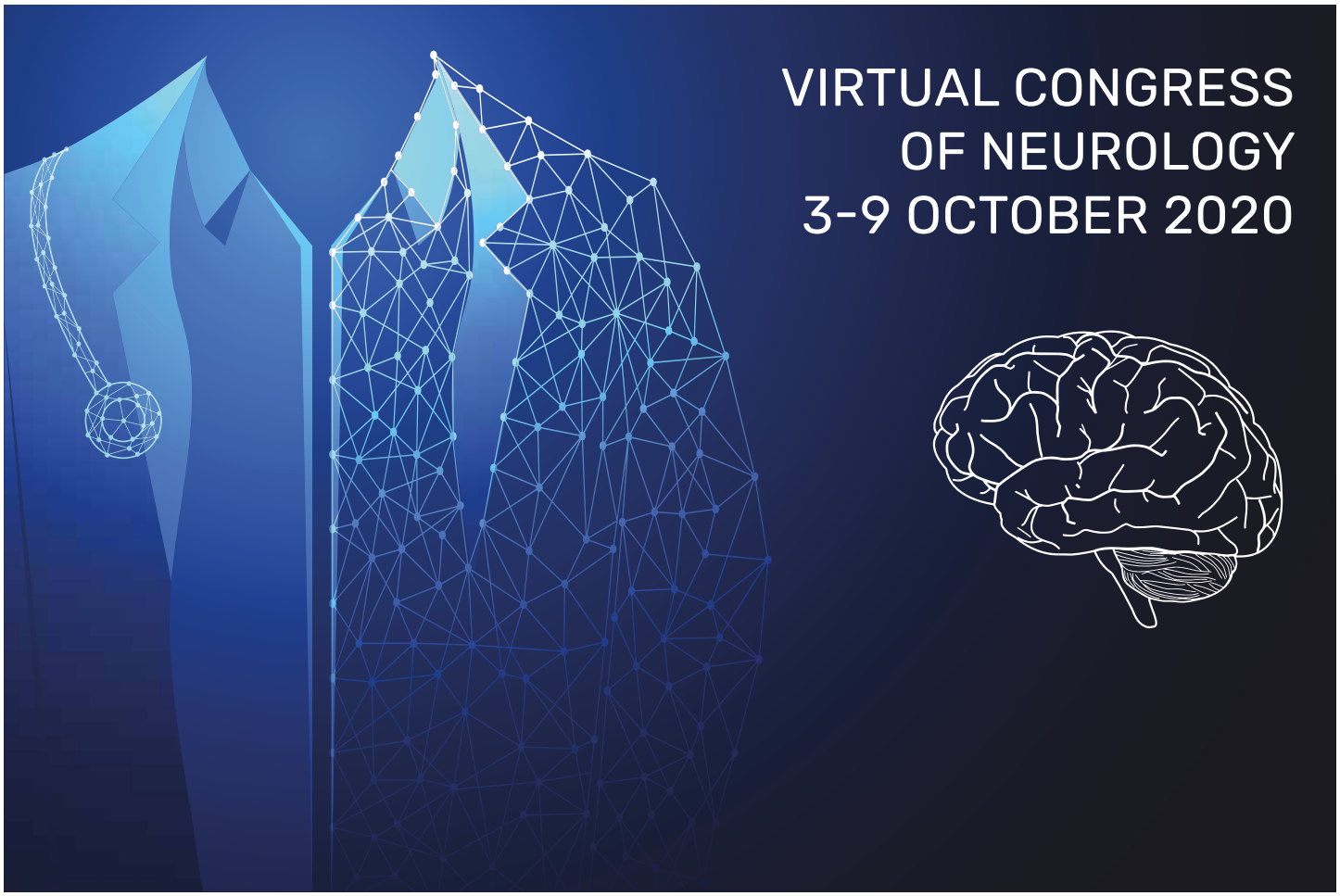
18th Migraine Trust International Symposium (MTIS)



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Summary of articles presented at the MTIS 2020 Virtual Meeting:

- OVERCOME study: Improvement of migraine using CGRP mAbs in a real-world setting.
- Remote electrical neuromodulation useful for adolescents with migraine.
- GLADIATOR trial: No new cardiovascular safety concerns with long-term use of lasmiditan.

And more

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1. Improvement of migraine using CGRP mAbs in a real-world setting

Most patients taking a calcitonin gene-related peptide (CGRP)-targeted monoclonal antibody (mAb) for the preventive treatment of migraine reported their migraine condition as better since starting the medication. This improvement appears relatively consistent across monthly headache day categories.

Real-world patient-reported outcome data is limited for patients who use a CGRP mAb for the preventive treatment of migraine. The current study, presented by Dr Robert Shapiro (University of Vermont, USA), assessed patient characteristics and patient-reported improvement among current users of CGRP mAbs [1].

Data was obtained in the last quarter of 2019 as part of the OVERCOME study via a web-based survey conducted in a representative US sample. Over 20,000 respondents were selected via a validated migraine diagnostic screener for International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria (95.1% of respondents) or via a self-reported healthcare professional migraine diagnosis (59.0% of respondents).

The current analysis evaluated a specific subpopulation of the respondents, namely those who had used a CGRP mAb for the preventive treatment of migraine within the past 3 months. A total of 950 patients (4.6%) reported ever using a CGRP mAb. The 586 patients (2.8%) currently using a CGRP mAb (mean age 38.9 years, 64.0% female, and 73.5% White) were asked to complete the Patient Global Impression of Improvement (PGI-I), which assessed the perceived improvement in their migraine condition since starting the current CGRP mAb. These patients had a mean monthly headache days of 7.6. Over half of the current CGRP mAb-users initiated their current treatment within the previous 3 months (55.1%). In addition, 62.6% of these patients reported use of an additional recommended migraine preventive medication (concomitant or switching) at some point during the same period.

Participants were also asked to complete the Migraine Disability Assessment (MIDAS) scale. Nearly half (49.5%) had severe migraine-related disability (MIDAS score ≥21), 22.9% moderate (11-20), 15.0% mild (6-10), and 12.6% little to none (≤5).

Unadjusted percentages of patients with PGI-I scores were reported overall and by monthly headache day categories (0-3, 4-7, 8-14, ≥15). Most respondents (79.2%, 95% CI 75.7-82.4%) reported their migraine condition as better since starting the CGRP mAb. These results were consistent across a range of monthly headache day categories.

These results are among the first real-world population-based patient-reported outcomes from those using CGRP mAbs for migraine prevention and suggest that these novel medications may positively impact patient-perceived improvement.

Future analyses should consider how other factors may influence patient-reported outcomes when using CGPR mAbs, including:

- migraine-related factors (e.g. baseline headache frequency, symptom severity, and cyclic disease fluctuations);
- medication-related factors (e.g. therapy duration, other preventive medication use, acute treatment optimisation, and switching between CGRP mAbs); and
- healthcare-related factors (e.g. location of care and access to medication).

1. Shapiro RE. CGRP monoclonal antibody use and patient-reported improvement of migraine: results of the OVERCOME study. MTIS 2020 Virtual Symposium, abstract MTV20-DP-002.

2. Similar treatment needs for high-frequency episodic and low-frequency chronic migraine

Data from the web-based CaMEO study indicate substantial overlap in the measures of burden and depression among respondents with high-frequency episodic migraine (8-14 monthly headache days (MHDs)) and those with low-frequency chronic migraine (15-23 MHDs). These findings suggest that the treatment needs of these 2 patient categories may be similar, suggesting that the 15-MHD threshold currently used for diagnosis of chronic migraine may merit reconsideration [1].

The 3rd edition of the International Classification of Headache Disorders (ICHD-3) defines chronic migraine as the occurrence of ≥15 MHDs for ≥3 months with criteria for migraine met on ≥8 days per month. Patients with <15 MHDs are considered to have episodic migraine. However, differences in migraine burden between patients with high-frequency episodic migraine and low-frequency chronic migraine have not been well characterised.

The CaMEO study was a longitudinal, web-based study that used quota sampling to identify respondents who met modified ICHD-3 migraine criteria. Data was provided by almost 17,000 respondents. Based on self-reported MHDs, 4 subgroups were defined:

- low- and moderate-frequency episodic migraine (0-7 MHDs);
- high-frequency episodic migraine (8-14 MHDs);
- low-frequency chronic migraine (15-23 MHDs); and
- high-frequency chronic migraine (≥24 MHDs).

The percentages of patients with severe disability (grade 4) or at least moderate disability (grade 3 or 4) based on the Migraine Disability Assessment Scale (MIDAS) were assessed in the 4 MHD subgroups, as well as severe (≥5)

or moderate-to-severe scores (≥3) on the Migraine Interictal Burden Scale (MIBS). Furthermore, the percentages of patients with moderate-to-severe depression –a score of ≥10 on the 9-item Patient Health Questionnaire– and moderate-to-severe anxiety –a score of ≥10 on the 7-item Generalised Anxiety Disorder scale– were assessed. All changes were statistically significant for the linear-by-linear association test (P<0.001).

Interestingly, substantial overlap between respondents with high-frequency episodic migraine and low-frequency chronic migraine was found for levels of moderate-to-severe disability, interictal burden, and depression.

Healthcare resource utilisation significantly increased across MHD categories (P<0.001), but was markedly similar between respondents with high-frequency episodic migraine and low-frequency chronic migraine. Similar findings were observed concerning utilisation of acute and preventive treatments. However, the rate of medication overuse was more than 20% higher among those with low-frequency chronic migraine versus high-frequency episodic migraine.

Consistent with prior research, this analysis demonstrated a strong linear relationship between MHD frequency and measures of migraine disease burden and healthcare resource utilisation, showing increases in all measures among patients with high-frequency episodic migraine compared with low-frequency chronic migraine.

1. Lipton RB. Exploring the boundaries between episodic and chronic migraine: results from the CaMEO study. MTIS 2020 Virtual Symposium, abstract MTV20-DP-009.

3. Nitroglycerin-induced cluster headache attacks characterised comprehensively

Results from the first single-blind, placebo-controlled study using intravenous nitroglycerin in cluster headache were presented at the MTIS 2020 Virtual Symposium [1]. Weight-adjusted intravenous nitroglycerin effectively and reliably induced cluster headache attacks, cranial autonomic symptoms, and non-headache symptoms in cluster headache patients.

Cluster headache is a primary headache disorder characterised by recurrent attacks of unilateral excruciating headache, ipsilateral cranial autonomic symptoms, and agitation. Attacks last 15-180 minutes and can recur up to 8 times a day.

Due to the episodic nature of cluster headache, nitroglycerin has been used as a method to induce cluster headache attacks for decades. However, the primary route of administration was sublingual, which has an unreliable bioavailability. Therefore, the current study used weight-adjusted intravenous nitroglycerin (0.5 µg/kg/min).

This single-blind, placebo-controlled study comprehensively investigated the stages of cluster headache attacks: non-headache symptoms, cranial autonomic symptoms, and pain onset. Participants were patients with episodic or chronic cluster headache and underwent 3 study visits in total: (i) during the first visit, 33 participants were unblinded and received intravenous nitroglycerin for 20 minutes; (ii) if an attack was triggered, they were asked to return for blinded visits either receiving nitroglycerin (n=25) or blinded placebo infusions (n=24), in random order; (iii) the clinical phenotype was recorded.

Nitroglycerin triggered cluster headache attacks in 79% of patients during the unblinded nitroglycerin visit and 76% during the blinded nitroglycerin visit. Nitroglycerin also induced non-headache symptoms and cranial autonomic symptoms with the attacks:

- non-headache symptoms occurred in 91% participants during the unblinded nitroglycerin visit, and 84% during the blinded nitroglycerin visit; and
- cranial autonomic symptoms occurred in 94% participants during the unblinded nitroglycerin visit, and 97% during the blinded nitroglycerin visit.

Time until the start of cluster headache attacks was shorter in the episodic cluster headache group compared with the chronic cluster headache group. During the nitroglycerin-induced cluster headache attacks, non-headache symptoms started early and were followed by cranial autonomic symptoms and pain. Finally, time until nitroglycerin-induced cluster headache attacks was shorter in the episodic group versus chronic cluster headache group. This observation highlights potential differences between subgroups of patients with cluster headache.

1. Wei DY. Placebo-controlled intravenous nitroglycerin phenotyping of acute attacks cluster headache. MTIS 2020 Virtual Symposium, abstract MTV20-DP-025.

4. Remote electrical neuromodulation useful for adolescents with migraine

Current acute treatments for migraine in adolescents are mostly pharmacological but have limitations. Remote electrical neuromodulation provides clinically meaningful relief of migraine pain and associated symptoms, offering a safe and effective non-pharmacological alternative for acute treatment in adolescents [1].

Migraine is a common disabling neurologic disorder in adolescents. The efficacy of pharmacological treatment is limited, can cause side effects, and may lead to medication overuse. There is thus a great unmet need

in this group for alternative acute treatments for migraine that are both effective and well tolerated.

Remote electrical neuromodulation is a novel acute treatment of migraine controlled by the patient. It stimulates upper arm peripheral nerves to induce conditioned pain modulation, an endogenous analgesic mechanism in which subthreshold conditioning stimulation inhibits pain in remote body regions. The remote electrical neuromodulation device Nerivio® is FDA-authorised for acute treatment of migraine with or without aura in adults.

The current open-label, single-arm, multicentre study assessed the efficacy and safety of this device in adolescents (aged 12-17 years) with migraine. Preventive treatment was allowed, if stable for ≥2 months and during the study. Enrolled were 60 patients, of whom 14 failed to meet the run-in criteria –having inadequate headache attacks– and 1 was lost to follow-up. Participants underwent a 4-week run-in phase during which the headaches were treated according to usual care and recorded in an electronic migraine diary. Eligible participants continued to an 8-week treatment phase in which they were asked to treat their headaches with the device. Pain severity levels, associated symptoms, and functional disability were recorded at treatment initiation, 2 and 24 hours post treatment.

A test treatment with remote electrical neuromodulation was completed by 39 participants. Pain relief and being pain-free at 2 hours were reported by 71.8% and 35.9% of participants, respectively. Both pain relief and pain-free responses were sustained at 24 hours in 90.9% of participants, as found in an exploratory analysis.

The following symptoms disappeared at 2 hours: nausea in 54.5%, photophobia in 41.9%, and phonophobia in 40.0% of participants. Furthermore, 69.7% of participants experienced improvement of functional ability at 2 hours. A single device-related adverse event was reported, namely a temporary sensation of pain in the arm.

Remote electrical neuromodulation provided clinically meaningful relief of migraine pain and associated symptoms in adolescents with migraine. Most participants achieved pain relief at 2 hours after treatment using the device in most of their treated attacks. In addition, it was well tolerated and safe. Hence, the results suggest that remote electrical neuromodulation can offer a safe and effective non-pharmacological alternative for acute treatment in adolescents with migraine.

1. Hershey AD. Remote electrical neuromodulation for the acute treatment of migraine in adolescents. MTIS 2020 Virtual Symposium, abstract MTV20-DP-031.

5. Concomitant preventive medication has no impact on efficacy of ubrogepant

Ubrogepant is an oral, small-molecule calcitonin gene-related peptide receptor (CGPR) antagonist, which is FDA-approved for the acute treatment of adult migraine patients with or without aura. Concomitant preventive medication use did not impact the efficacy of ubrogepant and was not associated with additional safety concerns.

Patients with migraine frequently need to take both acute and preventive medications. As ubrogepant is a novel acute treatment, the potential impact of concomitant preventive medication use on the safety and efficacy of ubrogepant is of clinical interest and was investigated in the current study [1].

ACHIEVE trials

In the phase 3 ACHIEVE I and ACHIEVE II trials, adults with a history of migraine with or without aura were included. Participants randomly received placebo or ubrogepant 25, 50, or 100 mg. Co-primary endpoints were (i) the percentage of patients with pain freedom at 2 hours after the initial dose; and (ii) the percentage of patients with freedom from most bothersome symptoms at 2 hours after the initial dose. These endpoints were evaluated in the subgroups with and without self-reported use of concomitant preventive medication.

After completion of the ACHIEVE trials, participants could enrol in a randomised, open-label, 52-week extension trial, in which they received either ubrogepant or placebo. A total of 2,247 participants from ACHIEVE I and II were enrolled in the extension, of whom 417 (18.6%) reported use of concomitant preventive treatments. Data from the 50 mg ubrogepant and placebo groups were pooled in the current analysis.

Safe and efficacious

In the long-term extension trial, no significant differences were observed for pain freedom, freedom from the most bothersome symptom, or pain relief at 2 hours between those who did and did not report use of concomitant preventive medication. However, numerically, a greater therapeutic gain was suggested to trend toward significance for those who reported concomitant preventive medication use compared with those who did not use preventive medication at the same time as ubrogepant use. Percentages of placebo responders for all outcome measures were greater among those not reporting use of preventive medication.

In the long-term extension study, treatment-emergent adverse events (AEs) in any dose group were reported by 74% and 68% of participants who did and did not report concomitant preventive medication use, respectively. Treatment-related AEs were reported in 8% and 11% between those who reported preventive medication use and those who did not, respectively.

A significant, acute treatment effect of ubrogepant was observed in both subgroups. No additional safety concerns were noted with

the use of concomitant preventive medications with ubrogepant. Taken together, the results indicate that ubrogepant is safe and efficacious in patients with migraine who are using concomitant preventive medications.

1. Blumenfeld AM. Efficacy and safety of ubrogepant in participants taking concomitant preventive medication. MTIS 2020 Virtual Symposium, abstract MTV20-DP-037.

6. No new cardiovascular safety concerns with long-term use of lasmiditan

Lasmiditan is a selective 5-HT1F receptor agonist that lacks the vasoconstrictive activity associated with other acute treatments for migraine. In an interim analysis of the long-term GLADIATOR trial, no vasoconstriction-related cardiovascular events occurred during the lasmiditan treatment-emergent period [1].

Previous studies showed that lasmiditan is associated with a low risk of cardiovascular treatment-emergent adverse events (AEs), specifically palpitations and tachycardia. No difference in cardiovascular treatment-emergent AE frequency in subjects with or without cardiovascular risk factors was found.

Patients who previously participated in phase 3, placebo-controlled, single-attack lasmiditan studies could be enrolled in the open-label, randomised GLADIATOR trial. These included patients with cardiovascular risk factors, coronary artery disease, arrhythmia, and uncontrolled hypertension. Participants received 100 or 200 mg lasmiditan either as a single dose within 4 hours after pain onset or as 2 doses within 2-24 hours after pain onset. To assess the long-term cardiovascular safety of lasmiditan for the acute treatment of migraine for up to 1 year, interim results were analysed.

In total, 19,058 migraine attacks were treated. Study median duration was 288 days. A total of 81% of patients had ≥1 cardiovascular risk factor, 0.3% had coronary artery disease, and 35% had low high-density lipoprotein (HDL) cholesterol.

As some cardiovascular events were likely not reported as treatment-emergent or were identified later, cardiovascular AE rates were assessed during 3 different time periods:

- treatment-emergent: <48 hours after the dose;
- intermediate: 48 hours until 1 week after the dose; and
- remote: >1 week after the dose.

No vasoconstriction-related cardiovascular events occurred in the treatment-emergent period. Such events were rarely observed; all were in the remote period, limiting clinical interpretation. Treatment-related cardiovascular events, specifically palpitations and tachycardia, were more frequent in the treatment-emergent period versus intermediate and remote periods. No cardiovascular safety concerns were identified during long-term use of lasmiditan, neither in patients with cardiovascular risk factors nor in elderly patients.

This interim analysis showed that no vasoconstriction-related cardiovascular events occurred during the lasmiditan treatment-emergent period. The cardiovascular safety of lasmiditan was generally consistent with data from single-attack studies.

1. Hochstetler H. Long-term cardiovascular safety of lasmiditan for the acute treatment of migraine for up to one year: interim results of an open-label phase 3 study (GLADIATOR). MTIS Virtual Symposium 2020, abstract MTV20-DP-039.

7. Less medication use and fewer doctor visits with galcanezumab in treatment-resistant migraine

Galcanezumab-treated patients with treatment-resistant migraine had clinically meaningful reductions in days with acute headache medication use. In addition, numerically fewer migraine-specific healthcare-professional visits were observed in patients taking galcanezumab in the CONQUER trial [1].

Treatment-resistant migraine is associated with decreased health-related quality of life and increased economic burden. CONQUER was a 3-month double-blind trial with 462 participants. Participants had treatment-resistant episodic or chronic migraine, and had failed 2-4 prior migraine preventive classes due to lack of effectiveness or unacceptable safety/tolerability. At baseline, mean use of acute headache medication was 12.3 days per month. Of all patients, 44.8% had acute headache medication overuse. The percentage of patients reporting migraine-specific healthcare resource utilisation at baseline in the galcanezumab and placebo groups were respectively:

- 40% and 50% healthcare-professional visits (HCP);
- 6% and 5% emergency-room (ER) visits; and
- 2% hospitalisations in both groups.

In the 3-month double-blind study phase, patients received galcanezumab (n=232; 120 mg/month following an initial 240 mg loading dose) or placebo (n=230). An optional 3-month open-label galcanezumab treatment followed.

Medication use

Acute headache medication use was self-reported daily with an e-diary and paper forms. In the double-blind period, mean reduction from baseline in mean use of acute headache medication was greater for the galcanezumab group (3.9–4.5 days) compared with placebo (0.4–1.0 days) in the first 3 months (P<0.001). During the open-label period, reductions from baseline ranged from -4.7 to -5.3 days; prior placebo group reductions were comparable to those observed in galcanezumab. Statistically

significant reductions were observed as early as month 1. Reductions were greatest for triptans, followed by NSAIDs and aspirin. Use of ergots, opioids, barbiturates, and anti-nausea medication was very low at baseline in this study population.

HCP and ER visits

Healthcare resource utilisation was reported at baseline (retrospectively for the previous 6 months) and at monthly visits. During the double-blind period, reductions from baseline of migraine-specific HCP visits were numerically greater with galcanezumab than placebo: -215.5 versus -155.3 per 100 person-years. During the open-label period, the prior placebo group reductions (-212.9) were similar to galcanezumab (-222.6). Migraine-specific ER visits decreased by two-thirds at month 3 in the galcanezumab group compared to nearly no reduction in the placebo group. For both groups, migraine-specific ER visits were <13 and hospitalisations were <2 per 100 person-years during the double-blind and open-label period.

1. Gómez JP. Effects of galcanezumab on acute medication use and health care resource utilization in patients with treatment-resistant migraine: results from a randomized, double-blind, placebo-controlled clinical trial (CONQUER). MTIS Virtual Symposium 2020, abstract MTV20-DP-035.

8. Real-world evidence reveals physicians' perception of erenumab

The TELESCOPE study provides real-world evidence data for erenumab –a first-in-class calcitonin gene-related peptide (CGRP) receptor inhibitor– in German headache centres. Based on the assessment of treating physicians, erenumab reduced the burden of migraine and increased quality of life (QoL) in >75% of their patients, with onset after the first injection in a majority of the patients.

Erenumab is approved for the preventive treatment of migraine in adults. Real-world data has become increasingly important for providing evidence of treatment effectiveness in clinical practice. TELESCOPE was an online survey, which took place from July until December 2019 in 45 German headache centres, collecting real-world data on erenumab treatment outcome from the physicians' perception in daily clinical routine [1].

This study captured data on the physician's perspective on erenumab treatment regarding therapy decision, patient profiles, and QoL in a broad range of migraine patients. In addition, physicians reported treatment effects and satisfaction with the outcome of 10-20 individual episodic and chronic migraine patients with ≥3 months of erenumab treatment per site. The 45 neurologists documented 542 patients.

The majority of neurologists considered restricted QoL (100% of physicians), monthly migraine days (MMDs; 98.8%), and number of previous prophylactic treatments (88.9%) as important reasons for initiating treatment with CGRP mAbs.

Treating physicians observed a reduced migraine burden and an improved QoL after treatment initiation with erenumab. The response rate and patient satisfaction were both reported as high (82.7% and 79.5%, respectively). According to the treating physicians' reports for all erenumab patients in the last quarter, the following endpoints were reported for erenumab:

- reduced headache intensity (77.4% of patients);
- improved QoL (75.5%); and
- reduced MMDs by half (66%).

Mean change in MMDs was -6.2 (12.1 vs 5.9) and mean change in acute medication days was -6.4 (11.5 vs 5.1). Treating physicians saw a response already after the first injection in 69.4% of patients.

1. Koch M. Real-world evidence data reveals the physicians' perception on erenumab therapy in German headache centers. MTIS 2020 Virtual Symposium, abstract MTV20-DP-044.

9. Early initiation of lasmiditan improves migraine outcomes

The open-label, 12-month, phase 3 GLADIATOR trial evaluated the efficacy of the novel, selective 5-HT1F receptor agonist lasmiditan in treating migraine attacks of mild versus moderate or severe pain severity [1]. Treating migraine attacks at mild pain showed a tendency to relatively better efficacy outcomes, suggesting that earlier dosing is beneficial.

It is recommended to treat acute migraine attacks early, when pain is mild. In 2 phase 3, placebo-controlled, single-attack clinical trials (SAMURAI and SPARTAN), lasmiditan was superior to placebo in treating moderate-to-severe migraine attacks. However, few mild attacks were studied in this phase 3 program.

The current analysis assessed data from the prospective, randomised, open-label, phase 3 trial GLADIATOR. Patients randomly received lasmiditan 100 or 200 mg. Data of almost 18,000 treated migraine attacks in nearly 2,000 patients was evaluated.

Two-thirds of attacks (65.1%) were treated when pain was moderate and one-third (33.3%) when pain was severe. A minority of attacks (1.5%) was treated when pain was mild. Average time from headache onset to treatment administration was 1.3 hours, which was not different for mild, moderate, or severe attacks.

Efficacy measures included the proportion of attacks with 2-hour pain freedom, 2-hour most-bothersome symptom freedom, and 24-hour sustained-pain freedom. In a relatively greater proportion of mild attacks, (sustained) pain freedom and freedom of most bothersome symptoms were achieved during treatment with lasmiditan.
One or more treatment-emergent adverse events (AE) were reported in 16.8% of mild migraine attacks, 14.3% of moderate attacks, and 10.2% of severe attacks. The most frequent treatment-emergent AE was dizziness, which was irrespective of headache intensity across the attacks.

Relatively better efficacy outcomes were observed when lasmiditan treatment was initiated at mild versus moderate or severe pain. Further research is needed to better understand the relationship of lasmiditan outcomes to time of administration in the course of migraine attacks.

1. Peres MF. Lasmiditan efficacy in mild versus moderate or severe migraine headaches. MTIS 2020 Virtual Symposium, abstract MTV20-DP-030.

10. Fremanezumab effective in patients with migraine and comorbid depression

Fremanezumab, a fully humanised monoclonal antibody that selectively targets calcitonin gene-related peptide (CGRP), was effective in patients with migraine and comorbid moderate-to-severe depression and was associated with improvement in depressive symptoms over long-term treatment and in patients with difficult-to-treat migraine [1].

Up to 30% of patients with episodic migraine and up to 57% of patients with chronic migraine have comorbid depression. Patients with migraine and comorbid depression experience reduced quality of life and may experience reduced efficacy with treatment.

FOCUS and HALO studies
In the 12-week, placebo-controlled FOCUS study, patients with episodic or chronic migraine and inadequate response to 2-4 prior migraine preventive medication classes were randomised to:

- quarterly fremanezumab: 675 mg in month 1 and placebo in months 2 and 3;
- monthly fremanezumab: 675 mg in patients with chronic migraine and 225 mg in patients with episodic migraine in month 1, and thereafter 225 mg in months 2 and 3; or
- matched monthly placebo.

In the 52-week HALO study, chronic migraine patients received monthly fremanezumab (225 mg monthly, with a starting dose of 675 mg) or quarterly fremanezumab (675 mg every 3 months).

For both studies, post-hoc subgroup analyses evaluated efficacy in patients with comorbid moderate-to-severe depression based on a Patient Health Questionnaire (PHQ)-9 score ≥10 at baseline. Changes from baseline in average monthly migraine days (MMDs), headache days of at least moderate severity (HDs), and PHQ-9 scores were evaluated in these subgroups.

12-week FOCUS study
In the 12-week FOCUS study, 154/838 (18.4%) randomised patients had moderate-to-severe depression. Mean reductions from baseline in MMDs and HDs were significantly greater with fremanezumab versus placebo at 12 weeks. During that period, fremanezumab treatment was also associated with greater mean reductions from baseline in the PHQ-9 score versus placebo, although those differences were not statistically significant.

52-week HALO study
In the 52-week HALO study, 219/1,103 (19.9%) of chronic migraine patients had moderate-to-severe depression. Compared with baseline, mean MMDs, HDs, and PHQ-9 score were reduced at week 52 after treatment with quarterly and monthly fremanezumab.

Fremanezumab was effective in patients with migraine and comorbid moderate-to-severe depression and was associated with improvement in depressive symptoms over long-term treatment and in patients with difficult-to-treat migraine.

1. Buse DC. Efficacy of fremanezumab in patients with migraine and comorbid depression. MTIS Virtual Symposium 2020, abstract MTV20-DP-065.

11. Long-term onabotulinumtoxinA improves quality of life in migraine

Real-world data from the PREDICT trial demonstrated that long-term onabotulinumtoxinA treatment improved health-related quality of life of patients with chronic migraine. In addition, onabotulinumtoxinA treatment reduced headache days, with high physician and patient satisfaction [1].

Chronic migraine can affect health-related quality of life and daily functioning, resulting in social and economic burden.

PREDICT was a 2-year, multicentre, prospective, observational study in Canadian adults who were naïve to botulinum toxins

for chronic migraine. The aim was to assess real-world long-term effects of onabotulinumtoxinA on quality of life in this patient population. OnabotulinumtoxinA treatment was recommended for injection every 12 weeks, up to 7 treatment cycles.

A total of 184 participants with an average age of 45 years, predominantly female (84.8%), and mostly Caucasian (94.6%) received ≥1 treatment with onabotulinumtoxinA.

At baseline, patients reported 20.9 headache days per month, which decreased over time by:
- -3.5 days at treatment 1;
- -6.5 days at treatment 4; and
- -6.3 days at treatment 7 (all timepoints vs baseline; P<0.0001).

Moderate-to-severe headache days also decreased from 12.9 days per month at baseline by:
- -3.4 days at treatment 1,
- -5.6 days at treatment 4, and
- -4.7 days at treatment 7 (all timepoints vs baseline; P<0.0001).

Significant increases in Migraine-Specific Quality of Life (MSQ) from baseline to treatment 4 (restrictive: 21.5, preventive: 19.5, emotional: 22.9) and at the final visit (restrictive: 21.3, preventive: 19.2, emotional: 27.4) were observed versus baseline. These differences exceeded the threshold for minimal clinically important differences (all P<0.0001).

With respect to safety, 77 patients (41.8%) reported 168 treatment-emergent adverse events (AEs). Of these, 38 treatment-emergent AEs in 22 patients (12.0%) were considered treatment-related. Only 4 patients (2.2%) reported 6 serious treatment-emergent AEs; none were considered treatment-related. No new safety signals were identified.

This real-world data demonstrated that long-term onabotulinumtoxinA treatment for chronic migraine improved health-related quality of life. In addition, onabotulinumtoxinA treatment reduced headache days, with high physician and patient satisfaction.

1. Boudreau G. OnabotulintoxinA treatment improved health-related quality of life in adults with chronic migraine: results from a prospective, observational study (PREDICT). MTIS Virtual Symposium 2020, abstract MTV20-DP-077.

12. Sustained shift in migraine status using galcanezumab

Galcanezumab resulted in a significant shift from chronic to episodic migraine status as well as from high- to low-frequency episodic migraine in patients with treatment-resistant migraine [1]. These sustained shifts, as found in the CONQUER trial, suggest that galcanezumab may result in reduced rates of disability and consequent lowering of the disease burden associated with chronic and high-frequency episodic migraine.

Due to higher disability, comorbidity, and healthcare resource utilisation, chronic migraine and high-frequency episodic migraine have a higher disease burden compared with low-frequency episodic migraine. CONQUER was a phase 3, multicentre, randomised controlled study in adult patients with treatment-resistant chronic or episodic migraine, who failed at 2-4 migraine-preventive medication categories over the past 10 years.

The current analysis aimed to assess the shift from chronic to episodic migraine status and from high- to (very) low-frequency episodic migraine. The following definitions were used:
- high-frequency episodic migraine: 8 to <15 migraine headache days per month with <15 headache days per month;
- low-frequency episodic migraine: 4 to <8 migraine headache days/month; and
- very-low-frequency episodic migraine: <4 migraine headache days/month.

At baseline, a total of 193 patients had chronic migraine and 198 patients had high-frequency episodic migraine. The mean number of headache and migraine headache days per month were 20.9 and 18.7 days, respectively, in chronic migraine patients and 10.8 and 9.3 days, respectively, in episodic migraine patients.

During the double-blind period, a significantly greater proportion of patients receiving galcanezumab versus placebo shifted from chronic to episodic migraine status:
- month 1, 49.0 versus 29.1 (P=0.008);
- month 2, 50.1 versus 25.7 (P=0.001); and
- month 3, 61.9 versus 32.1 (P≤0.001).

By the 3rd month, 39.9% of galcanezumab-treated patients versus 20.5% from the placebo group shifted from high- to low-frequency episodic migraine and sustained that shift at each of the 3 consecutive months of the double-blind period. This was seen in 9.8% versus 0% who shifted from high- to very low-frequency episodic migraine.

By month 6 –which corresponds to month 3 of the open-label extension period– 51.5% of patients in the galcanezumab/galcanezumab versus 46.7% (P=0.540) in the placebo/galcanezumab group had ≥3 consecutive months of shift from chronic to episodic migraine. The percentage of patients who shifted from high- to (very) low-frequency episodic migraine was:
- from high- to low-frequency episodic migraine: 60.2% versus 66.1% (P=0.413); and
- from high- to very low-frequency episodic migraine: 18.2% versus 22.5% (P=0.437).

Among patients with treatment-resistant migraine, treatment with galcanezumab resulted in a significant shift from chronic to episodic migraine status and from high- to low-frequency episodic migraine.

1. Kingston WS. Shift from chronic to episodic migraine status and high- to low-frequency episodic migraine status among patients with treatment-resistant migraine in a phase 3 galcanezumab study. MTIS Virtual Symposium 2020, abstract MTV20-DP-062.

13. Worldwide survey shows substantial burden of migraine

A survey from a large population of patients worldwide shows the substantial burden of migraine. These results indicate that migraine has a substantial negative impact on patients' lives and their familial, social, and professional environment.

As the second leading cause of years lived with disability, migraine is associated with a substantial personal burden for patients, their families, social circles, and employers. The current study aimed to evaluate patient perceptions of the impact and burden of migraine, as well as patient perception of migraine diagnosis and treatment, stigma, and migraine awareness and support [1].

A brief digital survey (~12 minutes) was completed by approximately 12,500 adult patients diagnosed with migraine who self-reported ≥4 days of migraine per month. Data was collected between November and December 2019 across 16 countries in Europe, South America, Asia, and Australia. The majority of patients was 25–54 years of age (74%) and female (73%).

A total of 70% of patients reported progression of migraine symptoms over time. Importantly, only 59% of patients reported to be satisfied with their prescription treatment for migraine. A comparable percentage of participants (61%) was satisfied with the physician treating their migraine.

Patients most commonly reported that migraine impacted the following areas of their lives:
- overall health and wellbeing (69%);
- social life (60%);
- work and career (56%); and
- relationship with family (39%).

Patients reported that the following people in their lives were the most impacted by their migraine:
- partner (68%);
- children (55%);
- parents (22%);
- employer (22%);
- friends (19%); and
- other family members (19%).

Almost half of the patients (46%) reported having hidden their migraine, most commonly from their employer (63%), family (49%), or friends (37%). A proportion of patients (44%) felt that the healthcare community could play the largest role in raising awareness of migraine.

These results indicate that migraine has a substantial negative impact on patients' lives and their familial, social, and professional environment and represents a substantial burden.

1. Mitsikostas DD. Patient perceptions of the impact and burden of migraine: an international survey of 12,545 patients across 16 countries. MTIS Virtual Symposium 2020, abstract MTV20-DP-089.

14. Long-term efficacy and safety of fremanezumab in treatment-resistant migraine

Fremanezumab, a fully-humanised monoclonal antibody that selectively targets calcitonin gene-related peptide (CGRP), demonstrated sustained efficacy up to 6 months and long-term tolerability in patients with episodic or chronic migraine who had an inadequate response to 2-4 classes of prior migraine preventive medications [1].

The double-blind, placebo-controlled, phase 3b FOCUS trial included patients with episodic or chronic migraine, who had an inadequate response to 2-4 prior classes of migraine preventive medications. The study included a 12-week double-blind period and 12-week open-label extension phase. Patients were initially randomised to:
- quarterly fremanezumab: 675 mg in month 1 and placebo in months 2 and 3;
- monthly fremanezumab: 675 mg in patients with chronic migraine and 225 mg in patients with episodic migraine in month 1, and thereafter 225 mg in months 2 and 3; or
- matched monthly placebo.

Study medication was given for 12 weeks. Previous results from the 12-week treatment period demonstrated that fremanezumab was effective and well tolerated.

During the open-label extension of FOCUS, the long-term efficacy and tolerability of fremanezumab were evaluated. Mean changes from baseline in monthly average migraine days during the 12-week open-label extension period was -4.7 in the placebo group, -5.1 in the quarterly fremanezumab group, and -5.5 in the monthly fremanezumab group. Mean changes in monthly average headache days of at least moderate severity were -4.5, -4.8, and -5.2, respectively.

The proportion of patients who achieved ≥50% reduction from baseline in monthly average migraine days was similar in patients continuing fremanezumab (quarterly, 45%; monthly, 46%) and switching from placebo (38%). Furthermore, substantial reductions in disability were observed with fremanezumab treatment, as well as sustained reductions in migraine-related symptoms, such as nausea or vomiting, photophobia, and phonophobia.

During the open-label extension period, regardless of the prior double-blind period treatment, proportions of patient-reported adverse events (AEs) were similar between patient groups. The most common AEs were injection-site related (erythema, induration, and pain). The incidence rates of AEs ranged from 2–5% with placebo and 3–6% with fremanezumab during the double-blind and open-label extension periods. No safety signals were identified.

The FOCUS study showed that fremanezumab demonstrated sustained efficacy up to 6 months and long-term tolerability in patients with episodic or chronic migraine who had an inadequate response to 2–4 classes of prior migraine preventive medications.

1. Ashina M. Long-term efficacy and safety of fremanezumab in patients with episodic and chronic migraine who had inadequate response to 2-4 prior migraine preventive medication classes: open-label extension of the phase 3B FOCUS study. MTIS Virtual Symposium 2020, abstract MTV20-DP-064.

15. Injection-site reactions with galcanezumab are mild and self-limiting

Injection-site reactions, most commonly pain and erythema, may occur with galcanezumab. This finding of the CONQUER trial is consistent with the overall safety profile of galcanezumab. Only one patient discontinued due to injection site erythema. No serious adverse events (AEs) related to injection sites were reported [1].

In previous phase 3 galcanezumab studies, injection-site reactions were the most frequently reported treatment-emergent AEs. In the CONQUER study, galcanezumab-treated patients received a 240 mg loading dose of galcanezumab followed by 120 mg per month. Patients were treated for up to 6 months with galcanezumab: 3 months double-blind period and 3 months during the open-label period. The mean age was 45.8 years, and the majority were female (85.9%) and White (81.7%). At baseline, patients had on average 13.2 migraine headache days per month and failed an average of 3.3 migraine preventive treatments over the past 10 years.

The objective of the current analysis was to characterise injection-site reactions in galcanezumab-treated patients aged 18-75 years with episodic or chronic migraine. Among 457 galcanezumab-treated patients, 10.9% had ≥1 treatment-emergent AE related to injection sites. Injection-site reactions occurring in >1.0% of patients were:

- pain (4.4%);
- erythema (4.2%);
- pruritis (2.0%);
- unspecified injection site reaction (1.8%); and
- induration (1.1%).

There were no serious AEs related to injection sites. Only 1 patient (0.2%) discontinued due to an injection site erythema, which was in the open-label portion of this trial. A severe treatment-emergent AE of injection site pain, as assessed by the injection site follow-up form, was reported by 1 patient. Most treatment-emergent AEs related to injection sites occurred on the day of injection, most often during the injection.

The staff at study locations was encouraged to offer comfort measures, such as cold compress, ice pack, or topical anaesthetic cream to the injection site before or after the injection. These comfort measures were used prior to 1.8% of injections and after 2.4% of injections.

The current analysis showed that injection-site reactions, most commonly pain and erythema, may occur with galcanezumab. These findings are consistent with the overall safety profile of galcanezumab. No serious AEs related to injection sites were reported. Furthermore, these AEs were self-limiting and resolved within the same day.

1. Stauffer VL. Characterization of injection-site reactions from the CONQUER study of galcanezumab in patients with treatment-resistant migraine. MTIS Virtual Symposium 2020, abstract MTV20-DP-053.