Monoclonal Antibodies in Migraine Prevention

The Science Behind VYEPTI™ (eptinezumab-jjmr)

Indication

VYEPTI is indicated for the preventive treatment of migraine in adults.

Important Safety Information

CONTRAINDICATIONS

VYEPTI is contraindicated in patients with serious hypersensitivity to eptinezumab-jjmr or to any of the excipients. Reactions have included angioedema.

Please see additional Important Safety Information on page 9.

Introduction

This document is intended to provide a brief overview of therapeutic monoclonal antibodies (mAbs), calcitonin gene-related peptide (CGRP), and migraine pathophysiology and the role of anti-CGRP mAbs in migraine prevention. In the upcoming sections, we cover information such as antibody structure and function, and what design features are taken into consideration when engineering a therapeutic mAb. We will also discuss the science behind VYEPTI (eptinezumab-jjmr), including pharmacokinetics and the theoretical mechanism of action (MOA), and how several important features of mAbs were intentionally utilized in the design of our molecule.

Monoclonal Antibodies

Antibodies are binding molecules that are synthesized during infection for clearance and neutralization of pathogens and toxins.[1] Antibodies are produced and secreted by B lymphocytes as part of the humoral immune response and occur in blood, gastric and mucus secretions, and in breast milk.[1,2] Antibodies that are secreted from B lymphocytes can be classified as polyclonal or monoclonal, which refers to the nature of the B cell population in which it was derived.[3] Exposure to antigens usually results in the stimulation, diversification, and propagation of many genetically different B cells. Antibodies found in serum are usually polyclonal and have a wide range of affinities and specificities.[3] Advancements in biotechnology have allowed the discovery of therapeutic monoclonal antibodies, which are derived from one population of antibodies (monoclonal) and have a unique affinity and specificity.[3] The ability to obtain pure mAbs in large amounts has been enhanced by basic research, and as a result, therapeutic antibodies have now become a predominant class of treatment for various human diseases.[4] In this section, we will highlight antibody structure and function and discuss how these properties are important considerations when creating safe and effective mAb therapies.

The first monoclonal antibody approved by the Food and Drug Administration (FDA) was in 1986.[4] Since then, antibodies have become a major class of treatment. Globally, there are at least 570 therapeutic mAbs that have been studied in clinical trials and 79 therapeutic mAbs that have been approved by the FDA.[4] The first mAbs developed were fully murine and they came with many limitations, including the possibility for a host immune response (immunogenicity) and poor pharmacokinetics **(Figure 1)**.[5] These limitations hindered long-term efficacy and required repeated administrations.[5] As a result, the development of chimeric antibodies was pursued. Chimeric antibodies contain mouse sequences in the variable regions, and the remaining sequences are human **(Figure 1)**.[5-7] These antibodies reduce, but do not eliminate, the risk of immunogenicity. In contrast, humanized mAbs replace most of the mouse sequences with human sequences, except for those found within the antigen binding complementarity-determining regions (CDRs), further reducing the risk of immunogenic effects **(Figure 1)**.[5-7] Fully human and humanized mAbs carry a lower risk for inducing immune responses in humans than mouse or chimeric antibodies.[8] Immunogenicity of humanized and fully human mAbs are nearly identical, with minor exceptions.[9] The advancement of mAb technology has incentivized the production of these therapeutic agents for the treatment of many

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vyepti™
(eptinezumab-jjmr)
100 mg/mL Injection for IV

EPT-B-100236

Lundbeck

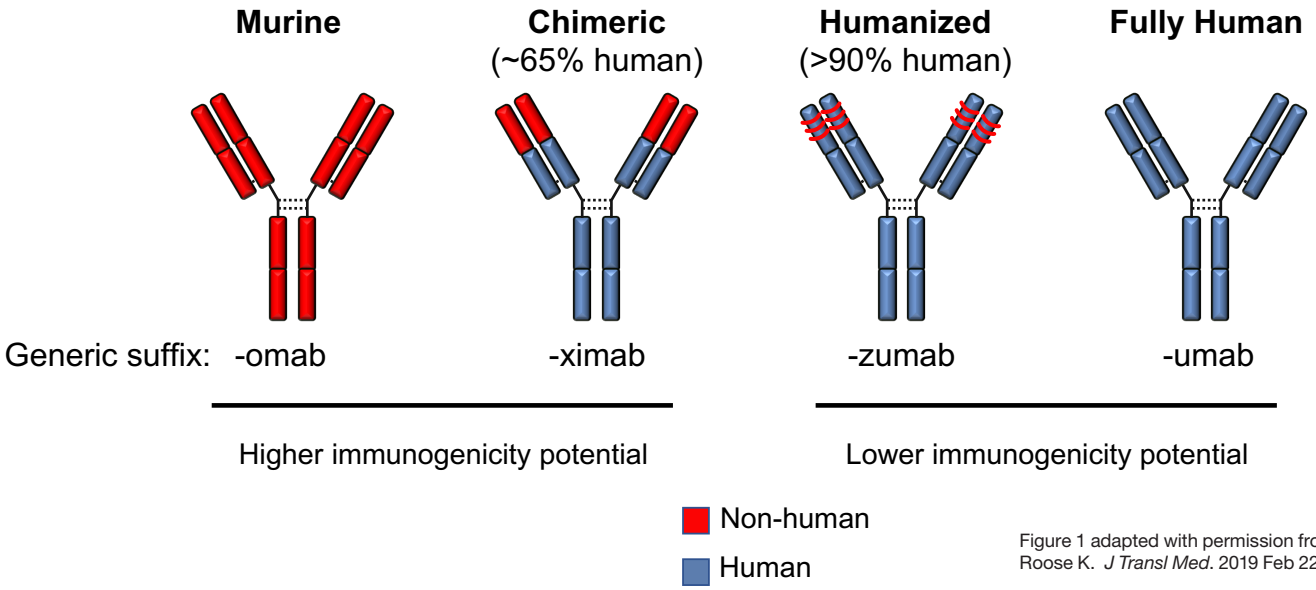


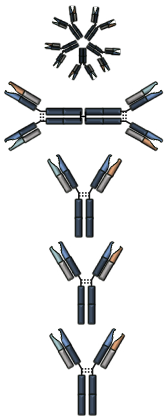
Figure 1 adapted with permission from Van Hoecke L, Roose K. *J Transl Med*. 2019 Feb 22;17(1):54.[6]

Figure 1: Humanization of mAbs and potential for immunogenicity.[5-7,9]
Murine mAbs have a higher potential for immunogenicity than those containing human fragments. Chimeric mAbs contain variable regions of murine origins, and the rest is human. Humanized mAbs only include the CDRs segments of murine origin. There is little difference in immunogenicity between human and humanized mAbs.

human diseases. In fact, mAbs are excellent treatment candidates for chronic diseases, like migraine, due to their low potential for off-target effects and long half-life.[10] Indeed, mAbs are an innovative therapeutic class for migraine.

In mammalian organisms, antibodies make up the immunoglobulin superfamily of proteins and can be divided into 5 classes (IgM, IgG, IgA, IgD, IgE) based on their physiochemical, structural, and immunologic attributes **(Figure 2)**.[1,2] IgMs are the first antibodies secreted during an immune response. They are secreted as pentamers with 10 antigen binding sites, which allow them to bind 10 antigens at a time, resulting in a fast clearance of pathogens.[1] IgA antibodies play an important role in the mucosal immune response. Their dimeric form allows them to cross epithelial barriers where they assist in immune responses within the digestive tract, nasal and bronchial mucosa, and in mammary and salivary glands.[1] IgE antibodies are

Figure 2: Antibody subclasses.[2]
Antibodies belong to 1 of 5 immunoglobulin classes.



- IgM- Attached to the surface of B cells or secreted into the blood. Responsible for early stages of immunity
- IgA- Circulates in mucus, saliva, tears, and breast milk
- IgE- Offers protection against parasitic worms. Responsible for allergic reactions
- IgD- Part of the B cell receptor. Activates basophils and mast cells
- IgG- Secreted by plasma cells in the blood. Able to cross the placenta into the fetus

Figure 2 adapted with permission from Molnar C, Gair J. Concepts of Biology: 1st Canadian Edition. Victoria, B.C.: BC campus; 2019. Retrieved from https://opentextbc.ca/biology.[2]

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

Hypersensitivity reactions: Hypersensitivity reactions, including angioedema, urticaria, facial flushing, and rash, have occurred with VYEPTI in clinical trials. Most hypersensitivity reactions occurred during infusion and were not serious, but often led to discontinuation or required treatment. Serious hypersensitivity reactions may occur. If a hypersensitivity reaction occurs, consider discontinuing VYEPTI, and institute appropriate therapy.

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involved in allergic reactions and readily bind mast cells in order to facilitate the release of histamine.[1] IgD also plays a role in allergic reaction and is known to stimulate basophils and mast cells to release antimicrobial factors during respiratory infections.[1] IgG antibodies are the most common antibodies found in circulation, making up about 80% of all antibodies.[1,2] Because they have several attributes that can be advantageous in a therapeutic setting, we will be focusing on IgG for the remainder of this review. Some of these attributes include having a high binding affinity to their target antigen and a substantially longer serum half-life (23 days) than other antibody isotypes.[1,3]

Antibodies have a molecular weight of 150 kilodaltons (kDa). These molecules are composed of 2 light and 2 heavy chains.[1] The heavy chains are partially bound to each other, making a Y formation that is flanked by 2 identical light chains.[2] Each light chain has a molecular weight of 25 kDa, and the heavy chain has a molecular weight of 50 kDa.[1] The antigen binding region is located at the top of the Y formation **(Figure 3)**. The heavy and light chains are separated into variable and constant regions, each with important effector functions.[1]

The variable region plays an important role in antigen recognition and binding. Within this variable region, there are 3 loops called the CDRs that are responsible for the specificity of the antibody-antigen interaction **(Figure 3)**.[11,12] The CDRs within the light and heavy chains come together during antigen binding to form the binding pocket.[12] In addition, the light and heavy chains are linked with a disulfide bond that is important for the stability of the variable region (Fab).[13] Interchain disulfide bonds that connect 2 heavy chains are critically important for the correct combination of heavy chains.[13] Under physiological conditions, structural integrity within an antibody is preserved by disulfide bonds.[13]

Crystallizable fragment (Fc) is the constant region that delineates the Ig isotype and binds to effector molecules.[13,14] For example, IgG binds the neonatal Fc receptor (FcRn), which allows IgG to have an increased serum half-life compared with other Ig isotypes.[14]

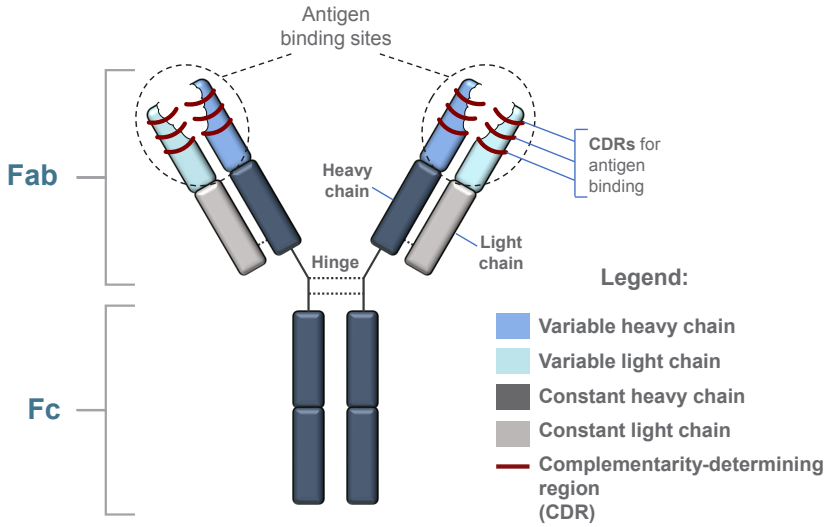

Figure 3: Antibody structure.[11,13]
Antibodies typically contain 2 identical heavy chains and 2 identical light chains. They are further characterized by antigen binding fragments (Fab) that are connected by a flexible region (hinge) to a constant region called the crystallizable fragment (Fc).

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ADVERSE REACTIONS

The most common adverse reactions (≥2% and at least 2% or greater than placebo) in the clinical trials for the preventive treatment of migraine were nasopharyngitis and hypersensitivity.

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FcRn is vital for the transfer of passive humoral immunity from mother to fetus.[14] However, FcRn is more widespread than initially suspected and continues to be expressed long after the neonatal period.[15] One postneonatal function for FcRn is to protect IgG from degradation, thereby increasing its half-life in serum **(Figure 4)**.[14,15] Experiments conducted in rats and humans identified that FcRn preferentially binds IgG under acidic conditions.[15] Animals deficient in the gene that encodes the FcRn receptor were unable to acquire IgG from maternal milk and had a low level of circulating IgG, demonstrating that these receptors are responsible for IgG protection.[15] FcRn is expressed by endothelial cells and circulating monocytes.[14,15] These cell types internalize serum IgG within an acidic endosomal compartment where IgG interacts with FcRn **(Figure 4)**. FcRn-bound IgG is recycled and released back into circulation, which enables an extended serum half-life. Any serum protein not bound to FcRn is not recycled and is destined for lysosomal degradation.[14] Engineering therapeutic antibodies to have an IgG backbone enables an extended serum half-life, which may have positive implications on their efficacy.[14,15]

CGRP and Migraine Pathophysiology

CGRP is a 37 amino acid neuropeptide first described in 1982.[16] The peptide is released from motor neurons at the neuromuscular junction and sensory neurons of the spinal cord.[16] In humans, CGRP has 2 isoforms, α-CGRP and β-CGRP, which only differ by 1 amino acid.[16] β-CGRP is mainly present in the enteric nervous system while α-CGRP is primarily found in sensory neurons.[16] CGRP plays an important role in maintaining the mucosal integrity of the gastrointestinal (GI) tract.[17] Indeed, the GI tract is highly innervated by β-CGRPergic fibers from the enteric nervous system, and blocking CGRP in the GI tract may contribute to inflammatory bowel disease.[16,17] GI motility is also modulated by CGRP, and inhibiting CGRP in the GI tract results in decreased motility and contraction, which can lead to constipation.[16,17] In addition to the GI tract, CGRP is also expressed in the heart, blood vessels, pituitary gland, thyroid, and lung, and is involved in many biologic functions, such as neuromodulation, vasodilation, cardiac contractility, bone growth, and mammalian development.[16] CGRP and its receptors are also expressed in both the peripheral and central nervous system (CNS), including the trigeminovascular pathways.[17]

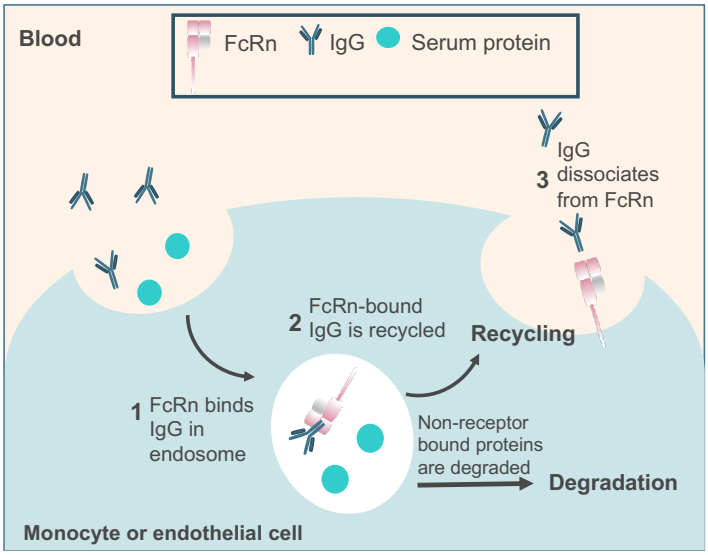

Figure 4: FcRn mediated IgG recycling.[14]
Neonatal Fc receptor is expressed by endothelial cells and circulating monocytes. Monocytes and endothelial cells internalize serum IgG, which then binds to FcRn in an endosomal compartment. FcRn recycles IgG back into circulation while non-receptor bound proteins are degraded.

Important Safety Information (cont'd)

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The release of CGRP from the trigeminal nerves is now thought to play a major role in migraine pathophysiology.[18] During all forms of vascular headaches, such as migraine (with or without aura) and cluster headaches, serum levels of CGRP are elevated.[18] Clinical studies have demonstrated that triptans return CGRP levels back to baseline and alleviate headache pain during an attack.[18] Further support for a role of CGRP in migraine pathogenesis was demonstrated by Lassen et al.[19] They showed that the infusion of CGRP induced headaches and migraine in susceptible individuals.[19]

CGRP is a potent vasodilator of the peripheral and cerebral blood vessels.[18] It is implicated in neurogenic inflammation and migraine pain.[18] It is believed that the major sites where anti-CGRP therapies play a role are those located outside of the blood brain barrier (BBB).[20] Anti-CGRP antibodies are very large molecules and are unable to pass the BBB. Therefore, anti-CGRP antibodies are excluded from accessing major sites of action within the CNS.[20] Instead, these therapies can potentially target areas outside of the BBB, including intracranial and extracranial blood vessels, dural mast cells, and peripheral parts of the trigeminal system.[20]

Interestingly, experiments with Evans blue revealed that the trigeminal ganglion is not protected by the BBB.[21] This suggests that the trigeminal ganglion is not protected by the BBB and can be reached by CGRP antagonists regardless of the molecule's ability to cross the BBB.[21] Other work demonstrated that CGRP was found on >50% of trigeminal neurons, and there is also wide distribution of CGRP receptors throughout the trigeminovascular system. Altogether, this supports a role for CGRP in migraine pathophysiology.[20]

It has been hypothesized that the pain sensitivity comes from nociceptive sensory fibers from the trigeminal nerve that innervate the meningeal blood vessels within the skull **(Figure 5)**.[22] As previously discussed, CGRP is released during migraine from trigeminal nerve fibers and ultimately results in vasodilation and neurogenic inflammation.[22] Migraine patients have increased CGRP levels both peripherally and centrally during a migraine attack.[22] Interestingly, CGRP levels were also shown to increase during the premonitory phase of migraine and continue to be elevated through the mild and moderate headache phase of the attack.[23] Experiments conducted using a triptan demonstrated that CGRP levels were not elevated during the premonitory phase of migraine

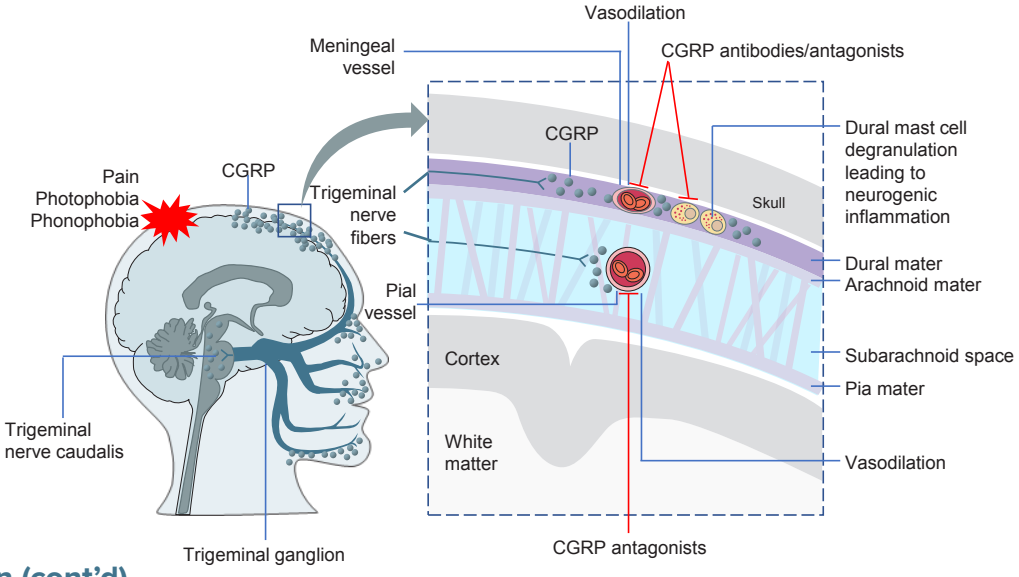

Figure 5:
CGRP role in migraine pathophysiology.[22]
CGRP is released from the trigeminal nerve fibers during a migraine and causes vasodilation and neurogenic inflammation.

Figure 5 adapted with permission from Russell FA, et al. *Physiol Rev.* 2014;94(4):1099-1142.[22]

Important Safety Information (cont'd)

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in subjects who did not respond to treatment.[23] This suggests that only attacks associated with elevated CGRP levels in saliva responded to a triptan therapy administered during moderate headache.[23] In this same study, the number of premonitory symptoms experienced by responders to triptans was less than those who did not respond to treatment.[23] These results support the hypothesis that a central, rather than a peripheral, mechanism is involved in the evolution of some migraine attacks.

Currently, there are 2 mechanisms by which migraine is hypothesized to be initiated. The first mechanism is explained in Figure 5 above, which involves trigeminal activation that leads to peripheral sensitization of the trigeminal afferents.[22,24] The second mechanism of migraine is centrally mediated and maintained. These attacks are believed to occur without significant peripheral nociceptive input and without excitatory activation of the peripheral nociceptive system.[25,26] Taking these 2 migraine pathophysiology models into consideration, if a migraine attack is propagated centrally, there may not be peripheral release of CGRP. This could explain why some migraine attacks may or may not be associated with CGRP release in the periphery.

Anti-CGRP antibodies are thought to remove the excessive CGRP that is released at the trigeminal sensory nerve fibers while anti-CGRP receptor antibodies block the receptor from signaling.[27] The goal of these therapies is to prevent nociceptive transmission, thereby decreasing headache frequency over time and improving migraine symptoms.[27,28] Indeed, mAbs have unique target specificity, avoiding off-target toxicities common to small molecules.[27] As outlined above, many mAbs have long terminal half-lives, and this pharmacokinetic profile results in less frequent dosing and mitigates the need for frequent oral dosing.[27] Although it is not completely understood how anti-CGRP mAbs exert their function, it is important to think about how the efficacy of anti-CGRP mAbs may be contingent upon the migraine attack being a result of activation of the peripheral nociceptive system which is outside of the BBB.[20,28]

It is worth noting that CGRP is not alone in its ability to trigger a migraine attack; other exogenous migraine triggers, such as nitroglycerin, pituitary adenylyl cyclase activating peptide, umbellulone (headache tree), ethanol, and others have also been demonstrated to induce migraine attacks.[29,30] Future studies are needed to characterize the roles of each of these and their potential interplay with CGRP in migraine pathophysiology.

Eptinezumab-jjmr Design Elements, Pharmacokinetics, and Mechanism of Action

Eptinezumab-jjmr was selected from several nonclinical monoclonal antibody candidates from rabbits that were immunized with CGRP. The clinical candidates were then further selected based on key factors, such as in vivo activity, adequate PK, and adequate drug stability **(Figure 6)**. Following the selection, the monoclonal antibody was humanized by grafting amino acids of rabbit origins onto human genes. It is important to point out that although a small number of rabbit amino acids are ultimately included in the monoclonal antibody, the rabbit structure and sequence usage are highly "human-like".[31]

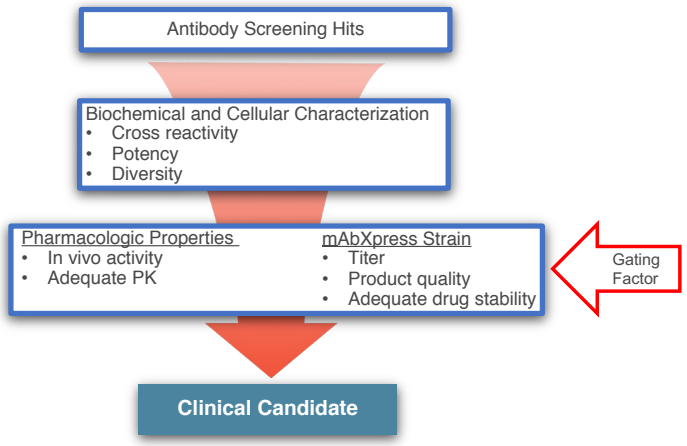

Figure 6: Pathway to eptinezumab-jjmr clinical candidate choice.[31] Nonclinical candidates were selected from rabbits immunized with CGRP. Candidates were further selected based off key gating factors.

Important Safety Information (cont'd)

ADVERSE REACTIONS

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Eptinezumab-jjmr was engineered on an IgG1 scaffold, designed for enhanced safety, increased bioavailability, and simplified manufacturing.[31] IgG1 antibodies are often used as backbone for Fc engineering strategies that aim to improve effector functions, stability, or pharmacokinetic properties of therapeutic antibodies.[32] IgG1 antibodies interact well with FcRn, protecting it from degradation and thereby extending its serum half-life.[14,15,32] IgG1 antibodies also have excellent biotechnologic characteristics, such as high production rates in transfectoma cells, easy and cost-effective purification, and the development of specific storage formulations for increased stability.[32] In order to help reduce immunogenicity, the structure of the antibody lacks N-linked carbohydrate crucial to FcR binding.[31] The interaction between Fc and its receptor is a glycan-glycan interaction that is significantly impacted by Fc-glycosylation. mAbs, which lack glycosylated Fc regions, tend to lose their effector functions.[33] Therefore, glycoengineering of mAbs can enhance therapeutic efficacy and safety.[33] Eptinezumab-jjmr is highly selective for CGRP and has minimal disassociation from the target.[31] In addition, it has a high binding affinity (Kd=4 pM) for soluble α-CGRP ligand.[31,34]

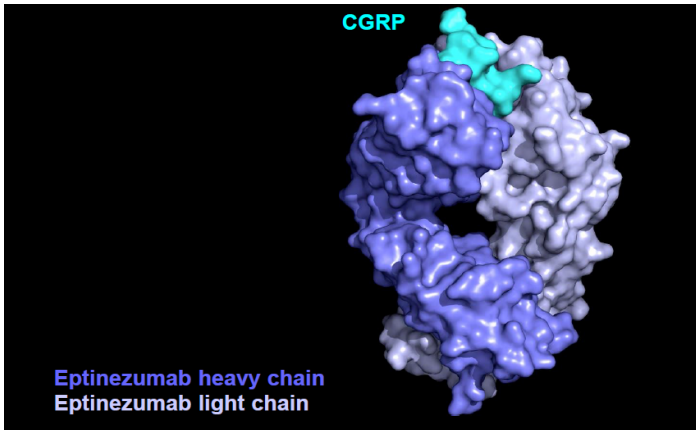

Figure 7: Overview of the eptinezumab-jjmr Fab: CGRP molecular structure shown in a space filling.[34]

Eptinezumab-jjmr binds to the C-terminal end of α-CGRP peptide with significant contributions from both heavy and light chain CDRs **(Figure 7)**.[34]

All 6 CDRs of eptinezumab-jjmr (H1, H2, H3, L1, L2, L3) make extensive contact with CGRP.[34] Eptinezumab-jjmr displays secondary structure elements, including an alpha helical turn and a network of hydrogen bonds.[34] The binding pocket interaction between eptinezumab-jjmr and CGRP consists of 5 hydrogen bonds and 25 hydrophobic interactions, most of which are between CGRP and the CDRs.[34] Eleven of the 12 CGRP amino acids visible in the crystal structure are in contact with the eptinezumab-jjmr Fab region **(Figure 8)**.

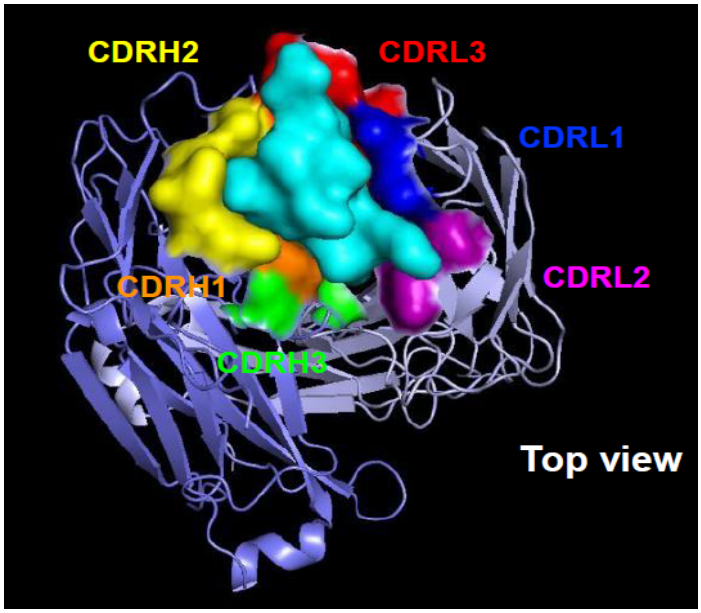

Figure 8: All 6 CDR loops in the eptinezumab-jjmr Fab region bind to CGRP.[34]

Understanding the eptinezumab: CGRP complex expands the understanding of how the mechanism of action of eptinezumab-jjmr works to sequester CGRP and prevent downstream biologic activity.

Important Safety Information (cont'd)

CONTRAINDICATIONS

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We can see that eptinezumab-jjmr was designed for optimal ligand binding. Eptinezumab-jjmr was also designed for increased bioavailability, rapid achievement of maximum serum concentration (C_{max}), and sustained inactivation of CGRP.[31,35] Indeed, population pharmacokinetics and an exposure response analysis demonstrated that eptinezumab-jjmr exhibits linear pharmacokinetics, achieving a C_{max} in approximately 30 minutes, coinciding with the end of IV administration.[35] Pharmacokinetic analyses of eptinezumab-jjmr support a dosing schedule of every 12 weeks, with no adjustment for patient characteristics. Duration of effect was demonstrated for both 100 mg and 300 mg doses.[35]

We conducted a study examining the pharmacokinetics of eptinezumab-jjmr during IV administration vs subcutaneous administration and found that the maximum mean concentration in plasma for IV administration was 36.0 ug/mL and was observed immediately on completion of the infusion.[36]

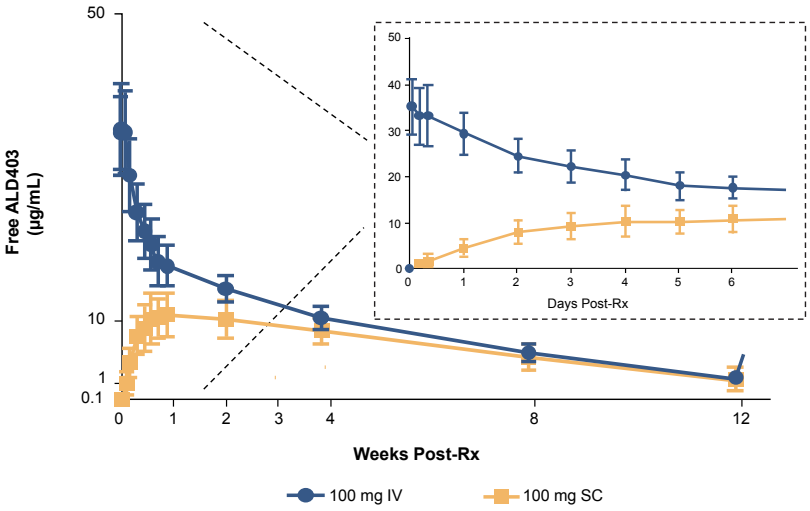

Figure 9: Mean free eptinezumab-jjmr concentration.[36]
IV administration resulted in immediate maximum plasma (36.0 ug/mL). Subcutaneous administration of eptinezumab-jjmr reached maximum concentration 6 days after administration (11 ug/mL).

Subcutaneous administration had an initial absorption phase that increased to a max concentration within approximately 6 days **(Figure 9)**. The mean maximal concentration achieved following the first subcutaneous administration was 11 ug/mL, and absolute bioavailability for subcutaneous administration was 73%.[36]

Summary

To summarize, CGRP is an extensively studied neuropeptide that has been implicated in the pathophysiology of migraine. The role of CGRP in migraine pain was supported by increased plasma levels of CGRP associated with painful migraine symptoms.[18] Additional evidence in support of CGRP's role in migraine arose when experiments demonstrated that infusion of CGRP could induce migraine attacks in susceptible individuals.[19] Identifying CGRP's role in migraine pathophysiology resulted in the development of anti-CGRP mAb therapies that offered a potential treatment for migraine. Eptinezumab-jjmr is an anti-CGRP mAb administered intravenously that results in 100% bioavailability at the end of the ~30-minute infusion. Eptinezumab-jjmr binds to CGRP ligand with high affinity, resulting in a potent and sustained inactivation of CGRP.[31,34]

The relationship between the pharmacodynamic activity and the mechanism(s) by which eptinezumab-jjmr exerts its clinical effects is unknown. However, our molecule has demonstrated a significant reduction in monthly migraine days in 2 phase 3 clinical trials and aims to elevate expectations with positive 75% and 100% responder rate results.[34] Eptinezumab-jjmr was intentionally designed to offer patients a fast, powerful, and sustained migraine treatment.

Important Safety Information (cont'd)

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Indication for VYEPTI (eptinezumab-jjmr) 100 mg/mL Injection

VYEPTI is indicated for the preventive treatment of migraine in adults.

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For more information, please see the Prescribing Information and Patient Information; or go to VYEPTIhcp.com.

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Please see Important Safety Information on page 9.
For more information, please see accompanying full Prescribing Information at the end of this document.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYEPTI safely and effectively. See full prescribing information for VYEPTI.

VYEPTI™ (eptinezumab-jjmr) injection, for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
VYEPTI is a calcitonin gene-related peptide antagonist indicated for the preventive treatment of migraine in adults (1)

----------DOSAGE AND ADMINISTRATION----------
- Must dilute before use. For intravenous infusion only (2.1, 2.2)
- Recommended dosage is 100 mg as an intravenous infusion over approximately 30 minutes every 3 months. Some patients may benefit from a dosage of 300 mg (2.1, 2.3)
- Dilute only in 100 mL of 0.9% Sodium Chloride Injection, USP (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 100 mg/mL solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------
VYEPTI is contraindicated in patients with serious hypersensitivity to eptinezumab-jjmr or to any of the excipients (4)

----------WARNINGS AND PRECAUTIONS----------
Hypersensitivity Reactions: Reactions have included angioedema, urticaria, facial flushing, and rash. If a hypersensitivity reaction occurs, consider discontinuing VYEPTI and initiate appropriate therapy (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥2% and 2% or greater than placebo) were nasopharyngitis and hypersensitivity (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck at 1-800-455-1141 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VYEPTI is indicated for the preventive treatment of migraine in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dosage is 100 mg administered by intravenous infusion every 3 months. Some patients may benefit from a dosage of 300 mg administered by intravenous infusion every 3 months.

2.2 Dilution Instructions

VYEPTI requires dilution prior to administration. Dilute only in 100 mL 0.9% Sodium Chloride Injection, USP. The infusion bags must be made of polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO). Use appropriate aseptic technique when preparing VYEPTI solution for intravenous infusion. VYEPTI single-dose vials contain no preservative; discard unused portion remaining in the vial.

Dilution

100 mg dose:

To prepare the solution, withdraw 1 mL of VYEPTI from a single-dose vial using a sterile needle and syringe. Inject the 1 mL content into a 100 mL bag of 0.9% Sodium Chloride Injection, USP.

300 mg dose:

To prepare the solution, withdraw 1 mL of VYEPTI from each of 3 single-dose vials using a sterile needle and syringe. Inject the resulting 3 mL content into a 100 mL bag of 0.9% Sodium Chloride Injection, USP.

Storage and Handling of Diluted Product

Gently invert the VYEPTI solution to mix completely. Do not shake. Following dilution, VYEPTI solution must be infused within 8 hours. During this time, VYEPTI solution should be stored at room temperature, 20°C to 25°C (68°F to 77°F). Do not freeze.

2.3 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 *[see Dosage Forms and Strengths (3)]*.

No other medications should be administered through the infusion set or mixed with VYEPTI. VYEPTI is for intravenous infusion only; infuse over approximately 30 minutes. Do not administer VYEPTI as an intravenous push or bolus injection. Use an intravenous infusion set with a 0.2 micron or 0.22 micron in-line or add-on sterile filter. After the infusion is complete, flush the line with 20 mL of 0.9% Sodium Chloride Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

VYEPTI is a clear to slightly opalescent, colorless to brownish-yellow solution available as follows:

- Injection: 100 mg/mL in a single-dose vial

4 CONTRAINDICATIONS

VYEPTI is contraindicated in patients with serious hypersensitivity to eptinezumab-jjmr or to any of the excipients in VYEPTI. Reactions have included angioedema *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema, urticaria, facial flushing, and rash, have occurred with VYEPTI in clinical trials. Most hypersensitivity reactions occurred during infusion and were not serious, but often led to discontinuation or required treatment. Serious hypersensitivity reactions may occur. If a hypersensitivity reaction occurs, consider discontinuing VYEPTI, and institute appropriate therapy *[see Contraindications (4) and Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of VYEPTI was evaluated in 2076 patients with migraine who received at least one dose of VYEPTI, representing 1615 patient-years of exposure; of these, 1524 patients were exposed to 100 mg or 300 mg. Across all doses, 1872 patients were exposed for at least 6 months and 991 patients were exposed for 12 months. In the placebo-controlled clinical studies (Study 1 and Study 2) of 1372 patients, 579 patients received at least one dose of VYEPTI 100 mg, 574 patients received at least one dose of VYEPTI 300 mg, and 588 patients received placebo *[see Clinical Studies (14)]*. Approximately 86% were female, 89% were white, and the mean age was 40.4 years at study entry.

The most common (incidence at least 2% and at least 2% greater than placebo) adverse reactions in the clinical trials for the preventive treatment of migraine were nasopharyngitis and hypersensitivity.

Table 1 summarizes the adverse reactions that occurred during Study 1 and Study 2.

Table 1. Adverse Reactions Occurring with an Incidence of at Least 2% for VYEPTI and at Least 2% Greater than Placebo in Studies 1 and 2

Adverse Reactions	VYEPTI 100 mg N=579 %	VYEPTI 300 mg 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.

In Study 1 and Study 2, 1.9% of patients treated with VYEPTI discontinued treatment because of adverse reactions *[see Warnings and Precautions (5.1)]*.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to eptinezumab-jjmr in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In patients receiving VYEPTI 100 mg or 300 mg every 3 months, the incidence of anti-eptinezumab-jjmr antibody development in Study 1 (up to 56 weeks) was 20.6% (92/447), and 41.3% (38/92) of those patients developed anti-eptinezumab-jjmr neutralizing antibodies. In Study 2 (up to 32 weeks), the incidence of anti-eptinezumab-jjmr antibody development was 18.3% (129/706), and 34.9% (45/129) of those patients developed anti-eptinezumab-jjmr neutralizing antibodies. In an open-label study with 84 weeks of treatment, 18% (23/128) of patients developed anti-eptinezumab-jjmr antibodies, and 39% (9/23) of those patients developed anti-eptinezumab-jjmr neutralizing antibodies.

Although the results from both studies showed no clear evidence of an impact from development of anti-eptinezumab-jjmr antibodies, including neutralizing antibodies, on the safety and efficacy profiles of VYEPTI, the available data are too limited to make definitive conclusions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on developmental risks associated with the use of VYEPTI in pregnant women.

No adverse developmental effects were observed following administration of eptinezumab-jjmr to pregnant animals at doses greater than those used clinically *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The estimated rate of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Animal Data

When eptinezumab-jjmr (0, 75, or 150 mg/kg) was administered weekly to female rats and rabbits by intravenous injection throughout organogenesis, no adverse effects on embryofetal development were observed. The higher dose tested (150 mg/kg) is 30 times the maximum recommended human dose (MRHD) of 300 mg, on a body weight basis (mg/kg).

When eptinezumab-jjmr (0, 75, or 150 mg/kg) was administered weekly to female rats throughout pregnancy and lactation, no adverse effects on pre- and postnatal development were observed. The higher dose tested (150 mg/kg) is 30 times the MRHD, on a mg/kg basis.

8.2 Lactation

Risk Summary

There are no data on the presence of eptinezumab-jjmr in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYEPTI and any potential adverse effects on the breastfed infant from VYEPTI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of VYEPTI did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

Eptinezumab-jjmr is a humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand. Eptinezumab-jjmr has an approximate molecular weight of 143 kD. Eptinezumab-jjmr is produced in *Pichia pastoris* yeast cells by recombinant DNA technology.

VYEPTI (eptinezumab-jjmr) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to brownish-yellow solution, for intravenous infusion. VYEPTI is supplied as a 100 mg/mL single-dose vial. Each mL contains 100 mg eptinezumab-jjmr formulated in L-histidine (1 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 80 (0.15 mg), sorbitol (40.5 mg), and Water for Injection, USP, at a pH of 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eptinezumab-jjmr is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor.

12.2 Pharmacodynamics

The relationship between the pharmacodynamic activity and the mechanism(s) by which eptinezumab-jjmr exerts its clinical effects is unknown.

12.3 Pharmacokinetics

Eptinezumab-jjmr exhibits linear pharmacokinetics and exposure increases proportionally with doses from 100 mg to 300 mg after intravenous administration. Steady-state plasma concentration is attained after the first dose with a once every 3-month dosing schedule.

Distribution

The central volume of distribution (Vc) for eptinezumab-jjmr is approximately 3.7 liters.

Metabolism & Elimination

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

The apparent clearance of eptinezumab-jjmr was 0.006 L/h, and the terminal elimination half-life was approximately 27 days.

Specific Populations

A population pharmacokinetic analysis assessing the effects of age, race, sex, and body weight did not suggest any clinically significant impact of these covariates on eptinezumab exposures.

Patients with Renal or Hepatic Impairment

No dedicated studies were conducted to assess the effects of renal or hepatic impairment on the pharmacokinetics of eptinezumab-jjmr. However, hepatic or renal impairment is not expected to affect the pharmacokinetics of eptinezumab-jjmr. A population pharmacokinetic analysis of integrated data from eptinezumab-jjmr clinical studies did not reveal clinically significant impact on pharmacokinetics of patients with hepatic or renal impairment.

Drug Interaction Studies

P450 Enzymes

Eptinezumab-jjmr is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Sumatriptan

The co-administration of a single dose of 300 mg eptinezumab-jjmr 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 significantly influence the pharmacokinetics of eptinezumab-jjmr or sumatriptan.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of eptinezumab-jjmr has not been assessed.

Mutagenesis

Genetic toxicology studies of eptinezumab-jjmr have not been conducted.

Impairment of Fertility

When eptinezumab-jjmr (0, 75, or 150 mg/kg) was administered weekly by intravenous injection to male and female rats prior to and during mating and continuing in females to gestation day 3-4, no adverse effects on fertility were observed. The higher dose tested (150 mg/kg) is 30 times the maximum recommended human dose of 300 mg, on a body weight basis (mg/kg).

14 CLINICAL STUDIES

The efficacy of VYEPTI was evaluated as a preventive treatment of episodic and chronic migraine in two randomized, multicenter, placebo-controlled studies, both with 6-month double-blind periods: one study in patients with episodic migraine (Study 1) and one study in patients with chronic migraine (Study 2). VYEPTI was administered by intravenous infusion every 3 months in both studies; however, the primary endpoint was measured at 12 weeks.

Study 1: Episodic Migraine

Study 1 (NCT02559895) included adults with a history of episodic migraine (4 to 14 headache days per month, of which at least 4 were migraine days). A total of 665 patients were randomized to receive placebo (N=222), 100 mg VYEPTI (N=221), or 300 mg VYEPTI (N=222) every 3 months for 12 months. Patients were allowed to use concurrent acute migraine or headache medications, including migraine-specific medications (i.e., triptans, ergotamine derivatives), during the trial.

The study excluded patients with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days over Months 1-3. Secondary endpoints included the percentages of patients with 50% or greater, and 75% or greater reductions from baseline in monthly migraine days over Months 1-3.

Patients had a median age of 39 years (range: 18 to 71 years), 84% were female, and 84% were white. The mean migraine frequency at baseline was approximately 8.6 migraine days per month and was similar across treatment groups.

VYEPTI treatment demonstrated statistically significant improvements compared to placebo for the primary efficacy endpoint, as shown in Table 2; secondary endpoints are also summarized in Table 2.

Table 2. Efficacy Endpoint Results in Study 1

	VYEPTI 100 mg N=221	**VYEPTI 300 mg N=222**	**Placebo N=222**
Monthly Migraine Days (MMD) – Months 1-3			
Change from baseline	-3.9	-4.3	-3.2
Difference from placebo	-0.7	-1.1	
p-value	0.018	<0.001	
≥50% MMD responders – Months 1-3			
% Responders	49.8%	56.3%	37.4%
Difference from placebo	12.4%	18.9%	
p-value	0.009*	<0.001	
≥75% MMD responders – Months 1-3			
% Responders	22.2%	29.7%	16.2%
Difference from placebo	6.0%	13.5%	
p-value	NS**	<0.001	

* Nominal statistical significance
** NS = Not statistically significant

Figure 1 shows the mean change from baseline in average monthly migraine days in Study 1. Patients treated with VYEPTI at both doses had greater mean decreases from baseline in mean monthly migraine days over Months 1-3 compared to placebo-treated patients.

Figure 1. Change from Baseline in Monthly Migraine Days in Study 1

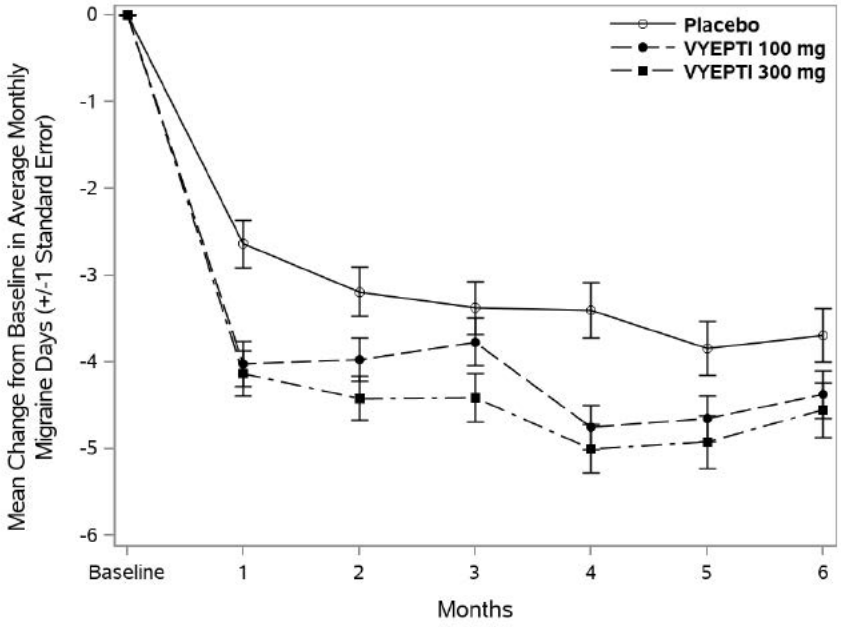


Figure 2 shows the distribution of change from baseline in mean monthly migraine days through Month 3 by treatment group in 2-day increments.

Figure 2. Distribution of Change from Baseline in Mean Monthly Migraine Days over Months 1 to 3 by Treatment Group in Study 1

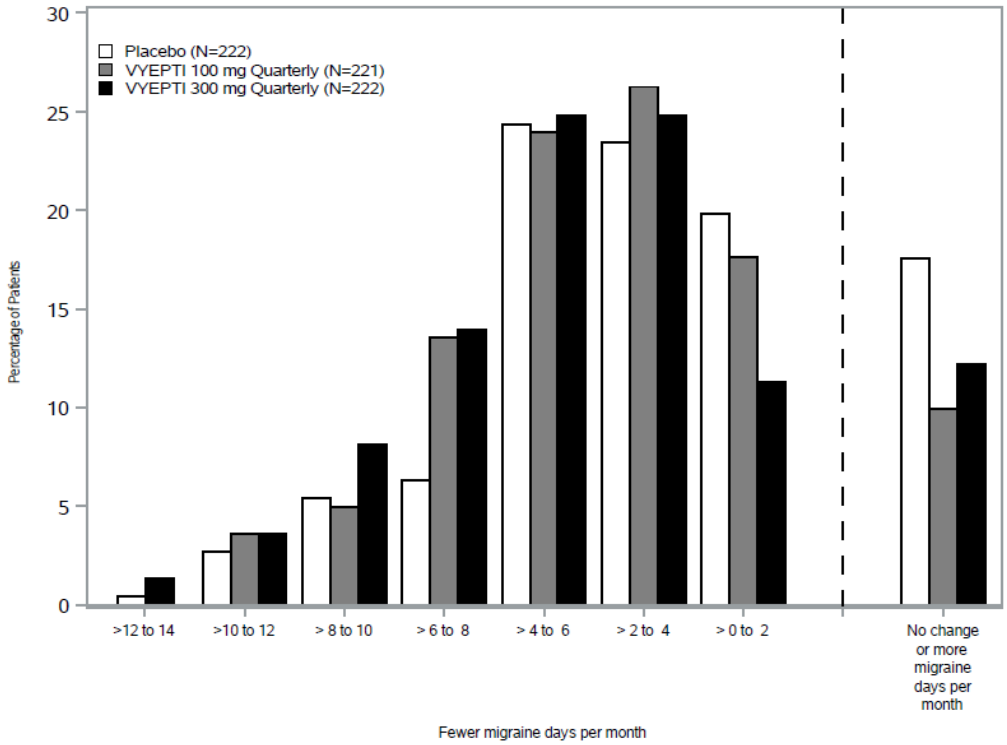
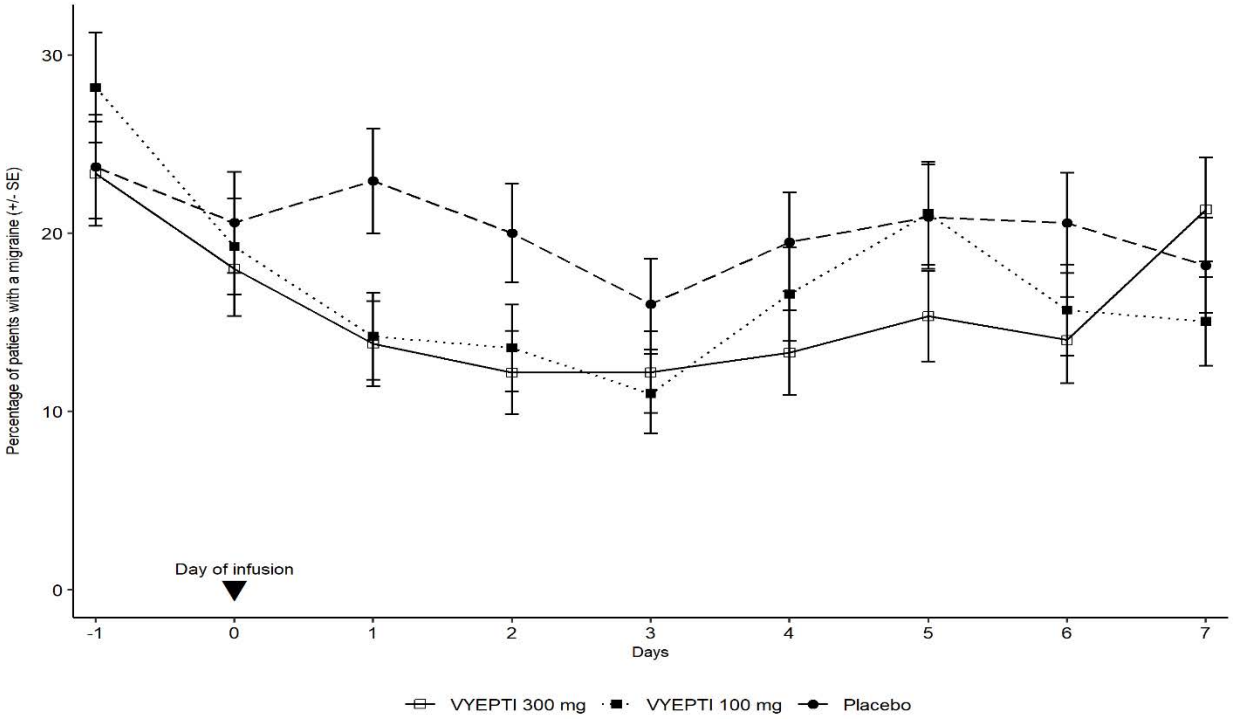


Figure 3 demonstrates that greater percentages of placebo-treated patients had migraines on most days during the first 7 days of treatment compared to VYEPTI-treated patients in Study 1.

Figure 3. Percentage of Patients with a Migraine from Day -1 (Day Prior to Infusion) to Day 7 in Study 1



Study 2: Chronic Migraine

Study 2 (NCT02974153) included adults with a history of chronic migraine (15 to 26 headache days per month, of which at least 8 were migraine days). A total of 1072 patients were randomized and received placebo (N=366), 100 mg VYEPTI (N=356), or 300 mg VYEPTI (N=350) every 3 months for 6 months. Patients were allowed to use and to continue an established stable regimen of acute migraine or headache preventive medication (except onabotulinumtoxinA). Patients with a dual diagnosis of chronic migraine and medication overuse headache attributable to acute medication overuse (triptans, ergotamine, or combination analgesics greater than 10 days per month) were included in the study population. Patients using opioids or butalbital-containing products greater than 4 days per month were not allowed.

The study excluded patients with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days over Months 1-3. Secondary endpoints included the percentages of patients with 50% or greater and 75% or greater reductions from baseline in monthly migraine days over Months 1-3.

Patients had a median age of 41 years (range: 18 to 65 years), 88% were female, and 91% were white. Forty-one percent of patients were taking concomitant preventive medication for migraine. The mean migraine frequency at baseline was approximately 16.1 migraine days per month and was similar across treatment groups.

VYEPTI treatment demonstrated statistically significant improvements compared to placebo for the primary efficacy endpoint, as shown in Table 3; secondary endpoints are also summarized in Table 3.

Table 3. Efficacy Endpoint Results in Study 2

	VYEPTI 100 mg N=356	VYEPTI 300 mg N=350	Placebo N=366
Monthly Migraine Days (MMD) – Months 1-3			
Change from baseline	-7.7	-8.2	-5.6
Difference from placebo	-2.0	-2.6	
p-value	<0.001	<0.001	
≥50% MMD responders – Months 1-3			
% Responders	57.6%	61.4%	39.3%
Difference from placebo	18.2%	22.1%	
p-value	<0.001	<0.001	
≥75% MMD responders – Months 1-3			
% Responders	26.7%	33.1%	15.0%
Difference from placebo	11.7%	18.1%	
p-value	<0.001	<0.001	

Figure 4 shows the mean change from baseline in average monthly migraine days for Study 2. Patients treated with VYEPTI at both doses had greater mean decreases from baseline in mean monthly migraine days over Month 1-3 compared to placebo-treated patients.

Figure 4. Change from Baseline in Monthly Migraine Days in Study 2

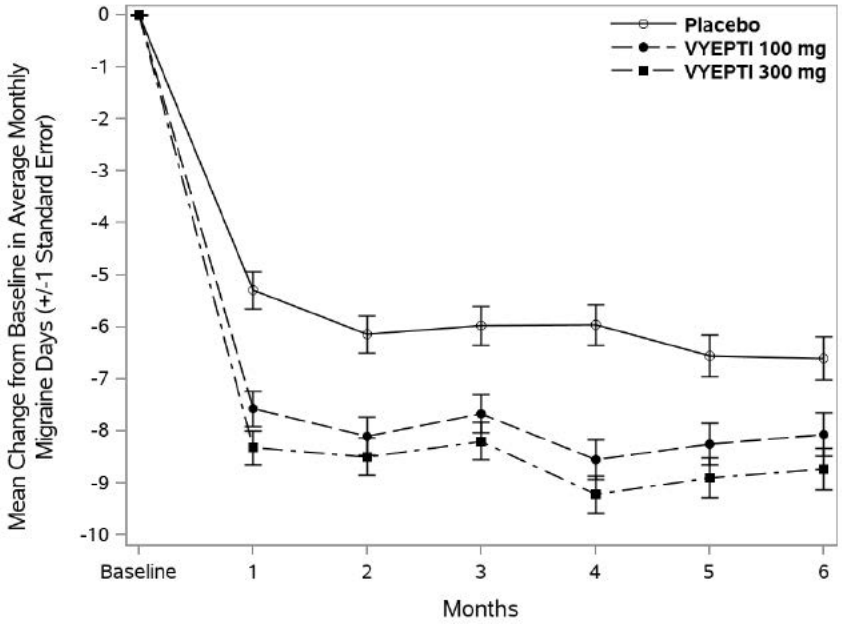


Figure 5 shows the distribution of change from baseline in mean monthly migraine days through Month 3 by treatment group in 3-day increments.

Figure 5. Distribution of Change from Baseline in Mean Monthly Migraine Days over Months 1-3 by Treatment Group in Study 2

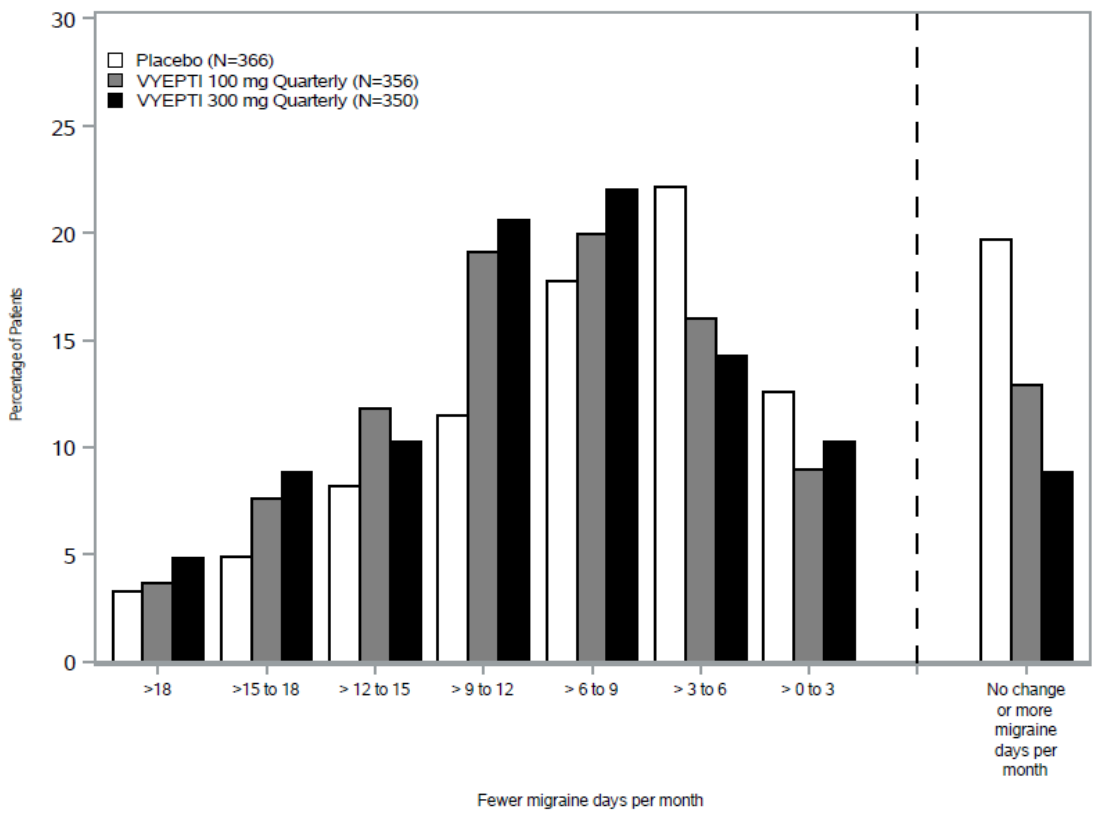
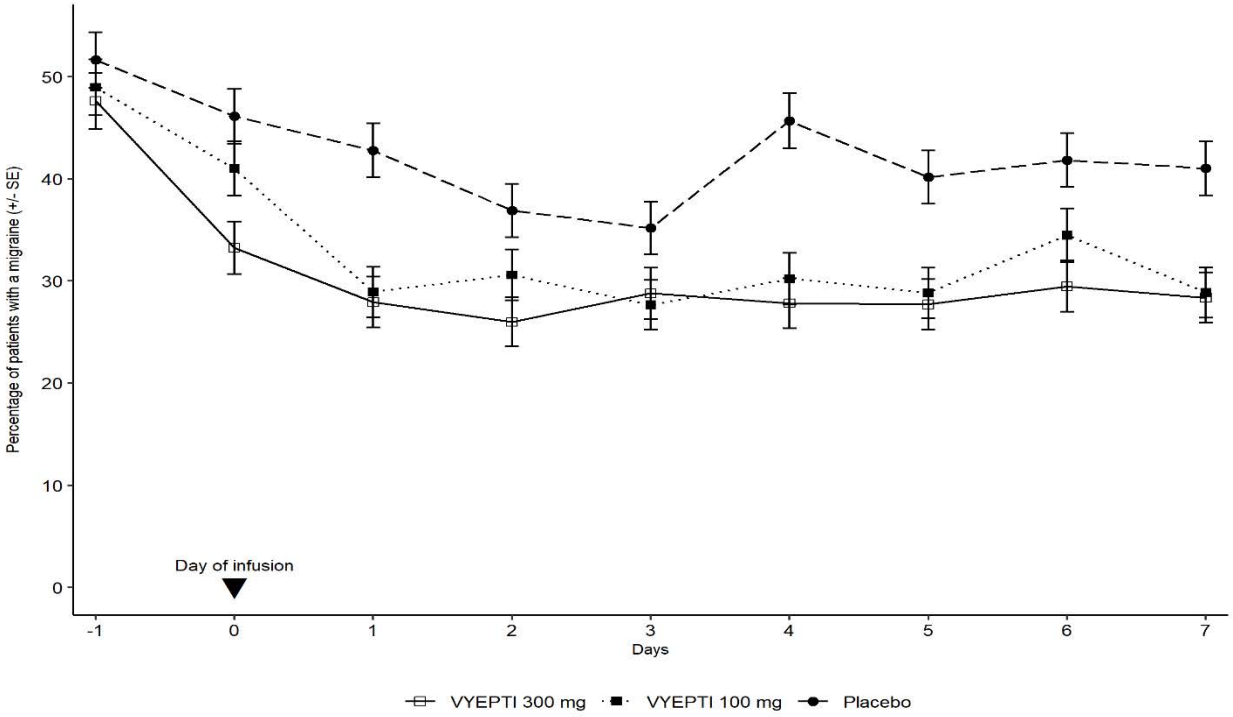


Figure 6 demonstrates that greater percentages of placebo-treated patients had migraines on individual days during the first 7 days of treatment compared to VYEPTI-treated patients in Study 2.

Figure 6. Percentage of Patients with a Migraine from Day -1 (Day Prior to Infusion) to Day 7 in Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VYEPTI (eptinezumab-jjmr) injection is a clear to slightly opalescent, colorless to brownish-yellow solution supplied as:

Carton containing one 100 mg/mL single-dose vial - NDC 67386-130-51.

16.2 Storage and Handling

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze or shake.

The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including angioedema, urticaria, facial flushing, and rash, can occur. Advise patients to contact their healthcare provider immediately if signs or symptoms of hypersensitivity reactions occur *[see Warnings and Precautions (5.1)]*.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Inform patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed *[see Use in Specific Populations (8.2)]*.

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