2) | -6.0 (4.0) | -6.0 (5.2) |
| *p value* | - | **0.001** | **0.001** | **0.001** |
| **Analgesic medication days** | 9.0 (2.0) | -7.0 (6.0) | -6.5 (6.5) | -5.0 (6.0) |
| *p value* | - | **0.005** | **0.004** | **0.004** |
| **Analgesic medication number** | 10.0 (2.0) | -6.0 (7.5) | -7.5 (8.0) | -6.0 (7.5) |
| *p value* | - | **0.007** | **0.005** | **0.006** |
| **MIDAS score** | 30.5 (31) | -18.0 (20.5) | -18.0 (35.2) | -18.0 (29.7) |
| *p value* | - | **0.003** | **0.002** | **0.002** |
| **HIT-6 score** | 67.0 (6.0) | -10.0 (13.2) | -20.0 (16.0) | -15.0 (19.2) |
| *p value* | - | **0.001** | **<0.001** | **<0.001** |
| *CM (n=67)* | | | | |
| **Monthly headache days** | 25.0 (14.0) | -11.0 (14.0) | -11.0 (17.0) | -11.0 (18.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| **Analgesic medication days** | 20.0 (18.0) | -10.0 (12.0) | -10.0 (13.0) | -10.0 (14.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| **Analgesic medication number** | 25.0 (18.0) | -13.0 (21.0) | -13.0 (14.0) | -14.0 (17.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| **MIDAS score** | 80.0 (65.0) | -47.0 (60.0) | -45.0 (57.0) | -45.0 (53.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |
| **HIT-6 score** | 67.0 (7.0) | -10.0 (15.0) | -11.0 (18.0) | -12.0 (18.0) |
| *p value* | - | **<0.001** | **<0.001** | **<0.001** |

*Abbreviations: CM, chronic migraine; HFEM, high frequency episodic migraine; IQR, interquartile range; LOCF, last observation carried forward; HIT-6, Headache Impact Test 6; MIDAS, Migraine Disability Assessment; SD, standard deviation. Baseline values are the same of observed data analysis but reported for data consistency. The changes are calculated using the Wilcoxon signed-rank test and expressed as median reduction [IQR]. All p values and reductions are vs baseline. Significative p values are reported in bold. IQR, interquartile range.*

**Table S4.** Response rate during fremanezumab treatment in HFEM, CM and overall populations (LOCF).

| | 3 months n (%) | 6 months n (%) | 12 months n (%) |
|---|---|---|---|
| **Overall population (n=83)** | | | |
| Response rate ≥30% | 57 (68.7) | 60 (72.3) | 58 (69.9) |
| Response rate ≥50% | 42 (50.6) | 51 (61.4) | 53 (63.8) |
| Response rate ≥75% | 19 (22.9) | 26 (31.3) | 25 (30.1) |
| Response rate 100% | 2 (2.4) | 4 (4.8) | 5 (6.0) |
| **HFEM (n=16)** | | | |
| Response rate ≥30% | 11 (68.7) | 13 (81.2) | 12 (75.0) |
| Response rate ≥50% | 9 (56.3) | 10 (62.5) | 11 (68.7) |
| Response rate ≥75% | 2 (25.0) | 6 (37.5) | 5 (31.3) |
| Response rate 100% | 2 (12.5) | 2 (12.5) | 2 (12.5) |
| **CM (n=67)** | | | |
| Response rate ≥30% | 46 (68.7) | 47 (70.1) | 46 (68.7) |
| Response rate ≥50% | 33 (49.3) | 41 (61.2) | 42 (62.7) |
| Response rate ≥75% | 15 (22.4) | 20 (29.9) | 20 (29.9) |
| Response rate 100% | 0 | 2 (3.0) | 3 (6.0) |

*Abbreviations: CM, chronic migraine; HFEM, high frequency episodic migraine; LOCF, last observation carried forward. Percentages are expressed on column total. HFEM and CM are part of the overall population. Response rate percentages are cumulative.*

**Table S5.** Univariable regressions with baseline selected variables for clinical response (defined as response rate ≥50% MHDs) at 3, 6 and 12 months.

| Univariable | 3 months | | | 6 months | | | 12 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95%CI | *p* value | OR | 95%CI | *p* value | OR | 95%CI | *p* value |
| Age (years) | 1.00 | 0.97-1.03 | 0.92 | 1.00 | 0.97-1.03 | 0.63 | 1.00 | 0.97-1.03 | 0.99 |
| Sex, *female* | 1.65 | 0.63-4.33 | 0.30 | 0.93 | 0.35-2.49 | 0.90 | 1.00 | 0.37-2.69 | 0.98 |
| Chronic migraine | 0.75 | 0.25-2.26 | 0.61 | 0.94 | 0.30-2.91 | 0.92 | 0.71 | 0.22-2.30 | 0.57 |
| Migraine duration (years) | 1.00 | 0.97-1.03 | 0.62 | 0.97 | 0.92-1.01 | 0.22 | 0.96 | 0.91-1.00 | 0.09 |
| Number of prior failures | 0.81 | 0.61-1.06 | 0.13 | 0.92 | 0.70-1.21 | 0.55 | 0.86 | 0.65-1.14 | 0.29 |
| Medication overuse | 1.62 | 0.63-4.14 | 0.30 | 1.25 | 0.48-3.23 | 0.63 | 1.35 | 0.52-3.50 | 0.52 |
| Monthly headache days | 0.96 | 0.91-1.01 | 0.17 | 0.96 | 0.91-1.02 | 0.24 | 0.97 | 0.95-1.03 | 0.44 |
| Analgesic medication days | 0.99 | 0.95-1.04 | 0.80 | 1.00 | 0.95-1.04 | 0.99 | 0.98 | 0.94-1.03 | 0.61 |
| Analgesic medication number | 0.99 | 0.98-1.01 | 0.70 | 0.98 | 0.96-1.00 | 0.09 | 0.98 | 0.96-1.00 | 0.07 |
| MIDAS score | 1.00 | 0.99-1.01 | 0.71 | 1.00 | 0.99-1.01 | 0.98 | 0.99 | 0.99-1.00 | 0.86 |
| HIT-6 score | 0.98 | 0.91-1.06 | 0.72 | 0.95 | 0.87-1.03 | 0.26 | 0.99 | 0.92-1.07 | 0.93 |

*Abbreviations: CI confidence interval; CM, chronic migraine; HFEM, high frequency episodic migraine; HIT-6, Headache Impact Test 6; MHDs, monthly headache days; MIDAS, Migraine Disability Assessment; OR, odds-ratio. Patients that discontinued treatment have been considered as non-responders for logistic regressions. For categorical variables, sex male, episodic migraine and absence of medication overuse have been used as reference.*