Summary Report of Benefit-Risk Assessment

VYEPTI CONCENTRATE FOR SOLUTION FOR INFUSION 100MG/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Eptinezumab
Product Registrant	Lundbeck Singapore Pte Ltd
Product Registration Number	SIN16325P
Application Route	Abridged evaluation
Date of Approval	16 Sep 21

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A INTRODUCTION

Vyepti Concentrate for Solution for Infusion is indicated for the prophylaxis of migraine in adults.

The active substance, eptinezumab, is a humanised monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor. Eptinezumab prevents the activation of CGRP receptors and hence the downstream cascade of physiological events linked to initiation, frequency and severity of migraine attacks.

Vyepti is available as a concentrate for solution for infusion, containing 100mg/ml of eptinezumab. Other ingredients in the vial are L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sorbitol and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, eptinezumab, is manufactured at Sandoz GmbH, Kundl, Austria. The drug product, Vyepti Concentrate for Solution for Infusion 100mg/ml, is manufactured at Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg Baden-Wuerttemberg, Germany.

Drug substance

Adequate controls have been presented for the raw materials, master cell bank and working cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Sandoz GmbH was adequate to support the approved storage condition and shelf life. The packaging is a 2L sterile polycarbonate bottle and a polypropylene cap with silicone rubber/polypropylene liner. The drug substance is approved for storage at ≤ -60°C with a shelf life of 36 months.

Drug product

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at 2 – 8ºC. The in-use period after opening is 8 hours at or below 25°C and is supported with appropriate data. The container closure system is Type I glass vials with a chlorobutyl rubber stopper with an aluminium seal and a flip-off plastic cap.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of eptinezumab was based on two pivotal studies, Study 006 and 011. These were Phase 3, randomised, multicentre, placebo-controlled studies in adult patients with episodic (Study 006, also referred to as PROMISE 1), and chronic (Study 011, PROMISE 2) migraine.

In Study 006, a total of 888 patients with episodic migraine were randomised in a 1:1:1:1 ratio to receive eptinezumab 30mg, 100mg, 300mg or placebo via intravenous (IV) infusion every 12 weeks, for a total of 4 infusions. The total duration of the study was 56 weeks, including a 48-week placebo-controlled treatment period followed by a safety follow-up after the last infusion at week 36. Patients were allowed to use concurrent acute migraine or headache medications, including migraine-specific medications (i.e., triptans, ergotamine derivatives). The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) over Weeks 1-12. The key secondary endpoints included ≥ 50% and ≥ 75% migraine responder rates (defined as the proportion of patients achieving at least the specified percent reduction in migraine days over Weeks 1-12), ≥ 75% migraine responder rate over Weeks 1-4, and the percentage of patients with a migraine on the day after the first dosing (Day 1).

There were 223 patients in the eptinezumab 30mg arm, 221 in the 100mg arm and 222 patients each in the 300mg and placebo arms. The majority of patients were female (84%), White (84%) with a median age of 39 years (18-71 years). The mean number of migraine days per month at baseline was 8.6 and was similar across treatment groups.

The statistical testing employed a fixed-sequence procedure for adjusting multiplicity to control the Type 1 error rate, with each endpoint tested at α=0.05 level of significance. Firstly, the primary and the key secondary endpoints on responder rates were evaluated for the eptinezumab 300mg dose. If a significant result ($p<0.05$) was achieved, the next step was to test the significance of the 100mg dose for the same endpoints. The procedure will then move

on to the remaining key secondary endpoint (percentage of patients with a migraine on the day after dosing) for both 300mg and 100mg. The eptinezumab 30mg arm was only tested if all of the preceding primary and secondary endpoints had reached statistical significance.

Summary of results in Study 006

Primary efficacy endpoint: Change from baseline in MMD over Weeks 1-12				
	Placebo (n=222)	**Eptinezumab 30mg (n=223)**	**Eptinezumab 100mg (n=221)**	**Eptinezumab 300mg (n=222)**
Baseline	8.4	8.7	8.7	8.6
Mean change	-3.2	-4.0	-3.9	-4.3
Difference vs placebo	-	-0.8	-0.7	-1.1
95% CI	-	(-1.4, -0.3)	(-1.3, -0.1)	(-1.7, -0.5)
p value	-	0.0046*	0.0182	0.0001
Key secondary endpoints				
≥ 75% responder rate over Weeks 1-4				
Responders	20.3%	30.0%	30.8%	31.5%
Difference vs placebo	-	9.8%	10.5%	11.3%
p value	-	0.0170*	0.0112	0.0066
≥ 75% responder rate over Weeks 1-12				
Responders	16.2%	24.7%	22.2%	29.7%
Difference vs placebo	-	8.4%	6.0%	13.5%
p value	-	0.0272*	0.1126	0.0007
≥ 50% responder rate over Weeks 1-12				
Responders	37.4%	50.2%	49.8%	56.3%
Difference vs placebo	-	12.8%	12.4%	18.9%
p value	-	0.0064*	0.0085*	0.0001
Percent of patients with a migraine on the day after dosing				
Migraine during baseline period	29.8%	31.0%	31.0%	30.8%
Day 1	22.5%	17.3%	14.8%	13.9%
p value	-	0.154*	0.0312*	0.0159*

*Nominal p value

A statistically significant reduction in MMD was demonstrated for patients in both eptinezumab 300mg and 100mg arms compared to placebo. The mean change from baseline in MMD over Weeks 1-12 was -4.3, -3.9, -4.0 and -3.2 for eptinezumab 300mg, 100mg, 30mg and placebo respectively, with a difference vs placebo of -1.1 days (95% CI: -1.7, -0.5, p=0.0001) and -0.7 days (95% CI: -1.3, -0.1, p=0.0182) for eptinezumab 300mg and 100mg. As statistical significance was not met in the test for the secondary endpoint, 75% migraine responder rate (Weeks 1-12), in the 100mg arm, sequential testing could not proceed further. Consequently, statistical significance could not be concluded for the primary endpoint for the 30 mg dose [difference vs placebo of -0.82 days (95% CI: -1.39, 0.25), nominal p value=0.0046)].

The results for the key secondary endpoints generally supported the primary efficacy endpoint for both eptinezumab 300 mg and 100 mg arms. In addition, a dose-dependent increase in responses was observed in the eptinezumab 300mg arm relative to the 100mg arm for the primary and key secondary endpoints.

In Study 011, a total of 1072 patients with chronic migraine were randomised in a 1:1:1 ratio to receive eptinezumab 100mg, 300mg or placebo via IV infusion every 12 weeks for a total of 2 infusions. The total duration of the study was 32 weeks, including a 24-week placebo-controlled treatment period followed by a safety follow-up after the last infusion at week 12. During the study, patients were allowed to continue an established stable regimen of acute migraine and headache preventive medication. The primary efficacy endpoint was change from baseline in MMD over Weeks 1-12. The key secondary endpoints were similar to those investigated in Study 006, with the addition of change from baseline in total score on the Headache Impact Test (HIT-6) at Week 12, reduction in migraine prevalence from baseline to week 4, and the change from baseline in acute migraine medication days over Weeks 1-12.

There were 356 patients in the eptinezumab 100mg arm, 350 patients in the 300mg arm and 366 patients in the placebo arm. The majority of patients were female (88%), White (91%) with a median age of 41 years (18 – 65 years). The mean migraine frequency at baseline was approximately 16.1 migraine days per month and was similar across treatment groups.

The statistical testing employed a fixed-sequence procedure for adjusting multiplicity to control the Type 1 error rate similar to that in Study 006. For the final key secondary endpoints in the sequence (change from baseline in acute medication use and change from baseline in HIT-6), only eptinezumab 300mg was included in the testing procedure.

A statistically significant reduction in MMD was demonstrated with both eptinezumab doses compared to placebo. The mean change from baseline in MMD over Weeks 1-12 was -8.2, -7.7 and -5.6 for eptinezumab 300mg, 100mg and placebo respectively, with a difference versus placebo of -2.6 days (95% CI: -3.5, -1.7, p<0.0001) and -2.0 days (95% CI: -2.9, -1.2, p<0.0001) for eptinezumab 300mg and 100mg.

Summary of results in Study 011

Primary efficacy endpoint: Change from baseline in MMD over Weeks 1-12			
	Placebo (n=366)	**Eptinezumab 100mg (n=356)**	**Eptinezumab 300mg (n=350)**
Baseline	16.2	16.1	16.1
Mean change	-5.6	-7.7	-8.2
Difference vs placebo		-2.0	-2.6
95% CI		(-2.9, -1.2)	(-3.5, -1.7)
p value vs placebo		<0.0001	<0.0001
Key secondary endpoints			
≥ 75% responder rate over Weeks 1-4			
Responders	15.6%	30.9%	36.9%
Difference vs placebo	-	15.3%	21.3%
p value	-	<0.0001	<0.0001
≥ 75% responder rate over Weeks 1-12			
Responders	15.0%	26.7%	33.1%
Difference vs placebo	-	11.7%	18.1%
p value	-	0.0001	<0.0001
≥ 50% responder rate over Weeks 1-12			
Responders	39.3%	57.6%	61.4%
Difference vs placebo	-	18.2%	22.1%
p value	-	<0.0001	<0.0001
Percent of patients with a migraine on the day after dosing			

Migraine during baseline period	58.0%	57.5%	57.4%
Day 1	42.3%	28.6%	27.8%
p value	-	<0.0001	<0.001
Reduction in Migraine prevalence			
Mean change	-18.8%	-27.1%	-29.8%
Difference vs placebo	-	-8.3%	-11.0%
95% CI	-	(-11.5%, - 5.1%)	(-14.2%, - 7.8%)
p value	-	<0.0001	<0.0001
HIT-6 score (Week 12)			
Mean change	-4.5	-6.2	-7.3
Difference vs placebo	-	-1.7	-2.9
95% CI	-	(-2.8, -0.7)	(-3.9, -1.8)
p value	-	0.0010*	<0.0001
Days per month with Acute Medication Use (Weeks 1-12)			
Mean change	-1.9	-3.3	-3.5
Difference vs placebo	-	-1.2	-1.4
95% CI	-	(-1.7, -0.7)	(-1.9, -0.9)
p value	-	<0.0001*	<0.0001

*Nominal p value as endpoints were not included in serial testing procedure for 100mg

Based on the fixed-sequence statistical testing procedure, eptinezumab 300mg demonstrated statistically significant improvements compared to placebo for all key secondary endpoints. Statistical superiority versus placebo was also met for most endpoints in the eptinezumab 100mg arm. The HIT-6 score and the change from baseline in acute monthly medication use were not included in the serial testing procedure hence statistical significant difference could not be concluded. Similar to Study 006, a dose-dependent increase in responses was observed in the eptinezumab 300mg arm relative to the 100mg arm for the primary and key secondary endpoints.

Overall, eptinezumab 100mg and 300mg demonstrated statistically significant and clinically meaningful improvements in the primary efficacy endpoint, MMD, compared to placebo in patients with both episodic and chronic migraine. This was supported by improvements in the key secondary endpoints, including ≥ 75% and ≥ 50% responder rates. In addition, a numerical benefit was observed for the 300mg dose compared to the 100mg dose for most endpoints.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of eptinezumab was based on safety data derived from studies 006 and 011 which included a total of 1372 patients exposed to eptinezumab and 588 patients exposed to placebo. The median exposure time to eptinezumab was 231 days compared to 227 days in the placebo arm.

Overview of safety profile in studies 006 and 011

	Placebo n=588 (%)	**Eptinezumab 30mg n=219 (%)**	**Eptinezumab 100mg n=579 (%)**	**Eptinezumab 300mg n=574 (%)**	**Eptinezumab (Pooled) n=1372 (%)**
Subjects with any Treatment-emergent adverse event (TEAE)	303 (51.5)	128 (58.4)	296 (51.1)	311 (54.2)	735 (53.6)

Subjects with any study drug related TEAE	48 (8.2)	24 (11.0)	68 (11.7)	85 (14.8)	177 (12.9)
Subjects with any serious TEAE	9 (1.5)	4 (1.8)	7 (1.2)	7 (1.2)	18 (1.3)
Subjects with any TEAE leading to study drug discontinuation	8 (1.4)	12 (5.5)	9 (1.6)	13 (2.3)	34 (2.5)
Subjects with any TEAE resulting in death	0	0	0	0	0

The overall incidence of TEAEs was comparable between the eptinezumab and placebo arms (51.1- 58.4% vs 51.5%). There was a dose-dependent increase in drug-related TEAEs (11.0% in the eptinezumab 30mg arm, 11.7% in the 100mg arm and 14.8% in the 300mg arm). The most common TEAEs that occurred with greater incidence in patients treated with any dose of eptinezumab compared to placebo were upper respiratory tract infection (7.3% in the eptinezumab 300mg arm, 6.4% for 100mg, 9.6% for 30mg vs 5.3% placebo), nasopharyngitis (8.2%, 6.2%, 6.4% vs 5.8%), nausea (3.0%, 1.9%, 4.1% vs 2.6%), fatigue (2.4%, 2.8%, 2.3% vs 1.4%), dizziness (2.3%, 2.6%, 3.7% vs 2.0%), urinary tract infection (2.8%, 1.9%, 1.8% vs 1.5%), arthralgia (2.4%, 1.7%, 1.4% vs 1.5%), back pain (1.6%, 2.4%, 1.8% vs 2.2%), influenza (3.1%, 0.9%, 1.4% vs 2.4%), cough (2.1%, 1.7%, 0.5% vs 1.2%), pain in extremity (0.7%, 0.5%, 2.3% vs 0.3%), and pyrexia (0.7%, 0.3%, 2.3% vs 0.5%). The majority of these TEAEs were mild to moderate in severity.

The rate of SAEs was low and comparable between the pooled eptinezumab and placebo arms (1.3% vs 1.5%). The SAEs reported in eptinezumab-treated patients included suicidal depression/ideation, seizure, serious migraine and cholecystitis (<0.1% each), which were not considered related to study treatment. No deaths were reported.

The main AE of special interest (AESI) reported with eptinezumab was hypersensitivity reactions. Hypersensitivity was reported in 1.4% of patients in the eptinezumab 300mg arm, 0.2% in the 100mg arm, 1.8% in the 30mg arm versus none in placebo. When also considering other TEAEs potentially related to hypersensitivity reactions (such as angioedema, urticaria, flushing/hot flushes, rash and pruritus), hypersensitivity reactions occurred in at an incidence of 2.6% in the eptinezumab 100 mg group, 3.8% in the eptinezumab 300 mg group, and 1.2% in the placebo group. The majority of the events were non-serious, mild or moderate in severity and occurred during the infusion. Anaphylactic reactions were not reported in Study 006 and 011, but have been reported in other studies. Warnings on potential serious hypersensitivity reactions including anaphylactic reactions have been included in the product labelling.

Overall, the safety profile of eptinezumab in the prophylaxis of migraine was considered acceptable. Appropriate warnings and precautions have been included in the product labelling to mitigate the safety concerns.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives. The current prophylactic treatments for migraine include topiramate, botulinum toxin and CGRP-inhibitors. There is a clinical need for treatment options to manage the frequency and severity of migraines to improve health outcomes and quality of life of migraine patients.

The efficacy of eptinezumab was supported by two pivotal Phase 3 studies which included patients with episodic or chronic migraine. A statistically significant reduction in MMD compared to placebo was demonstrated in both Study 006 (-1.1 and -0.7 for eptinezumab 300mg and 100mg) and Study 011 (-2.6 and -2.0). This was supported by consistent improvement compared to placebo for the key secondary endpoints, including ≥ 75% and ≥ 50% responder rates. While eptinezumab 300mg demonstrated numerical benefit compared to the 100mg dose for most efficacy endpoints in both Study 006 and 011, there was also a dose-dependent increase in drug-related TEAEs (14.8% vs 11.7%). Hence the recommended dosing regimen is eptinezumab 100mg every 12 weeks, with the option to administer the 300mg dose based on individual clinical response and tolerability.

Eptinezumab was generally well tolerated in the clinical studies, with a safety profile consistent with other CGRP-inhibitors. Most events were mild to moderate and generally manageable. AESIs such as hypersensitivity have been adequately described in the package insert.

Overall, the benefits of eptinezumab with respect to the clinically meaningful and statistically significant reduction in MMD outweighed the risks of adverse events associated with its use in the prophylaxis of episodic or chronic migraine. Appropriate warnings and precautions have been included in the package insert to mitigate the identified safety concerns.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of eptinezumab for the prophylaxis of migraine was deemed favourable and approval of the product registration was granted on 16 Sep 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

Portrait SmPC SINGAPORE Eptinezumab 100 mg/mL Concentrate for Solution for Infusion

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eptinezumab 100 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg/mL eptinezumab.

Eptinezumab is a humanised monoclonal immunoglobulin G1 (IgG1) antibody.

For the full list of excipients, see section 3.2

3. PHARMACEUTICAL FORM

3.1 Pharmaceutical form

Concentrate for solution for infusion.

The concentrate for solution for infusion is clear to slightly opalescent, colourless to brownish-yellow, with a pH of 5.5-6.1 and osmolality of 290-350 mOsm/kg.

3.2 List of excipients

Sorbitol

L-histidine

L-Histidine hydrochloride monohydrate

Polysorbate 80

Water for Injection

3.3 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section 3.7.

3.4 Shelf life

36 months

Following dilution, the VYEPTI solution for infusion (VYEPTI and 0.9% Sodium Chloride for Injection) must be infused within 8 hours (see Section 3.7).

3.5 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Keep the vial in the outer carton in order to protect from light.

Do not freeze or shake.

Following dilution, the VYEPTI solution for infusion (VYEPTI and 0.9% Sodium Chloride for Injection) may be stored at room temperature (at or below 25°C) or refrigerated at 2 to 8°C.

3.6 Nature and contents of container

Type I glass vial with chlorobutyl rubber stopper. The vial stopper is made without natural rubber latex.

Each Carton contains one vial.

3.7 Special precautions for disposal and other handling

The product requires dilution prior to administration. The dilution should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution for infusion.

The product contains no preservative and is intended for single use only and any unused product should be disposed.

Prior to dilution, the product (solution in the vials) should be inspected visually; do not use if the solution contains visible particulate matter or is cloudy or discoloured (other than clear to slightly opalescent, colourless to brownish-yellow).

For both the 100 mg and the 300 mg dose, a 100 mL bag of 0.9% Sodium Chloride for Injection should be used to prepare the VYEPTI solution for infusion as described below. No other IV diluents or volumes may be used to prepare the VYEPTI solution for infusion.

Gently invert the VYEPTI solution for infusion to mix completely. Do not shake.

Following dilution, VYEPTI solution for infusion must be infused within 8 hours. During this time, VYEPTI solution for infusion may be stored at room temperature (at or below 25°C) or refrigerated at 2 to 8°C. If stored at 2 to 8°C, allow the VYEPTI solution for infusion to warm to room temperature prior to infusion. DO NOT FREEZE.

100 mg dose:

To prepare the VYEPTI solution for infusion, withdraw 1.0 mL of VYEPTI from one single-use vial using a sterile needle and syringe. Inject the 1.0 mL (100 mg) content into a 100 mL bag of 0.9% Sodium Chloride for Injection

300 mg dose:

To prepare the VYEPTI solution for infusion, withdraw 1.0 mL of VYEPTI from 3 single-use vials using a sterile needle and syringe. Inject the resulting 3.0 mL (300 mg) content into a 100 mL bag of 0.9% Sodium Chloride for Injection.

Infusion administration instructions

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the liquid contains visible particulate matter or is cloudy or discolored.

Infuse VYEPTI 100 mg or 300 mg as prescribed, following dilution of the vial content in a 100 mL bag of 0.9% Sodium Chloride for Injection, over approximately 30 minutes. Use an intravenous infusion set with a 0.2 or 0.22 μm in-line or add-on filter. After the infusion is complete, flush the line with 20 mL of 0.9% Sodium Chloride for Injection.

Do not administer VYEPTI as a bolus injection.

No other medications should be administered through the infusion set or mixed with VYEPTI.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VYEPTI is indicated for prophylaxis of migraine in adults.

4.2 Posology and method of administration

As for other infusion treatments, VYEPTI treatment should be initiated and supervised by a healthcare professional.

Posology

The recommended dose is 100 mg administered by intravenous infusion every 12 weeks. Some patients may benefit from a dosage of 300 mg administered by intravenous infusion every 12 weeks. (see section 5.1).

Special Populations

Elderly (aged 65 years and over)

Although patients aged up to 75 years were included in one study, the clinical study program of VYEPTI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.The pharmacokinetics of Vyepti are not affected by age (see section 5.2).

Renal impairment/hepatic impairment

No dedicated hepatic or renal impairment studies were conducted to assess the effects of hepatic and renal impairment upon the pharmacokinetics of eptinezumab. Population pharmacokinetic analysis of integrated data from the VYEPTI clinical studies did not reveal any differences in patients with renal or hepatic impairment that would require dose adjustment. (see section 5.2).

Paediatric population

The safety and efficacy of eptinezumab in children below the age of 18 years has not yet been established. Currently no data are available.

Method of administration

Eptinezumab is for intravenous infusion only after dilution.

For instructions on dilution of the medicinal product prior to administration, see section 3.7.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 3.2.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Cardiovascular risk

Patients with a history of cardiovascular disease (e.g. hypertension, ischemic heart disease) were excluded from clinical studies (see section 5.1). No safety data are available in these patients.

Serious hypersensitivity

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported and may develop within minutes of the infusion. Most hypersensitivity reactions occurred during infusion and were not serious (see section 4.8). Serious hypersensitivity reactions may occur. If

a serious hypersensitivity reaction occurs, administration of VYEPTI should be discontinued immediately and appropriate therapy initiated.

4.5 Interaction with other medicinal products and other forms of interactions

Eptinezumab is not metabolized by cytochrome P450 enzymes. Therefore, interactions by eptinezumab with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are considered unlikely.

In healthy subjects, co-administration of a single dose of 300 mg eptinezumab administered as an intravenous infusion (over a period of 1 hour ± 15 min) with a single dose of 6 mg sumatriptan administered subcutaneously did not alter the pharmacokinetics of eptinezumab or sumatriptan.

Interactions with other drugs have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of eptinezumab in pregnant women. Animal studies with eptinezumab do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Human IgG is known to cross the placental barrier; therefore, eptinezumab may be transmitted from the mother to the developing fetus.

VYEPTI should not be used by pregnant women unless the expected benefit to the mother justifies the potential risk to the fetus.

Breast-feeding

There are no data on the presence of eptinezumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be excreted in breast milk; therefore, eptinezumab may be transmitted from the mother to the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYEPTI and any potential effects on the breastfed infant.

Fertility

The effect of eptinezumab on human fertility has not been evaluated. Animal studies with eptinezumab showed no impact on female and male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

VYEPTI is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

A total of over 2000 patients (more than 1,600 patient years) have been treated with VYEPTI in clinical studies. Of these, approximately 1,500 patients were exposed to 100 mg or 300 mg. Across all doses, 1872 patients were exposed for at least 24 weeks (two doses), 991 patients were exposed for 48 weeks (four doses), and 101 patients were exposed for up to two years (eight doses). In the placebo-controlled clinical studies (PROMISE 1 and PROMISE 2), 1372 patients received at least one dose of VYEPTI (including 579 patients receiving at least one dose of VYEPTI 100 mg and 574 patients receiving at least one dose of VYEPTI 300 mg), and 588 patients received placebo.

The most common adverse reactions in the placebo-controlled clinical studies (PROMISE 1 and PROMISE 2) for the preventive treatment of migraine were nasopharyngitis and hypersensitivity (see below). Most hypersensitivity reactions occurred during infusion and were not serious.

Infusion-site related adverse events occurred infrequently and in similar proportions of VYEPTI and placebo patients (< 2%) with no apparent relationship to VYEPTI dose. The most frequently occurring infusion-site related adverse event was infusion site extravasation, which occurred in < 1% of VYEPTI and placebo patients in PROMISE 1 and PROMISE 2.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification. Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100; rare (≥1/10,000 to <1/1,000; very rare (<1/10,000).

Table 1: List of Adverse Reactions in Clinical Studies and Post-marketing reports

System Organ Class	Adverse Reaction Preferred Term	Frequency Category
Infections and Infestations	Nasopharyngitis	Common
Immune system disorders	Hypersensitivity reactions	Common
	Anaphylactic reaction[1]	Rare

[1] Not reported in PROMISE 1 and PROMISE 2, but reported in other studies and in the post-marketing setting.

Description of selected adverse reactions

Nasopharyngitis

Approximately 8% of patients on 300 mg, 6% of patients on 100 mg and 6% of patients on placebo in PROMISE 1 and PROMISE 2 experienced nasopharyngitis. Nasopharyngitis was most frequent after the first dose of eptinezumab at any dose. The incidence decreased with subsequent doses and remained fairly steady thereafter.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported and may develop within minutes of the infusion (see section 4.4). The reported anaphylactic reactions have included symptoms of hypotension and respiratory difficulties, and have led to discontinuation of VYEPTI. Other hypersensitivity reactions, including angioedema, urticaria, flushing, rash and pruritus, were reported in approximately 4% of patients on 300 mg, 3% of patients on 100 mg and 1% of patients on placebo in PROMISE 1 and PROMISE 2.

Immunogenicity

In placebo-controlled pivotal clinical studies, PROMISE 1 and PROMISE 2, the incidence of anti-eptinezumab antibodies across both studies was 18% (105/579) and 20% (115/574) in patients receiving 100 mg and 300 mg every 12 weeks dosing, respectively. In both studies, the incidence of anti-eptinezumab antibodies peaked at Week 24, and thereafter showed a steady decline even after subsequent dosing every 12 weeks. The incidence of antibodies with neutralizing potential across both studies was 8.3% (48/579) and 6.1% (35/574) for the 100 mg and 300 mg treatment groups, respectively.

A long-term open label repeat dose study, PREVAIL, in 128 patients with chronic migraine consisted of a primary and secondary treatment phase in which up to eight IV infusions of VYEPTI 300 mg were administered over an 84-week period (one infusion every 12 weeks).

Overall 119 patients completed the primary treatment phase (4 infusions, from baseline up to 48 weeks) and 101 patients completed the secondary treatment phase (8 infusions; from baseline up to 96 weeks). Anti-drug antibodies (ADA) developed in 18% (23/128) of patients with an overall incidence of antibodies with neutralizing potential of 7% (9/128). 5.3% patients were ADA positive at week 48, 4% were ADA positive at week 72, and all patients, except one patient lost to follow-up, were ADA negative at week 104 (the last assessment in the study).

There was no evidence of impact of anti-eptinezumab antibody development on efficacy or safety in the clinical studies.

4.9 Overdose

There has been no experience of overdose with VYEPTI. Doses up to 1000 mg have been administered intravenously to humans without tolerability issues or clinically significant adverse reactions.

In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned.

ATC code: N02CD05

Mechanism of action

Eptinezumab is a humanized immunoglobulin G1 (IgG1) antibody that binds to α- and β- forms of human calcitonin gene-related peptide (CGRP) ligand with low picomolar affinity (4 and 3 pM K_D, respectively). This, in combination with the 100% bioavailability following an IV administration, translates into fast blockage of the biological effects of circulating CGRP in humans. As a result, eptinezumab prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation, frequency and severity of migraine attacks.

Eptinezumab is highly selective and does not bind to any of the related neuropeptides amylin, calcitonin, adrenomedullin and intermedin.

Pharmacodynamic effects

Pharmacodynamic activity characterized by inhibition of α-CGRP-mediated neurogenic vasodilation induced by topical capsaicin relative to baseline was evaluated following single or multiple administrations of eptinezumab in human volunteers. Mean neurogenic induced vasodilation was reduced by 41% following intravenous 100 mg eptinezumab administration compared to an increase of 12% for placebo on the day following treatment. For up to 12 weeks, the reduction persisted ranging from 20% to 50% for 100 mg eptinezumab while placebo ranged from a 20% increase to 0.20% reduction during the same period.

Clinical efficacy and safety

VYEPTI was evaluated for the preventive treatment of migraine in two pivotal placebo-controlled studies: PROMISE 1 was conducted in patients with episodic migraine (n=888) and PROMISE 2 in patients with chronic migraine (n=1072). Enrolled patients had a history of migraine (with or without aura) of at least 12 months, according to the International Classification of Headache Disorders (ICHD-II or III) diagnostic criteria.

The long-term safety of VYEPTI following repeated dosing for up to 2 years was further evaluated in patients with chronic migraine in an open-label study, PREVAIL, (n=128).

The efficacy of VYEPTI was also evaluated during a migraine attack occurring in patients who were candidates for prophylaxis of migraine: RELIEF was conducted in patients with migraine

as defined by ICHD-3 with ≥4 and ≤15 migraine days per month in the 3 months prior to screening (n=480).

PROMISE 1: Episodic Migraine

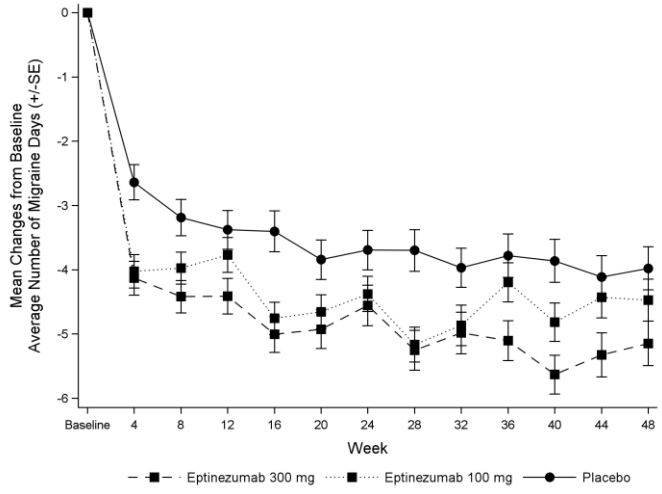
PROMISE 1 was a parallel group, double-blind, placebo-controlled global study to evaluate the efficacy and safety of VYEPTI for the preventive treatment of episodic migraine (defined as ≤ 14 headache days of which at least 4 migraine days during the past 3 months and confirmed during the 28-day screening period) in adults. A total of 665 patients were randomized to placebo (N=222), 100 mg eptinezumab (N=221), or 300 mg eptinezumab (N=222) every 12 weeks for 48 weeks (4 infusions). Patients were allowed concurrent acute migraine or headache medications, including migraine-specific medications (i.e., triptans, ergotamine derivatives), during the study. Regular use (greater than 7 days per month) of other treatments for the prevention of migraine was not allowed.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) over Weeks 1-12. The key secondary endpoints included ≥ 50% and ≥ 75% migraine responder rates defined as the proportion of patients achieving at least the specified percent reduction in migraine days over Weeks 1-12, ≥ 75% migraine responder rate over Weeks 1-4, and the percentage of patients with a migraine on the day after the first dosing (Day 1).

Patients had a mean age of 40 years (range: 18 to 71 years), 84% were women, and 84% were white. The mean number of migraine days per month at baseline was 8.6 and the rate of patients with a migraine on a given day was 30.7% during the screening period; both were similar across treatment groups.

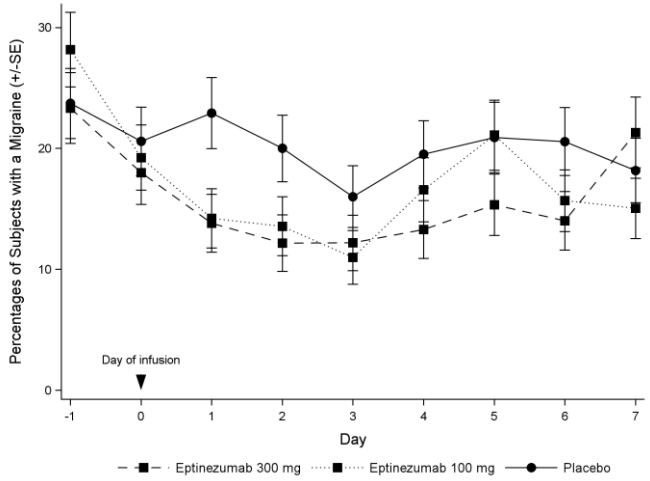
The 4-week results over Weeks 1-48, following four quarterly infusions of VYEPTI treatment are presented as changes from baseline in mean MMD (Figure 1). Both VYEPTI 100 mg and 300 mg treatment groups demonstrated statistically significant and clinically meaningful greater improvements from baseline to week 1-12 compared to placebo on mean MMD. For both doses of VYEPTI, a greater mean decrease in MMDs compared to placebo was sustained for all timepoints through Week 48.

Figure 1 Mean Changes from Baseline in Mean Monthly Migraine Days over Time in PROMISE 1 – Weeks 1-48



The daily results over the first week after the initial infusion of VYEPTI treatment are presented as percentages of patients with a migraine (Figure 2).

Figure 2: Percentages of Patients with a Migraine from Day -1 (Day Prior to Infusion) to Day 7 in PROMISE 1 – Days 1-7



For both doses of VYEPTI the preventive treatment benefit over placebo was observed as early as Day 1 post-infusion in a prespecified analysis. The percentage of patients with a migraine on the day after dosing were lower for both the 300 and the 100 mg groups relative to placebo (13.9% (p=0.0159) and 14.8% (p=0.0312)), respectively compared to 22.5% on Day 1.

VYEPTI treatment demonstrated statistically significant and clinically meaningful improvements for primary and key secondary efficacy endpoints, as summarized in Table 2.

Table 2: Primary and Key Secondary Efficacy Endpoint Results in PROMISE 1 (Episodic Migraine)

	VYEPTI 100 mg N=221	**VYEPTI 300 mg N=222**	**Placebo N=222**
Monthly Migraine Days (MMD) – Weeks 1-12			
Baseline	8.7	8.6	8.4
Mean Change	-3.9	-4.3	-3.2
Difference from placebo	-0.7	-1.1	
$CI_{95\%}$	(-1.3, -0.1)	(-1.7, -0.5)	
p-value vs placebo	0.0182	0.0001	
≥ 75% MMD responders – Weeks 1-4			
Responders	30.8%	31.5%	20.3%
Difference from placebo	10.5%	11.3%	
p-value vs placebo	0.0112	0.0066	
≥ 75% MMD responders – Weeks 1-12			
Responders	22.2%	29.7%	16.2%
Difference from placebo	6.0%	13.5%	
p-value vs placebo	0.1126	0.0007	
≥ 50% MMD responders – Weeks 1-12			
Responders	49.8%	56.3%	37.4%
Difference from placebo	12.4%	18.9%	
p-value vs placebo	0.0085	0.0001	
Percent of Patients with a Migraine on the Day After Dosing			
Migraine during the Baseline Period[a]	31.0%	30.8%	29.8%
Day 1	14.8%	13.9%	22.5%
p-value vs placebo	0.0312	0.0159	

[a] A baseline was the average over the 28-day screening period prior to receiving treatment

Additional secondary efficacy endpoints in PROMISE 1 substantiated results from the key efficacy endpoints. In line with the ≥ 50% and ≥ 75% migraine responder rates, 100% migraine responder rates

(average of 4-week means across Weeks 1-12) were higher for both doses of VYEPTI compared to placebo (100 mg and 300 mg: 11.4% and 16.8% vs placebo: 9.1%).

PROMISE 2: Chronic Migraine

PROMISE 2 was a parallel group, double-blind, placebo-controlled global study to evaluate the efficacy and safety of VYEPTI for the preventive treatment of chronic migraine (defined as ≥ 15 headache days, of which ≥ 8 were assessed as migraine days in the 3 months prior to screening and confirmed during the 28-day screening period) in adults. A total of 1,072 patients were randomized and received placebo (N=366), 100 mg eptinezumab (N=356), or 300 mg eptinezumab (N=350) every 12 weeks for 24 weeks (2 infusions). During the study, patients were allowed acute or preventive medication for migraine or headache on an established stable regimen (except for onabotulinumtoxinA). Patients with a dual diagnosis of chronic migraine and medication overuse headache (associated with the overuse of triptans, ergotamine, or combination analgesics > 10 days/month, or acetaminophen, acetylsalicylic acid, or non-steroidal anti-inflammatory drugs ≥ 15 days/month) confirmed during the 28 days screening period were included in the study population. Patients taking opioids or butalbital containing products > 4 days/month were excluded.

The primary efficacy endpoint was the change from baseline in mean MMD over Weeks 1-12. The key secondary endpoints included ≥ 50% and ≥ 75% migraine responder rates defined as the proportion of patients achieving the specified percent reduction in migraine days over Weeks 1-12, ≥ 75% migraine responder rate over Weeks 1-4, the percentage of patients with a migraine on the day after dosing, the reduction in migraine prevalence from baseline to Week 4, the change from baseline in the total score on the Headache Impact Test (HIT-6) at Week 12 (300 mg dose only), and the change from baseline in acute monthly migraine medication days, mean over Weeks 1-12 (300 mg dose only).

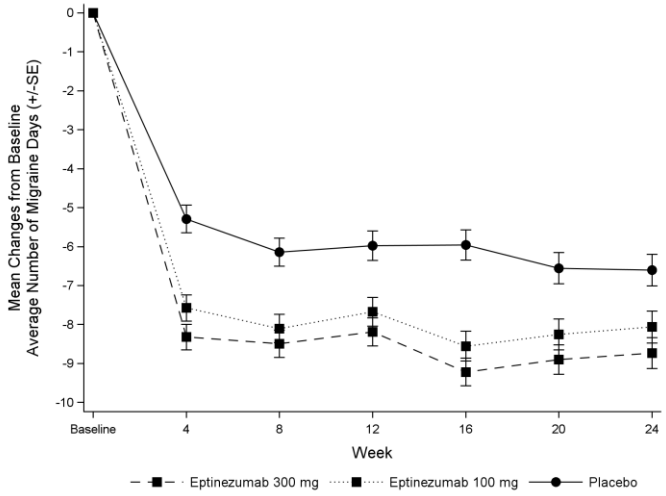
The HIT-6 is a self-administered questionnaire assessing the impact of headache on the functional status of patients with migraine. Interpretation of the impact of migraine on daily function by total score is as follows: 60-78 = Severe; 56-59 = Substantial, 50-55 = Some, and 36-49 = little to none.

A health-related quality of life secondary endpoint was the Short-Form Health Survey Version 2 (SF-36v2). The SF-36v2 measures functional health and well-being from the patient's point of view. It comprises 36 questions which cover eight domains of health measuring quality of life over the past 4 weeks. The eight sections measured are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.

Patients had a mean age of 41 years (range: 18 to 65 years), 88% were women, and 91% were white. Forty-one percent of patients were taking concomitant preventive medication for migraine. The mean number of migraine days per month at baseline was 16.1 and the rate of patients with a migraine on a given day was 57.6% during the screening period; both were similar across treatment groups.

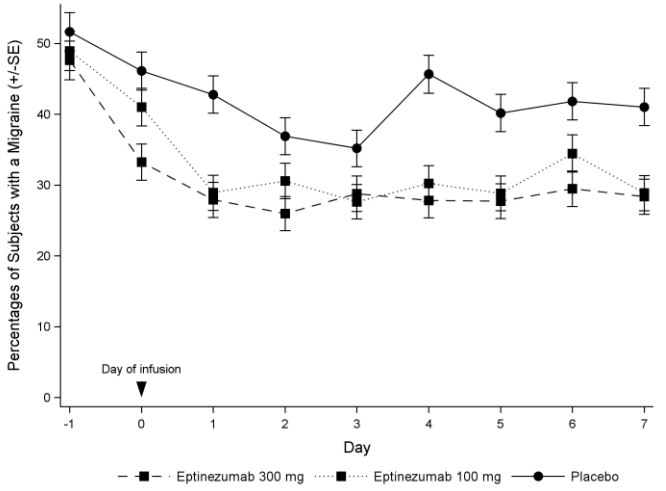
The monthly results over Weeks 1-24, following repeated VYEPTI infusions every 12 weeks are presented as changes from baseline in mean MMD (Figure 3). Both VYEPTI 100 mg and 300 mg treatment groups demonstrated statistically significant and clinically meaningful greater improvements from baseline to week 1-12 compared to placebo on mean MMD. For both doses of VYEPTI, a greater mean decrease in MMDs compared to placebo was sustained for all timepoints through Week 24.

Figure 3: Mean Changes from Baseline in Mean Monthly Migraine Days in PROMISE 2 - Weeks 1-24



The daily results over the first week after the initial infusion of VYEPTI treatment are presented as percentages of patients with a migraine (Figure 4).

Figure 4: Percentages of Patients with a Migraine from Day -1 (Day Prior to Infusion) to Day in PROMISE 2 – Days 1-7



A preventive treatment benefit over placebo for both doses of VYEPTI was observed as early as Day 1 post-infusion in a prespecified analysis. There was a statistically significant lower frequency in day 1 migraine for both the 300 and 100 mg groups compared to placebo (27.8% [p< 0.0001] and 28.6% [p<0.0001]), respectively, compared to 42.3%, on Day 1.

Eptinezumab treatment demonstrated statistically significant and clinically meaningful improvements for key efficacy endpoints as summarized in Table 3.

Table 3: Primary and Key Secondary Efficacy Endpoint Results in PROMISE 2 (Chronic Migraine)

	VYEPTI 100 mg N=356	**VYEPTI 300 mg N=350**	**Placebo N=366**
Monthly Migraine Days (MMD) – Weeks 1-12			
Baseline	16.1	16.1	16.2
Mean Change	-7.7	-8.2	-5.6
Difference from placebo	-2.0	-2.6	
$CI_{95\%}$	(-2.9, -1.2)	(-3.5, -1.7)	
p-value vs placebo	< 0.0001	< 0.0001	
≥ 75% MMD responders – Weeks 1-4			
Responders	30.9%	36.9%	15.6%
Difference from placebo	15.3%	21.3%	
p-value vs placebo	< 0.0001	< 0.0001	
≥ 75% MMD responders – Weeks 1-12			
Responders	26.7%	33.1%	15.0%
Difference from placebo	11.7%	18.1%	
p-value vs placebo	0.0001	< 0.0001	
≥ 50% MMD responders – Weeks 1-12			
Responders	57.6%	61.4%	39.3%
Difference from placebo	18.2%	22.1%	
p-value vs placebo	< 0.0001	< 0.0001	
Percent of Patients with a Migraine on the Day After Dosing			
Migraine during the Baseline Period[a]	57.5%	57.4%	58.0%
Day 1	28.6%	27.8%	42.3%
p-value vs placebo	< 0.0001	< 0.001	
Reduction in Migraine Prevalence[b] – Weeks 1-4			
Mean Change	-27.1%	-29.8%	-18.8%
Difference from placebo	-8.3%	-11.0%	
$CI_{95\%}$	(-11.5%, -	(-14.2%, -	

	5.1%)	7.8%)	
p-value vs placebo	< 0.0001	< 0.0001	
HIT-6 Score – Week 12[c]			
Baseline	65.0	65.1	64.8
Mean Change	-6.2	-7.3	-4.5
Difference from placebo	-1.7	-2.9	
$CI_{95\%}$	(-2.8, -0.7)	(-3.9, -1.8)	
p-value vs placebo	0.0010	< 0.0001	
Days per month with Acute Medication Use – Weeks 1-12[a,c]			
Baseline	6.6	6.7	6.2
Mean Change	-3.3	-3.5	-1.9
Difference from placebo	-1.2	-1.4	
$CI_{95\%}$	(-1.7, -0.7)	(-1.9, -0.9)	
p-value vs placebo	< 0.0001	< 0.0001	

[a] A baseline was the average over the 28-day screening period prior to receiving treatment
[b] Migraine prevalence: The average percent of patients with a migraine on any given day during baseline and the equivalent average rates over weeks 1, 2, 3, and 4
[c] The endpoint for the 100 mg dose was not a pre-specified key secondary endpoint.

Additional secondary efficacy endpoints in PROMISE 2 substantiated results from the key efficacy endpoints. In line with the ≥ 50% and ≥ 75% migraine responder rates, 100% migraine responder rates (average of 4-week means across Weeks 1-12) were higher for both doses of VYEPTI compared to placebo (100 mg and 300mg: 10.8% [0.8; 9.1] and 15.1% [6.2; 15.5] vs placebo: 5.1%).

Patients with medication overuse headache (MOH), other than those taking opioids or butalbital > 4 days/month, were enrolled in PROMISE 2: at baseline, 40.2% of the patients had MOH. In patients with chronic migraine, similar reductions in MMD (Mean for Weeks 1-12) were observed in patients with and without MOH at baseline. The mean change from baseline in MMD (Weeks 1-12) for the patients with MOH was for 300 mg: -8.6, 100 mg: -8.4, placebo: -5.4 and for patients without MOH was 300 mg: -8.1, 100 mg: -7.4, placebo:-6.1.The mean difference to placebo in change from baseline in MMD (Weeks 1-12) for the patients with MOH was (100 mg: -3.0 [-4.52; -1.49], 300 mg: -3.2 [95% CI: -4.75; -1.70] and for patients without MOH was (100 mg: -1.5 [-2.70; -0.31]), 300 mg: -2.4 [-3.59; -1.12].

RELIEF: Initiation of prophylaxis during a migraine attack

RELIEF was a randomized, parallel group, double-blind, placebo-controlled study to evaluate the efficacy of VYEPTI when initiated during a migraine attack occurring in patients who were candidates for prophylaxis of migraine as defined by ICHD-3 with ≥4 and ≤15 migraine days per month in the 3 months prior to screening. A total of 480 patients were randomized to receive a single infusion of

either VYEPTI 100 mg or placebo in a 1:1 ratio. Treatment was initiated within 1 to 6 hours on the onset of a qualifying migraine attack.

During the study, patients were allowed rescue medication, defined as any medication to treat migraine or migraine associated symptoms, any time after 2 hours post-start of VYEPTI infusion. During the study, patients were allowed to use prophylaxis medication for migraine or headache on an established stable regimen. Other anti-CGRP treatments were prohibited during the study.

The co-primary endpoints were time to headache pain freedom and time to absence of most bothersome symptom (selected among nausea, photophobia and phonophobia). The key secondary endpoints included headache pain freedom at 2 hours after the start of infusion and absence of most bothersome symptom at 2 hours after the start of infusion.

Patients had a mean age of 44 years (range: 18 to 75 years), 84% were women, and 86% were white. 16.4% of patients were taking concomitant preventive medication for migraine.

VYEPTI treatment demonstrated statistically significant and clinically meaningful improvements for primary and key secondary efficacy endpoints, as summarized in Table 4.

Table 4: Primary and Key Secondary Efficacy Endpoint Results in RELIEF (prophylaxis initiated during a moderate to severe migraine attack)

	VYEPTI 100 mg N=238	**Placebo N=242**
Time to Headache Pain Freedom		
Median time to headache pain freedom (hours)	4.0	9.0
Hazard ratio	1.54	
$CI_{95\%}$	(1.20, 1.98)	
p-value vs placebo	0.0006	
Time to Absence of Most Bothersome Symptom[a]		
Median time to headache pain relief (hours)	2.0	3.0
Hazard ratio	1.75	
$CI_{95\%}$	(1.41, 2.19)	
p-value vs placebo	< 0.0001	
Patients Achieving Headache Pain Freedom at 2 Hours after start of infusion		
Patients with freedom from headache pain	23.5%	12.0%
Odds Ratio	2.27	
$CI_{95\%}$	(1.39, 3.72)	
p-value vs placebo	0.0009	
Patients Who had Absence of Most Bothersome Symptom at 2 Hours Post Infusion		
Patients with absence of most bothersome symptom	55.5%	35.8%
Odds Ratio	2.25	
$CI_{95\%}$	(1.55, 3.25)	
p-value vs placebo	< 0.0001	

[a] The number of patients in the placebo group was 240 for this endpoint

The safety profile observed in RELIEF is consistent with the safety profile observed in the two pivotal placebo-controlled studies with VYEPTI (PROMISE 1 and 2).

PREVAIL: Long-term study

VYEPTI 300 mg was administered every 12 weeks by IV infusion in patients with chronic migraine in an open-label study for up to 2 years, with the primary objective of further evaluating the long-term safety following repeated doses of VYEPTI. Secondary objectives included characterization of the PK and immunogenicity profiles for VYEPTI (section 4.8) and evaluation of the therapeutic effect of VYEPTI on several patient reported outcomes relating to quality of life and headache impact including the Headache Impact Test (HIT-6). Patients had a mean age of 41.5 years (range: 18 to 65 years), 85% were women, and 95% were white. Thirty-six percent of patients were taking concomitant preventive medication for migraine. The mean number of migraine days per 28-day period in the 3 months preceding screening was 14.1 days. There were 128 enrolled and treated patients in this study. In total, 100 patients (78.1%) completed the study (Week 104). Overall, the results of this open-label clinical

study demonstrated that the effect of VYEPTI 300 mg administered by IV infusions every 12 weeks for the preventive treatment of migraine was demonstrated by reductions in headache impact, improvements in measures of health-related quality of life, and overall improvement in global impressions of change in migraine over 2 years of treatment in adults with chronic migraine. The safety profile was consistent with the safety profiles observed in randomized, placebo-controlled studies with VYEPTI.

Headache impact and health related Quality of Life

The impact of migraine headache was assessed via Headache Impact Test (HIT-6) and Short Form health survey (SF-36v2), respectively, in PROMISE-2 and PREVAIL.

In PROMISE-2, at baseline patients were severely impacted, with a mean total score of 65. At week 12, patients treated with eptinezumab showed a statistically significant improvement in the HIT-6 total score versus placebo compared to baseline. The mean change from baseline to week 12 was -6.2 ($p=0.0010$, nominal p value) for eptinezumab 100 mg, -7.3 ($p<0.0001$) for 300 mg, and -4.5 for placebo. The improvements were sustained over the entire treatment period and up to the safety follow-up, 20 weeks after the last infusion administration.

In the long-term study, PREVAIL, at baseline patients were severely impacted with a mean total HIT-6 of 65. The mean change from baseline through week 104 was -9.7 ($p<0.0001$).

In PROMISE-2, patients treated with VYEPTI showed improvement in physical (PCS) and mental (MCS) component summary scores of the SF-36v2 from baseline to Week 12 compared to placebo. The mean change from baseline to week 12 in MCS was 2.78 for 100 mg ($p = 0.0009$), 2.78 for 300 mg ($p = 0.0010$), and 0.93 for placebo. The mean change from baseline to week 12 in PCS was 3.79 for 100 mg ($p= 0.07$), 4.86 for 300 mg ($p < 0.0001$), and 3.03 for placebo.

In the long-term study, PREVAIL, patients treated with VYEPTI showed improvements in the physical and mental component summary scores of the SF-36v2: the mean change from baseline in MCS (baseline 51.3) was 3 ($p=0.0045$), and in PCS (baseline 46.7) was 4.3 ($p<0.0001$). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

Improvement in health-related quality of life and physical function was maintained in both studies through the entire study duration of 24 weeks and 104 weeks, respectively.

5.2 Pharmacokinetic properties

As eptinezumab is administered intravenously, it is 100% bioavailable. Eptinezumab exhibits linear pharmacokinetics and exposure increases proportionally with doses from 1 to 1000 mg. Steady-state is attained after the first-dose during a once every 12 weeks dosing schedule. Median time to maximum concentration (C_{max}) is 30 minutes (end-of-infusion), and the average terminal elimination half-life is 27 days. The mean accumulation ratios based on C_{max} and $AUC_{0\text{-}tau}$ are 1.08 and 1.15, respectively.

Absorption

VYEPTI is administered by intravenous infusion which bypasses extravascular absorption and is 100% bioavailable. Median time to peak concentration was attained at the end of infusion (30 minutes).

Distribution

The central volume of distribution (V_c) for eptinezumab was approximately 3.7 liters.

Biotransformation

Eptinezumab is expected to be degraded by proteolytic enzymes into small peptides and amino acids.

Elimination

Eptinezumab apparent clearance was 0.15 L/day, and the terminal elimination half-life was approximately 27 days.

Special populations

The pharmacokinetics of eptinezumab were not affected by age, gender, or race based on population pharmacokinetics. Therefore, no dose adjustment is needed.

A population pharmacokinetic analysis including 2123 subjects explored the effect of age, gender, ethnicity and body weight on the pharmacokinetics of eptinezumab. Relative to a 70 kg subject, steady state exposure of eptinezumab in a 190 kg subject was up to 52% lower, whereas is would be up to 50% higher in a 39 kg subject. However, from the exposure-response evaluation, there was no effect of body weight on the clinical outcome. No dose adjustment is needed based on body weight.

Renal or Hepatic Impairment

No dedicated hepatic or renal impairment studies were conducted to assess the effects of hepatic and renal impairment upon the pharmacokinetics of eptinezumab. Population pharmacokinetic analysis of integrated data from the VYEPTI clinical studies did not reveal any differences in patients with renal or hepatic impairment that would require dose adjustment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, or toxicity to reproduction and development.

Safety pharmacology and general toxicology

Safety pharmacology and general toxicity assessments after intravenous (IV) administration of eptinezumab once every 2 weeks for 6 months in cynomolgus monkeys identified the no-observed-adverse-effect-level (NOAEL) as the highest dose tested (150 mg/kg/dose). This supports a 103-fold or 123-fold safety margin, respectively, by C_{max} or AUC for the highest dose (300 mg) administered by IV infusion every 12 weeks in humans.

Genotoxicity and Carcinogenesis

As eptinezumab is unlikely to interact directly with DNA or other chromosomal material, evaluations for potential genotoxicity were considered unnecessary and not performed.

As no carcinogenicity risk has been identified by extensive evaluation of the literature related to inhibition of CGRP and as no eptinezumab-related proliferative findings were observed in long term studies in monkeys, carcinogenicity testing was considered unnecessary and not performed.

Reproductive and Developmental Toxicology

Eptinezumab administered by weekly IV at doses of 0, 75 or 150 mg/kg/dose showed no adverse effects on male or female fertility (rats), embryofetal development (rats and rabbits), postnatal survival, growth, or development during the pre- and postweaning period, including behavioral or reproductive performance (rats).

For all studies, the NOAEL was the highest dose tested (150 mg/kg) which is 35-fold higher than the highest recommended human dose, based on body weight.

6. MARKETING AUTHORISATION HOLDER

Product Registrant

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