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Appendix 1
Hovedkarakteristika for inkluderede studier

Studier med fremanezumab

TABLE 1 PHASE III HALO EM

Trial name	*HALO EM*
NCT number	*NCT02629861*
Objective	*The purpose of this study is to evaluate the efficacy, safety, and tolerability of monthly and quarterly subcutaneous (sc.) injections of fremanezumab compared with sc injections of placebo in patients with episodic migraine (EM).*
Publications – title, author, journal, year	*Effect of fremanezumab compared with placebo for prevention of episodic migraine, Dodick et al., JAMA, 2018*
Study type and design	*Randomized, double-blind, placebo-controlled, parallel-group phase 3 trial. Patients with episodic migraine were randomized 1:1:1 (stratified by sex, country, and baseline preventive migraine medication use) to receive (1) fremanezumab monthly, (2) a single higher dose of fremanezumab intended to support a quarterly dose regimen, or (3) placebo. Randomization was performed using electronic interactive response technology. Patients, investigators, the sponsor, and designated personnel were blinded to treatment assignments. The study is completed.*
Follow-up time	*Patients were seen at five scheduled visits for protocol-specified evaluations: at screening, baseline, weeks 4 and 8, and week 12.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Males or females aged 18 to 70 years, inclusive, with migraine onset at ≤50 years of age* • *Patient signs and dates the informed consent document* • *Patient has history of migraine according to International Classification of Headache Disorders, or clinical judgment suggests a migraine diagnosis* • *85% e-diary compliance* • *Total body weight between 99 and 265 lbs, inclusive* *Additional criteria apply, please contact the investigator for more information* ***Exclusion Criteria:*** • *Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator* • *Evidence or medical history of clinically significant psychiatric issues, including any suicide attempt in the past, or suicidal ideation with a specific plan in the past 2 years* • *History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [e.g., cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism*

<table>
<tr><td></td><td colspan="4">

- *Known infection or history of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection*
- *Past or current history of cancer in the last 5 years, except for appropriately treated nonmelanoma skin carcinoma*
- *Pregnant or nursing females*
- *History of hypersensitivity reactions to injected proteins, including monoclonal antibodies*
- *Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months or 5 half-lives, whichever is longer*

Additional criteria apply, please contact the investigator for more information
</td></tr>
<tr><td>Intervention</td><td colspan="4">*291 participants randomized to the fremanezumab 675 mg/placebo/placebo treatment (quarterly dosing) arm received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0, and placebo as a single 1.5-mL injection on Days 28 and 56.*

290 participants randomized to the fremanezumab 675/225/225 mg treatment (monthly dosing) arm received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) on Days 28 and 56.

294 participants received matching placebo.</td></tr>
<tr><td rowspan="6">Baseline characteristics</td><td colspan="4">*Baseline characteristics (total population)*</td></tr>
<tr><td>***Characteristic***</td><td>***Fremanezumab (monthly dosing)***</td><td>***Fremanezumab (quarterly dosing)***</td><td>***Placebo***</td></tr>
<tr><td>***Age, year, mean (SD)***</td><td>*42.9 (12.7)*</td><td>*41.1 (11.4)*</td><td>*41.3 (12.0)*</td></tr>
<tr><td>***Body mass index***</td><td>*26.2 (5.2)*</td><td>*27.0 (5.1)*</td><td>*27.2 (4.9)*</td></tr>
<tr><td>***Female sex, n (%)***</td><td>*244 (84.1)*</td><td>*251 (86.3)*</td><td>*247 (84.0)*</td></tr>
<tr><td>***Disease history***
Time since initial migraine diagnosis, year, mean (SD)
Current preventive medication use, n (%)
Current acute headache medication use, n (%)
Prior topiramate use, n (%)</td><td>

20.7 (12.9)
62 (21.4)
279 (96.2)
64 (22.1)</td><td>

20.0 (21.1)
58 (19.9)
281 (96.6)
51 (17.5)</td><td>

19.9 (11.9)
62 (21.1)
280 (95.2)
53 (18.0)</td></tr>
<tr><td>***Disease characteristics during 28-day prevention period***
Migraine days</td><td>

8.9 (2.6)</td><td>

9.3 (2.7)</td><td>

9.1 (2.7)</td></tr>
</table>

	Headache days of at least moderate severity	*6.8 (2.9)*	*7.2 (3.1)*	*6.9 (3.1)*
	Days with use of any acute headache medications	*7.7 (3.4)*	*7.8 (3.7)*	*7.7 (3.6)*
	Days with use of migraine-specific acute headache medications	*6.1 (3.1)*	*6.6 (3.1)*	*7.1 (3.0)*
	MIDAS score, mean (SD)	*38.0 (33.2)*	*41.7 (33.0)*	*37.2 (27.6)*
Primary and secondary endpoints	*The primary end point was the mean change from baseline (28-day pretreatment period) in the mean number of monthly migraine days during the 12-week period after the first injection.* *Secondary efficacy endpoints were:* • *the proportion of patients achieving at least a 50% reduction in the mean number of monthly migraine days from baseline to week 12* • *the mean change from baseline to week 12 in the monthly mean number of monthly days with use of any acute headache medications* • *the mean change from baseline to week 4 in the number of migraine days* • *the mean change from baseline to week 12 in mean number of monthly migraine days in patients not receiving concomitant migraine preventive medication* • *the mean change in the Migraine Disability Assessment (MIDAS) score.* *Adverse events and tolerability were assessed by evaluating reported adverse events, vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiratory rate), 12-lead electrocardiogram, clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis), physical examinations, and concomitant medication use. Suicidal ideation and behavior were assessed by the electronic Columbia-Suicide Severity Rating Scale. Systematic assessment of injection sites included examination for pain, erythema, induration, and ecchymosis immediately and 1 hour after dosing.*			
Method of analysis	*Efficacy analyses were conducted in the full analysis set, which included all randomized patients (intention-to-treat population). Analyses of adverse events were performed in all randomized patients who received at least 1 dose of study drug.* *The primary end point was analyzed using an analysis of covariance method. Ninety-five percent confidence intervals were constructed for the least-squares mean (LSM) differences between each fremanezumab group and the placebo group. The Wilcoxon rank-sum test was performed as the primary analysis if there was deviation from normality assumption as assessed by the Shapiro-Wilk test. The same analyses were used for relevant secondary end points. A mixed-effects repeated-measures analysis model was implemented as a sensitivity.*			
Subgroup analyses	*A small subgroup of patients (approximately 30%) was allowed to use concomitant migraine preventive medications. Analyses for the subgroup not receiving concomitant was performed; mean change from baseline (28-day run-in period) in the monthly*			

	average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug in patients not receiving concomitant migraine preventive medications.

TABLE 2 BIGAL ET AL., 2015 (EM)

Trial name	*A Multicenter Assessment of LBR-101 in High Frequency Episodic Migraine*
NCT number	*NCT02025556*
Objective	*The purpose of this study is to determine whether monthly subcutaneous administration of LBR-101 is safe and provides migraine prevention in subjects with high frequency episodic migraine.*
Publications – title, author, journal, year	*Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Bigal et al., Lancet Neurology, 2015*
Study type and design	*In this multicentre, randomised, double-blind, placebo-controlled, phase 2b study, we enrolled men and women (aged 18-65 years) from 62 sites in the USA who had migraine headaches 8-14 days per month. Using a randomisation list generated by a central computerized system and an interactive web response system, we randomly assigned patients (1:1:1; stratified by sex and use of concomitant preventive drugs) after a 28 day run-in period to three 28 day treatment cycles of subcutaneous 225 mg TEV-48125, 675 mg TEV-48125, or placebo. Investigators, patients, and the funder were blinded to treatment allocation. Patients reported headache information daily using an electronic diary. The study is completed.*
Follow-up time	*Time Frame: 12 weeks after first dose of blinded study drug*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Males or females aged 18 to 65 years of age.* • *A signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study including any known and potential risks and available alternative treatments.* • *Subjects fulfilling criteria for episodic migraine as per the Second Edition of The International Headache Society (Olesen and Steiner 2004), who experience migraine at high frequency as follows:* *- History of headaches on more than 8 days per month for at least 3 months prior to screening* *- Verification of headache frequency through prospectively collected baseline information during the 28-day run-in phase demonstrating headaches (of any type) on at least 8 days with a total of 8 to 14 days* fulfilling criteria for migraine.* **Operational definition for migraine and probable migraine days are presented in the statistical section of this protocol.* • *Body Mass Index (BMI) of 17.5 to 37.5 kg/m2, and a total body weight between 50 kg and 120 kg, inclusive.* • *Demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on a minimum of 22/28 days (80% compliance).*

	Exclusion Criteria: • *Subject has received onabotulinum toxin A for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the six months prior to screening.* • *Subject uses medications containing opioids (including codeine) or barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) on more than 4 days per month for the treatment of migraine or for any other reason.* • *Failed > 2 medication categories or > 3 preventive medications (within two medication categories) due to lack of efficacy for prophylactic treatment of episodic or chronic migraine after an adequate therapeutic trial* • *Treatment with an investigational drug or device within 30 days of study entry or any prior exposure to a monoclonal antibody targeting the CGRP pathway.*			
Intervention	*319 participants randomized to the subcutaneous LBR-101. The three arms are: Subcutaneous High Dose LBR-101 Administered Monthly x 3; Subcutaneous Low Dose LBR-101 Administered Monthly x 3; Subcutaneous Placebo Administered Monthly x 3. Between Jan 8, 2014, and Oct 15, 2014, 297 participants were enrolled: 104 were randomly assigned to receive placebo, 95 to receive 225 mg TEV-48125, and 96 to receive 675 mg TEV-48125.*			
Baseline characteristics	*Baseline characteristics (total population)*			
	Characteristic	***Placebo (n=104)***	***TEV-48125 225 mg (n=96)***	***TEV-48125 675 mg (n=97)***
	Age, years	*42·0 (11·6)*	*40·8 (12·4)*	*40·7 (12·6)*
	Height, cm	*165·3 (9·2)*	*165·1 (6·3)*	*166·2 (8·9)*
	Body mass index, kg/m²	*27·2 (5·2)*	*26·9 (5·2)*	*27·4 (5·1)*
	Female sex, n (%)	*92 (88%)*	*87 (91%)*	*82 (85%)*
	Preventive drug use (yes)	*28 (27%)*	*32 (34%)*	*26 (27%)*
	Discontinued past preventive drug use owing to absence of effi cacy	*28 (27%)*	*32 (33%)*	*28 (29%)*
	Patients using triptans ≥11 days per month	*13 (13%)*	*11 (12%)*	*7 (7%)*
	Migraine-days per month	*11·5 (2·24)*	*11·5 (1·9)*	*11·3 (2·2)*
	Headache-days per month	*12·4 (2·3)*	*12·6 (3·1)*	*12·5 (2·65)*
	Days using acute drugs per month	*10·4 (3·6)*	*10·4 (3·6)*	*9·8 (4·0)*
	Days using triptans per month	*8·5 (3·4)*	*8·2 (4·0)*	*6·9 (3·5)*

	Medium or severe headache-days per month	*9·8 (2·7)*	*10·0 (3·1)*	*9·6 (2·9)*
	Headache-hours per month	*82·1 (49·3)*	*76·1 (36·7)*	*80·4 (36·6)*
	Migraine Disability Assessment score	*48·4 (47·5)*	*45·7 (42·6)*	*48·4 (46·1)*
	Data are mean (SD) or number of patients (%)			
Primary and secondary endpoints	*The primary endpoints:* *1. Efficacy of two distinct doses of subcutaneous LBR-101 in the preventive treatment of HFEM, measured by mean change from baseline in the monthly migraine days during the 28-day post treatment period ending with week 12 [Time Frame: 12 weeks after first dose of blinded study drug]* *2. Evaluate the safety and tolerability (i.e.: by measuring the change from baseline in the frequency and severity of adverse events) of LBR-101 in the preventive treatment of HFEM. [Time Frame: 12 weeks after first dose of blinded study drug]* *Secondary efficacy endpoint: Efficacy of two distinct doses of subcutaneous LBR-101 in the preventive treatment of HFEM, measured by mean change from baseline on the number of days with headache of any severity during the 28-day post treatment period ending with week 12 [Time Frame: 12 weeks after first dose of blinded study drug]*			
Method of analysis	*Sample size and power were calculated for the primary endpoint to provide at least 90% power to detect a difference of 1·5 days between placebo and active treatment (SD 3 days).* *Change from baseline in the number of migraine-days in weeks 1–4, weeks 5–8, and weeks 9–12 was the dependent variable; preventive drug use (yes or no), sex, visit number, treatment, and treatment-by-visit interaction were fixed factors; acute drug use and years since onset of disease were covariates; and patient was treated as a random effect. We used an unstructured covariance matrix for repeated findings within patients and constructed 95% CIs for the least square mean difference between each group. Since MIDAS is used to assess disability during a 3 month period and was measured only twice (pre-treatment and after the last treatment), the change from baseline in total MIDAS scores to week 12 was analysed using an ANCOVA model with treatment group, baseline preventive drug use, and sex as fixed effects and baseline MIDAS total scores and years since onset of disease as covariates.* *The post-hoc analyses of the proportion of responders were done using χ^2 tests. All statistical tests were two-sided at a type I error (α) of 0·05. We used the Hochberg approach to adjust for multiplicity for the analysis of the primary and secondary efficacy variables. All efficacy variables were analysed for the intention-to-treat population, which included all participants who were randomly assigned to treatment group, received at least one dose of study drug, and provided at least one endpoint*			

	measurement. All treated participants were included in the safety analysis. We used SAS version 9.1.3 for all statistical analyses
Subgroup analyses	*N/A*

TABLE 3 PHASE III HALO CM

Trial name	*HALO CM*
NCT number	*NCT02621931*
Objective	*The purpose of this study is to evaluate the efficacy, safety, and tolerability of monthly and quarterly subcutaneous (sc.) injections of fremanezumab compared with sc injections of placebo in patients with chronic migraine (CM).*
Publications – title, author, journal, year	*Fremanezumab for the preventive treatment of chronic migraine. Silberstein et al., NEJM, 2017.*
Study type and design	*Randomized, double-blind, placebo-controlled, parallel-controlled, parallel-group trial phase 3 trial. Eligible patients were randomly assigned in a 1:1:1 ratio to receive either (1) a single higher dose of fremanezumab intended to support a quarterly dose regimen, (2) fremanezumab monthly, or (3) placebo. Patients, investigators, the sponsor, and trial staff were unaware of the trial-group assignments. The study is completed.*
Follow-up time	*Patients were seen at five scheduled visits for protocol-specified evaluations: at screening, baseline, weeks 4 and 8, and week 12.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Males or females aged 18 to 70 years, inclusive, with migraine onset at ≤50 years of age* • *Patient signs and dates the informed consent document* • *Patient has history of migraine according to International Classification of Headache Disorders, or clinical judgment suggests a migraine diagnosis* • *85% e-diary compliance* • *Total body weight between 99 and 250 lbs, inclusive* *Additional criteria apply, please contact the investigator for more information* ***Exclusion Criteria:*** • *Clinically significant haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator* • *Evidence or medical history of clinically significant psychiatric issues, including any suicide attempt in the past, or suicidal ideation with a specific plan in the past 2 years* • *History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [e.g. cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism*

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Known infection or history of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection
Past or current history of cancer in the last 5 years, except for appropriately treated nonmelanoma skin carcinoma
Pregnant or nursing females
History of hypersensitivity reactions to injected proteins, including monoclonal antibodies
Participation in a clinical study of a new chemical entity or a prescription medicine within 2 months prior to study drug administration or 5 half-lives, whichever is longer

Additional criteria apply, please contact the investigator for more information
</td></tr>
<tr><td>Intervention</td><td>
376 participants randomized to the fremanezumab 675 mg/placebo/placebo treatment (quarterly dosing) arm received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0, and placebo as a single 1.5-mL injection on Days 28 and 56.

379 participants randomized to the fremanezumab 675/225/225 mg treatment (monthly dosing) arm received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) on Day 0 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) on Days 28 and 56.

375 participants received matching placebo.
</td></tr>
<tr><td>Baseline characteristics</td><td>
Baseline characteristics (total population)
<table>
<tr><th>Characteristic</th><th>Fremanezumab (quarterly dosing)</th><th>Fremanezumab (monthly dosing)</th><th>Placebo</th></tr>
<tr><td>Age, year</td><td>42.0 ±12.4</td><td>40.6 ±12.0</td><td>41.4 ±12.0</td></tr>
<tr><td>Body mass index</td><td>26.6 ±5.4</td><td>26.5 ±5.1</td><td>26.5 ±5.0</td></tr>
<tr><td>Female sex, n (%)</td><td>331 (88)</td><td>330 (87)</td><td>330 (88)</td></tr>
<tr><td>Disease history
Time since initial migraine diagnosis, year
Current use of preventive medication, n (%)
Current use of acute headache medication, n (%)
Previous use of topiramate, n (%)
Previous use of onabotulinumtoxinA, n (%)</td><td>19.7 ±12.8
77 (2)
359 (95)
106 (28)
66 (18)</td><td>20.1 ±12.0
85 (22)
360 (95)
117 (31)
50 (13)</td><td>19.9 ±12.9
77 (21)
358 (95)
117 (31)
49 (13)</td></tr>
<tr><td>Disease characteristics during 28-day prevention period
Headache days</td><td>13.2 ±5.5</td><td>12.8 ±5.8</td><td>13.3 ± 5.8</td></tr>
</table>
</td></tr>
</table>

	Days with headache of any severity and duration	*20.4 ±3.9*	*20.3 ±4.3*	*20.3 ± 4.2*
	Migraine days	*16.2 ±4.9*	*16.0 ±4.3*	*16.4 ±5.2*
	Days of use of any acute headache medications	*13.1 ±6.8*	*13.1 ±7.2*	*13.0 ±6.9*
	Days of use of migraine-specific acute headache medications	*11.3 ±6.2*	*11.1 ±6.0*	*10.7 ±6.3*
	HIT-6 score	*64.3 ±4.7*	*64.6 ±4.4*	*64.1 ±4.8*
Primary and secondary endpoints	*The primary end point was the mean change in the average number of headache days per month, comparing the baseline 28-day preintervention period with the 12-week period after the first dose of the trial regimen.* *Secondary end points were* • *the mean change from baseline in the average number of migraine days per month* • *the percentage of patients with a reduction of at least 50% in the average number of headache days per month* • *the mean change from baseline in the average number of days per month in which acute headache medication was used during the 12-week period after the first dose.* • *the mean change from baseline in the number of headache days during the 4-week period after the first dose in all the patients and during the 12-week period after the first dose in patients not receiving concomitant preventive medication* • *the mean change in the score on the six-item Headache Impact Test (HIT-6; scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability) 15 from baseline (day 0) to 4 weeks after administration of the last dose of the trial regimen.* *Safety and side-effect profiles were evaluated according to reported adverse events, vital signs (systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate), physical examination, 12-lead electrocardiography, clinical laboratory tests (serum chemical, hematologic, coagulation, and urinalysis tests), systematic assessments of local injection-site reactions (erythema, induration, ecchymosis, and pain, all evaluated both immediately and 1 hour after dose administration), concomitant medication use, and suicidal ideation and behavior as assessed by means of scores on the electronic Columbia–Suicide Severity Rating Scale.*			
Method of analysis	*Efficacy analyses were conducted in the modified intention-to-treat population, which included all randomly assigned patients. Safety analyses included all randomly assigned patients who received at least one dose of a trial regimen.* *The primary end point was analyzed with the use of an analysis of covariance.* *The Wilcoxon rank-sum test was performed as the primary analysis if there was deviation from the normality assumption as assessed by means of the Shapiro–Wilk test. The same analyses were used for relevant secondary end points. For the*			

	percentage of patients with a reduction of at least 50% in the average number of headache days per month, the Cochran–Mantel–Haenszel test was used, with baseline use of preventive medication (yes or no) as a stratification variable.
Subgroup analyses	*A small subgroup of patients (approximately 30%) was allowed to use concomitant migraine preventive medications. Analyses for the subgroup not receiving concomitant was performed; mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug in patients not receiving concomitant migraine preventive medications.*

TABLE 4 BIGAL ET AL., 2015 (CM)

Trial name	*Assessment of LBR-101 In Chronic Migraine*
NCT number	*NCT02021773*
Objective	*The purpose of the study is to determine whether monthly subcutaneous administration of LBR-101 is safe and provides migraine prevention in patients with chronic migraine.*
Publications – title, author, journal, year	*Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Bigal et al., Lancet neurology, 2015*
Study type and design	*In this multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group phase 2b study, we enrolled men and women (aged 18-65 years) from 62 sites in the USA who had chronic migraine. Using a randomisation list generated by a central computerised system and an interactive web response system, we randomly assigned patients (1:1:1, stratified by sex and use of concomitant preventive drugs) to three 28-day treatment cycles of subcutaneous TEV-48125 675/225 mg (675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles), TEV-48125 900 mg (900 mg in all three treatment cycles), or placebo. Investigators, patients, and the funder were blinded to treatment allocation. The study is completed.*
Follow-up time	*Time frame: 12 weeks*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Males or females aged 18 to 65 years of age.* • *A signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study including any known and potential risks and available alternative treatments.* • *Chronic migraine meeting the diagnostic criteria listed in the International Classification of Headache Disorders (ICHD-III beta version, 2013)* • *Body Mass Index (BMI) of 17.5 to 37.5 kg/m2, and a total body weight between 50 kg and 120 kg inclusive.* • *Demonstrated compliance with the electronic headache diary during the run-in period headache data on a minimum of 22/28 days (80% diary compliance)* ***Exclusion Criteria:*** • *Onset of chronic migraine after the age of 50 years.*

<table>
<tr><td></td><td colspan="4">Subject has received onabotulinum toxin A for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 6 months prior to study entry.
Subject is using medications containing opioids (including codeine) or barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) on more than 4 days per month for the treatment of migraine or for any other reason.
Failed > 2 medication categories or > 3 preventive medications (within two medication categories) due to lack of efficacy for prophylactic treatment of episodic or chronic migraine after an adequate therapeutic trial
Treatment with an investigational drug or device within 30 days of study entry or any prior exposure to a monoclonal antibody targeting the CGRP pathway.</td></tr>
<tr><td>Intervention</td><td colspan="4">277 participants randomized to the subcutaneous LBR-101. Between Jan 8, 2014, and Aug 27, 2014, we enrolled 264 participants: 89 were randomly assigned to receive placebo, 88 to receive 675/225 mg TEV-48125, and 87 to receive 900 mg TEV-48125.</td></tr>
<tr><td rowspan="15">Baseline characteristics</td><td colspan="4">Baseline characteristics (total population)</td></tr>
<tr><td>Characteristic</td><td>Placebo (n=89)</td><td>TEV-48125 675/225 mg (n=88)</td><td>TEV-48125 900 mg (n=86)</td></tr>
<tr><td>Age, years</td><td>40·7 (11·5)</td><td>40·0 (11·6)</td><td>41·5 (12·9)</td></tr>
<tr><td>Height, cm</td><td>166·4 (8·1)</td><td>165·4 (8·3)</td><td>165·7 (7·6)</td></tr>
<tr><td>Body mass index, kg/m²</td><td>25·7 (4·5)</td><td>27·0 (5·2)</td><td>26·6 (5·3)</td></tr>
<tr><td>Female sex, n (%)</td><td>76 (85%)</td><td>76 (86%)</td><td>75 (86%)</td></tr>
<tr><td>Headache-hours of any severity per month</td><td>169·1 (113·11)</td><td>159·1 (90·73)</td><td>157·7 (108·16)</td></tr>
<tr><td>Headache-hours of at least moderate severity per month</td><td>91·90 (74·68)</td><td>90·7 (59·71)</td><td>96·20 (94·42)</td></tr>
<tr><td>Headache-days of at least moderate severity per month</td><td>13·9 (5·6)</td><td>13·8 (6·3)</td><td>13·1 (5·9)</td></tr>
<tr><td>Migraine-days per month</td><td>16·8 (5·0)</td><td>17·2 (5·4)</td><td>16·4 (5·3)</td></tr>
<tr><td>Days of acute drug use per month</td><td>15·7 (6·2)</td><td>15·1 (7·0)</td><td>16·2 (6·7)</td></tr>
<tr><td>Days of triptan use per month</td><td>10·0 (5·3)</td><td>9·2 (5·6)</td><td>11·8 (6·0)</td></tr>
<tr><td>Years of migraine</td><td>20·4 (13·1)</td><td>15·8 (11·2)</td><td>18·8 (12·2)</td></tr>
<tr><td>Preventive drug use (yes)</td><td>38 (43%)</td><td>35 (40%)</td><td>33 (38%)</td></tr>
</table>

	Data are mean (SD) or number of patients (%)
Primary and secondary endpoints	*The primary endpoints:* *1. Mean change from baseline in the number of monthly cumulative headache hours of any severity on headache days relative to the 28-day post-treatment period ending with week 12 [Time Frame: 12 weeks after first dose of blinded study drug]* *2. Safety as determined by the presence of Adverse events by treatment group [Time Frame: 12 weeks after first dose of blinded study drug]* *Secondary efficacy endpoint: Mean change from baseline in the number of headache days of at least moderate severity relative to the 28-day post-treatment period ending with week 12. [Time Frame: 12 weeks after first dose of blinded study drug]*
Method of analysis	*Sample size and power were calculated using the PASS version 11 statistical software developed by NCSS LLC (Kaysville, UT, USA). To detect with at least 80% power a mean change from baseline in the number of headache hours of at least 35 h (SD≤80), at least 30 h (SD≤60), or at least 25 h (SD≤40), we aimed to allocate at least 75 participants to each group. To impute values for missing calendar day entries in a given month, scores of months with 20–27-day entries were prorated. Scores for months with less than 10 days of diary data were estimated using a modified last observation carried forward approach, calculated as the patient's previous 28 day period mean value of day entries multiplied by the ratio of the mean for all patients in the same period and divided by the mean number of day entries for all patients in the previous 28 day period. Scores for months with 10–19 days of diary data were estimated using an average of both methods.* *The primary, secondary, and exploratory efficacy endpoints were analysed using the mixed-effects model repeated measurement (MMRM) analysis method. Change from baseline in the variable of interest (e.g., headache-hours) at weeks 1–4, weeks 5–8, and weeks 9–12 was the dependent variable; preventive drug use (yes or no), sex, visit number, treatment, and treatment-by-visit interaction were fixed factors; baseline value of the variable of interest and years since disease onset were covariates; and patient was treated as a random effect. We used unstructured covariance matrix for repeated findings within patients and constructed 95% CIs for the least square mean difference between groups.* *All statistical tests were two-sided at a type I error (α) of 0·05. We used the Hochberg approach to adjust for multiplicity for the analysis of the primary and secondary efficacy variables. All efficacy variables were analysed for the intention-to-treat population, which included all patients who were randomly assigned to treatment group, received at least one dose of study drug, and provided at least one endpoint measurement. We used SAS version 9.3 for all statistical analyses.*
Subgroup analyses	*A post-hoc subgroup analysis was performed indicating that there was a significant difference in number of days on which triptans were used between the placebo group and each of the TEV-48125 dose.*

TABLE 5 PHASE IIIB FOCUS

Trial name	*An Efficacy and Safety Study of Fremanezumab in Adults With Migraine (FOCUS)*
NCT number	*NCT03308968*
Objective	*The purpose of this study is to evaluate the efficacy, safety, and tolerability of monthly and quarterly subcutaneous (sc.) injections of fremanezumab compared with sc injections of placebo in patients with chronic migraine (CM) or episodic migraine (EM) who have responded inadequately to 2 to 4 classes of prior preventive treatments.*
Publications – title, author, journal, year	*Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomized, double-blind, placebo-controlled, phase 3b trial. Ferrari et al, Lancet, 2019.*
Study type and design	*A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled,Study With an Open-Label Period to Evaluate the Efficacy and Safety of Fremanezumab for the Prophylactic Treatment of Migraine in Patients With Inadequate Response to Prior Preventive Treatments, 838 men and women were enrolled (age 18-70 yr). The study consisted of three arms;* *Arm 1: fremanezumab monthly: During the double-blind period, participants with chronic migraine (CM) are administered Dosage A subcutaneous (sc) injection of fremanezumab at Week 0 (baseline) followed by Dosage B sc injections at Week 4 and Week 8 and participants with episodic migraine (EM) are administered Dosage B subcutaneous (sc.) injection of fremanezumab at Week 0 (baseline), Week 4, and Week 8 then followed by an open label period where all participants are administered Dosage B sc injection of fremanezumab at Weeks 12, 16 and 20. Intervention: fremanezumab.* *Arm 2: Fremanezumab quarterly: During the double-blind period, participants with chronic migraine (CM) and participants with episodic migraine (EM) are administered Dosage A sc injection of fremanezumab at Week 0 (baseline) followed by placebo sc injections at Week 4 and Week 8 followed by an open label period where all participants are administered Dosage B sc. injection of fremanezumab at Weeks 12, 16 and 20. Intervention: fremanezumab and placebo.* *Arm 3: Placebo Comparator: During the double-blind period, participants with chronic migraine (CM) and participants with episodic migraine (EM) are administered 3 placebo sc injections at Week 0, and 1 placebo injection at weeks 4 and 8 followed by an open label period where all participants are administered Dosage B sc. injection of fremanezumab at Weeks 12, 16 and 20. Intervention: fremanezumab and placebo.* *The study is completed.*
Follow-up time	*12 weeks*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *The patient has a diagnosis of migraine with onset at ≤50 years of age.* • *Body weight ≥45 kg* • *The patient has a history of migraine for ≥12 months prior to screening.* • *Women of childbearing potential (WOCBP) whose male partners are potentially fertile (i.e., no vasectomy) must use highly effective birth control methods for the duration of the study and the follow-up period and for 6.0 months after discontinuation of investigational medicinal product (IMP)*

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

Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [e.g., vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, acceptable birth control methods for the duration of the study and for 6.0 months after discontinuation of the investigational medicinal product (IMP).

Exclusion Criteria:

At the time of screening visit, patient is receiving any preventive migraine medications, regardless of the medical indication for more than 5 days and expects to continue with these medications.
Patient has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face, or neck during the 3 months before screening visit.
The patient has used an intervention/device (e.g., scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening.
The patient uses triptans/ergots as preventive therapies for migraine.
Patient uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (e.g., 81 mg) used for cardiovascular disease prevention is allowed.

</td></tr>
<tr><td>Intervention</td><td>838 participants randomized in blinded-fashion 1:1:1 into one of three treatments for the subgroup - two active treatments and one placebo treatment consisting of monthly injections for 3 months (up to week 12). Then all participants continue into an open-label extension of 3 months (weeks 13-week 24) during which everyone is administered sc injections of fremanezumab</td></tr>
<tr><td>Baseline characteristics</td><td>
Baseline characteristics (total population)
<table>
<tr><th>Characteristic</th><th>Placebo (n=279)</th><th>Quarterly fremanezumab (n=276)</th><th>Monthly fremanezumab (n=283)</th></tr>
<tr><td>Age, years</td><td>46.8 (11.1)</td><td>45.8 (11.0)</td><td>45.9 (11.1)</td></tr>
<tr><td>Height, cm</td><td>167.7 (9.0)</td><td>167.7 (8.1)</td><td>167.3 (7.7)</td></tr>
<tr><td>Body mass index, kg/m²</td><td>25.3 (4.1)</td><td>25.1 (4.1)</td><td>25.3 (4.3)</td></tr>
<tr><td>Female sex, n (%)</td><td>233 (84%)</td><td>229 (83%)</td><td>238 (84%)</td></tr>
<tr><td>Episodic migraine</td><td>112 (40%)</td><td>107 (39%)</td><td>110 (39%)</td></tr>
<tr><td>Chronic migraine</td><td>167 (60%)</td><td>169 (61%)</td><td>173 (61%)</td></tr>
<tr><td colspan="4">Number of previous preventive medication classes failed</td></tr>
<tr><td>2</td><td>142 (51%)</td><td>140 (51%)</td><td>133 (47%)</td></tr>
<tr><td>3</td><td>82 (29%)</td><td>85 (31%)</td><td>98 (35%)</td></tr>
<tr><td>4</td><td>54 (19%)</td><td>49 (18%)</td><td>50 (18%)</td></tr>
<tr><td>Monthly number of migraine days at baseline</td><td>14.3 (6.1)</td><td>14.1 (5.6)</td><td>14.1 (5.6)</td></tr>
<tr><td>Monthly number of headache days of at least moderate severity at baseline</td><td>12.8 (5.9)</td><td>12.4 (5.8)</td><td>12.7 (5.8)</td></tr>
</table>
</td></tr>
</table>

	Monthly days of use of any acute headache medication at baseline	*12.3 (6.3)*	*12.8 (6.2)*	*12.2 (6.0)*
	Data are mean (SD) or n (%)			
Primary and secondary endpoints	*The primary endpoint:* *Mean change from baseline in the monthly average number of migraine days during the double-blind period [Time Frame: Baseline (days -28 to 0), Treatment up to week 12]* *Secondary efficacy endpoint:* • *proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the double-blind period [Time Frame: Baseline, 12 weeks]* • *mean change from baseline in the monthly average number of headache days of at least moderate severity during the double-blind period [Time Frame: Baseline, 12 weeks]* • *mean change from baseline in the monthly average number of migraine days during the double-blind period [Time Frame: Baseline, 4 weeks]* • *proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the double-blind period [Time Frame: 4 weeks]* • *mean change from baseline in the monthly average number of days of use of any acute headache medications during the double-blind period [Time Frame: Baseline, 12 weeks]* • *mean change from baseline in the number of headache days of at least moderate severity during the double-blind period [Time Frame: Baseline, 4 weeks]* • *percentage of patients who did not complete study due to AEs [Time Frame: 12 weeks]* • *Percentage of Participants with Adverse Events [Time Frame: 12 weeks]*			
Method of analysis	*A sample size of 705 participants (235 per treatment group) completing the study was required for 90% power to show a difference of 1.8 in migraine days (assuming a common SD of 6 days) at an alpha level of 0.05. Assuming a 12% discontinuation rate, 268 participants per treatment group were planned for randomisation.* *The intention-to-treat analysis set comprised all randomly assigned participants. The safety analysis set comprised all randomly assigned participants who received at least one dose of study drug. Participants in the intention-to-treat analysis set who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessments for the primary outcome (modified intention-to-treat analysis set) were included in all efficacy analyses. The per-protocol analysis set was a subset of the modified intention-to-treat analysis set, including only participants who completed the study without important protocol deviations or any deviations or omissions in study drug administration.* *The primary efficacy outcome was analysed with an analysis of covariance (ANCOVA) method, with treatment, sex, region, special group of treatment failure, migraine classification, and treatment by migraine classification interaction as fixed effects; and baseline number of migraine days and years since onset of migraine as covariates. Sensitivity analyses were done with a mixed-effects repeated measures analysis model, including treatment, sex, region, special group of treatment failure, migraine*			

	classification, month, treatment-by-migraine classification interaction, treatment-by-month interaction, and treatment-bymigraine classification-by-month interaction as fixed effects; baseline value and years since onset of migraine as covariates; and participant as a random effect. The least-squares mean (LSM) change from baseline with standard error (SE) is presented for each treatment group, and the LSM difference versus placebo with 95% CI is presented for both fremanezumab dosing groups. Continuous secondary and exploratory efficacy outcomes were analysed similarly to the primary efficacy outcome. For the proportion of responders, a logistic regression model was used with the following effects: treatment, sex, region, special group of treatment failure (yes or no), and migraine classification (chronic or episodic). Stratification factors (as randomised) were used in the model. Participants who discontinued treatment early were considered non-responders for the overall analysis and for each month after discontinuation. *Odds ratios (ORs), 95% CIs for ORs, and p values are presented for each fremanezumab dosing group (quarterly and monthly doses). Adverse events were summarised by counts and percentages. Changes in laboratory, electrocardiogram (ECG), and vital signs measurements data were summarized descriptively. All values were compared with predefined criteria to identify potentially clinically significant values or changes.*
Subgroup analyses	*As part of prespecified exploratory analyses, the primary efficacy outcome was evaluated in subgroups of participants who had previously not responded to topiramate, onabotulinumtoxinA, valproic acid, and valproic acid plus two to three classes of preventive medications.*

Studier med komparatorer

Betablokkere (metoprolol/propranolol)

TABLE 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:

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

Patients must not have failed more than two previous adequate regimens of prophylactic medications for recurrent migraine episodes.
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

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</table>

	• Responder rate (response defined as at least a 50% reduction in average monthly migraine frequency) • 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

TABLE 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

<table>
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Psychiatric disorders
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</td></tr>
</table>

	- Number of working days lost due to migraine, - 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

TABLE 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

TABLE 9 SCHRADER ET AL., 2001

Trial name	*Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study*
NCT number	*Not stated in the publication*
Objective	*To determine the efficacy of an angiotensin converting enzyme inhibitor in the prophylaxis of migraine.*
Publications – title, author, journal, year	*Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo-controlled crossover study. Schrader et al., BMJ (Clinical research ed.), 2001*
Study type and design	*Double blind, placebo-controlled crossover study. After a four-week placebo run-in period to verify the frequency of attacks, patients were randomly allocated to take one tablet daily containing either 10 mg lisinopril (active) or placebo (inactive). The participants kept a daily diary in which they recorded the presence, severity, and, if appropriate, duration of symptoms in hours. Quality of life was assessed with a standardised questionnaire (SF-36). After each treatment period participants were also asked about the acceptability of the treatment ("If you could receive this treatment on prescription, would you like to continue with the treatment that you have used in the past 12 weeks?"). Participants were defined as compliant with treatment if they had adhered to the drug regimen (>80% of the tablets taken as determined by a tablet count at the end of the treatment period) and had given complete data in the diary.*
Follow-up time	*12 weeks*

Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Diagnosis of migraine with and without aura according to the criteria of the International Headache Society* • *Men and women aged between 18 and 60 year* • *Presence of migraine for more than a year* • *Onset of migraine before the age of 50 years* • *Attacks of migraine occurring two to six times a month.* ***Exclusion Criteria:*** • *Interval headache that the patient was unable to differentiate from migraine* • *Use of prophylactic drugs for migraine in the four weeks before randomization* • *Pregnancy or inability to use contraceptives* • *Decreased renal or hepatic function* • *Hypersensitivity to angiotensin converting enzyme inhibitors* • *History of angio neurotic oedema, and psychiatric disorder.*
Intervention	*Treatment period of 12 weeks with one 10 mg lisinopril tablet once daily for one week then two 10 mg lisinopril tablets once daily for 11 weeks, followed by a two week wash out period. Second treatment period of one placebo tablet once daily for one week and then two placebo tablets for 11 weeks. Thirty participants followed this schedule, and 30 received placebo followed by lisinopril.*
Baseline characteristics	*No baseline characteristics stated in the publication.*
Primary and secondary endpoints	*Primary end points: number of hours with headache, number of days with headache, number of days with migraine. Secondary end points: headache severity index, use of drugs for symptomatic relief, quality of life and number of days taken as sick leave, acceptability of treatment*
Method of analysis	*A Wilcoxon signed rank test was used to compare end point variables. For comparison of adverse events and acceptability we used a McNemar's matched pairs test A two-sided P<0.05 was considered significant A paired study including 55 subjects will have about 80% power to detect a group mean difference of 0.5 SD (with Student's t test).*
Subgroup analyses	*None*

Candesartancilexetil

TABLE 10 STOVNER 2014 (SE UNDER PROPRANOLOL).

TABLE 11 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

<table>
<tr><td>Publications – title, author, journal, year</td><td>Prophylactic treatment of Migraine with an Angiotensin II Receptor blocker. A Randomized Controlled Trial. Tronvik E, et al. JAMA 2003</td></tr>
<tr><td>Study type and design</td><td>Randomized double blind, placebo-controlled cross-over study</td></tr>
<tr><td>Follow-up time</td><td>12 weeks</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>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
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

TABLE 12 STOREY ET AL., 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:*** • *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 Page 32 of 50 titrated weekly in 25 mg increments over 8 weeks, to 200 mg. pr. day or to the maximum tolerated doses.*		
Baseline characteristics		*Topiramate N=19*	*Placebo N=21*
	Age, years (range)	*38.3 (19-62)*	*38.1 (24-56)*
	Female, n	*19*	*20*
	Male, n	*0*	*1*
	Migraine frequency per 28 days,n, (SD)	*5.14 (1.56)*	*4.37 (1.96)*
	Weight, lb (SD)	*170.8 (33,3)*	*181.0 (41.6)*

Primary and secondary endpoints	*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 endpoint:* • *mean percent reduction in migraine rate* • *the percentage of responders in each group*
Method of analysis	*Statistical Analysis: Not applicable since the endpoints for this application are not the same as those analysed in the publication*
Subgroup analyses	*N/A*

TABLE 13 MEI ET AL., 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:*** • *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 interictal period* • *those who had commenced any form of prophylactic therapy in the 2 months preceding trial.*		
Intervention	*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.*		
Baseline characteristics	*Patients completing the study*	*Topiramate N=35*	*Placebo N=37*
	Age, years (SD)	*39.,74 (12.02)*	*38.70 (11.04)*
	Female, n	*19*	*20*

	Male, n	*16*	*17*
	Frequencies of crises, n (SD)	*5.26 (1.29)*	*5.76 (0.98)*
Primary and secondary endpoints	*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 efficacy measures:* • *Effect of the quantity of symptomatic drugs taken during the period of therapy* • *Numbers of days of disability*		
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*		

TABLE 14 DIENER ET AL., 2004 (SE UNDER PROPRANOLOL).

TABLE 15 BRANDES ET AL., 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 months 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 Page 22 of 50 calendar day during which the patient experienced headache for at least 30 minutes.* • *Women 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 Criteria:*** • *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*

<table>
<tr><td></td><td colspan="5">• 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 (e.g., 600 mg/d), riboflavin at high doses (e.g., 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 colspan="5">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 rowspan="10">Baseline characteristics</td><td>Characteristic</td><td>Placebo N=114</td><td>Topiramate 50 mg/d N=117</td><td>Topiramate 100 mg/d N=120</td><td>Topiramate 200 mg/d N=117</td></tr>
<tr><td>Age, years</td><td>38.3</td><td>39.0</td><td>39.1</td><td>39.1</td></tr>
<tr><td>Men, n</td><td>20</td><td>20</td><td>11</td><td>11</td></tr>
<tr><td>Women, n</td><td>94</td><td>97</td><td>109</td><td>106</td></tr>
<tr><td>Monthly migraine frequency</td><td>5.6</td><td>5.4</td><td>5.8</td><td>5.1</td></tr>
<tr><td>MMD, Monthly migraine days</td><td>6.7</td><td>6.4</td><td>6.9</td><td>6.1</td></tr>
<tr><td>Monthly rescue medication used</td><td>5.8</td><td>5.7</td><td>6.2</td><td>5.8</td></tr>
<tr><td>Migraine duration, days</td><td>2.6</td><td>2.3</td><td>2.6</td><td>2.1</td></tr>
<tr><td>Monthly migraine severity</td><td>2.2</td><td>2.3</td><td>2.2</td><td>2.3</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="5">The primary efficacy measure:
• Change from baseline in mean monthly migraine frequency.
Secondary efficacy measures:</td></tr>
</table>

	• *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 mean, 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	*None*

TABLE 16 BRANDES ET AL., 2006

Trial name	*Assessing the Ability of Topiramate to Improve the Daily Activities of Patients With Migraine*
NCT number	*Not stated in the publication*
Objective	*To assess the impact of topiramate on the daily activities of patients with migraine.*
Publications – title, author, journal, year	*Assessing the Ability of Topiramate to Improve the Daily Activities of Patients With Migraine, Brandes et al., Mayo Clin Proc, 2006*
Study type and design	*Randomized, double-blind, placebo-controlled multicenter trial*
Follow-up time	*26 weeks.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Patients included in the trial ranged from 12 to 65 years of age (patients between 12 and 17 years of age did not participate in the SF-36 and MSQ surveys)* • *had at least a 6-month history of migraine with or without aura based on International Headache Society criteria.* • *To be eligible for the trial, patients must have experienced between 3 and 12 migraine attacks but no more than 15 headache days during the 28-day prospective baseline phase.* • *Women were required to be postmenopausal, surgically incapable of bearing children, or on a medically acceptable birth control regimen for at least 1 month before study entry* ***Exclusion Criteria:*** • *Reasons for exclusion from the trial included:*

	• *the presence of headaches other than migraine (such as episodic tension headaches or sinus headaches) and previous failure of more than 2 adequately dosed migraine preventive medications.* • *Patients in whom more than 2 preventive measures had failed are not representative of the target population for which the study was designed.* • *Onset of migraine after the age of 50 years* • *patients with a history of overuse of analgesics or specific agents for the treatment of migraine attacks before trial entry were excluded.* *Examples of medication overuse included more than 8 treatment episodes per month with ergot-containing medication or triptans or more than 6 treatment episodes per month with potent opioids (e.g., fentanyl, buprenorphine, hydromorphone, oxycodone). This approach excludes patients who might be rebounding from medication-overuse headache with possible confounding by withdrawal of medications.*				
Intervention	*Patients were allowed to continue taking acute migraine medications for the treatment of breakthrough attacks during the trial, but any currently used migraine preventive medications were tapered off during an initial washout period of up to 14 days. Patients who then completed the 28-day prospective baseline phase and met all entry criteria were assigned with equal chance to 1 of 4 treatment groups (50 mg/d, 100 mg/d, or 200 mg/d of topiramate or placebo) based on a schedule prepared before the study started. The randomization was balanced using permutated blocks across the 4 treatment groups and stratified by study center. An interactive voice response system was used to assign randomization numbers to patients and to assign study drug based on the randomization schedule. The 26-week,* *double-blind phase consisted of an 8-week titration and an 18-week maintenance period. All dosages of topiramate were initiated at 25 mg/d and increased by 25 mg weekly until patients reached their assigned or maximum tolerated dose, whichever was lower*				
Baseline characteristics	***Intent-to-treat population***	***Placebo (n = 114)***	***Topiramate, 50 mg/d (n = 117)***	***Topiramate, 100 mg/d (n = 120)***	***Topiramate, 200 mg/d (n = 117)***
	No. with no MSQ or SF-36 data*	*8*	*7*	*9*	*10*
	No. with available MSQ and SF-36 data	*106*	*110*	*111*	*107*
	Mean ± SD age (y)	*38.3±12.0*	*39.0±12.1*	*39.1±12.6*	*39.1±12.7*
	No. (%) male	*20 (18)*	*20 (17)*	*11 (9)*	*11 (9)*
	No. (%) female	*94 (82)*	*97 (83)*	*109 (91)*	*106 (91)*
	No. (%) white	*101 (89)*	*99 (85)*	*108 (90)*	*103 (88)*

	Mean ± SD migraine frequency per month	*5.6±2.2*	*5.4±2.4*	*5.8±2.6*	*5.1±2.0*
	**All 34 patients who did not provide Migraine Specific Questionnaire (MSQ) or Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) data were minors. Patients between 12 and 17 years of age did not participate in the SF-36 and MSQ surveys.*				
Primary and secondary endpoints	*Primary efficacy outcome: change in mean monthly migraine frequency.* *The study reports a priori specified analyses of the MSQ (version 2.1) and SF-36 (version 1.0) questionnaire data collected as part of the aforementioned 6-month, randomized, double-blind, placebo-controlled, pivotal topiramate efficacy trial.*				
Method of analysis	*A mixed-effects model with piecewise linear regression, which took into account variations in the availability of MSQ and SF-36 data throughout the double-blind phase, was used to assess between-group differences in outcome scores for the prospectively designated MSQ and SF-36 domains. This model included 2 random effects and allowed changes in the slope at 8 and 16 weeks. This model assumed that the data were missing at random, conditional on treatment, and all observed. A series of sensitivity analyses tested different assumptions that related to missing MSQ and SF-36 data (ie, data missing at random or data missing not at random, conditional on either the time in the double-blind phase of the study or time to last MSQ and SF-36 assessment). Results of these tests were insensitive to these assumptions (data not shown). Multiple end points within each topiramate dosage vs placebo treatment analysis were controlled for across the 4 prospectively designated domains (MSQ-RR, MSQ-RP, SF36-RP, and SF36-VT) using a sequentially rejective Bonferroni adjustment procedure.22 All P values were adjusted using this step-up procedure, as outlined by Hochberg.22 No adjustment for multiple comparisons was performed for each treatment group within a given measure. Possible associations between changes in the level of daily activity (the prospectively designated MSQ and SF-36 domains) and mean monthly migraine frequency were examined using the Spearman rank correlation, pooling all study medication groups.*				
Subgroup analyses	*None*				

TABLE 17 SILBERSTEIN ET AL., 2004

Trial name	*Topiramate in migraine Prevention*
NCT number	*Not stated in publication*
Objective	*To assess the efficacy and safety of Topiramate as a migraine-preventive therapy*
Publications – title, author, journal, year	*Topiramate in migraine prevention. Results of a large controlled trial. Silberstein SD et al. Arch Neurol 2004*
Study type and design	*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).*

<table>
<tr><td>Follow-up time</td><td colspan="5">Data from the 26 weeks double-blind treatment phase are presented.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td colspan="5">Inclusion:
• 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 colspan="5">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 rowspan="8">Baseline characteristics</td><td>Patients completing the study</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>
<tr><td colspan="5">Data shown are mean (SD), unless otherwise indicated.</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="5">Primary endpoint:
• Reduction in monthly migraine frequency across the 6 months treatment phase
Secondary endpoint:
• 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</td></tr>
<tr><td>Method of analysis</td><td colspan="5">The primary endpoint was analyzed 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</td></tr>
</table>

	discontinuing the study early, the average monthly migraine period rate was computed based on the migraine periods observed before discontinuation.
Subgroup analyses	*N/A*

TABLE 18 SILBERSTEIN ET AL., 2006

Trial name	*The impact of migraine on daily activities*				
NCT number	*Not stated in publication*				
Objective	*Assess the impact of migraine preventive therapy on patient-reported routine daily activities using the Migraine Specific Questionnaire (MSQ) and the Medical Outcomes Study Short Form-36 (SF-36) in patients with migraine who participated in a 26-week, randomized, double-blind, placebo-controlled trial of topiramate for migraine prevention*				
Publications – title, author, journal, year	*The impact of migraine on daily activities: effect of topiramate compared with placebo. Silberstein SD et al. Current Medical Research and Opinion 2006*				
Study type and design	*randomized, double-blind, placebo-controlled trial (MIGR-001)*				
Follow-up time	*26 weeks*				
Population (inclusion and exclusion criteria)	***Inclusion:*** • *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*				
Intervention	*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.*				
Baseline characteristics	*ITT-population*	*Topiramate 50 mg N= 117*	*Topiramate 100 mg N=125*	*Topiramate 200 mg N=112*	*Placebo N=115*
	Age, years (SD)	*40.2 (11.5)*	*40.6 (11.0)*	*40.5 (11.4)*	*40.4 (11.5)*
	Female, n	*107*	*112*	*94*	*103*
	Male, n	*10*	*3*	*18*	*12*
	MMD	*6.4 (2.7)*	*6.4 (2.7)*	*6.6 (3.1)*	*6.4 (2.6)*

	Weight	*75.7 (18.9)*	*78.9 (19.3)*	*76.7 (20.1)*	*75.6 (18.5)*
	Days of acute headache medication use pr. 28 days	*5.8 (2.5)*	*6.4 (2.7)*	*6.1 (3.1)*	*6.1 (3.0)*
	Data shown are mean (SD), unless otherwise indicated.				
Primary and secondary endpoints	*Primary endpoint:* • *Reduction in monthly migraine frequency across the 6-month treatment phase* *Secondary endpoint:* • *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	*A mixed-effects model with piecewise linear regression, which took into account variations in the availability of MSQ and SF-36 data throughout the double-blind phase, was used to assess between-group differences in the prospectively designated MSQ and SF-36 outcome scores. This model included two random effects and allowed changes in the slope at 8 and 16 weeks. The model allowed for a slope to describe the relationship from week 8 to week 16, and a slope to describe the relationship from week 16 to week 26. A sensitivity analysis, with different assumptions relating to missing MSQ and SF-36 data, was also performed jointly estimating the outcomes with time on the double-blind portion of the study and time to last MSQ or SF-36 assessment.*				
Subgroup analyses	*N/A*				

TABLE 19 SILBERSTEIN ET EL., 2006

Trial name	*Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults*
NCT number	*Not stated in publication*
Objective	*This paper evaluates 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 topiramate 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	*The pilot study had a randomized, double-blind, placebo-controlled design. Subjects were randomized in a 2:1 ratio to receive TPM 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.*
Follow-up time	*20 weeks*
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Subjects between the ages of 18 and 65 years were required to have a history of migraine with or without aura, as assessed by International Headache Society criteria, 1° for at least 12 months before screening.*

<table>
<tr><td></td><td colspan="3">

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:

Subjects were excluded from the study if they had previously failed to respond to TPM therapy or had taken preventive medication within 2 weeks (14 days) of the start of the prospective baseline period (defined in following section).
Also excluded were 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) were excluded.
Finally, 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 (e.g., triptan use on >8 days per month) also were excluded.
Receipt of injected corticosteroids, local anesthetics, or botulinum toxin within 60 days before screening was a cause for exclusion.
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.
Subjects who had 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 colspan="3">The intent-to-treat (ITT) population</td></tr>
<tr><td rowspan="6">Baseline characteristics</td><td>ITT-population</td><td>Topiramate (n= 138=</td><td>Placebo (n=73)</td></tr>
<tr><td>Age, years (SD)</td><td>39.9 (11.8)</td><td>41.7 (9.4)</td></tr>
<tr><td>Female, n</td><td>118 (85.5)</td><td>63 (86.3)</td></tr>
<tr><td>Weight, mean (SD), kg</td><td>74.6 (17.5)</td><td>80.7 (20.3)</td></tr>
<tr><td>No. of migraine episodes per month (28 days)</td><td>4.8 (1.5)</td><td>5.2 (1.7)</td></tr>
<tr><td>Migraine with aura, no. (%)</td><td>46 (33.3)</td><td>29 (39.7)</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The primary efficacy measure was the change in mean monthly migraine frequency.

Additional measures were the median percent reduction in monthly migraine frequency and the proportion of responders (those with ≥50%, ≥75%, or 100% reduction in monthly migraine frequency).</td></tr>
<tr><td>Method of analysis</td><td colspan="3">A sample size of 195 subjects (130 TPM, 65 placebo) was calculated to provide 90% power to detect a 1.0 difference in the mean reduction in monthly migraine frequency, assuming a common SD of 2.0, at the 5% (2-sided) significance level. Statistical analyses were conducted in the ITT population. For subjects who withdrew prematurely from the double-blind phase, the last available efficacy evaluation after baseline was carried forward. The per-protocol, analysisof-covariance (ANCOVA) model was used to assess the significance of the data for the primary and secondary efficacy measures. Comparisons of responder rates were performed</td></tr>
</table>

	using logistic regression. For ANCOVA and logistic regression, the mean prospective baseline migraine frequency was treated as a covariate, and treatment and center were treated as qualitative independent factors. *To provide proportional representation for each patient based on how long he or she remained in the study, a post hoc analysis of total migraine frequency during the entire double-blind phase was performed in the ITT population using an overdispersed Poisson regression model, in which the log of the duration of the double-blind phase was used as an offset. 11 In this regression model, the mean prospective baseline migraine frequency was treated as a covariate, and treatment and center were treated as qualitative independent factors. Correction for multiple comparisons was applied to the data derived from the prespecified analyses. This correction was not applied to the data derived from post hoc analyses, in which case nominal P values were provided*
Subgroup analyses	*A post hoc analysis in the subgroup of ITT subjects having migraine with aura (46 TPM, 29 placebo) suggested that TPM was associated with a significant reduction in monthly migraine frequency compared with placebo (-2.43 vs -0.79; P = 0.02)*

TABLE 20 SILBERSTEIN ET AL., 2007

Trial name	*To evaluate the efficacy and safety of topiramate (100 mg/day) compared with placebo for the treatment of chronic migraine.*
NCT number	*NCT00210912*
Objective	*To evaluate the efficacy and safety of topiramate (100 mg/day) compared with placebo for the treatment of chronic migraine.*
Publications – title, author, journal, year	*Efficacy and Safety of Topiramate for the Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial. Silberstein et al., Headache, 2007.*
Study type and design	*This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial (46 U.S. sites).* *The study consisted of a pre-treatment phase lasting up to 56 days, a double-blind treatment phase lasting 16 weeks, and a taper/exit period that lasted up to 2 weeks. The pre-treatment phase consisted of 2 study periods: a screening and washout period (day −56 to day −29), and a prospective baseline period (day −28 to day 0). The screening and washout period commenced at visit 1 and occurred within 28 days of the start of the prospective baseline period (visit 2). Patients were instructed to discontinue all preventive migraine medications for 14 to 28 days prior to visit 2and for the duration of the study. The prospective baseline period began on day−28 (visit 2), as soon as the patient completed the screening and washout period.* *The double-blind treatment phase consisted of a 4-week titration period and a 12-week maintenance period. During the titration period, subjects were given topiramate (or matching placebo) 25 mg/day once daily for 7 days, followed by weekly increases of 25 mg until either 100 mg/day of topiramate (or matching placebo) or a maximum tolerated dose was reached.*

Follow-up time	*12 weeks.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** *During the screening period, eligibility for participation in the study was determined. Adult subjects with a diagnosis of chronic migraine, defined according to Silberstein/ Lipton criteria for transformed migraine were identified. Subjects who met these criteria for chronic migraine during the screening period were required to meet additional criteria to proceed to randomization. Subjects were required to have at least 15 headache days per 28 days, defined as a calendar day during which they experienced head pain for at least 30 minutes. On at least half of these days, subjects were required to have experienced migraine with or without aura or migrainous headache[1]. Eligible subjects also were required to have a Migraine Disability Assessment (MIDAS) score of at least 11 at visit 1.* ***Exclusion Criteria:*** • *Previously failed more than 2 adequate trials of migraine preventive medications (adequate was defined as a trial of at least 3 months' duration at the recommended dose)* • *Previously failed an adequate trial of topiramate therapy due to lack of efficacy or adverse events* • *History of cluster headache or basilar, ophthalmoplegic, or hemiplegic migraines* • *Migraine onset after age 50* • *Overuse of acute migraine medication (defined in this trial as use in excess of 4 days per week during the prospective baseline period)* • *History of hepatic disorder or nephrolithiasis* • *Progressive neurologic disorder other than migraine* • *Pregnant or nursing* <u>Concomitant Headache medications:</u> *All preventive migraine treatments were discontinued at least 14 to 28 days prior to the prospective baseline period and for the duration of the study. Use of acute headache pain medications such as analgesics, nonsteroidal anti-inflammatory drugs, triptans, opioids, and ergot derivatives was permitted for symptomatic relief of headache but could not exceed 4 days per week during the maintenance period. The specific acute headache pain medications used were recorded in the daily headache record along with migraine episode information. As much as possible, subjects were to utilize the same acute medications throughout the study as those they had employed prior to enrolment.*
Intervention	*A total of 328 patients were randomized (topiramate, n = 165; placebo, n = 163), and 306 patients were included in the intent-to-treat population. Patients treated with topiramate has given a dose of 100 mg/day*
Baseline characteristics	*Baseline characteristics (intent-to-treat population)*

[1] *Migrainous headache was defined as moderate to severe headache with 1 or more of the following migraine features: unilateral pain or pain worse on 1 side of the head, pulsatile pain, photophobia and/or phonophobia, nausea and/or vomiting, or pain made worse by physical activity.*

	Characteristic	***Topiramate***	***Placebo***	***Total***
	Age, years			
	n	*153*	*153*	*306*
	Mean	*37.8*	*38.6*	*38.2*
	SD	*12.38*	*11.80*	*12.08*
	Median	*37.0*	*40.0*	*39.0*
	Min, Max	*18, 64*	*18, 74*	*18, 74*
	Sex, n (%)			
	Male	*25 (16.3)*	*20 (13.1)*	*45 (14.7)*
	Female	*128 (83.7)*	*133 (86.9)*	*261 (85.3)*
	Race, n (%)			
	White	*126 (82.4)*	*120 (78.4)*	*246 (80.4)*
	Black	*19 (12.4)*	*26 (17.0)*	*45 (14.7)*
	Asian	*1 (0.7)*	*2 (1.3)*	*3 (1.0)*
	Other	*7 (4.6)*	*5 (3.3)*	*12 (3.9)*
	Weight (kg)			
	n	*153*	*152*	*305*
	Mean	*80.00*	*76.84*	*78.43*
	SD	*20.276*	*22.221*	*21.292*
	Median	*76.64*	*72.79*	*74.38*
	Min, Max	*39.9, 154.2*	*46.3, 190.5*	*39.9, 190.5*
	Body mass index (kg/m^2)			
	n	*152*	*150*	*302*
	Mean	*29.161*	*27.965*	*28.567*
	SD	*6.9659*	*7.2853*	*7.1396*
	Median	*28.007*	*26.614*	*27.427*
	Min, Max	*15.69, 54.87*	*16.60, 57.57*	*15.69,57.57*
	Headache Characteristics (mean ± SD)	***Topiramate***	***Placebo***	
	Age at migraine onset, years	*19.0 ± 10.1*	*20.4 ± 10.5*	
	Duration of chronic migraine, Years	*9.3 ± 10.5*	*9.1 ± 10.6*	
	Baseline monthly rate of migraine or migrainous days	*17.1 ± 5.4*	*17.0 ± 5.0*	
	Baseline monthly rate of migraine Days	*15.2 ± 6.4*	*15.1 ± 5.8*	
	Baseline monthly rate of total headache days	*20.4 ± 4.8*	*20.8 ± 4.6*	
	Baseline number of days per month of acute medication use	*11.9 ± 7.0*	*11.4 ± 6.6*	
Primary and secondary endpoints	*The primary endpoint was the change from baseline in the mean monthly (28 day) number of migraine/migrainous days. The change from baseline in the mean monthly number of migraine days also was analyzed in addition to the percent change from baseline for these 2 efficacy parameters.*			

	A Secondary prespecified efficacy measures that were derived but will be detailed in a subsequent publication include: • *Categorical responder rates in the percent change from baseline in mean monthly number of migraine/migrainous, migraine, and total headache days* • *Change in the mean monthly rate of headache days* • *Change in monthly headache-free days* • *Reduction from baseline in the use of acute headache medications* • *Occurrence of associated symptoms of photophobia, phonophobia, and nausea* • *Absolute change in a Headache Index (which was defined as the sum of the product of daily average severity multiplied by headache duration for the day, divided by the number of days in the specified period. Severity was based on 5 categories: 1 = mild headache, easily ignored; 2= mild bothersome discomfort; 3 = moderate, painful; 4 = moderate, very painful; and 5 = severe, intensely painful) during the last 4 weeks of double-blind treatment compared with the prospective baseline period.* *Effects of study drug on MIDAS,22 Physician's Global Impression of Change, Subject's Global Impression of Change, and the Migraine-Specific Quality-of-Life Questionnaire were evaluated.* <u>*Safety and tolerability measures:*</u> *Safety measures included measurement of vital signs, serial physical and brief neurologic examinations, and clinical laboratory parameters (haematology, chemistry, and urinalysis). Women of childbearing potential had urine pregnancy tests. Spontaneously reported adverse events were collected and recorded at each visit. Treatment-emergent adverse events (TEAEs) were defined as those that were new in onset or aggravated in severity or frequency between the prospective baseline period and the conclusion of the double-blind treatment phase.* *The investigators recorded the date of onset, severity, and outcome of each adverse event, evaluated the possible relationship to treatment and recorded any action taken.*
Method of 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.* *Safety analyses were performed on all randomized subjects who received at least 1 dose* *of study medication and for whom at least 1 posttreatment safety measurement was available.* *The mean monthly rate of migraine/migrainous headache days and migraine headache days were analyzed with analysis of covariance models using a fixed-sequence (i.e., a gatekeeper approach) to control the overall Type I error rate at the 2-sided 5% level. Treatment and treatment center were qualitative design factors, with*

	baseline rate as a covariate. The first step involved an assessment of the change relative to baseline in the mean number of days per month with migraine/migrainous headache at the 2-sided 0.05 level of significance. If statistical significance was achieved, then the change in the mean monthly rate of migraine days could also be tested at the 2-sided 0.05 level. If significance again was achieved, then statistical significance would be declared at the 2-sided 0.05 level for both measures. If significance on the migraine/migrainous parameter was not achieved, then the formal testing procedure ended. Analyses of additional efficacy variables were not adjusted for multiplicity.
Subgroup analyses	*No subgroup was defined in this study.*

TABLE 21 SILBERSTEIN 2009 ET AL., 2009

Trial name	*A Study of the Effectiveness and Safety of Topiramate Versus Placebo for Preventing Chronic Migraine Headaches*
NCT number	*NCT00210912*
Objective	*The purpose of this study is to assess the safety and effectiveness of topiramate as compared to placebo for the prevention of headaches in patients with chronic migraine. Topiramate has been approved to prevent migraine headaches as well as in the treatment of epilepsy.*
Publications – title, author, journal, year	*Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Silberstein et al., Headache, 2009*
Study type and design	*This is a multicenter, randomized, double-blind, placebo-controlled, parallel group study of patients with chronic migraine. The Pretreatment Phase for the study will last up to 56 days and will consist of 2 study periods: a Screening/Washout Period (Day -56 to Day -29) and a Prospective Baseline Period (28 days). Medications being used to prevent migraines will be stopped for 14 to 28 days prior to the Prospective Baseline Period and for the rest of the study. The Prospective Baseline Period will begin on study Day -28 (Visit 2), and patients will maintain a daily headache record during this period. Those who move forward in the study must have had at least 15 headache days during this period, half of which need to be migraine headache days. Patients who finish the Prospective Baseline Period, who have the required rates of headache, and who continue to meet the remainder of the entry criteria will be randomized (like with the toss of a coin) to 1 of 2 treatment groups: topiramate 100 milligrams per day or placebo.* *The Double-Blind Phase will last 16 weeks. During the first 4 weeks, patients will titrate up to the topiramate dose of 100 milligrams per day or to the maximum tolerated dose, whichever is less. The next 12 weeks is the maintenance phase where you will continue to take the dose that you were taking at the end of the 4-week titration period. The primary hypothesis of this study is that the mean decrease in the number of migraine/migrainous headache days per month is greater in the topiramate group than in the placebo group and topiramate is generally well-tolerated.*
Follow-up time	*16 weeks.*
Population (inclusion and exclusion criteria)	***Inclusion:*** • *Diagnosis of chronic migraine*

	• *>=15 headache days per month in past 30 days* • *>= 15 headache days, half of which need to be migraine headaches during the prospective baseline period* • *MIDAS test score >= 11 at Visit 1* • *In generally good health* • *If female, using birth control* • *No abnormalities on neurological examination* ***Exclusion Criteria:*** • *Failed > 2 adequate trials of migraine prevention medications* • *Failed topiramate due to lack of effectiveness or adverse events* • *Daily headaches of severe intensity during past 30 days* • *Cluster, basilar, ophthalmoplegic, or hemiplegic migraines* • *Migraines started after age 50* • *Other pain greater than migraine pain* • *Use of drugs to treat migraines for > 4 days per week during the past month*
Intervention	*The intent-to-treat population consisted of 306 patients (topiramate, n = 153; placebo, n = 153)*
Baseline characteristics	*No baseline characteristics are presented in this study.*
Primary and secondary endpoints	*Primary efficacy measure: Change in the average number of days per month with migraine or migrainous headache by daily headache record.* *Secondary efficacy measure: Absolute change and % change from baseline in the headache index; change in the average daily and worst daily headache severity; quality of life assessments (MIDAS, MSQ, Physician's/Subject's global assessments of change.*
Method of analysis	*The proportions of subjects in the response categories for reductions of migraine, migraine/ migrainous and total headache days, and PGIC and SGIC were analyzed using the Cochran-MantelHaenszel test, stratified by center. The P values for the response rates, but not percent´s, were the result of a post hoc analysis. Changes from baseline to the final evaluations in scores on each MSQ domain (Role Function-Restrictive [RR], Role Function-Preventive [RP], and Emotional Function [EF]) were analyzed separately using the ANCOVA model, with treatment and center as qualitative independent factors and baseline value as a covariate. Changes from baseline to the final evaluations in MIDAS scores were analyzed using the ANCOVA model, with treatment and center as qualitative independent factors and baseline value as a covariate. In addition, the changes were categorized as "Worse," "No Change," and "Improved" and analyzed using the Cochran-Mantel Haenszel test, stratified by center. All statistical tests were performed at the 2-sided 0.05 level. No adjustments were made for multiplicity.*
Subgroup analyses	*N/A*

TABLE 22 DIENER ET AL., 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 in a randomized, double-blind, placebo-controlled trial.*
Publications – title, author, journal, year	*Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Diener et al., Cephalalgia, 2007.*
Study type and design	*Randomized, double-blind, placebo-controlled, parallel-group, multicentre trial of topiramate for the prevention of headache in patients with chronic migraine with and without medication overuse. The study is completed.*
Follow-up time	*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.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *Patients (18–65 years of age) were required to have a 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, with 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:*** • *Primary chronic headache or any secondary headache except medication overuse headache (MOH)* • *Experienced onset of migraine after age 50* • *Severe depression [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 and use of a carbonic anhydrase inhibitor* *Concomitant therapies: Patients were allowed to take acute rescue medications such as analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, opioids and ergot derivatives during any phase in the trial as usual. The use of acute rescue medication had to be specified, next to the migraine attack information, in the trial-specific patient diary.*
Intervention	*32 participants randomized to the topiramate arm, target dose of 100 mg/day (50 mg twice daily) at a rate of 25 mg/week. Study physicians could increase or decrease the target dose (within a range of 50–200 mg/day) during the first 12 weeks of the double-blind phase, depending on efficacy, tolerability, or both.* *27 participants randomized to the placebo arm*

<table>
<tr><td rowspan="7">Baseline characteristics</td><td colspan="4">Baseline characteristics (intent-to-treat population)</td></tr>
<tr><td>Characteristic</td><td>Topiramate</td><td>Placebo</td><td>P-value</td></tr>
<tr><td>Age, year</td><td>47.8 ± 9.4</td><td>44.4 ± 9.6</td><td>0.148</td></tr>
<tr><td>Gender (F/M), %</td><td>75/25</td><td>74/26</td><td>1.000</td></tr>
<tr><td>Mean number of migraine days/month</td><td>15.5 ± 4.6</td><td>16.4 ± 4.4</td><td>0.283</td></tr>
<tr><td>Patients with and without medication overuse</td><td>23/9</td><td>23/4</td><td>0.345</td></tr>
<tr><td>Beck Depression Inventory</td><td>9.0 ± 7.0</td><td>13.4 ± 8.8</td><td>0.064</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="4">The primary efficacy variable was the 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 end points were:

• 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), Headache Impact Test (HIT-6), and Migraine Disability Assessment (MIDAS) questionnaire scores

All three questionnaires were administered at start and end of the double-blind treatment phase; the MSQ and HIT-6 were also administered at 4 and 8 weeks in the double-blind phase

<u>Tolerability and safety measures</u>
Spontaneously reported treatment-emergent adverse events (TEAEs) were recorded. Vital signs, body weight changes and laboratory parameters, including bicarbonate, sodium, potassium and chloride, were measured at the start of the double-blind phase and at weeks 8 and 16. Fewer bicarbonate estimations were done compared with others since the bicarbonate measurement was added after the study had commenced.</td></tr>
<tr><td>Method of analysis</td><td colspan="4">Since the effect size of topiramate is unknown in subjects with chronic migraine, the following assumptions were made based on the results obtained in subjects with episodic migraine:
• First, the average number of migraine days would be between 15 and 28 at an average number of 20</td></tr>
</table>

	• *Second, there would be a 45% reduction in the number of migraine days on topiramate.* • *Third, there would be a 25% reduction in the number of migraine days on placebo, so the estimated effect size over placebo was four migraine days per month* • *Fourth, the SD was estimated of the change in the number of migraine days per month to be 5* *Under these assumptions two treatment groups of 29 subjects each would be needed to show a statistically significant difference between topiramate and placebo with a power of 0.80 and a = 0.05 (two-sided).* *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). Differences within a treatment group were tested using the Wilcoxon signed rank test (ordinal/continuous data). 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	*The subgroup of patients who were overusing acute medication (n = 46) consisted of 23 patients receiving topiramate and 23 receiving placebo There were no significant differences in demographics and baseline characteristics between the topiramate-treated and placebo-treated patients.* *It appeared, however, that triptans were the most commonly overused acute medications in the placebo group (96%, vs. 61% in the topiramate group), whereas the topiramate group had a higher rate of analgesic overuse (30%, vs. 9% in the placebo group). The modal dose of topiramate was assessed for each individual in this treatment subgroup. From these values, the calculated mean modal dose was 102 ± 17 (mg/day±SD).*

TABLE 23 INTERPID

Trial name	*INTREPID*
NCT number	*NCT00212810*
Objective	*The purpose of this study is to determine whether Topiramate is effective in preventing the development of chronic daily headache among patients with episodic migraine headaches.*
Publications – title, author, journal, year	*Topiramate intervention to prevent transformation of episodic migraine: The topiramate INTREPID study. Lipton et al., Cephalalgia, 2011*

Study type and design	*This is a randomized, double-blind, placebo-controlled multicenter study that will enrol patients 18-65 years old with an established history of migraine headaches who, in the 28 days prior to the study should have a migraine frequency of at least 10 but less than 15 migraine headache days per month, and less than 15 total headache days (migraine plus non migraine headaches) per month. The study duration will be approximately 26 weeks. The study is divided into 4 phases as follows: A Screening/Washout Phase that may last between 2-6 weeks, depending on whether you need to stop taking a medication that is not allowed in the study; A Baseline Phase lasting 4 weeks, at which time information will be collected on the migraine and non-migraine headaches you experience during this period; A double-blind Titration Phase lasting 4-6 weeks where all patients will be randomized to treatment with either Topiramate or placebo. If you are randomized to Topiramate, your dose will be gradually increased up to a dose of either 75 or 100 mg a day; A Maintenance Period lasting 20 weeks at which time you will continue on the dose you were taking at the completion of the Titration period; and a Taper/Exit phase, lasting 2 weeks, where you will gradually reduce the dose of study medication you were taking during the study.* *The study hypothesis is that the study drug will be more effective than placebo in preventing patients from transforming from episodic migraines to chronic daily headaches. Each patient will be asked to record their headache pain information and medication use on paper headache diaries. Patients will receive either Topiramate or placebo. The number of tablets of topiramate or placebo, will be gradually increased to either a minimum of 3 tablets/day or a maximum of 4 tablets/day. For those on Topiramate, 3 tablets would represent 75 mg and 4 tablets would represent 100 mg/day.*
Follow-up time	*26 weeks*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** • *To qualify for this study, you must be 18-65 years old* • *have a history of migraine headaches for at least 1 year* • *experience at least 10 but less than 15 migraine headache days and less than 15 total headache days/month* • *able to take oral medication* • *able to understand and sign the informed consent and to complete headache diaries.* ***Exclusion Criteria:*** • *You will not be able to participate in the study if you previously discontinued Topiramate because it did not make you feel better or it made you feel different* • *have migraine aura without headache* • *have a positive urine drug screen* • *have a history of kidney stones* • *have a history of suicide attempt* • *pregnant females* • *already on a migraine preventive medicine.*
Intervention	*A total of 385 patients were randomized. A total of 159 topiramate 100 mg/day subjects and 171 placebo subjects were efficacy-evaluable.*

<table>
<tr><td>Baseline characteristics</td><td colspan="3">Baseline characteristics</td></tr>
<tr><td></td><td>Characteristic</td><td>Topiramate (n=159)</td><td>Placebo (n=171)</td></tr>
<tr><td></td><td>Females (%)</td><td>138 (86.8)</td><td>156 (91.2)</td></tr>
<tr><td></td><td>Age (years ± SD)</td><td>39.6 (10.6)</td><td>40.9 (11.2)</td></tr>
<tr><td></td><td>BMI (kg/m^2)</td><td>30.2 (8.5) (N (n=158)</td><td>30.4 (8.4)</td></tr>
<tr><td></td><td>Age at migraine onset (years)</td><td>19.8 (10.0)</td><td>20.8 (10.8)</td></tr>
<tr><td></td><td>Number of headache days per 28 days</td><td>13.0 (2.5)</td><td>13.1 (2.6)</td></tr>
<tr><td></td><td>Number of migraine headache days per 28 days</td><td>11.6 (2.0)</td><td>11.8 (2.2)</td></tr>
<tr><td></td><td>Days of acute headache medication use per 28 days</td><td>8.6 (3.2)</td><td>8.6 (3.5)</td></tr>
<tr><td></td><td>Usual migraine headache pain intensity per 28 days (N, %)
- Mild
- Moderate
- Severe</td><td>
2 (1.3)
88 (55.3)
69 (43.4)</td><td>
2 (1.2)
90 (52.6)
79 (46.2)</td></tr>
<tr><td>Primary and secondary endpoints</td><td colspan="3">The primary efficacy parameter will be whether or not a patient experiences 15 or more headache days (migraine and non-migraine) during the last 28 days of the study.

Secondary end point: time to development of transformed migraine; occurrence of transformation as function of baseline headache days; change in the average rate of migraine days; percentage change in the average rate of migraine days;50%,75%, and 100% reduction in migraine days</td></tr>
<tr><td>Method of analysis</td><td colspan="3">The primary analysis of the primary efficacy measure, whether a subject reported 15 headache days per 28-day period at month 6, was analyzed based on the EE analysis set. Six 28-day periods during the double-blind phase were designated as months 1 through 6. For each subject, a binary outcome of whether 15 headache days/28 days was experienced or not experienced was determined for each month. A generalized linear mixed model (GLMM) using a logit link function was used to analyze this repeated binary outcome data. The standard assumption of local independence of repeated measures within a subject given the subject effect was made. Baseline monthly headache day rate was included as a covariate in the model. The null hypothesis tested was that the difference between treatment groups at month 6 as measured by the log odds ratio was 0. The marginal probability of reporting 15 headache days at each month was estimated by generating random normal deviates from the estimated normal distribution of the subject effect. A plot of the observed monthly probabilities of reporting 15 headache days against those predicted by the GLMM was generated.

The primary efficacy data variable was also analyzed using another statistical approach, the generalized estimating equation model for the EE analysis set. Secondary efficacy variables involving change from baseline and percent change in the mean 28-day rate during the double-blind phase were analyzed using analysis of</td></tr>
</table>

	covariance (ANCOVA) methodology with treatment and center as independent factors and baseline value (of the dependent) variable as a covariate. Categorical secondary variables were analyzed using the Cochran-Mantel-Haenszel test with modified ridit score, stratified by center. Analysis of time to the first reporting of 15 headache days per 28-day period, and time to the first reporting of 15 or more headache days, of which at least half were migraine, were analyzed using Kaplan-Meier (with a log rang test for treatment group difference) methodology and Cox's proportional hazards model, with baseline headache days or migraine headache days as a covariate.
Subgroup analyses	*No subgroup was defined in this study.*

TABLE 24 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 • 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

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

- 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>

TABLE 25 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 randomization lists with randomly permuted block lengths stratified according to center. Patients, treating clinicians and the outcome assessor were blinded.
Follow-up time	Data from the 12 week double-blind treatment period is presented.
Population (inclusion and exclusion criteria)	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,

<table>
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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 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.</td></tr>
<tr><td>Subgroup analyses</td><td>None</td></tr>
</table>

Valproat

TABLE 26 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; • 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.
Intervention	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

<table>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Placebo
N=115</th><th>Treatment 1
N=122</th></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 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.</td></tr>
<tr><td>Subgroup analyses</td><td>None</td></tr>
</table>

TABLE 27 JENSEN 1994

<table>
<tr><td>Trial name</td><td>Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study</td></tr>
<tr><td>NCT number</td><td>None</td></tr>
<tr><td>Objective</td><td>To evaluate if sodium valproate has a prophylactic effect in migraine without aura.</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>Sodium valproate has a prophylactic effect in migraine without aura:
A triple-blind, placebo-controlled crossover study. Jensen R, et al. Neurology 1994</td></tr>
<tr><td>Study type and design</td><td>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.</td></tr>
<tr><td>Follow-up time</td><td>Data from the 12 week triple-blind treatment phases is presented.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>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.</td></tr>
<tr><td>Intervention</td><td>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.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>Group A Valproate-Placebo
N=22</th><th>Group B Placebo-Valproate
N=21</th></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:</td></tr>
</table>

	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.
Method of analysis	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.
Subgroup analyses	None

TABLE 28 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. 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,

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

Subgroup analyses	None

TABLE 29 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 • 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
Intervention	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.
Baseline characteristics	<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>
Primary and secondary endpoints	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
Method of analysis	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.
Subgroup analyses	None

Botulinum type A toxin

TABLE 30 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

<table>
<tr><td></td><td>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= 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 ≤ .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</td></tr>
</table>

	prespecified type-1 error rate of .05 for the five variables that were prespecified as primary or secondary.
Subgroup analyses	None

TABLE 31 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

<table>
<tr><td></td><td>Institute, Cary, NC, USA) and was stored in a central server with access granted to the randomization programmers. The study is completed.</td></tr>
<tr><td>Follow-up time</td><td>Primary analysis after 24 weeks</td></tr>
<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</td></tr>
</table>

	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 • 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