Galcanezumab (LY2951742) CGRP Monoclonal Antibody for the Prevention of Migraine: Phase 2, Randomized, Double-Blind, Placebo-Controlled Studies, ART01 and CGAB

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Migraine

♦ Migraine

• Migraine is the 3rd most prevalent and 7th most debilitating neurological disease in the world²

• Migraine accounts for more than 50% of the disability attributable to all neurological diseases³
  – Affects 36 million people in the US
  – The cost to society in the US exceeds US$20 billion annually⁴

• Lifetime incidence of migraine is 43% for women and 18% for men⁵

4. Stewart WF et al. JAMA 2003;290:2443-54

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Migraine and Calcitonin Gene-Related Peptide (CGRP)¹

♦ CGRP is found throughout the trigeminovascular system and in central nervous system sites regarded as important in migraine pathogenesis²

♦ During spontaneous³,⁴ migraine and nitric oxide-triggered⁵,⁸ headache attacks, venous blood concentration of CGRP increases

♦ CGRP infusion can trigger a headache attack that is indistinguishable from a spontaneous attack in individuals with migraine⁶,⁷

♦ Small-molecule CGRP receptor antagonists have been shown to be efficacious in abortive and preventive migraine studies²,⁹

♦ In a POC study, galcanezumab demonstrated efficacy versus placebo in migraine prevention¹⁰


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Galcanezumab

♦ Preclinical

• A humanized monoclonal antibody that potently binds human CGRP ($K_D=31$ pM)
• Prevents CGRP-mediated biological effects (in vitro and in vivo)
• >10,000-fold selectivity for CGRP vs. related peptides (adrenomedullin, amylin, calcitonin, intermedin)

♦ Clinical (Phase 1)

• Well-tolerated after both single and repeat injections
• Linear and dose-proportional exposure
• Robust and durable pharmacodynamic effects

Galcanezumab for the Prevention of Migraine: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study: ART01

Dodick DW, Goadsby PJ, Spierings ELH, Scherer JC, Sweeney SP, Grayzel DS

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Galcanezumab ART01 Study: Objective

♦ To determine the efficacy and safety of galcanezumab for migraine prevention

Dodick DW et al. Poster presented at AHS 2014. Abstract LBP28
Galcanezumab ART01 Study: Methods

♦ Double-blind, randomized, placebo-controlled trial POC study of galcanezumab for the preventive treatment of migraine (NCT01625988)

♦ 35 sites in the US: randomized 218 patients (1:1) after 28 day baseline diary phase

♦ Dose: galcanezumab 150 mg subcutaneous (SC) Q2W
  • 6 injections over 12 weeks

♦ Patients with 4-14 migraine headache days/month

♦ No concomitant migraine preventive medications or overuse of acute migraine medications

♦ Objective: To determine the efficacy and safety of galcanezumab for migraine prevention

Dodick DW et al. Poster presented at AHS 2014. Abstract LBP28

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Galcanezumab ART01: Study Design

- **Screening and washout period**: 5-45 days
- **Baseline period**: 28-38 days
- **Treatment period**: 12 weeks; Visits 3-10
  - galcanezumab 150 mg SC Q2W
  - Randomization
- **Follow-up period**: 12 weeks; Visits 11-13
  - IVRS reporting of type, frequency, and severity of headaches

**Dosing**
- Week 1: 12345678910
- Week 2: 123456789101112131415161718192021222324


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Galcanezumab ART01 Study: Key Inclusion Criteria¹

♦ 18-65 years of age, inclusive

♦ History of migraine as defined by IHS ICHD-II guidelines (1.1 and 1.2)² of ≥1 year prior to enrollment, migraine onset prior to age 50, and a frequency of 4-14 MHDs per 28-day period

♦ Discontinued any medication or other treatment to prevent migraine headaches for ≥30 days prior to Visit 2 (Baseline)


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Galcanezumab ART01 Study: Key Exclusion Criteria

♦ Previous completion or withdrawal from this study or any other study investigating galcanezumab or other therapeutic antibodies that target CGRP

♦ History of chronic migraine or migraine subtypes including hemiplegic migraine, ophthalmoplegic migraine, and migraine with basilar type aura

♦ History of headache\textsuperscript{a} other than migraine or tension-type headache as defined by IHS ICHD-II within 12 months prior to randomization

♦ Evidence of significant active psychiatric disease

♦ ≥15 headache days (migraine, probable migraine, or nonmigraine) per 28-day period

♦ Failure to respond to >2 adequately dosed effective migraine prevention treatments

\textsuperscript{a}Eg, cluster headache or medication overuse headache


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Galcanezumab ART01 Study: Statistical Methods

- The study was designed to have 90% power to detect a treatment group difference of 1.2 migraine headache days per month when compared with placebo.
- Sample size assumes a two-sided test with 0.10 significance level and an intrapatient SD of 2 and an interpatient SD of 2.5; results are given with 90% CIs.
- A mixed-effects model of repeated measures was used, including patient baseline value, treatment, visit, and treatment-by-visit interaction as fixed effects, and patients as random effects.
- Analyses were by intention to treat.


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Galcanezumab ART01 Study: Patient Disposition

482 Patients screened\(^a\)  

218 Patients randomized

Assigned to placebo (N=110)

- Placebo (N=110)\(^b\) Included in analyses
  - 13 patients discontinued\(^b\)
    - 3 withdrew consent
    - 6 lost to follow-up
    - 2 noncompliant
    - 1 adverse event
    - 1 absence of efficacy
  
  - n=98 (89%) completed treatment period
  - n=97 (88%) completed follow-up period

Assigned to galcanezumab 150 mg

- Galcanezumab 150 mg (N=107)\(^b\) Included in analyses
  - 1 patient withdrew before treatment
  - 13 patients discontinued\(^b\)
    - 8 withdrew consent
    - 5 lost to follow-up
  
  - n=95 (89%) completed treatment period
  - n=93 (87%) completed follow-up period

\(^a\)264 ineligible: 115 excluded during screening or washout and 149 excluded during baseline assessment

\(^b\)Included in the safety and ITT populations


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### Galcanezumab ART01 Study: Demographics and Baseline Disease Characteristics

| Characteristic, mean value (SD)
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo (N=110)</strong></td>
</tr>
<tr>
<td>Age, years, mean</td>
</tr>
<tr>
<td>Women, %</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Ethnic origin, %</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>MHD</td>
</tr>
<tr>
<td>Migraine attacks</td>
</tr>
<tr>
<td>MHD plus probable MHD</td>
</tr>
<tr>
<td>Migraine severity</td>
</tr>
<tr>
<td>History of aura, %</td>
</tr>
</tbody>
</table>

---

²Values are mean (SD) unless otherwise indicated

²Per 28 days during the baseline period

²Rated by patients on scale of 1-3: 1=mild, 2=moderate, 3=severe

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Galcanezumab ART01 Study: Primary Efficacy Endpoint: Mean Change From Baseline in MHD During the Treatment Period

Bars show 90% CI; p-values not calculated for Months 1 and 2


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### Galcanezumab ART01 Study: Primary and Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Change From Baseline to Week 12</th>
<th>LS mean Difference (SE, 90% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Galcanezumab 150 mg Q2W</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHD</td>
<td>-4.2 (3.1)</td>
<td>-3.0 (3.0)</td>
<td>-1.2 (0.41, -1.9 to -0.6)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache days</td>
<td>-4.9 (4.1)</td>
<td>-3.7 (4.2)</td>
<td>-1.3 (0.50, -2.1 to -0.5)</td>
</tr>
<tr>
<td>Migraine attacks</td>
<td>-3.1 (2.4)</td>
<td>-2.3 (2.5)</td>
<td>-0.8 (0.29, -1.3 to -0.3)</td>
</tr>
<tr>
<td>MHD plus probable MHD</td>
<td>-4.8 (4.1)</td>
<td>-3.5 (4.2)</td>
<td>-1.3 (0.51, -2.2 to -0.5)</td>
</tr>
<tr>
<td>50% response rate (50% RR)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69/98 (70%)</td>
<td>47/104 (45%)</td>
<td>OR 2.88 (90% CI 1.78-4.69)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%), unless otherwise specified

<sup>a</sup>SD was not calculated

<sup>b</sup>Response rate analyzed in the ITT population by period

Galcanezumab ART01 Study: Secondary Efficacy Endpoint: Change From Baseline Headache Days per Month

Bars show 90% CI
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Galcanezumab ART01 Study: Secondary Efficacy Endpoint: Change From Baseline Migraine Attacks per Month

Bars show 90% CI
Galcanezumab ART01 Study: Secondary Efficacy Endpoint: Change From Baseline in Probable Migraine and Migraine Headache Days per Month
Galcanezumab ART01 Study: Percentage of Patients Reporting >50% Reduction in Monthly Migraine Headache Days

<table>
<thead>
<tr>
<th>% Responders,(^a) n (%)</th>
<th>Placebo n (%)</th>
<th>Galcanezumab n (%)</th>
<th>Odds Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>41 (37.3)</td>
<td>62 (57.9)</td>
<td>2.40</td>
<td>1.51;3.81</td>
</tr>
<tr>
<td>Month 2</td>
<td>47 (44.3)</td>
<td>66 (66.0)</td>
<td>2.25</td>
<td>1.41;3.59</td>
</tr>
<tr>
<td>Month 3</td>
<td>47 (45.2)</td>
<td>69 (70.4)</td>
<td>2.88</td>
<td>1.78;4.69</td>
</tr>
</tbody>
</table>

\(^a\)Responder is defined as a patient with a >50% reduction in migraine headache days

Dodick DW et al. Poster presented at AHS 2014. Abstract LBP28

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Galcanezumab ART01 Study: Response Rates for Monthly Migraine Headache Days at Month 3

a Exploratory post hoc analysis

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## Galcanezumab ART01 Study: Adverse Events Reported by ≥4% of Patients in Either Treatment Group

<table>
<thead>
<tr>
<th>Adverse Events (AE), n (%)</th>
<th>Placebo (N=110)</th>
<th>Galcanezumab 150mg Q2W (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>10 (9)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>7 (6)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (7)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (3)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>0 (0)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (3)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>0 (0)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8 (7)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>2 (2)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>5 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (9)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Toothache</td>
<td>1 (1)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

♦ Most AEs were mild or moderate in intensity; no patients in the galcanezumab group and one patient in the placebo group withdrew because of an AE


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Galcanzumab ART01 Study: Cardiovascular and Hepatic Safety¹

♦ No clinically meaningful ECG changes
♦ No QTcF >500 ms, no increase >60 ms
  • Maximum QTcF change was 42 ms in the galcanzumab-treated group, and 60 ms in placebo
  • Consistent with the negative Phase 1 multidose exposure QT analysis
♦ No evidence of hepatotoxicity
♦ No Hy’s Law cases²

¹Hy’s Law predicts serious hepatocellular injury; it provides screening thresholds: ALT or AST >3X ULN and total bilirubin >2X ULN and not primarily cholestatic; not caused by disease but by drug²

### Galcanezumab ART01 Study: Serious Adverse Events (SAE)\(^1\)

<table>
<thead>
<tr>
<th>Event</th>
<th>Last Dose to Event (Days)</th>
<th>Recovered (Yes, No)</th>
<th>Related (Yes, No)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral vascular disease</td>
<td>43</td>
<td>Yes, with sequelae</td>
<td>No</td>
<td>galcanezumab</td>
</tr>
<tr>
<td>Spontaneous abortion(^a)</td>
<td>78</td>
<td>NA</td>
<td>No</td>
<td>galcanezumab</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>73</td>
<td>Yes</td>
<td>No</td>
<td>placebo</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>12</td>
<td>Yes</td>
<td>No</td>
<td>placebo</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>7</td>
<td>Yes</td>
<td>No</td>
<td>placebo</td>
</tr>
<tr>
<td>Common bile duct stone / abdominal pain</td>
<td>55</td>
<td>Yes</td>
<td>No</td>
<td>placebo</td>
</tr>
</tbody>
</table>

\(^a\)One patient reported a pregnancy during the follow-up period, ~10 weeks after last treatment dose. The patient had a miscarriage ~2 weeks after the reported pregnancy; the miscarriage was listed as an SAE, and was considered ‘unrelated to treatment’ by the investigator\(^2\)


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2. Data on file, Eli Lilly and Company
Galcanezumab ART01 Study: Conclusions

♦ Compared with placebo, galcanezumab significantly reduced the mean number of migraine headache days (MHD) over the 3-month study period

♦ All adverse events (AEs) were mild to moderate in intensity, there were no serious treatment-related AEs, and no patients withdrew from the galcanezumab group because of an AE

♦ Compared to placebo, galcanezumab reduced monthly migraine attacks, MHD and probable MHD, total headache days, and demonstrated improved responder rates

♦ High responder rates in the galcanezumab group: 70% of patients experienced greater than 50% reduction in migraine headache, 49% experienced greater than 75% reduction, and 32% of patients experienced complete elimination of migraine attacks at Month 3 of treatment

ART01 Post Hoc Analysis: Efficacy of Galcanezumab in Subgroups of Patients With Migraine of Different Frequency

Skljarevski V, Ferguson M, Oakes T, Tanaka Y, Zhang Q, Due M, Martinez J
Post hoc analyses using data from the ART01 study were conducted in adult patients randomly assigned to galcanezumab or placebo for 12 weeks.

Subgroups were examined based on the number of MHD during the baseline period from 5 to 10:

- ≥5 vs <5 MHD
- ≥6 vs <6 MHD
- ≥7 vs <7 MHD
- ≥8 vs <8 MHD
- ≥9 vs <9 MHD
- ≥10 vs <10 MHD

50% response rates based on the number of MHD were also examined for the same subgroups.

Skljarevski V et al. Poster presented at CONy 2016
Galcanezumab Post Hoc Analyses of Subgroups Based on the Number of MHD During the Baseline Period: Statistical Analyses

- For each subgroup separately, for change from baseline in MHD, a mixed model repeated measures analysis method was used with the following covariates: treatment, baseline MHD, pooled investigator, period, treatment-by-period interaction, baseline MHD-by-period interaction.

- For 50% response rate, a categorical, pseudo-likelihood-based repeated measures model was used and the covariates included: treatment, period, baseline, treatment-by-period interaction.
Galcanezumab ART01 Post Hoc Analysis: Mean Change From Baseline MHD in Subgroups of Patients With ≥5, 6, or 7 MHD/Month at Baseline

≥5 Baseline MHD

≥6 Baseline MHD

≥7 Baseline MHD

* p<.05; ** p<.01

Skljarevski V et al. Poster presented at CONy 2016
Galcanezumab ART01 Post Hoc Analysis: Mean Change From Baseline in MHD in Subgroups of Patients With ≥8, 9, or 10 MHD/Month at Baseline

Mean Change From Baseline in MHD

≥8 Baseline MHD

≥9 Baseline MHD

≥10 Baseline MHD

*p<.05

Skljarevski V et al. Poster presented at CONy 2016

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Galcanezumab ART01 Post Hoc Analysis: 50% Response Rates at Month 3 in Subgroups of Patients With ≥5, 6, 7, 8, 9, or 10 MHD/Month at Baseline

Skljarevski V et al. Poster presented at CONy 2016
Galcanezumab ART01 Post Hoc Analysis: High-Frequency Subgroup Conclusions

♦ The galcanezumab effect appears to be maximized for the high-frequency subgroup (≥8 MHD)

♦ In addition, the ≥8 MHD subgroup may provide for highest assay sensitivity in migraine prevention trials
Onset of Efficacy of Galcanezumab in Migraine Prevention: a Post Hoc Analysis From a Phase 2a Study of a Monoclonal Antibody to Calcitonin Gene-Related Peptide

Goadsby PJ, Dodick DW, Martinez J, Ferguson M, Oakes T, Tanaka Y, Ni X, Zhang Q, Due M, Skljarevski V
ART01 Post Hoc Analyses: Onset of Efficacy for Galcanezumab

♦ The ART01 study provided preliminary evidence of efficacy of galcanezumab (LY2951742) in migraine prevention

♦ These post hoc analyses were performed to determine the onset of efficacy of galcanezumab weekly over the 12-week treatment period

♦ To assess the onset of efficacy, daily data reflecting if the patient had a migraine headache (“yes” vs. “no”) during the 12-week treatment period were aggregated into the number of migraine headache days (MHD) for each weekly interval

♦ Onset of efficacy was defined as the first week in which galcanezumab was statistically superior to placebo in reduction of MHD per week

For derivation of weekly MHD, weekly baseline value was calculated as number of MHD per 28-day period at baseline divided by 4.

For postbaseline data, firstly biweekly injection schedules at Weeks 0, 2, 4, 6, 8, and 10 were used to cut daily data into biweekly intervals.

Biweekly intervals were divided into 2 equal weekly intervals by identifying the midpoint.

Change from baseline in weekly MHD was analyzed with MMRM analyses with fixed covariate of treatment, weeks, treatment-by-week interaction, and baseline weekly number of migraine headache days.

Least squares means (LSMeans) of weekly treatment differences were calculated based on the MMRM.

Weekly migraine/probable migraine headache days (MHD/pMHD), as well as weekly headache days were derived and analyzed similarly.
Galcanezumab ART01 Onset of Efficacy: Mean Change in Weekly Migraine Headache Days (MHD) Normalized From Baseline

Values shown are LS Means with 90% CI
*p<.05


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Galcanezumab ART01 Onset of Efficacy: Mean Change in Weekly Migraine or Probable Migraine Headache Days (pMHD) Normalized From Baseline

Values shown are LS Means with 90% CI
*p<.05

Galcanezumab ART01 Onset of Efficacy: Mean Change in Weekly Headache Days Normalized From Baseline

Values shown are LS Means with 90% CI
*p<.05
Headache days ≥4 hours


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Galcanezumab ART01 Onset of Efficacy: Limitations

♦ Studies were not designed specifically to evaluate weekly efficacy outcomes

♦ Calculations for weekly change in MHD may not be representative of those patients who have fewer migraines per month (eg, 4) than those with higher-frequency MHD

♦ The evaluation of changes in migraine frequency over the course of a week may not accurately reflect overall changes in migraine frequency for a patient in general

  • Migraine frequency is variable and weekly assessment of migraine frequency is not considered as reliable as monthly assessment of migraine frequency

  • In particular, calculations for weekly change in MHD in patients who have migraine frequency at the lower end of the range (eg, 4 MHD/month) may have a greater risk for inaccurate frequency interpolations than those with higher frequency MHD

These post hoc analyses suggest evidence of onset of efficacy of galcanezumab in this trial as early as one week.
Efficacy and Safety of Galcanezumab in a Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study in Patients With Migraine: CGAB

Oakes TM, Zhang Q, Ferguson MB, Skljarevski V, Martinez JM, Johnson KW, Schacht AL, Due MR, Goadsby PJ, Dodick DW

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In this Phase 2b study, patients 18-65 years of age with 4-14 MHD and ≥2 migraine attacks per month were randomized (2:1:1:1:1) to placebo or 1 of 4 galcanezumab dose groups (5, 50, 120, and 300 mg) SC Q4W¹

The primary objective was to assess whether at least one dose of galcanezumab was superior to placebo in the prevention of migraine headache as measured by migraine headache days¹

This study was conducted at 40 sites in the US²

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2. https://clinicaltrials.gov/ct2/show/study/NCT02163993#locn
Galcanezumab CGAB Study: Study Periods

♦ The study consisted of 4 periods

- SPI: screening period to assess inclusion/exclusion criteria and discontinuation of any excluded medications
- SPII: a baseline period to record the frequency, duration, symptoms, and severity of migraine headaches
- SPIII: double-blind, placebo-controlled treatment period of 12 weeks with injection of galcanezumab or placebo Q4W
- SPIV: follow-up period of an additional 12 weeks for continued safety assessment
Galcanezumab CGAB Study: Study Design

Study Period I
Screening
5-45 days

Study Period II
Baseline
28-38 days

Study Period III
Treatment

placebo

galcanezumab 5 mg

galcanezumab 50 mg

galcanezumab 120 mg

galcanezumab 300 mg

IVRS reporting of type, frequency, and severity of headaches

Week
Visit
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Dosing

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Oakes TM et al. Poster presented at AHS 2016. Abstract PS42
Galcanezumab CGAB Study: Key Inclusion/Exclusion Criteria\(^1\)

**Inclusion Criteria:**
- History of migraine as defined by IHS ICHD-3 beta guidelines (1.1 and 1.2)\(^2\) of ≥1 year prior to enrollment, migraine onset prior to age 50, and a frequency of 4-14 MHDs per 28-day period as determined during the baseline period\(^3\)
  - ≥2 migraine attacks of ≥30 minutes per 28-day period

**Exclusion Criteria:**
- Current use or any prior exposure to any CGRP antibody, any antibody to the CGRP receptor, or antibody to nerve growth factor (NGF)
- History of migraine subtypes including hemiplegic migraine, ophthalmoplegic migraine, and migraine with brainstem aura
- Failure to respond to >2 adequately dosed effective migraine prevention treatments
- Medication overuse headache
- Concomitant use of other migraine preventive treatments

2. IHS Cephalalgia 2013;33:629-808
3. Data on file, Eli Lilly and Company

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Galcanezumab CGAB Study: Statistical Methods

♦ Analyses of primary efficacy measure:
  • Primary analysis: a Bayesian dose-response model with hierarchical logistic regression to model dose response curve and a time course hierarchical model for longitudinal data
  • Supported analysis: an MMRM method using SAS® MIXED procedure

♦ Analyses of longitudinal response rate:
  • A categorical, pseudo-likelihood-base repeated measures analysis using SAS® GLIMMIX procedure

♦ Analyses of categorical safety measures:
  • Fisher’s exact test

♦ Analysis of the MSQ v2.1 and HIT6
  • ANCOVA at LOCF endpoint
Galcanezumab CGAB Study: End Points

♦ Galcanezumab was evaluated for the following:

- **Primary Efficacy Endpoint:** Change from baseline in number of migraine headache days (MHD; at Month 3)
- **Secondary endpoints:**
  - Change from baseline in MHD (Months 1-3)
  - Change from baseline in MHD plus probable MHD (Months 1-3)
  - Overall change from baseline in MHD over Months 1-3
  - 50% response rate (RR 50) for MHD (Months 1-3)
  - Change from baseline to Month 3 in MSQ v2.1 and HIT6
Galcanezumab CGAB Study: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=137)</th>
<th>GMB 5 mg (N=68)</th>
<th>GMB 50 mg (N=68)</th>
<th>GMB 120 mg (N=70)</th>
<th>GMB 300 mg (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean</td>
<td>39.5</td>
<td>41.4</td>
<td>39.6</td>
<td>40.6</td>
<td>40.8</td>
</tr>
<tr>
<td>Gender (female), %</td>
<td>79.6</td>
<td>80.9</td>
<td>89.7</td>
<td>84.3</td>
<td>83.6</td>
</tr>
<tr>
<td># of migraine headache days/month, mean</td>
<td>6.6</td>
<td>6.7</td>
<td>6.4</td>
<td>7.0</td>
<td>6.7</td>
</tr>
<tr>
<td># of migraine and probable migraine headache days/month, mean</td>
<td>8.0</td>
<td>8.6</td>
<td>8.3</td>
<td>8.7</td>
<td>8.0</td>
</tr>
<tr>
<td># of migraine attacks/month, mean</td>
<td>4.7</td>
<td>4.6</td>
<td>4.4</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>Severity of migraine headache/month, mean&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.3</td>
<td>2.4</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

There were no statistically significant differences between treatment groups

<sup>a</sup>Headache severity is evaluated on a 1-3 scale

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Galcanezumab CGAB Study: Patient Disposition for Treatment Phase (Study Period III)

- Placebo (N=137):
  - 11 patients (8%) discontinued\(^a\)
  - 2 lost to follow-up
  - 1 physician decision
  - 2 protocol violation
  - 6 patient decision
  - 126 patients completed SPIII

- GMB 5 mg (N=68):
  - 9 patients (13%) discontinued\(^a\)
  - 1 adverse event
  - 3 lost to follow-up
  - 1 protocol violation
  - 6 patient decision
  - 59 patients completed SPIII

- GMB 50 mg (N=68):
  - 2 patients (3%) discontinued\(^a\)
  - 1 lost to follow-up
  - 1 patient decision
  - 66 patients completed SPIII

- GMB 120 mg (N=70):
  - 8 patients (11%) discontinued\(^a\)
  - 3 lost to follow-up
  - 1 protocol violation
  - 1 patient decision
  - 62 patients completed SPIII

- GMB 300 mg (N=67):
  - 5 patients (8%) discontinued\(^a\)
  - 1 adverse event
  - 1 lost to follow-up
  - 2 protocol violation
  - 1 patient decision
  - 62 patients completed SPIII

\(^a\)Discontinued SPIII for any reason

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The primary objective of the study was met: The posterior probability (99.6%) of greater improvement for galcanezumab 120 mg compared with placebo met the prespecified threshold for the mean change from baseline in the number of migraine headache days at Month 3.

<table>
<thead>
<tr>
<th>Treatment (Q4W)</th>
<th>N</th>
<th>Posterior Mean Change from Baseline (90% CI)</th>
<th>Posterior Mean Change</th>
<th>Probability (GMB-PBO&lt;0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (PBO)</td>
<td>134</td>
<td>-3.66 (-4.12, -3.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMB 5 mg</td>
<td>65</td>
<td>-4.23 (-4.84, -3.63)</td>
<td>-0.57</td>
<td>0.915</td>
</tr>
<tr>
<td>GMB 50 mg</td>
<td>68</td>
<td>-3.92 (-4.50, -3.33)</td>
<td>-0.25</td>
<td>0.730</td>
</tr>
<tr>
<td>GMB 120 mg</td>
<td>69</td>
<td>-4.80 (-5.24, -4.20)</td>
<td>-1.14</td>
<td>0.996</td>
</tr>
<tr>
<td>GMB 300 mg</td>
<td>66</td>
<td>-4.28 (-4.91, -3.65)</td>
<td>-0.62</td>
<td>0.916</td>
</tr>
</tbody>
</table>

Oakes TM et al. Poster presented at AHS 2016. Abstract PS42
Galcanezumab CGAB Study Primary Efficacy Endpoint: Change From Baseline in Number of Migraine Headache Days (Months 1-3)

Oakes TM et al. Poster presented at AHS 2016. Abstract PS42

*p-value ≤.05

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Galcanezumab CGAB Study Secondary Endpoint: Change From Baseline in Number of Migraine Plus Probable Migraine Headache Days (Months 1-3)

*p-value ≤.05

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Galcanezumab CGAB Study Secondary Endpoint: Overall Change From Baseline in MHD Over Months 1-3

*p-value=0.018

Error bars represent 95% CI

Oakes TM et al. Poster presented at AHS 2016. Abstract PS42
Galcanezumab CGAB Study Secondary Endpoint: Estimated Percentage of Patients Reporting 50% Response Rate (RR 50) for MHD at Months 1-3

* p-value ≤ .05

Oakes TM et al. Poster presented at AHS 2016. Abstract PS42

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Galcanezumab CGAB Study Quality of Life: Change From Baseline to Month 3 in MSQ v2.1 and HIT6

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=133)</th>
<th>GMB 5 mg (N=63)</th>
<th>GMB 50 mg (N=67)</th>
<th>GMB 120 mg (N=63)</th>
<th>GMB 300 mg (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIT-6 Total Score</strong></td>
<td>-7.26</td>
<td>-9.26</td>
<td>-8.46</td>
<td>-9.95*</td>
<td>-8.27</td>
</tr>
</tbody>
</table>

* p≤.05
**p≤.001
### Galcanezumab CGAB Study: TEAE During Treatment Phase (SPIII) With ≥5% in Any GMB Arm and >Placebo

<table>
<thead>
<tr>
<th>TEAEs, %</th>
<th>Placebo (N=137)</th>
<th>GMB 5 mg (N=68)</th>
<th>GMB 50 mg (N=68)</th>
<th>GMB 120 mg (N=70)</th>
<th>GMB 300 mg (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with ≥1 TEAE</strong></td>
<td>51.1</td>
<td>60.3</td>
<td>45.6</td>
<td>51.4</td>
<td>47.8</td>
</tr>
<tr>
<td><strong>Injection site pain</strong></td>
<td>2.9</td>
<td>8.8</td>
<td>8.8</td>
<td>14.3*</td>
<td>13.4*</td>
</tr>
<tr>
<td><strong>Upper respiratory tract infection</strong></td>
<td>8.8</td>
<td>10.3</td>
<td>11.8</td>
<td>11.4</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>Nasopharyngitis</strong></td>
<td>2.2</td>
<td>11.8*</td>
<td>4.4</td>
<td>8.6</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Dysmenorrhea</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1.8</td>
<td>6.6*</td>
<td>0</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>2.9</td>
<td>1.5</td>
<td>2.9</td>
<td>0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

<sup>*p-value < .05 compared with placebo</sup>

<sup>aFor females only. N=109 for placebo; N=55 for GMB 5 mg; N=61 for GMB 50 mg; N=59 for GMB 120 mg; N=56 for GMB 300 mg</sup>

Treatments administered Q4W

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**Galcanezumab CGAB Study: TEAE During Post-treatment Phase (SPIV) With ≥1% in Any GMB Arm and >Placebo**

<table>
<thead>
<tr>
<th>TEAEs, %</th>
<th>Placebo (N=125)</th>
<th>GMB 5 mg (N=61)</th>
<th>GMB 50 mg (N=66)</th>
<th>GMB 120 mg (N=63)</th>
<th>GMB 300 mg (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 TEAE</td>
<td>28.0</td>
<td>27.9</td>
<td>28.8</td>
<td>27.0</td>
<td>32.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.0</td>
<td>1.6</td>
<td>4.6</td>
<td>1.6</td>
<td>1.54</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2.4</td>
<td>3.3</td>
<td>1.5</td>
<td>1.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0</td>
<td>0</td>
<td>4.6</td>
<td>0</td>
<td>3.1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0.8</td>
<td>0</td>
<td>1.5</td>
<td>0</td>
<td>4.6</td>
</tr>
<tr>
<td>Influenza</td>
<td>0.8</td>
<td>0</td>
<td>1.5</td>
<td>3.2</td>
<td>0</td>
</tr>
<tr>
<td>Neck pain</td>
<td>0</td>
<td>1.6</td>
<td>3.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0.8</td>
<td>0</td>
<td>0</td>
<td>3.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Treatments administered Q4W

Oakes TM et al. Poster presented at AHS 2016. Abstract PS42
### Table: Serious Adverse Events (SAEs) during Treatment (SPIII) or Post-treatment (SPIV) Phase

<table>
<thead>
<tr>
<th>SAEs&lt;sup&gt;a&lt;/sup&gt; During Treatment Phase, %</th>
<th>Placebo (N=137)</th>
<th>GMB 5 mg (N=68)</th>
<th>GMB 50 mg (N=68)</th>
<th>GMB 120 mg (N=70)</th>
<th>GMB 300 mg (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 SAE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.4</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAEs&lt;sup&gt;a&lt;/sup&gt; During Post-treatment Phase %</th>
<th>Placebo (N=125)</th>
<th>GMB 5 mg (N=61)</th>
<th>GMB 50 mg (N=66)</th>
<th>GMB 120 mg (N=63)</th>
<th>GMB 300 mg (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 SAE</td>
<td>0</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>0</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>None of the SAEs were judged related to treatment<sup>2</sup>

Following database lock, an additional SAE, ankyloglossia congenital, in a male infant of a paternal pregnancy case, was reported (the father was treated with GMB 300 mg); this event was not considered to be related to study drug.

Treatments dosed Q4W

2. Data on file, Eli Lilly and Company

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In this dose ranging study, the two highest doses of galcanezumab are efficacious in patients with episodic migraine.

Galcanezumab was well tolerated with the majority of patients completing the study.

Larger trials are needed to confirm these findings.