CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761119Orig1s000

SUMMARY REVIEW

Summary Review

Date	February 21, 2020
From	Heather Fitter, MD Nick Kozauer, MD Billy Dunn, MD
Subject	Summary Review
BLA #	761119
Applicant	Lundbeck Seattle BioPharmaceuticals, Inc.
Date of Submission	December 26, 2018
PDUFA Goal Date	February 21, 2020
Proprietary Name	Vyepti
Established or Proper Names	Eptinezumab
Dosage Form	Solution for intravenous (IV) injection (100 mg/mL)
Applicant Proposed Indication/Population	Prevention of migraine in adults
Applicant Proposed Dosing Regimen(s)	100 mg IV infusion every 3 months; 300 mg IV infusion every 3 months
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	Preventive treatment of migraine in adults
Recommended Dosing Regimen(s)	100 mg IV infusion every 3 months; 300 mg IV infusion every 3 months

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Eptinezumab is a humanized monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) ligand, and prevents CGRP 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 preventive treatment of migraine. Three drugs in the anti-CGRP class were approved recently for this indication: erenumab (May 2018), fremanezumab (September 2018), and galcanezumab (September 2018). These three drugs are given by subcutaneous (SC) administration either monthly or quarterly, while eptinezumab is given intravenously (IV) quarterly. 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 eptinezumab was demonstrated in two adequate and well-controlled studies, one study in patients with episodic migraine and one study in patients with chronic migraine. Both studies used a well-validated and clinically interpretable primary endpoint, the number of monthly migraine headache days. The episodic migraine study tested three doses, 30 mg, 100 mg, and 300 mg given IV every three months, while the chronic migraine study tested two doses, 100 mg and 300 mg given IV every three months. The applicant is not proposing to market the 30 mg dose. All doses studied demonstrated efficacy on the primary endpoint. Although the 30 mg and 100 mg dose performed similarly in the episodic migraine study, due to the benign safety profile of all doses, and the lack of efficacy data to support the 30 mg dose for chronic migraine (since it was not included in the CM study), the doses of 100 mg and 300 mg are recommended for both populations. There was a dose-response relationship for efficacy seen in both studies between the 100 mg and the 300 mg dose.

In patients with episodic migraine, treatment with eptinezumab led to a reduction in approximately 4 migraine days/month, whereas placebo treated patients had a reduction of approximately 3 migraine days/month, both groups improving on average, from a baseline rate of about 8-9

days/month. The mean treatment effect (the difference between eptinezumab and placebo), approximately 1 fewer migraine day/month, is similar to that observed with drugs already approved for the preventive treatment of episodic migraine.

In patients with chronic migraine, treatment with eptinezumab led to a reduction in approximately 7-8 migraine days/month, whereas placebo treated patients had a reduction of approximately 6 migraine days/month, both groups improving on average, from a baseline rate of 16 migraine days/month. The mean treatment effect (the difference between eptinezumab and placebo), approximately 1-2 fewer migraine days/month, is similar to that observed with drugs already approved for the preventive treatment of chronic migraine. Findings on secondary endpoints, such as the 50% responder rate at 3 months and the 75% responder rate at 3 months were supportive of the primary endpoint in both studies.

The safety profile of eptinezumab was characterized in the two controlled efficacy studies, one study that included blinded dosing every 3 months for 12 months (although for the last 6 months the applicant was not blinded to the treatment assignment) and the other study that included blinded dosing for 6 months followed by an open-label safety study for 6 months. In addition, two double-blind controlled Phase 2 trials were also analyzed for safety. Common adverse events in clinical trials that occurred in at least 2% of eptinezumab-treated patients and at least 2% greater than placebo included nasopharygitis and hypersensitivity. The clinical trials included generally younger, healthy patients and effectively excluded patients with major cardiovascular (CV) or cerebrovascular disease. The data provided with this application do not support the need for CV restrictions with the use of eptinezumab; however, these data are too limited to definitively establish the CV safety of eptinezumab.

The risk/benefit profile of eptinezumab is acceptable and supports approval for the preventive treatment of migraine in adults. There is no evidence to suggest that eptinezumab is more effective than other FDA-approved drugs for this indication; however, eptinezumab is the first CGRP antagonist to be approved for IV injection. Labeling will clearly convey the generally favorable safety profile demonstrated in this application including a small increase in the incidence of nasopharyngitis and hypersensitivity as compared with placebo. Labeling will also include a Warning and Precaution for hypersensitivity reactions, largely consistent with other drugs of this class, and supported by the current safety data from the development program.

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	Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 second highest cause of disability in the Global Burden of Disease Study in 2016. The prevalence of 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 the preventive treatment of migraine: erenumab, fremanezumab, glacanezumab, topiramate, propranolol, timolol, and valproate are approved for the preventive treatment of migraine in adults and onabotulinumtoxinA is approved for prophylaxis of chronic migraine. In addition, many drugs and supplements are used off-label for the preventive treatment of migraine. • Erenumab, fremanezumab, and galcanezumab are monoclonal antibodies in the same therapeutic class as eptinezumab (CGRP antagonist), but these other products are administered as subcutaneous (SC) injections: erenumab and glacanezumab are 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, fremanezumab, and glacanezumab are monoclonal antibodies in the same therapeutic class as eptinezumab, are administered as SC injections, while eptinezumab will be administered via an IV route. There may be a number of patients that will benefit from an intravenously administered CGRP antagonist option in cases where an injection by the patient or a caregiver are not feasible.
Benefit	• The efficacy of eptinezumab was demonstrated in two adequate and well-controlled clinical studies (Studies CLIN-006 and CLIN-011). The studies used a well-validated and clinically meaningful endpoint to establish efficacy, a reduction in monthly migraine days. • Results are summarized in the table below; comparisons between the eptinezumab (100 mg and 300 mg) groups and placebo are statistically significant.	The mean treatment effect of eptinezumab can be summarized as follows: for episodic and chronic migraine, the mean decreases in migraine headache days, relative to placebo, were approximately 10-14% and 12-15%, respectively. This treatment effect is similar to that of other products approved for the preventive treatment of migraine

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Baseline</th><th>On treatment</th><th>Change from baseline</th></tr>
<tr><td colspan="4">Study CLIN-006 (episodic migraine)</td></tr>
<tr><td>Placebo</td><td>8.4</td><td>5.4</td><td>3</td></tr>
<tr><td>Eptinezumab 100 mg</td><td>8.7</td><td>4.7</td><td>4</td></tr>
<tr><td>Eptinezumab 300 mg</td><td>8.6</td><td>4.3</td><td>4.3</td></tr>
<tr><td colspan="4">CLIN-011 (chronic migraine)</td></tr>
<tr><td>Placebo</td><td>16.2</td><td>10.5</td><td>5.7</td></tr>
<tr><td>Eptinezumab 100 mg</td><td>16.1</td><td>8.5</td><td>7.6</td></tr>
<tr><td>Eptinezumab 300 mg</td><td>16.1</td><td>7.9</td><td>8.2</td></tr>
</table>

Relative to placebo, the mean effect of eptinezumab treatment for episodic migraine was approximately a 10-14% reduction in migraine days, whereas for chronic migraine, there was approximately a 12-15% reduction in migraine days.
Like the many other approved drugs with the indication of “preventive” treatment of migraine or migraine “prophylaxis,” eptinezumab is not likely to render patients migraine-free.

</td><td>(effect size over placebo of approximately 1 to 2 days per month). Like the many approved drugs with the indication of “preventive” treatment of migraine, or migraine “prophylaxis,” eptinezumab is not likely to render patients migraine-free.

Eptinezumab is administered quarterly, which could be a convenience factor for some patients. Approved oral agents are given at least daily; erenumab, glacanezumab, and fremanezumab are approved for monthly administration, while fremanezumab also has a quarterly dosing option.

Eptinezumab offers an alternative to patients who do not tolerate, or do not have an adequate response to, currently marketed drugs.</td></tr>
<tr><td>Risk and Risk Management</td><td>

The most common treatment emergent adverse events (TEAEs) in the pooled Phase 3 controlled clinical trials of eptinezumab-treated patients included nasopharyngitis and hypersensitivity, all occurring at a relatively low incidence.
There were no patients in the controlled trials that experienced serious adverse events (SAEs) that were clearly related to the use of eptinezumab.
The rate of adverse dropouts was low but there were 13 patients overall that discontinued study drug due to hypersensitivity reactions and 3 patients that discontinued drug due to hypertension.
Clinical trials included generally younger, healthy patients and

</td><td>There were no significant safety findings that would preclude approval of eptinezumab. Adequate labeling and enhanced pharmacovigilance will address the identified safety issues.

The data submitted with this application do not support the need to include CV restrictions in labeling. However, these data are also insufficient to definitively establish the CV safety of eptinezumab.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	effectively excluded patients with major CV disease. • Based on either the proposed mechanism of action or previous safety issues seen with CGRPs, safety issues of concern for eptinezumab were CV effects, gastrointestinal effects, and hepatotoxicity. No clear safety signals were detected upon review of these issues. • No serious safety issues outside of several serious cases of hypersensitivity were related to the use of eptinezumab. Other uncertainties • The risk of adverse outcomes in pregnancy has not been characterized. • Safety and efficacy in pediatric migraine patients has not been established.	Because the risk of adverse outcomes in pregnancy has not been characterized, and because eptinezumab will be used in women of childbearing potential, a pregnancy registry and a pregnancy outcomes study will be postmarketing requirements. Since safety and efficacy of eptinezumab in pediatric migraine patients has not been established, studies to evaluate eptinezumab in pediatric migraine patients will be required under the Pediatric Research Equity Act (PREA). There should be enhanced pharmacovigilance with periodic evaluation of CV events, cerebrovascular events, hypertension, and constipation.

2. Background

This review discusses the data presented by Lundbeck (the applicant) in support of a new biologics license application (BLA) for eptinezumab solution for intravenous (IV) 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 associated 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 range 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.

Chronic migraine (CM) is defined as 15 or more headache days per month, with features of migraine headache on ≥8 days per month. Patients with 14 or fewer migraine headache days per month are defined as having episodic migraine (EM). Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders (ICHD). Many products are FDA-approved for the preventive treatment of migraine in adults. Drugs approved for the preventive treatment of migraine prior to 2010 had an indication without a reference to episodic or chronic migraine populations; this distinction first became commonly used approximately in 2004. Therefore, while topiramate, valproate, timolol, and propranolol are indicated for the preventive treatment of migraine (referred to as the prophylaxis of migraine headache in some older labels), the first drug to include an indication specific to the preventive treatment of chronic migraine was onabotulinumtoxinA, which was approved for that indication (refered to as prophylaxis) in 2010. Recently (2018), three monoclonal antibodies targeting the CGRP system have been approved for the preventive treatment of both chronic and episodic migraine; erenumab (Aimovig) targeting the CGRP receptor, and fremanezumab (Ajovy) and galcanezumab (Emgality) targeting the CGRP peptide.

The applicant provides data from two placebo-controlled efficacy trials, Studies CLIN-006, in patients with episodic migraine and CLIN-011, in patients with chronic migraine. The Division communicated with the applicant during development that a single positive study for the preventive treatment of episodic migraine and a single positive study for the preventive treatment of chronic migraine would allow for an indication statement for eptinizumab for the preventive treatment of migraine. Three doses of eptinezumab were evaluated between these studies: 30, 100, and 300 mg, administered every 3 months; however, the applicant only proposes the 100 mg and 300 mg doses for marketing.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Leslie Rivera Rosado (refer to her review for the entire OPQ list of participants in the review of this application). Eptinezumab is a humanized IgG1 monoclonal antibody consisting of two identical light chains and two identical heavy chains. The light chain and heavy chain variable regions are comprised of both human and humanized rabbit sequences. Eptinezumab recognizes and blocks binding of CGRP to its receptor.

The eptinezumab drug substance is packaged in a (b) (4). OPQ states that storage conditions are recorded to be (b) (4) months at (b) (4) °C.

The review of manufacturing information provided in the application leads to the conclusion that the methodologies and processes used for drug substance and drug product manufacturing, release, and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective. The drug product portion of this BLA was also reviewed from a sterility assurance and product quality microbiology standpoint and is recommended for approval.

In addition, the immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in the presence of eptinezumab at plasma concentrations.

The OPQ review team has determined that the data submitted in this application are adequate to support the conclusion that the manufacture of Vyepti is well controlled and leads to a product that is pure and potent. OPQ recommend that this product be approved for use under the conditions specified in labeling.

4. Nonclinical Pharmacology/Toxicology

The primary nonclinical reviewer for this application was Dr. Richard Siarey, with Dr. Lois Freed performing the secondary review.

Dr. Siarey states that nonclinical studies of IV eptinezumab consisted of general toxicology rat and monkey studies, which included safety pharmacology assessments, a rat fertility study, rat and rabbit embryofetal development studies, and a rat pre- and postnatal development study. The Division agreed that only a monkey chronic 6-month study was needed. No adverse effects of IV eptinezumab were observed in either the rat 4-week or monkey 6-month general toxicology studies; the no observed adverse effect levels (NOAELs) were determined to be 100 mg/kg/week and 150 mg/kg every 2 weeks, respectively.

The nonclinical review concludes that these exposures provide an adequate safety margin to the maximum proposed human dose of 300 mg/day. No adverse effects of IV eptinezumab were observed in any of the reproductive and development studies. The Division accepted the

justification from the applicant not to conduct carcinogenicity studies. Overall, no adverse findings were observed in the toxicology studies. Refer to Dr. Siarey's review of this BLA for a detailed discussion of these studies.

Drs. Siarey and Freed conclude that the nonclinical data are adequate to support approval of this BLA.

5. Clinical Pharmacology

The primary reviewers for the Office of Clinical Pharmacology (OCP) review were Drs. Gopichand Gottipati and Atul Bhattaram. Dr. Sreedharan Sabarinath was the team leader. The OCP review states that the clinical pharmacology information included in this BLA supports approval of 100 mg and 300 mg administered IV once every three months (quarterly) for the preventive treatment of migraine.

Drs. Gottipati and Bhattaram do not suggest any dose adjustments based on age, race, sex, bodyweight, renal or hepatic impairment, food-intake, or drug/transporter mediated interactions.

There were major manufacturing changes for both the drug substance and drug product, including changes in the manufacturing site and in the scale-up process between the commercial and clinical trial formulations. A pharmacokinetic (PK) bridging study (CLIN-014) was conducted by the applicant and the Office of Study Integrity and Surveillance (OSIS) conducted an inspection. OSIS noted that drug concentrations obtained using dilution factors greaer than 100-fold in the study were not reliable and could not be used for regulatory purposes; however, the CMC review team noted that the differences in product quality attributes between the clinical and commercial formulations were minor and that the likelihood of these findings impacting PK was low. Thus, Study CLIN-014 was not considered necessary to bridge between the commercial and the clinical trial formulations.

Mechanism of Action
Drs. Gottipati and Bhattaram state that eptinezumab is a fully humanized monoclonal immunoglobulin G1 (IgG1) targeted against the CGRP ligand and block both α- and β-CGRP isoforms from binding to the receptor.

Absorption
Eptinezumab is administered intravenously.

Distribution
The volume of distribution of eptinezumab is 3.6 liters.

Metabolism and Elimination
Eptinezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Since monoclonal antibodies do not

typically undergo metabolism by the cytochrome P450 system, no drug interaction studies were conducted.

Specific Populations
Generally, IgG monoclonal antibodies undergo elimination via intracellular catabolism so hepatic impairment is not expected to significantly impact the disposition of eptinezumab. In addition, renal elimination of monoclonal antibodies is generally low. Therefore, the applicant did not conduct dedicated renal or hepatic impairment studies to evaluate the effect of these conditions on the PK of eptinezumab. Since the impact of renal/hepatic impairment is unlikely to be clinically relevant, the OCP review concludes that no dose adjustments are recommended based on renal or hepatic impairment.

Immunogenicity
Drs. Gottipati and Bhattaram state that the final immunogenicity database consisted of 1993 subjects from 4 clinical studies in which ADA results were available. Three hundred and sixteen subjects (15.9%) demonstrated treatment emergent anti-eptinezumab antibody responses (i.e., ADA-positive status), while 124 (6.2%) developed neutralizing antibodies (NAb) against eptinezumab. Overall, the impact of ADA status and ADA titer quartiles were generally consistent across dose levels and CM/EM populations. Lower eptinezumab trough levels were not associated with lower efficacy. Similar results were observed for NAb status. Despite these findings, the OCP review notes that the available data regarding the relationship of ADA development to safety or efficacy are too limited to make definitive conclusions.

Dosing
The recommended dosing regimens are eptinezumab 100 mg or 300 mg administered once every 3 months as an IV infusion over 30 minutes in 100 mL of 0.9% sodium chloride injection.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Emily Freilich conducted the clinical efficacy review for this application. Dr. Steve Bai conducted the biometrics review and Dr. Kun Jin was the biometrics team leader.

The applicant conducted two placebo-controlled efficacy trials (Table 1), one in episodic migraine patients and the other in chronic migraine patients: Study ALD403-CLIN-006 (Study CLIN-006) and Study ALD403-CLIN-011 (Study CLIN-011), respectively.

Table 1: Pivotal Clinical Efficacy Studies

	Population	Timepoint of Primary Endpoint Analysis	Doses	Location
Study CLIN-006	Episodic Migraine	12 weeks	30 mg, 100 mg, or 300 mg	2 countries (including US)
Study CLIN-011	Chronic Migraine	12 weeks	100 mg or 300 mg	13 countries (including US)

Study CLIN-006

Study CLIN-006 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of eptinezumab for the preventive treatment of episodic migraine. Patients were randomized in a 1:1:1:1 ratio to receive either 30 mg eptinezumab, 100 mg eptinezumab, 300 mg eptinezumab, or placebo. The double-blind treatment period was 24 weeks, but the primary endpoint was measured at 12 weeks. During the next 24 weeks (24-48), patients and investigators were blinded, but the applicant was not; therefore, the data from the last 24 weeks can only be used to support safety but not efficacy, while the data from the first 24 weeks can be used to support the primary efficacy endpoint and the persistence of any response.

Patients eligible for enrollment into Study CLIN-006 were adults 18-75 years of age with at least a one-year history of migraine with or without aura. Patients had to have 14 or fewer headache days in each 28-day period in the 3 months prior to screening, of which at least 4 had to be migraine days. In addition, patients had to be diagnosed with migraine before the age of 50 years. Patients with cardiovascular disease, hypertension on day 0 (defined as BP greater than 140/90), neurological disease, cerebrovascular disease, diabetes, Raynaud's disease, or an abnormal electrocardiogram (ECG) at screening or day 0 were excluded. In addition, patients previously dosed with any monoclonal antibody targeting the CGRP pathway were excluded.

The primary endpoint used to evaluate efficacy was the change in the frequency of migraine days over weeks 1-12. The protocol also included the following secondary endpoints, and included a plan to control for multiple comparisons: 75% responder rate for weeks 1-4, 75% responder rate for weeks 1-12, 50% responder rate for weeks 1-12, and the percentage of patients with a migraine on the day after dosing. In addition, the change in acute migraine medication days from weeks 1-12 was evaluated as an exploratory endpoint.

The full analysis population was used for the efficacy analyses, and was defined by the applicant as all randomized patients who received at least 1 dose of study drug. Missing data for the eDiary was handled as follows: If the diary had been completed at least 21 days in a 28-day interval, then normalization was used. If the diary had been completed less than 21 days in the 28-day interval, then the results for the 28-day interval was a weighted function of the observed data for the current four-week interval and the results from the previous interval.

The applicant used a serial procedure to control Type 1 error. First, the primary and key secondary endpoints (except percentage of patients with migraine on the day after dosing) were evaluated for the 300 mg dose, then the 100 mg dose, and then the percentage of patients

with migraine on the day after dosing was evaluated for the 300 mg dose, then the 100 mg dose. Then, the primary and key secondary endpoints were tested for the 30 mg dose.

Study CLIN-011

Study CLIN-011 was identical in design to Study CLIN-006, except the eptinezumab doses studied in CLIN-011 were 100 mg or 300 mg and the population studied was chronic migraine patients. In Study CLIN-011, the duration of the double-blind placebo controlled portion of the study was 24 weeks, but the primary endpoint was measured at 12 weeks. Study CLIN-011 had an optional open-label safety extension trial (CLIN-005) trial and enrollment was offered to all participants in the double-blind portion of the trial. In addition, Study CLIN-011 had the following additional key secondary endpoints: reduction in migraine prevalence from baseline to week 4, change from baseline in the Headache Impact Test (HIT)-6, and change in the acute migraine medication usage. Study CLIN-011 was conducted in 13 countries, while CLIN-006 was conducted in 2 countries.

The testing sequence to control for Type I error was different, as well. The primary endpoint was tested for the 300 mg dose, followed by one grouping of key secondary endpoints (75% responder rate, percentage of subjects with a migraine on the day after dosing), then another grouping of secondary endpoints (migraine prevalence day 1-28 post-dose, 50% responder rate), followed by testing of the 100 mg dose group's primary endpoint, and the two subgroups of secondary endpoints in the same order as was used for the 300 mg dose, followed by testing of the key secondary endpoint regarding acute medication usage and the change from baseline in the HIT-6 for only the 300 mg dose.

Results

Studies CLIN-006 and CLIN-011

The median age of the patients in both trials was 38-41 years. Eighty to 90% of patients were female, and 88 to 93% were White. Demographic characteristics were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups in both trials. The median duration of migraine history was 15-18 years. In Study CLIN-006, the mean number of migraine days/month during the baseline period was 8-9 days, and the mean number of headache days/month during the baseline period was 10 days. For Study CLIN-011, the mean number of migraine days/month during the baseline period was 16 days, and the mean number of headache days/month during the baseline period was 20-21 days.

Primary endpoint

Table 2 presents the results of the primary efficacy analyses and the key secondary analyses for Studies CLIN-006 and CLIN-011.

Table 2: Study CLIN-006 and CLIN-011-Primary and Key Secondary Endpoints (source: Dr. Freilich's review Table 39)

	STUDY CLIN-006				STUDY CLIN-011		
	Treatment Group				Treatment Group		
Primary Efficacy Endpoint	Eptinezumab 300 mg N = 222	Eptinezumab 100 mg N = 221	Eptinezumab 30 mg N = 223	Placebo N = 222	Eptinezumab 300 mg N = 350	Eptinezumab 100 mg N = 356	Placebo N = 366
Baseline Migraine Days	**8.6**	**8.7**	**8.7**	**8.4**	**16.1**	**16.1**	**16.2**
Mean Change from baseline in Monthly Migraine Days	**-4.29**	**-3.88**	**-4.01**	**-3.19**	**-8.2**	**-7.7**	**-5.6**
Treatment effect^	**-1.11** (p-value = 0.0001)	**-0.69** (p-value = 0.0181)	**-0.82** (p-value = 0.0046)**		**-2.59** (p-value < 0.0001)	**-2.03** (p-value < 0.0001)	
Key Secondary Endpoints							
75% Responder Rate Weeks 1-4 (%)	31.5	30.8	30.0	20.3	36.9	30.9	15.6
Treatment effect^	11.3 (p-value = 0.006)	10.5 (p-value = 0.0112)	9.8 (p-value = 0.017)**		21.3 (p-value < 0.0001)	15.3 (p-value < 0.0001)	
75% Responder Rate Weeks 1-12(%)	29.7	22.2	24.7	16.2	33.1	26.7	15.0
Treatment effect^	13.5 (p-value = 0.0007)	6.0 (p-value = 0.113)*	8.4 (p-value = 0.027)**		18.1 (p-value < 0.0001)	11.7 (p-value = 0.0001)	
50% Responder Rate Weeks 1-12(%)	56.3	49.8	50.2	37.4	61.4	57.6	39.3
Treatment effect^	18.9 (p-value = 0.0001)	12.4 (p-value = 0.0085)**	12.8 (p-value = 0.0065)**		22.1 (p-value < 0.0001)	18.2 (p-value < 0.0001)	
Percentage of Pts with Migraine on Day 1	13.9	14.8	17.3	22.5	27.8	28.6	42.3
Treatment effect^	-8.6 (p-value = 0.0159)**	-7.7 (p-value = 0.0312)**	-5.2 (p-value = 0.1539)*		-13.9 (p-value < 0.0001)	-13.2 (p-value < 0.0001)	
Migraine Prevalence Reduction Weeks 1-4	n/a	n/a	n/a		-29.8	-27.1	-18.8
Treatment effect^					-11.0 (p-value < 0.0001)	-8.26 (p-value < 0.0001)	
HIT-6 Change Over Weeks 9-12	n/a	n/a	n/a		-7.5	n/a	-4.3
Treatment effect^					-2.88 (p-value < 0.0001)		
Acute Migraine Med Reduced Weeks 1-12	n/a	n/a	n/a		-3.5	n/a	-1.9
Treatment effect^					-14 (p-value < 0.0001)		

*^Treatment effect = difference from placebo; n/a-not pre-specified, *not significant, ** nominally significant*

Drs. Bai and Freilich both conclude that treatment with eptinezumab resulted in statistically significant reductions in the number of migraine days for weeks 1-12, as compared to placebo. There was a mean difference from placebo of -1.11 days for eptinezumab 300 mg and of -0.69

days for eptinezumab 100 mg; both comparisons represent statistically significant improvements over placebo based on the multiplicity decision rule. Although similar numerical results were obtained for the 30 mg group (mean difference of -0.82 as compared to placebo), this result was only considered to be nominally significant based on the lack of Type I error control, since the secondary endpoints for the 100 mg and 300 mg arms were tested in the hierarchy prior to the testing of the primary endpoints for the 30 mg arm.

Dr. Bai reports that in Study CLIN-006 nearly all patients remained in the study through week 12, with fewer than 10 patients (less than 5%) in the 100 mg or 300 mg groups not attending the week 12 visit, and 17 placebo patients (less than 3%) not attending the week 12 visit. Results of sensitivity analyses based on the missing data imputation rule provided results that were consistent with those of the primary endpoint.

Secondary Endpoints
Table 2 summarizes the results of the analyses of the secondary efficacy endpoints from both clinical trials.

In Study CLIN-006, the 75% responder rate over weeks 1-4 demonstrated a statistically significant improvement for eptinezumab 300 mg and 100 mg, as compared to placebo, while the eptinezumab 30 mg group could only be considered nominally significant when compared to placebo, due to the lack of Type I error control. The 75% responder rate over weeks 1-12 demonstrated a statistically significant improvement for eptinezumab 300 mg over placebo. Eptinezumab 100 mg was not statistically significant for the 75% responder rate over weeks 1-12, as compared with placebo. The lack of statistical significance on this endpoint for the 100 mg puts in question the clinical meaningfulness of the statistically significant findings of the 75% responder rate through weeks 1-4 at the 100 mg dose. For a preventive treatment, the goal is sustained treatment, rather than a treatment effect that is seen early and diminishes quickly. Yet, the 75% responder rate endpoint over weeks 1-12 was nominally significant for the 30 mg dose. The 50% migraine responder rate over weeks 1-12 demonstrated a statistically significant improvement for eptinezumab 300 mg over placebo, but was nominally significant as compared to placebo for the 100 mg and 30 mg groups.

The applicant included “the percentage of subjects with a migraine on the day after dosing” as a key secondary endpoint in both trials. There was extensive discussion regarding this endpoint during development. The Division expressed a concern that presenting only the results of this analysis on day 1 after treatment would potentially be misleading, if such an effect was not consistent throughout the first weeks/month of treatment. To support the interpretation of this analysis, the Division asked the applicant to provide the observed data for each study that indicated the percentages of patients in each treatment arm with a migraine on each of the first 30 days of treatment, respectively. This trend consistently favored drug in both trials, with tighter confidence intervals in the chronic migraine trial, as would be expected given that more overall events had occurred. Based on these findings, the Division determined that it would be acceptable to present a figure in labeling showing these percentages by treatment day for the first week of treatment for each study, respectively, to illustrate the early onset of efficacy with respect to prevention.

Study CLIN-011 also demonstrated statistically significant results favoring both doses of eptinezumab tested, as compared to placebo, for the 75% responder rate over weeks 1-4, the 75% responder rate over weeks 1-12, the 50% responder rate over weeks 1-12, the percentage of patients with a migraine on the day after dosing, and the reduction in migraine prevalence from baseline to week 4. The additional secondary endpoints, a reduction in the HIT-6 test and a reduction in acute migraine medication usage, were only tested in the eptinezumab 300 mg dose, yet these analyses also demonstrated statistically significant improvements in the 300 mg dose as compared to placebo.

Efficacy by Subgroups

Dr. Bai performed analyses of the treatment effect across subgroups for both Studies CLIN-006 and CLIN-011 and concludes that the efficacy trends observed in the primary efficacy analyses appeared to be similar across all subgroups (age, gender, race, and region). Overall, the reductions from baseline in the eptinezumab 300 mg group were more robust and consistent across the analyzed subgroups compared to the eptinezumab 100 mg group.

Efficacy Conclusions

The applicant has provided substantial evidence of the effectiveness of eptinezumab for the preventive treatment of migraine based on the results from two adequate and well-controlled investigations. One study was conducted in patients with episodic migraine and the other study was conducted in patients with chronic migraine. There is well-established precedent for positive efficacy trials for the preventive treatment of migraine in the episodic and chronic migraine populations, respectively, to be mutually supportive. These two studies demonstrated a reduction in migraine days over a 12-week period from baseline in eptinezumab groups as compared to placebo. Findings on the secondary endpoints measuring responder rates (75% and 50% reductions from baseline) were generally supportive of the efficacy demonstrated in the primary endpoint analyses.

A reduction in HIT-6 was demonstrated in the eptinezumab 300 mg group as compared to placebo in Study CIN-011, but was not evaluated in regard to other doses in that study, or in Study CLIN-006. (b) (4) The applicant also measured a reduction in the use of acute migraine medication with eptinezumab 300 mg as compared to placebo in Study CLIN-011, but this was not evaluated for the 100 mg arm, nor was this evaluated in Study CLIN-006.

The 100 mg and 300 mg doses are effective and should be described in labeling. Although the 30 mg dose had a similar numerical treatment effect in most cases to the 100 mg dose, the applicant is not proposing marketing of the 30 mg dose. Due to the lack of concerning safety signals for the 100 mg and 300 mg doses, and any clear dose-dependent safety findings, there is not a compelling reason to recommend marketing of the 30 mg dose.

8. Safety

Dr. Emily Freilich conducted the clinical safety review of this application.

As discussed by Dr. Freilich, the overall exposure to eptinezumab exceeds the minimum number of subjects recommended by the International Council for Harmonization (ICH) E1 Guideline for chronically administered medications. She reports that 2,076 subjects were exposed to at least one dose of eptinezumab, of which 1,372 were exposed in the pivotal efficacy clinical trials and 823 received at least one dose of eptinezumab 100 mg, the highest dose proposed for marketing.

Dr. Freilich notes that this development program allowed patients up to the age of 75 to enroll, but that there is only a small proportion of patients (1.2%) over the age of 65; therefore, safety evaluations in the elderly population are limited.

There were no obvious demographic imbalances between active treatment and placebo when considering, gender, age, race, ethnicity, or weight.

Deaths and Serious Adverse Events (SAEs)
Dr. Freilich reports that there were no deaths reported during the eptinezumab development program.

She notes that in the pivotal efficacy trials overall SAEs were balanced between the eptinezumab (1.3%) and placebo (1.5%) groups. There were 3 patients that experienced suicide-related SAEs. Two patients reported suicidal ideation on the 100 mg eptinezumab arm, and 2 patients reported suicide attempts, one on 100 mg eptinezumab (the same patient that had also previously reported suicidal ideation) and the other patient was in the 300 mg eptinezumab arm. Review of the narratives suggest that all cases were confounded based on prior history of post-traumatic stress disorder (PTSD) or depression, and in two cases the patients had a prior history of both conditions. One patient (300 mg arm) who experienced a suicide attempt was an 18-year-old female with a history of depression and anxiety, reportedly stable at the time of study initiation. She received two doses (last on (b) (6)) and on (b) (6), was hospitalized due to a suicide attempt. She reported that she was having difficulty with family relations and this seemed to be a significant stressor that contributed to the suicide attempt. The Columbia-Suicide Severity Rating Scale was administered during the clinical trials, and there were not significant numbers of abnormal reporting on this scale during development. Overall, there is no clear association between eptinezumab treatment and an increased risk of suicidal ideation/attempts.

Four patients discontinued eptinezumab due to the following respective SAEs: acute kidney injury, stomal hernia, rhabdomyolysis (all three on 30 mg), and seizure (300 mg). All cases are confounded. The seizure occurred in a 47-year-old female that experienced a generalized tonic-clonic seizure approximately 7 weeks after taking her last dose of eptinezumab. The case narrative reports that the treating neurologist concluded that the etiology of the seizure was a possible toxic-metabolic abnormality, although the specific abnormality was not identified. It

seems that this etiology was further supported by an electroencephalogram (EEG) consistent with mild encephalopathy.

Dr. Freilich did not identify any SAEs in the controlled trials that clearly seemed to be related to the use of the study drug. She notes that all SAEs reported were confounded by other factors and selected cases are discussed in detail in her review.

Discontinuations

There were 42 patients who had study drug withdrawn due to adverse events (AEs), 2.5% in the eptinezumab group and 1.4% in the placebo group. The only treatment-emergent adverse events (TEAEs) that occurred in more than 1 patient that led to study drug discontinuation was hypersensitivity (13 patients) and hypertension (3 patients). Four of the 42 discontinuations were due to the previously described SAEs.

There were no cases of anaphylaxis during the controlled trial, but one patient experienced angioedema. Another patient experienced an SAE of anaphylactoid reaction which began several minutes post-infusion and required treatment to terminate the reaction. After review of this case, it appears that this patient also experienced facial edema. The applicant states that this reaction should be coded as allergic reaction and infusion reaction of grade 2/moderate severity because there were no clinical signs of respiratory or cardiovascular manifestations to meet the definition of anaphylaxis.

One patient that had a history of mild hypertension developed worsening hypertension that was classified as grade 2/moderate. The increased blood pressure was noted at week 4, and he was started on metoprolol at week 5. At the week 28 visit, the metoprolol was increased and the decision was made to discontinue study drug. The second patient had a baseline blood pressure of 122/88, but had an unscheduled visit prior to his first dose of eptinezumab with a blood pressure of 144/100. On the day of dosing, his baseline blood pressure was 122/88, which increased to 140/99 after dosing, and 142/107 at week 4. At the week 8 visit, the patient was started on lisinopril and discontinued from the study. The third patient that was recorded as discontinuing study medication due to an increased blood pressure, was also the patient that reported an SAE of suicide attempt. His blood pressure at screening was 140/80 and by week 28 it increased to 161/90 and remained elevated through week 36 at which time the investigator decided to discontinue study drug. Of note, at week 24 (the time of the suicide attempt) he had a positive urine screen for cocaine, which is known to be associated with elevated blood pressure.

There was one reported case of serotonin syndrome, but this occurred 9 months after the patient's last dose of eptinezumab, and was attributed to the use of concomitant medications in close proximity to the event of tramadol, bupropion, and escitalopram. This case is not likely related to the use of study drug.

Treatment Emergent Adverse Events (TEAEs)

The Table below modified, from Dr. Freilich's review, summarizes the most common TEAEs from the pivotal efficacy trials.

Table 3: Common TEAEs that Occurred in ≥ 1% of treatment population and ≥ 1% greater than placebo in any treatment arm (≥ 2% than placebo in bold)

Adverse Event	All Eptinezumab Treated Patients				Placebo N = 588 (%)	Greatest Risk Difference
	30 mg N = 219 (%)	100 mg N = 579 (%)	300 mg N = 574 (%)	All Doses N = 1372 (%)		
Infections and infestations						
Nasopharyngitis	**6**	**6**	**8**	**7**	**6**	**2**
Respiratory Tract infection	**12**	**7**	**9**	**9**	**8**	**5**
Urinary Tract Infection	2	2	3	2	2	1
Diarrhoea	2	1	2	2	1	1
Influenza	2	1	3	2	2	1
Rhinorrhoea	0	1	1	1	0	1
Nervous System Disorders						
Dizziness	**4**	**3**	**2**	**3**	**2**	**2**
Fatigue	**2**	**3**	**2**	**3**	**1**	**2**
Anxiety	2	1	1	1	0	1
Immune System Disorders						
Hypersensitivity reactions*	**3**	**1**	**2**	**2**	**0**	**3**
Food Allergy	1	0	0	0	0	1
Cardiovascular Disorders						
Palpitations	1	0	0	0	0	1
Gastrointestinal Disorders						
Nausea	4	2	3	3	3	1
Cholelithiasis	0	1	0	1	0	1
Constipation	1	1	1	1	0	1
General and Systemic Disorders						
Weight Increased	1	1	1	1	0	1
Joint Pain	2	2	3	2	2	1
Pain in Extremity	**2**	**1**	**1**	**1**	**0**	**2**
Muscle Strain	1	1	0	1	0	1
Contusion	1	1	0	1	0	1

**Includes the Preferred Terms: Hypersensitivity, as well as pruritus and flushing/hot flush that occurred only on day of dosing*
Source: Reviewer's analysis of ISS ADAE dataset (PSS population)

The following table includes common AEs that occurred at greater than or equal to 2% in the eptinezumab group and greater than or equal to 2% over placebo. This is the table that will be included in Section 6 of the prescribing information.

(b) (4)

Adverse Reactions	VYEPTI 100 mg (b) (4) N=579 %	VYEPTI 300 mg (b) (4) N=574 %	Placebo N=588 %
Nasopharyngitis	6	8	6
Hypersensitivity reactions*	1	2	0

**Hypersensitivity reactions includes multiple related adverse event terms, such as hypersensitivity, pruritus, and flushing/hot flush that occurred on the day of dosing.*

Laboratory Findings

Dr. Freilich reports that there were very few TEAEs related to laboratory findings and that they occurred in less than 0.3% of the eptinezumab patients and in a similar proportion in placebo patients. No SAEs were related to laboratory values, and review of laboratory findings did not demonstrate any significant changes from baseline values in active treatment compared to placebo exposed patients.

Since hepatotoxicity was a special safety signal of concern, Dr. Freilich's review contains a detailed discussion of this issue. Dr. Freilich reports that there were no patients in the safety database that met criteria for Hy's law. In both eptinezumab and placebo arms, there were infrequent reports of elevated liver enzymes or bilirubin with no trends over time, no apparent dose-response relationship in laboratory values, or changes from baseline in the clinical pivotal studies. The shift table (refer to Table 5) provided below demonstrates that similar percentages of patients on both treatment and placebo had laboratory results that shifted from normal to abnormal. Overall, Dr. Freilich concludes that there is no clinically meaningful signal for hepatic injury in this safety database.

Table 5: Studies CLIN-006 and CLIN-011-Shift Table for Liver Function Tests (source: Dr. Freilich's review Table 49)

Laboratory parameter and shift	All Eptinezumab Treated Patients				Placebo N = 588 (%)
	30 mg N = 219 (%)	100 mg N = 579 (%)	300 mg N = 574 (%)	All Doses N = 1372 (%)	
Alanine Aminotransferase (ALT)					
Normal to High	18	8	10	10	10
Normal to High (> 3x ULN)	1	1	1	1	0
Aspartate Aminotransferase (AST)					
Normal to High	9	7	6	7	5
Normal to High (> 3x ULN)	0	0	0	0	0
Bilirubin					
Normal to High	3	2	2	2	1
Number of patients n (%) with Bili > 2x ULN	1 (0)	1 (0)	1 (0)	3 (0)	1 (0)

Vital Signs

Dr. Freilich reports that, overall, the mean vital signs were comparable at baseline for the eptinezumab and placebo treatment arms. The post-baseline vital signs were also comparable, with no significant differences between eptinezumab and placebo patients, and no dose-related changes noted.

Electrocardiogram (ECG)

Dr. Freilich reports that in the controlled pivotal efficacy trials, the means for the ECG parameters were comparable between treatment arms and placebo at baseline and at all post-baseline evaluations. The mean changes from baseline were small and similar between treatment arms. There were no dose-related trends. Similar proportions of patients who received eptinezumab (0.4%) and patients who received placebo (0.4%) had a shift in any post-baseline ECG from normal to abnormal clinically significant, and one patient each in treatment and placebo groups shifted from abnormal not clinically significant to abnormal clinically significant.

There were 3 TEAEs of T-wave inversion that occurred in 3 patients receiving 300 mg eptinezumab. The other ECG-related TEAEs occurred in one patient each and included Q wave abnormal (100 mg), ST segment depression (100 mg and placebo), ST-T segment elevation (30 mg). Three placebo patients also had ECG-related changes including T wave amplitude decreased (2 patients) and T wave abnormal (1 patient). After review of these cases, Dr. Freilich concludes that there are no ECG-related safety signals identified in the eptinezumab database.

Dr. Freilich notes that since this is a biologic monoclonal antibody, a thorough QTc study was not required. Instead, the applicant provided summary statistics for the QTcF. Dr. Freilich states that no patient in the controlled pivotal efficacy studies had a QTcF interval that was > 500 msec. The incidence of QTcF intervals >450 and ≤ 480 msec, or QTcF > 480 msec and ≤ 500 msec were similar in the eptinezumab and placebo groups. There were 2 patients in the treatment arm that had a QTcF > 480 msec and ≤ 500 msec.

The largest mean increase from baseline in QTcF was 4 msec. There were similar proportions of patients in the treatment arms and placebo who had an increase from baseline of QTcF > 30 ms or > 60 ms with no dose-response noted. Dr. Freilich concludes that eptinezumab does not appear to have any notable effect on the TQTc.

Safety Areas of Special Interest

Cardiovascular Risk

Dr. Freilich did not identify any potential CV or cerebrovascular safety concerns in regard to toxicity associated with the use of eptinezumab. She notes that the safety database included only 1.2% over the age of 65 years, and that the patients enrolled had a low incidence of CV or cerebrovascular disease, so the interpretability of these safety data in regards to patients over 65 years of age or patients with CV or cerebrovascular disease is limited.

Dr. Freilich concludes that the current database does not support an increased CV risk with eptinezumab and therefore recommends not including any CV restrictions in labeling; however, these data are also insufficient to definitively establish the CV safety of eptinezumab, and enhanced pharmacovigilance in the postmarketing setting will be required. Dr. Freilich also recommends enhanced pharmacovigilance for hypertension due to the identification of two patients that discontinued due to hypertension without an alternate explanation for the etiology of the hypertension.

Suicidality and Depression

In the controlled trials, Dr. Freilich notes a numeric imbalance in the number of patients reporting suicide-related TEAEs on treatment (11) as compared to placebo (3), yet the overall incidence of these events is similar, 0.5% and 0.4% respectively. In addition, there were 4 SAEs of suicidal ideation and suicide attempt reported in 3 patients. All cases seemed to be confounded. All the cases but one occurred in the chronic migraine database, and the incidence of depression and suicidality in the chronic migraine population is higher than that of the overall migraine population.

Gastrointestinal Toxicity and Liver Toxicity

Constipation was identified as a safety signal of interest due to literature identifying the gastrointestinal system as a target organ for CGRP. In addition, other products in this class have been associated with constipation. Dr. Freilich reports that in the pivotal studies population, the incidence of constipation in the treatment arm was more than 2 times the incidence in the placebo arm (refer to Table 3); however, the overall incidence was low throughout the studies. None of the reports of constipation were serious or severe, and none led to discontinuation of treatment.

Regarding abdominal pain, there were equal numbers of TEAEs in both the treatment arm and placebo arm, and there were no abdominal pain-related SAEs, and none led to discontinuation. There was one severe TEAE of abdominal pain reported in a patient who received placebo.

Table 6: Studies CLIN-006 and CLIN-011-Incidence of Gastrointestinal TEAEs (source: Dr. Freilich's review Table 58)

Adverse Event	All Eptinezumab Treated Patients				Placebo N = 588 (%)
	30 mg N = 219 (%)	100 mg N = 579 (%)	300 mg N = 574 (%)	All Doses N = 1372 (%)	
Gastrointestinal Disorders SOC	**13.7**	**7**	**11.1**	**9.8**	**8.7**
Abdominal pain, all	1.8	1.7	1.7	1.7	1.4
Constipation	1.4	0.7	1.2	1.0	0.3

Although the overall incidence of constipation in this safety database is low, the incidence was 2-3 times higher in the eptinezumab groups as compared to the placebo groups; therefore, Dr. Freilich recommends enhanced postmarketing pharmacovigilance for constipation.

Liver toxicity was also identified as a special safety signal of concern in this development program. Dr. Freilich reports that there were 19 patients who had a total of 21 events coded to "hepatic events," which included hepatic enzymes increased or bilirubin increased. Of these 19 patients, 6 received placebo (1%) and 13 received eptinezumab (0.9%). There was a trend towards increased events with the higher dose, but no conclusions could be made since the overall incidence was so low. None of these events led to study drug discontinuation, none were considered SAEs, and there was 1 event graded as a severe TEAE. Therefore, no clear signal of liver toxicity was identified in the eptinezumab safety database.

Hypersensitivity

Hypersensitivity was observed with other CGRP antagonist monoclonal antibodies recently approved; therefore, it was identified as a safety signal of interest for this application. In the controlled trials, there were 14 reported TEAEs of hypersensitivity in the active treatment arm (13 leading to discontinuations) and none reported in the placebo arm. In addition, 14 patients reported pruritus in the active treatment arm, with none reported in the placebo arm. Four of these patients reported this event on the day of dosing, which makes them likely to be due to hypersensitivity. An additional 5 patients reported "flushing" on the day of dosing that Dr. Freilich reports may be related to an infusion reaction or an immune mediated hypersensitivity reaction. When grouping adverse event terms that appear to be related to hypersensitivity reactions, there is an imbalance of these events between active treatment (1-2%) and placebo (0%). Although most of these cases were reported as mild or moderate, there were several patients that required treatment with either epinephrine, solumedrol, or diphenhydramine to terminate the reaction. One event was associated with angioedema while another was identified as an anaphylactoid reaction (SAE) and was associated with facial edema. Including a Warning and Precaution for Hypersensitivy in labeling is warranted.

Safety Conclusions

The safety profile of eptinezumab is acceptable for the preventive treatment of migraine. There are no safety issues that preclude approval.

There are no SAEs that clearly seem related to eptinezumab use. The overall incidence of adverse events is low, but eptinezumab is associated with nasopharyngitis and hypersensitivity and these events should be described in a common adverse events table in the label. In addition, a Warning and Precaution section should be included for Hypersensitivity Reactions due to the increased incidence seen in this safety database. In addition, enhanced pharmacovigilance is recommended for cardiovascular events, cerebrovascular events, hypertension, and constipation. The reasoning for this enhanced pharmacovigilance is explained below: There are theoretical concerns that patients on this class of drug (CGRP antagonists) may be at increased risk of cerebrovascular or cardiovascular events due to the proposed mechanism of action of CGRP in relation to compensatory vasodilation in the face of ischemia, and although a signal was not identified in the current database, the data are limited in that patients with a history of cardiovascular or cerebrovascular disease were not included, and patients over the age of 65 years were not well represented. It is noted that three patients discontinued due to hypertension and two cases were not confounded. Regarding suicidality, although there were 3 patients that reported suicide-related events defined as SAEs on treatment, these cases were confounded, and there was no clear association between this risk and treatment. In addition, although the overall incidence of constipation was low in this database, the incidence on eptinezumab was twice that of placebo, and serious cases of constipation have been reported with other drugs of this class.

The risks of eptinezumab can be accurately conveyed with labeling.

A pregnancy registry and pregnancy outcome studies will be required. Pediatric studies under the Pediatric Research Equity Act (PREA) for patients with episodic migraine 6-17 years of age and chronic migraine 12-17 years of age will be required.

9. 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 two adequate and well-controlled studies using clinical trial designs similar to those of trials for previously approved drugs for the acute treatment of migraine. Moreover, the safety profile was acceptable for the preventive treatment of migraine.

10. Pediatrics

Eptinizumab was discussed at a Pediatric Review Committee (PeRC) meeting on January 7, 2020, and agreement was reached on the applicant's plan (b) (4) In addition, PeRC agreed to a post-approval deferral of trials in pediatric patients age 6 to 17 for episodic migraine and a deferral of trials in pediatric patients age 12 to 17 for chronic migraine. Please refer to Section 14 of this memo for the required pediatric postmarketing studies.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Dr. Cara Alfaro was the primary OSI reviewer for this application and Dr. Phillip Kronstein was the team leader. Dr. Alfaro states that three clinical sites were inspected in support of this BLA, specifically for Studies CLIN-006 and CLIN-011. Overall, Dr. Alfaro concludes that the studies appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the respective indication. No significant inspectional findings were noted. The OSI review notes that at one site approximately 14% of patients enrolled in one of the studies had been randomized to the incorrect migraine severity stratum. The applicant submitted updated datasets with the corrected strata randomization and an analysis of the primary endpoint using the updated datasets was consistent with the original findings. At another site, there were 2 unblinding events that involved 6 patients for Study CLIN-006 and 4 unblinding events involving 6 patients for Study CLIN-011. The statistical reviewer performed a sensitivity analysis excluding the 12 patients for whom an unblinding event was identified and the results were consistent with those of the original analysis.

Controlled Substance Staff (CSS)
Dr. Joshua Hunt conducted the CSS reveiw for this product during the IND stage and determined that a formal review for the BLA was not needed unless the review team identifies any abuse-related concerns associated with this drug. Dr. Hunt stated that absent any unexpected new abuse-related signals in the future, it was not necessary to include Section 9 in the prescribing information. Dr. Freilich queried the safety database for eptinezumab and did not identify a signal for abuse-related events.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Chad Morris was the primary reviewer and Dr. Briana Rider was the Team Leader for the DMEPA review. DMEPA concludes that the final agreed-upon prescribing information (PI), Patient Package Insert (PPI), and carton and container labeling are acceptable.

Dr. Morris reviewed the proposed proprietary name, Vyepti, and concludes that this name is acceptable.

12. Labeling

See the final negotiated product label. Agreement was reached with the applicant on labeling.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The Division of Risk Management (DRM) has determined that a REMS is not necessary for eptinezumab.

Pharmacovigilance
There should be enhanced pharmacovigilance postmarketing with periodic evaluation of cardiovascular events, cerebrovascular events, hypertension, and constipation.

Postmarketing Requirements (PMRs)

PMR-1 A nonclinical juvenile animal toxicology study in rat (ongoing).

PMR-2 A Phase 1, single-arm, single-dose, pediatric pharmacokinetic study to evaluate eptinezumab in pediatric migraine patients ages 6 through 11 years. The primary objective will be to characterize the pharmacokinetic profile of eptinezumab compared to adult migraine patients, with additional secondary pharmacokinetic and safety endpoints. Immunogenicity will also be assessed through development of specific anti-eptinezumab antibodies.

PMR-3 A randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of eptinezumab in patients with episodic migraine age 6 through 17 years. The study will include an initial double-blind treatment phase (minimum of 3 months) followed by an open-label extension phase for a minimum of 9 months duration. Of the total number of patients enrolled in this trial, a minimum of 25% of patients will be in the 6-11-year age group. There will be a similar number of patients in the 12-14 year old age range, and the 15-17 year old age range. This study is to be submitted as a Special Protocol Assessment (SPA).

PMR-4 A randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of eptinezumab in patients with chronic migraine age 12 through 17 years. The study will include an initial double-blind treatment phase (minimum of 3 months), followed by open-label extension phase for a minimum of 9 months duration. There will be a similar number of patients in the 12-14 year old age range, and the 15-17 year old age range. This study is to be submitted as a Special Protocol Assessment (SPA).

PMR-4 A prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Vyepti during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Vyepti 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-5 A pregnancy outcomes study using a different study design than provided for in PMR-4 (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 Vyepti 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/

NICHOLAS A KOZAUER on behalf of HEATHER D FITTER
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WILLIAM H Dunn
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