Safety and Tolerability Findings from an Open-Label Safety Study of Galcanezumab in Patients with Episodic or Chronic Cluster Headache

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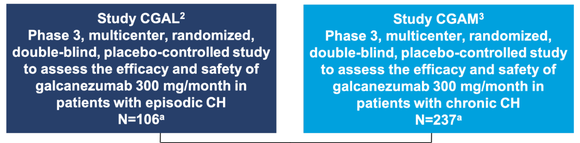
OBJECTIVE

- Cluster headache (CH) is a disabling primary headache disorder characterized by episodic attacks of intense unilateral headache and the frequent association of autonomic symptoms, such as lacrimation, conjunctival injection, and nasal congestion[1]
- Galcanezumab is a humanized IgG4 monoclonal antibody that binds calcitonin gene-related peptide (CGRP) and prevents its biological activity without blocking the CGRP receptor
- The objective of this Phase 3b, open-label study (Study CGAR; NCT02797951) was to evaluate the safety of galcanezumab within the context of expected medical practice in patients with episodic or chronic CH through assessment of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs),[a] as well as suicidal ideation and behaviors

[a]Any adverse event that results in death, is life-threatening, or places the participant at immediate risk of death from the event as it occurred; requires or prolongs hospitalization; causes persistent or significant disability or incapacity; results in congenital anomalies or birth defects; or is another condition that investigators judge to represent significant hazards.

STUDY DESIGN



[a]Only patients completing the double-blind and post-treatment follow-up (washout) periods of CGAL or CGAM were eligible to enroll in CGAR. Participation in CGAR was optional for eligible patients.
[b]Dosing was no more frequent than once per month, and the investigator could choose not to dose galcanezumab for 1 or more months at their clinical discretion based on clinical efficacy
[c]This study did not have a single specified end of study definition; rather, the study continued in a specific region until sponsor decision based on approval or nonapproval from a regulatory agency in the country or region where the patient was enrolled.
[d]Galcanezumab-treatment time is composed of monthly dosing intervals, that is, the time from a galcanezumab dose to the next monthly visit.
[e]Off-treatment time is the time between the first monthly visit that a dose was not administered and the dosing reinitiation visit.

KEY RESULT

Summary of Safety Findings During Both the Galcanezumab-treatment and Off-treatment Time

Category	n (%)
Death	1 (0.6)[a]
≥1 SAE	17 (10.4)[b]
Discontinuations due to an adverse event	5 (3.1)[c]
≥1 TEAE	119 (72.6)[d]
Likely hypersensitivity related	12 (7.3)[e]
Injection site reaction	19 (11.6)[f]
Upper respiratory tract infection related	49 (29.9)[g]
Treatment-emergent anti-drug antibodies (TE ADA+)	4 (2.8)[h]

[a]Death due to suicide 46 days after receiving the last dose of galcanezumab; considered not treatment or study related by the investigator.
[b]One SAE (constipation) was considered treatment or study related by the investigator.
[c]One adverse event that led to study discontinuation (angioedema) was considered treatment or study related by the investigator.
[d]Most were of mild or moderate severity.
[e]Comprised pruritus (1.8%), rash (1.8%), seasonal allergy (1.8%), eczema (1.2%), and injection site urticaria (1.2%). Most events were mild or moderate in severity; one severe (angioedema and pruritus, resolved the same day).
[f]Most common were injection site induration (4.3%), injection site erythema (3.7%), and injection site pain (3.1%). Most events were mild or moderate in severity; two severe (injection site pruritus and injection site pain, both resolved in 3 days).
[g]Most commonly recorded as nasopharyngitis (22.0%), sinusitis (4.3%), tonsilitis (2.4%), and upper respiratory tract infection (2.4%). All events were mild or moderate in severity.
[h]Patients with TE ADA+ postbaseline conditional on patients without TE ADA+ in parent study (N=144).

CONCLUSIONS

- Galcanezumab 300 mg had a favorable safety profile
  - TEAEs reported by 10 or more patients included nasopharyngitis, influenza, back pain, arthralgia, and bronchitis
  - Most patients reported TEAEs as moderate or mild in severity
  - Low frequency of discontinuation due to adverse events
  - No new safety issues were identified
  - The safety profile in this study was consistent with that observed in previous Phase 3 CH studies
- Limitations: Study drug was provided and it is unknown how this might have influenced the decision to administer a dose of galcanezumab within the conduct of this study

Additional Results

Baseline Patient Characteristics

- Mean age of the patients was 48.3 years (range, 23-66 years), and 79% were ≥40 years old; 75% were men, 85% were white, and 79% were from Europe
- 32% of patients were from the episodic CH Study CGAL, and 68% were from the chronic CH Study CGAM
- Overall, 92% of patients were taking ≥1 concomitant medication, the most common of which was sumatriptan (45%), followed by verapamil (34%) and oxygen (29%)

Exposure to Galcanezumab and Patient Disposition

- Mean duration of exposure 475 days (range, 28-1211 days)
- Of the 164 treated patients, 96 went through uninterrupted monthly dosing, defined as consecutive doses from first dose until patient discontinuation
- The majority of patients (71%) continued in the study until approval or nonapproval from their respective regulatory agency; lack of efficacy (12%) and patient withdrawal (9%) were the other most common reasons for discontinuation

Table 1: Most Frequently Reported TEAEs During the Galcanezumab-treatment and Off-treatment Time

TEAE (≥4% of Patients)	n (%)
Nasopharyngitis	36 (22.0)
Influenza	16 (9.8)
Back pain	11 (6.7)
Arthralgia	11 (6.7)
Bronchitis	10 (6.1)
Diarrhea	8 (4.9)
Hypertension	8 (4.9)
Cluster headache	8 (4.9)
Depression	7 (4.3)
Injection-site induration	7 (4.3)
Sinusitis	7 (4.3)

- Based on maximum severity, 20.1% of patients reported ≥1 TEAE of no greater than mild severity, 37.8% reported ≥1 TEAE of moderate severity, and 14.6% reported ≥1 severe TEAE

Table 2: SAEs During Galcanezumab-treatment and Off-treatment Time

SAE	n (%)[a]
Cluster headache	3 (1.8)
Constipation[b]	1 (0.6)
Chest discomfort	1 (0.6)
Sarcoidosis	1 (0.6)
Gastroenteritis	1 (0.6)
Exposure to household chemicals	1 (0.6)
Rib fracture	1 (0.6)
Cartilage injury	1 (0.6)
Tibia fracture	1 (0.6)
Intervertebral disc degeneration	1 (0.6)
Bladder neoplasm	1 (0.6)
Lung adenocarcinoma	1 (0.6)
Sciatica	1 (0.6)
Completed suicide	1 (0.6)
Ureterolithiasis	1 (0.6)
Arterial occlusive disease	1 (0.6)

[a]One patient reported 2 SAEs (gastroenteritis and cluster headache).
[b]Considered treatment or study related by the investigator.

Columbia-Suicide Severity Rating Scale (C-SSRS)

- During galcanezumab-treated and off-treatment time, 2 patients (1.2%) experienced suicidal ideation ("wish to be dead") but did not have emergence of suicidal behavior
- One patient died due to suicide 46 days after receiving the last dose of galcanezumab
  - The patient's mental status was good during the study
  - No history of anxiodepression
  - Negative C-SSRS assessments at all visits
  - Judged by the investigator to be due to severe family trouble and not treatment or study related

Other Safety Findings

- There were no clinically meaningful findings based on changes in laboratory parameters, weight, and temperature
- Hypertension was one of the most common preexisting conditions at baseline, and increase in systolic blood pressure or diastolic blood pressure was observed in <10% of patients
- No clinically meaningful changes in heart rate, PR, QRS intervals, or QTc prolongation were observed with galcanezumab

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Immunogenicity - Treatment-emergent Anti-drug Antibodies (TE ADA+)[a]

- Of 159 patients who were evaluable for TE ADA in CGAR, 8 patients met TE ADA+ criteria postbaseline
  - 4 patients were TE ADA+ during the parent study and 2 were TE ADA+ at only CGAR baseline
  - 2 patients met TE ADA+ criteria postbaseline who had not previously met it during the parent study or at CGAR baseline: 1 patient who received placebo in Study CGAL and 1 patient who received galcanezumab in Study CGAL
- No hypersensitivity events were reported by patients who met TE ADA+ criteria in CGAR

[a]Defined as ADA "Not Present" at baseline and ≥1 "Present" postbaseline with a titer of at least 1:20 or ADA "Present" at baseline and ≥1 "Present" postbaseline with a 4-fold or greater increase in titer.

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