Appendix 1
Hovedkarakteristika for inkluderede studier

Studier med erenumab

TABEL 1 STUDIE 295 (CM, TEPPER 2017)

Trial name	**A Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) in Chronic Migraine Prevention**
NCT number	NCT02066415
Objective	To evaluate the effect of erenumab compared to placebo on the change from baseline in the number of monthly migraine days in adults with chronic migraine.
Publications – title, author, journal, year	**Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Tepper S, et al. Lancet Neurol. 2017** Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Ashina M, et al. Cephalalgia 2018 Early onset of efficacy with erenumab in patients with episodic and chronic migraine. Schwedt T, et al. J Headache Pain 2018 Efficacy of erenumab in patients with chronic migraine achieving ≥50% Response: Subgroup analysis of a double-blind, randomized study. Dolezil D, et al. MTIS 2018, 17th biennial Migraine Trust International Symposium, London, UK, 06–09 Sep. 2018. Digital poster MTIS2018-110 Patient-reported outcomes in chronic migraine patients with prior prophylactic treatment failure receiving placebo or erenumab: Subgroup analysis of a pivotal randomized study. Lanteri-Minet M, et al. MTIS 2018, 17th biennial Migraine Trust International Symposium, London, UK, 06–09 Sep. 2018. Digital poster MTIS2018-066 Efficacy of erenumab for the treatment of patients with chronic migraine in presence of medication overuse. Tepper SJ, et al. 18th International Headache Congress, Vancouver, Canada, 07-10 Sep. 2017. Digital poster EO-01-013
Study type and design	This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2 study. trial. Enrolled patients were assigned 3:2:2 to placebo, erenumab 70 mg or erenumab 140 mg monthly for 3 months (12 weeks) via interactive response technology. The investigators, patients and sponsor were masked to treatment assignment. Participants who completed the 12-week double-blind treatment phase of Study 20120295 were eligible to enroll in an open-label extension study (Study 20130255; NCT02174861). The study is completed.
Follow-up time	Patients were followed up for safety for 12 weeks after end of treatment. Results from the 12 week double-blind phase of the study are presented here.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • History of at least 5 attacks of migraine without aura and/or migraine with visual sensory, speech and/or language, retinal or brainstem aura.

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History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine day.
≥ 4 distinct headache episodes, each lasting ≥ 4 hours OR if shorter, associated with use of a triptan or ergot-derivative on the same calendar day based on the eDiary calculations.
Demonstrated at least 80% compliance with the eDiary.

Exclusion Criteria:

History of cluster headache or hemiplegic migraine headache
Unable to differentiate migraine from other headaches
Failed > 3 medication categories due to lack of efficacy for prophylactic treatment of migraine.
Received botulinum toxin in head or neck region within 4 months prior to screening.
Used a prohibited migraine prophylactic medication, device or procedure within 2 months prior to the start of the baseline phase

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<tr><td>Intervention</td><td>656 patients were randomly assigned to placebo (n=281), erenumab 70 mg (n=188) and erenumab 140 mg (n=187). Participants received subcutaneous injections on day 1 and at weeks 4 and 8 by in the double-blind treatment phase.
609 patients continued in the follow up study, where all patients received erenumab by subcutaneous injections. The study is completed.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo (n=160)</th><th>Erenumab 70 mg (n=107)</th></tr>
<tr><td>Age (years) (SD)</td><td>41,4 (10,0)</td><td>42,4 (9,9)</td></tr>
<tr><td>Sex</td><td></td><td></td></tr>
<tr><td>Women</td><td>132 (83%)</td><td>82 (77%)</td></tr>
<tr><td>Men</td><td>28 (18%)</td><td>25 (23%)</td></tr>
<tr><td>Body-mass index (kg/m2)</td><td>25,9 (4,9)</td><td>25,8 (4,9)</td></tr>
<tr><td>Ethnic origin</td><td></td><td></td></tr>
<tr><td>White</td><td>142 (89%)</td><td>103 (96%)</td></tr>
<tr><td>Black</td><td>13 (8%)</td><td>2 (2%)</td></tr>
<tr><td>Asian</td><td>2 (1%)</td><td>1 (1%)</td></tr>
<tr><td>Other*</td><td>3 (2%)</td><td>1 (1%)</td></tr>
<tr><td>Region</td><td></td><td></td></tr>
<tr><td>North America</td><td>85 (53%)</td><td>58 (54%)</td></tr>
<tr><td>Europe</td><td>75 (47%)</td><td>49 (46%)</td></tr>
<tr><td>Age at migraine onset (years) (SD)</td><td>21,2 (10,9)</td><td>21,7 (9,9)</td></tr>
<tr><td>Disease duration (years)</td><td>20,7 (11,5)</td><td>21,5 (11,7)</td></tr>
<tr><td>Previous preventive therapy</td><td></td><td></td></tr>
<tr><td>Naive</td><td>94 (59%)</td><td>60 (56%)</td></tr>
<tr><td>Previous therapies</td><td>66 (41%)</td><td>47 (44%)</td></tr>
<tr><td>Treatment failure†</td><td>60 (38%)</td><td>34 (32%)</td></tr>
<tr><td>Other</td><td>6 (4%)</td><td>13 (12%)</td></tr>
<tr><td>Monthly migraine days</td><td>8,8 (2,7)</td><td>8,6 (2,5)</td></tr>
<tr><td>Monthly migraine attacks</td><td>5,4 (1,5)</td><td>5,4 (1,5)</td></tr>
<tr><td colspan="3">Data are mean (SD) or number (%). Data are for all randomised patients in the full analysis set. Some percentages do not total 100% because of rounding. *Other includes native Hawaiian or other Pacific Islander, multiple ethnic origins, or other. †Treatment failure includes discontinuation because of lack of efficacy or adverse reaction.</td></tr>
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Primary and secondary endpoints	Primary Endpoint: • Change From Baseline in Monthly Migraine Days Secondary Endpoints: • Percentage of Participants With at Least a 50% Reduction in Monthly Migraine Days From Baseline • Change From Baseline in Monthly Acute Migraine-specific Medication Treatment Days • Change From Baseline in Cumulative Monthly Headache Hours • Number of Participants With Adverse Events • Number of Participants Who Developed Antibodies to Erenumab
Method of analysis	The randomisation analysis set included all patients who were randomly assigned to treatment or placebo in the study. The efficacy analysis set included patients in the randomisation analysis set who received at least one dose of investigational product and completed at least one post-baseline monthly electronic diary measurement. For all analyses, patients were analysed according to the randomised treatment. A sequential testing procedure, specifically the hierarchical gate-keeping procedures and Hochberg method, was used to maintain the two-sided study-wise type I error at 0.05 for the two erenumab doses and the primary and secondary endpoints. The test for erenumab superiority in the primary endpoint (change from baseline in mean monthly migraine days) was tested separately at a significance level of 0.04 for the erenumab 70 mg group and 0.01 for the erenumab 140 mg group. If the primary endpoint was significantly different from placebo at each dose level, the secondary endpoints were to be tested separately using the Hochberg method at the same significance levels. If the secondary endpoints were significantly different for an erenumab treatment group compared with placebo, the corresponding significance level was to be carried over to the hypothesis testing of the primary endpoint for the other erenumab treatment group, if it was not significantly different from placebo under the original significance level (0.04 for the 70 mg group and 0.01 for the 140 mg group). If the secondary endpoints were negatively correlated, the Holm method was used for the corresponding tests rather than the Hochberg method. For the primary endpoint at week 12, the least-squares mean at each timepoint was calculated with a linear mixed effects model including treatment group, baseline monthly migraine days, stratification factors (region [North America vs Europe] and medication overuse [presence vs absence]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The continuous secondary endpoints were analysed with the same method as for the primary endpoint. We reported the least-squares mean change from baseline for each treatment group, treatment difference compared with placebo, 95% CI, and p values for pairwise comparison. For the 50% responder secondary endpoint, we used a stratified Cochran-Mantel-Haenszel test after the missing data were imputed as non-response. We reported adjusted odds ratios (OR) compared with placebo, 95% CI, and p values. The safety analysis set included all randomly assigned patients who received at least one dose of investigational product. For all analyses, patients were analyzed according to the randomized treatment.
Subgroup analyses	Pre-specified (failed ≥1 and failed ≥2) and post-hoc (failed ≥ 3) subgroup analyses were conducted, based on number of prior treatment failure(s). Effect (change in monthly migraine days, MMD, and MSMD and ≥50% and ≥75 responder rates) in patients who had failed ≥1, ≥2) or ≥3 prior treatments due to lack of efficacy and/or tolerability was compared to that of the overall study population. For continuous endpoints, adjusted analyses utilized a generalized linear mixed model, which included treatment, visit, treatment by visit interaction, the two stratification factors (region and medication overuse status) and baseline value as covariates, and assumed a first-order autoregressive covariance structure. Observed data were used in analyses without imputation for missing data. For dichotomous endpoints, odds ratios were estimated

	from a stratified Cochran- Mantel-Haenszel test after imputation of missing data as nonresponse. The main study was not designed or powered to compare differences in efficacy between subgroups. A post-hoc analysis was conducted, based on responders versus non-responders (response defined as ≥50% reduction in MMD). Effect (MMDs, migraine-specific medication treatment days (MSMD), the Headache Impact Test (HIT-6™) scores, Migraine Disability Assessment (MIDAS) scores, and Migraine-Specific Questionnaire (MSQ) scores) was compared between responders and non-responders. Furthermore, a subgroup analysis was performed in patients with medication overuse at baseline. Data were presented in congres abstracts.

TABEL 2 STRIVE (EM, GOADSBY 2017)

Trial name	**Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) in Migraine Prevention (STRIVE)**
NCT number	NCT02456740
Objective	The primary objective of the study was to evaluate the effect of erenumab compared to placebo on the change from baseline in monthly migraine days.
Publications – title, author, journal, year	**A Controlled Trial of Erenumab for Episodic Migraine, Goadsby PJ et al. NEJM 2017** Migraine-related disability, impact, and health-related quality of life among patients with episodic migraine receiving preventive treatment with erenumab. Buse DC, et al. Cephalalgia 2018 Early onset of efficacy with erenumab in patients with episodic and chronic migraine. Schwedt T, et al. Journal of Headache and Pain 2018 Efficacy Outcomes in Responder and Non-responder Patients With Episodic Migraine Treated Preventively With Erenumab in the STRIVE Study. Brössner G, et al. 2018, 17th biennial Migraine Trust International Symposium, London, UK, 06–09 Sep. Digital poster. Link til abstract: MTIS2018-074 side 136
Study type and design	This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trial. Enrolled patients were assigned 1:1:1 to placebo or erenumab 70 mg or 140 mg monthly for 6 months (24 weeks) by centrally executed randomization with the use of an interactive voice or Web response system. Randomization was stratified by region and according to the use of migraine-preventive medication. The investigators, patients and sponsor were masked to treatment assignment. Following the double-blind treatment, patients were re-randomized 1:1 to continue treatment with either 70 mg or 140 mg erenumab every 4 weeks until week 48 with actual dose blinded. The study is completed.
Follow-up time	Following completion of the open-treatment phase of the study (28 weeks), patients were followed up for safety for 12 weeks. Results from the double-blind phase of the study are presented here.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • History of migraine (with or without aura) for ≥ 12 months prior to screening according to the International Headache Society (IHS) International Classification of Headache Disorders (ICHD-3) classification • Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening and during baseline

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Headache frequency: < 15 headache days per month on average across the 3 months prior to screening and baseline
Demonstrated at least 80% compliance with the eDiary.

Exclusion Criteria:

Older than 50 years of age at migraine onset
History of cluster headache or hemiplegic migraine headache
Unable to differentiate migraine from other headache
No therapeutic response with > 2 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial
Used a prohibited medication, device, or procedure within 2 months prior to the start of the baseline phase or during the baseline phase
Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase. If only 1 prophylactic medication is used, the dose must be stable within 2 months prior to the start of the baseline phase and throughout the study

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<tr><td>Intervention</td><td>A total of 955 patients underwent randomization (317 to the 70 mg erenumab group, 319 to the 140 mg erenumab group, and 319 to the placebo group), and 858 patients (89.8%) completed the 6-month double-blind treatment phase.
845 patients entered the open-treatment phase and were re-randomized 1:1 to either 70 mg erenumab (n=421) and 140 mg erenumab (n=424). Treatment was given by subcutaneous injection every 4 weeks.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristics</th><th>Placebo (N=319)</th><th>Erenumab, 70 mg (N=317)</th><th>Erenumab, 140 mg (N=319)</th></tr>
<tr><td>Age (range) – yr</td><td>41,3±11,2 (18-65)</td><td>41,1±11,3(18-63)</td><td>40,4±11,1(19-65)</td></tr>
<tr><td>Female sex – no. (%)</td><td>274 (85,9)</td><td>268 (84,5)</td><td>272 (85,3)</td></tr>
<tr><td>Geographic region – no. (%)</td><td></td><td></td><td></td></tr>
<tr><td>North America</td><td>158 (49,5)</td><td>150 (50,2)</td><td>160 (50,2)</td></tr>
<tr><td>Other†</td><td>161 (50,5)</td><td>158 (49,8)</td><td>159 (49,8)</td></tr>
<tr><td>Age at migraine onset – yr</td><td>21,2 ±10,2</td><td>21,4±11,0</td><td>20,7±9,9</td></tr>
<tr><td>Acute headache medication use – no. (%)</td><td></td><td></td><td></td></tr>
<tr><td>Migraine-specific‡</td><td>191 (59.9)</td><td>179 (56.5)</td><td>192 (60.2)</td></tr>
<tr><td>Non-migraine-specific</td><td>244 (76.5)</td><td>243 (76.7)</td><td>256 (80.3)</td></tr>
<tr><td>Migraine-preventive medication use – no. (%)§</td><td></td><td></td><td></td></tr>
<tr><td>No current or previous use</td><td>178 (55.8)</td><td>175 (55.2)</td><td>187 (58.6)</td></tr>
<tr><td>Previous use only</td><td>131 (41.1)</td><td>133 (42.0)</td><td>124 (38.9)</td></tr>
<tr><td>Current use¶</td><td>10 (3.1)</td><td>9 (2.8)</td><td>8 (2.5)</td></tr>
<tr><td>History of preventive treatment failure – no. (%)‖</td><td>127 (39.8)</td><td>127 (40.1)</td><td>116 (36.4)</td></tr>
<tr><td>Lack of efficacy</td><td>90 (28.2)</td><td>89 (28.1)</td><td>83 (26.0)</td></tr>
<tr><td>Unacceptable side Effects</td><td>78 (24.5)</td><td>65 (20.5)</td><td>62 (19.4)</td></tr>
<tr><td>Assessment of migraine during baseline phase</td><td></td><td></td><td></td></tr>
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	Migraine days per Month	8,2±2,5	8,3±2,5	8,3±2,5
	Headache days per month	9,3±2,6	9,1±2,6	9,3±2,5
	Migraine attacks per Month	5,1±1,5	5,2±1,5	5,2±1,4
	Days of use of acute migraine-specific medication per month‡	3,4±3,4	3,2±3,4	3,4±3,5
	Monthly MPFID everyday-activities score**	13,7±9,1	14,0±8,9	13,1±8,3
	Monthly MPFID physical-impairment score**	12,2±9,4	12,6±9,6	12,0±9,0
	Plus–minus values are means ±SD. Data in the table are for the full analysis set (all patients who underwent randomization). There were no significant between-group differences in baseline characteristics. Percentages may not total 100 because of rounding. † Other includes Austria, Belgium, the Czech Republic, Finland, Germany, the Netherlands, Poland, Slovakia, Sweden, Turkey, and the United Kingdom. ‡ During the baseline phase, 557 patients (58.5%) used triptan-based medications and 4 patients (0.4%) used ergotamine-based medications (safety analysis set). § The summary of treatment with migraine-preventive medications is based on actual data collected rather than on randomization stratification. ¶ The use of one stable migraine-preventive medication was allowed, in accordance with a late protocol amendment. Three patients (0.3%) used topiramate; 7 (0.7%) used beta blockers; 7 (0.7%) used tricyclic antidepressants; 4 (0.4%) used serotonin–norepinephrine reuptake inhibitors; 1 (0.1%) used flunarizine, verapamil, or lomerizine; 2 (0.2%) used lisinopril or candesartan; and 3 (0.3%) used other medications. ‖ Treatment-failure categories were not mutually exclusive; a patient could be included in both categories. ** The Migraine Physical Function Impact Diary (MPFID) contains a 7-item everyday-activities domain and a 5-item physical-impairment domain, as well as a global question to assess the overall effect of migraines. The scores were averaged over a period of 1 month and then linearly transformed to a 100-point scale, with higher scores representing greater migraine burden on functioning.			
Primary and secondary endpoints	<u>Primary Endpoint:</u> • Change From Baseline in Mean Monthly Migraine Days to the Last 3 Months of the Double-blind Treatment Period <u>Secondary Endpoints:</u> • Percentage of Participants With at Least a 50% Reduction From Baseline in Monthly Migraine Days in the Last 3 Months of the Double-blind Treatment Phase (50% response rate) • Change From Baseline in Monthly Acute Migraine-specific Medication Treatment Days to the Last 3 Months of the Double-blind Treatment Period • Change From Baseline in Mean Monthly Average Physical Impairment Domain Score Measured by MPFID in the Last 3 Months of the Double-blind Treatment Phase • Change From Baseline in Mean Monthly Average Impact on Everyday Activities Score Measured by MPFID in the Last 3 Months of the Double-blind Treatment Phase			

Method of analysis	The full analysis set in the final protocol included all the patients who underwent randomization. The efficacy end points are reported with the use of the following efficacy analysis set: patients who received at least one dose of erenumab or placebo and had at least one postbaseline measurement for migraine days per month during the double-blind treatment phase, analyzed according to randomly assigned trial regimen. The efficacy analysis set meets the criteria for a full analysis set. The primary end point and continuous secondary end points were analyzed with the use of a linear mixed-effects model without any imputation of with multiple imputation under missing-at-random and missing-not-at-random assumptions. For the secondary end point of a 50% or greater reduction in mean migraine days per month, a stratified Cochran–Mantel–Haenszel test was used after imputation of missing data as nonresponse. Sensitivity analyses for this end point included a generalized linear mixed-effects model without any imputation of missing data. The significance of the between-group differences with regard to the primary and secondary end points was determined after multiplicity adjustment with a prespecified hierarchical gatekeeping procedure and Hochberg-based testing procedures to maintain the two-sided, study-wise, type I error rate at an alpha level of 0.05. The primary end point was tested separately for each erenumab dose at an alpha level of 0.04 for 70 mg and of 0.01 for 140 mg. First-tier and second-tier secondary end points were then tested sequentially. The safety analysis set included all the patients who underwent randomization and received at least one dose of erenumab or placebo, analyzed according to randomly assigned trial regimen unless the dose received throughout the double-blind treatment phase differed from the one that had been randomly assigned
Subgroup analyses	A post-hoc subgroup analysis was conducted, based on number of prior treatment failure(s). Effect (change in monthly migraine days, MMD, and ≥50% responder rate) in patients who had failed ≥1 (n=369) or ≥2 (n=161) prior treatments due to lack of efficacy and/or tolerability was compared to that of the overall study population. P values for subgroup analysis are descriptive and not adjusted for multiple comparisons. Furthermore, subgroup analyses were performed in patients achieving or not achieving response, defined by ≥50% reduction from baseline in MMD. Data were presented in abstracts.

TABEL 3 ARISE (EM, DODICK 2018)

Trial name	**Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) Compared to Placebo in Migraine Prevention (ARISE).**
NCT number	NCT02483585
Objective	To evaluate the effect of erenumab compared to placebo on the change from baseline in monthly migraine days, in adults with episodic migraine.
Publications – title, author, journal, year	**ARISE: A Phase 3 randomized trial of erenumab for episodic migraine, Dodick et al, Cephalalgia, 2018.**
Study type and design	This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trial. Enrolled patients were assigned 1:1 to placebo or erenumab 70 mg monthly for 3 months (12 weeks) by centrally executed randomization with the use of an interactive response system. The investigators, patients and sponsor were masked to treatment assignment. Following the double-blind treatment, all patients continued on 70 mg until week 36. The study is completed.
Follow-up time	A safety follow-up visit was completed 12 weeks after last dose of investigational product. Results from the double-blind phase of the study are presented here.

<table>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion Criteria:
• History of migraines (with or without aura) for ≥ 12 months
• Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening
• Headache (i.e., migraine and non-migraine headache) frequency: < 15 headache days per month on average across the 3 months prior to screening
• Demonstrated compliance with the eDiary
Exclusion Criteria:
• Older than 50 years of age at migraine onset.
• History of cluster headache or hemiplegic migraine headache.
• Unable to differentiate migraine from other headaches
• No therapeutic response with > 2 categories for prophylactic treatment of migraine after an adequate therapeutic trial.
• Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase. If only 1 prophylactic medication is used, the dose must be stable within 2 months prior to the start of the baseline phase and throughout the study
• Used a prohibited medication, device, or procedure within 2 months prior to the start of the baseline phase or during the baseline phase.
• Received botulinum toxin
• Anticipated to require any excluded medication, device, or procedure during the study.
• Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain).
• History of major psychiatric disorder.
• History of seizure disorder or other significant neurological conditions other than migraine.
• Human immunodeficiency virus (HIV) infection by history.
• Myocardial infarction (MI), stroke, transient ischemic attack (TIA), unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening.
• The subject is at risk of self-harm or harm to others. Previously randomized into an AMG 334 study.
• Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures.</td></tr>
<tr><td>Intervention</td><td>A total of 577 patients underwent randomization (286 to 70 mg erenumab and 291 to placebo), and 546 patients (95%) completed the 3-month double-blind treatment phase. 538 patients entered the open-treatment phase where all patients were treated with 70 mg erenumab. Treatment was given by subcutaneous injection every 4 weeks.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo
n=291</th><th>Erenumab 70 mg
n=286</th></tr>
<tr><td>Age, years</td><td>42±12</td><td>42±11</td></tr>
<tr><td>Female sex, no (%)</td><td>247 (84,9)</td><td>245 (85,7)</td></tr>
<tr><td>White race, no (%)†</td><td>259 (89,0)</td><td>259 (90,6)</td></tr>
<tr><td>Weight, kg</td><td>76±19</td><td>77±19</td></tr>
<tr><td>Body-mass index‡</td><td>27,4±6,1</td><td>27,4±6,3</td></tr>
<tr><td>Age at onset of migraine, years</td><td>22±11</td><td>21±10</td></tr>
<tr><td>Duration of disease, years</td><td>20±12</td><td>22±13</td></tr>
<tr><td>History of aura (yes), no (%)</td><td>144 (49,5)</td><td>146 (51,0)</td></tr>
<tr><td>Prior prophylactic therapy (yes), no (%)</td><td></td><td></td></tr>
<tr><td>Naïve</td><td>150 (51,5)</td><td>144 (50,3)</td></tr>
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	Prior use only	125 (43,0)	123 (43,0)
	Current use	16 (5,5)	19 (6,6)
	Acute headache medication use no (%)		
	no (%)	283 (97,3)	280 (97,9)
	Migraine-specific	174 (59,8)	178 (62,2)
	Non-migraine-specific	236 (81,1)	224 (78,3)
	History of any prior preventive treatment use, no (%)	132 (45,4)	134 (46,9)
	History of any prior preventive treatment failure§	115 (87,1)	117 (87,3)
	Baseline period		
	Monthly migraine days	8,4±2,6	8,1±2,7
	Monthly migraine attacks	5,2±1,5	5,1±1,5
	Monthly headache days	9,3±2,7	9,1±2,7
	Monthly acute migraine specific medication days	3,4±3,6	3,7±3,6
	Monthly MPFID impact on everyday activities score¶	13,2±8,9	12,6±8,6
	Monthly MPFID physical impairment score¶	11,5±9,2	10,8±9,1
	*Plus-minus values are mean standard deviation. †Race was self-reported. ‡The body-mass index is the weight in kilograms divided by the square of the height in meters. §Failure due to lack of efficacy or poor tolerability. ¶MPFID scores range from 0–100, with higher scores indicating greater impact. ¶MPFID: Migraine Physical Function Impact Diary.		
Primary and secondary endpoints	Primary Endpoint: • Change From Baseline in Monthly Migraine Days at Week 12 Secondary Endpoints: • Percentage of Participants With at Least a 50% Reduction From Baseline in Monthly Migraine Days at Week 12 (≥50% responders) • Change From Baseline in Monthly Acute Migraine-specific Medication Treatment Days at Week 12 • Percentage of Participants With at Least a 5-point Reduction From Baseline in Average Impact on Everyday Activities Domain Score Measured by MPFID at Week 12 • Percentage of Participants With at Least a 5-Point Reduction From Baseline in Average Impact on Physical Impairment Domain Score Measured by MPFID at Week 12 • Number of Participants With Adverse Events • Number of Participants Who Developed Antibodies to erenumab		
Method of analysis	The full analysis set included all patients who were randomized in the study. The efficacy analysis set included all patients who received at least one dose of randomized treatment and had at least one change from baseline measurement for MMD during the double-blind treatment phase, analyzed according to randomized treatment. Continuous variables were analyzed using a linear mixed effects model including treatment group, baseline value, stratification factors (region and preventive migraine		

	medication status), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. Dichotomous variables were analyzed using a stratified Cochran-Mantel-Haenszel test and using non-responder imputation, in which missing data was assumed to be non-response. The safety-analysis set, which included all randomized patients who received one or more doses of investigational product, was used to analyze adverse event incidence rates according to randomized treatment group unless a patient received an incorrect dose throughout the entire double-blind treatment phase.
Subgroup analyses	None.

TABEL 4 LIBERTY (EM, REUTER 2018)

Trial name	**A Study Evaluating the Effectiveness of AMG 334 Injection in Preventing Migraines in Adults Having Failed Other Therapies (LIBERTY)**
NCT number	NCT03096834
Objective	The purpose of this study is to determine if AMG 334 is effective in treating migraines in patients who have unsuccessfully failed other preventive migraine treatments.
Publications – title, author, journal, year	**Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomized, double-blind, placebo-controlled, phase 3b study. Reuter U et al. Lancet 2018** Effect of erenumab on patient-reported outcomes in patients with episodic migraine with 2-4 prior preventive treatment failures: Results from the LIBERTY study. Goadsby PJ, MTIS 2018, 17th biennial Migraine Trust International Symposium, London, UK, 06–09 Sep. Digital poster MTIS2018-078
Study type and design	This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trial. Enrolled patients were assigned 1:1 to placebo or erenumab 140 mg monthly for 3 months (12 weeks) via interactive response technology. The investigators, patients and sponsor were masked to treatment assignment. Following the double-blind treatment, all patients are continuing on open treatment of 156 weeks. The study is ongoing..
Follow-up time	After end of treatment patients are followed up for 12 weeks. Data from the double blind phase of the study are presented here.
Population (inclusion and exclusion criteria)	Inclusion Criteria: •Documented history of migraine in the 12 months prior to screen •4-14 days per month of migraine symptoms •>=80% diary compliance during the Baseline period •Failure of previous migraine prophylactic treatments (2, 3 or 4 treatments) Exclusion Criteria: •>50 years old at migraine onset •Pregnant or nursing •History of cluster or hemiplegic headache •Evidence of seizure or psychiatric disorder •Score of 19 or higher on BDI •Active chronic pain syndrome •Cardiac or hepatic disease

Intervention	A total of 246 patients underwent randomization (121 to 140 mg erenumab and 125 to placebo). Patients who completed the double-blinded treatment phase, could enter an open-label treatment phase. Treatment was given by subcutaneous injection every 4 weeks.
Baseline characteristics	

	Erenumab group (n=121)	Placebo group (n=125)
Age, years	44,6 (10,5)	44,2 (10,6)
Sex		
Male	24 (20%)	22 (18%)
Female	97 (80%)	103 (82%)
Race		
White	112 (93%)	115 (92%)
Non-white	9 (7%)	10 (8%)
Ethnicity*		
Hispanic or Latino	9 (7%)	10 (8%)
Non Hispanic or Latino	104 (86%)	109 (87%)
Weight, kg	72,8 (14,4)	72,1 (16,2)
Body-mass index, kg/m^2	25,0 (4,2)	24,9 (5,1)
Number of previous unsuccessful preventive migraine treatments†		
Two	43 (36%)	52 (42%)
Three	44 (36%)	49 (39%)
Four	33 (27%)	23 (18%)
Previous unsuccessful preventive drugs‡		
Amitriptyline	49 (40%)	63 (50%)
Candesartan	26 (21%)	26 (21%)
Flunarizine	32 (26%)	38 (30%)
Lisinopril	2 (2%)	0
Metoprolol	46 (38%)	48 (38%)
Propranolol	60 (50%)	51 (41%)
Topiramate	105 (87%)	104 (83%)
Valproate	43 (36%)	25 (20%)
Venlafazine	6 (5%)	7 (5%)
Others§	9 (7%)	13 (10%)
Monthly migraine days	9,2 (2,6)	9,3 (2,7)
Aura		
Present	42 (35%)	45 (36%)
Not present	79 (65%)	80 (64%)
Monthly headache days	10,1 (2,8)	10,1 (2,7)
Randomisation by strata		
4-7 monthly migraine days	36 (30%)	38 (30%)
8-14 monthly migraine days	85 (70%)	87 (70%)
Acute headache medication use¶		
Migraine-specific	102 (84%)	109 (87%)
Only non-migraine specific	13 (11%)	14 (11%)
Monthly acute migraine-specific medication days	4,8 (2,9)	4,4 (2,8)

Data are mean (SD) or n (%). *Ethnicity data were missing for eight patients in the erenumab group and 11 in the placebo group. †One patient in each group had unsuccessfully used fewer than two preventive treatments. ‡Does not include patients considered unsiitable for treatment. §Includes cinnarizine, indoramin, nadolol, oxetorone, and pizotifen. ¶Six patients in the erenumab group and two in the placebo group did not use acute headache medication at baseline.

Primary and secondary endpoints	Primary Endpoint: • Percentage of patients with a 50% response in the reduction of Monthly Migraine Days (MMD) at month 3 Secondary Endpoint: • Change in the number of monthly migraine days (MMDs) from baseline to month 3 • Change in the Migraine Physical Function Impact Diary (MPFID) "impact on everyday activities" domain score from baseline to month 3 • Change in the MPFID "physical impairment" domain score from baseline to month 3 • Change in the number of monthly acute migraine-specific medication treatment days • Percentage of patients with a 75% response • Percentage of patients with a 100% response
Method of analysis	The full analysis set, which was used for efficacy analyses, included all randomly assigned patients who started their study medication, completed at least one post-baseline monthly migraine day measurement in the double-blind treatment phase, and were analyzed based on the pre-planned randomized treatment. For the primary endpoint, the Cochran-Mantel-Haenszel test was used to measure the association between 50% responder rate and treatment group; analysis was stratified by migraine frequency, with a one-sided significance level of 0·025 (0·05 two-sided). ORs, 95% CIs, and two-sided p values are reported. Patients with missing data for monthly migraine days at month 3 of the double-blind treatment phase were imputed as non-responders. The continuous change from baseline efficacy endpoints (least-square means) was analyzed with a linear mixed-effects model, including treatment group, baseline value, stratification factors, study visit, and the interaction of treatment group with study visit, without any imputation for missing data. The dichotomous secondary efficacy endpoints derived from corresponding continuous endpoints were analyzed with the stratified Cochran-Mantel-Haenszel test after imputation of missing data as non-response. Estimates (treatment difference or OR) of erenumab compared with placebo with associated 95% CI and p values are reported. The safety analysis set included all randomly assigned patients who received at least one dose of study drug. Analyses were based on actual treatment received.
Subgroup analyses	A post-hoc subanalysis was conducted, based on number of prior treatment failure(s). Effect (≥50% responder rate, ≥75% responder rate, change in monthly migraine days, MMD, and in HR QOL parameters) was compared between erenumab and placebo in patients who had failed ≤2 (n=43 for erenumab and n=52 for placebo) or >2 (n=76 for erenumab and n=72 for placebo) prior treatments due to lack of efficacy and/or tolerability. Dichotomous variables were analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (4-7 vs 8-14 migraine days at Baseline) after missing data are imputed as non-response (NRI). Continuous variables were analyzed using a linear mixed effects model which included treatment group, baseline value, stratification factor, subgroup factor, the interaction of treatment group with subgroup, scheduled visit, and the interaction of treatment group with scheduled visit.

TABEL 5 STUDY 178, PHASE 2 (EM, SUN 2016)

Trial name	**A Phase 2 Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) in Migraine Prevention**
NCT number	NCT01952574
Objective	A phase 2 study to evaluate the effect of erenumab compared to placebo on the change from baseline in monthly migraine days in participants with episodic migraine.
Publications – title, author, journal, year	**Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial, Sun et al., Lancet Neurol, 2016.** Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study, Ashina et al., Neurology, 2017.
Study type and design	A multi-center, randomized, double-blind, placebo-controlled. Phase 2 study. Patients were randomly assigned in a 3:2:2:2 to monthly subcutaneous placebo, AMG 334 7 mg, AMG 334 21 mg, or AMG 334 70 mg using a sponsor-generated randomization sequence centrally executed by an interactive voice response or interactive web response system. The investigators, patients and sponsor were masked to treatment assignment. An analysis of the double-blind phase of the study was performed with a data cutoff date of 25 September 2014. After completing the 12 week study, patients could enroll in an open-label extension study (OLE) and continue treatment with AMG 332 70 mg. A pre-planned interim analysis was conducted when all participants had completed the 1-year open label follow-up. This OLE study is currently ongoing.
Follow-up time	Median exposure of erenumab was 575 days (range 28-882 days) at the time of the pre-planned interim analysis of the OLE study.
Population (inclusion and exclusion criteria)	Inclusion Criteria: • History of migraine for more than12 months prior to screening • Migraine frequency: ≥ 4 and ≤ 14 migraine days per month in each of the 3 months prior to screening and during baseline phase • Headache frequency: < 15 headache days per month (with > 50% of the headache days being migraine days) in each of the 3 months prior to screening and during baseline phase • Demonstrated at least 80% compliance with the eDiary during baseline phase Exclusion Criteria: • Older than 50 years of age at migraine onset • History of cluster headache or basilar or hemiplegic migraine headache • Unable to differentiate migraine from other headaches • No therapeutic response with > 2 of the following eight medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. Medication categories are: ○ Category 1: Divalproex sodium, sodium valproate ○ Category 2: Topiramate ○ Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol) ○ Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline) ○ Category 5: Venlafaxine, desvenlafaxine, duloxetine, milnacipran ○ Category 6: Flunarizine, verapamil ○ Category 7: Lisinopril, candesartan ○ Category 8: Butterbur, feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)

<table>
<tr><td></td><td>

- Overuse of acute migraine medications in any month during the 3 months prior to screening or during screening

</td></tr>
<tr><td>Intervention</td><td>483 patients were randomly assigned to placebo (n=160), AMG 334 7 mg (n=108), AMG 334 21 mg (n=108), or AMG 334 70 mg (n=107).
Participants received subcutaneous injections on day 1 and at weeks 4 and 8 by in the double-blind treatment phase.
383 patients continued in the follow up study, where all patients received 70 mg erenumab (AMG 334) by subcutaneous injections every 4 weeks for up to 5 years.
225 patients are currently still on treatment (as of 15 November 2018)</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo (n=160)</th><th>Erenumab 70 mg (n=107)</th></tr>
<tr><td>Age (years)</td><td>41,4 (10,0)</td><td>42,6 (9,9)</td></tr>
<tr><td>Sex</td><td></td><td></td></tr>
<tr><td>Women</td><td>132 (83%)</td><td>82 (77%)</td></tr>
<tr><td>Men</td><td>28 (18%)</td><td>25 (23%)</td></tr>
<tr><td>Body-mass index (kg/m^2)</td><td>25,9 (4,9)</td><td>25,8 (4,9)</td></tr>
<tr><td>Ethnic origin</td><td></td><td></td></tr>
<tr><td>White</td><td>142 (89%)</td><td>103 (96%)</td></tr>
<tr><td>Black</td><td>13 (8%)</td><td>2 (2%)</td></tr>
<tr><td>Asian</td><td>2 (1%)</td><td>1 (1%)</td></tr>
<tr><td>Other*</td><td>3 (2%)</td><td>1 (1%)</td></tr>
<tr><td>Region</td><td></td><td></td></tr>
<tr><td>North America</td><td>85 (53%)</td><td>58 (54%)</td></tr>
<tr><td>Europe</td><td>75 (47%)</td><td>49 (46%)</td></tr>
<tr><td>Age at migraine onset (years)</td><td>21,2 (10,9)</td><td>21,7 (9,9)</td></tr>
<tr><td>Disease duration (years)</td><td>20,7 (11,5)</td><td>21,5 (11,7)</td></tr>
<tr><td>Previous preventive therapy</td><td></td><td></td></tr>
<tr><td>Naive</td><td>94 (59%)</td><td>60 (56%)</td></tr>
<tr><td>Previous therapies</td><td>66 (41%)</td><td>47 (44%)</td></tr>
<tr><td>Treatment failure†</td><td>60 (38%)</td><td>34 (32%)</td></tr>
<tr><td>Other</td><td>6 (4%)</td><td>13 (12%)</td></tr>
<tr><td>Monthly migraine days</td><td>8,8 (2,7)</td><td>9,6 (2,5)</td></tr>
<tr><td>Monthly migraine attacks</td><td>5,4 (1,5)</td><td>5,4 (1,5)</td></tr>
<tr><td colspan="3">Data are mean (SD) or number (%). Data are for all randomised patients in the full analysis set. Some percentages do not total 100% because of rounding. *Other includes native Hawaiian or other Pacifi c Islander, multiple ethnic origins, or other. †Treatment failure includes discontinuation because of lack of effi cacy or adverse reaction.</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td><u>Primary Endpoint:</u>

- Change From Baseline in Monthly Migraine Days at Week 12

<u>Secondary Endpoints:</u>

- Percentage of Participants With at Least a 50% Reduction From Baseline in Monthly Migraine Days at Week 12 (50% responder rate)
- Change From Baseline in Monthly Migraine Attacks at Week 12

Endpoints for OLE study:

- Change in monthly migraine days
- Achievement of ≥50%, ≥70% and 100% reduction in monthly migraine days

</td></tr>
<tr><td>Method of analysis</td><td>Patients in the full analysis set were analyzed according to randomized treatment, regardless of the treatment received. The efficacy analyses were done using a subset of the full analysis set, defined as all randomly assigned patients who received at least one dose of investigational product during double-blind treatment and had at least 4 migraine days during the baseline period.
For the primary endpoint and the secondary endpoint of change in monthly migraine attacks at week 12, the least squares mean at each time point was calculated from a generalized linear mixed-effect model for repeated measures. The primary endpoint</td></tr>
</table>

	was adjusted for multiple comparisons using a sequential testing procedure, which allowed for the testing of each of the AMG 334 doses against placebo from the highest to lowest dose groups to control the study-wise type I error. Statistical testing was only done for the next lower dose group if there was a significant difference between the higher dose group and placebo. For the secondary endpoint of the proportions of patients with at least a 50% reduction in monthly migraine days, adjusted odds ratios (ORs) were calculated from a generalized linear mixed model for repeated measures. The stratification factor of region (North America vs Europe) and baseline value for the corresponding endpoint were included in the model as covariates for all efficacy analyses and the pairwise comparison of treatment differences, and linear trend in the treatment groups were tested from the model using observed data without any missing data imputation. The study wise type I error was not controlled for the secondary endpoints in this phase 2 study, and thus for these endpoints nominal p values were reported without adjustment for multiple testing. The safety analysis set included all randomly assigned patients who received at least one dose of investigational product and were analyzed based on actual treatment received.
Subgroup analyses	N/A

Studier med komparatorer

Betablokkere (metoprolol/propranolol)

TABEL 6 DIENER 2004

Trial name	**Topiramate in migraine prophylaxis Results from a placebo-controlled trial with propranolol as an active control**
NCT number	Not stated in publication
Objective	To evaluate the efficacy and safety of two doses of topiramate (100 and 200 mg/d) vs placebo for migraine prophylaxis, with immediate-release propranolol (160 mg/d) as an active control.
Publications – title, author, journal, year	**Topiramate in migraine prophylaxis - Results from a placebo-controlled trial with propranolol as an active control, Diener HC, et al. J Neurol 2004**
Study type and design	A randomized, double-blind, parallel-group, multicenter trial conducted in 13 countries. The trial included four phases: baseline, core double-blind, blinded extension, and taper/exit. The study is completed.
Follow-up time	26 week core double blind phase, blinded extension phase for up to 12 months. Data from the core double blind phase are presented.
Population (inclusion and exclusion criteria)	Inclusion: • Age 12 and 65 years • Established history of migraine with or without aura for at least one year, according to International Headache Society (IHS) criteria • 3 to 12 migraine headaches (periods) • No more than 15 headache days (including migraine days) Exclusion: • Patients must not have failed more than two previous adequate regimens of prophylactic medications for recurrent migraine episodes.

<table>
<tr><td></td><td>

- History of asthma, bradyarrhythmia, uncontrolled diabetes, and any other limitations to the use of beta-blockers

</td></tr>
<tr><td>Intervention</td><td>

A total of 575 subjects were randomized; of these, 568 contributed efficacy data after randomization and were included in the intent-to-treat cohort for the efficacy analyses; 570 contributed to the safety analyses . The trial included four phases: baseline, core double-blind, blinded extension, and taper/exit.
The baseline phase consisted of a 14-day washout period during which any prophylactic migraine medications were discontinued and a 28-day prospective baseline period during which subjects completed daily records of headache activity/symptoms and rescue medication usage.

During the titration period, the initial daily dose of TPM (25 mg/d) or PROP (20 mg/d) was titrated upwards in weekly increments of 25 mg/d (TPM) or 20 mg/d (PROP) until achieving either the assigned dose or maximum tolerated dose, whichever was lower. After completing titration, subjects continued receiving the stable dose of study medication until the end of the maintenance period.
Only subjects who completed the entire 26-week core double-blind phase were eligible to enter the blinded extension phase. All other subjects were discontinued from the trial.
Subjects who were eligible to enter the blinded extension phase received the same dose of study medication that was achieved during the core double-blind phase. During this phase, subjects continued to receive study medication for up to 12 months after the last subject was randomized, or until they were withdrawn.
At the end of treatment, regardless of the phase, study medication was tapered over period of up to 7 weeks.

</td></tr>
<tr><td>Baseline characteristics</td><td>

<table>
<tr><th></th><th>Placebo
N=143</th><th>Topiramate
100 mg/d
N=139</th><th>Topiramate
200 mg/d
N=143</th><th>Propranolol
160 mg/d
N=143</th></tr>
<tr><td>Age, mean</td><td>40.3</td><td>39.8</td><td>42.6</td><td>40.6</td></tr>
<tr><td>Male</td><td>34</td><td>29</td><td>28</td><td>24</td></tr>
<tr><td>Female</td><td>109</td><td>110</td><td>115</td><td>119</td></tr>
<tr><td>Mean body weight, kg</td><td>71.2</td><td>70.8</td><td>70.2</td><td>68.9</td></tr>
<tr><td>MMD (mean monthly migraine days)</td><td>6.1</td><td>5.8</td><td>6.2</td><td>6.1</td></tr>
<tr><td>Monthly days of rescue medication</td><td>5.3</td><td>5.0</td><td>5.5</td><td>5.4</td></tr>
<tr><td>Migraine attack rate</td><td>4.1</td><td>3.6</td><td>4.0</td><td>3.9</td></tr>
</table>

</td></tr>
<tr><td>Primary and secondary endpoints</td><td>

Primary endpoints:

- The change in mean monthly migraine frequency from the baseline phase relative to the double-blind treatment phase.
- Comparison of topiramate with placebo with respect to change in monthly (28-day) migraine frequency averaged over the entire core double-blind phase vs the frequency at baseline.

Secondary Endpoints:

- Change in number of migraine days per month
- Change in the average monthly rate of rescue medication use in days
- Responder rate (response defined as at least a 50% reduction in average monthly migraine frequency)

</td></tr>
</table>

	• Onset of action (defined as the earliest monthly time point when a statistically significant difference in the primary efficacy endpoint between the placebo and topiramate treatment groups was detected and consistently.
Method of analysis	Efficacy analyses were conducted on the intent-to-treat cohort, which was defined as those randomized patients who had at least 1 post-baseline efficacy assessment. The primary efficacy endpoint is the change in average monthly migraine frequency (based on migraine periods). Efficacy endpoints were analyzed using a linear model with baseline value as a covariate and analysis center and treatment as factors. The least squares means, which are means adjusting for the variables in the statistical model, were used to compare treatment groups.
Subgroup analyses	N/A

TABEL 7 DIENER 1996

Trial name	**Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol**
NCT number	Not stated in publication
Objective	To test the hypothesis that cyclandelate is more effective than placebo in the prophylaxis of migraine using the minimal effective dosage of 1200 mg/day, and as a secondary hypothesis, investigate the comparative efficacy with propranolol (120 mg/day).
Publications – title, author, journal, year	**Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. Diener HC et al, Cephalalgia:16:441-7,1996**
Study type and design	A randomized, parallel-group, double-blind multicenter study. The study is completed. Patients who fulfilled the entry criteria entered a 4-week baseline period without any prophylactic treatment. Those who recorded 2-10 attacks on their migraine headache diaries during the baseline period qualified for randomization (randomization ratio =3 : 2 : 3) to cyclandelate, placebo or propranolol. To avoid early withdrawals due to initial side effects, treatment started with a 2-week run-in period at a dosage of 400 mg tid cyclandelate placebo or 40 mg tid propranolol. This was followed by a 12-week period of active prophylaxis at a dosage of 400 mg tid cyclandelate, placebo or 40 mg tid propranolol. At the end of the study and prior to breaking the code, the attending physician evaluated all migraine headache diaries, blinded to the number and total duration of migraine attacks at baseline and in the last 4 weeks of prophylaxis. This diary database was used for primary analysis
Follow-up time	20 weeks (primary analysis)
Population (inclusion and exclusion criteria)	Inclusion criteria: • Patients between the age 18 and 60 years • Male or female • Migraine with and/or without aura according to the IHS criteria • Migraine history of at least 12 months' duration • A mean number of 2-10 migraine attacks per month within the last 3 months prior to the study Exclusion criteria: • Pregnant or lactating women • Psychiatric disorders

<table>
<tr><td></td><td>

Concomitant non-migraine headaches 23 times per month within the last 3 months
Intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks preceding the tria
Specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder)
Intake of drugs to treat migraine attacks>12 days/month. Prior to study entry and at the end of the treatment

</td></tr>
<tr><td>Intervention</td><td>A total of 214 ITT patients in 17 centres were randomized after completing the baseline period, 81 patients (37.9%) were treated with cyclandelate, 55 (25.7%) with placebo and 78 (36.4%) with propranolol. Forty patients had to be excluded from the ITT analysis for various reasons and 174 patients (cyclandelate n=67, placebo n =39, propranolol n =68) remained for the PI' analysis.
The study had a 2-week run-in period at a dosage of 400 mg tid cyclandelate placebo or 40 mg tid propranolol. This was followed by a 12-week period of active prophylaxis at a dosage of 400 mg tid cyclandelate, placebo or 40 mg tid propranolol.
The study ended with a 2-week run-out period to avoid early recurrence of migraine, using the same dosages as in the run-in period. Additional medication to treat acute migraine attacks was allowed for up to 12 days/month for the duration of the study, including the baseline period. Patients were required to come for a check-up visit at the end of the baseline
period and at weeks 10, 14, 18 and 20.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Cyclandelate N=81</td><td>Propranolol N=78</td><td>Placebo N=55</td></tr>
<tr><td>Mean Age</td><td>39</td><td>40</td><td>39</td></tr>
<tr><td>Woman</td><td>66</td><td>60</td><td>41</td></tr>
<tr><td>Men</td><td>15</td><td>18</td><td>14</td></tr>
<tr><td>No of patients with acute migrane medication
- Analgesics/antirheumatics
- Specific migraine drugs</td><td>
55
46</td><td>
51
49</td><td>
36
32</td></tr>
<tr><td>Mean number of attacks/4 weeks
≤ 4 attacks</td><td>4
3</td><td>4
3</td><td>4
3</td></tr>
<tr><td>Additional medication under attacks
-Never
- Sometimes
-Every Day</td><td>
6
23
52</td><td>
3
24
51</td><td>
2
15
38</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoints:
- "Rate of responders", i.e. patients with ≥50% reduction in the number of migraine attacks
- Mean "migraine duration" in hours.

Secondary endpoints:
- The efficacy of propranolol versus placebo and equivalent efficacy of cylandelate compared to propranolol.
- change in intensity of headache
- Intake of analgesics or migraine drugs
- Number of working days lost due to migraine,</td></tr>
</table>

	- frequency and severity of adverse events.
Method of analysis	Not applicable since the endpoints for this application are not the same as those analyzed in the publication
Subgroup analyses	N/A

TABEL 8 STOVNER 2014

Trial name	**A Comparative study of candesartan vs. propranolol for migraine prophylaxis: A randomized triple-blind, placebo-controlled study**
NCT number	NCT008846663
Objective	To determine whether the effect of candesartan for migraine prevention, shown in one previous study, could be confirmed in a new study, and if so, whether the effect was comparable to that of proparanolol (non-inferiority analysis), and whether adverse events were different.
Publications – title, author, journal, year	**A Comparative study of candesartan vs. propranolol for migraine prophylaxis: A randomized triple-blind, placebo-controlled study, Stovner etal, Cephalalgia 2014**
Study type and design	The study was designed as a placebo-controlled double-blind, double cross-over trial, with a four-week open baseline period, and three 12-week treatment periods with a four-week wash-out period between each treatment period.
Follow-up time	12 weeks
Population (inclusion and exclusion criteria)	Inclusion criteria: I • age 18–65 years • migraine with or without aura or or chronic migraine • ≥ 2 migraine attacks per month during the last three months beforeinclusion, and ≥ 2 migraine attacks during the four week baseline period documented in the diary • Debut of migraine ≥ 1 year prior to inclusion, and before the age of 50 Exclusion criteria: • interval headache not distinguishable from migraine • chronic tension-type or other headache occurring on ≥ 15 days/month • pregnancy, nursing or not using contraceptives in fertile women • heart conduction block or other significant abnormality on electrocardiogram; heart rate <54 (sitting, after three minutes' rest) asthma or diabetes; decreased hepatic or renal function • hypersensitivity to active substances • history of angioneurotic oedema • psychiatric illness • use of daily migraine prophylactics less than four weeks prior to start of study • having tried ≥ 3 prophylactic drugs against migraine during the last 10 years • previous use of PRO or CAN in adequate doses (≥ 16 mg or ≥160 mg) and duration (≥6 weeks) • previous discontinuation of CAN or any beta-blocker because of AEs; • current use of antihypertensive medication • use of rizatriptan 10 mg tablet; regular ergotamines or opioids use • consistent failure to respond to any acute migraine medication • alcohol or illicit drug dependence

Intervention	In a randomized, triple-blind, double cross-over study, 72 adult patients with episodic or chronic migraine went through three 12-week treatment periods on either candesartan 16 mg, propranolol slow-release 160 mg, or placebo.
Baseline characteristics	<table><tr><td></td><td>Whole population N=72</td></tr><tr><td>Age in years (SD)</td><td>31 (11)</td></tr><tr><td>Females, n (%)</td><td>59 (82)</td></tr><tr><td>Mean duration of headache history in years (SD)</td><td>19 (11)</td></tr><tr><td>Mean number of attacks per month (SD)</td><td>4.8 (3.6)</td></tr><tr><td>Mean number of migraine days per four weeks (SD)</td><td>4.9 (3.0)</td></tr></table>
Primary and secondary endpoints	Primary endpoint: Migraine days per 4 weeks. Secondary endpoints: • Headache days per four weeks • Headache hours per four weeks • headache intensity • doses of analgesics per four weeks
Method of analysis	All statistical tests were between treatment periods, and did not include baseline data. MMD was tested with Wilcoxon's paired signed rank test. Subjects fulfilling mITT-requirements were included in the main analysis.
Subgroup analyses	N/A

Lisinopril

Der er ikke identificeret relevante studier med lisinopril.

Candesartancilexetil

TABEL 9 STOVNER 2014 (SE UNDER PROPRANOLOL).

TABEL 10 TRONVIK 2003

Trial name	**Prophylactic treatment of Migraine with an Angiotensin II Receptor blocker**
NCT number	Not stated in publication
Objective	To determine whether treatment with the angiotensin II receptor blocker Candesartan is effective as a migraine-prophylactic drug
Publications – title, author, journal, year	**Prophylactic treatment of Migraine with an Angiotensin II Receptor blocker. A Randomized Controlled Trial. Tronvik E, et al. JAMA 2003**
Study type and design	Randomized double blind, placebo-controlled cross-over study
Follow-up time	12 weeks
Population (inclusion and exclusion criteria)	Inclusion criteria: • Age 18-65 • migraine occurrence with/without aura according to IHS criteria.at a rate of 2-6 attacks pr. Month • Debut 1 year prior randomization, before age 50 Exclusion criteria: • Headache not distinguishable from migraine

<table>
<tr><td></td><td>

- Pregnancy/nursing
- Hepatic impairment
- History of angioneurotic edema, psychiatric illnes

Use of daily migraine prophylactic 12 weeks prior to study.
</td></tr>
<tr><td>Intervention</td><td>Placebo run in period of 4 weeks, followed by two 12-week treatment periods separated by 4 weeks of placebo washout. 30 patients were randomized to assign to receive 16 mg candesartan/day in the first treatment period, followed by 1 placebo tablet/day in the second period. Remaining 30 received placebo followed by candesartan.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>IIT population
N=57</td></tr>
<tr><td>Women, n</td><td>45</td></tr>
<tr><td>Age, women. Years (SD)</td><td>42 (11)</td></tr>
<tr><td>Age, men. Years (SD)</td><td>48 (13)</td></tr>
<tr><td></td><td>8.4 (3.9)</td></tr>
<tr><td>Migraine days per 4 weeks (SD)</td><td>5.7 (2.9)</td></tr>
<tr><td>Headache days per 4 weeks (SD)</td><td>8.4 (3.9)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary: Number of days with headache per 4 weeks
Secondary:

- Hours with headache per 4 weeks
- days with migraine per 4 weeks
- hours with migraine per 4 weeks

headache severity index, level of disability, dosis of triptans, doses of analgetics, acceptability of treatment, days of sick leave, and QOL in the SF 36 questionnaire</td></tr>
<tr><td>Method of analysis</td><td>All statistical tests were between treatment periods, and did not include baseline data. MMD was tested with Wilcoxon’s paired signed rank test. The analysis was based on the ITT analysis set.</td></tr>
<tr><td>Subgroup analyses</td><td>N/A</td></tr>
</table>

Topiramat

TABEL 11 BRANDES 2004

Trial name	**Topiramate for migraine prevention a randomized controlled trial**
NCT number	Not stated in publication
Objective	To assess the efficacy and safety of topiramate for migraine prevention in a large controlled trial
Publications – title, author, journal, year	**Topiramate for migraine prevention a randomized controlled trial. Brandes JL, et al. JAMA 2004**
Study type and design	A 26-week, multicenter, randomized, double blind, placebo-controlled study conducted during outpatient treatment. The study is completed.
Follow-up time	26 weeks (primary analysis)
Population (inclusion and exclusion criteria)	Inclusion: • Established history of migraine with or without aura for at least 6 month before screening. • Age 12 to 65 years • Between 3 and 12 migraines but not more than 15 headache days per 28 days during the prospective baseline phase. A headache day was defined as a

<table>
<tr><td></td><td>calendar day during which the patient experienced headache for at least 30 minutes.
• Woman were required to be post menopausal, surgically incapable of bearing children, or practicing a medically acceptable method of birth control for at least 1 month before study entry.
Exclusion:
• Headache other than migraine, episodic tension or sinus headache
• Failed to respond to more than 2 adequate previous regimens of migraine-preventive medications
• Onset of migraine occurred after age 50 years
• Overuse of analgesics or specific agents for acute treatments of migraine episodes
• Continued use of following medication during the study: Beta blockers, tricyclic antidepressiva, antiepileptics,calcium channel blockers, monoamine oxidase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) daily, magnesium supplements at high doses (eg, 600 mg/d), riboflavin at high doses (eg, 100 mg/d), corticosteroids, local anesthetics, botulinum toxin, or herbal preparations such as feverfew or St John’s wort. Nonpharmacologic prophylactic approaches started at least 1 month before the prospective baseline phase could be continued throughout the study.
• Patients with a history of nephrolithiasis
• Patients who had participated in a topiramate study or had taken topiramate for more than 2 weeks.
• Patients who had received an experimental drug or used an experimental device within 30 days of screening also were</td></tr>
<tr><td>Intervention</td><td>After evaluation for inclusion and exclusion criteria, eligible patients entered a washout period of up to 14 days, during which any migraine-preventive medications were tapered. This period was followed by a prospective baseline phase of 28 days, during which headache and medication record information completed by patients was reviewed.
During the baseline phase, patients were permitted to take rescue medication.
Patients who completed the prospective baseline phase and met all entry criteria were randomized to 1 of 4 treatment groups according to a computer- generated randomization schedule: placebo or topiramate at 50 mg/d, 100 mg/d, or 200 mg/d. Randomization was balanced by using permuted blocks of 4 and stratified by center. Patients and clinicians were blinded to study medication.
Patients randomized to topiramate started at a dose of 25 mg/d; the daily dose was increased by 25 mg weekly (for a total of 8 weeks) until patients reached either their assigned dose or maximum tolerated dose, whichever was less. Patients then continued receiving that amount for 18 weeks in 2 divided doses (morning and evening). Patients who completed the 18-week maintenance period or who exited the double-blind phase for lack of efficacy were eligible to enter an open-label extension after a blinded transition period of 7 weeks. In the event of tolerability problems, patients were given the opportunity to reduce study medication by a maximum of 2 dose levels during the entire 26- week treatment phase.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo N=114</th><th>Topiramate 50 mg/d N=117</th><th>Topiramate 100 mg/d N=120</th><th>Topiramate 200 mg/d N=117</th></tr>
<tr><td>Age</td><td>38.3</td><td>39.0</td><td>39.1</td><td>39.1</td></tr>
<tr><td>Men</td><td>20</td><td>20</td><td>11</td><td>11</td></tr>
<tr><td>Woman</td><td>94</td><td>97</td><td>109</td><td>106</td></tr>
</table>
</td></tr>
</table>

	Monthly migraine frequency	5.6	5.4	5.8	5.1
	MMD, Monthly migraine days	6.7	6.4	6.9	6.1
	Monthly rescue medication use,d	5.8	5.7	6.2	5.8
	Migraine duration, days	2.6	2.3	2.6	2.1
	Monthly migraine severity	2.2	2.3	2.2	2.3
Primary and secondary endpoints	The primary efficacy measure: • Change from baseline in mean monthly migraine frequency. Secondary efficacy measures: • Responder rate (proportion of patients with ≥50% reduction in monthly migraine frequency) • Reductions in mean number of monthly migraine days • Severity, duration, and days a month requiring rescue medication • Adverse events. • The month of onset of preventive treatment action was assessed.				
Method of analysis	Efficacy analyses were conducted on the intent-to-treat population, which was defined as randomized patients who had at least 1 post baseline efficacy assessment. For patients discontinuing early, the mean monthly migraine frequency during the entire double-blind treatment phase and the cumulative monthly periods were computed according to the migraine periods observed before discontinuation. The primary and secondary continuous efficacy measure was assessed with a linear model, with treatment and analysis center as factors and the baseline value as a covariate. Estimates of treatment effects are based on the treatments' least squares means, which are the means adjusted for the variables in the statistical model. Analyses were done with SAS (version 6.12; SAS Institute Inc, Cary, NC) at a significance level of .05.				
Subgroup analyses	N/A				

TABEL 12 DIENER 2007

Trial name	**Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study**
NCT number	Not stated in publication
Objective	The aim of this study was to evaluate the efficacy and tolerability of topiramate for the prevention of chronic migraine.
Publications – title, author, journal, year	**Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study, Diener HC et al., Cephalalgia 2007**
Study type and design	A randomized, double blind, placebo controlled, parallel group, multi-center trial of topiramate for the prevention of headache in patients with chronic migraine with and without medication overuse.

<table>
<tr><td></td><td>A prospective, 4-week baseline phase was followed by a 16-week, double-blind treatment phase, which consisted of a 4-week titration and 12-week treatment period. The taper-down phase lasted up to 7 weeks.
Computer randomization was used prior to study start.
The study is completed.</td></tr>
<tr><td>Follow-up time</td><td>16 weeks (4 weeks titration og 12 weeks treatment)</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria:
Patients 18–65 years of age
Diagnosis of chronic migraine that satisfied the second edition of The International Classification of Headache Disorders criteria of ≥15 migraine headache days per 4 weeks, at least during the last 3 months prior to trial entry
An established migraine history for at least 1 year
Patients could be included if they had ≥12 migraine days in the prospective baseline period
Exclusion criteria
Patients were excluded if they presented with another primary chronic headache or any secondary headache except medication overuse headache (MOH).
Patients who experienced onset of migraine after age 50
Patients who were severely depressed (Beck Depression Inventory (BDI) scale score≥30)
Patients taking antidepressants unless the antidepressant was used at a stable dose for at least 3 months prior to trial entry and the patient intended to continue the antidepressant throughout the trial.
Patients taking any migraine prophylactic drug unless the drug had been used for at least 3 months (at a stable dose for at least 1 month) prior to trial entry and was continued throughout the trial.
Prior history of topiramate use
Use of other anticonvulsants within 30 days of trial entry
Use of a carbonic anhydrase inhibitor.</td></tr>
<tr><td>Intervention</td><td>The total ITT population (n = 59) consisted of 32 patients receiving topiramate and 27 patients receiving placebo.
Topiramate and placebo, identical tablets produced by the manufacturer, were titrated to the target dose of 100 mg/day (50 mg twice daily) at a rate of 25 mg/week. The dose of topiramate was required to remain stable during the last 4 weeks of the double-blind phase at the time when data for the primary end-point were collected. Randomization was stratified according to presence or absence of medication overuse in the baseline period.

Patients were allowed to take acute rescue medications such as analgesics, non-steroidal antiinflammatory drugs (NSAIDs), triptans, opioids and ergot derivatives during any phase in the trial as usual.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo
N=27</th><th>Topiramate
N=32</th></tr>
<tr><td>Age, years</td><td>44.4</td><td>47.8</td></tr>
<tr><td>Gender (F/M), %</td><td>74/26</td><td>75/25</td></tr>
<tr><td>MMD (Mean number of migraine days/month)</td><td>16.4</td><td>15.5</td></tr>
<tr><td>Patients with and without medication overuse</td><td>23/4</td><td>23/9</td></tr>
<tr><td>Beck depression Inventory</td><td>13.4</td><td>9.0</td></tr>
</table>
</td></tr>
</table>

Primary and secondary endpoints	Primary endpoints • Change in the mean number of monthly migraine days from baseline to the last 4 weeks of the double-blind phase. A migraine day was defined as a calendar day with symptoms of a migraine attack lasting at least 30 min. Secondary endpoints • Change in monthly migraine days from baseline to the entire double-blind phase • The percentage of patients with ≥50% reduction in the mean number of monthly migraine days (categorical responder rates) • Change from baseline in the mean number of days of acute medication intake • Patient satisfaction ratings with the efficacy and tolerability of the treatment they received • Mean changes from baseline on the Migraine-Specific Quality of Life Questionnaire (MSQ, Version 2.1) • Mean change from baseline on Headache Impact Test (HIT-6) • Mean change from baseline on Migraine Disability Assessment (MIDAS) questionnaire scores.
Method of analysis	Efficacy analyses were performed on the intent-to-treat (ITT) population, which consisted of all randomized patients who received at least one post baseline efficacy evaluation. Differences between treatment groups (topiramate vs. placebo) were compared using the Wilcoxon two-sample test for ordinal/continuous data, and interpreted at the 5% significance level (two-tailed comparison). Fisher's exact test was used to assess differences between nominal data. For patients who dropped out, data from the last visit available were carried forward only for the end-point visit. Data have not been corrected for multiple comparisons
Subgroup analyses	N/A

TABEL 13 DIENER 2004 (SE UNDER PROPRANOLOL).

TABEL 14 LIPTON 2011

Trial name	**The topiramate INTREPID study**
NCT number	Not stated in publication
Objective	Evaluate whether topiramate prevents development of chronic daily headache (CDH, ≥15 headache days/month) in adults with high-frequency episodic migraine (HFEM, 9 - 14 migraine headache days /month). Secondary objective, to assess the efficacy of topiramate as preventive migraine treatment in this population.
Publications – title, author, journal, year	**Topiramate intervention to prevent transformation of episodic migraine: The topiramate INTREPID study. Lipton RB et al. Cephalgia 2011**
Study type and design	Multicenter, RCT, double blind, placebo controlled study comparing topiramate 100 mg/day and placebo for 26 weeks.
Follow-up time	Primary analysis after 26 weeks double blind treatment.
Population (inclusion and exclusion criteria)	Inclusion criteria: • adults, 18-65 years/age • established history of migraine headache for 12 min. month before screening

<table>
<tr><td></td><td>Exclusion criteria:
Previously failed more than two adequate trials of medication from different migraine prophylactics.
Any migraine medication use six weeks before visit 2.</td></tr>
<tr><td>Intervention</td><td>Patients were randomized to topiramate 100 mg/day (n=188) or placebo (n=197)</td></tr>
<tr><td>Baseline characteristics</td><td><table>
<tr><td>Efficacy evaluable analysis set</td><td>Topiramate N= 159</td><td>Placebo N=171</td></tr>
<tr><td>Age, years (SD)</td><td>39.6 (10.6)</td><td>40.9 (11.2</td></tr>
<tr><td>Female, n (%)</td><td>138 (86.8)</td><td>156 (91.2)</td></tr>
<tr><td>BMI, kg/m2 (SD)</td><td>30,2 (8.5)</td><td>30,4 8.4)</td></tr>
<tr><td>Headache days per 28 days, n (SD)</td><td>13.0 (2.5)</td><td>13.1 (2.6)</td></tr>
<tr><td>Migraine days per 28 days, n (SD)</td><td>11.6 (2.0)</td><td>11.8 (2.2)</td></tr>
<tr><td>Days of acute headache medication use per 28 days</td><td>8.6 (3.2)</td><td>8.6 (3.5)</td></tr>
</table></td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary: Onset of new-onset of CDH at month 6.
Secondary:
Number of migraine days per 28 days
Number of headache days per 28 days</td></tr>
<tr><td>Method of analysis</td><td>The analyses were based on the ITT analysis set which comprised randomized subjects who received at least 1 dose of study drug and at least 1 post-dose efficacy assessment. Secondary efficacy variables were analyzed using an analysis of variance (ANCOVA) model with treatment, center and baseline value as explanatory variables.</td></tr>
<tr><td>Subgroup analyses</td><td>N/A</td></tr>
</table>

TABEL 15 MEI 2004

Trial name	**Topiramate in migraine prophylaxis: a Randomized double blind versus placebo study**
NCT number	Not stated in publication
Objective	To evaluate the efficacy and tolerability of topiramate, given at the dose of 100 mg/day in the prophylactic treatment of migraine
Publications – title, author, journal, year	**Topiramate in migraine prophylaxis: a Randomized double blind versus placebo study, Mei et al., Neurol Sci, 2004**
Study type and design	Randomized double blind versus placebo
Follow-up time	16 weeks double blind treatment
Population (inclusion and exclusion criteria)	Inclusion criteria: • Diagnosed Migraine with/without aura • Frequency of crises ranging from 2 to 6 in a month Exclusion criteria: • Renal pathologies • women taking oral contraceptives • potential fertile sexual active women not using contraceptives • those who presented episodes indistinguishable from migraine without aura in the intercritical period • those who had commenced any form of prophylactic therapy in the 2 months preceding trial.

<table>
<tr><td>Intervention</td><td>Patients were randomized using a computer-generated random number scheme to topiramate (n=58) or placebo (n=57).
TPM started at a dose of 25 mg/day, increased by 25 mg weekly until 100 mg (first 4 weeks). Patients continued on 100 mg for 12 weeks, then decreased by 25 mg weekly.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td>Patients completing the study</td><td>Topiramate N=35</td><td>Placebo N=37</td></tr>
<tr><td>Age, years (SD)</td><td>39.,74 (12.02)</td><td>38.70 (11.04)</td></tr>
<tr><td>Gender</td><td></td><td></td></tr>
<tr><td>Female, n</td><td>19</td><td>20</td></tr>
<tr><td>Male, n</td><td>16</td><td>17</td></tr>
<tr><td>Frequencies of crises, n (SD)</td><td>5.26 (1.29)</td><td>5.76 (0.98)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary efficacy measures: reduction of mean migraine headache frequency compared to baseline and proportion of subjects responding to treatment (≥50% reduction in migraine headache frequency)
Secondary:
Effect of the quantity of symptomatic drugs taken during the period of therapy
Numbers of days of disability</td></tr>
<tr><td>Method of analysis</td><td>Not applicable since the endpoints for this application are not the same as those analysed in the publication</td></tr>
<tr><td>Subgroup analyses</td><td>N/A</td></tr>
</table>

TABEL 16 SILBERSTEIN 2007

Trial name	**Efficacy and safety of Topiramate for the treatment of Chronic Migraine: A randomized, Double blind, Placebo Controlled Trial**
NCT number	Not stated in publication
Objective	To evaluate the efficacy and tolerability of topiramate, given at the dose of 100 mg/day compared with placebo
Publications – title, author, journal, year	**Efficacy and safety of Topiramate for the treatment of Chronic Migraine: A randomized, Double blind, Placebo Controlled Trial, Silberstein, Headache, 2007**
Study type and design	Randomized, double-blind, placebo-controlled, parallel-group, multicenter trial with topiramate versus placebo. The study consisted of a pretreatment phase lasting up to 56 days, a double-blind treatment phase lasting 16 weeks and a taper/exit period lasting up to 2 weeks
Follow-up time	Data from the 16 weeks double-blind treatment phase are presented.
Population (inclusion and exclusion criteria)	Inclusion criteria: - Adults with a diagnosis of CM according to Silberstein/Lipton criteria for transformed migraine - At least 15-headache days per 28 days - A MIDAS score of at least 11 at visit 1. Exclusion criteria: - Previously failed more than 2 adequate migraine preventive medication (incl. topiramate) - History of cluster headache - Migraine onset after age 50 - Overuse of acute medication - History of hepatic disorder, progressive neurologic disorder, pregnancy or nursing

<table>
<tr><td>Intervention</td><td>Eligible patients were randomized and assigned sequentially 1:1 to either topiramate or placebo at the end of the prospective baseline period. 165 received topiramate and 163 received placebo</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td>IIT population</td><td>Topiramate N=153</td><td>Placebo N=153</td></tr>
<tr><td>Age, years. Mean (SD)</td><td>37.8 (12.38)</td><td>37.6 (11.80)</td></tr>
<tr><td>Gender</td><td></td><td></td></tr>
<tr><td>Female</td><td>83.7 %</td><td>86.9%</td></tr>
<tr><td>Race</td><td></td><td></td></tr>
<tr><td>Caucasian</td><td>82.4%</td><td>78.45%</td></tr>
<tr><td>Black</td><td>12.4%</td><td>17.0%</td></tr>
<tr><td>Weight, kg. Mean (SD)</td><td>80.0 (20.3)</td><td>76.8 (22.2)</td></tr>
<tr><td>Monthly rate of migraine days</td><td>15.2 (6.4)</td><td>15.1 (5.8)</td></tr>
<tr><td>Monthly rate of total headache days</td><td>20.4 (4.8)</td><td>20.8 (4.6)</td></tr>
<tr><td>Number of days per month of acute medication use</td><td>11.9 (7.0)</td><td>11.4 (6.6)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoint: Change in mean monthly migraine frequency pr. 28 days, during the entire double blind phase, compared with the prospective baseline period in the ITT population, which included all randomized subjects who received ≥ 1 dose of study drug and provided ≥ post baseline efficacy evaluation.
Secondary endpoints:
median percent reduction in monthly migraine frequency
proportion of responders (those with≥ 50, ≥75%, or 100% reduction in monthly migraine frequency).</td></tr>
<tr><td>Method of analysis</td><td>Statistical Analysis
Analyses of treatment effectiveness were performed on the intent-to-treat population (full analysis set), which consisted of all randomized subjects who received at least 1 dose of study medication and provided at least 1 post randomization efficacy evaluation. The mean monthly rate of migraine/migrainous headache days and migraine headache days were analyzed using an analysis of covariance (ANCOVA) with treatment and center were qualitative design factors, and baseline rate as a covariate.</td></tr>
<tr><td>Subgroup analyses</td><td>N/A</td></tr>
</table>

TABEL 17 SILBERSTEIN 2006

Trial name	**Efficacy and Tolerability of Topiratmate 200 mg/d in the prevention of migraine with /without aura in adults: A Randomized Placebo controlled, Double blind 12 week Pilot study**
NCT number	Not stated in publication
Objective	The paper evaluates the efficacy and safety data from a pilot study of TPM 200 mg/d as preventive therapy in adult subjects with a history of migraine with or without aura.
Publications – title, author, journal, year	**Efficacy and Tolerability of Topiratmate 200 mg/d in the prevention of migraine with/without aura in adults: A Randomized Placebo controlled, Double blind 12 week Pilot study", Silberstein et al, Clinical Therapeutics 2006**
Study type and design	Multicenter, randomized, double blind, placebo controlled, parallel-group, out patient trial. The trial consists of an up to 4 weeks screening/washout period, a 4 week prospective baseline period, and a 20 week double blind treatment phase, which included an 8 weeks titration phase and a 12 week maintenance phase.
Follow-up time	Data from the 20 week double blind treatment phase is presented.

<table>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria:
Subjects between the ages of 18 and 65 years
a history of migraine with or without aura, as assessed by International Headache Society criteria, 1° for at least 12 months before screening.
Subjects must have experienced an average of 3 to 8 migraine episodes per month (defined as 28 days) for 3 months (84 days) before screening. For the purposes of this study, a migraine episode was defined as the period from the onset of painful symptoms to the resolution of pain or 24 hours after onset, whichever was sooner. Migraine pain that recurred within 24 hours was considered part of the same episode.
Exclusion criteria:
previously failed to respond to topiramate therapy
had taken preventive medication within 2 weeks (14 days) of the start of the prospective baseline period
subjects who had >15 headache days per month during the 3 months before screening, during screening, or during the prospective baseline period
subjects with a diagnosis of cluster headache; basilar, ophthalmoplegic, hemiplegic, or transformed migraine; or migraine aura exclusively (without headache)
subjects who had previously failed to respond to >2 adequately dosed migraine preventive medications, had migraine onset after the age of 50 years, or overused acute migraine treatment (eg, triptan use on >8 days per month)
receipt of injected corticosteroids, local anesthetics, or botulinum toxin within 60 days before screening
women of childbearing age were required to be using an approved method of birth control or to abstain from sexual intercourse
pregnant or lactating women were excluded
serum alanine and/or aspartate aminotransferase levels >2 times the upper limit of the normal range were excluded, as were subjects with active liver disease.</td></tr>
<tr><td>Intervention</td><td>Subjects who met the eligibility criteria were randomized 2:1 to topiramate 200 mg/d or placebo. The double-blind treatment phase consisted of an 8-week titration period (25 mg/d for the first week, followed by weekly increases of 25 mg) and a 12-week maintenance period. In total 213 patients were randomized, 140 to topiramate and 73 to placebo.</td></tr>
<tr><td>Baseline characteristics</td><td><table>
<tr><td>IIT</td><td>Topiramate: 200 mg
N= 138</td><td>Placebo:
N=73</td></tr>
<tr><td>Age, years Mean (SD)</td><td>39.9 (11.8)</td><td>41.7 (9.4)</td></tr>
<tr><td>Gender no.</td><td></td><td></td></tr>
<tr><td>Female, n (%)</td><td>118 (85.5)</td><td>63 (86.3)</td></tr>
<tr><td>Male, n (%)</td><td>20 (14.5)</td><td>10 (13.7)</td></tr>
<tr><td>Weight, kg. Mean (SD)</td><td>74.6 (17.5)</td><td>80.7 (20.3)</td></tr>
<tr><td>No. of migraine episodes per 28 days
Mean (SD)
Range</td><td>
4.8 (1.5)
2-8</td><td>
5.2 (1.7)
2-9</td></tr>
</table></td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoint: change in mean monthly migraine frequency.
Secondary endpoints:
median percent reduction in monthly migraine frequency
proportion of responders (≥50%, ≥75%, or 100% reduction in monthly migraine frequency)</td></tr>
</table>

Method of analysis	Not applicable since the endpoints for this application are not the same as those analysed in the publication.
Subgroup analyses	N/A

TABEL 18 SILBERSTEIN 2004

<table>
<tr><td>Trial name</td><td>Topiramate in migraine Prevention</td></tr>
<tr><td>NCT number</td><td>Not stated in publication</td></tr>
<tr><td>Objective</td><td>To assess the efficacy and safety of Topiramate as a migraine-preventive therapy</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>Topiramate in migraine provention. Results of a large controlled trial. Silberstein SD et al. Arch Neurol 2004</td></tr>
<tr><td>Study type and design</td><td>A 26 weeks, randomized, double blind, placebo-controlled study.
The study consisted of a 28 day prospective baseline phase.
The double-blind phase was divided into titration (8 weeks) and maintenance (18 weeks).</td></tr>
<tr><td>Follow-up time</td><td>Data from the 26 weeks double-blind treatment phase are presented.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria.
Patients age 12-65 years with 3-12 migraines during the prospective 28-day baseline phase.
Women needed to be post –menopausal, surgically incapable of childbearing or, or using contraceptives.
Exclusion criteria:
Headaches other than migraine
failed previously 2 migraine preventive drugs
had migraine onset after age 50.
>8 treatment days pr. month of ergots or triptans
used B-blockers, tricyclic anti-depressants, AED´s. ACE inhibitors etc.
patients with renal impairments
patients who had participated in previous topimarate study,
patients who had used topimarate for 2 weeks or longer
patients who had used an experimental drug or device within 30 days prior screening</td></tr>
<tr><td>Intervention</td><td>469 patients composed the IIT population. Participants were randomized to placebo or topiramate, 50, 100 or 200 mg/WK to the assigned dose or as tolerated in 8 weeks; Maintenance therapy continued for 18 weeks.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Topiramate 50 mg N= 117</td><td>Topiramate 100 mg N=125</td><td>Topiramate 200 mg N=112</td><td>Placebo N=115</td></tr>
<tr><td>Age, years (SD)</td><td>40.2 (11.5)</td><td>40.6 (11.0)</td><td>40.5 (11.4)</td><td>40.4 (11.5)</td></tr>
<tr><td>Female; n</td><td>107</td><td>112</td><td>94</td><td>103</td></tr>
<tr><td>Male; n</td><td>10</td><td>3</td><td>18</td><td>12</td></tr>
<tr><td>MMD</td><td>6.4 (2.7)</td><td>6.4 (2.7)</td><td>6.6 (3.1)</td><td>6.4 (2.6)</td></tr>
<tr><td>Weight</td><td>75.7 (18.9)</td><td>78.9 (19.3)</td><td>76.7 (20.1)</td><td>75.6 (18.5)</td></tr>
<tr><td>Days of acute headache medication use pr. 28 days</td><td>5.8 (2.5)</td><td>6.4 (2.7)</td><td>6.1 (3.1)</td><td>6.1 (3.0)</td></tr>
</table>
Data shown are mean (SD), unless otherwise indicated.</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoint:
Reduction in monthly migraine frequency across the 6 month treatment phase
Secondary endpoints:</td></tr>
</table>

	• time to onset of action • the proportion of patients responding (≥50% reduction in monthly migraine frequency) • Mean change in migraine days per month • mean change in days with rescue medication per month
Method of analysis	The primary endpoint was analysed using a linear model with treatment and analysis center as factors and baseline value as covariate. The least square means, which are means adjusted for the variables in the statistical model, were used to compare treatment groups. Efficacy analyses were conducted on the intent to treat population, Which was defined as those randomized patients who had at least 1 post baseline efficacy assessment. For subjects discontinuing the study early, the average monthly migraine period rate was computed based on the migraine periods observed before discontinuation.
Subgroup analyses	N/A

TABEL 19 STOREY 2001

Trial name	**Topiramate in migraine Prevention: A double blind placebo Controlled Study**
NCT number	Not stated in publication
Objective	To evaluate the efficacy of Topiramate in the preventive treatment of episodic migraine
Publications – title, author, journal, year	**Topiramate in migraine Prevention: A double blind placebo Controlled Study, Storey, Headache, 2001**
Study type and design	Single center double blind, placebo-controlled randomized trial to evaluate the efficacy and safety of topiramate for the preventive treatment of migraine. The study consisted of a 4-week baseline phase, an 8-week titration phase and an 8 week maintenance phase.
Follow-up time	16 weeks double blind treatment
Population (inclusion and exclusion criteria)	Inclusion criteria: • men and women aged 18-65 years • diagnosed with migraine – with or without aura, based on IHD criteria • migraine throughout a period of 1 year, with a frequency of two or more/month • negative pregnancy test 72 hours prior study medication • two or more migraines per 28 days during the baseline phase Exclusion criteria: • Patients were excluded from the study if they required medication for the symptomatic relief of migraine within a 24 hours period, plus three times per week • If presented with a history of more than 12 tension type headaches pr. month and unable to distinguish between headache and migraine • If they met the DSM-IV, criteria for any substance related disorder within 12-month prior screening visit • Usage of any experimental drug 30 days prior study entry • History of renal calculi, Multiple Sclerosis, or a history of any medical condition, that would expose them to an increased risk of significant AE´s to interfere with the assessment of efficacy and safety of the trial
Intervention	At the end of the 4-week baseline phase, eligible patients were randomized 1:1 to topiramate (n=19) or placebo (n=20). Topiramate or matched placebo was given and

<table>
<tr><td></td><td>titrated weekly in 25 mg increments over 8 weeks, to 200 mg. pr. day or to the maximum tolerated doses.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Topiramate N=19</td><td>Placebo N=21</td></tr>
<tr><td>Age, years (range)</td><td>38.3 (19-62)</td><td>38.1 (24-56)</td></tr>
<tr><td>Gender</td><td></td><td></td></tr>
<tr><td>Female</td><td>19</td><td>20</td></tr>
<tr><td>Male</td><td></td><td>1</td></tr>
<tr><td>Migraine frequency per 28 daysn, (SD)</td><td>5.14 (1.56)</td><td>4.37 (1.96)</td></tr>
<tr><td>Weight, lb (SD)</td><td>170.8 (33,3)</td><td>181.0 (41.6)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoint: The mean reduction in the 28 days migraine rate during the entire double blind phase (week5-20). The 28 day migraine rate was determined by dividing the number of migraines in the in the period and multiplying by 28.
Secondary endpoints:
• mean percent reduction in migraine rate
• the percentage of responders in each group</td></tr>
<tr><td>Method of analysis</td><td>Statistical Analysis:
Not applicable since the endpoints for this application are not the same as those analysed in the publication</td></tr>
<tr><td>Subgroup analyses</td><td>N/A</td></tr>
</table>

TCA (amitriptylin/nortriptylin)

TABEL 20 COUCH 2011

Trial name	**Amitriptyline in the Prophylactic Treatment of Migraine and Chronic Daily Headache**
NCT number	Not stated
Objective	To compare amitriptyline with placebo in the treatment of intermittent migraine and chronic daily headache
Publications – title, author, journal, year	**Amitriptyline in the Prophylactic Treatment of Migraine and Chronic Daily Headache. Couch JR, el al. Headache 2011**
Study type and design	This study was a double-blind, placebo controlled, study comparing amitriptyline in doses of 25-100 mg/day, depending on the tolerance of the patient, with a matched placebo. Patients received placebo for 4 weeks (Period A – baseline period). After 4 weeks patients with at least 2 moderate or worse migraine headaches during Period A could be randomized into the double-blind period of 5-20 weeks (Periods B and C). Patients were randomized to either amitriptyline or placebo therapy on a 1:1 basis in blocks of 4 subjects. During Periods B and C the patient received pills that were identical to each other and identical to those dispensed in Period A, which contained either amitriptyline 25 mg or placebo. The first 4 weeks (Phase B) was a dose titration phase, and the following 12 weeks (Phase C) was a dose maintenance phase.
Follow-up time	Data from the 20-week double-blind treatment phase is presented.
Population (inclusion and exclusion criteria)	Inclusion criteria Patients between 18 and 70 years of age with at least two moderate or worse migraine headaches per month Exclusion criteria

<table>
<tr><td></td><td>

absence of migraine headache
secondary headache
pregnant females or nursing mother
known allergy to amitriptyline
urinary retention, glaucoma, any cardiac disease, sustained hypertension
subjects taking guanethidine or monoamine oxidase inhibitors
prostatic hypertrophy
thyroid disease or taking thyroid medication
seizure disorder
patients taking any known preventative antimigraine agent including methysergide, propranolol, cyproheptadine, antianxiety agents, or other tricyclic antidepressants.

</td></tr>
<tr><td>Intervention</td><td>Placebo or amitriptyline in doses of 25-100 mg/day, depending on the tolerance of the patient. 194 patients received amitriptyline and 197 received placebo</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Placebo
N=197</td><td>Amitriptyline
N=194</td></tr>
<tr><td>Age (years)</td><td>35,7</td><td>34,1</td></tr>
<tr><td>Male (n)</td><td>34 (17%)</td><td>40 (21%)</td></tr>
<tr><td>Female (n)</td><td>163 (83%)</td><td>154 (79%)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The major efficacy measures for this study are the frequency, duration, and severity of headaches

Headache frequency was measured as number of days per 4 weeks with a headache of any degree of severity.

Duration was measured in hours.

Headache severity was measured on a 5-point scale as follows: disabling (4) – a headache so severe the patient must lie down; severe (3) – a headache severe enough that usual activity is diminished by 50% or more; however, some activity is possible; moderate (2) – a headache that limits usual activity by less than 50%; mild (1) – a headache that is present but does not limit activity; no headache (0).</td></tr>
<tr><td>Method of analysis</td><td>Not applicable since the endpoints for this application are not the same as those analysed in the publication</td></tr>
<tr><td>Subgroup analyses</td><td>None</td></tr>
</table>

TABEL 21 GONCALVES 2016

Trial name	**Double Blind Randomized Study Controlled by Placebo and Amitriptylin to Evaluate the Efficacy of Melatonin in the Preventive Treatment of Migraine**
NCT number	NCT01357031
Objective	The purpose of this study was to determine the effectiveness of melatonin 3 mg compared to placebo and amitriptyline 25 mg in the preventive treatment of migraine.
Publications – title, author, journal, year	**Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. Gonçalves AL, et al. J Neurol Neurosurg Psychiatry 2016**
Study type and design	The study was a randomized, multicenter, parallel-group study. Melatonin 3 mg was compared with amitriptyline 25 mg and placebo. The study consisted of a 4-week period to established baseline measures followed by a 12-week treatment period. Randomization was performed centrally with the use of

<table>
<tr><td></td><td>randomization lists with randomly permuted block lengths stratified according to center. Patients, treating clinicians and the outcome assessor were blinded.</td></tr>
<tr><td>Follow-up time</td><td>Data from the 12 week double-blind treatment period is presented.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion Criteria:
age of 18–65 years;
migraine with or without aura criteria according to the International Classification of Headache Disorders, third edition, β-version12 for at least 1 year
age of onset before 50 years,
at least three migraine headache attacks or four migraine headache days (defined as any occurrence of migraine headache pain of at least 30 min in duration with acute treatment) per month,
presents with migraine or non-migraine headache attacks <15 days per month during each of the 3 months prior to the screening visit and the reference period.
Migraine diagnosis was performed by a trained neurologist headache specialist.
Women were eligible if they were unable to bear children or if they were not pregnant and using adequate contraception.
Exclusion criteria:
history of psychiatric disorder (in the past or present);
ergotamine, triptan, opioid, or combination medication intake for >10 days per month, or simple analgesic intake for >15 days per month for >3 months;
in use of preventive medications such as β-blockers, tricyclic antidepressants, calcium channel blockers, antiepileptic drugs, bupropion, serotonergic norepinephrine reuptake inhibitors; and were unable to discontinue the treatment
had previously taken melatonin, amitriptyline or agomelatine;
had uncontrolled hypertension (ie, sitting systolic blood pressure >160 mm Hg or sitting diastolic blood pressure >90 mm Hg) at the screening visit or at randomization.</td></tr>
<tr><td>Intervention</td><td>Patients were randomized 1:1:1 to amitriptyline 25 mg/day (n=59), melatonine 3 mg/day (n=60) and placebo (n=59)</td></tr>
<tr><td>Baseline characteristics</td><td><table><tr><td></td><td>Placebo
N=59</td><td>Amitriptyline
N=59</td></tr><tr><td>Age (years)</td><td>36.6</td><td>37.2</td></tr><tr><td>Female (n)</td><td>45 (76.3%)</td><td>44 (74.6%)</td></tr><tr><td>BMI Kg/m2</td><td>24.6</td><td>411</td></tr></table></td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary efficacy outcome measure was frequency in number of migraine headache days per month comparing baseline with the past 4 weeks of treatment. Secondary end points included
reduction in migraine intensity, attack duration,
number of analgesics used and
percentages of patients with greater than 50% reductions in migraine headache days.</td></tr>
<tr><td>Method of analysis</td><td>Efficacy data were analyzed for the intention-to-treat population, defined as randomized patients who received at least one dose of the study medication and provided at least one post-baseline efficacy assessment. Missing days as non-migraine headache days. An analysis of covariance (ANCOVA) model was used to test the null</td></tr>
</table>

	hypothesis of no difference between placebo and the average of the values for the three groups. Results were summarized using the adjusted mean and SE for each treatment group, a 95% CI for the change from baseline for each treatment group, a model estimate of the difference between each active treatment group and placebo, a 95% CI for the difference, and an associated p value and adjusted p value for the difference. Analysis of the primary end point was carried out using a combination of a sequential method and a Hochberg procedure to maintain the experiment-wise α level of 0.05.
Subgroup analyses	None

Valproat

TABEL 22 FREITAG 2002

Trial name	**A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis**
NCT number	Not stated in publication
Objective	To evaluate the efficacy and safety of extended-release divalproex sodium compared with placebo in prophylactic monotherapy treatment of migraine headache.
Publications – title, author, journal, year	**A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Freitag FG, et al. Neurology 2002.**
Study type and design	This was a 17-week multicenter, double-blind, randomized, placebo-controlled, parallel-group study consisting of three phases: a 4-week baseline phase; a 12-week double-blind experimental phase; and a 1-week double-blind termination phase. During the baseline phase, subjects maintained a headache diary in which headache activity was recorded. Subjects compliant in maintaining a headache diary and who had at least two migraine headache attacks (separated by a headache-free interval of at least 24 hours) during the 4-week baseline phase were eligible to be randomized. Following the 4-week baseline phase, eligible subjects were randomly assigned in a 1:1 ratio at each center to receive either extended-release divalproex sodium or identical gray ovaloid placebo tablets, and entered into the 12-week experimental phase. The experimental phase consisted of a 2-week dose titration/adjustment period followed by a 10-week fixed-dose treatment period. Headache diaries were used to collect information regarding the start and end times, characteristics, and symptomatic medication usage associated with each headache attack. Headache attacks separated by any headache-free interval were to be reported separately. Based on review of the diaries, the headache type of each attack was determined by the investigator per the IHS diagnostic criteria. The tolerability and safety of study medication were monitored through adverse event reporting and assessments of prior and concurrent medication, physical and brief neurologic examinations, routine laboratory evaluations, and serum pregnancy tests for women of childbearing potential.
Follow-up time	Data from the 12-week double-blind experimental phase are presented.
Population (inclusion and exclusion criteria)	Inclusion criteria: • Men or woman more 12 years or older • More than two migraine headache attacks during a 4-week baseline period Exclusion criteria: • Women who were lactating or pregnant • subjects who had headaches an average of _15 days per month; had ever experienced cluster headaches;

<table>
<tr><td></td><td>

had previously received an adequate course of treatment with valproate or divalproex sodium for migraine headaches
had a CNS neoplasm or infection, demyelinating disease, degenerative neurologic disease, or progressive CNS disease
had failed more than two adequate trials of prophylactic antimigraine regimens
or who had received prophylactic antimigraine medication within five half-lives of that medication before entering the baseline phase.

</td></tr>
<tr><td>Intervention</td><td>Subjects initiated treatment on 500 mg once daily for 1 week, and the dose was then increased to 1,000 mg once daily with an option, if intolerance occurred, to permanently decrease the dose to 500 mg during the second week. 122 patients was randomized to active treatment and 101 patients completed</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Placebo
N=115</td><td>Treatment 1
N=122</td></tr>
<tr><td>Age (years)</td><td>41.3</td><td>39.8</td></tr>
<tr><td>Male (n)</td><td>25 (22%)</td><td>25 (20%)</td></tr>
<tr><td>Female (n)</td><td>90 (78%)</td><td>97 (80%)</td></tr>
<tr><td>Weight (kg)</td><td>74.5</td><td>74.39</td></tr>
<tr><td>Height (cm)</td><td>166.88</td><td>166.88</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary efficacy variable was the experimental phase reduction from baseline (i.e., the baseline phase) in 4-week migraine headache rate. The 4-week rates for the experimental and baseline phases were calculated for each subject as the number of migraine headaches during the study phase multiplied by the ratio of 28 days to the actual number of days in the phase.
The principal secondary variables were the experimental phase percent reduction from baseline in 4-week migraine headache rate, assessing both actual percentages and the proportion of subjects achieving at least a 50% reduction, and the experimental phase reduction from baseline in the number of migraine headache days per 4 weeks.
Other secondary variables included the experimental phase changes from baseline in the proportions of migraine headaches treated with particular classes of symptomatic medications (e.g., triptans).</td></tr>
<tr><td>Method of analysis</td><td>The primary and secondary efficacy variables chosen for the current study were specified in the protocol and were based on (or were slight modifications of) variables included in the IHS committee guidelines for controlled trials of drugs in migraine,14 including the committee’s recommended use of the 4-week migraine headache rate as the primary efficacy variable and the 24-hour headache free rule in calculating the migraine headache rates. Per this rule, migraine headache attacks separated by a _24-hour headache-free interval were combined and considered as a single migraine headache in calculations of 4-week migraine headache rates. The efficacy data set was an intent-to-treat data set that included all data from randomized subjects who received study drug and provided at least one headache evaluation during the experimental phase.

The primary efficacy variable was the experimental phase reduction from baseline (i.e., the baseline phase) in 4-week migraine headache rate. The 4-week rates for the experimental and baseline phases were calculated for each subject as the number of migraine headaches during the study phase multiplied by the ratio of 28 days to the actual number of days in the phase.

The principal secondary variables were the experimental phase percent reduction from baseline in 4-week migraine headache rate, assessing both actual percentages</td></tr>
</table>

	and the proportion of subjects achieving at least a 50% reduction, and the experimental phase reduction from baseline in the number of migraine headache days per 4 weeks. The nonparametric van Elteren method of linearly combining Wilcoxon test results from individual investigators, using weights recommended by Lehmann, was the protocol-specified primary analysis method for the continuous variables. Ninety-five percent CI of weighted treatment differences in means for these variables were derived using the analogous protocol-specified alternative analysis method, an analysis of variance (ANOVA) model that weighted treatment differences at each investigator site inversely proportional to the variance of the estimated treatment group difference.
Subgroup analyses	None

TABEL 23 JENSEN 1994

Trial name	**Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study**
NCT number	None
Objective	To evaluate if sodium valproate has a prophylactic effect in migraine without aura.
Publications – title, author, journal, year	**Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study. Jensen R, et al. Neurology 1994**
Study type and design	A triple-blind, dose-controlled, crossover study in patients with migraine without aura. After a 4-week medication-free run-in period, patients eligible for inclusion were randomized to sodium valproate or placebo. After randomization, all patients were given three apparently identical tablets per day during the entire trial. The treatment periods were separated by a 4-week wash-out period with three placebo tablets per day. Thereafter, the patients were shifted to either placebo or sodium valproate in a similar 12-week treatment period.
Follow-up time	Data from the 12 week triple-blind treatment phases is presented.
Population (inclusion and exclusion criteria)	Inclusion • a diagnosis of migraine without aura, a history of migraine for at least 1 year • 2 to 10 days with migraine per month • age between 18 and 70 years • women of childbearing potential had to use adequate contraceptive measures throughout the study. Exclusion criteria • daily headache • more than six attacks per year of migraine with aura • cluster headache or trigeminal neuralgia • other neurologic, somatic, or psychiatric diseases • other migraine prophylaxis • any form of drug abuse or dependency, including daily ergotamine or large amounts of plain analgesics • previous participation in more than two migraine drug trials.
Intervention	Randomization assigned 22 patients to the sodium valproate-placebo sequence (group A) and 21 patients to the placebo-sodium valproate sequence (group B). Doses of valproate was 1000-1500 mg based on serum valproate level.

<table>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Group A Valproate-Placebo
N=22</td><td>Group B Placebo-Valproate
N=21</td></tr>
<tr><td>Age</td><td></td><td></td></tr>
<tr><td>Mean (years)</td><td>45</td><td>47</td></tr>
<tr><td>Range</td><td>28-58</td><td>27-62</td></tr>
<tr><td>Male/Female</td><td>4/18</td><td>2/19</td></tr>
<tr><td>Frequency of migraine/4 weeks</td><td></td><td></td></tr>
<tr><td>Mean</td><td>6.3</td><td>6.8</td></tr>
<tr><td>Range</td><td>(3-10)</td><td>(4-10)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoints:
The mean number of days with migraine during sodium valproate as compared with the placebo period.
Secondary endpoints:
Frequency of tension-type headache, headache intensity, headache duration, and drug consumption.
Responders defined as those patients for whom the frequency of migraine days was reduced to 50% or less when compared with the baseline period.</td></tr>
<tr><td>Method of analysis</td><td>Patients who dropped out of the trial after randomization were excluded from the statistical analysis, but reasons for dropping out were recorded. The primary efficacy variable was the treatment effect, i.e., the mean number of days with migraine during sodium valproate
as compared with the placebo period. Other variables were considered secondary. A nonparametric statistical test, Wilcoxon’s rank sum test, was used to test the treatment effect. A 5% level of significance was used.</td></tr>
<tr><td>Subgroup analyses</td><td>None</td></tr>
</table>

TABEL 24 KLAPPER 1997

Trial name	**Divalproex sodium in migraine prophylaxis: a dose-controlled study**
NCT number	None
Objective	To evaluate the efficacy and safety of divalproex sodium (DVPX) when used as prophylactic monotherapy in patients with migraine.
Publications – title, author, journal, year	**Divalproex sodium in migraine prophylaxis: a dose-controlled study. Klapper J et al. Cephalalgia 1997**
Study type and design	Design: Multicenter, double-blind, placebo-controlled, parallel group. During a 4-week (single-blind) baseline phase (BP), patients received placebo and completed a headache diary. Patients completing the BP who had experienced at least two migraine attacks during this period were randomized to one of four treatment groups (placebo, or either 500 mg, 1000 mg, or 1500 mg DVPX) in a 1 : 1 : 1 : 1 ratio within each study center. The experimental phase (EP) lasted 12 weeks, the first 4 weeks for dose escalation to randomized dose, and the remaining 8 weeks for maintenance at that dose.
Follow-up time	Data from the 12 week double-blind experimental phase are presented.
Population (inclusion and exclusion criteria)	Inclusion criteria: Patients 16 years or older were eligible to enroll in the study if they had suffered migraine attacks with or without aura (as defined by the International Headache Society criteria) for at least **6** months prior to the study and had averaged at least two migraine attacks per month during the previous **3** months.

<table>
<tr><td></td><td>Patients previously untreated for migraine or patients who, in the opinion of the investigator, had previously failed no more than two adequate trials (e.g. at least 1 month of treatment at a full therapeutic dose) of prophylactic therapy were eligible. Patients already receiving prophylactic treatment were required to discontinue these medications and complete a washout period of a length equivalent to at least five half-lives of the medication prior to enrollment.
Exclusion criteria:
Patients were excluded from the study if they experienced other headache types (i.e. interval headaches) on more than 15 days per month, had migraines which were always unassociated with headache, or had cluster headaches.
Also excluded were pregnant women, women of child-bearing potential not practicing effective birth control, patients previously treated with valproate,
and patients with a significant medical or psychiatric disorder, particularly one requiring medication that could have confounded data interpretation.
Disallowed concomitant medications included beta-adrenergic blocking agents, tricyclic antidepressants, calcium channel blockers, monoamine oxidase inhibitors, methysergide maleate, lithium carbonate, phenobarbital, phenytoin, arbamazepine, warfarin, and any of the following used on a daily basis: ergotamine preparations, non-steroidal anti-inflammatory agents, analgesics, benzodiazepines, or cyproheptadine hydrochloride.
Treatment with symptomatic medications was allowed on an as-needed basis for treatment of individual headaches during the study, but was to average less than 3 days per week.</td></tr>
<tr><td>Intervention</td><td>Patients were randomized to receive a valproate daily dose of 500 (n=45), 1000 (n=43), or 1500 (n=44) mg, or to placebo (n=44).
The EP began with a 4-week dose titration period and was followed by an 8-week dose maintenance period. The initial daily dose for DVPX-treated patients was 250 mg. The daily dose was then increased by 250 mg every 4 days (every 8 days for the 500 mg group) until the assigned randomized dose was achieved, at which time study medication was taken twice daily in equal, divided doses, morning and evening. The dose then remained fixed at the randomized dose throughout the remainder of the study.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo

N=44</th><th>Divalproex sodium 500 mg N=45</th><th>Divalproex sodium 1000 mg N = 43</th><th>Divalproex sodium 1500 mg N = 44</th></tr>
<tr><td>Age (years)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>40.2</td><td>40.2</td><td>40.2</td><td>40.2</td></tr>
<tr><td>Range</td><td>(19-67)</td><td>(19-67)</td><td>(19-67)</td><td>(19-67)</td></tr>
<tr><td>Gender</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Female</td><td>91%</td><td>93</td><td>88%</td><td>84%</td></tr>
<tr><td>Race</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Caucasian</td><td>89%</td><td>89%</td><td>89%</td><td>89%</td></tr>
<tr><td>Black</td><td>7%</td><td>7%</td><td>7%</td><td>7%</td></tr>
<tr><td>Other</td><td>5%</td><td>5%</td><td>5%</td><td>5%</td></tr>
<tr><td>Weight</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean (kg)</td><td>68.4</td><td>68.4</td><td>68.4</td><td>68.4</td></tr>
<tr><td>Range</td><td>(37.2-109.5)</td><td>(37.2-109.5)</td><td>(37.2-109.5)</td><td>(37.2-109.5)</td></tr>
<tr><td>Years with migraine</td><td>21.0</td><td>20.6</td><td>23.7</td><td>21.3</td></tr>
<tr><td>Previously used other prophylactic antimigraine medications</td><td>55%</td><td>56%</td><td>56%</td><td>45%</td></tr>
</table>
</td></tr>
</table>

Primary and secondary endpoints	The primary efficacy variable was the 4-week migraine attack frequency (i.e. the number of migraine attacks, with or without aura, during the EP' multiplied by the ratio of 28 days to the actual number of days the patient was treated). • The proportional reduction from baseline in migraine attack frequencies was also evaluated. Other headache characteristics evaluated included • the duration and peak severity of migraine attacks that continued to occur • the numbers of days per 4 weeks with migraine attacks that impair usual activities or necessitating symptomatic medication, and • the 4-week attack frequencies of migraines with nausea, vomiting, photophobia and/or phonophobia and of all non-migraine headache types combined.
Method of analysis	Not applicable since the endpoints for this application are not the same as those analysed in the publication
Subgroup analyses	None

TABEL 25 MATHEW 1995

Trial name	**Migraine Prophylaxis With Divalproex**
NCT number	None
Objective	To compare the effectiveness and safety of divalproex sodium (Depakote) and placebo in the prophylaxis of migraine headache.
Publications – title, author, journal, year	**Migraine prohylaxis with Divalproex. Mathew NT, et al. Arch Neurol. 1995**
Study type and design	The investigation was conducted as a randomized, placebo controlled, double-blind, parallel-group, multicenter study, designed to compare the efficacy and safety of divalproex with that of placebo in the prophylaxis of migraine headache. The study was divided into two phases: a baseline phase (4 weeks) and treatment phase (12 weeks with 4-week dose adjustment and 8-week maintenance). Patients were randomized to groups receiving divalproex or placebo in a 2:1 ratio of divalproex to placebo within each center. Total duration of the study was 16 weeks.
Follow-up time	Data from the 12 week double-blind treatment phase is presented.
Study type and design	The investigation was conducted as a randomized, placebo controlled, double-blind, parallel-group, multicenter study, designed to compare the efficacy and safety of divalproex with that of placebo in the prophylaxis of migraine headache. The study was divided into two phases: a baseline phase (4 weeks) and treatment phase (12 weeks with 4-week dose adjustment and 8-week maintenance). Patients were randomized to groups receiving divalproex or placebo in a 2:1 ratio of divalproex to placebo within each center. Total duration of the study was 16 weeks.
Follow-up time	Data from the 12 week double-blind treatment phase is presented.
Population (inclusion and exclusion criteria)	Inclusion criteria: • 16 to 75 years of age • have suffered migraine episodes with or without aura per International Headache Society criteria for 6 or more months previously; • migraine frequency was required to be two or more episodes per month for the previous 3 months

<table>
<tr><td></td><td>
the patient had not received prophylactic treatment previously or had failed no more than two adequate trials, in the investigator's opinion, of established prophylactic antimigraine regimens.
Exclusion criteria:

only migraine episodes unassociated with headache
chronic daily headaches or tension-type headaches occurring more than 15 days per month
cluster headaches
a history of any significant medical or psychiatric disorder (particularly one that would confound data interpretation or required medication whose known effects included antimigraine prophylaxis)
a history of poor compliance with previous medication regimens
a history of previous valproate use
women of child bearing potential

</td></tr>
<tr><td>Intervention</td><td>Patients were randomized to groups receiving divalproex or placebo in a 2:1 ratio of divalproex (n=70) to placebo (n=37). Treatment with divalproex sodium was started at a dose of 250 mg/d; doses were then titrated upward at recommended increments of 250 mg every other day (or 250 mg every third day for patients weighing <60 kg) with the goal of achieving a trough plasma valproate sodium concentration of approximately 70 to 120 mg/L. The dose of placebo was adjusted in a similar fashion to maintain the blind.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Placebo
N=37</td><td>Valproate
N=70</td></tr>
<tr><td>Age (years)</td><td>43</td><td>47</td></tr>
<tr><td>Female %</td><td>73</td><td>80</td></tr>
<tr><td>Duration of migraine diagnosis</td><td colspan="2">25</td></tr>
<tr><td>Previous prophylactic treatments</td><td colspan="2">1.3</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>
The primary outcome measure was the 4-week migraine headache frequency (ie, the number of migraine headaches, with or without aura, per 4 weeks) during the treatment phase.
Secondary outcomes:

proportion of patients with a reduction of 50% or more in 4-week migraine headache frequencies compared with the baseline phase
the average duration of episodes
the average severity of episodes at peak intensity (peak severity)
the average severity related to functional ability (assessment of functional restriction)
the average symptomatic medication usage (measuring usage days of each medication summed across medications) per episode
the 4-week frequencies of migraine headaches with associated nausea, vomiting, aura, photophobia, and phonophobia
the number of days per 4 weeks with migraine headaches

</td></tr>
<tr><td>Method of analysis</td><td>Analyses were performed using all data from randomized patients. The nonparametric Van Elteren method of linearly combining Wilcoxon test results from individual investigators, using weights recommended by Lehmann, was the method used to compare treatment groups with respect to the primary efficacy outcome measure. The Cochran-Mantel-Haenszel statistic was used to compare treatment groups with respect to the proportion of patients with a 50% or greater reduction in 4-week migraine headache frequencies. All hypothesis tests were two tailed, and values of .05 or less were considered significant.</td></tr>
<tr><td>Subgroup analyses</td><td>None</td></tr>
</table>

TABEL 26 SARCHIELLI 2014

<table>
<tr><td>Trial name</td><td>Sodium valproate in migraine without aura and medication overuse headache: A randomized controlled trial</td></tr>
<tr><td>NCT number</td><td>None</td></tr>
<tr><td>Objective</td><td>To assess the efficacy, safety and tolerability of sodium valproate (800mg/day) compared with placebo in medication overuse headache patients with a history of migraine without aura.</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>Sodium valproate in migraine without aura and medication overuse headache: A randomized controlled trial. Sarchielli P, et al. European Neuropsychopharmacology 2014</td></tr>
<tr><td>Study type and design</td><td>A double-blind placebo-controlled study. Treatment included a 4-week baseline period, during which no study medication was given), followed by a 6-day in patient detoxification phase (in which abused drugs were promptly discontinued) and a 12-week double-blind treatment period, with valproate 800mg/day or placebo. After the detoxification phase, the patients were advised to discontinue the overused medication.
Eligible patients who completed the prospective baseline period and detoxification phase were sequentially assigned in a 1:1 ratio to either VPA or placebo and received a random computer- generated medication code number, in compliance with a permuted block randomization design. Neither the patients nor the clinic staff were aware of the study medication assigned.</td></tr>
<tr><td>Follow-up time</td><td>Data from the 12-week double-blind treatment period are presented.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion criteria:
Outpatients aged 18–65 year
Established past history of episodic migraine without aura, and a diagnosis of medication overuse headache according to the International Headache Society revised criteria (Silberstein et al., 2008) during the previous 3 months with all other causes of secondary headache ruled out
Patients had to be willing to comply with all appointments for clinic visits, tests, and with the procedures required by the protocol, and had to have returned the informed consent form.
Females were eligible only if of non-childbearing potential or using an adequate contraceptive method
Exclusion criteria:
Patients taking a headache-prevention medication during the month preceding enrollment
Known allergic reactions to drugs
Assuming prohibited concomitant therapy (other antiepileptic drugs; tricyclic antidepres- sants; anticoagulants; neuroleptics; abused benzodiazepines)
History or suspicion of alcohol abuse or illicit drug use in the previous 2 years
Past or present history of a serious illness, or metabolic disorder</td></tr>
<tr><td>Intervention</td><td>44 patients received valproate 800 mg and 44 patients received placebo.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo
N=44</th><th>Amitriptyline
N=44</th></tr>
<tr><td>Female</td><td>35 (79.5%)</td><td>34 (77.3%)</td></tr>
<tr><td>Male</td><td>9 (20.5%)</td><td>10 (22.7%)</td></tr>
<tr><td>Age 18-34</td><td>5</td><td>8</td></tr>
<tr><td>Age 35-44</td><td>20</td><td>14</td></tr>
<tr><td>Age 45-54</td><td>13</td><td>17</td></tr>
<tr><td>Age 55-64</td><td>6</td><td>5</td></tr>
</table>
</td></tr>
</table>

	BMI < 18	24	27
	BMI 18-24,9	14	9
	BMI 25-29,9	1	2
	BMI ≥ 30	5	5
	Headache duration < 10 years	6 (13.6%)	7 (15.9%)
Primary and secondary endpoints	Primary endpoint: the proportion of patients with ≥ 50% reduction in headache days per month (responder rate) from the prospective 4-week baseline phase to the last 4 weeks of the 3-month treatment. Secondary endpoints: • the number of days with headache • headache intensity • the monthly frequency, duration and severity of headache attacks • the number of days per month with acute medications		
Method of analysis	Descriptive statistics were reported as counts and percentages, mean and standard deviation (SD) or median and range. Categorical and continuous variables were compared between the two groups with the Fisher Exact test or the ChiSquare test as appropriate and the Wilcoxon–Mann–Whitney Test. Changes in headache frequency, number of days with acute medications, and number of rescue drugs were compared using Analysis of Variance for repeated measures. Correlations within patients were modeled using the "unstructured" correlation matrix. The results of ANOVA have been displayed as "treatment", "time" and "treatment _time" effects. Wilcoxon–Mann–Whitney and the signed-rank tests were used to assess differences between and within each group. Multivariable logistic regression models were applied on the primary end point to adjust for possible confounders or imbalances in the two groups (age, sex, disease duration, chronicity duration, co-morbidities and antecedent surgeries). Results are reported as ORs (odds ratios) and 95% confidence intervals (95%CIs). The Poisson distribution for count data was used to assess incidence and 95% CI of adverse events in the two arms. Statistical analyses were performed in both the intent-to-treat (ITT) and completers populations. All efficacy outcomes in the ITT population were assessed using the last observation carried forward (LOCF) approach. Results reported in this work always refer to the ITT population		
Subgroup analyses	None		

Botox

TABEL 27 AURORA 2010. PREEMPT 1.

Trial name	**PREEMPT I**
NCT number	NCT00156910
Objective	This is the first of a pair of studies designed to assess efficacy, safety and tolerability of onabotulinumtoxinA (BOTOX®) as headache prophylaxis in adults with chronic migraine.
Publications – title, author, journal, year	**OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT I trial, Aurora SK. et al. Cephalalgia, 2010.** Pooled analyses: • OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Aurora SK, et al. Headache 2011

	• Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. Silberstein SD, et al. J Neurol Neurosurg Psychiatry 2015 • OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Dodick DW, et al. Headache. 2010 • OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Aurora SK et al. Acta Neurol Scand 2014 • Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine. Diener H et al. European Journal of Neurology 2014 • OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine, Lipton R.B. et al. Neurology, 2011 • OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: Pooled results from the PREEMPT randomized clinical trial program Lipton RB et al. Cephalalgia 2016 • The impact of onabotulinumtoxinA on severe headache days: PREEMPT 56-week pooled analysis. Matharu M et al. The Journal of Headache and Pain 2017
Study type and design	Phase III with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Enrolled patients were randomly assigned 1:1, Randomization was stratified based on the frequency of acute headache pain medication intake during the 28-day baseline as yes/no overuse of acute headache pain medications, where medication overuse–yes was defined as intake during baseline of simple analgesics on 15 days, or other medication types or combination of types for 10 days, with intake 2 days/week from the category of overuse. The randomization sequence was generated using SAS programming language (SAS Institute, Cary, NC, USA). Randomization programmers had access to the central server, where the randomization sequence was kept. The study is Completed.
Follow-up time	Primary analysis after 24 weeks
Population (inclusion and exclusion criteria)	Inclusion Criteria: • Frequent migraine (≥15 headache days per month) • ≥4 distinct headache episodes lasting ≥4 hours • ≥50% of baseline headache days migraine/probable migraine days Exclusion Criteria: • Previous use of botulinum toxin of any serotype or immunization to any botulinum toxin serotype • Any medical condition that puts the patient at increased risk with exposure to BOTOX • Diagnosis of complicated migraine, chronic tension-type headache, hypnic headache, hemicrania continua, new daily persistent headache • Use of prophylactic headache medication within 28 days prior to week -4 • Unremitting headache lasting continuously throughout the 4-week baseline period • Known or suspected Temporomandibular Disorders (TMD) • Diagnosis of fibromyalgia • Beck depression inventory score >24 at week-4 • Psychiatric problems that may have interfered with study participation
Intervention	• Biological: Botulinum Toxin Type A Two treatment sessions in the double-blind phase and three treatment sessions in the open-label extension phase. Total minimum dose is 155 U with 31 fixed-site,

<table>
<tr><td></td><td>fixed dose injections across seven specific head/neck muscle areas with the total maximum dose of 195 U with 39 head/neck injections.

Other Name: BOTOX®

• Other: Placebo (saline)

Two treatment sessions in the double-blind phase. Total minimum dose in 155 U with 31 fixed-site, fixed dose injections across seven specific head/neck muscle areas and the total maximum dose is 195 U with 39 head/neck injections.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo
N= 338</th><th>Botulinum Toxin Type A
N= 341</th></tr>
<tr><td>Age</td><td>42.1</td><td>41.2</td></tr>
<tr><td>Female, %</td><td>85.8</td><td>89.1</td></tr>
<tr><td>Monthly migarine days</td><td>19.1 (4.1)</td><td>19.1 (4.0)</td></tr>
<tr><td>% patients with 1 or more prophylaxis</td><td>64.2</td><td>59.5</td></tr>
<tr><td>Mean BMI</td><td>27.3</td><td>26.7</td></tr>
<tr><td>% patients with medication overuse</td><td>69.8</td><td>66.3</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary endpoint in PREEMPT 1 was mean change from baseline in frequency of headache episodes for the 28-day period ending with week 24.

Secondary:
• Frequency of headache days (defined as a calendar day [00:00 to 23:59] when the patient reported 4 continuous hours of headache diary episode)
• Migraine days (defined as a calendar day with 4 continuous hours of headache meeting ICHD-II criteria for migraine 1.1, 1.2, or 1.6)
• Migraine episodes (defined as patient-reported headache with a start and stop time indicating that the pain lasted 4 continuous hours and met ICHD-II criteria for migraine 1.1, 1.2, or 1.6)
• Overall acute headache pain medication use (all categories; referred to hereafter as acute pain medication intakes)</td></tr>
<tr><td>Method of analysis</td><td>All efficacy analyses used the intent-to-treat population, which included all randomized patients. Analysis of covariance (ANCOVA) of the change from baseline, with the same variable’s baseline values as covariate, with main effects of treatment group and medication overuse strata.

Scores for months with ≥20 days of diary data were prorated to 28-day equivalents. Scores for months with <10 days of diary data were estimated using a modified last observation carried forward (mLOCF) methodology. This involved the substitution of the patient’s previous 28-day period score multiplied by the ratio of the mean across all patients in the 28-day period of interest divided by the mean across all patients in the previous 28-day period. Scores for months with 10–19 days of diary data were estimated using an average of the prorated and mLOCF estimates. The mLOCF method of imputation of missing data was prespecified, but sensitivity analyses were also done (e.g., using observed data without imputation). For binomial variables, the between-group comparisons were done with Pearson’s Chi-square or Fisher’s exact tests, except that logistic regression with the same variable’s baseline as covariate was used for variables with baseline imbalance. A two-sided test with $p \leq .05$ was considered to be statistically significant. No control of the type-1 error rate for multiple secondary endpoints was prespecified in PREEMPT 1. Therefore, a highly conservative Bonferroni adjustment was applied to compare the week 24 p values to a critical level of .01, which adjusted the prespecified type-1 error rate of .05 for the five variables that were prespecified as primary or secondary.</td></tr>
</table>

Subgroup analyses	None

TABEL 28 DIENER 2010. PREEMPT 2.

Trial name	**PREEMPT II**
NCT number	NCT00168428
Objective	This is the second of a pair of studies designed to assess efficacy and safety of onabotulinumtoxinA (BOTOX®) for prophylaxis of headaches in adults with chronic migraine.
Publications – title, author, journal, year	**OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial, Diener H.C. et al. Cephalalgia, 2010** Pooled analysis: • OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Aurora SK, et al. Headache 2011 • Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. Silberstein SD, et al. J Neurol Neurosurg Psychiatry 2015 • OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Dodick DW, et al. Headache. 2010 • OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Aurora SK et al. Acta Neurol Scand 2014 • Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine. Diener H et al. European Journal of Neurology 2014 • OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine, Lipton R.B. et al. Neurology, 2011 • OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: Pooled results from the PREEMPT randomized clinical trial program Lipton RB et al. Cephalalgia 2016 • The impact of onabotulinumtoxinA on severe headache days: PREEMPT 56-week pooled analysis. Matharu M et al. The Journal of Headache and Pain 2017
Study type and design	Phase III with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Qualified subjects were randomized (1:1) in a double-blind fashion to onabotulinumtoxinA or placebo. Randomization was stratified based on the frequency of acute headache pain medication use during baseline (designated as ‘‘medication overuse–yes’’ or ‘‘medication overuse–no’’), with treatments balanced in blocks of four within each medication-overuse stratum for each investigator site. The randomization sequence was generated using SAS programming language (SAS Institute, Cary, NC, USA) and was stored in a central server with access granted to the randomization programmers. The study is completed.
Follow-up time	Primary analysis after 24 weeks

<table>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion Criteria:
Frequent migraine (≥15 headache days per month)
≥4 distinct headache episodes lasting ≥4 hours
≥50% of baseline headache days migraine/probable migraine days
Exclusion Criteria:
Previous use of botulinum toxin of any serotype or immunization to any botulinum toxin serotype
Any medical condition that puts the patient at increased risk with exposure to BOTOX
Diagnosis of complicated migraine, chronic tension-type headache, hypnic headache, hemicrania continua, new daily persistent headache
Use of prophylactic headache medication within 28 days prior to week -4
Unremitting headache lasting continuously throughout the 4-week baseline period
Known or suspected TMD
Diagnosis of fibromyalgia
Beck depression inventory score >24 at week-4
Psychiatric problems that may have interfered with study participation</td></tr>
<tr><td>Intervention</td><td>Biological: Botulinum Toxin Type A
Two treatment sessions in the double-blind phase and three treatment sessions in the open-label extension phase. Total minimum dose is 155 U with 31 fixed-site, fixed dose injections across seven specific head/neck muscle areas with the total maximum dose of 195 U with 39 head/neck injections.
Other Name: BOTOX®
Other: Placebo (saline)
Two treatment sessions in the double-blind phase. Total minimum dose in 155 U with 31 fixed-site, fixed dose injections across seven specific head/neck muscle areas and the total maximum dose is 195 U with 39 head/neck injections.</td></tr>
<tr><td>Baseline characteristics</td><td><table><tr><th></th><th>Placebo
N= 358</th><th>Botulinum Toxin Type A
N= 347</th></tr><tr><td>Age</td><td>41.0</td><td>40.9</td></tr><tr><td>Female, %</td><td>84.6</td><td>86.2</td></tr><tr><td>MMD (SD)</td><td>18.7 (4.1)</td><td>19.2 (3.9)</td></tr><tr><td>% patients with 1 or more prophylaxis</td><td>66.2</td><td>64.0</td></tr><tr><td>Mean BMI</td><td>27.1</td><td>26.7</td></tr><tr><td>% patients with medication overuse</td><td>69.8</td><td>66.3</td></tr></table></td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary efficacy endpoint was mean change from baseline in frequency of headache days for the 28-day period ending with week 24.

Secondary:
Frequency of migraine days (defined as a calendar day with ≥4 continuous hours of headache meeting ICHD-II criteria for migraine 1.1, 1.2 or 1.6)
Frequency of moderate/severe headache days (defined as a calendar day with 4 continuous hours of headache and a maximum severity of moderate or severe, per the patient diary among all headache episodes reported on that day regardless of duration)
Monthly cumulative headache hours on headache days
Proportion of patients with severe (≥60) Headache Impact Test (HIT)-6 score</td></tr>
</table>

	• Frequency of headache episodes (defined as patient-reported headache with a start and stop time indicating that the pain lasted ≥4 continuous hours).
Method of analysis	All efficacy analyses used the intent-to-treat population, which included all randomized patients. For each primary and secondary variable, prespecified comparisons between treatment groups were done by analysis of covariance of the change from baseline, with the same variable's baseline value as a covariate, with main effects of treatment group and medication overuse strata. The baseline covariate adjustment was prespecified as the primary analysis; sensitivity analyses (e.g., rank-sum test on changes from baseline without a baseline covariate) were also performed. Scores for months with at least 20 days of diary data were prorated to 28-day equivalents. Scores for months with less than 10 days of diary data were estimated using a modified last observation carried forward (mLOCF) methodology. This involved the substitution of the patient's previous 28-day period score multiplied by the ratio of the mean across all patients in the 28-day period of interest divided by the mean across all patients in the previous 28-day period. Scores for months with 10–19 days of diary data were estimated using an average of the prorated and the mLOCF estimates. The mLOCF method of imputation of missing data was prespecified, but sensitivity analyses were also done (e.g., using observed data, without imputation). For binomial variables, the between-group comparisons were done with Pearson's Chi-square or Fisher's exact tests, except that logistic regression, with the same variable's baseline as covariate, was used for variables with baseline imbalance. A two-sided test with $p \leq .05$ was considered statistically significant. To control the type 1 error rate for multiple secondary endpoints in the amended PREEMPT 2 protocol and analysis plan, a fixed-sequence gate-keeping approach was used for the five ranked secondary variables at the week 24 primary visit. If the p value of a secondary endpoint was not ≤.05, the tests of any lower-ranked secondary endpoints were not considered statistically significant, regardless of individual p value.
Subgroup analyses	None

TABEL 29 FREITAG 2008

Trial name	**Botulinum Toxin Type A in the treatment of Chronic Migraine Without Medication Overuse**
NCT number	None.
Objective	The objective of this study was to assess the efficacy and safety of Botulinum Toxin Type A compared with placebo in the treatments of chronic migraine not associated with medication overuse headache
Publications – title, author, journal, year	**Botulinum toxin type a in the treatment of chronic migraine without medication overuse, Freitag FG. et al. Headache, 2008**
Study type and design	This was a double-blind, parallel-group, placebo-controlled randomized study. 28 days screening phase, 16 week study. Patients were blind to their treatment allocation and randomized to active or placebo treatment using a list generated in Microsoft Excel (Redmond, WA, USA). The study medication BoNTA or placebo was prepared by a registered nurse in the research department familiar with the preparation of BoNTA following the preassigned randomization schedule. The research nurse responsible for the monitoring of the patient, review of diary logs, and completion of case report forms was different from the nurse preparing the study medication.
Follow-up time	Primay analysis after 16 weeks.

<table>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion Criteria:
Frequent migraine (≥15 headache days per month)
≥4 distinct headache episodes lasting ≥4 hours
6 month chronic migraine history
Stable preventive medications for 60 days
Exclusion Criteria:
Previous use of botulinum toxin of any serotype for any therapeutic reason.
Myasthenia gravis, Eaton-Lambert syndrome, Amyotrophic lateral sclerosis,
Other disorder of neuromuscular function, Use of aminoglycoside antibiotics
Curare-like agents, Other agents that might interfere with neuromuscular function
Patients with diagnoses of migraine beginning for the first time after age 50 years, cluster headaches or basilar, ophthalmoplegic, or hemiplegic migraine, exclusively having migraine aura without headache
Patients with a more painful condition than their migraine pain, progressive neurological disorders, or a structural disorder of the brain from birth, trauma, or past infection.
Patients who had received injections or oral corticosteroids within 30 days prior to the baseline diary initiation visit
Patients with a significant major psychiatric disorder (eg, major depression) or receiving antipsychotic medication, or who had a Beck Inventory of Depression Scores greater than 24
Patients who have received an investigational drug or used an investigational device within 30 days of study entry</td></tr>
<tr><td>Intervention</td><td>Biological: Botulinum Toxin Type A (BOTOX®, Allergan, Inc., Irvine, CA, USA) 100 U or placebo (sterile saline).</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo

N= 21</th><th>Botulinum Toxin Type A
N= 20</th></tr>
<tr><td>Age, years (range)</td><td>42.4 (22-55)</td><td>42.2 (19-64)</td></tr>
<tr><td>Female/male</td><td>15/6</td><td>15/5</td></tr>
<tr><td>Caucasian/other</td><td>20/1</td><td>18/2</td></tr>
<tr><td>Monthly migraine episodes, n</td><td>14.6</td><td>13.8</td></tr>
<tr><td>Monthly headache days, n</td><td>23</td><td>23</td></tr>
<tr><td>Acute medication doses per month, n (range)</td><td>21 (5-36)</td><td>19 (5-46)</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary efficacy parameter was the change in monthly migraine episode frequency per 4-week assessment period compared with baseline. Secondary efficacy parameters also assessed change from the baseline by 4-week assessment periods for the BoNTA and placebo groups.

Secondary:
Change in number of total headache days
The headache index (HAI) (the HAI being calculated by multiplying the maximal severity of a headache in a headache days times the duration of the headache in fraction of the 24-hour day the headache was experienced by the patient, summing the total of all the headaches for the evaluation period then dividing by the number of the days in the evaluation period).
The 50% responder rate (the percentage of patients who experience a 50% or greater reduction in their monthly migraine episode frequency)
Change in the amount of acute medication used</td></tr>
</table>

	• Change in MIDAS, and change in the Headache Pain Specific Quality of Life measure. Safety and tolerability (AEs) in each treatment group.
Method of analysis	Not applicable since the endpoints for this application are not the same as those analyzed in the publication
Subgroup analyses	None