Efficacy of fremanezumab in refractory chronic migraine patients: Real-world data from the Hull Migraine Clinic, UK

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Research Article

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Abstract

Background:

Fremanezumab is an anti-calcitonin gene-related peptide monoclonal antibody efficacious for chronic migraine prophylaxis. We evaluated real-world prophylactic efficacy of fremanezumab for refractory chronic migraine in a United Kingdom specialist centre (Hull Migraine Clinic).

Methods:

289 adult chronic migraineurs commenced fremanezumab with prospective follow-up, maintaining headache diaries for ≥1 month pre-fremanezumab initiation and continuously thereafter. Patients failed 6 median previous prophylactics. We measured monthly headache days, migraine days, headache-free days, analgesia medication days, triptan days and Headache Impact Test-6 scores at baseline and during treatment.

Results:

All outcomes significantly improved in results of 182 patients at 4-month follow-up (p<0.0001), with reduced median monthly headache days (by 9 days), migraine days (by 10 days) and Headache Impact Test-6 (by 14.5 points). 80% patients achieved ≥30% migraine reduction, whilst 68% and 42% patients achieved >50% and >75% reduction. 58%, 39% and 17% patients achieved ≥30%, >50% and >75% headache day reduction. OnabotulinumtoxinA-unresponsive patients exhibited substantial responses, with 78%, 66% and 39% patients achieving ≥30%, >50% and >75% migraine reduction. Medication-overuse did not affect responses. 45% patients achieved <15 headache days in any month, and 65% achieved <8 migraine days in any month. 37% achieved both outcomes. In multivariate analyses, baseline headache-freedom and lower Headache Impact Test-6 score associated with ≥30% migraine reduction (p<0.05), whilst baseline headache-freedom and lower migraine-days associated with achieving <15 headache days in any month (p<0.01).

Conclusion:

Fremanezumab demonstrates real-world efficacy at 4 months in highly-refractory and onabotulinumtoxinA-unresponsive chronic migraine, irrespective of medication-overuse. Baseline headache-freedom, lower migraine-days and lower Headache Impact Test-6 score heralded superior responses.

Introduction

Chronic migraine (CM), defined by the International Classification of Headache Disorders 3rd-Edition (ICHD3) as headaches occurring ≥15 days/month for >3 months with migrainous headaches on ≥8 days/month, is a disabling condition with significant morbidity affecting 1.4–2.2% of the population (1, 2). Prophylaxis is the mainstay management strategy. However, oral prophylactics do not specifically

target its molecular pathophysiology, whilst patients are often unresponsive or intolerant of multiple treatments, incurring additional comorbidities in the process including medication-overuse headache (MOH), defined by ICHD3 as headaches occurring ≥15 days/month in patients with pre-existing headache disorder and regular overuse of ≥1 acute/symptomatic headache treatment medications for >3 months (1). Moreover, oral prophylaxis adherence is inconsistent, ranging between 19–79% at 6 months (3). In the UK, CM unresponsive to ≥3 oral prophylactics is eligible for onabotulinumtoxinA (4). However, despite these therapeutics, an estimated 5–31% of CM remains unresponsive to all existing preventatives (5).

Anti-calcitonin gene-related peptide (CGRP) and CGRP receptor monoclonal antibodies constitute a novel preventative class specifically targeting migraine pathophysiology. Fremanezumab is a humanised anti-CGRP monoclonal antibody efficacious for episodic migraine (EM) and CM prophylaxis in the Phase 3, randomised, double-blind, placebo-controlled HALO studies (6, 7). Monthly and quarterly fremanezumab significantly reduced headache and migraine days and acute analgesia use at 12-weeks in the HALO CM trial and 12-months in a trial-extension study (6, 8). Fremanezumab was approved by the US Food and Drug Administration (2018) for adult migraine prophylaxis (9), by the European Medicines Agency (2019) for migraine prophylaxis in adults with ≥4 migraine days/month (10), and by the UK National Institute of Health and Care Excellence (NICE) for prophylaxis of CM unresponsive to ≥3 prophylactics (2020), with treatment cessation if <30% migraine frequency improvement after 12 weeks treatment (11).

However, real-world fremanezumab efficacy data is sparse. Existing studies incorporated CM patients with lower baseline headache and migraine days than typically encountered in specialist headache centres (6, 12). Moreover, whilst erenumab demonstrated efficacy as an anti-CGRP therapy in onabotulinumtoxinA-refractory CM, real-world fremanezumab data in this cohort is lacking (13). Furthermore, novel HALO *post-hoc* analysis suggested >50% fremanezumab-treated CM patients reverted to EM at 3 months, potentially enabling patients to safety self-medicate with abortive therapies without specialist neurology input and warrants real-world correlation (14).

In this prospective audit, we report real-world efficacy outcomes of monthly fremanezumab treatment in a CM cohort refractory to an average of >6 preventatives, including onabotulinumtoxinA, in a large UK specialist headache centre (Hull Migraine Clinic).

Methods

Audit participants:

289 adult patients fulfilling the ICHD3 CM diagnostic criteria from the Hull Migraine Clinic, a large UK tertiary headache centre, commenced fremanezumab according to NICE guidance between November 2020 and April 2021. All patients had failed ≥3 preventatives including amitriptyline, nortriptyline, propranolol, atenolol, topiramate, candesartan, venlafaxine, sodium valproate, flunarizine, pizotifen, gabapentin, pregabalin, greater occipital nerve block, external trigeminal nerve stimulation (Cefaly),

external vagal nerve stimulation (GammaCore), and onabotulinumtoxinA. Medication failure was defined as discontinuation due to absence of headache frequency, duration or severity reduction after ≥12-weeks, or intolerance. OnabotulinumtoxinA failure indicated <30% sustained monthly headache-day reduction after ≥2-cycles (4). Patients discontinued onabotulinumtoxinA before fremanezumab with ≥3 months' washout period. Oral prophylaxis continuation was at patient and clinician discretion. Failure of 3 prophylaxis classes with 8 debilitating headache days/month for ≥3-months indicated resistant migraine, whilst failing all prophylaxis classes indicated refractory migraine according to European Headache Federation proposals (15). Those with medication-overuse (MO), namely non-opiate use ≥15 days/month or triptan use ≥10 days/month for >3 months, were included to accurately reflect the nature of real-world refractory patients (1). Fremanezumab was offered after discussion of all available untried preventative strategies. All patients gave their consent to participate in our study. However, as an audit under national guidelines, formal research ethics committee review was not required (https://www.hra-decisiontools.org.uk/research).

Audit design:

We ascertained baseline demographics including migraine onset age, CM duration, presence of aura and previous prophylactics including onabotulinumtoxinA. All patients self-administered monthly subcutaneous fremanezumab 225mg from pre-filled autoinjector syringes after training, with first follow-up at 4 months post-study initiation (1 month after the third dose). Patients maintained a headache diary for ≥30 days before fremanezumab initiation and continuously thereafter, recording monthly headache days (MHD), migraine days (MMD), crystal-clear headache-free days (HFD), acute analgesia medication (AMD) and triptan use days (TD), and Headache Impact Test-6 (HIT-6) score to assess migraine impact on quality-of-life (16). Diary completion was mandatory for treatment continuation, as per our usual clinical practice. Headache-day was defined as a day with any headache of any severity; migraine-day was one with headaches fulfilling ICHD3 migraine criteria; and crystal-clear headache-free day was a day without any head pains. Data from the 30 days immediately before first fremanezumab dose served as baseline parameters for each patient.

For each patient at 4-month follow-up, the data for all outcomes (MHD, MMD, HFD, AMD, TD and HIT-6) from the month containing their best MHD result on fremanezumab served as their post-treatment data. We calculated pre- and post-fremanezumab cohort medians and change medians for each outcome. We correlated baseline MHD and MMD with % MHD and MMD reductions for each patient. At 4-month follow-up, we calculated proportion of patients achieving ≥30%, >50% and >75% MHD and MMD reductions from baseline. We ascertained proportion of patients achieving MHD <15 days in any treatment month as early indicator of reversion to EM headache frequency in any month, those achieving MMD<8 days in any treatment month as indicative of adequate migraine frequency reduction to one manageable with acute analgesia without incurring MO, and those achieving both outcomes. Adverse events (AEs) during treatment were noted. Patients with <30% MMD reduction after 12-weeks treatment discontinued fremanezumab according to NICE guidance.

We assessed MHD, MMD, HFD and HIT-6 outcomes, proportions of patients achieving ≥30%, >50% and >75% MHD and MMD reductions, and proportions achieving MHD <15 in any treatment month, MMD<8 in any treatment month and both outcomes in three subanalyses in: a) patients with and without baseline headache-freedom to elucidate possible efficacy differences; b) onabotulinumtoxinA-refractory patients to establish fremanezumab efficacy in this important cohort; and c) patients with and without baseline MO to ascertain its possible impact on fremanezumab efficacy.

Statistical analysis:

We compared baseline and post-fremanezumab MHD, MMD, HFD, AMD, TD and HIT-6 outcomes for the cohort and within each subanalysis group using Wilcoxon's signed-rank test, since all pre- and post-treatment outcomes significantly deviated from normal distribution in the Kolmogorov-Smirnov goodness-of-fit test (p<0.05). Categorical variables including MHD, MMD, HFD, AMD, TD, HIT-6 are presented as median and interquartile ranges (IQR), and continuous variables as mean ± standard deviation (SD). Spearman's rank correlation coefficient assessed correlations between baseline MHD and MMD and % MHD and MMD reductions, with R^2 goodness-of-fit calculation. In subanalyses, inter-group comparisons of median changes for non-normally distributed variables were performed using the Mann-Whitney U test. Continuous variables were compared using unpaired Student's t-test. Dichotomous variables between groups were compared using Fisher's two-tailed exact test. Bonferroni correction of the p value was applied for multiple comparisons as indicated.

Univariate logistic regression was performed to identify all variables significantly associated with ≥30% MMD reduction and MHD<15 days in any treatment months, which were further analysed using multivariate logistic regression. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. For each variable, p<0.05 indicated statistical significance. Statistical analysis was performed using GraphPad Prism (Version 9.2.0, GraphPad Software, San Diego, California, USA).

Results

Patient demographic characteristics:

Table 1: Baseline clinical characteristics of study patients who completed 4-month follow-up

Figure 1: Cohort use of previous migraine prophylactics

Of 289 total patients, we report the outcomes of 182 patients who completed 3 injections and 4-month follow-up. Baseline characteristics of these patients and prior prophylactics used are summarised (Table 1, Figure 1).

a) Cohort fremanezumab efficacy outcomes:

Table 2a: Changes in monthly headache days, monthly migraine days, crystal-clear headache-free days, analgesia use and HIT-6 score post-fremanezumab treatment

Table 2b: Numbers and proportions of patients achieving ≥30%, >50% and >75% reductions from baseline monthly headache days and baseline monthly migraine days post-fremanezumab treatment

Table 2c: Numbers and proportions of patients achieving MHD <15 in any month, MMD <8 in any month, MHD <15 in any month and MMD <8 in any month, and number and proportion of patients with 0 baseline headache-free days achieving ≥1 headache-free days post-fremanezumab treatment

Figure 2: Cohort changes in monthly headache days, migraine days and crystal-clear headache-free days post-fremanezumab treatment

Figure 3: Changes in acute analgesia and triptan use and HIT-6 score post-fremanezumab treatment

At 4-month follow-up, median MHD reduction from baseline was 9 days, MMD reduction was 10 days and HFD increase was 9 days (all $p<0.0001$) (Table 2a, Figure 2a–c). 38 (45%) of 84 patients without baseline headache-freedom achieved ≥1 HFD post-fremanezumab (Table 2c, Figure 2d). These demonstrate significant MHD, MMD and HFD improvements after 3 fremanezumab doses.

We assessed correlation between baseline MHD and MMD and individual patient response magnitudes. Baseline MHD negatively correlated with % MHD reduction ($r = -0.410$, $R^2 = 17\%$, $p<0.0001$) and % MMD reduction ($r = -0.155$, $R^2 = 2\%$, $p=0.0416$) (Figure 2e, f). Baseline MMD demonstrated no correlation with % MMD reduction ($r = -0.119$, $p=0.13$, data not shown). Therefore, fewer baseline headache days statistically associated with superior % MHD and MMD reduction responses, with minimal clinical significance. Baseline MMD bore no correlation with % MMD reduction magnitude.

We next evaluated ≥30%, >50% and >75% MHD and MMD reduction from baseline to quantify the proportion of patients meeting UK continuation criteria and who experienced significant fremanezumab responses (Table 2b, Figure 2g). 105 (58%), 70 (39%) and 31 (17%) patients achieved ≥30%, >50% and >75% MHD reduction. 145 (80%) patients achieved ≥30% MMD reduction, thereby meeting UK fremanezumab continuation criteria. 124 (68%) and 76 (42%) achieved >50% and >75% MMD reduction. 46 (25%) achieved ≥30% MMD reduction without achieving ≥30% MHD reduction (not shown). Overall, sizeable proportions of patients experienced large-magnitude MHD and MMD improvements, with greater response for MMD reduction and 80% patients eligible for treatment continuation beyond 3 months.

To contextualise real-world fremanezumab utility, we evaluated the proportion of patients achieving MHD <15 days or MMD<8 days in any treatment month (Table 2c, Figure 2h). 82 (45%) patients achieved MHD <15 days in any treatment month, indicating reversion to headache frequency of EM for ≥1 months. 119 (65%) achieved MMD <8 days in any treatment month, indicating migraine frequency reduction to a level manageable with acute analgesia without risking MO. Moreover, 67 (37%) achieved both outcomes. Therefore, within 3 months of fremanezumab initiation, substantial proportions of our cohort

demonstrate early headache improvement towards EM reversion and migraine frequency reduction to one safely manageable with abortive therapies.

Post-fremanezumab, median AMD reduction was 5 days, TD reduction was 0 days and HIT-6 reduction was 14.5 (all $p<0.0001$) (Table 2a, Figures 3a–c). These demonstrated significantly reduced acute analgesia and triptan use to a frequency below that which predisposes to MO, and significantly improved quality-of-life.

b) Fremanezumab efficacy in patients with and without baseline headache-freedom:

Table 3a: Baseline clinical characteristics of patients with and without baseline headache-freedom

Table 3b: Treatment outcomes post-fremanezumab in patients with and without baseline headache-freedom

Figure 4: Treatment outcomes in patients with and without baseline headache-freedom

We compared treatment outcomes between patients with and without baseline headache-freedom. Patients without baseline headache-freedom exhibited significantly greater baseline MHD, MMD and HFD but similar other baseline characteristics, including proportion with baseline medication-overuse and HIT-6 score (Table 3a). Both groups achieved significant post-fremanezumab MHD, MMD, HFD and HIT-6 improvements (all $p<0.0001$). Patients with baseline headache-freedom experienced significantly greater median MHD reduction and HFD gain compared to those without, with significantly greater percentages achieving ≥30%, >50% and >75% MHD reductions, MHD <15 days in any month, MMD <8 days in any month, and both outcomes, but no significant difference in median MMD reduction or percentages achieving significant MMD reductions. Similar percentages of patients stopped medication-overuse post-fremanezumab in both groups (Table 3b, Figure 4a–j). Therefore, those with baseline headache-freedom demonstrate greater headache improvement independent of medication-overuse reductions, suggesting baseline headache-freedom as a potential response prognosticator.

c) Fremanezumab efficacy in onabotulinumtoxinA-unresponsive patients:

Table 4a: Baseline clinical characteristics of onabotulinumtoxinA-unresponsive patients

Table 4b: Treatment outcomes in onabotulinumtoxinA-unresponsive patients

We evaluated treatment efficacy in 166 onabotulinumtoxinA-unresponsive patients (Table 4a). Overall, fremanezumab induced significant headache, migraine, headache-free days and HIT-6 improvements in onabotulinumtoxinA-refractory patients (Table 4b).

d) Fremanezumab efficacy in patients with and without baseline analgesia medication overuse:

Table 5a: Clinical characteristics of patients with and without baseline analgesia MO

Table 5b: Treatment outcomes in patients with baseline MO

Table 5c: Treatment outcomes in patients without baseline MO

Table 5d: Treatment outcome comparisons in patients with and without MO

We next compared treatment outcomes between patients with and without baseline MO. The two groups exhibited similar baseline characteristics including MHD, MMD, HFD and HIT-6 score (Table 5a). Post-fremanezumab, 58 (82%) with baseline MO reverted to non-MO with cessation of non-opioid and triptan overuse. Both groups achieved significant improvement in all outcomes, with no significant inter-group differences in median improvement for any outcomes (Tables 5b, c, d). Overall, fremanezumab demonstrated similar efficacy in patients with and without MO.

e) Factors associated with fremanezumab response:

Table 6a: Univariate and multivariate logistic regression analysis of patient factors associated with achieving ≥30% MMD reduction from baseline post-treatment and fremanezumab continuation

Table 6b: Univariate and multivariate logistic regression analysis of patient factors associated with achieving MHD <15 days/month in any treatment month post-fremanezumab

We investigated potential predictive factors for treatment responses, including ≥30% baseline MMD reduction (enabling fremanezumab continuation), and MHD<15 in any month (Table 6a, b). ≥30% baseline MMD reduction associated with baseline HFD (OR 2.789, p=0.0461) and HIT-6 score (OR 0.918, p=0.0282) in multivariate regression analysis, indicating baseline headache-freedom and lower HIT-6 scores independently associated with ≥30% MMD response. Achieving MHD <15 in any treatment month associated with baseline HFD ≥1 (OR 4.564, p=0.0003) and MMD (OR 0.923, p=0.008) in multivariate regression analysis, signifying baseline HFD ≥1 and lower baseline MMD independently associated with headache frequency reversion to that of EM in any treatment month. Other characteristics including migraine duration, medication-overuse, previous prophylactics or onabotulinumtoxinA were not associated with either outcome.

f) Safety and tolerability:

37 (20%) patients discontinued fremanezumab due to inefficacy. Injection site irritation and rash was the only AE reported in 5 (3%) patients. No patients discontinued fremanezumab due to AEs (data not

shown).

Discussion

Table 7a: Comparison between Hull experience and other salient studies of fremanezumab in chronic migraine

Table 7b: Comparison between Hull experience and other salient studies of anti-CGRP monoclonal antibodies in chronic migraine

a) Cohort fremanezumab efficacy outcomes:

We provide the first real-world evidence of fremanezumab efficacy in improving headache outcomes within 3-months of fremanezumab initiation in highly-refractory and onabotulinumtoxinA-unresponsive CM patients, regardless of medication-overuse. Those with baseline headache-freedom exhibited greater responses than those without, whilst baseline headache-freedom, lower MMD and lower HIT-6 associated with superior responses.

Compared to randomised controlled trials (Table 7a), our results corroborate the 12-week HALO trial of fremanezumab efficacy in CM (6). Our 9 days median MHD reduction, 10 days MMD reduction, 5 days AMD reduction and 14.5 points HIT-6 reduction exceeded the 4.6 and 4.3 days headache reduction, 5.0 and 4.9 days migraine reduction, 4.2 and 3.9 days analgesia use reduction and 6.8 and 6.4 points HIT-6 reduction in the HALO monthly and quarterly fremanezumab groups. Similar proportions achieved >50% MHD reduction (39% in our cohort, versus 41% and 38% in both HALO groups). Post-hoc analysis demonstrated 59% and 22% of HALO responders achieving >50% and >75% MMD reduction with monthly fremanezumab at 3-months, compared to 68% and 42% in our cohort. Monthly fremanezumab also reduced analgesia use by 6.7 days and HIT-6 by 8.2 points (17). However, HALO patients were less refractory, having used only ≤1 previous preventatives and exhibiting 20.3 days/month with any headache, 12.8 designated “headache days” (day with moderate-to-severe headaches lasting ≥4 hours, or requiring triptan/ergot use) and 16.2 monthly migraine days at baseline. In a mixed cohort (61% CM) unresponsive to 2–4 prophylactics, the FOCUS study demonstrated 3.5 days MMD reduction and 3.6 days moderate-to-severe headache day reduction compared to placebo at 12-weeks, with 34% and 12% achieving >50% and >75% MMD reductions. Subgroup analysis demonstrated 3.8 days MMD reduction in CM patients (18). However, unlike our study, FOCUS studied CM and EM patients as a mixed cohort, with a CM subset analysis providing the most direct comparisons to our results. For other anti-CGRP therapeutics, the Phase 3b CONQUER trial of CM unresponsive to 2–4 preventative classes showed galcanezumab reduced MHD by 6.7 and MMD by 6.6 days at 3-months (end of double-blind phase) (19). In the REGAIN trial in CM unresponsive to ≤3 prophylactics, monthly galcanezumab reduced monthly migraine days by 4.8 and 4.6 days with 120mg and 240mg dosing, respectively, with 28% and 7–9% achieving >50% and >75% MMD reductions (20). However, REGAIN excluded onabotulinumtoxinA-

refractory patients. Overall, compared to trials with less-refractory patients who tried fewer previous preventatives, we observe greater outcome improvements in our more refractory cohort.

Our results substantiate those of real-world and open-label extension (OLE) studies of anti-CGRP migraine prophylaxis (Table 7b). A real-world study of 587 fremanezumab-treated CM patients (baseline MHD 16.4 days, MMD 14.7 days) reported MHD and MMD reductions of 8.0 (49%) and 7.9 (54%) days at 3-months, and 10.8 (66%) and 10.1 (69%) days at 6-months, consistent with our results (abstract data, 12). In a real-world study of CM patients unresponsive to 8.4 prophylactics on average (91% onabotulinumtoxinA-refractory), erenumab reduced MHD and MMD by 6.3 and 6.0 days at 3-months, and 6.8 and 7.5 days at 6-months. 49%, 35% and 18% patients achieved ≥30%, ≥50% and ≥75% MMD reduction at 3-months, lower than the 80%, 68% and 42% in our cohort (21). In GARLIT, a real-world study of CM unresponsive to a median of 5 prophylactics, galcanezumab reduced baseline MHD by 12 days to 8 days and HIT-6 by 12 points to 58 at 3-months, with 67% and 33% achieving >50% and >75% MHD reduction, and 14 days MHD reduction, 13 points HIT-6 reduction and 64% and 38% achieving >50% and >75% MHD reduction at 6-months (22). OLE of FOCUS to 24-weeks demonstrated 4.5–5.2 days moderate-to-severe headache day reduction, 4.7–5.5 days MMD reduction, and 38–46% and 16–20% achieving >50% and >75% MMD reductions (23). In CONQUER OLE, galcanezumab reduced MHD by 6.6–8.3 and MMD by 6.5–8.2 days at 6-months in CM unresponsive to 2–4 preventative classes (24). In REGAIN OLE, monthly galcanezumab reduced monthly headache days by 6.5–7.3 days at 6-months and 8.0–9.0 days at 12-months, with 45–46% and 53–57% achieving >50% MHD reduction (abstract data) (25). Overall, our more-refractory cohort demonstrated slightly greater improvements to these studies.

We assessed MHD<15 days/month responses as early indication of EM reversion, and MMD<8 days/month responses to reflect adequate migraine frequency reduction to one manageable with analgesia without risking MO. 45% achieved MHD<15 in any month, 65% achieved MMD<8 in any month, and 37% achieved both outcomes. However, real-world fremanezumab EM reversion data is lacking. Defining EM reversion as average MHD<15 over 3-months or MHD<15 days in all 3 months, both HALO post-hoc analysis and FOCUS demonstrated 53–54% and 34% EM reversion with monthly fremanezumab according to either definition (14, 26). A post-hoc trial extension of erenumab, defining EM conversion as <45 headache days during each of multiple 12-week periods over the entire study, demonstrated 53.1% EM conversion after 12 weeks treatment (27). Similarly, GARLIT demonstrated EM conversions of 74% at 3-months and 77% at 6-months with galcanezumab in the real-world (22). However, our more refractory cohort will likely require longer treatment durations than other studies to achieve EM reversion over 3 consecutive months.

b) Fremanezumab efficacy in patients with and without baseline headache-freedom:

We are the first to demonstrate better outcomes in patients with baseline headache-freedom compared to those without, with no previous studies evaluating impact of headache-freedom on anti-CGRP therapeutic

outcomes. We show significantly greater MHD reduction (+10 days), percentages achieving ≥30%, >50% and >75% MHD reduction (+32%, +25%, +21%), MHD <15 in any month (+41%), MMD <8 in any month (+42%) and both outcomes (+44%) in those with baseline headache-freedom, suggesting baseline headache-freedom may predict superior anti-CGRP therapy response. Given migraines often co-exist with other cephalalgias, patients without headache-freedom may harbour both a fremanezumab-responsive migraine and a second, less-responsive, chronic daily headache, as illustrated by 25% of our cohort exhibiting ≥30% migraine response without headache-day reduction. Chronic daily headaches may further predispose to MOH, complicating management. Alternatively, psychosocial factors may affect perception of headache improvement and subsequent reporting.

c) Fremanezumab efficacy in onabotulinumtoxinA-unresponsive patients:

We demonstrated significant fremanezumab efficacy in onabotulinumtoxinA-unresponsive patients, with median MHD and MMD reductions of 8 and 9 days, 78% achieving ≥30% MMD reduction and 12-point HIT-6 reduction. In a real-world study of onabotulinumtoxinA-unresponsive patients refractory to 5.5 preventatives on average, 3 months of erenumab reduced headache days limiting daily activity by 6.4 days, triptan use by 3.4 days and HIT-6 by 7.1 points, and improved headache-free days by 5.7 days (13). Although lacking head-to-head comparisons, these suggest anti-CGRP therapies may be highly-efficacious in onabotulinumtoxinA-refractory CM. Consequently, one might consider anti-CGRP antibodies before onabotulinumtoxinA for CM prophylaxis on efficacy grounds, with additional advantage of self-administration minimising face-to-face interactions during pandemic. Recent studies further suggest anti-CGRP therapies and onabotulinumtoxinA yield greater efficacy in combination than either alone (28, 29). Therefore, anti-CGRP therapies and onabotulinumtoxinA may hold a complementary and synergistic future relationship, with each potentially useful for treating patients unresponsive to the other, with combination therapy for highly-refractory patients. However, future direct efficacy and safety comparisons in trials are necessary to define their precise relationship.

d) Fremanezumab efficacy in patients with and without baseline medication-overuse:

We provide the first real-world evidence of similar fremanezumab efficacy in patients with and without MO for all outcomes measured, with 82% with MO reverting to non-MO. These corroborate clinical trial subanalysis results for fremanezumab (HALO), galcanezumab (REGAIN) and erenumab demonstrating similar headache, migraine and HIT-6 improvements, and real-world results showing similar proportions achieving ≥50% MHD or MMD reduction after 6 months of erenumab or galcanezumab, in those with and without MO (30–33). Therefore, current evidence suggests anti-CGRP therapies are similarly efficacious, regardless of MO.

e) Determinants of fremanezumab response:

We identified headache-freedom, lower MMD and lower HIT-6 score at baseline associating with fremanezumab response and reversion to EM headache frequency for ≥1 months. Two real-world studies demonstrated lower baseline analgesia use, MMD and HIT-6 predicted >50% MMD response post-erenumab, partially corroborating our results (34, 35). In comparison, HALO post-hoc analysis found greater acute analgesia, oral preventative and previous topiramate/onabotulinumtoxinA usage in post-fremanezumab non-reverters compared to EM reverters (LiptonRef14). Other studies identified MOH duration, number of previous prophylactics, CM duration and psychological factors associating with negative erenumab response (36, 37). Previous preventative-use did not constitute a treatment response discriminator in our cohort, likely due to numerous previous preventatives (including onabotulinumtoxinA) tried by most of our patients. Our results suggest baseline headache-freedom as key predictor of anti-CGRP therapy response and EM reversion, alongside lower baseline MMD and HIT-6 scores.

f) Fremanezumab safety and tolerability:

Our cohort tolerated fremanezumab well, with 5 patients reporting injection-site reactions as the only AE and no AE-related treatment discontinuations, compared to 71% developing AEs (96% mild), 41% developing injection-site reactions and 2% treatment discontinuation due to AEs at 12-weeks in the HALO monthly fremanezumab group (6). Our patients reported no symptoms raising concerns for liver function derangements, cardiovascular/cerebrovascular AEs or infections, observed in the 12-month HALO extension study (8). Therefore, fremanezumab demonstrates high safety and tolerability in our cohort.

g) Strengths and limitations of our audit:

Our main strengths are a sizeable, real-world, highly-refractory CM population unresponsive to an average of >6 prophylactics, including 91% unresponsive to onabotulinumtoxinA, with detailed follow-up enabling comprehensive and multidimensional clinical data capture. Limitations include non-randomisation and reliance on subjective reporting with potential for reporting/attrition bias. Furthermore, although baseline MHD negatively correlated with % MHD and MMD reductions statistically, R^2 goodness-of-fit analysis indicated poor clinical predictive value. Nevertheless, our study is important in demonstrating real-world fremanezumab efficacy in highly-refractory and onabotulinumtoxinA-unresponsive patients, with or without MO, and identifying baseline headache-freedom as a treatment-response determinant warranting validation in future studies.

Conclusion

We report real-world fremanezumab efficacy in improving headache and quality-of-life outcomes at 4-months in highly-refractory and onabotulinumtoxinA-unresponsive CM, with or without MO. Patients with

baseline headache-freedom exhibited greater responses than those without. Headache-freedom, lower MMD and lower HIT-6 at baseline may predict superior responses.

Study Highlights

- Fremanezumab improves all major headache outcomes at 4-months in real-world chronic migraineurs unresponsive to >6 prophylactics on average, with 80% achieving ≥30% migraine reduction.
- Fremanezumab significantly improves outcomes in onabotulinumtoxinA-unresponsive patients, with 78% achieving ≥30% migraine reduction.
- Headache-freedom, lower monthly migraine days and lower HIT-6 score at baseline associated with superior responses.
- Fremanezumab maintains similar efficacy, irrespective of baseline medication-overuse.

Declarations

Ethics approval and consent to participate:

All patients gave their consent to participate in our study. However, as an audit under national guidelines, formal research ethics committee review was not required (https://www.hra-decisiontools.org.uk/research).

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests:

Fan Cheng- none.

Qinyao Wu- none.

Mariam Hussain- none.

Victoria Wilkinson- none.

Lisa Wilson- none.

Modar Khalil- none.

Fayyaz Ahmed has been on the advisory board of Allergan, Teva, Lundbeck, Novartis and Eli Lilly, for which he has been paid honorarium donated to registered charities i.e., the British Association for the Study of Headache, Migraine Trust and the Anglo-Dutch Migraine Association.

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Authors' contributions:

FC contributed to patient evaluation, data collection, database maintenance, data analysis and interpretation and wrote the manuscript. QW contributed to data collection, extraction and database maintenance. MH, VW and LW contributed to patient evaluation and data collection. FA, MK, VW and LW contributed to data collection and database maintenance. FA and MK contributed to critical revision of the manuscript and for important intellectual concepts.

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Tables

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Figures

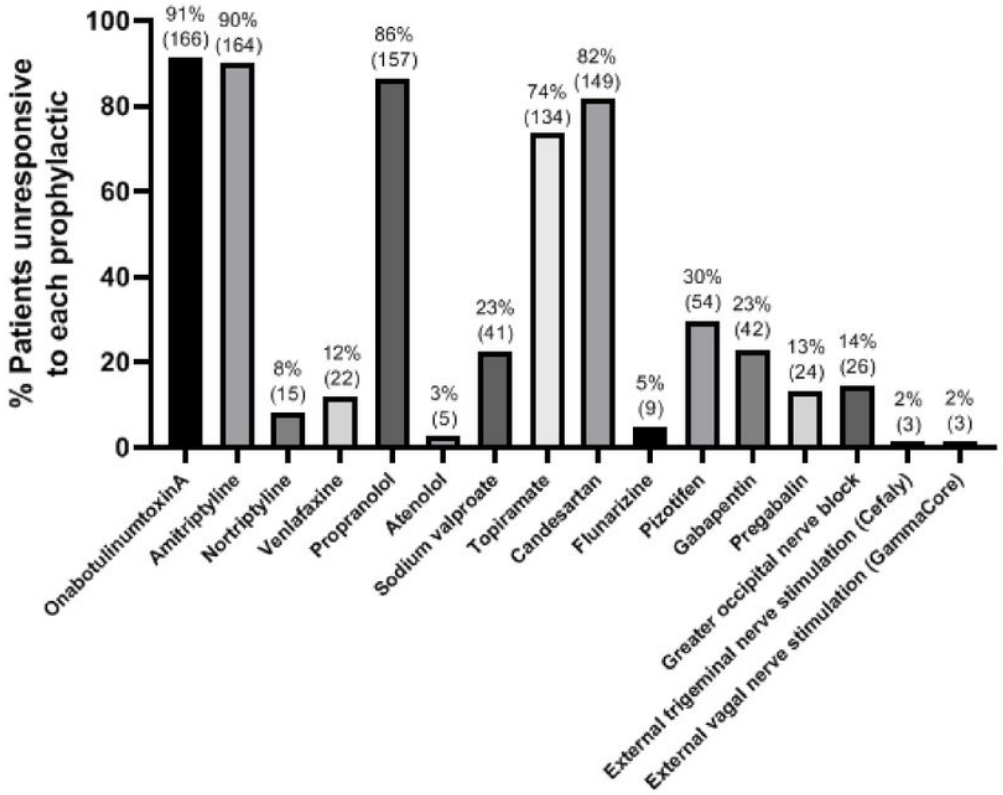

Figure 1

Cohort use of previous migraine prophylactics. Percentage and number (in parentheses) of patients who tried and were unresponsive to each migraine prophylactic.

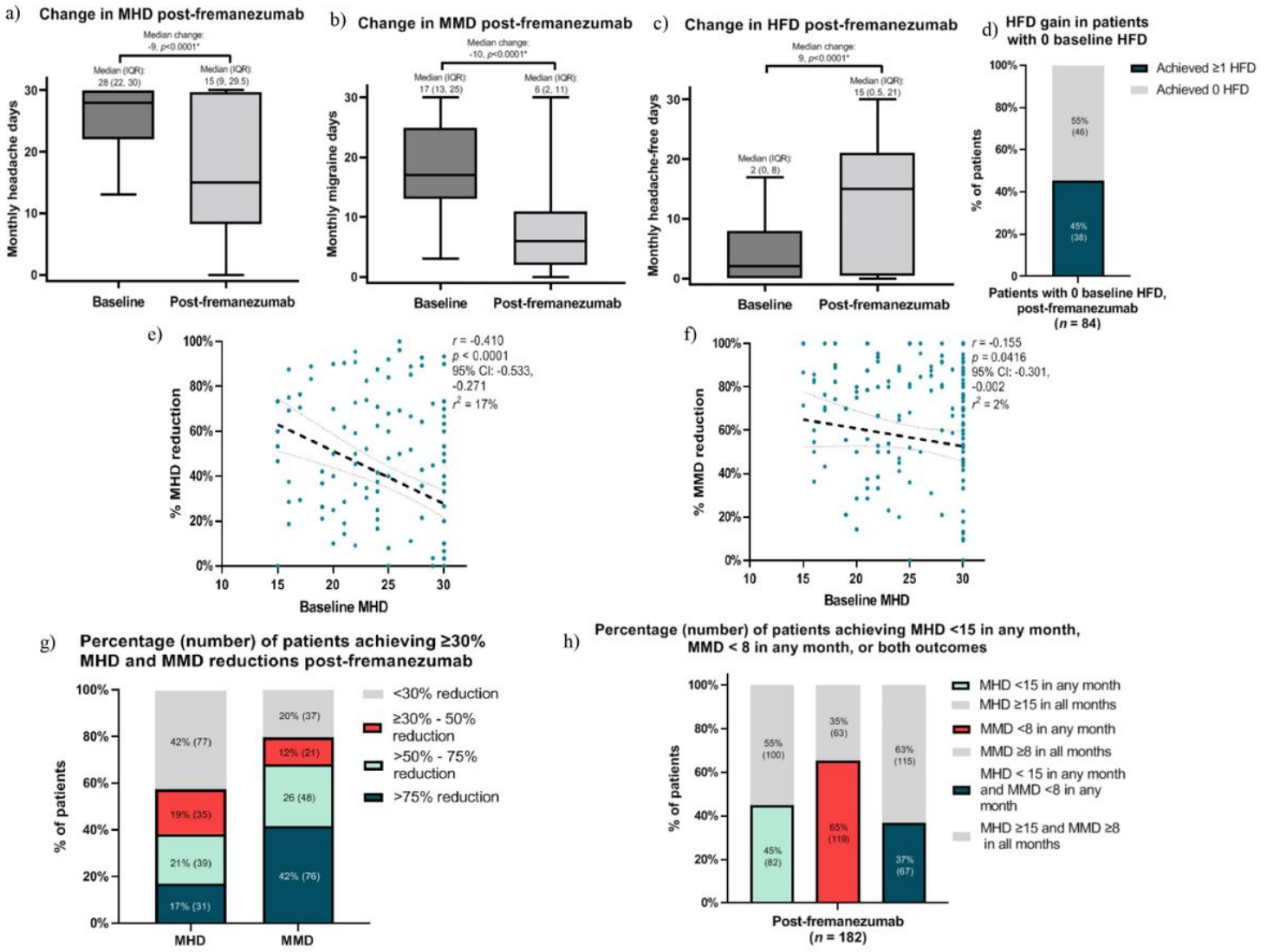

Figure 2

Cohort changes in MHD, MMD and HFD post-fremanezumab treatment. (a–c) Change in MHD (a), MMD (b) and HFD (c) (Wilcoxon signed-rank test). Bonferroni correction for multiple comparisons set at $p < 0.05/6 = 0.008$ for statistical significance. * denotes $p<0.008$. d) Percentage and number (in parentheses) of patients without baseline headache-freedom achieving ≥1 HFD during treatment. (e–f) Correlation of baseline MHD and % MHD reduction from baseline (e) and correlation of baseline MMD and % MMD reduction from baseline (f) for all patients (Spearman's rank correlation coefficient, $p<0.05$). (g–h) Percentage and number (in parentheses) of patients achieving: ≥30%, >50% and >75% MHD and MMD reduction from baseline (g), MHD<15 in any treatment month, MMD<8 in any treatment month, or MHD<15 in any treatment month and MMD<8 in any treatment month (h).

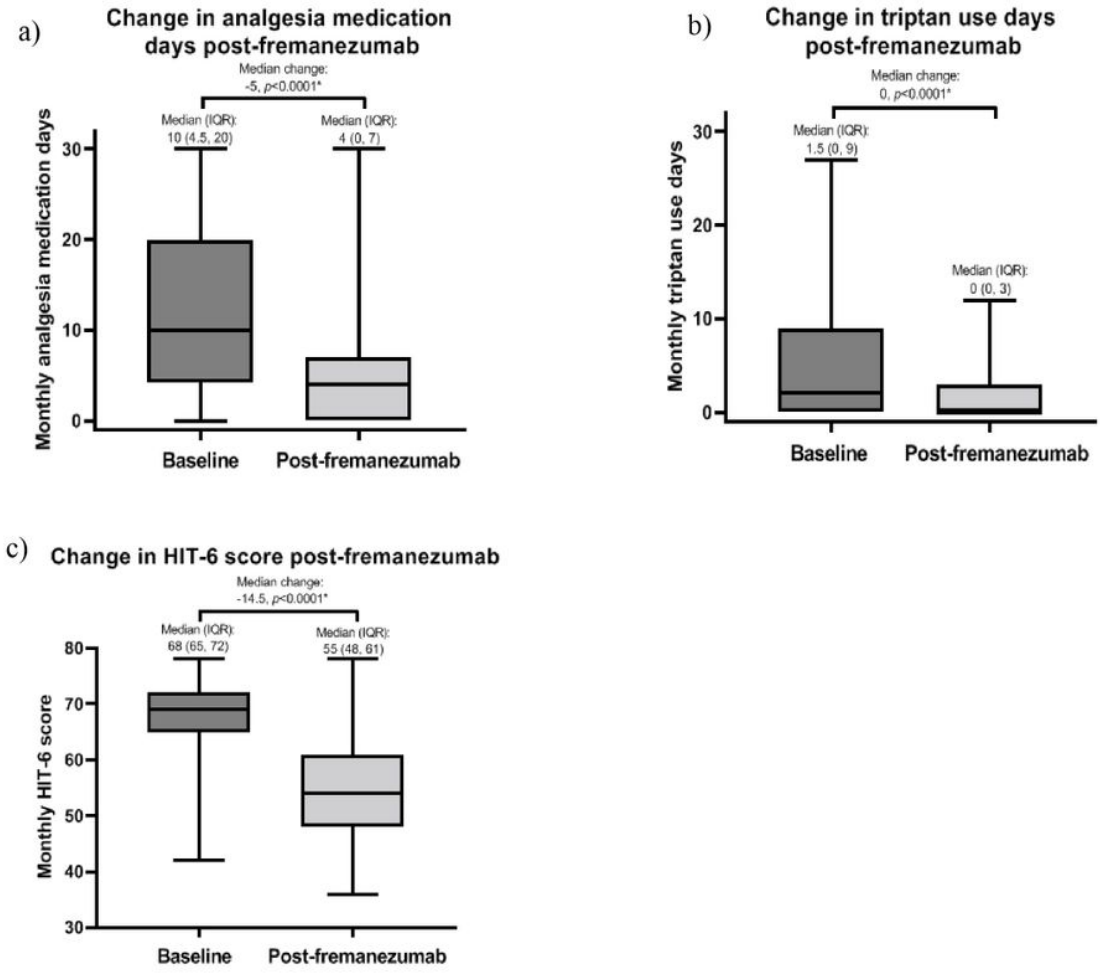

Figure 3

Changes in analgesia use and HIT-6 post-fremanezumab treatment. (a – c) Change in acute analgesia medication use days (a), triptan use days (b) and HIT-6 score (Wilcoxon signed-rank test). Bonferroni correction for multiple comparisons set at $p < 0.05/6 = 0.008$ for statistical significance. * denotes $p<0.008$.

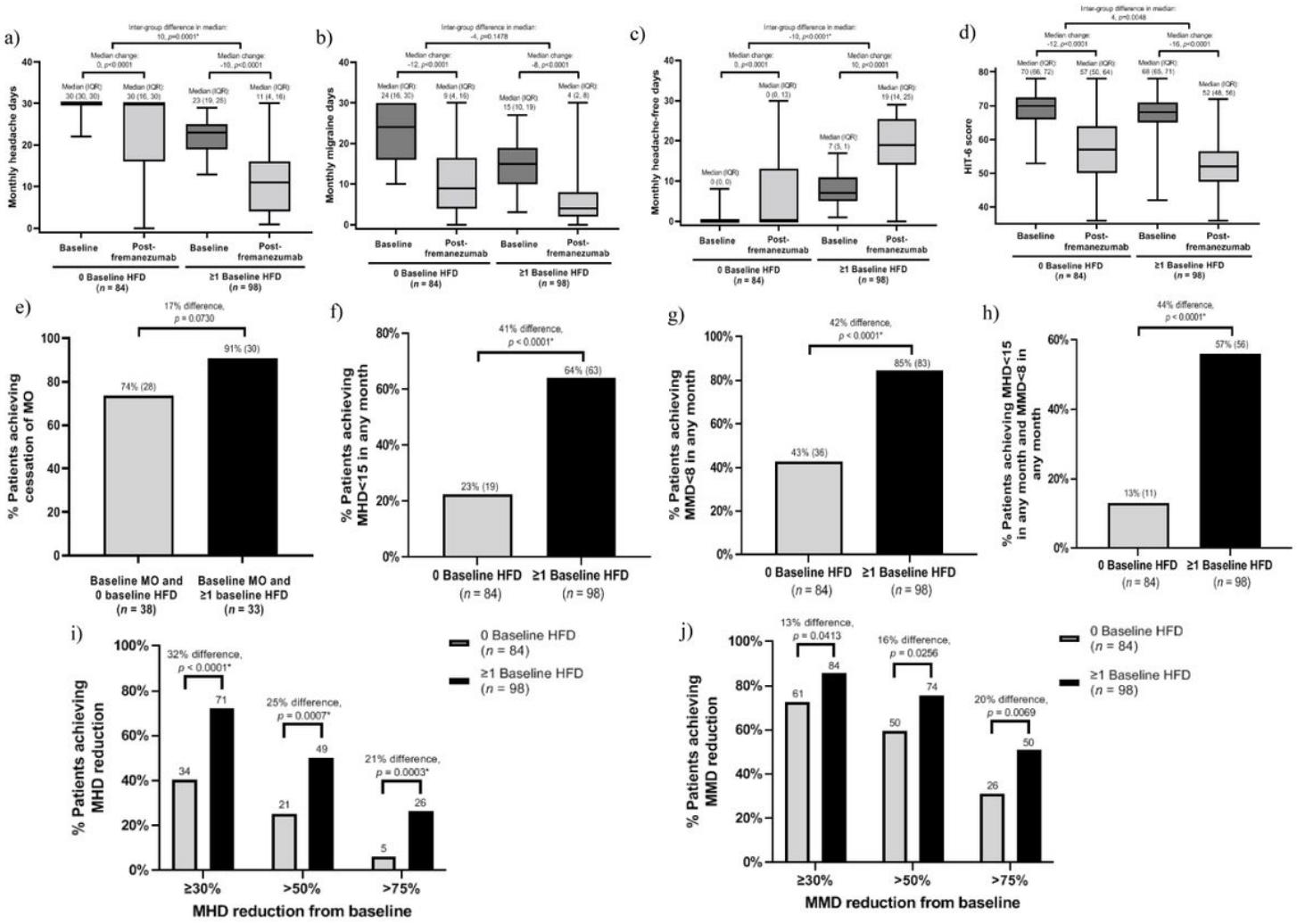

Figure 4

Treatment outcomes in patients with or without baseline headache-freedom. (a–d) Change in MHD (a), MMD (b), HFD (c) and HIT-6 score (d). Intra-group and inter-group MHD, MMD, HFD and HIT-6 comparisons made using Wilcoxon signed-rank test and Mann Whitney U test, respectively. e) Percentage and number (in parentheses) of patients with baseline medication-overuse (MO) achieving cessation of MO post-fremanezumab. (f–j) Percentage and number (in parentheses) of patients achieving MHD<15 in any treatment month (f), MMD<8 in any treatment month (g), and both outcomes (h), and ≥30%, >50% and >75% reduction of baseline MHD (i) and MMD (j). Inter-group comparisons of dichotomous variables made using Fisher's two-tailed exact test. Bonferroni correction for multiple comparisons set at $p < 0.05/14 = 0.004$ for statistical significance. * denotes $p<0.004$.

Supplementary Files

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