CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Joint Supervisory Review

Date	September 27, 2018
From	Heather Fitter, MD; Eric Bastings, MD; Ellis Unger, MD
Subject	Joint Supervisory Review
BLA #	BLA 761063
Applicant	Eli Lilly and Company
Date of Submission	September 27, 2017
PDUFA Goal Date	September 27, 2018
Proprietary Name	Emgality
Established or Proper Names	Galcanezumab-gnlm
Dosage Form	Solution for subcutaneous (SC) injection 120mg
Applicant Proposed Indication/Population	Prophylaxis of migraine headache in adults
Applicant Proposed Dosing Regimen	120 mg SC injection monthly, with a 240-mg loading dose as the initial dose
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	Preventive treatment of migraine in adults

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Galcanezumab is a humanized monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) ligand, preventing binding to its receptor. The applicant provided information supporting safety and efficacy in patients with both chronic migraine (i.e., at least 15 headache days/month, with features of migraine headache on at least 8 days/month) and episodic migraine (i.e., up to 14 migraine headache days/month).

There are several FDA-approved drugs for the prophylaxis of migraine. Two drugs in this class were approved this year for the preventive treatment of migraine: erenumab in May 2018 and fremanezumab in September 2018. Like galcanezumab, fremanezumab binds to the CGRP ligand, whereas erenumab binds to the CGRP receptor. Topiramate, propranolol, valproate, and timolol are approved for the prophylaxis of migraine, and onabotulinumtoxinA is approved for the prophylaxis of chronic migraine in adults. Of note, the distinction between episodic and chronic migraine did not exist at the time of approval of topiramate, propranolol, valproate, and timolol (the diagnostic entity of chronic migraine was introduced in the international classification of headache in 2004), and their labels, therefore, do not include mention of episodic or chronic migraine (but the trial populations consisted mostly of patients who would now be described as having episodic migraine).

The efficacy of galcanezumab was demonstrated in three adequate and well-controlled studies, two in patients with episodic migraine, and one in patients with chronic migraine. The studies used a well-validated and clinically interpretable primary endpoint, the number of monthly migraine headache days. All three studies tested two doses of galcanezumab (120 mg and 240 mg), given monthly.

Both doses of galcanezumab tested were similarly effective in both patient populations. In patients with episodic migraine, treatment with galcanezumab led to about 4 to 5 fewer migraine headache days/month, whereas placebo-treated patients had approximately 2 to 3 fewer migraine headache days/month, both groups improving, on average, from a baseline rate of about 9 days/month. The mean treatment effect size (the difference between galcanezumab and placebo), approximately 2 fewer migraine headache days/month, is similar to that observed with drugs already approved for episodic migraine.

In patients with chronic migraine, treatment with galcanezumab led to about 5 (mean) fewer migraine headache days/month, while placebo-treated patients had about 3 (mean) fewer days/month, both groups improving from a mean baseline of about 19 days/month. The treatment effect of galcanezumab (mean effect of approximately 2 headache days/month) was similar to that of onabotulinumtoxinA, erenumab and fremanezumab, the three products currently approved for the preventive treatment of chronic migraine. It is noteworthy that a fraction of galcanezumab-treated patients experienced relatively large reductions in migraine headache days; however, there is no way to identify these patients prospectively.

No serious safety issues were identified in the galcanezumab safety database. It should be noted, however, that the trials enrolled generally young, healthy, female patients, and excluded patients older than 65 years and those with significant cardiovascular disease. The most frequent adverse event in controlled clinical trials was injection site reactions (in about 18-23% on galcanezumab-treated patients vs. 13% on placebo). A

few cases of hypersensitivity reactions, including rash, dyspnea and/or pruritus, were reported in patients treated with galcanezumab, leading to study withdrawal. There were no reported cases of angioedema or anaphylaxis. A warning will be included in labeling regarding the risk of hypersensitivity reactions, and glacanezumab will be contraindicated in patients with a history of serious hypersensitivity reaction.

As CGRP is a vasodilator, a theoretical concern has been raised in the literature that inhibition of CGRP could impair protective vasodilation in patients with tissue ischemia or infarction. FDA conducted an evaluation of available published literature to investigate the potential for antagonism of CGRP to induce vasoconstriction or adversely affect coronary vessel size, coronary blood flow, or myocardial infarct size under experimental conditions. The results of this evaluation suggest that regulation of vascular tone in healthy patients and those with cardiovascular risk factors involves multiple endogenous factors, of which CGRP is only one, and that there is limited understanding of the role of CGRP in normal hemodynamic processes or in the response to ischemia or infarction. It was concluded, therefore, that there is insufficient information to dismiss the theoretical concerns, but that additional basic research would be needed to further understand the role of CGRP in these processes. Without a better understanding, it is not likely that nonclinical studies of galcanezumab could be designed and conducted that would provide useful information; therefore, a post marketing study to assess the cardiovascular safety of glacanezumab will not be required.

The risk/benefit profile of galcanezumab is clearly favorable for patients with episodic or chronic migraine. Absent head-to-head studies comparing galcanezumab to currently approved therapies, it is not possible to determine whether galcanezumab has greater efficacy than those products, but it is clear that galcanezumab will be an important addition to the migraine preventive treatment armamentarium, as it is the third drug of a new therapeutic class, and will offer a treatment alternative to patients with episodic or chronic migraine.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headaches are also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, and various degrees of cognitive impairment are often present. Migraine attacks typically last from 4 to 72 hours in adults. About one-third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as a migraine aura. • Migraine was found to be the sixth highest cause of disability in the Global Burden of Disease Study in 2013. The prevalence of	Migraine is a serious and at times disabling condition that can impact the quality of patients' lives.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	migraine is approximately 9% in males and 20% in females in the U.S., thus resulting in a major impact to public health.	
Current Treatment Options	• There are several FDA-approved therapies for preventive treatment of migraine: erenumab, fremanezumab, topiramate, propranolol, timolol, and valproate are approved for the preventive treatment of migraine in adults and onabotulinumtoxinA is approved for prophylaxis of chronic migraine. The other preventive treatments listed above, with the exception of erenumab and fremanezumab, have a number of contraindications, warnings and precautions, as well as side effects limiting their use. In addition, many drugs and supplements are used off-label for migraine prophylaxis. • Erenumab and fremanezumab are monoclonal antibodies in the same therapeutic class as galcanezumab (CGRP antagonist), administered as subcutaneous injections: erenumab is administered monthly and fremanezumab is administered monthly or quarterly. OnabotulinumtoxinA is recommended to be administered intramuscularly every three months, and all the other medications are to be taken orally, one to three times per day.	Approved treatments are moderately effective. Although many drugs have indications that include the word "preventive" or "prophylaxis," generally none renders patients migraine-free. Erenumab and fremanezumab, monoclonal antibodies in the same therapeutic class as galcanezumab, were approved earlier this year. Medications approved for the preventive treatment of migraine have a number of side effects, and some patients lack a tolerable drug to reduce the frequency of their monthly migraines.
Benefit	• The efficacy of galcanezumab was demonstrated in three adequate and well-controlled clinical studies: Studies CGAG and CGAH in patients with episodic migraine; Study CGAI in patients with chronic migraine. Patients in all three studies were randomized to receive subcutaneous injections of either a 240-mg loading dose of galcanezumab followed by a 120-mg dose monthly, 240-mg monthly, or placebo monthly, over a 6-month treatment period in the episodic migraine studies, and a 3-month treatment period in the chronic migraine study. The studies used a well-validated and clinically interpretable primary endpoint, the mean change from baseline in the monthly average number of migraine headache days. • Results are summarized in Table 1 below; comparisons between the galcanezumab groups and placebo are highly statistically significant. The 120-mg and 240-mg dose groups had similar	The mean treatment effect of galcanezumab can be summarized as follows: for episodic and chronic migraine, the mean decreases in migraine headache days, relative to placebo, were approximately 20% and 10%, respectively. This treatment effect is similar to that of other products approved for the preventive treatment of migraine (effect size over placebo of approximately 1 to 2 days per month). And like the many approved drugs with the indication of "preventive" treatment of migraine, or migraine "prophylaxis," galcanezumab is not likely to render

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	efficacy in both episodic migraine and chronic migraine. **Table 1: The Monthly Average Number of Migraine Headache Days, by Treatment Group** • Relative to placebo, the mean effect of galcanezumab treatment for episodic migraine was approximately a 20% reduction in migraine days, whereas for chronic migraine, there was approximately a 10% reduction in migraine days. • Like the many other approved drugs with the indication of "preventive" treatment of migraine or migraine "prophylaxis," galcanezumab is not likely to render patients migraine-free.	patients migraine-free. Galcanezumab is administered monthly, which could be a convenience factor for some patients. Approved oral agents are given at least daily; erenumab and fremanezumab are also approved for monthly administration, while fremanezumab has a quarterly dosing option. Galcanezumab offers an alternative to patients who do not tolerate, or do not have an adequate response to, currently marketed drugs.

	Baseline	On treatment	Change from baseline
Study CGAG (episodic migraine)			
Placebo	9.1	6.3	-2.8
Galcanezumab 120 mg	9.2	4.5	-4.7
Galcanezumab 240 mg	9.1	4.5	-4.6
Study CGAH (episodic migraine)			
Placebo	9.2	6.9	-2.3
Galcanezumab 120 mg	9.1	4.8	-4.3
Galcanezumab 240 mg	9.1	4.9	-4.2
Study CGAI (chronic migraine)			
Placebo	19.6	16.8	-2.7
Galcanezumab 120 mg	19.4	14.6	-4.8
Galcanezumab 240 mg	19.2	15.0	-4.2

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Risk • No serious safety issues were identified with a clear causal relationship to galcanezumab. • The most common adverse reaction was injection site reaction, occurring in 18% of patients treated with galcanezumab 120 mg, vs. 13% on placebo. These reactions were generally self-limited. A few cases of hypersensitivity reactions, including dyspnea, rash and pruritus, were reported in patients treated with galcanezumab. There were no reported cases of angioedema or anaphylaxis. • CGRP is a vasodilator, and there is a theoretical concern from animal studies that CGRP inhibition could impair protective vasodilation in patients with tissue ischemia or infarction. We conducted an evaluation of available published literature to investigate the potential for CGRP antagonism to induce vasoconstriction or adversely affect coronary vessel size, coronary blood flow, or myocardial infarct size under experimental ischemic conditions. The results of this evaluation suggest that the regulation of vascular tone in healthy patients and those with cardiovascular disease involves multiple factors, of which CGRP is only one, and that there is limited understanding of the role of CGRP in normal hemodynamic processes or in the response to ischemia or infarction. It was concluded, therefore, that there is insufficient information to dismiss the theoretical concerns, but that additional basic science research is needed to understand further the role of CGRP in these processes. Without a better understanding, it is unlikely that nonclinical studies of galcanezumab could be designed and conducted that would provide useful information; therefore, no postmarketing study will be required to assess the cardiovascular safety of galcanezumab. A review of cardiovascular events, ECGs, and vital signs in the galcanezumab database did not identify a cardiovascular risk to patients; however, the number of patients was too small to be very reassuring, and the patients in the development program generally had few cardiovascular risk	Galcanezumab has an acceptable safety profile for the migraine population. Aside from injection site reactions, no major safety issues related specifically to galcanezumab have been identified to date. Based on experimental data in animals, there is a theoretical concern that CGRP receptor blockade with galcanezumab could precipitate ischemic events in patients with underlying cardiovascular disease. Regulation of vascular tone in healthy patients and those with cardiovascular risk factors involves multiple endogenous factors, of which CGRP is only one, and that there is limited understanding of the role of CGRP in normal hemodynamic processes or in response to ischemic events. Considering the current state of knowledge, no postmarketing study to assess further the cardiovascular safety of galcanezumab is recommended. The applicant's plan to defer the study of pediatric patients age 6-17 years for episodic migraine, and age 12-17 years for chronic migraine, is acceptable. A pregnancy registry study must also be conducted. Routine pharmacovigilance is appropriate for galcanezumab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	factors. Isolated ischemic events were reported in galcanezumab clinical studies, but the rate of these events was no greater than the background rate in this patient population. • Liver toxicity was an area of special interest because liver toxicity has been observed with an oral CGRP antagonist in development, and there are concerns about a class effect. There was no evidence of liver toxicity attributable to galcanezumab in the safety database. • The risk of adverse outcomes in pregnancy has not been characterized. The following PMRs will be required: • A pregnancy registry study • Pediatric studies in patients age 6-17 years	

2. Background

This memo discusses the data presented by Eli Lilly and Company in support of a new biologics license application (BLA) for galcanezumab solution for subcutaneous injection, a calcitonin gene-related peptide (CGRP) inhibitor proposed for the preventive treatment of migraine.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headache is also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, with various degrees of cognitive impairment often present. Migraine attacks typically last between 4 to 72 hours in adults. About one-third of individuals with migraine experience transient neurological symptoms before and/or during a migraine attack, referred to as migraine aura.

Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders (ICHD). The second edition (2004) of that classification introduced the diagnostic entity of chronic migraine, defined as ≥15 headache days per month, with features of migraine headache on ≥8 days per month. Patients with ≤14 migraine headache days per month are defined as having episodic migraine. The distinction between episodic and chronic migraine did not exist prior to 2004, and all drugs approved for migraine prophylaxis prior to 2010 have an indication without reference to the episodic or chronic nature of migraine. The first drug to include an indication specific to the prophylaxis of chronic migraine was onabotulinumtoxinA, which was approved for that indication in 2010. Although there is clearly a continuum and overlap between episodic and chronic migraine, differences in epidemiology, biological mechanisms, and treatment response have been described, and it is noteworthy that multiple adequate and well-controlled studies failed to show the efficacy of onabotulinumtoxinA for the treatment of episodic migraine, whereas it was shown to be effective for chronic migraine. Erenumab and fremanezumab are monoclonal antibodies that received marketing authorization for the preventive treatment of migraine in adults earlier this year. Whereas erenumab binds to the CGRP receptor, fremanezumab and galcanezumab bind to the CGRP ligand.

The Division had extensive interactions with the applicant during the development program with respect to the design of the clinical studies. The Division stated that trial results from a single study in patients with episodic migraine and a single study in patients with chronic migraine could support an application for both populations. The applicant provides data from three efficacy studies, two episodic migraine studies with a 6-month treatment period, and one chronic migraine study with a 3-month treatment period. Two doses were evaluated in the three pivotal efficacy studies; 120 mg and 240 mg monthly. Patients in the 120-mg group were to receive an initial loading dose of 240 mg, with 120 mg administered once-monthly thereafter.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Yan Wang (refer to her review for the entire OPQ list of participants in the review of this application). Galcanezumab is a humanized IgG4 kappa monoclonal antibody that binds to the CGRP ligand and blocks its binding to the CGRP receptor. Galcanezumab is produced in genetically engineered Chinese Hamster Ovary (CHO) cells. The overall molecular weight of galcanezumab is 146,940 Daltons. The galcanezumab drug product is supplied at 120 mg/1 mL as a single-dose, sterile, preservative-free, clear and colorless to slightly yellow solution for subcutaneous (SC) injection (b) (4) assembled into prefilled syringe (PFS), or assembled into an autoinjector (prefilled pen).

Dr. Reyes Candau-Chacon was the primary reviewer for the manufacturing process of galcanezumab bulk drug substance from a microbiological quality perspective, and she recommends approval. Dr. Jessica Hankins reviewed the drug product portion of this BLA, and recommends approval from a product quality microbiology and sterility assurance perspective.

Dr. Yan Wang performed the primary review, and Dr. Joel Welsch was the team leader for the evaluation of assays for galcanezumab, anti-drug antibodies (ADA), and neutralizing anti-drug antibodies (Nabs) for this application. They conclude that the assay for measurement of galcanezumab in plasma is acceptable. The assays for measurement of ADA and Nabs were also found acceptable.

OPQ concludes that the manufacture of galcanezumab by the applicant is well controlled and leads to a product that is pure and potent. OPQ recommends approval of galcanezumab for human use under the conditions specified in the package insert.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Edward Nesti, with Dr. Lois Freed performing the secondary review. As discussed by Dr. Freed, Dr. Nesti has concluded that the nonclinical studies conducted by the applicant support approval of galcanezumab for the preventive treatment of migraine in adults.

Dr. Freed discusses in her memorandum the concerns that were raised regarding potential adverse effects of chronic CGRP antagonism in humans, specifically, the potential for galcanezumab to induce a direct vasoconstrictive effect on coronary arteries and/or to inhibit compensatory vasodilation in coronary vessels that occurs in response to an acute ischemic event.

Dr. Freed discusses in her memorandum that because of the potent vasodilatory properties of CGRP, concerns were raised regarding long-term antagonism of CGRP in humans, particularly in patients with cardiovascular disease or risk factors. The applicant was asked to provide a review of relevant published literature and other data available to them. Since this request was made, the Agency has conducted an evaluation of available published literature, primarily on a

well-established probe ($CGRP_{(8-37)}$), to investigate the potential for antagonism of CGRP to induce coronary vasoconstriction, or to adversely affect coronary blood flow or myocardial infarct size under ischemic conditions. The results of this evaluation suggest that regulation of vascular tone in healthy patients and those with cardiovascular risk factors involves multiple endogenous factors, of which CGRP is only one, and that there is limited understanding of the role of CGRP in normal hemodynamic processes or in the response to ischemia or infarction. It was concluded, therefore, that there is insufficient information to dismiss the theoretical concerns, but that additional basic science research would be needed to further understand the role of CGRP in these processes. Without a better understanding of the role of the CGRP system under physiological and pathophysiological conditions, it is unlikely that nonclinical studies of galcanezumab could be designed and conducted that would provide useful information; therefore,a postmarketing study to assess the cardiovascular safety of galcanezumab will not be required.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Bilal AbuAsal (the primary reviewer), Dr. Sabarinath Sreedharan (the clinical pharmacology team leader), Dr. Gopichand Gottipati, and Dr. Kevin Krudys.

Dosing
Similar efficacy and safety were demonstrated for both 120-mg (with a 240-mg loading dose) and 240-mg once-monthly regimens of galcanezumab in episodic and chronic migraine patients (see Clinical/Statistical - Efficacy below). Injections sites in the clinical trials included the abdomen, thigh, back of the upper arm, and buttocks. Site of injection was not found to be a significant covariate in the population PK analysis.

Pharmacokinetics
OCP notes that following a single subcutaneous (SC) dose of 120 mg or 240 mg of galcanezumab, peak plasma concentrations are achieved by 5 to 7 days. Galcanezumab exposure increases proportionally with doses in the range of 120 to 240 mg. The expected half-life of galcanezumab is 27 days.

Food Effect
Galcanezumab is administered by the SC route; therefore, food-drug interactions are not anticipated.

Intrinsic Factors
No clinically significant pharmacokinetic differences were noted by age, race or sex. Body weight was the only significant covariate affecting the PK of galcanezumab, with increased clearance with increasing body weight. Body weight, however, was not identified as a statistically significant covariate on efficacy.

Galcanezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Therefore, dedicated clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the PK of

galcanezumab were not conducted. Based on a population PK analysis, neither bilirubin concentration nor creatinine clearance significantly influenced the apparent clearance of galcanezumab. Therefore, no dose adjustment is recommended for body weight, sex, age, renal or hepatic impairment.

Drug-drug Interactions
Monoclonal antibodies typically do not undergo metabolism by the cytochrome P450 system and are unlikely to be affected by drug transporters; therefore, no drug interaction studies were conducted with galcanezumab.

Pharmacometrics
OCP conducted a pharmacometric analysis to assess galcanezumab's dose-exposure response. There was a clear difference in exposure for the two dose levels tested, 120 mg and 240 mg, but the exposure response analysis showed no apparent relationship between efficacy and galcanezumab concentration, consistent with the lack of a dose-response observed in the efficacy studies (Table 2).

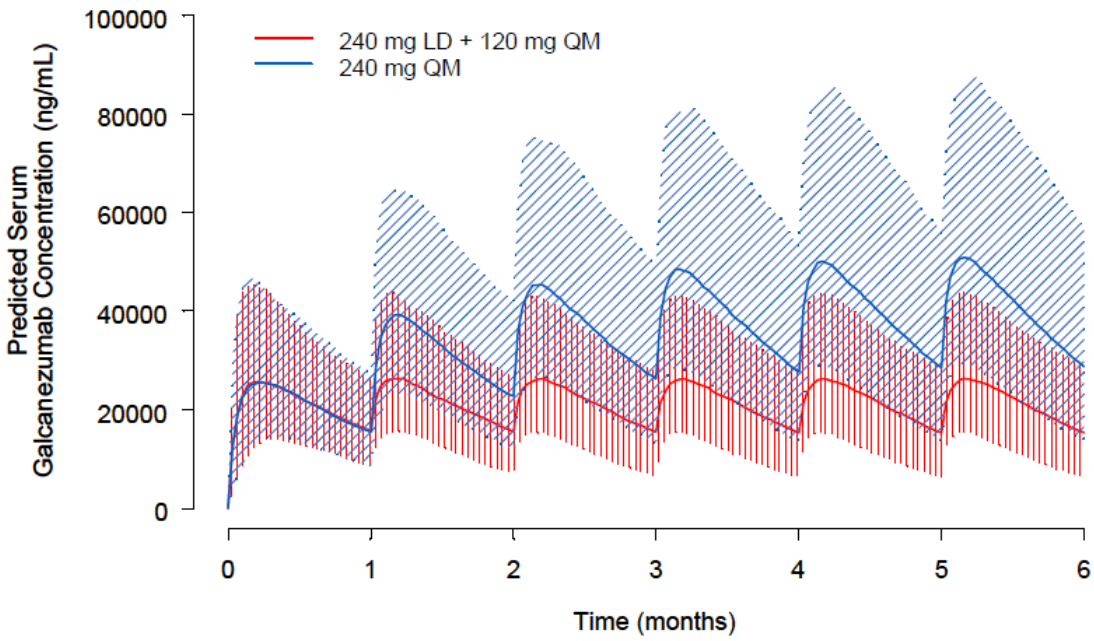
Table 2: Mean Difference Between Galcanezumab and Placebo in the Number of Monthly Migraine Headache Days for the Three Pivotal Efficacy Studies Individually

Study	Dose	LS Mean Difference vs Placebo (95% CI)
CGAG	120 mg	-1.9 (-2.5, -1.4)
	240 mg	-1.8 (-2.3, -1.2)
CGAH	120 mg	-2.0 (-2.5, -1.5)
	240 mg	-1.9 (-2.4, -1.4)
CGAI	120 mg	-2.1 (-2.9, -1.3)
	240 mg	-1.9 (-2.7, -1.0)

Source: Adapted from Applicant's Integrated Summary of Efficacy (ISE); Figure ISE.8.1

Dr. AbuAsal also reviewed the results of a Phase 2 study in migraine patients, which included four doses of galcanezumab (5, 50, 120, 300 mg given every 4 weeks) and placebo. Monthly doses under 120 mg did not have robust efficacy. Interestingly, the 120-mg monthly dose did not show a statistically significant improvement relative to placebo at Months 1 and 2, but did so at Month 3. The 300-mg dose showed significant separation from placebo at Month 1 and 2, but not at Month 3. Based on this observation, a 240-mg loading dose was selected for the Phase 3 trials, to achieve steady-state concentrations by Month 1 (refer to Figure 1 below).

Figure 1 : Model Predicted Galcanezumab Concentration-time Profiles after a 240-mg Loading Dose followed by 5 Consecutive Once-monthly 120-mg Doses, or 6 Consecutive Once-monthly 240-mg doses



Abbreviations: LD = loading dose; QM = once monthly.
Solid line is the median response. Shaded region represents the 90% prediction interval (PI) of galcanezumab concentrations calculated from 500 simulation iterations.

Source: Applicant Population PK/PD report: Figure 10.1

Immunogenicity
The overall incidence of anti-drug antibody (ADA) across the Phase 3 studies with treatment periods up to 12 months was about 12.5%; titers were low in most patients. Most patients who developed ADA had the presence of neutralizing anti-drug antibodies (Nab). The presence of ADA, irrespective of titer and Nab, did not seem to affect the PK, efficacy, or safety of galcanezumab in those patients. Although these data do not demonstrate an impact of ADA development on the efficacy or safety of galcanezumab in these patients, the available data are too limited to make definitive conclusions.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Suhail Kasim was the clinical reviewer for this application. Dr. Junshan Qiu was the biometrics reviewer, and Dr. Kun Jin was the biometrics team leader. Dr. Sarrit Kovacs was

the primary reviewer, and Dr. Wen-Hung Chen was the team leader from the Clinical Outcomes Assessment (COA) team. For this application, the COA staff conducted a review of the Migraine-Specific Quality of Life Questionnaire (MSQ)–Role Function–Restrictive domain, a patient-reported outcome (PRO), which was designed to evaluate the functional impact of migraine.

The applicant conducted three pivotal placebo-controlled efficacy trials (Table 3): two trials in episodic migraine (EM) [Study I5Q-MC-CGAG (referred to as CGAG in this memo) and Study I5Q-MC-CGAH (referred to as CGAH in this memo)] and one trial in chronic migraine (CM) [I5Q-MC-CGAI (referred to as CGAI in this memo)].

Table 3: Clinical Efficacy Studies

	Population	Double-blind treatment period	Dosing regimen
Study CGAG	Episodic migraine	6 months	120-mg monthly, with a 240-mg loading dose, or 240-mg monthly, or placebo
Study CGAH	Episodic migraine	6 months	Same as above
Study CGAI	Chronic migraine	3 months	Same as above

The primary endpoint for the three pivotal efficacy trials was the mean change from baseline in the monthly average number of migraine headache days (MHD). The primary endpoints, as well as the key secondary endpoints (described below), were identical for all three studies, but the timing of evaluation of endpoints was different. In addition, the prespecified sequential testing order to provide control of the type-1 error rate differed between the episodic and chronic migraine trials (see additional description below). In the episodic migraine trial, the endpoints were measured over the course of the 6-month double-blind treatment period, while in the chronic migraine trial, the key endpoints were evaluated over the 3-month double-blind treatment period.

All 3 studies included a novel patient-reported outcome (PRO) developed to assess the functional impact of migraine, the Migraine Specific Quality of life Questionnaire (MSQ) Role Function-Restrictive domain. Dr. Kovacs, from the Clinical Outcome Assessment (COA) staff in the Office of New Drugs (OND), describes the new PRO as a self-administered instrument that consists of 14 items that address 3 independent domains: 1) Role Function-Restrictive, 2) Role Function-Preventive, and 3) Role Function-Emotional. This instrument consists of 7 items designed to measure the impact of migraine on daily activities. Raw scores for each item range from 7 to 42; transformed scores are then generated for each domain, ranging from 0 to 100, with higher scores indicating less impact of migraine on patients' daily lives. The prespecified analysis for the MSQ Role function-Restrictive domains scores was based on transformed scores. The restrictive domain is specifically proposed to measure the impact of migraine on work or daily activities, relationships with family and friends, leisure time, productivity, concentration, energy and tiredness. This instrument was designed with a 4-week recall period. The applicant provided data supporting the 4-week recall period for this instrument. Dr. Kovacs concludes that the MSQ v2.1 Role Function–Restrictive domain's

content validity, psychometric properties, and performance are acceptable in the context of use, and that the evidence submitted by the applicant is sufficient to demonstrate that the MSQ v2.1 Role Function-Restrictive domain is adequate to assess the impact of migraine on daily activities.

Studies CGAG and CGAH (Episodic Migraine)

Studies CGAG and CGAH were randomized, double-blind, placebo-controlled trials in patients with episodic migraine, and both had the same design. Subjects eligible for enrollment were adults 18 to 65 years of age with a history of migraine with or without aura for ≥ 12 months, and who experienced ≥ 4 to < 15 migraine headache days/month. Subjects on other preventive treatments for migraine and subjects with medication-overuse headache (defined as headaches occurring ≥ 15 days per month associated with regular use of acute headache medications) were excluded. Subjects were also excluded if they had ECGs showing abnormalities compatible with acute cardiovascular events, a serious cardiovascular risk, or had a history of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, stroke, deep vein thrombosis, or pulmonary embolism within 6 months of screening. Patients were also excluded if they had a planned cardiovascular surgery or percutaneous coronary angioplasty.

After a one-month baseline period, eligible patients were randomized in a 2:1:1 ratio to receive placebo, galcanezumab 120 mg SC monthly with a 240-mg initial loading dose, or galcanezumab 240 mg SC monthly for 6 months. After participation in the double-blind portion of the trial, patients were offered enrollment into either a 12-month open-label (fixed dose) safety study, or a 4-month safety follow-up period (off study medication).

The primary endpoint for studies CGAG and CGAH was the mean change from baseline in the monthly average number of migraine headache days (MHD).

Key secondary endpoints in studies CGAG and CGAH were (as ordered in the analysis plan): 1) change from baseline in monthly average MHD; 2) the proportion of patients with ≥50% reduction from baseline in monthly MHD; 3) the proportion of patients with ≥75% reduction from baseline in monthly MHD; 4) mean change from baseline in monthly migraine headache days with acute migraine medication taken; 5) the change from baseline in the Role Function-Restrictive domain scores of the MSQ; 6) the proportion of patients with 100% reduction from baseline in monthly MHD; and 7) the mean change from baseline in the Patient Global Impression-Improvement (PGI-S) score.

To control the overall type-1 error rate, the primary and key secondary endpoints were tested using an overall super chain procedure multiple-testing approach providing control of the familywise type-1 error rate at a 2-sided 0.05 alpha level, with alpha propagation techniques.

Efficacy analyses were modified intent-to-treat, based on patients who had received at least one dose of investigational product and completed at least one change from baseline measurement in monthly migraine days during the double-blind treatment period.

For the repeat measure analyses, missing data were handled by estimating the treatment effect using a restricted likelihood estimation, which incorporates the observed data based on an assumption of missing at random (MAR). The robustness of the primary analysis conclusions, using these MAR assumptions, was tested in a systematic way by using different assumptions, based on a possibility that the data were not missing at random.

For analyses using Analysis of Covariance (ANCOVA) model, the procedure used to handle missing data depended on how the endpoint was being measured. For endpoints that were measured as change from baseline over the entire treatment period, imputation was based on the average monthly value observed during months when this value was measured. For endpoints that were measured as change from baseline to the end of treatment, change from baseline to last observation carried forward (LOCF) was used.

CGAI (Chronic Migraine)

Study CGAI was a 3-month randomized, double-blind, placebo-controlled trial in patients with chronic migraine. Eligible subjects were adults 18 to 65 years of age with a history of migraine with or without aura who experienced ≥15 headache days per month, with ≥8 migraine days per month. Patients with medication overuse headache were eligible for enrollment. A subset of patients (up to 15%) could use one concomitant migraine preventive treatment. The study had the same cardiovascular exclusions as the episodic migraine studies.

After a one-month baseline period, eligible subjects were randomized in a 1:1:1 ratio to placebo, galcanezumab 120 mg SC monthly with an initial 240-mg bolus, or galcanezumab 240 mg SC once-monthly. After participation in the double-blind portion of the trial, patients were offered enrollment in a 9-month open-label (flexible-dose) safety study (Study I5Q-MC-CGAJ) or a 4-month safety follow-up period (off study medication). During the flexible-dose portion of the open-label safety study, investigators could select a monthly dose of 120 mg or 240 mg at their discretion, but all patients received the 240-mg bolus as the initial dose.

The primary endpoint and key secondary endpoints were identical to those in the episodic migraine trials, except that evaluations for this trial were done over the 3-month double-blind treatment period, rather than over the 6-month double-blind treatment period of the episodic migraine trials. The pre-specified multiple testing procedure for controlling type-1 error was slightly different in the chronic migraine study than in the episodic migraine studies. The pre-specified testing order for key endpoints in the chronic migraine trial was as follows: 1) change from baseline in monthly average MHD; 2) the proportion of patients with ≥50% reduction from baseline in monthly MHD; 3) the proportion of patients with ≥75% reduction from baseline in monthly MHD; 4) the mean change from baseline in monthly migraine headache days with acute migraine medication taken; 5) the mean change from baseline in the Role Function-Restrictive domain scores of the MSQ; 6) the mean change from baseline in the PGI-S score; and 7) the proportion of patients with 100% reduction from baseline in monthly MHD. In the episodic migraine trial, the PGI-S was tested at step 7 and the proportion of patients with 100% reduction from baseline in monthly MHD was tested at step 6. This study handled missing data in the same way as in the episodic migraine studies.

Results

In the three pivotal efficacy studies, the median age of the subjects was between 38 and 43 years. Eighty-one to 86% of subjects were female, and 68 to 82% were Caucasian. Demographics and baseline disease characteristics were generally balanced between treatment groups. The mean number of MHD at baseline was 9 days in the episodic migraine population and 19 days in the chronic migraine population, and similar in the various treatment groups in each study.

Patients in the episodic migraine trials could not use a concomitant preventive migraine treatment in addition to the study medication, but in the chronic migraine study, 13-15% of patients were using a concomitant preventive treatment for migraine.

Change from Baseline in Monthly Average Number of Migraine Headache Days (Primary Efficacy Endpoint)

Study CGAG (Episodic Migraine)

For Study CGAG, Dr. Qiu reports that the overall mean changes from baseline in the number of MHD were -4.7 and -4.6 days for galcanezumab 120 mg and 240 mg, respectively, compared with -2.8 days for placebo. The adjusted mean treatment difference was -1.9 days between galcanezumab 120 mg and placebo and -1.8 days between galcanezumab 240 mg and placebo, $p<0.001$ for both (see Table 4).

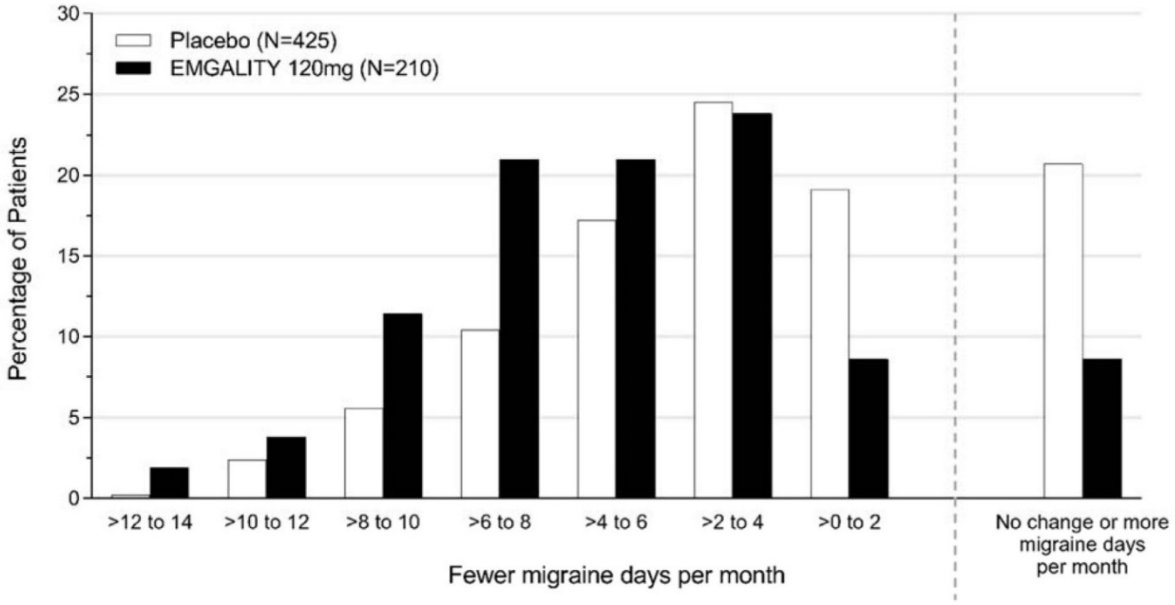
Table 4: Study CGAG – Primary Efficacy Endpoint: Change from Baseline in the Monthly Average Number of Migraine Headache Days

	Placebo (n=425)	Galcanezumab 120 mg (n=210)	Galcanezumab 240 mg (n=218)
Overall			
Baseline	9.1	9.2	9.1
LS mean (SE)	-2.81 (0.24)	-4.73 (0.29)	-4.57 (0.29)
95% CI	(-3.28,-2.34)	(-5.31, -4.16)	(-5.15, -3.99)
Comparison with placebo			
LS mean (SE)		1.92 (0.28)	-1.76 (0.28)
95% CI		(-2.48,-1.37)	(-2.31, -1.20)
p-value		< 0.001	< 0.001

Adapted from Applicant's Table CGAG 11.3, Clinical Study Report

Figure 2 shows a distribution of changes from baseline in mean MHD in bins of 2 days, by treatment group, in Study CGAG. A leftward shift (toward improvement) is evident for galcanezumab relative to placebo.

Figure 2: Study CGAG – Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 6 by Treatment Group



Source: Applicant, verified by FDA

Study CGAH (Episodic Migraine)

For Study CGAH, Dr. Qiu reports that the overall mean changes from baseline in the number of MHD were -4.3 and -4.2 days for galcanezumab 120 mg and 240 mg, respectively, compared with -2.3 days for placebo. The adjusted mean treatment difference was -2.0 days between galcanezumab 120 mg and placebo and -1.9 days between galcanezumab 240 mg and placebo, $p<0.001$ for both (see Table 5).

Table 5: Study CGAH – Primary Efficacy Endpoint: Change from Baseline in the Monthly Average Number of Migraine Headache Days

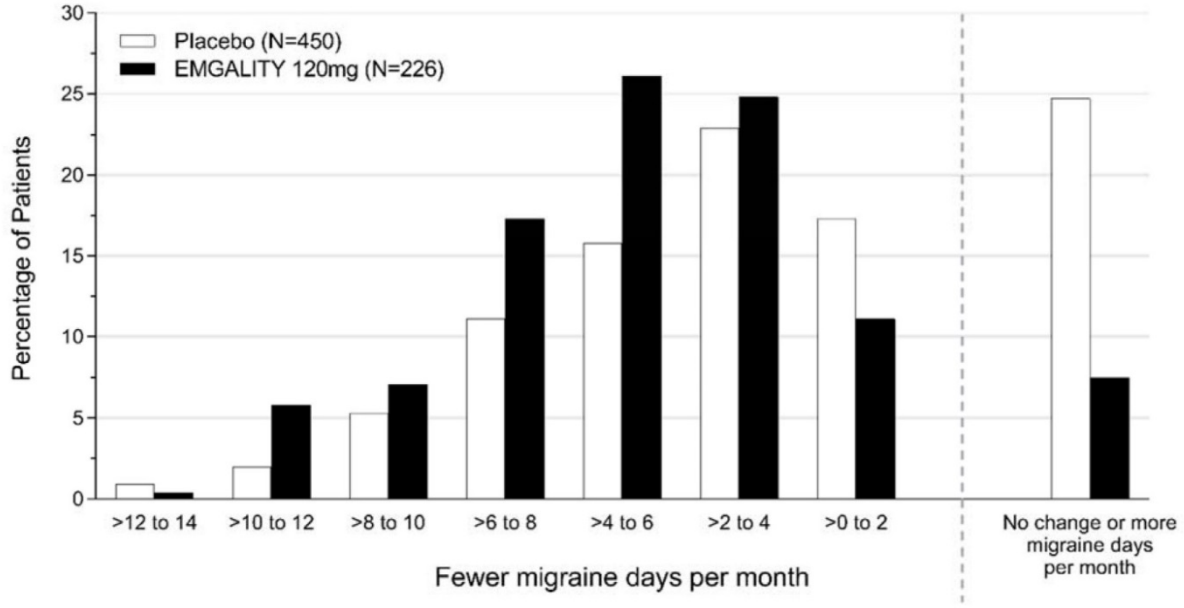
	Placebo (n=450)	Galcanezumab 120 mg (n=226)	Galcanezumab 240 mg (n=220)
Overall			
Baseline	9.2	9.1	9.1
LS mean (SE)	-2.28 (0.20)	-4.29 (0.25)	-4.18 (0.26)
95% CI	(-2.67,-1.88)	(-4.79, -3.80)	(-4.68, -3.67)
Comparison with placebo			
LS mean (SE)		-2.02 (0.27)	-1.90 (0.27)
95% CI		(-2.55,-1.48)	(-2.44, -1.36)
p-value		< 0.001	< 0.001

Adapted from Applicant's table CGAH 11.3, Clinical Study Report

Dr. Kasim notes in his review that the treatment effect seen in both episodic migraine studies, CGAG and CGAH, was consistent throughout all 6 months of the trial.

Figure 3 shows a distribution of changes from baseline in mean MHD in bins of 2 days, by treatment group, in Study CGAH. As in Study CGAG, a leftward shift (towards improvement) is evident.

Figure 3: Study CGAH-Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 6 by Treatment Group



Source: Applicant, verified by FDA

Study CGAI (Chronic Migraine)

For Study CGAI, Dr. Qiu reports that the overall mean changes from baseline in the number of MHD were -4.8 and -4.6 days for galcanezumab 120 and 240 mg, respectively, compared with -2.8 days for placebo. The adjusted mean treatment difference was -2.1 days between galcanezumab 120 mg and placebo and -1.9 days between galcanezumab 240 mg and placebo, $p<0.001$ for both (see Table 6).

Table 6: Study CGAI – Primary Efficacy Endpoint: Change from Baseline in the Monthly Average Number of Migraine Headache Days

	Placebo (n=538)	Galcanezumab 120 mg (n=273)	Galcanezumab 240 mg (n=274)
Overall			
Baseline	19.6	19.4	19.2
LS mean (SE)	-2.74 (0.36)	-4.83 (0.44)	-4.18 (0.26)
95% CI	(-3.45,-2.03)	(-5.69, -3.97)	(-4.68, -3.67)

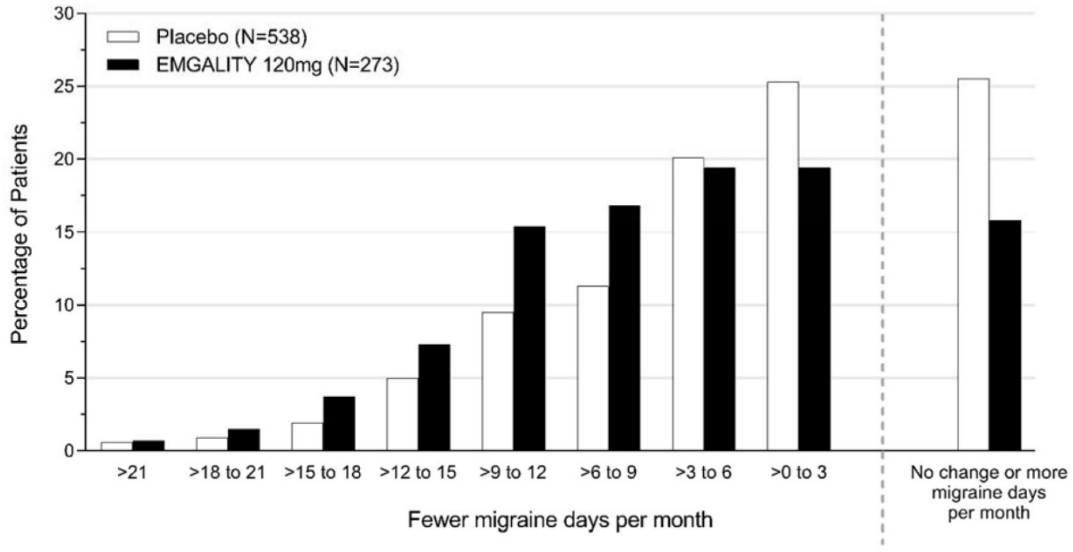
	Placebo (n=538)	Galcanezumab 120 mg (n=273)	Galcanezumab 240 mg (n=274)
Comparison with placebo			
LS mean (SE)		-2.09 (0.42)	-1.88 (0.42)
95% CI		(-2.92,-1.26)	(-2.71, -1.05)
p-value		< 0.001	< 0.001

Adapted from Applicant's table CGAI 11.3, Clinical Study Report

Dr. Kasim notes that the treatment effect was consistent throughout all 3 months of the study.

Figure 4 shows a distribution of changes from baseline in mean MHD in bins of 3 days, by treatment group. Three-day bins were used in this analysis, in contrast to 2-day bins for the EM studies, because the number of monthly migraine days is greater in CM patients than in EM patients. As in the EM studies, a leftward shift (towards improvement) is evident.

Figure 4: Study CGAI – Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 3 by Treatment Group



Source: Applicant, verified by FDA

Key Secondary Endpoints

Study CGAG (Episodic Migraine)

The secondary endpoints described in Table 7 were prespecified and controlled for multiplicity. In Study CGAG, galcanezumab demonstrated statistically significant differences from placebo in the proportions of patients who demonstrated ≥50%, ≥75%, and 100% reductions in mean MHD, for both doses (p<0.001). A statistically significant (p<0.001) difference was also demonstrated in the mean change from baseline in the number of monthly migraine headache days with use of acute migraine medication between the galcanezumab

groups and placebo. In addition, galcanezumab demonstrated a statistically significant difference from placebo in the change from baseline in the score for the MSQ Role Function–Restrictive domain ($p<0.001$). Of note, approximately 15% of patients became migraine-free on galcanezumab (100% reduction in MHD), vs. 6% in the placebo group.

Table 7: Study CGAG – Key Secondary Efficacy Analyses

Statistic	Episodic Migraine Study CGAG (Months 1 to 6)		
	Placebo (N=425)	Galcanezumab	
		120 mg (N=210)	240 mg (N=208)
Reduction of at least 50% in monthly average number of migraine days			
% responder, SE	38.6 (1.7)	62.3 (2.4)	60.9 (2.5)
p-value		<0.001	<0.001
Reduction of at least 75% in monthly average number of migraine days			
% responder, SE	19.3 (1.4)	38.8 (2.4)	38.5 (2.4)
p-value		<0.001	<0.001
100% reduction in monthly average number of migraine days			
% responder, SE	6.2 (0.8)	15.6 (1.6)	14.6 (1.6)
p-value		<0.001	<0.001
Change from baseline in mean number of monthly migraine headache days with use of acute migraine medication			
	Placebo (N=425)	120 mg (N=210)	240 mg (N=208)
Baseline	7.4	7.4	7.3
LS mean change from baseline (SE)	-2.15 (0.21)	-3.96 (0.25)	-3.76 (0.26)
Comparison with Placebo			
LS mean (SE)		-1.81 (0.24)	-1.61 (0.24)
95% CI		(-2.28, -1.33)	(-2.09, -1.14)
p-value		<0.001	<0.001
MSQ Role Function-Restrictive Domain scores (months 4 to 6)			
	Placebo (N=377)	120 mg (N=189)	240 mg (N=184)
Baseline	52.9	51.4	48.8
LS mean change from baseline (SE)	24.7 (1.1)	32.4 (1.3)	32.1 (1.3)
Comparison with Placebo			
LS mean change (SE)		7.7 (1.3)	7.4 (1.3)
95% CI		5.2, 10.3	4.8, 10.0
p-value		<0.001	<0.001

Source: Applicant Tables CGAG 11.4, 11.8, ISE Table 8.5, CSR

Study CGAH (Episodic Migraine)

A similar magnitude of effect is seen in study CGAH as compared to study CGAG when evaluating the secondary endpoints described in Table 8 below.

In Study CGAH, there were statistically significant differences between both doses of galcanezumab and placebo in the proportions of patients who demonstrated a ≥50%, ≥75%, or

100% reduction from baseline in the average number of MHD ($p<0.01$). A statistically significant difference ($p<0.001$) was also demonstrated in the mean change from baseline in monthly MHD with use of acute medication between both doses of galcanezumab and placebo. In addition, there was a statistically significant difference in the change from baseline in the MSQ Role Function–Restrictive domain score between both doses of galcanezumab and placebo ($p<0.001$). In both episodic migraine efficacy trials, results with the 240-mg dose of galcanezumab were similar to those with the 120-mg dose. Of note, 12 to 14% of patients became migraine-free on galcanezumab (100% reduction in MHD), vs. 6% in the placebo group.

Table 8: Study CGAH – Key Secondary Efficacy Analyses

Statistic	**Episodic Migraine Study CGAH (Months 1 to 6)**		
	Placebo (N=450)	**Galcanezumab**	
		120 mg (N=226)	**240 mg (N=220)**
Reduction of at least 50% in monthly average number of migraine days			
% responder, SE	36 (1.7)	59.3 (2.4)	56.5 (2.5)
p-value		<0.001	<0.001
Reduction of at least 75% in monthly average number of migraine days			
% responder, SE	17.8 (1.3)	33.5 (2.3)	34.3 (2.3)
p-value		<0.001	<0.001
100% Reduction in monthly average number of migraine days			
% responder, SE	5.7 (0.7)	11.5 (1.4)	13.8 (1.5)
p-value		<0.001	<0.001
Mean change from baseline in mean number of monthly migraine headache days with use of acute migraine medication			
	Placebo (N=450)	120 mg (N=226)	240 mg (N=220)
Baseline	7.6	7.5	7.5
LS mean change (SE)	-1.85 (0. 18)	-3.67 (0.22)	-3.63 (0.23)
Comparison with Placebo			
LS mean (SE)		-1.82 (0.24)	-1.78 (0.24)
95% CI		-2.29, -1.36	-2.25, -1.31
p-value		<0.001	<0.001
MSQ Role Function-Restrictive Domain scores (months 4 to 6)			
	Placebo (N=396)	120 mg (N=213)	240 mg (N=210)
Baseline	51.3	52.4	51.8
LS mean change from baseline (SE)	19.7 (0.9)	28.5 (1.2)	27.0 (1.2)
Comparison with Placebo			
LS mean change (SE)		8.8 (1.3)	7.4 (1.3)
95% CI		6.3, 11.3	4.9, 9.9
p-value		<0.001	<0.001

Source: Applicant tables CGAH 11.4, 11.8, ISE table 8.5, CSR

Study CGAI (Chronic Migraine)

For the galcanezumab 240-mg dose group, Dr. Kasim reports that the key secondary study endpoints were met for 50% and 75% reductions from baseline MHD, mean change from baseline in the number of monthly migraine days with use of headache medication, and the change from baseline in MSQ role function-restrictive domain endpoints. For the next test in the sequence, however, 100% reduction of MHD, the results were not statistically significant.

For galcanezumab 120 mg, only the key secondary endpoint of the reduction from baseline of at least ≥50% in MHD (50% responders) was statistically significant after multiplicity adjustment. Per the prespecified multiple testing procedure, because the *p*-value observed for the comparison of the 75% responder rate for the 120-mg dose versus placebo (p=0.031) was higher than the multiplicity-adjusted alpha level (0.025), and because no alpha could be recycled from galcanezumab 240 mg to 120 mg (because the analysis for 100% responders for galcanezumab 240 mg was not statistically significant), further hierarchical testing for the 120-mg dose was stopped. Thus, all remaining items in the 120-mg testing sequence (i.e., mean change from baseline in the number of monthly migraine headache days with use of acute migraine medication, the change from baseline in MSQ Role Function-Restrictive domain scores, and 100% responder rate,) are considered not statistically significant after multiplicity adjustment, regardless of *p*-value, which are nominal only (Table 9).

Table 9: Study CGAI- Key Secondary Efficacy Analyses

Statistic	Chronic Migraine Study CGAI (Months 1 to 3)		
	Placebo (N=538)	Galcanezumab	
		120 mg (N=273)	240 mg (N=274)
Reduction of at least 50% in monthly average number of migraine days			
% responder, SE	15.4 (1.6)	27.6 (2.7)	27.5 (2.6)
p-value		<0.001	<0.001
Reduction of at least 75% in monthly average number of migraine days			
% responder, SE	4.5 (0.9)	7.0 (1.4)	8.8 (1.7)
p-value		0.031 (NS @ >0.025)	<0.001
100% reduction from baseline in Migraine Headache Days			
% responder, SE	0.5 (0.3)	0.7 (0.4)	1.3 (0.6)
p-value		0.597*	0.058*
Mean change from baseline in mean number of monthly migraine headache days with use of acute migraine medication			
	Placebo (N=538)	120 mg (N=273)	240 mg (N=274)
LS mean (SE)	-2.23 (0.33)	-4.74 (0.40)	-4.25 (0.40)
Comparison with Placebo			
LS mean (SE)		-2.51 (0.38)	-2.01 (0.38)
95% CI		(-3.27, -1.76)	(-2.77, -1.26)
p-value		<0.001*	<0.001
MSQ Role Function-Restrictive Domain scores (at Month 3)			
	Placebo (N=494)	120 mg (N=252)	240 mg (N=253)
Baseline	38.4	39.3	38.9

Statistic	Chronic Migraine Study CGAI (Months 1 to 3)		
	Placebo (N=538)	Galcanezumab	
		120 mg (N=273)	240 mg (N=274)
LS mean change from baseline (SE)	16.8 (1.18)	21.8 (1.41)	23.1 (1.6)
Comparison with Placebo			
LS mean change (SE)		5.1 (1.5)	6.3 (1.7)
95% CI		(2.1, 8.0)	(3.0, 9.6)
p-value		<0.001 *	<0.001
* nominal p-value			

Source: Applicant tables CGAI 11.4, 11.7, ISE table 8.5, CSR

MSQ Role Function-Restrictive Domain

Dr. Kovacs reviewed the anchor-based empiric cumulative distribution function (eCDF) figures for the episodic migraine trials and estimated a clinically meaningful within-patient improvement threshold of between 28.6 and 32.4 points. In the chronic migraine study, she estimates the clinically meaningful within-patient improvement threshold to be 28.6 points. Dr. Kovacs concludes that the eCDF curves showed a separation between placebo and both (120-mg and 240-mg) galcanezumab treatment groups in both episodic migraine trials, and that the MSQ v2.1 Role Function-Restrictive domain score changes fall within the estimated thresholds for clinically meaningful improvement. In the chronic migraine trial, there was less separation between the galcanezumab 120 mg and the placebo arm curves, but a more consistent separation between the 240-mg galcanezumab curve and placebo.

The MSQ-Role Function Restrictive domain analysis was a pre-specified secondary endpoint and there was control of the type-1 error for all three pivotal efficacy trials. The prespecified analysis for the episodic migraine trials yielded statistically significant results when the 120 mg galcanezumab group was compared to placebo. In the chronic migraine trial, however, because hierarchical testing stopped prior to testing of this secondary endpoint, this analysis yielded only nominally significant findings. Refer to Table 7, Table 8, and Table 9 for the results of the analyses of the MSQ-Role Function-Restrictive domain scores in the pivotal trials.

Efficacy by Subgroups

There was no meaningful difference in the magnitude or direction of the treatment effect based on age, gender, race or body mass index (see primary review).

Efficacy Conclusions

The applicant has provided substantial evidence of effectiveness of galcanezumab based on three adequate and well-controlled investigations. These studies demonstrated significant reductions in mean MHD in patients treated with galcanezumab, compared with those who received placebo. In the episodic migraine trials, treatment benefits were demonstrated in all secondary endpoints. In the chronic migraine trial, results for the secondary endpoints were less consistent. Efficacy was similar in both populations for galcanezumab 240 mg and galcanezumab 120 mg. The magnitude of change observed in the primary endpoint is modest (1.8-2.1 days/month over placebo), but consistent with treatment effects observed with

previously approved migraine preventive treatments. Considering the similar efficacy of the two doses tested and the relatively flat dose-exposure response, the labeling will recommend a dose of 120 mg once-monthly, with an initial 240-mg loading dose.

8. Safety

Dr. Maria L. Villalba conducted the clinical safety review, with Dr. Sally Jo Yasuda as the safety team leader.

As discussed by Dr. Villalba, the overall exposure to galcanezumab exceeds the minimum numbers of patients recommended by the International Council for Harmonization (ICH) E1 Guideline for chronically administered medications. She reports that 3156 subjects have been exposed to at least one dose of galcanezumab (including 419 healthy volunteers, and subjects in studies for other indications, e.g., 151 patients in cluster headache or osteoarthritis studies). Seven hundred and thirty-five patients were exposed to galcanezumab 120 mg for ≥ 6 months, and 167 patients for 12 monthly doses. One thousand one hundred and eighty-five patients were exposed to galcanezumab 240 mg for ≥ 6 months, and 359 patients for 12 monthly doses, through the time of the 3-month safety update report. Two hundred sixty-six patients received 12 monthly doses of either galcanezumab 120 mg or 240 mg and also completed the 4-month post-treatment follow-up. No patients received > 12 doses of galcanezumab in this development program. Dr. Villalba notes that there was limited exposure in patients with cardiovascular risk factors. She also notes that there is limited information provided on patients 65 years and older, as these patients represented only 1% of the population in the database.

Deaths

(b) (4)

patient was a 36 year-old healthy male volunteer with no concomitant medications and an unremarkable past medical history, who received a single dose of galcanezumab 240 mg, and died 15 days after this dose. He did not report any AEs during his outpatient visits through day 12. On day 15, he was found "face down in the water next to a yacht slip." There were no signs of trauma, and toxicology results were negative for alcohol and common drugs of abuse. The autopsy report states he had pulmonary congestion, and concluded that he died of accidental drowning, yet Dr. Villalba notes there was no mention of water in the lungs in the autopsy report. Dr. Villalba speculates that this patient may have experienced sudden death from unknown causes. She concludes that the cause of the death is undetermined and the relationship to study drug is unknown. Dr. Yasuda agrees that the relationship to the study drug is unknown.

Serious Adverse Events (SAEs)

In the controlled trial database, 42 serious adverse events were reported in 37 subjects. Dr. Villalba notes that SAEs were reported at similar frequencies among galcanezumab-treatment

groups (2.3%), and slightly more than on placebo (1.3%), but most SAEs occurred in only 1 patient. A query of related SAEs was conducted that combined closely related event terms. The only SAEs reported in >1 galcanezumab-treated patient were cancers (3 vs. 0), pancreatitis (acute/alcoholic; 3 vs. 0), and nephrolithiasis/renal colic (2 vs. 0).

The system-organ-classes (SOCs) with the most SAEs were neoplasm (0.5% galcanezumab, none in placebo) and gastrointestinal disorders (0.4% galcanezumab and 0.2% placebo). The incidence of cardiovascular serious adverse events was similar in all 3 treatment groups: 0.3%, 0%, and 0.1% for galcanezumab 240 mg, galcanezumab 120 mg, and placebo, respectively.

In a Phase 2 trial, there was a patient with cardiovascular risk factors who had thromboembolic events resulting in an above-knee amputation. Dr. Villalba believes that there is biological plausibility that such an event may be related to galcanezumab. Dr. Yasuda concludes that a contribution of CGRP inhibition cannot be ruled out, yet there is not strong evidence for a supporting role either.

Across controlled and uncontrolled trials, there were 3 seizures reported as SAEs and 2 non-SAE seizures. Most of the cases were confounded, and therefore it cannot be determined whether these events were related to galcanezumab; however, the rate of seizures in this database were no greater than the background rate in this population. Overall, there is not a signal for seizures in this database.

AEs Leading to Study Discontinuation

In the controlled trials, Dr. Villalba notes that 56 patients discontinued or were withdrawn from studies because of an adverse event; 17 (2.4%) on galcanezumab 120 mg, 14 (1.9%) on galcanezumab 240 mg, and 25 (1.7%) on placebo. Most AEs resulted in discontinuation in only 1 patient. The most common AEs leading to discontinuation among galcanezumab patients were injection site reactions/erythema/swelling (0.2% for galcanezumab 120 mg and 0.4% for galcanezumab 240 mg, vs. 0% for placebo), and hepatic enzyme increased (0.3% for galcanezumab 240 mg and 0% for galcanezumab 120 mg, vs. 0% for placebo).

Severe Adverse Events

Dr. Villalba notes that the percentage of patients with severe AEs was similar in placebo and each galcanezumab treatment group across the controlled trials (approximately 7.4% in each group). The largest differences were related to injection site pain. Across controlled and uncontrolled trials, severe injection site pain occurred in approximately 1% on galcanezumab.

Adverse Events of Any Severity

Dr. Villalba reports that the most commonly reported treatment-emergent adverse event (TEAE) across controlled trials (at least 2% and at least 2% greater than placebo) was injection site reactions (see Table 10). In controlled trials in migraine, injection site reactions occurred in 18 to 23% of patients in galcanezumab groups vs. 13% on placebo. There was no significant difference in the percentage of patients experiencing TEAEs by treatment group in the controlled trials, with 67% in the galcanezumab 240 mg group, 65% in the glacanezumab 120 mg group, and 61% in placebo.

Table 10: Studies CGAG, CGAH and CGAI – Adverse Drug Reactions Occurring with an Incidence of at least 2% for AJOVY and 2% Greater than Placebo in (up to 6 Months of Treatment)

	Placebo N=1451 n (%)	Galcanezumab	
		120 mg N=705 n (%)	240 mg N=730 n (%)
Injection site reactions	183 (13)	129 (18)	166 (23)

Source: Dr. Villalba's review, Table 23

Laboratory Findings

In the controlled trials, Dr. Villalba identified no clinically meaningful differences or consistent trends between galcanezumab and placebo in changes from baseline in chemistry, hematology, coagulation, or urinalysis laboratory parameters.

In the controlled trials, the frequencies of ALT ≥3X the upper limit of normal (ULN) were 1%, 0.7% and 0.6 % for galcanezumab 240 mg, galcanezumab 120 mg, and placebo, respectively. The frequency of AST ≥3X ULN was 0.7%, 0.2% and 0.2% for galcanezumab 240 mg, galcanezumab 120 mg and placebo, respectively. There were no Hy's law cases. Based on these data, there is no evidence that galcanezumab causes liver toxicity.

Vital signs

In the controlled trials, analyses of change from baseline for heart rate, blood pressure, temperature, and weight showed no significant differences between galcanezumab and placebo.

ECG changes

Dr. Villalba reports that there were no changes from baseline in mean heart rate, PR interval, QRS interval, or QTc as compared to placebo across the controlled trials. In addition, outlier analyses did not identify a safety signal. Overall, there was no important signal for ECG abnormalities in the galcanezumab database. A dedicated thorough QT study was not required for this monoclonal antibody.

Immunogenicity

At baseline, Dr. Villalba reports that 7 to 11% of all patients were anti-drug antibody positive, and 4 to 6% were neutralizing antibody positive. Following treatment, ADA positivity was detected in 14-15% of patients on galcanezumab, and 2% of patients on placebo. Neutralizing antibody was present in almost 99% of galcanezumab-treated patients who became ADA positive, and approximately 66% of patients on placebo who became ADA positive. The available data regarding the relationship of ADA development and safety are too limited to make definitive conclusions. Dr. Villalba also notes that no patient has been re-exposed to galcanezumab after stopping galcanezumab, so that the safety of stopping and restarting this product has not been studied.

Safety Areas of Special Interest

Cardiac Effects

Multiple published reports state that CGRP is a potent vasodilator. A theoretical concern has been raised in experimental literature that inhibition of CGRP could impair adaptive/protective vasodilation in patients with significant coronary artery disease, cerebrovascular disease and peripheral vascular disease. To address these concerns, the applicant submitted a review of the relevant published literature on the biology of CGRP and its role in the cardiovascular system (see Nonclinical Pharmacology/Toxicology, above). Our review of cardiovascular events, ECGs, and vital signs measurements in the galcanezumab database does not identify a clear cardiovascular risk to patients. There were isolated cases of ischemic events reported in the database, but the rate of these cases was no greater than the background rate in this patient population. There were no clinically meaningful changes from baseline in vital signs or ECG measurements in controlled studies, or differences in outlier measurements for systolic or diastolic blood pressure in controlled studies.

Hepatic Safety

Based on the hepatotoxicity seen in certain small molecule CGRP antagonists, hepatotoxicity was identified as a potential safety signal. Drs. Villalba and Yasuda conclude that the review of this database does not suggest a risk of liver toxicity with galcanezumab.

Injection Site Reactions

In the controlled trials, Dr. Villalba identified that the incidence of injection site reactions was increased for galcanezumab 240 mg (21%), galcanezumab 120 mg (18%) as compared to placebo (13%) in the controlled trials. Most events were mild to moderate in severity, and resolved within 2 weeks. Dr. Villalba notes that injection site reactions could occur at any time during treatment and that a dose-response trend was apparent in the incidence of injection site reactions between galcanezumab 240 mg and 120 mg.

Hypersensitivity

Dr. Villalba identified that the incidence of treatment-emergent hypersensitivity was greater for galcanezumab (3.4%) than placebo (2.3%) in the controlled trials. Although most of the events were transient and mild or moderate in severity, they were severe in 0.3% of patients on both doses of galcanezumab, as compared to 0% on placebo. Approximately 0.1% and 0.4% of patients on galcanezumab 240 mg and galcanezumab 120, respectively, discontinued because of an hypersensitivity reaction, vs. 0% on placebo. There were no serious adverse events of hypersensitivity in the controlled trials, but in open-label studies, 0.3% of patients on galcanezumab 120 mg reported hypersensitivity as a serious adverse event, and 0.4% reported a severe hypersensitivity reaction. There were no cases of angioedema or anaphylaxis. Dr. Villalba recommends including a contraindication for patients with a history of serious hypersensitivity, and describing hypersensitivity in the Warnings and Precautions section of labeling. I agree with these recommendations.

Suicidality

Dr. Villalba found no signal for suicidality in this database.

Human Carcinogenicity or Tumor Development

Dr. Villalba's states that the overall safety database did not suggest that galcanezumab increases the risk of tumor development. In the controlled trials, there were 7 neoplasms, including 5 malignancies on galcanezumab 120 mg, with none occurring on galcanezumab 240 mg or placebo. Three of these malignancies presented within the first 31 days post-treatment, with another at Day 185 and another at Day 246. Four additional malignancies occurred in the open-label period, and all occurred within one year of treatment. No clusters of similar types of malignancies were identified in the database. In the controlled trials, the malignancies identified were breast, cervix, nipple, colon, and tonsillar. In the open-label portion of the study, the malignancies identified were lung, tongue, melanoma, and squamous cell carcinoma. Given the variable types of malignancies and the reports of these adverse events within a relatively short time-frame after initial drug exposure (within one year), it is unlikely that galcanezumab played a role in the development of these neoplasms. In addition, there is no evidence to suggest that chronic treatment with galcanezumab would increase the risk of carcinogenesis, based on data from pharmacology and chronic toxicology studies and an assessment of the literature regarding CGRP.

9. CDRH

Dr. Keith Marin conducted the CDRH review and Dr. John McMichael was the team leader. They both recommend approval. Galcanezumab is proposed for administration in both a prefilled syringe and autoinjector. Both devices were found acceptable by CDRH.

Compliance with Quality System Requirements

Dr. Katelyn Bittleman conducted the review for the Office of Compliance and Dr. Anzia Rahman was the Lead Reviewer. Dr. Bittleman concludes that galcanezumab is approvable from the perspective of the applicable quality system requirements. She states that the documentation review of this application for compliance with the quality systems requirements showed no deficiency. No facility inspections for compliance were needed for this approvability determination.

10. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because it was clear that the applicant had provided substantial evidence of effectiveness from three adequate and well-controlled studies, using clinical trial designs similar to those for previously approved migraine drugs. Moreover, the safety profile was deemed acceptable for the treatment of migraine, without controversial issues.

11. Pediatrics

Galcanezumab was discussed at a PeRC meeting on August 22, 2018. Agreement was reached with the applicant's plan for requesting a partial waiver for patients 0 to less than 6 years of age and deferral for patients 6 to 17 years of age. Please refer to Section 14 of this memo for the required pediatric postmarketing studies.

12. Other Relevant Regulatory Issues

Office of Scientific Investigations
Dr. Cara Alfaro conducted the review for the Office of Scientific Investigations. Four clinical sites were inspected, in addition to the Clinical Research Organization (CRO), (b) (4) in support of this BLA. Dr. Alfaro reports that the studies appear to have been conducted adequately and the data generated by those sites appear acceptable. The final compliance classification for three sites was No Action Indicated (NAI), but the final compliance classification for one site was Voluntary Action Indicated (VAI), due to drug accountability issues. The final compliance classification of the CRO was NAI.

Controlled Substance Staff
The Controlled Substance Staff reviewer for this application was Dr. Joshua Hunt. Dr. Hunt concludes that there is no abuse signal or data requiring further review of this application. He recommends that the prescribing information does not include Section 9.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Ebony Whaley conducted the DMEPA review, and Dr. Lolita White was the Team Leader. The prescribing information, instructions for use (IFU), container labels, and carton labeling were reviewed to determine their acceptability from a medication error perspective. Dr. Whaley recommended modifications to the prescribing information, IFU and carton and container, which were communicated to the applicant. The applicant agreed to these changes.

Dr. Whaley included an Appendix in her review that references previous DMEPA reviews that document the lack of a requirement to perform a Human Factor (HF) validation study for this product. A HF validation study is not necessary because information from a HF validation study for another product was able to be leveraged to support the use of this product.

Dr. Chad Morris reviewed the proposed proprietary name, Emgality, and concluded that this name is acceptable. Dr. Morris also reviewed the nonproprietary name suffix "gnlm," and concluded that the suffix is devoid of meaning format and acceptable. Dr. Morris recommends that the nonproprietary name be revised throughout draft labels and labeling to "galcanezumab-gnlm."

13. Labeling

Agreement was reached with the applicant on labeling. Section 9 (abuse and dependence) can be omitted.

14. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
A REMS is not necessary for this product.

Postmarketing Requirements (PMRs)

PMR 3498-1 Deferred pediatric randomized, double-blind, placebo-controlled trial to assess PK (Part A), and efficacy and safety (Part B) under PREA for the preventive treatment of episodic migraine in children and adolescents ages 6 through 17 years. Part A includes an option to enroll in an open-label safety extension phase (9 months), followed by a post treatment phase (4 months). Part B includes a double-blind treatment phase (3 months) and an open-label safety extension phase (9 months), followed by a post treatment period (4 months). This study is to be submitted as a special protocol assessment (SPA).

PMR 3498-2 Deferred pediatric randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the preventive treatment of chronic migraine in adolescents ages 12 through 17 years. This study includes a double-blind treatment phase (3 months) and an open-label safety extension phase (9 months), followed by a post treatment period (4 months). This study is to be submitted as a special protocol assessment (SPA).

PMR 3498-3 Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Emgality during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Emgality before or during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR 3498-4 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3392-3 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to Emgality during pregnancy compared to an unexposed control population.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HEATHER D FITTER
09/27/2018

ERIC P BASTINGS
09/27/2018

ELLIS F UNGER
09/27/2018
I contributed substantially to the writing of this memorandum and agree with its content.