11 November 2021
EMA/9446/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vyepti

International non-proprietary name: eptinezumab

Procedure No. EMEA/H/C/005287/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Administrative information

Name of the medicinal product:	Vyepti
Applicant:	H. Lundbeck A/S Ottiliavej 9 2500 Valby DENMARK
Active substance:	Eptinezumab
International Non-proprietary Name/Common Name:	Eptinezumab
Pharmaco-therapeutic group (ATC Code):	antimigraine preparations, calcitonin gene-related peptide (cgrp) antagonists (N02CD)
Therapeutic indication(s):	VYEPTI is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month
Pharmaceutical form:	Concentrate for solution for infusion
Strength:	100 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

ADA	Anti-drug antibody
AESI	Adverse event of special interest
AUC	Area under the curve
CCS	Container closure system
CDR	Complementary determining region
CI	Confidence interval
α-CGRP	α-Calcitonin Gene-related Peptide
CL	Clearance
CLcr	Creatinine clearance
CM	Chronic migraine
Cavg	Average plasma concentration
Cmax	Maximum plasma concentration
Ctrough	Lowest plasma concentration before next dose
CRL	Charles River Laboratories
CV	Coefficient of variation
DLC	Demonstration lot campaign
DP	Drug product
ECL	Electrochemiluminescence
ELISA	Enzyme-linked Immunosorbent Assay
EM	Episodic migraine
F	Bioavailability
GOF	Goodness of fit
HC	High concentration control
HRP	Horse radish peroxidase
IgG	Immunoglobulin G1
ISR	Incurred sample analysis
IV	Intravenous
Ka	Absorption constant
Kd	Dissociation constant
LC	Low concentration control
MMD	Monthly migraine days
MRD	Minimum required dilution
MSD	Mesoscale Discovery
NAb	Neutralizing antibody
PEI	Polyethylenimine
pI	Isoelectric point
PK	Pharmacokinetics
PD	Pharmacodynamics
R	Accumulation ratio
RS	Reference standard
RE	Residual error
RSE	Relative standard error
RT	Room temperature
SC	Subcutaneous

SD	Standard deviation
SmPC	Summary of product characteristics
SPEAD	Solid phase extraction with acid dissociation
T1/2	Half-life
TEAE	Treatment emergent adverse event
Tmax	Time at which maximum plasma concentration is reached
TMB	3,3′,5,5′-Tetramethylbenzidine
V	Volume of distribution
VLC	Validation lot campaign
VPC	Visual predictive check

1. Background information on the procedure

1.1. Submission of the dossier

The applicant H. Lundbeck A/S submitted on 16 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Vyepti, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Vyepti is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-C1-002243-PIP01-17 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance eptinezumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal

product previously authorised within the European Union.

1.6. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Bruno Sepodes

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Liana Gross-Martirosyan

The application was received by the EMA on	16 November 2020
The procedure started on	24 December 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	27 October 2021

to all CHMP and PRAC members on	
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vyepti on	11 November 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Migraine is a complex and multifaceted brain disorder. Two main categories can be identified, based mainly on the frequency of attacks: episodic migraine (EM), defined as less than 15 headache days per month and chronic migraine (CM), defined as the patient having 15 or more headache days per month, with at least five attacks fulfilling criteria for migraine with or without aura. However, there is a substantial overlap in terms of symptoms between the two forms, as well as pathophysiology and burden of disability, which make preventive treatment one of the key strategies for migraine management.

Migraine is very common and has two major subtypes based on specific features and symptoms that accompany each attack: migraine without aura (the most frequent form) and migraine with aura, in which transient focal neurological symptoms usually precede or sometimes accompany the headache. There are trigger factors that include hypo-hyper activity, hunger, sleep deprivation, exposure to intense or pulsatile light, depressed mood, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain which migraineurs experience hours or even days before the headache, or during its resolution. Migraine without aura is the most common form of primary headaches. Headache typically is recurrent and lasts 4 to 72 hours, has unilateral location, pulsating quality, moderate to severe intensity and aggravated with routine activity, associated or not to nausea, phono- or photophobia. Migraine with aura needs the coexistence of fully reversible aura symptoms spreading over at least 5 minutes with 5 to 60 minutes duration and followed by headache. In the early stage of an attack, the accompanying premonitory symptoms may be associated with hypothalamic involvement (Maniyar FH, 2014).

2.1.2. Epidemiology

Including both EM and CM, migraine has a one-year prevalence of 15-18% worldwide, with extensive financial yearly burden on global economies, ranging from $19.6 in the United States to €27 billion in the European Union. It was ranked as the third most prevalent disorder and sixth-highest specific cause of disability worldwide by the WHO (Global Burden of Disease Study, 2013).

Migraine predominantly affects females with a 3:1 ratio, with a peak of incidence between the ages of 25 to 55 years, thus it may profoundly impact upon quality of life and productivity. In fact, due to the neurological deficits experienced in the acute phase (such as nausea, vomiting, light and/or sound sensitivity, need to be isolated from the outer world including workplace and school), as well as the aftermath following an attack that lasts for hours or days, subjects experience a condition of true restrictive lifestyle. The vast majority (approximately 90%) of migraine sufferers have a reduced ability to function, and one-third require bed rest during migraine attacks (Lipton et al. 2007).

Migraine has a significant impact on the population, as each year, about 2.5 % of patients with EM develop new-onset CM (Manack et al., 2011). Demographic and comorbidity data outline some clinical differences among subjects with CM and EM, being EM patients more frequently overweight and younger, unemployed and with and anxious-depressed mood (Blumenfield et al 2010), whereas in several CM patients there are risk factors like painkillers abuse as well as different response to treatments, both preventive and abortive.

Comorbidities of migraines include, but are not limited to, psychiatric and medical conditions such as depression and vascular disorders (Buse et al, 2010; Bigal et al, 2009).

2.1.3. Aetiology and pathogenesis

Over the past two decades, new theories apart from the classical neurovascular theory, have tried to elucidate the pathogenesis of migraine while focusing on activation of the trigeminovascular system (Goadsby et al., 2002), cortical hyperexcitability (Coppola et al., 2002), and dysregulation of brainstem regions involved in antinociception and vascular control. The so called trigeminal durovascular afferent pathway has undergone in-depth analyses through immunohistochemistry and functional brain imaging, starting from the knowledge that pain-sensitive structures such as the intracranial blood vessels and the meninges, especially the dura mater, are supplied with sensory nerve fibres (Pietrobon & Striessnig, 2003) by the ophthalmic ramus of the first branch of the trigeminal nerve. They arise from pseudounipolar neurons located in the trigeminal ganglion (Link et al., 2008) projecting onto second order sensory neurons in the trigeminal nucleus caudalis in the brain stem and its related extensions down to the C2-level called the trigeminocervical complex (Goadsby, 2007).

In light of this, several experiments have tried to elucidate the details behind each of the four phases in which a migraine attack is classically subdivided: the premonitory, aura, headache, and postdrome phases. There is wide consensus over the notion that migraine attacks are the results of a cyclic disorder of brain sensory processing, which is influenced by genetic and environmental factors. The premonitory phase involves brain stem and diencephalic systems that modulate afferent signals and explain photophobia or phonophobia, followed by pain up to the resolution or postdromal phase. A dysfunction of central pain processing in the interictal state has been gathered from the hypometabolism of central pain processing areas including bilateral insula, bilateral anterior and posterior cingulate cortex, left premotor and prefrontal cortex, and left primary somatosensory cortex as revealed by ^{18}F-FDG and BOLD-fMRI imaging studies.

The major classes of medicines identified thus far, such as triptans, serotonin 5-HT1B/1D receptor agonists, calcitonin gene-related peptide (CGRP) modulators, including receptor antagonists and monoclonal antibodies, gepants, ditans, 5-HT1F receptor agonists glurants, mGlu5 modulators would exert their main effect at this stage of the whole process.

With regard to CGRP, this neuropeptide is abundant in perivascular trigeminal nerve fibres by which is activated, especially during migraine attacks, and shows the capability of dilating intracranial and extracranial blood vessels while modulating vascular nociception at central level. As such, CGRP may play an important role in the pathophysiology of migraine and, conversely, blockade of CGRP receptors as well as its own peripheral circulation may contribute to abort migraine.

Elevated blood concentrations of CGRP have been associated with migraine (Edvinsson and Goadsby 1994; Bigal et al. 2013). In addition, CGRP infusions can induce migraine-like attacks in individuals with a history of migraine (Lassen et al. 2002; Hansen et al. 2010).

CGRP peptide can directly exert excitatory effects on nociceptive neurons leading to sensitisation or activation of neurons in pain signalling pathways, suggesting that it can drive maladaptive processes in peripheral nerves that induce peripheral sensitisation and ultimately pain. It can also facilitate the effects of other pain transmitters including glutamate and substance P (Ma et al. 2010).

The rationale in using CGRP mAbs stands behind the possibility to target smooth muscle cells on blood vessels and neurons and glial cells outside the blood–brain barrier, contributing to halt vasodilation, mast cell

degranulation, neurogenic inflammation, and possibly peripheral pain sensitization in migraine (Russel FA et al, 2014).

2.1.4. Clinical presentation, diagnosis

Migraine is a chronic condition, albeit prolonged remissions are frequently observed. The diagnosis of migraine is based on patient history and follows the International Headache Society (HIS) diagnostic criteria, now at their ICHD-3 beta revision.

According to the definition of common migraine (migraine without aura or hemicrania simplex, coded with 1.1 in the ICHD-3 beta) patients must have *at least 5 recurrent attacks lasting 4-72 hours (untreated or unsuccessfully treated) and the headache must have at least 2 of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs). In addition, during the headache the patient must have had at least 1 between nausea and/or vomiting, photophobia and phonophobia*. These features must not have been attributable to another disorder.

With regard to prognosis, migraine is a rather benign condition and is not associated with an increased risk of death. The natural history of migraine may slightly change according to the exact type of headache and usually ranges from complete resolution, to symptoms continuation with gradually less or even worsening intensity and frequency over time. Generally Episodic Migraine tend to convert to chronic migraine provided that medication overuse has taken place in the meantime.

The presence of aura may double the risk for ischemic stroke (Kurth et al., 2012). Increase risk for migraine has been linked to young adult age, female gender, use of hormonal birth control, and smoking, whereas the absence of aura does not appear to constitute a risk factor for specific conditions. Generally, the severity and frequency of migraine attacks tend to diminish with increasing age.

2.1.5. Management

The goals of migraine treatment are to relieve pain, restore function, reduce headache frequency, reduce excessive overuse of acute medications and prevent the progression of EM to CM. Pharmacological interventions for the treatment of migraine include acute (symptomatic) treatments and preventive medications. The latter are indicated for all patients with CM as well as for a subset of individuals with EM who have frequent or very prolonged attacks, significant disability, or contraindications to acute therapy.

In the management of migraine, among the first steps to be taken there is the reduction or, if possible, the elimination of the exposure to triggers. This can be done through several ways that include diet and physical exercise. If control of these stimuli is ineffective in preventing the onset of the migraine crisis, and if intense pain prevents normal daily activities, it is possible to resort to drug therapy.

Treatment of acute phase.

The goal of the "acute" migraine therapy is to calm the pain once it has arisen and quickly limit the appearance of the associated symptomatology. The most commonly used medications to reduce migraine-related pain are analgesics.

Anti-inflammatory drugs. The recommended initial treatment for mild to moderate symptoms is based on drugs belonging to the pharmacological class of NSAIDs, such as paracetamol, acetylsalicylic acid, ibuprofen,

diclofenac and naproxen with variable pain-relieving effects over migraine symptoms intensity and duration. These drugs should be used only when needed, on a full stomach and for short periods, given their high association with side effects (such as gastritis, liver and kidney disorders) and their tendency to decrease their effectiveness over time. Analgesics tend to be more effective when taken at the first signs of a migraine attack; in this way, in fact, they can perform their analgesic effect before the most serious symptoms occur. NSAIDs may be prescribed in combination with antiemetics, if there is also nausea and vomiting, or with other molecules (for example: paracetamol, acetylsalicylic acid and caffeine).

Triptans. If ordinary analgesics do not help alleviate migraine symptoms, triptans are the next pharmacological option. The triptan class consists of several drugs with different absorption and pain activity characteristics. Their activity takes place on serotonin receptors, preventing the propagation of pain. In particular, these drugs determine the contraction of blood vessels in the brain, counteracting the dilation that occurs during the migraine attack (and which is considered part of the process underlying the migraine). The effect of triptans is rapid and can significantly reduce the severity and duration of symptoms; even in this case, the best result is obtained if they are taken when the pain is still mild. Sumatriptan is the most commonly used triptan.

Ergotamine and derivatives. Ergotamine and dihydroergotamine are old-generation drugs used only in cases of particularly disabling or refractory migraine. These medicines appear to be equally effective as triptans: they carry out a vasoconstrictive action and contrast the phase of cranial vasodilation responsible for the appearance of migraine. However, they can create serious side effects and can accentuate nausea.

Other drugs include several possible pharmacological options not specific for migraine, such as analgesics, narcotics, opioids and barbiturates. Since these drugs can be addictive, they are less suitable for migraine treatment and should be taken only occasionally, when the specific basic therapy is not effective.

Preventive Therapy

Even though the standard of care in migraine prophylaxis can be highly variable among centers and countries, preventive therapy is useful if migraine occurs with a certain frequency and / or particularly severe symptoms. The goal is to reduce the frequency and severity of migraine attacks.

Several classes of drugs have been successfully adopted as preventive therapies; "older" preventive treatments for migraine include:
(i) anti-hypertensive agents: beta-blockers (propranolol, metoprolol and timolol) and calcium antagonists (verapamil) act by modulating the tone of blood vessels and regulating the mechanisms involved in pain;

(ii) antidepressants (amitriptyline, nortriptyline, etc.): they act at the central level acting mainly on the serotonin receptors, involved in the onset of migraine and through myorelaxation of districts involved in tension-type headache
(iii) antiepileptics drugs (gabapentin, topiramate, valproic acid, etc.): appear to act on the threshold of pain and on cerebral hyperexcitability.
(iv) onabotulinum toxin type A: the administration of this drug through several subcutaneous injections in specifically identified points over the head and neck muscles are useful in cases of chronic migraine only (not indicated for the Episodic Migraine). The effect may last up to 3 months and generally it has to be repeated.

Each type of drug is more effective when used in conjunction with other medical recommendations, such as changes in diet and lifestyle, physical activity and relaxation exercises. A frequent complication of Medication overuse (MO) can lead to additional headache as that requires a combination of pharmacological and non-

pharmacological approaches. Prophylactic treatments that reduce acute medication use may therefore reduce the risk of MO.

However, these "older" treatment options in part require long titration periods with a delayed onset of efficacy, daily drug intake, and an often poor tolerability.

Epidemiologic studies suggest that among patients with chronic migraine, up to 80% were no longer on their medication after 12 months (Hepp et al. 2015) and such a high prophylactic treatment discontinuation seems to be due to poor tolerability and insufficient clinical response, that calls into question acute medication overuse, disease progression, and increased disability.

In this frame, and similarly to other chronic conditions, there is need for novel, more specifically target-oriented prophylactic agents for migraine (Goadsby 2013; Diener et al. 2015; Pike et al. 2016).

An innovative preventive treatment option has been introduced recently with the class of CGRP-targeting therapies. The rapid onset of treatment effect and the less frequent administration scheme, in conjunction with a good tolerability and safety profile are meaningful advances of these new therapies.

2.2. About the product

Eptinezumab is a humanized anti-(calcitonin gene-related peptide) (CGRP) monoclonal IgG1 antibody (anti-CGRP mAb).

Eptinezumab binds to α- and β- forms of human calcitonin gene-related peptide (CGRP) ligand with low picomolar affinity (4 and 3 pM KD, respectively). This, in combination with the 100% bioavailability following an IV administration, translates into fast blockage of the pharmacological 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 commercial drug product is supplied as a sterile, non-pyrogenic, aqueous concentrate for solution for infusion. Each milliliter of drug product contains 100 mg of eptinezumab and the solution is formulated with a target pH of 5.8. Eptinezumab is administered as intravenous (IV) infusion after dilution of the concentrate.

The proposed indication for eptinezumab was prophylaxis of migraine in adults who have at least 4 migraine days per month.

2.3. Type of Application and aspects on development

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) Vyepti is presented as a concentrate for solution for infusion containing 100mg of eptinezumab as active substance per mL (1mL per vial).

Other ingredients are: sorbitol (E420), L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, and water for injections (WfI).

Eptinezumab is administered as intravenous (IV) infusion after dilution of the concentrate. The product is presented as a single-use preservative-free solution and is supplied in Type I glass vials with chlorobutyl rubber stopper.

2.4.2. Active Substance

2.4.2.1. General information

Eptinezumab is a recombinant humanised anti-(calcitonin gene-related peptide) (CGRP) monoclonal IgG1 antibody (anti-CGRP mAb).

Eptinezumab is a soluble protein consisting of four polypeptide chains, two identical heavy chains and two identical light chains. The light and heavy chain variable regions are comprised of both human and humanised rabbit sequences. The expected molecular weight is 143283 Daltons.

Eptinezumab is a monoclonal antibody that binds to α- and β- forms of human calcitonin gene-related peptide (CGRP) ligand with low picomolar affinity (4 and 3 pM KD, respectively). Blockage of α-CGRP leads can lead to attenuated pain transmission and induction of the nociceptive state in the brain, thereby being a good target for the treatment of migraine. There are several monoclonal antibodies already approved in the EU for the treatment of migraine targeting α-CGRP or its receptor, which supports the proposed mode of action for eptinezumab.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturer(s)

Eptinezumab is manufactured at Sandoz GmbH, Biochemiestrasse 10, Kundl 6250, Austria. Testing sites and responsibilities have been included and provided. The GMP documentation is available either by GMP-certificates and/or by the EudraGMDP document reference numbers indicated in the application form. The GMP documentation for US sites is considered sufficient. Master cell bank (MCB) and working cell banks (WCB) have been established under GMP conditions.

Description of manufacturing process and process controls

A narrative description of the active substance manufacturing process has been provided, consisting of an upstream and a downstream part. Eptinezumab is produced in a yeast-based (*Pichia pastoris*) expression system using conventional fermentation and downstream purification processes.

The upstream process of eptinezumab bulk drug substance (BDS) comprises 3 individual steps, which are all related to the *Pichia pastoris*-based microbial fermentation procedure: the inoculum preparation step, the seed fermentation step, and the production fermentation step. In-process controls (IPCs) have been defined for the inoculum and production fermentation step. Adequate acceptance criteria have been provided.

The downstream process of the eptinezumab manufacture for commercial use is conducted at the bulk drug substance (BDS) manufacturer's production facility and consists of 7 steps, which can be divided into 2 process units: isolation (first centrifugation/flocculation, second centrifugation/filtration, and capture) and purification.

Pichia pastoris cells are first removed by centrifugation, and the supernatant is treated with a flocculating agent resulting in the flocculation of impurities. These are removed by a second centrifugation step followed by filtration of the resulting supernatant. Capture of the monoclonal antibody by protein A purification represents the final isolation step in the manufacturing process of eptinezumab BDS.

Further purification of eptinezumab is accomplished by the use of 2 additional, consecutive chromatography stepsFinally, the resulting solution is ultrafiltered/diafiltered followed by eptinezumab bulk drug substance (BDS) filled into bottles and stored frozen.

The description of the manufacturing process steps is accompanied by flow charts indicating the process parameters and process controls. Target operating set points are defined for several process parameters at each step as either critical or non-critical. In-process controls (IPCs) have been defined for all steps. Adequate acceptance criteria have been provided.

Reprocessing and/or reworking of manufacturing process steps is not permitted as part of the manufacturing process.

The batch numbering system is considered adequate. A unique number is generated for each individual batch. The unique batch number is included in all issued records for this batch to ensure traceability.

Control of materials

Raw materials used for the cell culture and purification process are listed together with their quality standard (in-house, Ph. Eur., USP/NF) and their intended use. Safety information for biologically sourced materials has been provided. No starting material of animal or human origin is used during inoculum preparation or fermentation of eptinezumab. A comprehensive description of all raw materials used during the manufacture of eptinezumab BDS and their corresponding quality requirements have been provided.

Raw materials used for cell bank generation or used in the active substance manufacturing process have been provided in a tabular format. The compendial or non-compendial materials are sourced from qualified and approved sources inspected, sampled and tested under appropriate conditions and according to the respective acceptance criteria. Based on a risk assessment, raw materials are either considered critical or non-critical. Non-critical materials may be sourced from different manufacturers upon appropriate source qualification measures. Critical materials will not be replaced without further assessment. All chromatographic resins, the bottle used for storage as well as the final filter cartridge used for filtration of BDS prior to filling are defined as critical.

A traditional two-tiered cell banking system was established. The cell banks were sufficiently characterised. No evidence of microbial contamination was observed.

Stability of the cell banks and the genetic integrations were demonstrated through End of Production (EOP) and Limit of *In Vitro* Cell Age End-of-Production Cell (LIVCA) testing.

The validated LIVCA duration includes pilot scale fermentation process duration plus a duplicated seed expansion process. The validated limit of *in vitro* cell age for the MCB and is population doublings from the thaw of a vial from MCB through the end of production has been established.

New eptinezumab WCBs will be manufactured from the same MCB in accordance with approved manufacturing records and using the same process steps. For future WCBs, the number of cells in the cell banks should be based on the quantity of cells used to manufacture the supportive batches and current commercial batches. The Applicant is recommended, to revise the variability of the cell counting. Taking the new method variability into account, the cell number for new cell banks should be recalculated and the suitability of the LIVCA justified.

Control of critical steps and intermediates

Process Parameters (PP) and In-Process Controls (IPC), which have the potential to affect Critical Quality Attributes (CQAs) of eptinezumab BDS are classified as critical and are thus has to be monitored/controlled to ensure consistent quality of eptinezumab BDS.

The in-process control program includes process monitoring and verification activities to ensure that operational/performance parameters and quality attributes are maintained in a state of control with minimal risk to process and Process parameters represent process inputs whereas quality attributes focus on process outputs. Criticality determination for process parameters is based on the parameter's ability to impact any identified critical quality attributes. The control strategy incorporates alert limits, action limits and acceptance criteria representing increased control levels for the PPs, CPPs, IPCs and CIPCs. Adequate limits or acceptance criteria are in place.

CPPs and CIPCs are provided for upstream and downstream manufacturing process of eptinezumab bulk drug substance (BDS) in a comprehensive and clear way. Overall CPPs and CIPCs have been identified which were justified and supported by process characterisation data. Non-critical PPs and their acceptable ranges have been sufficiently described. Furthermore, maximal process intermediate storage duration based on validation studies have been defined.

Process validation and/or evaluation

The eptinezumab active substance manufacturing process has been validated by conducting several consecutive commercial-scale Process Performance Qualification (PPQ) batches and with the equipment intended for the commercial active substance manufacturing process. All CPPs/PPS as well as CIPCs/IPCs and process monitors met their predefined acceptance criteria or ranges.

The upstream manufacturing process consistency and reproducibility for eptinezumab production was shown by time courses of performance-indicating parameters regarding the production fermentation step. No deviations occurred during the upstream process manufacturing steps of the PPQ BDS batches. Therefore, it is demonstrated that each individual upstream process steps – and thus the complete upstream manufacturing process – is stable and controlled.

The downstream manufacturing process of eptinezumab BDS was evaluated for process consistency, process- and product-related impurity / substance clearance, as well as bioburden and endotoxin control.

For the process consistency, critical as well as non-CPPs and IPCs defining and characterizing the entire downstream manufacturing process performance complied with the ranges and limits predefined in the PPQ protocol. Although some deviations to the validation protocol and process deviations occurred during the

downstream manufacturing process of the PPQ runs, none was assessed to negatively impact the validity of the PPQ study / process performance, nor the final BDS quality. This is acceptable.

A filling homogeneity study demonstrated that the eptinezumab concentration and quality is maintained throughout the filling process. Protocol and process deviations were reported at several steps and sufficient justifications have been provided.

Process- and product-related impurity clearance to adequate levels was also demonstrated during PPQ runs. Microbial control of the manufacturing process was shown to be effective as all bioburden and endotoxin IPC limits were met. Intermediate hold periods have been adequately set based on stability data from the PPQ, and additional data from validation lot campaign (VLC) batches as well as a laboratory scale study performed during demonstration lot campaign (DLC). The stability of solutions and media used during up- and down-stream processing has been sufficiently investigated including microbial control and adequate storage conditions set.

Chromatography resin and UF/DF membrane lifetime/reuse is concurrently validated at scale using adequate pre-defined protocols. Initial lifetimes were set based on laboratory scale evaluations.

Shipping validation of the active substance was performed. The distance and transportation time sufficiently covered normal transportation from the manufacturing site to the filling site.

Manufacturing process development

Three versions of the active substance manufacturing process have been used during the clinical development: Process 1 (C1), Process 2 (C2) (Clinical) and Process 2 (C2) (Commercial). The active substance manufacturing history has been described in sufficient detail.

To support comparability between the different manufacturing processes two formal ICHQ5E compliant comparability evaluations were performed. An initial comparability assessed early (C1) to late phase (C2) processes and a commercial comparability, which assessed late phase (C2) to commercial phase process (C2). Furthermore, a Phase 1 clinical comparative pharmacokinetic study was also performed as part of the overall assessment of the comparability of the commercial finished product to the clinical finished product.

A risk assessment has been performed to identify eptinezumab critical quality attributes. The approach has been sufficiently described and is considered adequate. CQAs have been defined as mandatory by default due to compendial requirements or regulatory expectations or as non-mandatory using a scoring scheme. Impact and uncertainty scores were defined for four product impact categories (PICs) including efficacy, PK/PD, immunogenicity, and safety. The impact score is multiplied by the uncertainty score to create a severity score. QAs above a defined severity limit (SL) are defined as CQAs. The final list of CQAs is considered acceptable.

Process characterisation was performed using small-scale models which were sufficiently qualified. The upstream characterisation development justification studies were divided into fermentation process and clarification and harvest characterisation. Based on the prior CQA risk assessment adequate process parameters have been characterised. In most cases one-factor at a time (OFAT) experiments or design-of experiments (DOE) have been conducted.

Based on the data and effects from the characterisation studies commercial process parameters have been established. The set parameter ranges are acceptable.

Down-stream process characterisation studies were performed. Based on the data and effects from the characterisation studies commercial process parameters have been established. The set parameter ranges are acceptable.

A Host Cell Protein (HCP) assay and potency assay was developed and sufficiently validated.

Characterisation

Elucidation of Structure and Other Characteristics

Characterisation of the eptinezumab BDS was performed on several C2 batches (from the demonstration lot campaign - pivotal and commercial scale batches) using state-of-the art methods. The selection of the BDS batches and methods used is considered adequate. In general, all relevant properties of eptinezumab have been investigated. Sufficient information on how the extinction coefficient of eptinezumab, which is used for the protein concentration method, has been provided.

Impurities

The impurities of eptinezumab were divided into process- and product-related impurities. The biological activity of eptinezumab was characterised. The results support the mechanism of action and clinical relevance of eptinezumab.

A risk assessment of extractables and leachables was performed and no high-risk components were identified. Elemental impurities were investigated in line with ICH Q3D and no elemental impurity level was identified requiring additional controls.

All variants are characterised and controlled at release and during stability testing, which is considered acceptable.

2.4.2.3. Specification

The release specification for eptinezumab active substance include tests for general characteristics and physicochemical properties, identity, quantity, purity and impurities, process-related impurities, potency, microbial safety, and general attributes.

For the compendial methods (colour, bacterial endotoxins, bioburden, pH, osmolality) reference has been made to the respective Ph. Eur monographs. For the internal methods, a reference to the respective in-house reference is provided. Overall, the set of release parameters tested complies with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008.

The specification set for the eptinezumab active substance are considered adequate and justified.

Analytical procedures

Compendial methods and non-compendial analytical procedures are used to control the manufacture of eptinezumab bulk drug substance. The analytical methods employed have been described is sufficient detail.

Batch analyses

Batch release data are presented for several eptinezumab bulk drug substance batches manufactured according to the intended commercial manufacturing process. In addition, release data was also presented for eptinezumab bulk drug substance previously manufactured with C1, C2.0 or C2.1 previous process and from several commercial manufacturing campaign.

Data from batch release, shows consistent and comparable quality of BDS across all batches through process development. All the BDS batches comply with the pre-established specifications valid at the time of testing.

Justification of specification

The eptinezumab specifications were established to confirm the overall quality, safety, purity, and potency of the eptinezumab BDS and to focus on the critical quality attributes (CQAs) that ensure the safety and efficacy of the resulting finished product. The selected specification tests and acceptance criteria are in agreement with the regulatory requirements from the Ph. Eur. and the guideline ICH Q6B. Specification acceptance criteria were developed and justified based on regulatory requirements, as well as accumulated batch release and stability data from all representative batches made at both the clinical-scale manufacturing site and the commercial-scale manufacturing site. For each test parameter a discussion is provided. Sufficient and adequate information have been provided.

Reference standards of materials

A two-tiered system with primary and working reference standards (PRS and WRS) has been established for eptinezumab. The history of the reference standards (RS) used during development has been provided. The current primary RS was used for the establishment of the working RSs and is used for the annual requalification of working RSs. The currently used primary RS was derived from an eptinezumab source lot (BDS batch) that was produced using pivotal clinical (late phase) manufacturing process. Qualification data demonstrated its suitability as primary RS. The qualification and stability acceptance criteria for future primary and working standards have been provided. Both RS are re-qualified annually, which is adequate.

Reference standard has been qualified as the initial working RS, which originates from eptinezumab BDS batch, which was manufactured using the commercial manufacturing process. Suitability as working RS has been demonstrated based on adequate qualification data.

Protocols for the establishment of future PRS and WRS have been provided. Future PRS and WRS will be sourced from commercial scale eptinezumab BDS batches and will be established after qualification against the existing primary reference standard.

To mitigate the risk of drifts in biological activity/potency the working RS are tested against the primary RS. The data of the working RS is calibrated against the primary RS results using a statistical approach. In conclusion, detailed information on the reference standards has been provided and overall, the strategy is considered adequate.

Container closure system

The container closure system (CCS) of eptinezumab BDS are translucent leak-proof bottle with a silicone-lined polypropylene (PP) closure with white colourant.

Incoming CCS batches are sufficiently inspected. The CCS shows adequate BDS protection based on available stability data. Durability in shipment was shown during transport validation studies. A simulated extractable study was performed. In conclusion no risk from extractables and leachables was identified.

The container primary closure system is in compliance to the Ph. Eur. requirements. Overall, the suitability and safety of the BDS CCS is described in sufficient detail and considered acceptable.

2.4.2.4. Stability

The eptinezumab active substance stability program includes several primary and supportive batches.

In line with ICH Q5C, the batches were tested under long-term and accelerated conditions. Data currently available for the primary and supportive batches under long-term conditions and under accelerated conditions support the initial claimed shelf life under long-term conditions.

The photostability studies conducted demonstrate that the active substance is sensitive to light however the commercial packaging provides adequate protection from light.

It can be concluded that the used analytical methods are sufficiently stability indicating. An adequate post-approval stability protocol has been provided and it has been committed that all stability studies will be completed and that a minimum of one batch of eptinezumab AS will be put on long-term stability at the recommended storage condition every year that manufacturing of such batches occurs. This is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Finished Medicinal Finished Product

Eptinezumab concentrate for solution for infusion, 100 mg/mL (finished product) is a clear to slightly opalescent, colourless to brownish-yellow, sterile, nonpyrogenic, aqueous liquid preparation for intravenous administration. It is supplied in aseptically filled single use vials nominally containing 100 mg per 1 mL (1 mL per vial) of eptinezumab. The inactive ingredients are: L-histidine/L-histidine monohydrochloride, sorbitol, polysorbate 80 and water for injections. Excipients are compendial and compatibility of excipients was demonstrated.

The finished product contains no antimicrobial agents or preservatives. No overage is used in the finished product formulation.

Pharmaceutical development

The active substance is diluted to final bulk finished product with a dilution buffer which composition is identical to the one used to formulate the active substance. The excipients are suitable for parenteral administration and are globally used in approved biopharmaceutical finished products.

In accordance with ICH Q8 and ICH Q11, the Quality Target Product Profile (QTPP) were defined for eptinezumab active substance/ finished product development. Considerations for the QTPP include, the intended use, route of administration, dosage form, delivery system, dosage strength, and active substance/ finished product quality criteria (e.g., potency, appearance, stability, and drug release) appropriate for the intended marketed product.

Different stability screening studies were conducted to support the buffer, stabilizer, pH, and surfactant identified for the eptinezumab finished product.

Manufacturing process development

The finished product used for clinical trials has been manufactured at one manufacturer and the finished product manufacturing process was subsequently transferred as part of late stage development to a commercial manufacturing facility of another manufacturer for commercial finished product production.

The comparability exercise is focused on equality of safety and efficacy of eptinezumab finished product manufactured at different sites. Additionally, comparability was demonstrated in a Phase 1 comparative pharmacokinetic clinical study by PK profile comparison.

All finished product lots manufactured meet the proposed commercial specification limits through six months for long-term samples and have comparable profiles for all stability indicating parameters or have attributes that were assessed as comparable for all methods.

Extensive product quality data and comparative profiles were evaluated to provide assurance that quality and safety of the finished products is comparable.

Container closure system

The container closure system for the finished product is a Type 1 glass vial closed with a chlorobutyl rubber stopper, and secured with a seal with a flip-off plastic cap.

Compatibility of the primary packaging materials, the vial and stopper, with the finished product has been demonstrated during primary and supporting stability studies. The containers are in compliance with applicable requirements for Type 1 glass vials. Adsorption of the product onto container surfaces, including the stopper, is not evident by the consistent results of the protein concentration observed in the stability studies.

Safety of container and closure is assured through certification by the manufacturer that the glass vials and the elastomeric closure used for the manufacture of the finished product comply with Ph. Eur. and USP requirements.

An assessment of the potential impact of contact between the proposed commercial container closure system (vial/stopper) and the finished product was performed with respect to extractables as potential leachables. The proposed container closure system is adequate for the finished product.

2.4.3.2. Manufacture of the product and process controls

Manufacturer(s)

Information on the manufacturing sites for the eptinezumab finished product and their responsibilities have been sufficiently provided. According GMP certification is available.

Batch formula

A batch formula for eptinezumab concentrate for solution for infusion finished product has been provided.

Description of manufacturing process and process controls

The finished product eptinezumab concentrate for solution for infusion, 100 mg (1 mL per vial) is manufactured according to a standard manufacturing process for monoclonal antibodies.

1) Thawing eptinezumab bulk drug substance (BDS); 2) Pooling eptinezumab BDS (optional step); 3) Formulating finished product solution; 4) Pre-filtration for bioburden reduction; 5) Sterile filtration, aseptic

filling, and stoppering of vials; 6) Sealing, visual inspection, and labelling; and 7) Storage of vials and shipment.

Sampling for finished product testing is performed. The filled and sealed vials are stored at 2-8°C.

The filled vials are 100% visually inspected following USP and Ph. Eur. Defective vials are rejected. After visual inspection the vials are placed into storage at 2-8°C under quarantine. After visual inspection, vials are labeled and packed.

Tabular overviews of IPCs as well as hold and processing times have been provided. IPCs have been provided with acceptance criteria. Filter integrity of filters for bioburden reduction filtration before and after filling is tested via bubble point.

Controls of critical steps and intermediates

Evaluation of critical process parameters was based on historical manufacturing and development data. This evaluation resulted in the identification of critical process parameters and in-process tests (CIPTs), and critical in-process controls (CIPCs). Both CIPTs and CIPCs are used to assess the process consistency and process performance; they are distinguished by the timing of testing. CIPTs are performed after the manufacture of the batch, whereas CIPCs are performed in real-time and inform the operation of the process to the next process step. In-line sterile filtration is controlled by filter integrity testing via bubble point and total aerobic microbial count (TAMC) and total yeasts and molds count (TYMC). Bioburden analysis by TAMC and TYMC met the established acceptance criteria. Filing is controlled by volume and in-line weighing. The capping is controlled automatically by a sensor. A justification for each IPC was provided.

Holding and processing times for eptinezumab finished product have been presented and adequately justified.

Process validation and/or evaluation

Separate original validation reports have been provided: bacterial retention validation report and filter compatibility test report. Process performance qualification runs performed to validate thawing, pooling, compounding, filtration, filling and aseptic processing have been completed successfully.

Several consecutive finished product batches were successfully manufactured using the proposed minimum and maximum manufacturing batch sizes. All in-process control and release data of the PPQ-batches fulfilled the predefined acceptance criteria. The finished product manufacturing control strategy (with in-process tests and operational ranges specified) was shown to be suitable for controlling the process and the resulting finished product.

Sufficient information on the batch numbering system for the finished product bulk batch as well as for the finished product batch has been provided.

Media fill runs have been performed to validate the aseptic processes. The results of these media fills show that the pre-defined acceptance criteria are met, and the aseptic filling process is documented to be validated.

Process performance qualification of finished product manufacturing has been evaluated in full compliance with cGMP requirements to demonstrate the consistency and reliability of the manufacturing process of eptinezumab finished product. Validation of thawing, pooling, compounding, filtration, filling and aseptic processing has been completed successfully. All in-process control and release data of the PPQ batches fulfilled the predefined acceptance criteria and the release specification. PPQ confirmed the process design and demonstrated that the commercial manufacturing process performs as expected.

A hold and processing time verification study has been further conducted as part of the PPQ. Results of this study support the specified hold times as the processing and hold times did not affect the purity of the finished product solution. No increase in endotoxin or bioburden was observed.

Furthermore, homogeneity within batches was determined as part of the PPQ. Samples to evaluate batch homogeneity were taken at the beginning, middle, and end of filling and were tested. Based on results from the PPQ batches, batch homogeneity was demonstrated reproducibly throughout the filling process.

Dye leak test and vacuum decay test were used to assess effectiveness of container closure components (container closure integrity test, CCIT). Data from both tests demonstrate integrity of the container closure system.

Bacterial retention validation and filter chemical compatibility were performed at filter membrane disc and the full device. Chemical compatibility evaluation has been successfully passed.

Impact of simulated shipping stress on finished product quality was also analysed. The finished product is not sensitive to extreme transport stresses – no degradation or significant particle formation was observed when compared with data from the lot not subjected to transport stress.

A packaging performance testing and distribution simulation has been performed additionally, demonstrating that the system-maintained integrity after packaging and labeling, handling, distribution and storage.

In conclusion, the validation results demonstrate the consistency of the finished product manufacturing process through the evaluation of controlled parameters, in-process controls and tests, and the compliance of finished product batches to release specifications. The process validation demonstrates the manufacturing process operates in a robust and controlled manner which consistently produces finished product in accordance with the required product quality attributes.

2.4.3.3. Product specification

The release specification for eptinezumab finished product include tests for general characteristics and physicochemical properties, identity, quantity, purity and impurities, potency, microbial safety, and general attributes.

The specifications have been set in line with the Ph. Eur. monograph for monoclonal antibodies for human use and Ph. Eur. monograph for parenteral preparations. Excipients added during manufacture of the finished product comply with compendial monographs.

No excipients of human or animal origin used in the manufacture of the finished product.

The outcomes of the risk assessment for each of the potential elemental impurities source indicate that under the current control strategy, the worst-case theoretical concentrations for all elemental impurities are well below the permitted daily exposure limits and no additional routine process testing or controls are deemed necessary. The assumptions and worst-case theoretical calculations used in the risk assessment were confirmed by testing three separate batches of vialed finished product for elemental impurities content.

A risk assessment for the presence of potential extractable and leachables from the manufacturing equipment used over the active substance and finished product manufacturing process has been provided. The risk assessment focused on the vial and stopper as these components of the primary container closure system are the higher risk components. This is endorsed. In respect to potential extractables and leachables originated

from the equipment used during manufacturing of the finished product, all the key elements were identified as potential sources and declarations from the respective suppliers presented reassuring the safety of the components of the equipment used in this respect.

Analytical procedures

The analytical procedures for the finished product are identical with those performed to analyse the BDS, with some exceptions e.g. container closure integrity, which are solely applicable to the finished product. These two non-compendial analytical methods are described with the principle of method and presentation of the results evaluation with sufficient detail.

Established pharmacopoeial analytical procedures were verified for one or more parameters. The successful completion of the verification provides assurance that the compendial analytical procedures used to control eptinezumab finished product are suitable for their intended use.

Non-compendial analytical procedures were validated following a defined protocol with pre-defined acceptance criteria in accordance with the principles of ICH Q2R (R1).

Overall, the validation data presented for the analytical methods are acceptable and demonstrate the suitability of the analytical procedures for their intended use.

Batch analyses

Batch release data are presented for eptinezumab finished product PPQ batches manufactured according to the intended commercial manufacturing process. In addition, release data are presented for the finished product batches manufactured with the previous process. The results demonstrate that the different manufacturing processes are able to deliver eptinezumab finished product with consistent quality. All test results are well within acceptance criteria and complied with the specifications set at the time the batches were tested. No out-of-specification (OOS) results occurred. Batches derived from the different developmental phases are comparable with regard to release data.

Characterisation of impurities

For container closures extractables and leachables impurities have been presented. The product-related impurities present or potentially present in eptinezumab finished product are the same as those present or potentially present in eptinezumab active substance except for sub-visible particulates and elemental impurities. Sub-visible particles in eptinezumab finished product have been assessed with the principles of Ph. Eur. 2.9.19 and USP <787>.

The outcome of the risk assessment for the potential elemental impurities, conducted in line with ICH Q3D, indicate that under the current control strategy, the worst-case theoretical concentrations for all elemental impurities are well below the permitted daily exposure limits and no additional routine process testing or controls are deemed necessary. The assumptions and worst-case theoretical calculations used in the risk assessment were confirmed by testing three separate batches of vialed finished product for elemental impurities content.

A risk assessment concerning the potential presence of nitrosamines in the product has been provided. Based on this assessment the Applicant concluded that there is no risk associated with nitrosamines for the finished product, and this conclusion can be agreed.

Justification of specification(s)

Adequate justifications have been provided for the finished product specifications and are endorsed.

Reference standard

The eptinezumab working reference standard for testing eptinezumab finished product is the same as the one used for testing eptinezumab active substance (see discussion on the AS section).

Container closure system

The primary container closure system is a Type I glass vial with a rubber stopper kept in its position by an aluminum seal with a flip-off plastic cap. Vial and stopper comply with compendial requirements.

The specifications of the glass vial, rubber stopper, and flip-off seal along with the technical drawings have been provided. The vial complies with monograph 3.2.1 for "Glass containers for pharmaceutical use" of Ph. Eur. and vial stopper complies with the monograph 3.2.9 for "rubber closures" of Ph. Eur. The quality of vial, stopper, and seal is controlled by the manufacturer/supplier. Certificates analysis (CoA) of all the components of the Container Closure System have been provided.

Suitability of the CCS has been studied by investigation of extractables and leachables potentially present in the finished product.

Study details and results have been provided showing that levels of leachables emanating from the CCS remain at or below the analytical evaluation threshold or applicable limit.

Container closure integrity of the CCS combination has been verified by either dye ingress testing or vacuum decay.

2.4.3.4. Stability of the product

A shelf life of 3 years when stored at 2°C - 8°C is claimed for the finished product.

The primary (several PPQ batches) and several supportive stability studies included long-term (5 ± 3°C) and accelerated (25 ± 2°C/60 ± 5% RH) conditions, in accordance with ICH Q1A(R2) and Q5C requirements. For the long-term storage condition (5 ± 3 °C and protected from light), stability study results for the finished product batches are available through 36 months and through 24 to 36 months for supportive batches. For the accelerated storage condition (25 ± 2°C/60 ± 5% RH), stability study results are available through 6 months for primary batches and supportive batches.

Forced degradation and photostability studies support the recommended storage condition at 2°C - 8°C with protection from light. Placement of the primary finished product container in a coated paperboard carton provides protection of the finished product from photo exposure.

Currently, long-term data through 36 months are available for all primary lots of eptinezumab finished product. In addition, results of supportive stability lots are available showing similar trends. Based on the stability results the claimed shelf life of 3 years when stored at 2°C - 8°C for the finished product is considered acceptable.

In-use stability data has been provided for the finished product diluted in 0.9% NaCl injection and supports storage up to 8h at 2ºC-25ºC. As stated in the SmPC 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 (below 25°C) or refrigerated at 2°C - 8°C.

2.4.3.5. Adventitious agents

TSE compliance

Vyepti active substance and finished product are overall manufactured without animal- or human-derived materials. Likewise, the raw materials used for cell banking are not of animal origin.

TSE/BSE statements from the active substance, finished product and cell bank manufacturers have been provided. It is furthermore stated that any future working cell bank will also be prepared in compliance with the 'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products' EMEA/410/01, current revision.

There are no excipients of animal origin. Confirmation has been provided that materials used during manufacture of Vyepti have been evaluated regarding TSE safety and were compliant to EMA/410/01. Some equipment contained animal tallow-derived materials, however, they are also stated to comply with EMEA/410/01. In summary, Vyepti has been shown to be free of TSE risk substances and overall in compliance with EMA/410/01, current revision.

Virus safety

Vyepti is expressed in the yeast *Pichia pastoris*. *Pichia pastoris* is not a potential host for the amplification of viruses that are infectious for human or animal cells. Therefore, no virus safety testing on cell banks and unprocessed bulk has been performed and the purification process was not validated for its virus reducing capacity. This approach is in compliance with current guidelines.

No materials of human or animal origin are used in the whole manufacturing process and none of the excipients are of human or animal origin. In summary, the viral safety of Vyepti has been sufficiently demonstrated.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant is recommended to revise the variability of the cell counting method and recalculate the cell number for new cell banks and the suitability of the LIVCA justified.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Vyepti is considered acceptable when used in accordance with the conditions as defined in the SmPC.

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated.

The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

2.4.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The Applicant is recommended to revise the variability of the cell counting method. Taking the new method variability into account, the cell number for new cell banks should be recalculated and the suitability of the LIVCA justified.

2.5. Non-clinical aspects

2.5.1. Introduction

The Applicant submitted a comprehensive dossier of non-clinical studies in support of this application.

2.5.2. Pharmacology

Primary pharmacodynamics

The applicant has demonstrated that eptinezumab binds to human α-CGRP and β-CGRP with high affinity (pM range); specificity for CGRP was demonstrated based on the lack of binding to related proteins (calcitonin, adrenomedullin, intermedin and amylin). Binding affinity of eptinezumab to human, rat and rabbit CGRP forms was found to be comparable, except for a lower affinity to rabbit α-CGRP. Functional activity of eptinezumab was demonstrated in a cell-based assay of CGRP-induced accumulation of intracellular cAMP. In this assay, eptinezumab inhibited accumulation of intracellular cAMP induced by human, rat and rabbit α- and β-CGRP with comparable potency in the low nM range. In vitro reactivity of eptinezumab to cynomolgus CGRP was not assessed; this is accepted since human and cynomolgus CRGP have identical amino acid sequences.

In vivo activity of eptinezumab was demonstrated in a model of capsaicin-induced increase in dermal blood flow in rats and cynomolgus monkeys and a model of vasodilation induced intradermal injection of CRGP in rabbits. In all studies, eptinezumab reduced the dermal vasodilation response to challenge (capsaicin or CGRP). There are no animal models for migraine; thus, the evidence for a therapeutic effect are derived from the clinical data.

Secondary pharmacodynamics

The applicant has not provided data on secondary pharmacodynamics. However, the binding of eptinezumab to proteins related to CGRP has been assessed as part of the primary pharmacodynamics. No binding to related proteins was detected, confirming the specificity of eptinezumab to CGRP and indicating a low risk for off-target functions.

Fc-dependent effector function by eptinezumab was addressed as part of the analytical characterisation of the molecule. Due to deletion of the N-glycosylation site in the heavy chain of the molecule and absence of Fc N-glycosylation, eptinezumab has no measurable binding to low-affinity Fc gamma receptors (RIIA, RIIB/C, RIIIA and RIIIB) and only weak binding to the high-affinity receptor FcγRI (approx. 40x lower compared to human IgG). Due to this Fc modification and the soluble nature of CGRP, eptinezumab does not mediate Ab-dependent cellular toxicity or complement-dependent cytotoxicity.

CGRP is a molecule with pleiotropic functions. While the applicant has evaluated the effect of eptinezumab in CGRP-mediated vasodilation, the effect of eptinezumab on other functions of CGRP has not been assessed. A risk assessment regarding potential consequences upon on-target blockade of such additional CGRP functions has not been submitted. Nevertheless, specific theoretical risks associated with blockade of CGRP-dependent signalling (i.e. cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebro-vascular accident, transient ischemic attack, angina, unstable and poorly controlled hypertension; use in pregnancy including those at risk of pre-eclampsia) have been included in the RMP. Therefore, a discussion on secondary pharmacodynamic effects, i.e. blockade of CGRP-mediated functions other than vasodilation, is not warranted.

Safety pharmacology

Assessment of safety pharmacology endpoints as part of the general toxicity studies did not reveal effects of eptinezumab on the central nervous system, the cardiovascular and respiratory system and renal system.

2.5.3. Pharmacokinetics

The pharmacokinetics of evinacumab were evaluated in rats and cynomolgus monkeys as part of the single-dose toxicity and repeated-dose toxicity studies after IV administration. This reflects the proposed clinical route of administration (IV).

Throughout development, different PK assays were used for detection of eptinezumab in plasma. The first generation ECL assay measured total eptinezumab while the second generation assay measured free or partially free eptinezumab. Anti-drug antibodies were measured using solid phase extraction with acid dissociation followed by direct ECL detection. A bridging ECL method was used in the juvenile rat study. Neutralising Ab were detected using a competitive ligand binding assay. All methods were appropriately validated.

In both rats and cynomolgus monkeys the PK characteristics of eptinezumab after single IV administration were typical for a monoclonal antibody. There were no notable gender differences. Exposure to eptinezumab was generally dose-proportional. Plasma concentration profiles were consistent with IV administration, i.e. with a rapid Tmax and an apparent mono-exponential decline. Volume of distribution was low, indicating that eptinezumab does not distribute substantially beyond the vascular compartment.

After repeated IV administration, limited accumulation was observed. In rats, the accumulation ratio in AUC was approx. 1.50 to 2.22 after once weekly dosing for 4 weeks. In cynomolgus the accumulation ratio in AUC was approx. 2.03 to 2.61-fold with once weekly dosing for 4 weeks and approx. 2.60 with dosing every 2 weeks for a 26-week period.

2.5.4. Toxicology

Toxicity studies with eptinezumab were conducted in rats, cynomolgus monkeys and rabbits. These species are considered pharmacologically relevant based on the affinity and functional activity of eptinezumab against CGRP from these species.

Single- and repeat-dose toxicity

General toxicity of eptinezumab was evaluated in single-dose and repeat-dose studies in rats and cynomolgus monkeys. Short-term studies (up to 28 days) were conducted in both species while the chronic toxicity was evaluated in cynomolgus only. This is acceptable in accordance with ICH S6(R1).

In Sprague Dawley rats, eptinezumab was well tolerated when administered once weekly at doses of up to 100 mg/kg IV for 4 weeks. No adverse effects were observed. As calculated by the assessor, exposure in the high-dose group was approx. 50x greater than the maximum clinical exposure (at 300 mg IV, Q12W).

In cynomolgus monkeys, eptinezumab at doses of up to 100 mg/kg Q1W for 4 weeks and up to 150 mg/kg Q2W for 6 months was well tolerated. There were no toxicological findings of importance for the safety assessment. Of note, there were no eptinezumab-related effects on the cardiovascular and respiratory system. In the chronic toxicity study, exposure in the high-dose group was > 100x greater than the maximum clinical exposure. One low-dose female exhibited an anaphylactoid-like reaction and died within approximately 30 minutes after eptinezumab administration on Day 71 (6th dose). This anaphylactoid reaction was associated with the presence of high levels of ADA. As immunogenicity to a human protein in animals is not predictive for clinical immunogenicity, the finding is not considered indicative of a clinical risk.

Genotoxicity and carcinogenicity

Genotoxicity studies have not been conducted in accordance with ICH S6(R1).

In accordance with ICH S6(R1) the applicant has provided a product-specific carcinogenicity risk assessment taking into account non-clinical data for eptinezumab and a literature review on the potential role of CGRP in tumorigenesis and its effect on the immune system. Literature data show that CGRP has a pro-angiogenic role and is rather immunosuppressive. Both factors would support tumour growth. Since blockade of CGRP would prevent these effects, the carcinogenic risk associated with eptinezumab is considered low.

Reproductive and developmental toxicity

Reproductive and developmental toxicity of eptinezumab was evaluated in rats and rabbits.

In the fertility and early embryonic development study, both male and female rats were treated with eptinezumab at doses of up to 150 mg/kg IV Q1W, from prior to mating, throughout mating, and up to day 3/4 post coitum (females) and up to week 9 (males).

With regard to reproductive performance in males, there were no eptinezumab-related effects on mating, fertility or sperm assessment at doses up to 150 mg/kg. In females, there were no eptinezumab-related effects on estrous cycles, mating index or conception rate. In mated females, the numbers of corpora lutea, implantation sites, live embryos and resorptions were unaffected by the administration of eptinezumab. There appeared to be a greater percentage of pre-implantation losses in the eptinezumab-treated females (10.82% at 75 mg/kg, 7.46% at 150 mg/kg) compared to the control group (2.39%). However, rates of pre-implantation losses in the eptinezumab-treated groups were close to the historical average of the test facility, while the average rate of the control group was lower than the historical average. Thus, the finding is not considered related to eptinezumab.

The effect of eptinezumab on embryo-fetal development was assessed in SD rats and in NZW rabbits. In rats, eptinezumab was administered IV at 0, 75 and 150 mg/kg on GD 6, 12 and 18; animals were necropsied on GD21. Results from the DRF and pivotal study were consistent. There was no evidence of embryo-fetal mortality, alteration in growth or structural abnormalities and the maternal and the fetal NOAEL is 150 mg/kg, the highest dose administered. At this dose, the average expected maternal Cmax value was 4473 µg/ml, which is 36x higher than the Cmax in humans at the maximum clinical dose. In rabbits, eptinezumab

was administered IV at 0, 75 and 150 mg/kg on GD7, 13 and 20; animals were sacrificed on GD29. Again, results from the DRF and pivotal studies were consistent. They showed no evidence of embryo-fetal mortality, alteration in growth or structural abnormalities. The maternal and fetal NOAEL is 150 mg/kg. This corresponded to an average maternal Cmax value of 4116 µg/ml which is 33x higher than the Cmax in humans at the maximum clinical dose.

In the pre-/post-natal development study, rats were treated once weekly from GD6, throughout gestation up to LD20 with eptinezumab at doses of 0, 75 and 150 mg/kg IV. In maternal F0 animals, no eptinezumab-related effects were observed on delivery endpoints or pup survival. The only finding was a greater food consumption in lactating females at 150 mg/kg up to LD14. This coincided with greater pup body weights on PND 14 to 17. As these effects were small and transient, it is agreed that they are not adverse. In F1 off-spring from eptinezumab-treated maternal animals, no eptinezumab-related effects were observed on fetal and post-natal development, including sexual maturation. Based on these results, the maternal and the off-spring NOAEL is considered to be 150 mg/kg.

Juvenile animal toxicity

In line with the agreed PIP, juvenile animal studies were performed to assess the toxicity of eptinezumab treatment including its impact on bone development since literature data indicate that CGRP may play a role in regulation of bone metabolism (Irie et al., 2002). Juvenile rats were treated once weekly from PND 28 through PND 43 (DRF study) or PND 91 (pivotal study) at doses up to 150 mg/kg IV. The pivotal study was followed by a 6-week treatment-free period. Both studies have a general repeat-dose toxicity design; additional assessment of developmental landmarks, behavioural performance and bone measurements were included in the pivotal study.

In the pilot study, eptinezumab was well tolerated without adverse effects. In the pivotal study, there were two unscheduled deaths including 1 control animal. Based on a lack of an identifiable cause of death and the overall low incidence, none of these deaths were attributed to eptinezumab, which is agreed. There were no eptinezumab-related effects on developmental parameters and behavioural performance. As regards bone development, there were not eptinezumab-related changes in long bone measurements in vivo and ex vivo. There were no eptinezumab-related changes at the end of the treatment period with regard to bone mineral density in distal femur metaphysis, mid-femur diaphysis and lumbar vertebral body as determined by pQCT densitometry at doses up to 150 mg/kg. Thus, the juvenile study did not reveal an impact of eptinezumab on bone development in juvenile rats. Although the proposed indication includes only adult patients, the outcome of the study conducted in juvenile rats is communicated in section 5.3 of the SmPC.

Local tolerance

Local tolerance to IV administration of eptinezumab was assessed as part of the general repeat-dose toxicity studies in rats and cynomolgus monkeys. In both studies there were no gross- or eptinezumab-related microscopic lesions at the IV injection sites. Dedicated studies were performed to assess local tolerance to IM injection in rats and to SC injection in rats and cynomolgus monkeys. Eptinezumab was well tolerated; there were no gross pathology findings at the IM and SC injection sites; microscopic findings were generally considered to be related to the injection procedure.

Immunotoxicity

Immunotoxicity of eptinezumab was assessed based on immunophenotyping of PBMC in the cynomolgus chronic toxicity study. As there were no eptinezumab-related changes additional immunotoxicity studies are not warranted.

Impurities

Polyethyleneimine (PEI) is used during manufacture of eptinezumab and some residual PEI is present in the eptinezumab drug substance. Thus, the potential toxicity of PEI was evaluated in rats. Animals were administered PEI at 80 µg/kg IV on days 1, 8 and 15; main study animals were euthanised one day after the last dose, recovery animals after a 2-week treatment-free period. In this 2-week study, PEI was well tolerated; the administered 80 µg/kg/dose is considered the NOAEL. This is agreed.

The maximum limit for residual PEI as specified in accordance with ICH Q3A is 1 µg/mg eptinezumab. This translates to a maximum PEI dose of 4.3 µg/kg based on 300 mg eptinezumab/70 kg human. Thus, the PEI dose at NOAEL in rats is approx. 18x higher than the maximum anticipated dose in humans. However, the human equivalent dose to the rat NOAEL is 12.9 µg/kg which is only 3x higher than the maximum anticipated dose in humans. This is a rather low margin.

In study report ALD518-001-TOX, a literature review is mentioned based on which a maximum safe PEI dose for a 60 kg human was calculated as 5.6 mg. This corresponds to a PEI dose of 93 µg/kg, which is approx. 21x higher than the maximum anticipated PEI dose in humans. This literature-based review was requested to further support the current specification for residual PEI of "≤ 1.0 µg/mg". The Applicant responded that this review did not find literature reporting non-clinical NOAEL for parenteral administration of PEI and that the safe parenteral dose (5.6 mg for 60 kg individual) was calculated based on publicly available oral LD50 values for mice and rats.

In addition, the applicant justified the specification for residual PEI, by calculating a safe human dose, based on the cumulative PEI dose administered in the rat toxicity study ALD518-001-Tox. This is accepted, given that eptinezumab will be administered every 3 months only. According to the Applicant's calculation a safety margin of 7.7-fold can be derived. Taken together, the limit for residual PEI (≤ 1.0 µg/mg) is sufficiently justified and accepted.

2.5.5. Ecotoxicity/environmental risk assessment

Eptinezumab is a monoclonal antibody consisting of natural amino acids, and is therefore not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

The eptinezumab primary pharmacodynamics programme is appropriate and sufficient. These study adequately support the use of rats, rabbits and cynomolgus for the safety assessment of eptinezumab.

A discussion on secondary pharmacodynamics taking into account potential consequences of blocking the pleiotropic functions of GCRP has not been submitted. This is accepted given that specific theoretical risks associated with blockade of CGRP-dependent signalling (i.e. cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebro-vascular accident, transient ischemic attack, angina, unstable and poorly controlled hypertension; use in pregnancy including those at risk of pre-eclampsia) have been included in the RMP.

The effects of eptinezumab on safety pharmacology endpoints were assessed as part of the general toxicity studies in rats and cynomolgus monkeys. Importantly, there were no effects on cardiovascular endpoints and respiration rate in cynomolgus monkeys. It is agreed that these studies did not identify any safety concerns.

In the repeat-dose toxicity studies in rats and cynomolgus monkeys, eptinezumab was generally well tolerated. In all studies the NOAEL was the highest-dose administered, resulting in sufficient exposure margins to the exposure in humans at the maximum anticipated clinical dose.

A product-specific carcinogenicity risk assessment was provided taking into account non-clinical data for eptinezumab and a literature review on the potential role of CGRP in tumorigenesis and its effect on the immune system. It is agreed that the carcinogenic risk associated with eptinezumab is low.

A comprehensive reproductive and developmental toxicity programme was conducted in rats and rabbits. These studies did not reveal any adverse effects on fertility, pregnancy outcome or embryo-fetal development. This is reflected in the SmPC, section 5.3.

In line with the agreed PIP, juvenile animal studies were performed to assess the impact of eptinezumab on bone development. To this end, juvenile rats were treated from PND28 through PND 91. The study did not identify any eptinezumab effects on bone development. The outcome of the juvenile study is communicated in section 5.3 of the SmPC.

Polyethyleneimine (PEI) is used during manufacture of eptinezumab and some residual PEI is present in the eptinezumab drug substance. The potential toxicity of this impurity was studied in a 2-week study in rats. PEI was well tolerated in this study; thus; the current specification for residual PEI in the eptinezumab drug substance is sufficiently supported.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, eptinezumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on non-clinical aspects

From the non-clinical point of view, the marketing authorisation application for eptinezumab is considered approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Listing of Eptinezumab Efficacy Studies in Patients with Migraine

Study Number	Diagnosis	Objectives of Study	Study Design and Type of Control	Number of Subjects Treated (Full Analysis Population)	Treatment Schedule	Study Duration[a]
Pivotal Studies						

006	Episodic migraine	Efficacy; Safety; PK; Immunogenicity	parallel group; double-blind; placebo controlled	***4 treatment groups:*** 222 placebo 223 active (30 mg) 221 active (100 mg) 222 active (300 mg)	***4 total infusions:*** day 0 week 12 week 24 week 36	56 weeks
011	Chronic migraine	Efficacy; Safety; PK; Immunogenicity	parallel group; double-blind; placebo controlled	***3 treatment groups:*** 366 placebo 356 active (100 mg) 350 active (300 mg)	***2 total infusions:*** day 0 week 12	32 weeks
Supportive Studies						
002	Episodic migraine	Safety; Efficacy; PK; Immunogenicity	parallel group; double-blind; placebo controlled	***2 treatment groups:*** 82 placebo 81 active (1000 mg)	Single infusion	24 weeks
005	Chronic migraine	Dose response; Safety; Duration of effect; PK; Immunogenicity	parallel group; double-blind; placebo controlled; dose-ranging	***5 treatment groups:*** 116 placebo 123 active (10 mg) 117 active (30 mg) 118 active (100 mg) 114 active (300 mg)	Single infusion	49 weeks

Abbreviations: PK = pharmacokinetic

[a] Duration of the study following the first treatment.

Source: ALD403-CLIN-002 CSR, ALD403-CLIN-005 CSR, ALD403-CLIN-006 CSR, ALD403-CLIN-011 CSR.

2.6.2. Clinical Pharmacology

2.6.2.1. Pharmacokinetics

Pharmacokinetic and pharmacodynamic data on eptinezumab were collected in a total of 10 clinical studies (see Table 1; pivotal studies ALD403-CLIN-006 and ALD403-CLIN-011 are not listed, although these studies also contributed to PK/PD data). Single doses of 1 to 1000 mg IV and 100 mg SC and multiple doses of 30 mg, 100 mg and 300 mg IV were investigated.

The proposed standard dose for this application is 100 mg eptinezumab administered by intravenous infusion every 12 weeks, while some patients may also benefit from a dosage of 300 mg administered by intravenous infusion every 12 weeks.

Table 1: Summary of Clinical Studies Contributing Pharmacokinetic and Pharmacodynamic Data

Study Number (Module Number)	PK/PD Objectives	Study Design	Treatments	Population Studied	Number of Subjects Treated
ALD403-CLIN-001 (5.3.3.1)	Part A: To determine PK and PD of eptinezumab Part B: To determine PK of eptinezumab when administered with sumatriptan vs sumatriptan alone	Randomized double-blind, placebo-controlled	Part A: Placebo or eptinezumab 1, 3, 10, 30, 100, 300, or 1000 mg IV Placebo or eptinezumab 100 mg SC Subjects were administered a single dose on Day 1 Part B: Placebo or eptinezumab 300 mg Subjects were administered a single IV infusion in combination with sumatriptan 6 mg administered SC on Day 1	Part A: Healthy adult male and female subjects Part B: Healthy adult females Adult males and females with history of migraine	Total: 104 Part A: Active: 61 Placebo: 31 Part B: Active: 6 Placebo: 6
ALD403-CLIN-002 (5.3.5.1)	To determine the PK of eptinezumab	Randomized, double blind, placebo-controlled, parallel-group	Eptinezumab 1000 mg Placebo Subjects were administered a single IV infusion on Day 0	Adult males and females with frequent episodic migraines	Total: 163 Active: 81 Placebo: 82
ALD403-CLIN-005 (5.3.5.1)	To determine the PK of a single-dose of eptinezumab administered IV	Randomized, double-blind, placebo-controlled, parallel-group, dose-response	Eptinezumab 10 mg Eptinezumab 30 mg Eptinezumab 100 mg Eptinezumab 300 mg Placebo Subjects were administered a single IV infusion on Day 0	Adult males and females with chronic migraine	Total: 616 10 mg: 130 30 mg: 122 100 mg: 123 300 mg: 120 Placebo: 121
ALD403-CLIN-007 (5.3.5.1)	To determine the PK and PD of IM administration of eptinezumab and placebo in healthy subjects	Randomized, double-blind, placebo-controlled	Group A: 100 mg/mL eptinezumab IM, placebo SC, placebo IV Group B: 100 mg/mL eptinezumab SC, placebo IM, placebo IV Group C: 100 mg eptinezumab IV, placebo IM, placebo SC Group D: 300 mg eptinezumab IM, placebo SC, placebo IV Group E: Placebo IM, placebo SC, placebo IV Subjects received 3 injections on Day 1 and on Day 84 (total of 6 injections)	Healthy adult male and female subjects	Total: 60 Group A: 13 Group B: 12 Group C: 12 Group D: 12 Group E: 11
ALD403-CLIN-010 (5.3.4.2)	To assess effects of eptinezumab on human energy metabolism To determine free eptinezumab concentrations	Randomized, double-blind, placebo-controlled, parallel-group	Eptinezumab 100 mg Placebo Subjects were administered a single IV infusion on Day 0	Overweight and obese adults, male and female, who are otherwise healthy	Total: 24 100 mg: 16 Placebo: 8
ALD403-CLIN-012 (5.3.4.2)	To assess effects of eptinezumab on insulin sensitivity To determine free eptinezumab concentrations	Randomized, double-blind, placebo-controlled, parallel-group	Eptinezumab 100 mg Placebo Subjects were administered a single IV infusion on Day 1	Adult male and female subjects with T1DM who were receiving stable insulin therapy via a continuous subcutaneous insulin infusion pump.	Total: 21 100 mg: 14 Placebo: 7

Study Number (Module Number)	PK/PD Objectives	Study Design	Treatments	Population Studied	Number of Subjects Treated
ALD403-CLIN-013 (5.3.5.2)	To evaluate the PK and immunogenicity of repeat doses of ALD403 administered IV to subjects with chronic migraine	Phase 3, open-label, repeat doses	ALD403 300 mg injection Subjects were administered 4 IV infusions of ALD403 on Day 0 and at Weeks 12, 24, and 36 in the primary treatment phase. Subjects who received all 4 infusions of ALD403 in the primary treatment phase and entered the secondary treatment phase received up to 4 additional infusions at Weeks 48, 60, 72, and 84 for a total of 8 infusions over the 2 treatment phases.	Adult males and females with diagnosis of migraine at ≤50 years of age with history of chronic migraine ≥1 year	Total: 128
ALD403-CLIN-014 (5.3.1.2)	To assess comparative PK, additional PK endpoints of commercial vs clinical drug product (Test vs Reference)	Randomized, double-blind, parallel-group	Eptinezumab Reference 300 mg Eptinezumab Test 300 mg Subjects were administered a single IV infusion on Day 0	Healthy adult males and females	Total: 165

IM = intramuscular; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous, T1DM = type 1 diabetes mellitus.

Pharmacokinetic data analysis

The concentrations of free eptinezumab were listed and summarized by timepoint and dose group, and descriptive statistics were provided. Plots of the individual concentrations of eptinezumab, and plots of the mean or median concentrations were presented over time (linear and log-scales). Non-compartmental analyses using PhoenixTM WinNonLin® (v 6.1 or higher) were carried-out to derive PK parameters such as Cmax, Tmax, AUC, t1/2, λZ, CL, Vd. PK parameters were summarized including arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum, median, maximum, geometric mean, and geometric CV. PK data analyses are considered appropriate.

Population PK modelling

Pharmacokinetics of eptinezumab were further described using a population PK modeling approach. The PK dataset only included PK information related to IV administration of eptinezumab. Overall, a total of 8 clinical studies (CLIN-001, CLIN-002, CLIN-005, CLIN-006, CLIN-010, CLIN-011, CLIN-012, and CLIN-013) comprising 2123 patients and healthy volunteers were included in the population PK analysis. The size of the database is deemed appropriate.

The final population PK model was a 2-compartment model with linear elimination. In general, high variability of eptinezumab PK parameters was observed. Body weight, CLcr, disease (healthy, episodic or chronic migraine), sex and baseline MMD were identified as significant covariates explaining the variability of eptinezumab CL and/or V (Table 6).

Table 6: Stepwise Covariate Analysis

Step	Model	OFV	#Param	Delta 1	Delta 2
Base	2-CPT Model, Mixed error, Block Eta Vp and CLp[a]	274166.0	11	NA	NA
Forward Search					
Step 1	+Weight on CL & CLp (Fitted)	273136.7	12	-1029.3	-1029.3
Step 2	+Weight on Vc & Vp (Fitted)	272836.9	13	-1329.1	-299.8
Step 3	+DS on V	272717.3	15	-1448.7	-145.3
Step 4	+DS on CL	272635.0	17	-1531.0	-82.3
Step 5	+CL_{cr}_cap on CL	272594.8	18	-1571.2	-40.2
Step 6	+MDBase on CL	272584.0	19	-1582.0	-10.8
Step 7	+Sex on V	272561.2	20	-1604.8	-22.8
Backward Search	During the backward elimination, none of the covariates were removed.				

[a]Correlation between BSV of CLp and Vp was observed.
Forward: Forward covariate analyses; statistically significant decrease of objective function (OFV) at $p<0.05$ (Delta 1 of 3.84, for one degree of freedom (i.e., one parameter difference) between covariate and base models were selected for inclusion.
Backward: During the backward elimination, none of the covariates were removed. Backward covariate deletion process; the full model underwent the backward deletion process which consisted of the removal of covariates one at a time in a stepwise manner using likelihood ratio test (LRT) (at $p <0.001$ Delta 1 of 10.84 for one degree of freedom and 13.8 for two degrees of freedom).
#Param: number of parameters, N/A: Not applicable; OFV= objective function value; V: volume of distribution; Delta1: Difference between the OFV value for the tested model and the base model without any covariates; Delta2: Difference between the OFV value for the tested model and the previous model without the additional covariate; MDBase= baseline MMD

The number of covariates included suggests an over-parameterization of the model. In general, it appears unexpected that disease state and baseline MMD are significant covariates influencing eptinezumab PK. In the clinical studies, healthy subjects usually presented lower Cmax and AUC when compared to migraine patients, while CL and V seemed to be slightly increased in the healthy. The root cause of the described exposure differences has not been identified, but it is assumed to be due to variability associated with study-to-study factors and/or the bioanalytical methodology.

PK parameters derived from the final population PK model are described in table 7.

Table 7: Population PK Parameters of Eptinezumab Derived from the Final PK Model

Parameter	Estimate	RSE%	BSV%	RSE%	Shrinkage
CL (L/h)	0.00620	0.8	29.0	4.4	9.0%
× (WT/70)$^{\theta}$	0.709	2.8	N/A		
×exp Θ if EM	-0.231	-2.6			
× exp Θ if CM	-0.272	-2.8			
× (MDBase/13.0)$^{\theta}$	0.044	2.3			
× (CL_{cr_cap}/118)$^{\theta}$	0.162	3.5			
Vc (L)	3.636	1.1	31.0	2.3	20.2%
× (WT/70)$^{\theta}$	0.544	3.7	N/A		
× expΘ if EM	-0.311	-2.8			
× expΘ if CM	-0.422	-3.0			
× expΘ if Male	0.091	2.7			
CLp× (WT/70)$^{\theta}$ (L/h)	0.039	2.2	111.3	5.7	56.8%
Vd× (WT/70)$^{\theta}$ (L)	2.012	1.4	34.8	4.6	29.2%
Error Model					
Additive (ng/mL)	37.5	5.7	N/A		
Prop Error (%)	25.2				

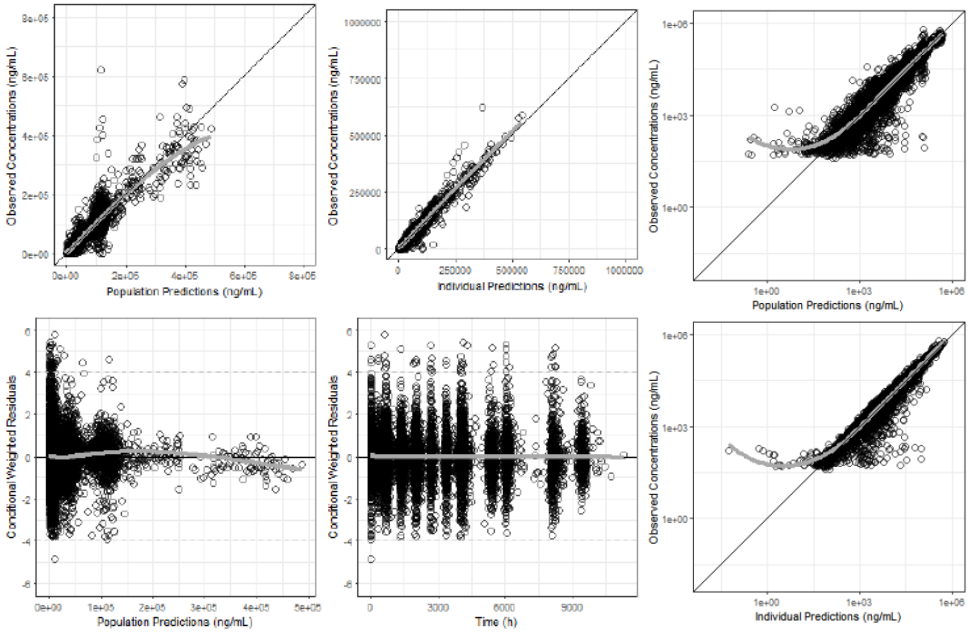
For continuous covariates (weight, MDBASE, CL_{cr_cap}), a power model standardized by the median was used. For the categorical covariates (disease state, sex) an exponentiated factor relative to the reference category was used.
BSV= Between-subject variability; CL= systemic clearance; CM: chronic mirgraine; CLcr_cap: creatinine clearance capped at 150 mL/min; CV= coefficient of variation; CLp= inter-compartmental clearance; EM: episodic migraine; MDBase=baseline MMD; RSE= relative standard error; Vc= central volume of distribution; Vp= peripheral volume of distribution; WT= body weight (kg).
Note 1: BSV% were calculated as $\sqrt{e^{omega}x100}$.
Note 2: The full omega block for the final model is presented in Appendix 1.6.1.

Evaluation and Qualification of Models

The quality-of-fit of the model was evaluated using a standard model discrimination process including statistical criteria as well as pertinent graphical representations of goodness-of-fit. The population PK model derived after the covariate analysis was validated using visual predictive checks on the observed time-concentrations profiles.

Goodness-of-fit (GOF) plots derived with the final population PK model of eptinezumab are presented in the figure below.

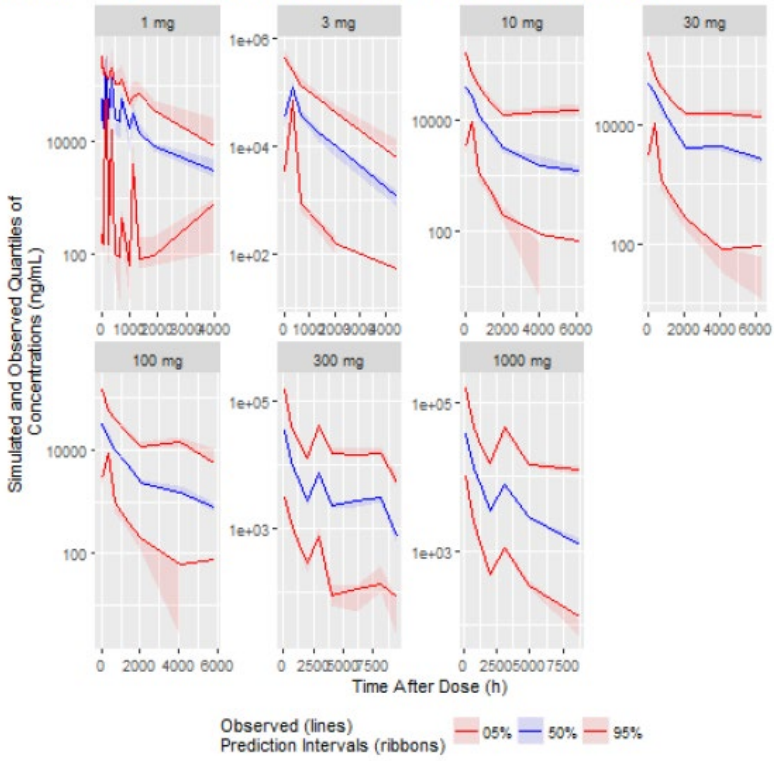
Goodness-of-Fit for Final Model of Eptinezumab



GOF plots reveal an overestimation of low eptinezumab concentrations and a slight underestimation of high eptinezumab concentrations. In general, only few data were available for doses below 10 mg. Given the departure from linearity detected at lower dose levels (≤ 10 mg), target-mediated drug disposition is suspected. Therefore, the selected population PK model does not adequately fit the low eptinezumab concentrations included.

The visual predictive check (VPC) semi-log plots of eptinezumab concentrations are presented in Figure 1.10.2.

1.10.2. Visual Predictive Check by Study – Semi-Log Plots



Observed median and upper/lower 90th percentiles of observed eptinezumab concentrations were contained within the model-predicted ranges (shaded areas).

Ultimately, it is agreed that the model provides acceptable estimations of eptinezumab exposure for the relevant doses (100 mg and 300 mg) of this application.

Absorption

In study ALD403-CLIN-001, the absolute bioavailability of SC ALD403 (100 mg) was calculated by AUC SC (Cohort I) /AUC IV (predicted) to be 70.33%. However, results on eptinezumab PK and bioavailability after SC administration are not considered relevant for this application, since eptinezumab is presently intended to be solely administered via the IV route. Similarly, PK data from the SC route of administration were not included in the population PK model. As a consequence, no estimation of Ka or F was conducted.

Bioequivalence

Study ALD403-CLIN-014 compared the PK of the Commercial Drug Product (Test) to the eptinezumab Clinical Drug Product (Reference, C2.0). In principle, in vivo comparable PK can be concluded as the 90% CI for the rations of the LSM for AUC0-inf and Cmax are contained inside the acceptance 80-125% interval. The incidence of treatment-emergent ADA-positive subjects was higher for eptinezumab commercial DP compared to eptinezumab clinical DP. The applicant considered that these observed differences can be related to the small sample size and have no clinically meaningful relevance.

Distribution, Metabolism and Elimination

Apparent clearance and central volume of distribution of eptinezumab estimated in the population PK analysis was 0.15 L/d and 3.64 L, respectively. These values correspond to typical values described for CL and Vd of

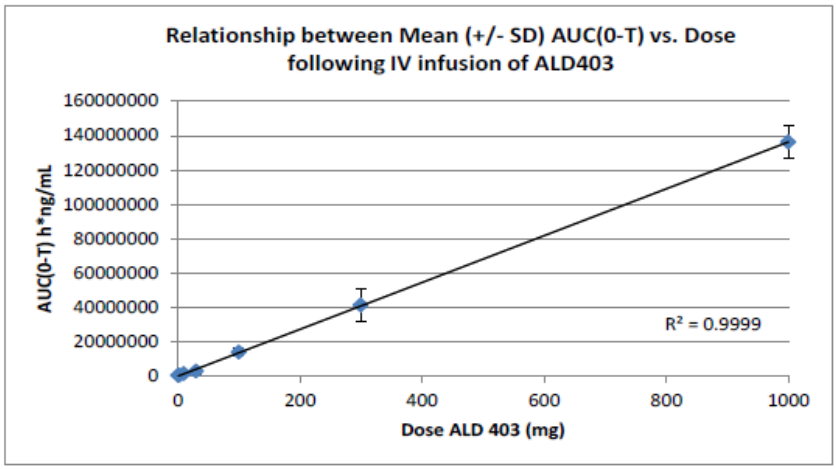
monoclonal antibodies and indicate minimal extravascular distribution of free eptinezumab and relatively slow elimination from the plasma compartment. Half-life of eptinezumab was determined to be 27 days.

Like other therapeutic antibodies, eptinezumab is expected to be primarily metabolized via proteolytic catabolism. Due to its large molecular size, renal excretion of intact eptinezumab is unlikely.

Dose proportionality and time dependency

In **study ALD403-CLIN-001**, the relationship between dose and AUC(0-T) following single IV administration of 3, 10, 30, 100, 300, or 1000 mg eptinezumab was shown to be linear (Figure 4 below).

Figure 4: Relationship between Mean (±SD) Free ALD403 $AUC_{(0-T)}$ and Dose following Intravenous Infusion of ALD403



In **study ALD403-CLIN-005**, dose proportionality for eptinezumab pharmacokinetics was evaluated by comparison of descriptive statistics of dose normalized parameters Cmax, AUC0-tlast, and AUC0-inf between dose levels (Table 15) and statistical Hummel power analysis (Table 16).

Table 15. Summary of Dose Normalized Free ALD403 Pharmacokinetics Parameters (PK Population)

Parameter	Statistic	ALD403 300 mg	ALD403 100 mg	ALD403 30 mg	ALD403 10 mg
C_{max}/D	n	114	115	110	117
(ng/mL/mg)	Mean (SD)	386.3 (101)	403.8 (178.2)	390.8 (189.2)	472.7 (250.1)
	CV%	26.2	44.1	48.4	52.9
	Median	367.3	358.4	368	406.3
	Min, Max	226, 846	196, 1490	34.1, 1950	153, 1520
	Geo Mean (CV%)	374.8 (59.2)	378.3 (298.5)	360.4 (1263.5)	428.6 (964.0)
$AUC_{0-tlast}$/D	n	114	115	110	117
(h*ng/mL/mg)	Mean (SD)	233200 (68310)	223800 (83030)	214800 (93300)	259300 (147700)
	CV%	29.3	37.1	43.4	57.0
	Median	230300	206400	215600	227300
	Min, Max	1020, 404000	1210, 562000	273, 594000	1260, 1040000
	Geo Mean (CV%)	209100 (415.7)	197200 (428.1)	163100 (24754.9)	213600 (1047.1)
AUC_{0-inf}/D	n	109	105	92	102
(h*ng/mL/mg)	Mean (SD)	242200 (59280)	234600 (77840)	239900 (84310)	293700 (148500)
	CV%	24.5	33.2	35.1	50.6
	Median	237700	222600	241300	263800
	Min, Max	96400, 405000	84800, 575000	18400, 597000	93500, 1090000
	Geo Mean (CV%)	234600 (8.3)	222400 (14.8)	222900 (33.4)	268700 (24.6)

Table 16. Hummel Power Analysis of Dose Proportionality for Free ALD403 Pharmacokinetics Parameters (PK Population)

		Power Model	90% Confidence Interval	
Parameter	Coefficient	Estimate	Lower Limit	Upper Limit
C_{max} (ng/mL)	Intercept	6.026	5.909	6.143
	Slope	0.973	0.945	1.001
$AUC_{0-\infty}$ (h*ng/mL)	Intercept	12.520	12.422	12.619
	Slope	0.962	0.939	0.985

Both methods demonstrated that pharmacokinetics of IV administered eptinezumab exhibited linearity in response to dose increase in the tested range of 10 mg to 300 mg.

However, at dose levels ≤ 10 mg, target mediated drug disposition is suspected, given the slight departure from linearity detected at the lower dose level (10 mg) in the population PK model and the higher CL values determined in study ALD403-CLIN-001 for eptinezumab doses of 1 – 10 mg.

Referring to the population PK analysis, an accumulation ratio of 1.08 and 1.15 for Cmax and AUC(0-τ) for dosing of 100 mg or 300 mg eptinezumab every 12 weeks was determined. This is in line with the expectation of nearly no accumulation (AR calculated = 1.13) if the estimated elimination half-life of 27 days in the context of the 3-monthly dosing interval is considered.

Variability

Moderate to high interindividual variability as assessed by %CV was observed in the clinical studies conducted in patients with EM and/or CM. In study ALD403-CLIN-005, variability of both AUC parameters was within levels of 30% to 50%. In study ALD403-CLIN-006, intersubject variability of AUC0-2016, AUC0-last, and Cmax after single (first) dose ranged from 36.1 to 83.4%. At steady state after multiple dosing, intersubject variability of AUC0-last, AUC0-τ, and Cmax was 42.8 to 66.9%. In study ALD403-CLIN-011, intersubject variability of AUC0-last, AUC0-2016, and Cmax ranged from 27.8% to 36.6%. In study ALD403-CLIN-013, intersubject variability of AUC and Cmax ranged from 39 – 72%.

Referring to the population PK analysis, variability could be explained by the covariates body weight, CLcr, disease (healthy, CM or EM patients), and baseline migraine days. In the final population PK model, relative standard error (RSE) values were less than 20% for the estimated parameters. Residual variability of the model was rather low (additive error = 37.5 ng/mL and proportional error = 25.2 %).

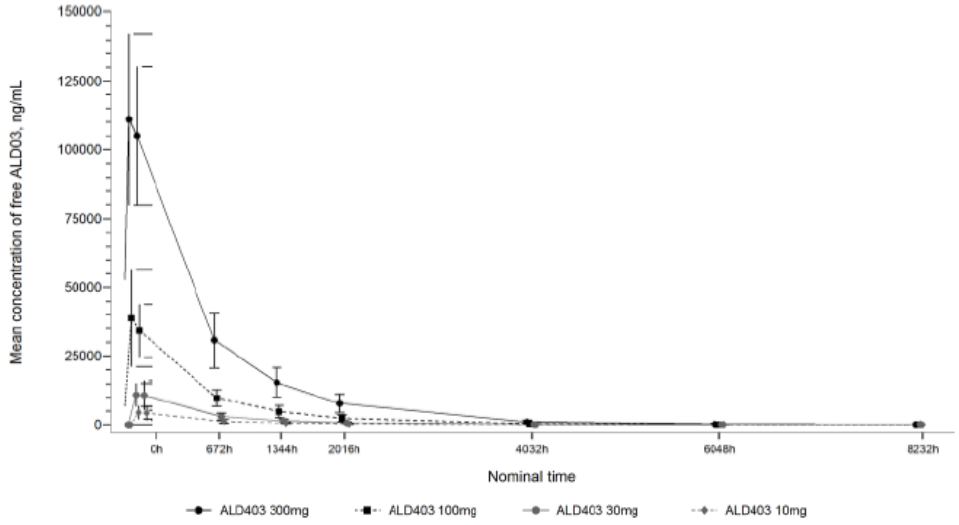
PK in migraine patients

Study ALD403-CLIN-005 (single dose PK)

This was a parallel-group, double-blind, randomized, placebo-controlled, dose-ranging study conducted in subjects with chronic migraine. Subjects were equally randomized to receive either eptinezumab 10, 30, 100, 300 mg, or placebo. Blood samples for PK analysis were drawn at pre-dose, immediately post-dose (after infusion), and 4 hours post-end of infusion on Day 0, and during visits at Weeks 4, 8, 12, 24, 36, and 49.

Mean (±SD) plasma concentration versus time plots for free eptinezumab in linear scale are presented in Figure 4 below.

Figure 4. Mean (±SD) Free ALD403 Plasma Concentration vs Time Curves on Linear Scales (PK Population)



Pharmacokinetic parameters for free eptinezumab are presented Table 14 below.

Table 14. Summary of Free ALD403 Pharmacokinetics Parameters (PK Population)

Parameter	Statistic	ALD403 300 mg	ALD403 100 mg	ALD403 30 mg	ALD403 10 mg
C_{max} (ng/mL)	n	114	115	110	117
	Mean (SD)	115200 (31100)	39800 (17500)	11720 (5678)	4739 (2506)
	CV%	27.0	44.0	48.4	52.9
	Median	109400	35410	11040	4063
	Min, Max	41000, 254000	17200, 149000	1020, 58500	1530, 15200
	Geo Mean (CV%)	111400 (26.4)	37310 (34.7)	10810 (44.0)	4296 (43.7)
T_{max} (h)	n	114	115	110	117
	Median	1.25	1.17	1.315	1.25
	Min, Max	0.5, 5.42	0.58, 5.43	0.92, 5.83	0.85, 5.5
$AUC_{0\text{-tlast}}$ (h*ng/mL)	n	114	115	110	117
	Mean (SD)	69630000 (21010000)	21990000 (7728000)	6441000 (2799000)	2600000 (1480000)
	CV%	30.2	35.1	43.5	56.9
	Median	69090000	20590000	6469000	2294000
	Min, Max	307000, 121000000	121000, 40400000	8190, 17800000	12600, 10400000
Geo	Mean (CV%)	62110000 (86.4)	19450000 (84.7)	4891000 (183.5)	2140000 (103.6)
$AUC_{0\text{-inf}}$ (h*ng/mL)	n	109	105	92	102
	Mean (SD)	72300000 (18460000)	23030000 (7104000)	7193000 (2531000)	2945000 (1487000)
	CV%	25.5	30.8	35.2	50.5
	Median	71300000	22180000	7239000	2638000
	Min, Max	19600000, 121000000	8480000, 40500000	553000, 17900000	935000, 10900000
	Geo Mean (CV%)	69670000 (29.4)	21920000 (33.2)	6682000 (45.3)	2694000 (41.8)

$t_{½z}$ (h)	n	109	106	93	102
	Mean (SD)	679.1 (151.5)	660.1 (243.9)	651.2 (169.3)	710.2 (374.1)
	%CV	22.3	36.9	26.0	52.7
	Median	687.3	618.8	650.7	678.2
	Min, Max	175, 1200	199, 2530	322, 1500	282, 3970
λ_z (1/h)	n	109	106	93	102
	Mean (SD)	0.00109 (0.0003761)	0.001159 (0.0004111)	0.001131 (0.0002854)	0.001087 (0.0003147)
	%CV	34.5	35.5	25.2	28.9
	Median	0.001008	0.00112	0.001065	0.001022
	Min, Max	0.000578, 0.00396	0.000274, 0.00348	0.000464, 0.00215	0.000175, 0.00246
CL (mL/h)	n	109	105	92	102
	Mean (SD)	4.399 (1.345)	4.753 (1.677)	5.185 (5.472)	4.005 (1.527)
	CV%	30.6	35.3	105.5	38.1
	Median	4.208	4.493	4.144	3.791
	Min, Max	1.13, 10.4	1.74, 11.8	1.67, 54.3	0.915, 10.7
	Geo Mean (CV%)	4.22 (29.6)	4.495 (34.1)	4.487 (45.3)	3.721 (41.7)
V_z (mL)	n	109	105	92	102
	Mean (SD)	4162 (1106)	4221 (1509)	4765 (5470)	3969 (2176)
	CV%	26.6	35.7	114.8	54.8
	Median	4091	3983	3895	3728
	Min, Max	1060, 9780	1980, 13700	1550, 54400	1160, 17200
	Geo Mean (CV%)	4018 (28.1)	4022 (30.8)	4102 (44.2)	3578 (46.6)

Study ALD403-CLIN-006 (multiple dose PK)

This was a Phase 3, parallel group, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of the repeat doses of eptinezumab administered intravenously compared to placebo in subjects with FEM. Subjects were randomly assigned to 1 of 3 eptinezumab treatment groups (30, 100, or 300 mg of eptinezumab) or placebo treatment in a 1:1:1:1 ratio.

Administration of study drug included 4 total IV infusions of eptinezumab or placebo on Days 0, 84 (Week 12), 168 (Week 24), and 252 (Week 36). The PK analysis included evaluations of concentration-time profiles for free eptinezumab on the following days: predose on Day 0, and at Weeks 4, 8, 12, 16, 20, 24, 36, 48, and 56.

Following single and multiple doses, after reaching peak levels, mean concentration values of free eptinezumab declined with a relatively slow elimination phase over an approximately 12-week period. Due to limited blood sampling occasions, the peak concentration levels observed did not represent a true Cmax, which would be expected to occur toward the end of the infusion, and Cmax and AUC were expected to underestimate the eptinezumab exposure. However, plasma free eptinezumab concentrations generally increased with increasing doses of eptinezumab. Overall, the mean plasma predose concentrations of free eptinezumab appeared to achieve steady state within approximately 12 weeks after dosing.

Summaries of plasma free eptinezumab PK parameters derived for each eptinezumab dose after single and multiple doses are presented in Table 29 and Table 30.

Table 29: Mean (CV) Plasma ALD403 Pharmacokinetic Parameters After a Single IV Administration of ALD403 in Subjects With Frequent Episodic Migraines

Plasma PK parameters	ALD403 300 mg Mean (CV); N	ALD403 100 mg Mean (CV); N	ALD403 30 mg Mean (CV); N
N	216	213	206
$AUC_{0\text{-last}}$ (h*µg/mL)	32745 (41.0);216	10464 (41.2);213	3639 (77.6);206
$AUC_{0\text{-}2016}$ (h*µg/mL)	33289 (39.6);208	10595 (39.5);203	3804 (76.1);188
C_{max} (µg/mL)	30.6 (36.1);216	10.0 (54.1);213	3.64 (83.4);206
t_{max} (h)[a]	672.46 (574.12; 1394.00);216	672.35 (575.60; 2093.62);213	671.68 (525.98; 1413.97);206
C_{trough} Day 84 (µg/mL)	8.29 (59.1);209	2.54 (58.4);204	0.829 (94.4);190

Table 30: Mean (CV) Plasma ALD403 Pharmacokinetic Parameters After Multiple IV Administrations of ALD403 in Subjects With Frequent Episodic Migraines

	Mean (CV); N		
Plasma PK parameters	ALD403 300 mg	ALD403 100 mg	ALD403 30 mg
N	203	199	184
$AUC_{0\text{-last}}$ (h*µg/mL)	40737 (44.2);203	12941 (44.8);199	4170 (60.9);184
$AUC_{0\text{-}\tau}$ (h*µg/mL)	41715 (44.2);191	13332 (44.2);186	4297 (59.4);175
C_{max} (µg/mL)	36.8 (42.8);203	11.7 (53.2);199	4.01 (66.9);184
t_{max} (h)[a]	672.08 (0.00; 1342.53);203	672.60 (0.00; 1966.67);199	671.28 (0.00; 1966.42);184
C_{min} (µg/mL)	7.98 (59.0);203	2.47 (64.3);199	0.692 (80.7);184
t_{min} (h)[a]	0.00 (0.00; 2015.92);203	0.00 (0.00; 2015.97);199	0.00 (0.00; 2015.97);184
$C_{trough\ Day\ 168}$ (µg/mL)	9.58 (64.7);192	3.44 (148.4);187	1.01 (113.3);175
ARAUC	1.63 (285.8);189	1.58 (220.7);180	1.36 (60.3);166
ARC_{max}	1.56 (285.1);201	1.39 (122.2);196	1.36 (73.3);177

Population PK analysis

The PK population consisted of a total of 2123 subjects treated with eptinezumab. The population consisted primarily of females (83.8%) and categorized as white race sub-type (88.5%). Median (range) age and body weight in the PK population were 39.0 years (18 to 71 years) and 74.2 kg (39.2 to 190 kg), respectively. Based upon the estimated glomerular filtration rate (eGFR) prior to treatment, the majority of subjects had normal eGFR (55.3%) or mild decrease in eGFR (41.9%). The average monthly migraine days (MMD) during the 28-day screening period was approximately 14 days for subjects dosed with eptinezumab 10-300 mg (studies CLIN-005, -006 and -011). The majority of subjects were ADA negative (83.8%) compared to 13.1% of subjects who were ADA positive, and approximately 2.5% had no ADA results available. Descriptive statistics of PK parameters of eptinezumab following a single 30-minute to 1-hour IV infusion and following multiple dose 30-minute to 1-hour IV infusions are presented by dose in Table 8 and Table 11/12, respectively.

Table 8: Descriptive Statistics – PK Parameters of Eptinezumab following a 30-minute to 1-h IV Infusion by Dose – Single Dose

PK Parameter	Eptinezumab Dose (mg)						
	1 (n=4)	3 (n=6)	10 (n=130)	30 (n=336)	100 (n=727)	300 (n=833)	1000 (n=87)
$AUC_{0\text{-}12wk}$ (h*µg /mL)							
Mean (CV%)	158 (57.9)	251 (24.4)	2050 (47.3)	5770 (41.1)	17900 (29.0)	54500 (27.7)	164000 (24.0)
Median [Min, Max]	125 [90.9, 292]	271 [137, 312]	1830 [819, 7480]	5360 [1240, 21000]	17400 [6350, 55700]	52900 [15400, 122000]	162000 [98100, 271000]
C_{max} (µg/mL)							
Mean (CV%)	0.279 (59.0)	0.460 (29.7)	4.32 (56.8)	12.4 (38.6)	37.3 (28.1)	114 (27.7)	348 (22.4)
Median [Min, Max]	0.219 [0.156, 0.520]	0.512 [0.196, 0.572]	3.58 [1.72, 21.5]	11.5 [2.65, 38.8]	35.9 [13.2, 128]	111 [29.8, 360]	346 [210, 574]
C_{avg} (µg/mL)							
Mean (CV%)	0.0785 (57.9)	0.124 (24.4)	1.02 (47.3)	2.87 (41.2)	8.95 (29.3)	27.2 (27.8)	81.3 (24.0)
Median [Min, Max]	0.0619 [0.0451, 0.145]	0.134 [0.0681, 0.155]	0.908 [0.406, 3.71]	2.67 [0.613, 10.4]	8.69 [3.19, 28.3]	26.2 [7.67, 60.5]	80.1 [48.7, 134]
C_{trough} (µg/mL)							
Mean (CV%)	0.0232 (60.2)	0.0333 (18.8)	0.294 (50.6)	0.821 (55.4)	2.66 (46.1)	8.06 (42.4)	23.3 (34.7)
Median [Min, Max]	0.0182 [0.0129, 0.0435]	0.0331 [0.0245, 0.0419]	0.276 [0.100, 1.12]	0.732 [0.0879, 3.76]	2.52 [0.363, 8.31]	7.40 [0.845, 21.1]	22.9 [9.82, 43.9]

$AUC_{0\text{-}12wk}$: area under the curve from time zero to 12 weeks; C_{avg}: average concentrations; C_{max}: maximum concentrations; C_{trough}: concentration observed at the end of the dosing interval (12 weeks).
Note: A total of 5 subjects received IV infusions over approximately 2 h.

Table 11: Descriptive Statistics – PK Parameters of Eptinezumab following a 30-minute to 1-h IV Infusion of Eptinezumab by Dose – Steady-State

PK Parameter	Eptinezumab Dose (mg)						
	1 (n=4)	3 (n=6)	10 (n=130)	30 (n=336)	100 (n=727)	300 (n=833)	1000 (n=87)
$AUC_{0\text{-}\tau}$ (h*µg/mL)							
Mean (CV%)	183 (60.0)	282 (23.0)	2350 (47.5)	6640 (43.3)	20800 (32.1)	63100 (30.1)	187000 (25.4)
Median [Min, Max]	143 [103, 345]	300 [165, 351]	2110 [906, 7990]	6180 [1320, 25400]	20000 [7030, 60000]	60500 [18500, 142000]	181000 [107000, 318000]
$C_{ss,av}$ (µg/mL)							
Mean (CV%)	0.0910 (60.0)	0.140 (23.0)	1.17 (47.5)	3.29 (43.3)	10.3 (32.1)	31.3 (30.1)	93.0 (25.4)
Median [Min, Max]	0.0708 [0.0512, 0.171]	0.149 [0.0819, 0.174]	1.05 [0.450, 3.96]	3.06 [0.655, 12.6]	9.93 [3.49, 29.7]	30.0 [9.18, 70.3]	89.6 [53.1, 158]
$R_{ac}(AUC_\tau)$							
Mean (CV%)	1.15 (1.92)	1.13 (3.27)	1.14 (3.98)	1.14 (6.55)	1.15 (7.69)	1.15 (6.27)	1.14 (3.79)
Median [Min, Max]	1.15 [1.13, 1.18]	1.12 [1.10, 1.20]	1.14 [1.06, 1.28]	1.13 [1.02, 1.63]	1.14 [1.01, 2.08]	1.14 [1.01, 1.78]	1.14 [1.07, 1.23]
$R_{ac}(C_{max})$							
Mean (CV%)	1.10 (0.675)	1.09 (2.83)	1.08 (2.42)	1.08 (2.93)	1.08 (3.66)	1.08 (3.17)	1.08 (2.12)
Median [Min, Max]	1.10 [1.09, 1.10]	1.08 [1.07, 1.15]	1.08 [1.03, 1.17]	1.07 [1.01, 1.24]	1.08 [1.01, 1.43]	1.08 [1.01, 1.29]	1.08 [1.04, 1.12]

$AUC_{0\text{-}\tau}$: area under the concentration-time curve during a dosing interval (12 weeks) at steady-state; $C_{ss,av}$: average steady-state drug concentrations during a dosing interval; $R_{ac}(AUC_\tau)$: Accumulation ratio based on AUC_τ; $R_{ac}(C_{max})$: Accumulation ratio based on C_{max}.
Note: A total of 5 subjects received IV infusions over approximately 2 h.

Table 12: Descriptive Statistics – PK Parameters of Eptinezumab following a 30-minute IV Infusion of Eptinezumab by Dose – Steady-State

PK Parameter	Eptinezumab Dose (mg)						
	1 (n=0)	3 (n=0)	10 (n=11)	30 (n=26)	100 (n=384)	300 (n=483)	1000 (n=2)
$C_{max,ss}$ (µg/mL)							
Mean (CV%)	N/A	N/A	4.92 (36.3)	12.7 (34.8)	40.9 (26.6)	125 (29.2)	333 (0.965)
Median			4.59	11.4	39.4	121	333
[Min, Max]			[3.42, 9.71]	[7.09, 26.4]	[14.1, 83.1]	[33.1, 368]	[330, 335]
T_{max} (h)							
Median	N/A	N/A	0.75	0.75	0.50	0.50	0.77
[Min, Max]			[0.75, 0.80]	[0.72, 0.80]	[0.43, 0.80]	[0.33, 0.78]	[0.75, 0.78]
C_{trough} (µg/mL)							
Mean (CV%)	N/A	N/A	0.378 (39.3)	0.925 (56.7)	3.39 (52.1)	9.87 (47.0)	26.4 (12.2)
Median			0.357	0.754	3.13	9.08	26.4
[Min, Max]			[0.183, 0.710]	[0.162, 2.31]	[0.368, 14.7]	[0.970, 29.2]	[24.1, 28.6]

After a single IV administration of the to be marketed 100 mg and 300 mg dose, Cmax was 37.3 µg/mL and 114 µg/mL and AUC(0-12wk) was 17900 µgxh/mL and 54500 µgxh/mL. These values largely correspond to the values obtained by noncompartmental analysis in the individual studies. At steady state after 3-monthly dosing of eptinezumab, the population PK model predicted a Cmax of 40.9 µg/mL and 125 µg/mL and AUC(0-τ) of 20800 µgxh/mL and 63100 µgxh/mL for the 100 mg and 300 mg dose, respectively. Steady state was also analysed by noncompartmental analysis in study 006. However, due to infrequent sampling in this study the values for Cmax and AUC were underestimated, explaining the lower values (Cmax = 11.7 µg/mL and 36.8 µg/mL and AUC(0-τ) = 12941 µgxh/mL and 40737 µgxh/mL for the 100 mg and 300 mg dose) as compared to the population PK model derived PK parameters. Ctrough after single dosing was 2.66 µg/mL and 8.06 µg/mL for the 100 mg and 300 mg eptinezumab dose, respectively. Ctrough at steady state was 3.39 µg/mL and 9.87 µg/mL for the 100 mg and 300 mg eptinezumab dose, respectively.

Overall, PK of eptinezumab was consistent across the individual studies conducted in both healthy volunteers and migraine patients. Slightly higher eptinezumab exposure was observed in patients with chronic migraine as compared to healthy subjects (see Table 4 below). However, it is agreed that this difference is not considered clinically relevant, given the absence of safety results suggesting limits for maximum eptinezumab exposure and the relatively flat exposure response relationship seen in treatment with eptinezumab.

Table 4: Free Eptinezumab Pharmacokinetic Parameters after 300 mg IV Infusion – Comparison of Healthy Subjects (Study ALD403-CLIN-014) and Subjects with Chronic Migraine (Study ALD403-CLIN-005 and ALD403-CLIN-013)

		ALD403-CLIN-014 (Healthy Subjects)		ALD403-CLIN-005 (Subjects with Chronic Migraine)	ALD403-CLIN-013 (Subjects with Chronic Migraine)
Parameter (units)	Statistic	300 mg (Commercial)	300 mg (Clinical)	300 mg	300 mg
C_{max} (µg/mL)	N	80	85	114	125
	Mean (±SD)	106.3 (±30.880)	102.0 (±40.039)	115.2 (±31.100)	106 (±75.941)
	Min, Max	58.1, 265	17.1, 318	41.0, 254.0	16.0, 620
T_{max} (h)	N	80	85	114	125
	Median	2.50	2.50	1.25	0.72
	Min, Max	0.50, 24.5	0.22, 190.0	0.50, 5.42	0.50, 1.45
AUC_{0-t} (µg*h/mL)	N	80	85	114	125
	Mean (±SD)	55379.9 (±17014.36)	52066.8 (±15242.54)	69630.0 (±21010.00)	53163.2 (±20567.84)
	Min, Max	18763, 120465	8425, 95946	307, 121000	11415, 156229
$AUC_{0-\infty}$ (µg*h/mL)	N	77	83	109	113
	Mean (±SD)	59734.9 (±20180.51)	56187.4 (±16830.88)	72300.0 (±18460.00)	60135 (±25161.20)
	Min, Max	26327, 143816	8783, 112058	19600, 121000	13181, 194467
$t_{½}$ (h)	N	77	83	109	113
	Mean (±SD)	637.5 (±181.84)	648.5 (±154.93)	679.1 (±151.5)	673.9 (±170.95)
	Min, Max	137, 1183	185, 1097	175, 1200	299, 1251

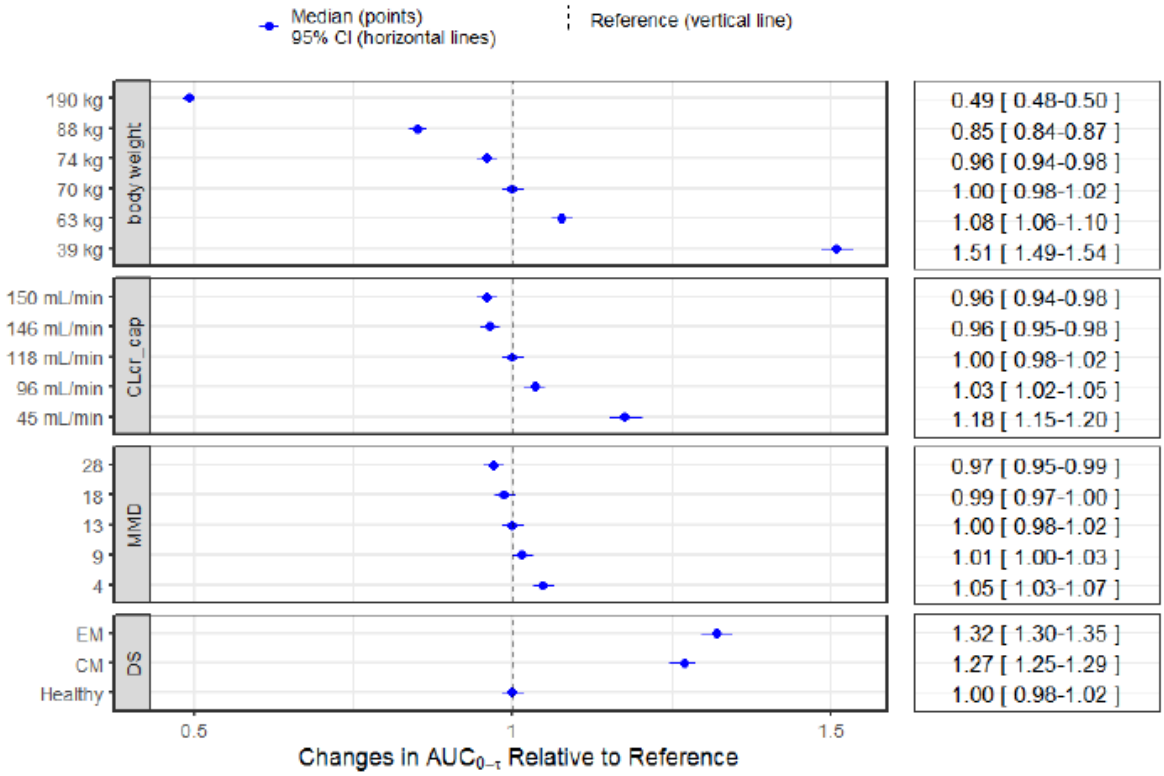
$AUC_{0-\infty}$ = area under the concentration-time curve calculated from time zero to infinity; AUC_{0-t} = area under the concentration-time curve calculated from time zero to the last measured time point; C_{max} = observed maximum concentration; h = hour; Max = maximum; mg = milligram; Min = minimum; mL = milliliter; µg = microgram; $t_{½}$ = terminal elimination half-life; T_{max} = time to C_{max}.

PK in special populations

In general, intact monoclonal antibodies with high molecular weight of about 150 kDa are not eliminated via renal excretion. Furthermore, eptinezumab is expected to be primarily metabolized via proteolysis at the cellular level. It is therefore not anticipated that renal or hepatic impairment might significantly influence the exposure of eptinezumab.

The population PK model was used to assess the impact of a variety of covariates on eptinezumab PK. Weight, CLcr (capped at a physiological value of 150 mL/min), disease (healthy, CM or EM patients), and baseline MMD were the most important covariates describing the variability of eptinezumab CL. Body weight, disease (healthy, CM or EM patients) and sex were the covariates describing the variability of Vc for eptinezumab.

Figure 3: Forest Plot: Geometric Mean Ratios and 90% CIs for the Effect of Covariates on Eptinezumab Exposure at Steady-State ($AUC_{0-\tau}$)



The most prominent effect on eptinezumab exposure was observed for body weight: Depending on body weight compared to the standard 70-kg subject, eptinezumab AUC at steady state was up to approx. 50% higher or lower. Still, the applicant concludes that no dose adjustment for body weight is required, given the absence of safety results suggesting limits for maximum exposure, and the relatively flat exposure response relationship for eptinezumab. For a better understanding of the impact of body weight on eptinezumab exposure, the applicant provided analyses of AUC distribution across bins of body weight (≤49, 50-59, 60-69, 70-79, 80-89, 90-99, 100-109, 110-119, 120-129, 130-139, ≥140 kg). For the 300 mg dose, and based on the individual clearances, the mean predicted AUCinf would vary from 82000 ug*h/L for patients with less than 49 kg to 41000 ug*h/L for patient with more than 140 kg. Based on these values, the individual mean predicted AUCinf would vary from 27000 ug.h/L for patients with less than 49 kg to 14000 ug*h/L for patient with more than 140 kg for the 100 mg dose. Based on the PopPK/PD analysis previously presented, the AUC resulting in 90% of the maximum effect would be 10700 – 13300 ug*h/L. The AUC50 is 1190 – 1480 ug*h/L. From this, it is predicted that the exposure in all the situations would be above the AUC90 threshold, meaning that no need for increasing dose by weight is anticipated.

In addition, results were further discussed in light of the exposure-response relationships in terms of both efficacy and safety. The applicant provided subgroup analyses of the primary analyses for Studies 006 and 011, and a similar ANCOVA for Study 005, based on weight quartiles. No consistent pattern of response in the different weight groups was obvious. Response patterns were generally not the same across studies, and in several cases the largest difference across weight categories was seen among the placebo groups. In part, the eptinezumab 100 mg and 300 mg groups appeared to have similar numerical reductions in MMDs for the highest weight quartile, suggesting that both doses work equally also in the highest weight quartile. Overall,

it seems that the 100 mg and 300 mg doses are both under the plateau area of efficacy and a weight based dosing approach seems not necessary. Besides, exposure-safety analysis of TEAEs by quartiles of AUC did not reveal a relationship between exposure and incidence of TEAEs.

Finally, the effect of body weight on eptinezumab exposure is adequately reflected in section 5.2 of the SmPC.

No other covariates were considered to be cause for clinical concern given the relatively small estimated effect sizes of these factors (i.e., less than 1.5-fold changes in AUC relative to the reference AUC0-τ in a typical patient). Since no data in patients with severe renal impairment are available, this information was requested to be included in section 5.2 of the SmPC.

Race, impaired hepatic function, gender and age were studied as covariates in the population PK model but were not found to significantly influence eptinezumab CL or V, which was further confirmed by boxplot analyses of eptinezumab AUC by stage of hepatic impairment, by sex, by race, and by age group.

Eptinezumab PK in children has not been investigated.

Interactions

No formal DDI studies have been performed with eptinezumab. This is acceptable considering that eptinezumab as monoclonal antibody is not metabolized via cytochrome P450 (CYP) enzymes and is not expected to induce or inhibit CYP enzymes. In study ALD403-CLIN-001, eptinezumab was co-administered with sumatriptan. Differences in exposure of eptinezumab, if co-administered with sumatriptan, were marginal and not considered clinically relevant.

		Cohort H 6/5 0M/6F	HV 28.5 [20-50]	Eptinezumab 300 mg IV	99.9 (77.6-111.0)	2.50 (1.50-5.00)	42775 (13253)	51142 (10176)	24 (20-27)	6.1 (4.7-7.8)	4.97 (3.47-5.90)
		Cohort F 8/6 8M/0F	HV 26.8 [21-41]		93.2 (66.0-176.4)	2.80 (1.50-9.00)	39967 (5601)	47560 (5344)	30 (18-44)	6.4 (5.2- 7.1)	6.45 (4.40-10.20)

Study No Country	Product ID/ Batch No.	No. Subjects Entered[a]/ Completed (M/F)	HV/P Age: Mean [range] or (SD)	Treatments	Free Eptinezumab Pharmacokinetic Parameters						
					C_{max} (µg/mL) Mean (range)	T_{max} (h) Median (range)	AUC_{0-t} (µg*h/mL) Mean (SD)	$AUC_{0-\infty}$ (µg*h/mL) Mean (SD)	$t_{½}$ (d) Mean (range)	CL (mL/h) Mean (range)	V_z (L) Mean (range)
ALD403-CLIN-001	ALD403 IV: 1-FIN-1269 ALD403 SC: 1-FIN-1382	Cohort H 6/5 0M/6F	HV 28.5 [20-50]	Eptinezumab 300 mg IV	99.9 (77.6-111.0)	2.50 (1.50-5.00)	42775 (13253)	51142 (10176)	24 (20-27)	6.1 (4.7-7.8)	4.97 (3.47-5.90)
		Cohort F 8/6 8M/0F	HV 26.8 [21-41]		93.2 (66.0-176.4)	2.80 (1.50-9.00)	39967 (5601)	47560 (5344)	30 (18-44)	6.4 (5.2- 7.1)	6.45 (4.40-10.20)
		Cohort I 12/9 12M/0F	HV 24.8 [21-35]	Eptinezumab 100 mg SC	10.0 (4.7-13.3)	97.40 (95.90-478.10)	9385 (1454)	10978 (1897)	24 (7-37)	9.4 (7.4-13.9)	7.59 (2.15-12.60)
		Part B 6/5 M2/F4	HV or P 21.8 [20-24]	Eptinezumab 300 mg IV + ST 6 mg SC	94.2 (63.6-129.0)	3.00 (1.50-13.10)	46925 (17609)	55281 (17757)	24 (16-33)	5.6 (3.5-7.5)	4.53 (2.74-5.88)

Similarly, sumatriptan PK was not affected by co-administration of eptinezumab.

Exposure relevant for safety evaluation

At steady state after 3-monthly dosing of eptinezumab, the population PK model predicted a Cmax of 40.9 µg/mL and 125 µg/mL and AUC(0-τ) of 20800 µgxh/mL and 63100 µgxh/mL for the 100 mg and 300 mg dose, respectively.

2.6.2.2. Pharmacodynamics

Eptinezumab is a humanized anti calcitonin gene-related peptide (CGRP) IgG1 monoclonal antibody (mAb) that is being developed as an intravenous (IV) formulation for the preventive treatment of migraine with an early onset of effect. The CGRP is a member of the calcitonin family of peptides; eptinezumab inhibits both α-CGRP and β-CGRP from binding to its receptor.

Inhibiting the biological activity of CGRP to effectively prevent migraine is supported in the scientific literature and clinical studies with the anti-CGRP small molecule (gepant) class of drugs and anti-CGRP monoclonal antibodies. In migraine patients, the administration of CGRP induces migraine headaches in the majority of patients, whereas it induces headaches, but not migraine in healthy subjects (Lassen et al, 2002). Research demonstrates that α-CGRP dilates intracranial and extracranial blood vessels, and regulates mast cell degranulation, that during migraine, result in secretion of vasoactive, proinflammatory, and neurosensitizing mediators potentially contributing to migraine pathogenesis (Moskowitz, 1990; Theoharides, 2005).

The applicant did not provide clinical pharmacodynamic studies as proof-of-concept for the mechanism of action of eptinezumab, unlike other anti-CGRP mAbs already approved. CGRP levels were not assessed, neither in Phase 1 clinical trials nor in in vivo non-clinical primary pharmacology studies. Although the measurement of CGRP levels would provide a more adequate PK/PD and dose/exposure-effect relationship, it can be accepted that CIDBF model provides an indirect relation with inhibition of CGRP-induced pain and can be used as surrogate PD endpoint. The joint analysis of this surrogate PD endpoint along with efficacy results can be considered as a valid approach.

Skin blood flow assessment

In study ALD403-CLIN-001, the inhibition of α-CGRP-mediated neurogenic vasodilation induced by topical capsaicin application following single or multiple administrations of eptinezumab in healthy subjects was investigated as a proof of concept and in order to help inform early dose selection.

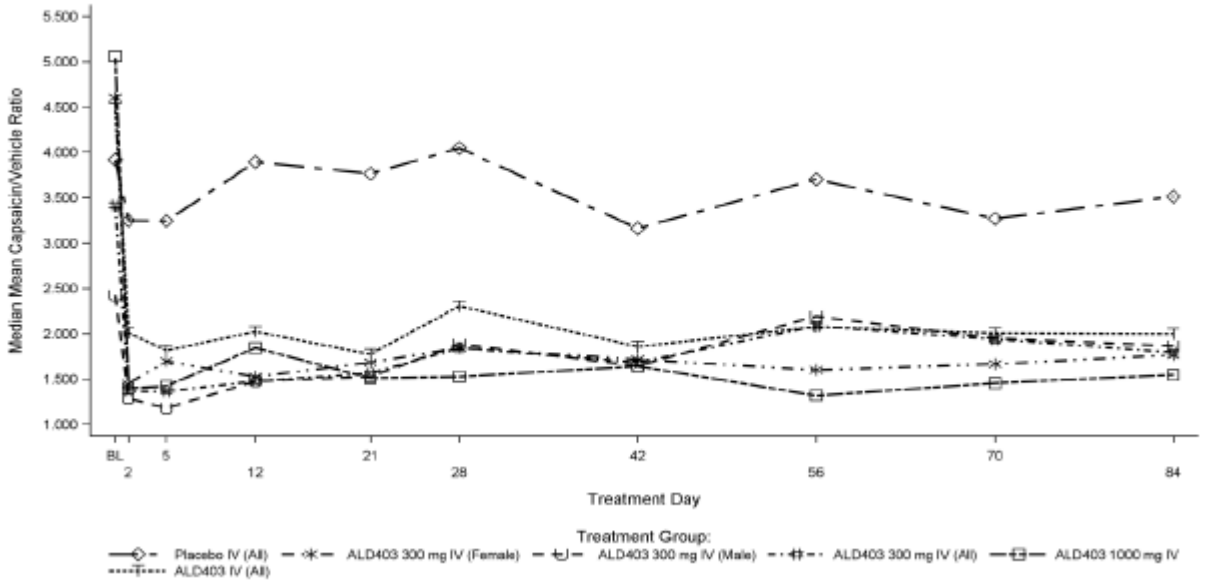
Dermal perfusion was evaluated following the topical application of capsaicin or vehicle solution on the right volar forearm of each subject prior to treatment (baseline), and on study days 2, 5, 12, 21, 28, 42, 56, 70, and 84. The ratio of capsaicin/vehicle dermal perfusion values post-treatment was compared to baseline values. A summary of the skin flow microcirculation assessment following IV dosing with eptinezumab is presented in Table 10 below.

Table 10: Skin flow microcirculation assessment – Median Capsaicin/Vehicle Ratio (Median % Change from Baseline) - IV ALD403

Dose of ALD403	1 mg IV (N=6)	3 mg IV (N=6)	10 mg IV (N=5)	30 mg IV (N=6)	100 mg IV (N=6)	300 mg IV Female (N=6)	300 mg IV Male (N=8)	1000 mg IV (N=6)	Placebo IV (N=25)
Baseline	4.3	5.3	3.8	5.0	3.3	4.6	2.4	5.1	3.9
Day 2	3.8 (-12%)	4.8 (-25%)	4.5 (20%)	2.5 (-45%)	1.4 (-62%)	1.4 (-63%)	1.3 (-45%)	1.4 (-63%)	3.2 (-10%)
Day 5	3.0 (-20%)	4.0 (-35%)	3.3 (-10%)	2.0 (-60%)	1.7 (-60%)	1.7 (-58%)	1.2 (-44%)	1.4 (-68%)	3.2 (-4%)
Day 12	3.2 (-14%)	4.2 (-33%)	2.8 (-33%)	2.1 (-53%)	1.4 (-60%)	1.5 (-61%)	1.5 (-22%)	1.8 (-60%)	3.9 (-9%)
Day 21	3.6 (-4%)	4.6 (-15%)	4.1 (2%)	2.7 (-39%)	1.4 (-61%)	1.7 (-47%)	1,5 (-26%)	1.5 (-63%)	3.8 (-4%)
Day 28	4.3 (7%)	5.2 (-14%)	2.5 (-20%)	1.8 (-61%)	2.0 (-48%)	1.8 (-51%)	1.9 (-20%)	1.5 (-65%)	4.0 (2%)
Day 42	3.2 (4%)	3.4 (-35%)	1.6 (-62%)	3.4 (-37%)	1.6 (-49%)	1.7 (-46%)	1.6 (-37%)	1.6 (-64%)	3.2 (2%)
Day 56	3.9 (-18%)	4.4 (-17%)	1.8 (-21%)	3.3 (-38%)	1.9 (-43%)	1.6 (-51%)	2.2 (-28%)	1.3 (-69%)	3.7 (-1%)
Day 70	3.0 (-23%)	3.6 (-37%)	4.9 (+16%)	3.6 (-31%)	2.3 (-49%)	1.7 (-57%)	2.0 (-12%)	1.5 (-65%)	3.3 (6%)
Day 84	2.8 (-24%)	5.3 (-12%)	3.8 (9%)	1.8 (-57%)	1.7 (-45%)	1.8 (-55%)	1.9 (-17%)	1.5 (-64%)	3.5 (-12%)

Following dosing with 1, 3 or 10 mg IV eptinezumab, the median capsaicin/vehicle dermal perfusion ratios post-treatment were generally similar to subjects dosed with IV placebo. Following dosing with 30, 100, 300, and 1000 mg IV eptinezumab, the median capsaicin/vehicle ratios post-treatment were reduced by approximately 12 to 69 percent when compared to pre-treatment baseline values and when compared to placebo (Figure 6).

Figure 6: Median Skin Flow Microcirculation Assessment Over Time following dosing with 300 mg and 1000 mg IV ALD403, compared to IV placebo.



This study is considered acceptable for demonstration of proof of concept. However, a clear dose-dependent effect on reduction of dermal vasodilation may not be construed from the data.

Immunogenicity

The immune response to treatment with eptinezumab was investigated in 5 clinical studies (Figure 1). ADA results are available from 2074 subjects. Eptinezumab dose levels ranged from 10 to 1000 mg, administered in up to 4 doses at intervals of 12 weeks via intravenous infusion, for the preventive treatment of migraine in subjects with episodic or chronic migraine. The scheduled duration of ADA monitoring extended up to 56 weeks in the Phase 3 studies, with provision to extend this with a 6-month follow-up period for subjects with a confirmed ADA positive result at the End-of-Study visit.

The incidence of ADA and NAb, as well as ADA titer at each sampling time point were investigated. In addition, ADA specificity was determined and the impact of the presence of ADA and NAb on eptinezumab PK (Ctrough), efficacy (change in frequency of monthly migraine days) and safety was analysed.

Figure 1: Overview of Clinical Studies in Eptinezumab Immunogenicity Database

Clinical immunogenicity database:
Total Number of subjects treated with eptinezumab = **2076**
Total Number of subjects with ADA results = **2074**

- **Phase 3, Randomized, Double-Blind, Placebo-controlled studies:**
  - **-006** Frequent Episodic Migraine; 4 doses of 30, 100, or 300 mg eptinezumab or placebo at 12-week intervals; number of subjects treated with eptinezumab = **666**
  - **-011** Chronic Migraine; 2 doses of 100 or 300 mg eptinezumab or placebo at Day 0 and at week 12; number of subjects treated with eptinezumab = **706**
- **Phase 3, Open-label Safety study:**
  - **-013** Chronic Migraine; 4 doses of 300 mg eptinezumab at 12-week intervals; number of subjects treated with eptinezumab = **128**
- **Phase 2, Randomized, Double-Blind, Placebo-controlled study:**
  - **-005** Chronic Migraine; single doses of 10, 30, 100, or 300 mg eptinezumab or placebo; number of subjects treated with eptinezumab = **495**
- **Phase 1b, Randomized, Double-Blind, Placebo-controlled study:**
  - **-002** Frequent Episodic Migraine; single dose of 1000 mg eptinezumab or placebo; number of subjects treated with eptinezumab = **81**

The overall incidence of treatment-emergent ADA and neutralizing antibody (NAb) detected in these studies was 15.9% and 6.2% respectively. The prevalence of pre-existing ADA was 0.7%. Highly consistent profiles were observed across all 5 clinical studies, with onset of detectable ADA at 8 weeks and maximal ADA frequency and ADA titer detected at the 24-week time-point, regardless of eptinezumab dose level or number of doses. However, considering the drug tolerance level of the ADA assay and the resulting questionable reliability of early ADA results (2 and 4 weeks after administration of eptinezumab), it is not unexpected that the onset of detectable ADA was generally observed later in time (i.e. at Week 8). After Week 24, ADA and NAb signals declined despite additional doses of eptinezumab.

ADA signals were mainly reactive with the complementary determining regions (CDRs) of eptinezumab, rather than the immunoglobulin G1 (IgG1) framework or fragment crystallisable (Fc) region or Pichia-derived glycan.

Table 118: Overall ADA Positive and NAb Positive Incidence in Studies ALD403 CLIN 005, -006, -011, and -013 (Safety Population)

Statistic	Clinical Study[a]				Overall
	-006	-011	-013 Part 1	-005	
Total number of patients with ADA results, N	666	706	128	493	1993
ADA positive subjects, n (%)[b]	119 (17.9)	129 (18.3)	22 (17.2)	59 (12.0)	329 (16.5)
Pre-existing, n (%)	3 (0.5)	6 (0.8)	0	4 (0.8)	13 (0.7)
Treatment emergent, n (%)	**116 (17.4)**	**123 (17.4)**	**22 (17.2)**	**55 (11.2)**	**316 (15.9)**
NAb positive subjects, n (%)[c]	52 (7.8)	45 (6.4)	9 (7.0)	18 (3.7)	124 (6.2)

Apparent mean concentration of eptinezumab in plasma just prior to next administration (Ctrough) values at all time-points were lower for the ADA positive subpopulation compared to the ADA negative subpopulation (see Table 71 for exemplary results from study ALD403-CLIN-006). Considering that ADA interference with the PK assay was observed during validation of the PK assay, the apparent reduction in Ctrough may reflect a combination of ADA interference in the assay and enhanced clearance. It is difficult to distinguish which of these factors predominantly contributes to the reduction of eptinezumab trough concentrations. However, it is suggested that the extent of reduction of eptinezumab exposure in ADA-positive subjects is not clinically meaningful, given that neither ADA-positive nor NAb-positive status appeared to influence efficacy in either the 100 or 300 mg treatment groups.

Table 71: Mean C_{trough} by ADA Status for Subjects Treated with 100 or 300 mg Eptinezumab (PK Population)

Sample time-point	300 mg eptinezumab			100 mg eptinezumab		
	Mean C_{trough} for ADA negative, ng/mL (n)	Mean C_{trough} for ADA positive, ng/mL (n)	C_{trough} as % for ADA positive / ADA negative	Mean C_{trough} for ADA negative, ng/mL (n)	Mean C_{trough} for ADA positive, ng/mL (n)	C_{trough} as % for ADA positive / ADA negative
Week 12	8726.6 (163)	6320.5 (46)	72.4%	2828.0 (160)	2168.1 (44)	76.7%
Week 24	10292.3 (148)	6896.4 (43)	67.0%	3876.2 (147)	1900.1 (41)	49.0%
Week 36	9784.6 (141)	6825.5 (42)	69.8%	3064.0 (138)	2221.2 (40)	72.5%
Week 48	9573.0 (135)	7154.4 (40)	74.7%	2453.3 (132)	2170.3 (39)	88.5%

In both pivotal Phase 3 studies (ALD403-CLIN-006 and -011), the change in monthly migraine days by ADA status was remarkably consistent for the ADA- and NAb-positive vs. ADA- and NAb-negative subpopulations at both the 100 and 300 mg eptinezumab dose levels from baseline to Week 24 (see boxplots in Figure 22 and 24, exemplary results from study ALD403-CLIN-006). Statistical analysis of covariance (ANCOVA) taking

all dose levels into account, did not reveal any difference in efficacy for the weeks 1-12 and weeks 13-24 treatment periods or from baseline to Week 24 (see Table 74 for exemplary results from study ALD403-CLIN-006).

Figure 22: Boxplot of Change in Monthly Migraine Days by ADA Status, 12-Week Interval and Treatment (Full Analysis Population), 100 mg eptinezumab

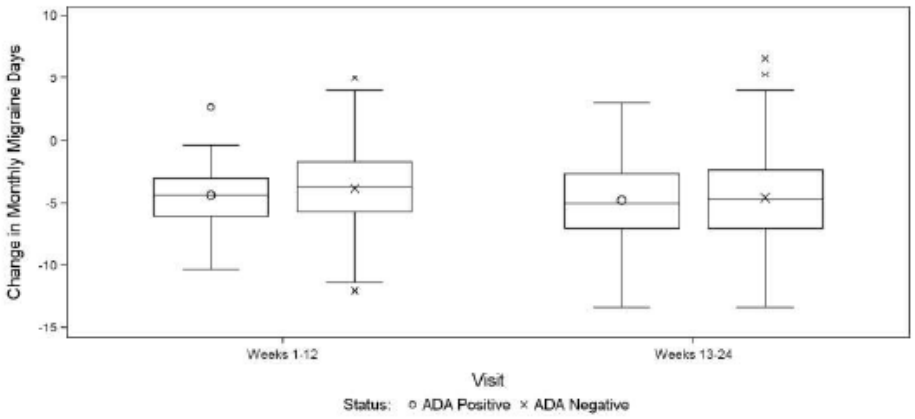


Figure 24: Boxplot of Change in Monthly Migraine Days by NAb Status, 12-Week Interval and Treatment (Full Analysis Population), 100 mg eptinezumab

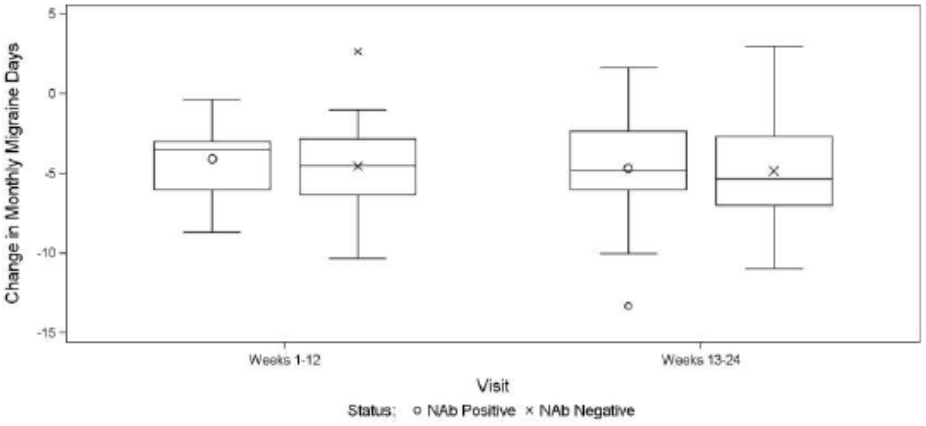


Table 74: Analysis of Change in Monthly Migraine Days by ADA status (Full Analysis Population, all dose levels combined) in Study ALD403-CLIN-006

Interval	ADA positive N=119	ADA negative N=599
Weeks 1-12		
Change from Baseline[a]		
Estimated Mean	-4.4	-4.3
Mean Diff. from ADA negative	-0.08	
95% CI	(-0.70,0.54)	
p-value	0.8022	

Weeks 13-24		
Change from Baseline[a]		
Estimated Mean	-4.9	-4.9
Mean Diff. from ADA negative	0.08	
95% CI	(-0.62,0.78)	
p-value	0.8201	
Weeks 1-24		
Change from Baseline[a]		
Estimated Mean	-4.6	-4.6
Mean Diff. from ADA negative	0.00	
95% CI	(-0.62,0.62)	
p-value	0.9972	

Apart from a single case of anaphylaxis reported in study -013 (but not meeting the clinical criteria defined by Sampson et al 2006), there was only a small number of Grade 1 or 2 adverse events that were coded to the preferred term (PT) of hypersensitivity observed in any of the 5 migraine studies. In the safety populations for studies ALD403-CLIN-005, -006, -011 and -013, 24 out of a total of 1995 (1.2%) eptinezumab-treated subjects were reported to have a treatment-emergent mild or moderate adverse event that was coded to the PT of hypersensitivity. The majority of these subjects were ADA negative throughout the treatment period. No cases of severe hypersensitivity reactions were observed.

There was no apparent relationship to pre-existing or treatment-emergent ADA or NAb positive status, ADA titer category or eptinezumab dose level. There was no evidence for a risk of immune complex-related hypersensitivity, consistent with the relatively low ADA titers observed for all eptinezumab dose levels. There was no relationship between the ADA or NAb signals and incidence or severity of other Adverse Events of Special Interest (AESI). No clear pattern was seen for the relationship between ADA-positivity (as compared to ADA negative patients) and TEAE or AESI at the evaluated eptinezumab doses.

In line with the results obtained from analyses of the impact of ADA status on efficacy and safety of eptinezumab, the following information is provided in the SmPC: "There was no evidence of impact of anti-eptinezumab antibody development on efficacy or safety in the clinical studies". A brief description of the effect of ADA positivity on eptinezumab exposure was added to the SmPC.

Overall, across all studies a certain degree of variability appears to exist in terms of patients developing anti-drug antibodies (ADA) with neutralizing capacity (neutralizing antibodies – nAbs). The applicant was asked to justify this variability according the study/subjects characteristics. The applicant was further asked to discuss the impact of ADA/nAb formation in PD/efficacy endpoints, with a post-hoc analysis of these endpoints in the subset of patients that developed ADA/nAbs, analysing the level of ADA/nAbs with PK/PD parameters. In response, the applicant adequately justified the concerns raised, not only with the consistency in timing and duration of immunogenicity responses but also with a statistical analysis showing no relation between ADA-positive/Nab-positive status with efficacy.

At the time of the initial submission, no data on ADA development after the last dosing of eptinezumab at week 36 were available, given that a maximum of 4 doses (Week 1, 12, 24 and 36) was given in study -006 and results were only available for the primary treatment phase of study -013 (secondary treatment phase of this study is ongoing). Since eptinezumab is generally intended as long-term treatment, 1-year

immunogenicity data were required. In response, the applicant provided immunogenicity results from the secondary treatment phase of study ALD403-CLIN-013. ADA incidence during the secondary treatment phase further decreased as compared to the highest ADA incidence observed at Week 24. At Week 48, 5.3% (6 of 113 patients with ADA results) were ADA positive and at Week 72, 4.0% (4 of 101 patients with ADA results) were ADA positive. At Week 104, ADA results were available for 96 patients and finally all patients presented to be ADA negative, confirming that ADA response is transient in patients treated with eptinezumab. Similarly, the percentage of NAb positive samples decreased during the secondary treatment phase and was zero already at Week 72.

A moderate event of hypersensitivity occurred in one patient during the Week 60 infusion, however, this patient was found to be ADA negative. Thus, the data provided for the secondary treatment phase confirm that there is no relationship between ADA positivity and hypersensitivity reactions.

In addition, there was no indication for an impact of immunogenicity or NAbs on the efficacy or on the maintenance of efficacy following 8 repeated infusions of eptinezumab.

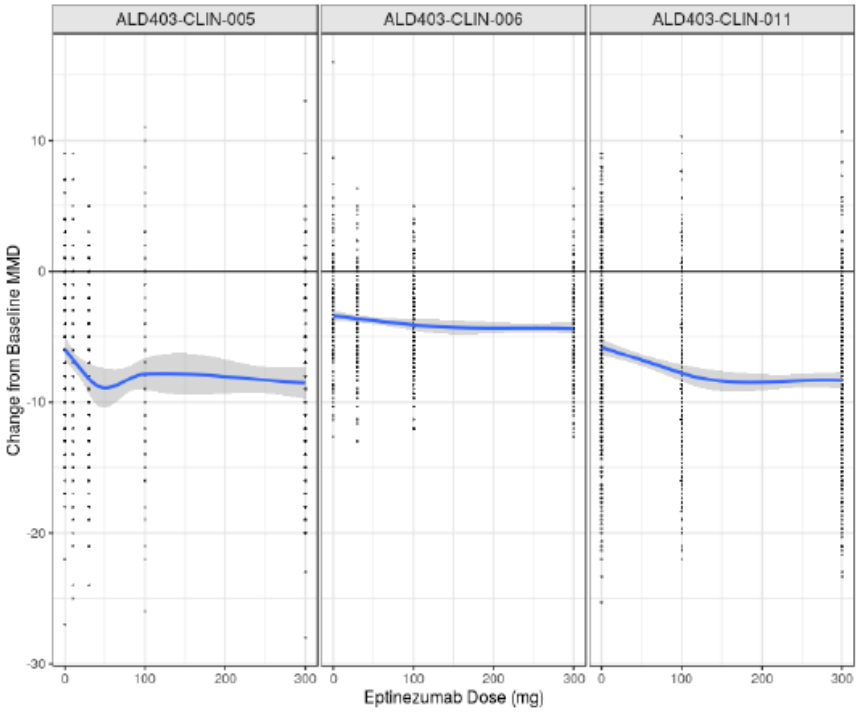
Relationship between plasma concentration and effect

The exposure-response relationships on selected endpoints were assessed in approximately 2543 patients dosed with placebo or IV eptinezumab 10-300 mg in a total of 3 clinical studies (CLIN-005, -006 and -011). Individual PK parameters derived with the final population PK model were used to derive both individual exposure metrics of eptinezumab (i.e., area under the curve from time 0 to 12 weeks [AUC0-12wk], maximum concentration [Cmax], individual trough concentration [Ctrough], average concentration [Cavg]). PD endpoints included the change in frequency of monthly migraine days (MMD) (continuous variable) and responder rate rates (categorical variable) in 28-day intervals.

Primary Endpoint: Change in frequency of MMD

As shown in Figure 6, the treatment benefit defined by the change from baseline migraine days is pronounced at dose levels 100 mg and higher.

Figure 6: Dose-Response Relationship – Change in Frequency of MMD over Weeks 1-12 by Study



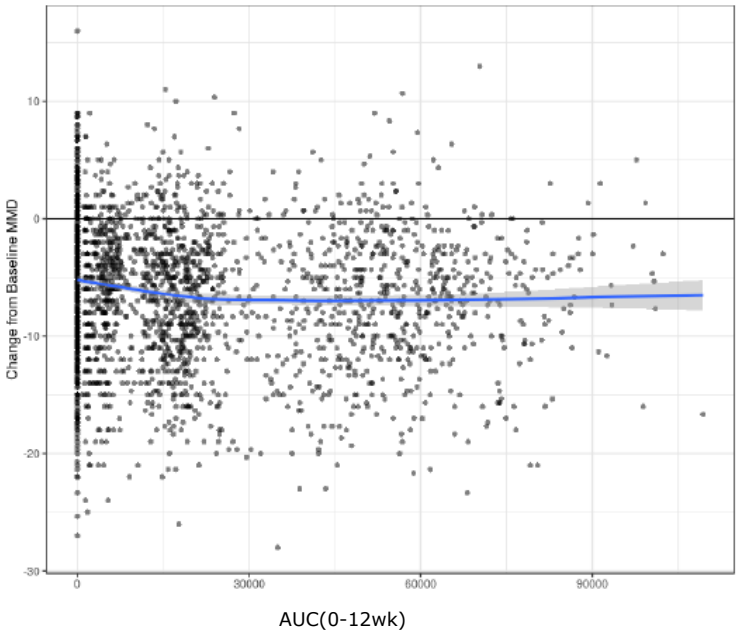
Legend: Solid line with gray shaded area: smooth (loess) regression and 95% confidence interval.

The number of migraines days decreased from baseline with increasing eptinezumab dose. The dose-response relationship appeared to be steeper for study CLIN-005 compared to studies CLIN-006 and CLIN-011.

Subsequently, exposure-response relationships analysis was performed. The relationship between the change in frequency of MMD over Weeks 1-12 versus key metrics of exposure (i.e., AUC0-12wk, Cmax, Ctrough, Cavg) was derived. The exposure response with AUC0-12wk is presented in Figure 8.

From the exposure-response (ER) relationship plot, it is noticed that the treatment benefit is nominal at lower AUC0-12wk. An AUC0-12wk of 15 000 hr*µg/mL or higher tends to present sustained decrease in migraine days compared to baseline. This AUC0-12wk of 15,000 hr*µg/mL corresponds to an average AUC0-12wk from the 100 mg dose.

Figure 8: Exposure-Response Relationship – Change in frequency of MMD (Weeks 1-12)



The number of migraine days decreased from baseline with increasing eptinezumab exposure over Weeks 1-12. Similar decreases in number of migraine days were observed for increasing Cmax, Cavg and Ctrough (data not shown). Several statistical functions were tested to model the relationship of eptinezumab exposure and change in migraine days using a placebo-anchored approach (i.e., for placebo, AUC was set to 0). The saturable inhibitory Emax model describing the relationship between the PK parameters of eptinezumab and change in frequency of MMD over Weeks 1-12 resulted in a statistically significant decrease in the objective function value relative to the statistical linear model.

This model is described as follows:

Reduction of Migraine Days: E0 + Imax × AUC/(AUC50 + AUC)

Imax is the maximum inhibitory effect, AUC50 is the AUC achieving the half-maximal change in effect and AUC is the area under the curve for eptinezumab. The model was stratified by disease status (CM or EM).

Results of the inhibitory Emax model are summarized below in Table 14:

Table 14: Inhibitory E_{max} model Derived Parameters: PK/PD Exposures Correlation of Change in frequency of MMD at Weeks 1-12 versus Eptinezumab Exposure Metrics at Single Dose

Eptinezumab Exposure Metric	Disease State	EC_{50} (CV%)	EC_{90}[a]	Mean (CV%) PK Parameters following a Single Dose[b]		
				30 mg	100 mg	300 mg
$AUC_{0\text{-}12wk}$ (hr*µg/mL)	CM	1480 (85.6)	13300	5770 (41.1)	17900(29.0)	54500(27.7)
	EM	1190 (225.7)	10700			
C_{max} (µg/mL)	CM	3.78 (84.0)	34.0	12.4 (38.6)	37.3 (28.1)	114 (27.7)
	EM	2.54 (228.4)	22.8			
C_{trough} (µg/mL)	CM	0.109 (105.6)	0.983	0.821 (55.4)	2.66 (46.1)	8.06 (42.4)
	EM	0.183 (187.7)	1.65			
C_{avg} (ng/mL)	CM	745 (85.7)	6710	2870 (41.2)	8950 (29.3)	27200(27.8)
	EM	585 (227.3)	5260			

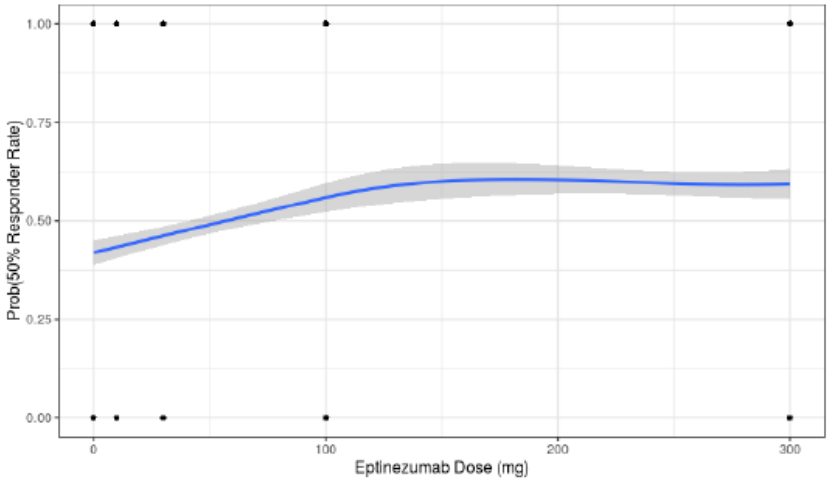
Treatment with 100 or 300 mg eptinezumab provided exposure (AUC0-12wk, Cmax, Ctrough, or Cavg) that exceeded all EC90 estimates for the CM and EM groups. Exposure following the administration of 30 mg eptinezumab was insufficient to meet the EC90 estimates.

Key Secondary Endpoints: 50% and 75% migraine responder rate

A logistic regression analyses was performed to explore associations with eptinezumab exposures (e.g., AUC0-12Wk / Ctrough / Cmax/ Cavg) and the various categorical endpoints: 75% migraine responder rate (Weeks 1-4), 75% migraine responder rate (Weeks 1-12), and 50% migraine responder rate (Weeks 1-12). Presented are responder rates from Week 1-12.

Dose-response relationships were explored prior to performing exposure-response analysis. Dose-response relationships for 50% migraine responder rate over Weeks 1-12 are presented in Figure 13.

Figure 13: Dose-Response Relationship: 50% Migraine Response Rate over Weeks 1-12

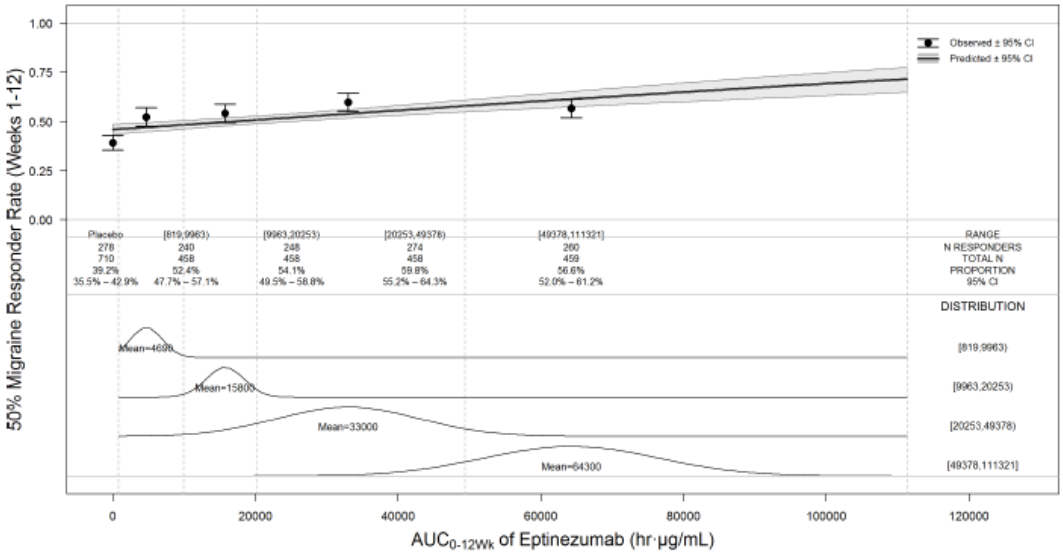


Legend: Solid line with gray shaded area: smooth (loess) regression and 95% confidence interval.

The probability of 50% responder rate over Weeks 1-12 increased with increasing eptinezumab dose.

The probability of 50% responder rate over Weeks 1-12 as a function of eptinezumab AUC is presented in Figure 15.

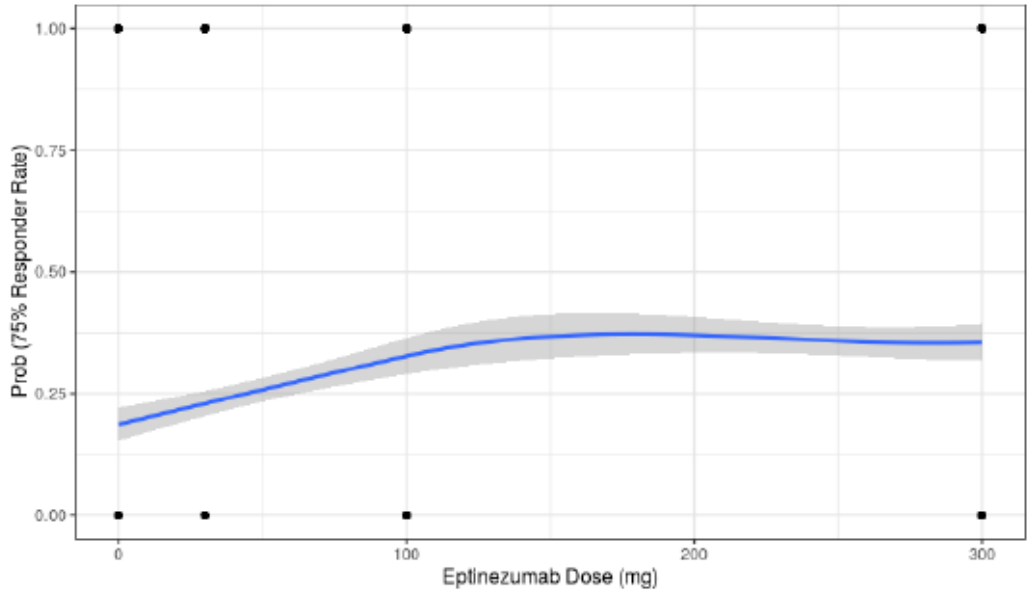
Figure 15: Exposure-Response Relationship: 50% Migraine Responder Rate (Weeks 1-12) vs. $AUC_{0\text{-}12wk}$



Considerable responses are observed with placebo (39%). This observation has already been described in clinical studies with other anti-CGRP antibodies. The observed 50% responder rate for the first, second, third, and fourth quartiles of AUC0-12wk were 52%, 54%, 60% and 57%, respectively, and were higher than placebo.

Dose-response relationships for 75% migraine responder rate over Weeks 1-12 are presented in Figure 16.

Figure 16: Dose-Response Relationship: 75% Migraine Response Rate over Weeks 1-12

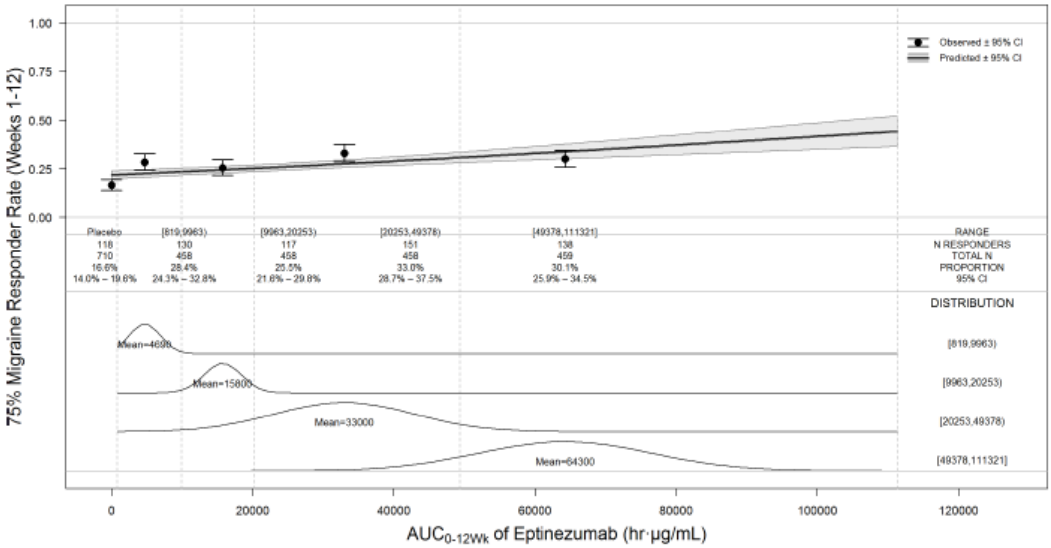


Legend: Solid line with gray shaded area: smooth (loess) regression and 95% confidence interval

The probability of 75% responder rate over Weeks 1-12 increased with increasing eptinezumab dose.

The probability of 75% responder rate over Weeks 1-12 as a function of eptinezumab AUC0-12wk is presented in Figure 18.

Figure 18: Exposure-Response Relationship: 75% Migraine Responder Rate vs. $AUC_{0\text{-}12wk}$ (Weeks 1-12)



The observed 75% responder rate was 17% for placebo. The observed 75% responder rate for the first, second, third, and fourth quartiles of AUC0-12wk) were 28%, 26%, 33% and 30%, respectively, and were higher than placebo.

The third quartile of AUC0-12wk (mean AUC0-12wk = 33,000 hxµg/mL) appeared to show a higher probability of response for all key secondary endpoints, compared to the first and second quartiles of AUC0-12wk (mean AUC0-12wk = 4690 hxµg/mL and 15,800 hxµg/mL, respectively). The fourth quartile of AUC0-12wk mean AUC0-12wk = 64.300 hxµg/mL) showed no further improvement for all key secondary endpoints. The applicant argues that the third quartile corresponds to the 100 mg dose, however, this is not fully agreed, since AUC0-12wk was 17,900 hxµg/mL for the 100 mg dose (min-max-range: 6350-55,700 hxµg/mL). The exposure after single administration of 100 mg eptinezumab is therefore somewhat lower than the exposure described for the third quartile (33,000 hxµg/mL with min-max-range: 20,253-49378 hxµg/mL). Still, it is agreed that a plateau effect is observed somewhere between the 100 mg and 300 mg dose. Referring to the overall exposure-response analyses conducted, the estimated difference in treatment benefit comparing the 100 mg and 300 mg eptinezumab dose and corresponding exposure appears marginal or not obvious at all. However, the primary and secondary endpoints analysed in the pivotal efficacy trials consistently revealed slightly higher efficacy of the 300 mg dose as compared to the 100 mg dose. This is not evident from the provided exposure-efficacy analyses; however, differential conclusions may relate to the rather small differences in efficacy which may not have been discriminable due to the width of the scale. Additionally, as mentioned above, the quartiles (3rd and 4th) depicted in the exposure-response analysis for the secondary endpoints do not entirely match the exposure reached after dosing with 100 mg and 300 mg eptinezumab.

No exposure-safety analyses have been conducted. For a thorough assessment of the appropriateness of the intended dosing regimens and for a better discrimination between the different dosing regimens, the applicant was asked to analyse the relationship of eptinezumab exposure with relevant adverse events. The requested exposure-safety analysis was provided in response to the D120 LoQ. Except for the SOC Gastrointestinal disorders in Study 011 showing increased TEAE incidences with increasing AUC quartile intervals, no apparent relationship was seen in the incidences of TEAEs by SOC and AUC quartile intervals in

Studies 006 and 011. The pattern of increasing GI disorders with increasing AUC quartiles was not seen in Study 006, therefore this finding is not considered clinically meaningful - also accounting for the fact that TEAE incidences in the SOC Gastrointestinal disorders for the all eptinezumab (8.4%) and placebo (7.9%) groups in Study 011 were found to be similar.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Overall, pharmacokinetics of eptinezumab has been extensively studied and adequately characterized throughout 10 clinical studies and a population PK analysis.

Assay methods developed for the quantification of eptinezumab plasma concentrations and the determination of ADA and NAb directed against eptinezumab were adequately validated. For the PK assay, questions raised on the cross-site comparability study, interference with ADA, and long-term stability were adequately addressed in response to the D120 LoQ. For the ADA and NAb assay, concerns regarding the drug tolerance level and interference with haemolysis were demonstrated not to result in non-reliability or misinterpretation of overall study data.

For description of eptinezumab PK and exposure-response analysis, a population PK model was developed which included IV data from 8 clinical studies comprising 2123 patients and healthy volunteers. The final population PK model was a 2-compartment model with linear elimination. Some weaknesses of the model have been identified. For instance, the number of covariates included suggests over-parameterization and the applicant was asked to elucidate on the biological plausibility of the covariates disease state and baseline MMD being significant predictors of eptinezumab PK. However, the root cause of the exposure differences seen for disease state and baseline MMD could not be identified, but was assumed to be due to variability associated with study-to-study factors and/or the bioanalytical methodology. Exposure differences due to disease state and baseline MMD were generally small and considered not clinically relevant. In the GOF and VPC plots, some deviations are evident. Low eptinezumab concentrations are overestimated and high eptinezumab concentrations are slightly underestimated by the model. Nevertheless, the model seems to provide acceptable estimations of eptinezumab exposure for the relevant doses (100 mg and 300 mg) of this application.

Eptinezumab is presently intended to be solely administered as IV infusion with 100% bioavailability. Apparent clearance and central volume of distribution of eptinezumab estimated in the population PK analysis was 0.15 L/d and 3.64 L, respectively. These values are typical for monoclonal antibodies and indicate minimal extravascular distribution of free eptinezumab and relatively slow elimination from the plasma compartment. Half-life of eptinezumab was 27 days.

After IV administration of eptinezumab doses ranging from 10 mg to 300 mg, dose proportionality was demonstrated. However, at dose levels ≤ 10 mg, departure from PK linearity was detected and target mediated drug disposition is suspected. The accumulation ratio for 3-monthly dosing of 100 mg or 300 mg eptinezumab was predicted to be 1.08 – 1.15.

Moderate to high interindividual variability as assessed by %CV was observed in the clinical studies conducted in patients with EM and/or CM. In the population PK analysis, variability was largely explained by the covariates body weight, CLcr, disease (healthy, CM or EM patients), and baseline migraine days.

The PK of eptinezumab was overall consistent across the individual studies conducted in both healthy volunteers and migraine patients. Slightly higher exposure of eptinezumab was observed in patients with chronic migraine as compared to healthy subjects, which is not considered clinically relevant. At steady state after 3-monthly dosing of eptinezumab, the population PK model predicted a Cmax of 40.9 µg/mL and 125 µg/mL and AUC(0-τ) of 20800 µgxh/mL and 63100 µgxh/mL for the 100 mg and 300 mg dose, respectively. According to visual assessment of the predose plasma levels, steady state was achieved by Week 12 after the first eptinezumab administration.

Body weight, CLcr (capped at a physiological value of 150 mL/min), disease (healthy, CM or EM patients), sex, and baseline MMD were the most important covariates describing the variability of eptinezumab CL and V. The most prominent effect on eptinezumab exposure was observed for body weight, which is now adequately reflected in the SmPC. It was demonstrated that eptinezumab exposure in all bins of body weight was predicted to be above the AUC90 threshold (AUC resulting in 90% of the maximum effect), meaning that no need for increasing dose by weight is anticipated. Overall, it seemed that the 100 mg and 300 mg doses are both under the plateau area of efficacy and a weight based dosing approach is not necessary. Exposure-safety analysis of TEAEs by quartiles of AUC did not reveal a relationship between exposure and incidence of TEAEs. Since no data in patients with severe renal impairment are available, this information was added to section 5.2 of the SmPC. Boxplot analyses were provided indicating no significant impact of hepatic impairment, sex, race, and age on the exposure of eptinezumab. No data are available on eptinezumab PK in children.

Pharmacodynamics

A skin blood flow test measuring the inhibition of topical capsaicin-induced vasodilation after treatment with eptinezumab was conducted as proof of concept. However, the applicant did not provide clinical pharmacodynamic studies as proof-of-concept for the mechanism of action of eptinezumab, unlike other mAbs already approved. CGRP levels were not assessed, neither in Phase 1 clinical trials nor in in vivo non-clinical primary pharmacology studies. Ultimately, the CIDBF model is deemed acceptable to provide an indirect relation with inhibition of CGRP-induced pain and can be used as surrogate PD endpoint. The joint analysis of this surrogate PD endpoint along with efficacy results can be considered as a valid approach.

Immunogenicity of eptinezumab was investigated in 2074 subjects from 5 clinical studies. Overall, ADA and NAb response to eptinezumab was comprehensively analysed. The overall treatment emergent ADA incidence was 15.9% across the studies, 6.2% subjects in the overall safety population were determined to be NAb-positive.

Ctrough was lower in ADA- and NAb-positive subjects as compared to ADA- and NAb-negative subjects. This information was requested to be included in the SmPC. However, the extent of reduction of eptinezumab exposure in ADA-positive subjects was not considered clinically meaningful, given that neither ADA-positive nor NAb-positive status appeared to influence efficacy in either the 100 or 300 mg treatment groups. Furthermore, no relationship of the presence of ADA and the occurrence of adverse events (with special focus on hypersensitivity reactions) was described. No clear pattern was seen for the relationship between ADA-positivity (as compared to ADA negative patients) and TEAE or AESI at the evaluated eptinezumab doses.

Since eptinezumab is generally intended as long-term treatment, immunogenicity results from the secondary treatment phase of study ALD403-CLIN-013 were requested and provided in response to the D120 LoQ. ADA incidence during the secondary treatment phase further decreased as compared to the highest ADA incidence observed at Week 24. Similarly, the percentage of NAb positive samples decreased during the secondary

treatment phase. The data from the secondary treatment phase further confirmed that there is no impact of ADA or NAb positivity on efficacy or adverse events (hypersensitivity reactions).

Exposure-efficacy analyses

Exposure-response analyses included the investigation of dose-and exposure-response relationships for change in frequency of MMD over weeks 1-12 and the analysis of the probability of 50% and 75% responder rate over Weeks 1-4 and weeks 1-12 versus key metrics of exposure (i.e., AUC0-12Wk, Cmax, Ctrough and Cavg). Overall, dose- and exposure-response analyses of primary and secondary efficacy endpoints demonstrated a trend toward increased efficacy with increased exposure, although response curves were rather flat and considerable responses have also been observed with placebo. This observation has already been described in clinical studies with other anti-CGRP antibodies.

The estimated difference in treatment benefit comparing the 100 mg and 300 mg eptinezumab dose and corresponding exposure appears marginal. However, the primary and secondary endpoints analysed in the pivotal efficacy trials consistently revealed slightly higher efficacy of the 300 mg dose as compared to the 100 mg dose.

For better discrimination between the different dosing regimens and in order to rationally define a target exposure range, the applicant provided analyses of the relationship between eptinezumab exposure and relevant adverse events. No apparent relationship was seen in the incidences of TEAEs by SOC and AUC quartile intervals in Studies 006 and 011.

2.6.4. Conclusions on clinical pharmacology

Overall, pharmacokinetics of eptinezumab has been adequately characterized. Immunogenicity of eptinezumab was extensively and sufficiently analysed.

Pharmacodynamic proof of concept was demonstrated in a skin blood flow test. Exposure-response analyses were provided revealing a trend toward increased efficacy with increased exposure, and no apparent relationship in the incidences of TEAEs and AUC quartile intervals.

2.6.5. Clinical efficacy

In order to demonstrate the efficacy of eptinezumab, used as an intravenous (IV) formulation, for the preventive treatment of migraine, the Applicant provided data from 4 eptinezumab studies:

• Two of the studies are pivotal and administered multiple infusions of eptinezumab: episodic migraine Study ALD403-CLIN-006 (hereafter referred to as Study 006) and chronic migraine Study ALD403-CLIN-011 (hereafter referred to as Study 011).

• Two of the studies are supportive and administered 1 infusion of eptinezumab: episodic migraine Study ALD403-CLIN-002 (hereafter referred to as Study 002) and chronic migraine Study ALD403-CLIN-005 (hereafter referred to as Study 005).

Dose-response study

Study 005: A Parallel Group, Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Phase 2 Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of ALD403 Administered Intravenously in Patients with Chronic Migraine

Study 005 was a parallel group, double-blind, randomized, placebo-controlled trial. Subjects were randomized into one of four ALD403 dose levels (10 mg, 30 mg, 100 mg, or 300 mg) or placebo in a 1:1:1:1:1 ratio. Randomization was stratified by baseline migraine days (< 20 and ≥ 20 days) and medication overuse status (medication overuse vs. no medication overuse).

Subjects completed a Headache eDiary daily for 28 days from screening until randomization to determine certain eligibility criteria, and the baseline migraine results. There was approximately a week between randomization and dosing. Subjects were asked to complete a daily eDiary through 48 weeks post dose.

Dosing occurred on Day 0. After dosing, visits occurred approximately every four weeks through 3 months post-dose and approximately every 12 weeks through 49 weeks postdose.

The total study duration was approximately 54 weeks with visits at screening, Day 0, and Weeks 4, 8, 12, 24, 36, and 49. Additionally, phone calls were made by site staff to subjects at weeks 2, 16, 20, 28, 32, 40 and 44.

The primary objective of the study was to evaluate the dose response of a single dose of ALD403 administered IV in patients with chronic migraine, measured as 75% migraine responder rate.

Secondary objectives included the evaluation of the safety of ALD403 administered IV compared with placebo in patients with chronic migraine, the duration of effect of ALD403 administered IV in patients with chronic migraine, and the pharmacokinetics (PK) and immunogenicity of ALD403 administered IV in patients with chronic migraine.

665 patients were randomly assigned to treatment with either ALD403 (n = 531) or placebo (n = 134). Overall, 49 (7.4%) patients were randomized but not treated.

Table 6. Populations for Analysis

	ALD403 300 mg n (%)	**ALD403 100 mg n (%)**	**ALD403 30 mg n (%)**	**ALD403 10 mg n (%)**	**Placebo n (%)**	**Overall n (%)**
Randomized Patients	131	133	134	133	134	665
Safety Population[a]	121 (92.4)	122 (91.7)	122 (91.0)	130 (97.7)	121 (90.3)	616 (92.6)
Modified Full Analysis Population	114 (87.0)	118 (88.7)	117 (87.3)	123 (92.5)	116 (86.6)	588 (88.4)
Site 165 Patients[b]	6 (4.6)	5 (3.8)	5 (3.7)	7 (5.3)	5 (3.7)	28 (4.2)
PK Population[a]	120 (91.6)	122 (91.7)	122 (91.0)	129 (97.0)	NA	493 (74.1)

Baseline characteristics were generally similar across treatment groups.

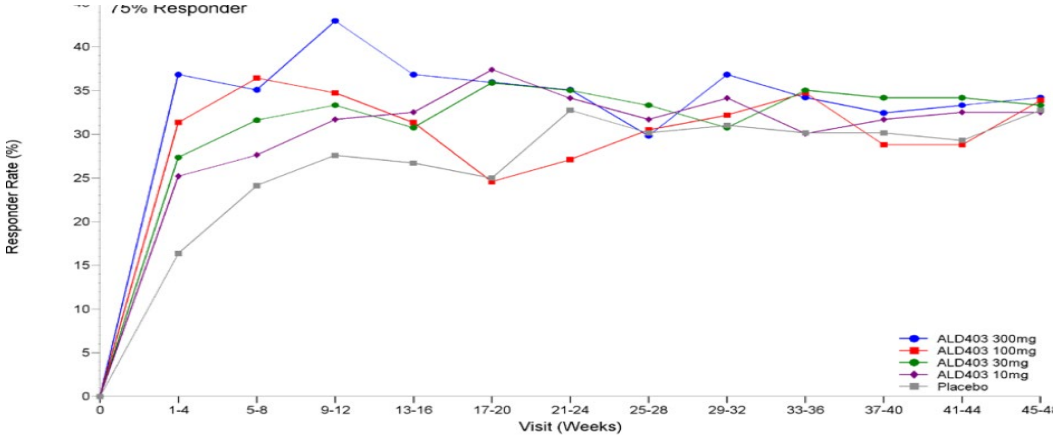
Primary efficacy analysis

The ALD403 groups had higher response rates overall for the **responder endpoints (50%, 75%, and 100%)** than placebo up to Week 12. Differences from placebo for the ALD403 10 mg group were generally not statistically significant for the study endpoints. The differences were in general greatest at Weeks 1 to 4 and less pronounced up to Week 12.

The greatest 75% migraine response rate was observed with ALD403 300 mg-treated patients (33.3% vs placebo 20.7%). For the study's primary efficacy endpoint, more ALD403-treated patients were 75% migraine responders over Weeks 1 to 12 (33.3%, 31.4%, 28.2%, and 26.8% for 300 mg, 100 mg, 30 mg, and 10 mg, respectively) than placebo-treated patients (20.7%). The difference between the 300 mg ALD403 and placebo treatment groups was statistically significant (95% CI) (p = 0.0330) as was the difference between the 100 mg ALD403 and placebo treatment groups (p = 0.0715; 10% alpha decision rule).

The 75% migraine responder rates for Weeks 1-4 for the ALD403 groups were generally similar to those observed for Weeks 1-12 though the differences from placebo for Weeks 1-4 were larger (20.5%, 15.0%, 11.0%, and 8.8% for 300 mg, 100 mg, 30 mg, and 10 mg, respectively).

Figure 1 presents line plots for the 75% migraine responder rate by 4-week intervals for each treatment group up to Week 49:

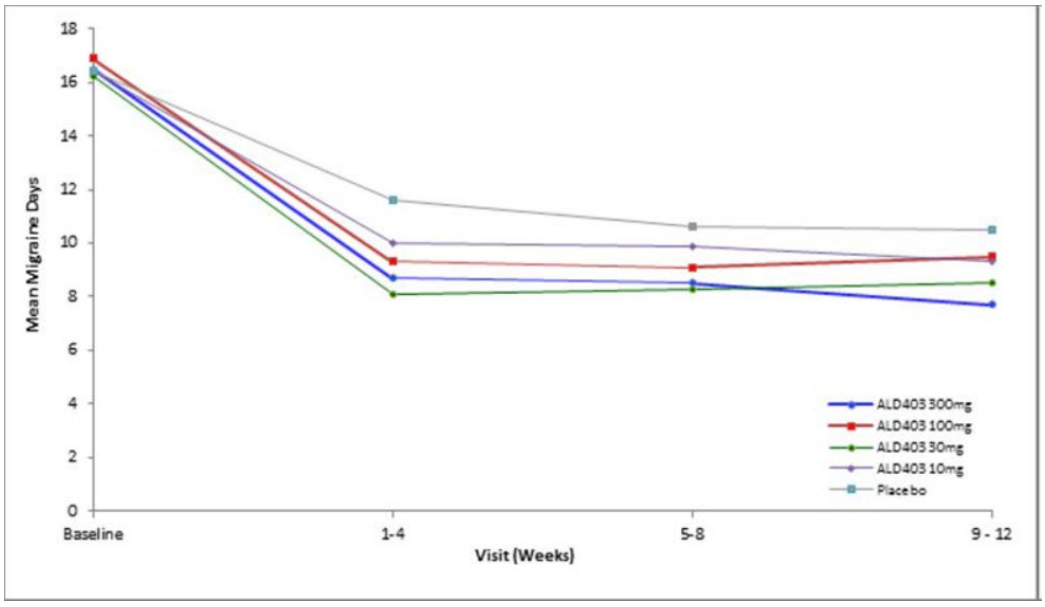


Secondary efficacy measures

Secondary efficacy measures included 50% headache responder rates, 100% migraine responder rates, and change from baseline of migraine days. These measures were supportive for the primary efficacy analyses.

With regard to the secondary efficacy endpoint "change from baseline in monthly migraine frequency", the 30 mg dose was numerically slightly better than the 100 mg dose until week 8. However, this effect was not statistically significant, and was not maintained until week 12.

Figure 3. Mean Number of Migraine Days vs 4 Week Interval (Modified Full Analysis Population)



Conclusion

Overall, all doses tested (10, 30, 100, 300 mg) performed better than placebo, with a trend in favour for the 300 mg dose, and the 100 mg and 30 mg dose performing highly similar. Based on these data, the range of doses chosen for further testing in phase 3 clinical trials is acceptable. However, based on these phase 2 data, it appears as if at least some patients with chronic migraine might also have responded to a repeat 30 mg dosing regimen. This 30mg dose however was not followed further in the phase 3 clinical trial in chronic migraine patients, although it is likely that some patients would have responded to this lower dose. Of note, there were more patients pre-treated with migraine prophylactics in the 300 mg group compared to the other arms. Imbalances were especially observed for betablockers, valproate, and botox, which could argue for an overall more difficult-to-treat population in the 300 mg arm. This might have influenced efficacy results.

Main study(ies)

The efficacy profile of eptinezumab was established in 2 pivotal Phase 3, randomized, double-blind, placebo-controlled studies, named ALD403-CLIN-006 (Frequent Episodic Migraine, recruiting patients with 4 to 14 MHDs/month at baseline) and ALD403-CLIN-011 (Chronic Migraine, recruiting patients with ≥15 to ≤26 headache days of which at least 8 with features of migraine). Up to six (Study 011) and 12 months (Study 006) of placebo-controlled data are available from the 2 pivotal studies.

Key inclusion criteria in the 2 pivotal studies specified that subjects be adults with a history of migraine with or without aura. Exclusion criteria were generally similar across both studies, with minor differences due to the disease state (EM or CM). 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) were included in Study 011.

The following dose regimes of IMP were evaluated, given once every 12 weeks as an intravenous infusion:

Study 006: 30 mg, 100 mg, 300 mg eptinezumab or placebo in a 1:1:1:1 ratio.

Study 011: 100 mg, 300 mg eptinezumab or placebo in a 1:1:1 ratio.

Study ALD403-CLIN-006: Frequent Episodic Migraine

Methods

Study Participants

The study included anti CGRP mAb-naïve, male and female patients between 18 and 75 years of age with a diagnosis of frequent episodic migraine (defined as ≤14 headache days of which at least 4 had to be migraine days in each 28-day period in the 3 months prior to screening). Subjects did not regularly use prophylactic headache medication. Patients with a history of complicated migraine, chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic, and familial hemiplegic migraine, as well as subjects with cardiovascular disease, neurological disease, cerebrovascular disease, diabetes, or Raynaud's disease were excluded from study participation.

The study was primarily conducted in the USA, and in few study sites in the Republic of Georgia.

Treatments

Patients were assigned to the 4 treatment arms (30, 100, 300 mg eptinezumab or placebo) in a 1:1:1:1 ratio. The doses of eptinezumab (30, 100, 300 mg) or placebo were reconstituted by unblinded personnel in a total volume of 100 mL 0.9% saline. Doses were administered intravenously over a period of 1 hour (±15 minutes) on Day 0 and at Weeks 12, 24, and 36, by the blinded investigator or designee. Subjects were monitored for 4 hours after the end of the infusion.

The eptinezumab dose ranges evaluated in this study included all doses that tested superior to placebo in the phase 2 study program.

Any concomitant prophylactic headache medication was prohibited through week 24. Concomitant barbiturate and opioid medication, as well as codeine was restricted, but not prohibited. It is not clear, to which extend these medications were actually used across treatment groups and whether endpoint analyses might have been affected.

Objectives

Primary objective

The primary objective of the study was to evaluate the efficacy of repeat doses of ALD403 administered intravenously compared to placebo in subjects with FEM.

Secondary objective

The secondary objectives of this study were to evaluate the safety of repeat doses of ALD403 administered intravenously compared to placebo and to evaluate the pharmacokinetics (PK) and immunogenicity of repeat doses of ALD403 administered intravenously to subjects with FEM.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint was „Change in frequency of migraine days (Weeks 1-12)". The primary efficacy analysis was therefore conducted at Week 12 after the first dose of study drug.

[Originally, another primary endpoint, namely "75% responder rate (weeks 1-12)", was chosen. The primary endpoint was changed to "Change in frequency of migraine days (weeks 1-12)" with amendment no.3 in 2016.]

Key secondary endpoints

Key secondary efficacy endpoints included:

- 75% migraine responder rate (Weeks 1-4)
- 75% migraine responder rate (Weeks 1-12)
- 50% migraine responder rates (Weeks 1-12)
- Percentage of subjects with a migraine on the day after dosing

Randomisation and blinding (masking)

Randomization was planned to occur 29 to 35 days after the screening visit after eligibility assessments are completed and eligibility verified. Sites were planned to complete the randomization in an Interactive Web or Voice Response System (IWRS or IVRS) and the randomization assignment was planned to be obtained by the clinical trial site's unblinded pharmacist or Investigational Product consignee. Subjects were planned to be randomized in equal ratios to one of the dose groups. Stratified permuted block randomization was planned to be used, stratified by migraine days during the screening period (≤9 days vs. >9 days).

Statistical methods

Primary analysis populations

The Full Analysis Population was planned to be used for efficacy analyses. This set was planned to include all randomized subjects who received Investigational Product/placebo. Subjects were planned to be summarized within the treatment group to which they were randomized.

Outcome variable

The primary outcome was defined as the change from baseline in monthly migraine days (Weeks 1-12), where the baseline monthly migraine days were planned to be measured over a 28 days period after screening (i.e. before randomization) and the monthly migraine days up to week 12 were planned to be the average of the monthly migraine days in each 4 week period up to week 12 (i.e. the average of the migraine days in week 1-4, 5-8 and 9-12).

Initially, 75% response on week 1-12 was defined as primary outcome measure. A responder was planned to be defined as a subject who achieves a ≥75% reduction in migraine headache days when response rates for each of the four week intervals (1-4, 5-8, 9-12) are averaged.

Primary analysis model

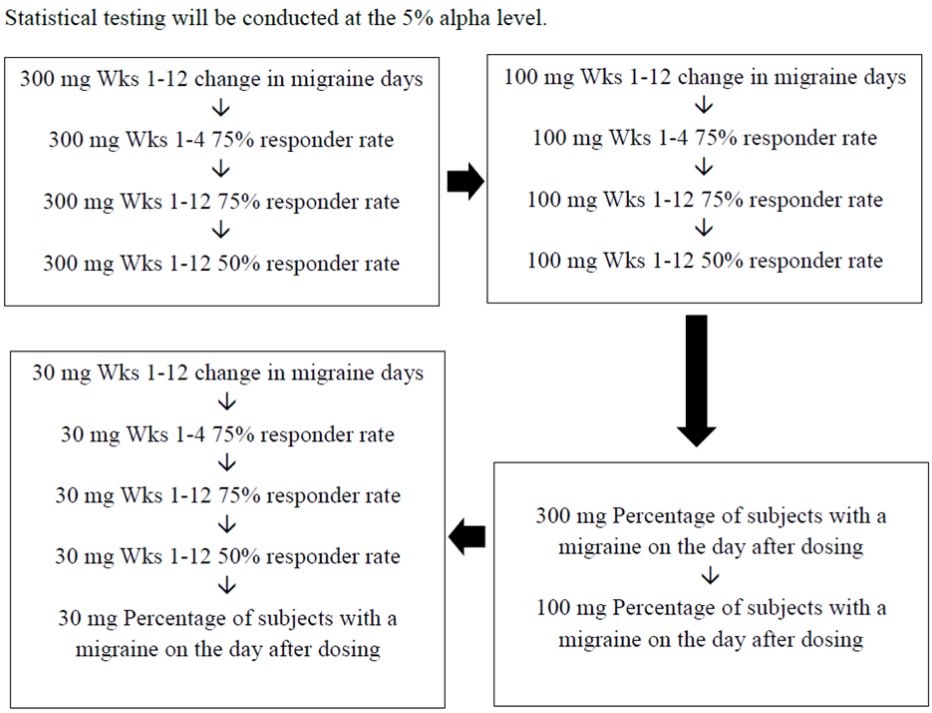
An ANCOVA model was planned to be used to test for a difference between treatment arms. This model was planned to include the change from baseline measure as the response variable. Treatment and the

stratification variable: baseline migraine days (continuous predictor) were planned to be included as independent variables.

For the key secondary endpoints (including the initially planned primary 75% responder rate) a CMH test was planned. The tests was planned to be stratified by the randomization stratification factor.

Significance level and multiplicity

The significance level was planned to be 5% two-sided. Multiplicity due to different dose-levels and several key secondary endpoints was planned to be addressed by an hierarchical testing procedure, displayed in the following figure:



Of note, the hierarchy was amended several times. Initially it was planned to test only the 75% responder rate hierarchically in all dose levels as compared to placebo in decreasing order (300 mg, 100 mg, 30 mg). In amendment 1, hierarchical testing of key secondary endpoints was introduced, where key secondary endpoints would be tested in each dose level after rejection of the primary null hypothesis for that dose level. The test of key secondary endpoints was planned to be conducted in parallel to the primary endpoint in the next lower dose level. This was again changed in amendment 3, which planned to hierarchically test primary and key secondary endpoints for each dose level before moving on to the next lowest dose level. In amendment 4 this was again changed to include the key secondary endpoint percentage of subjects with migraine on the day after dosing in the highest and second highest does level, before moving on to the lowest dose.

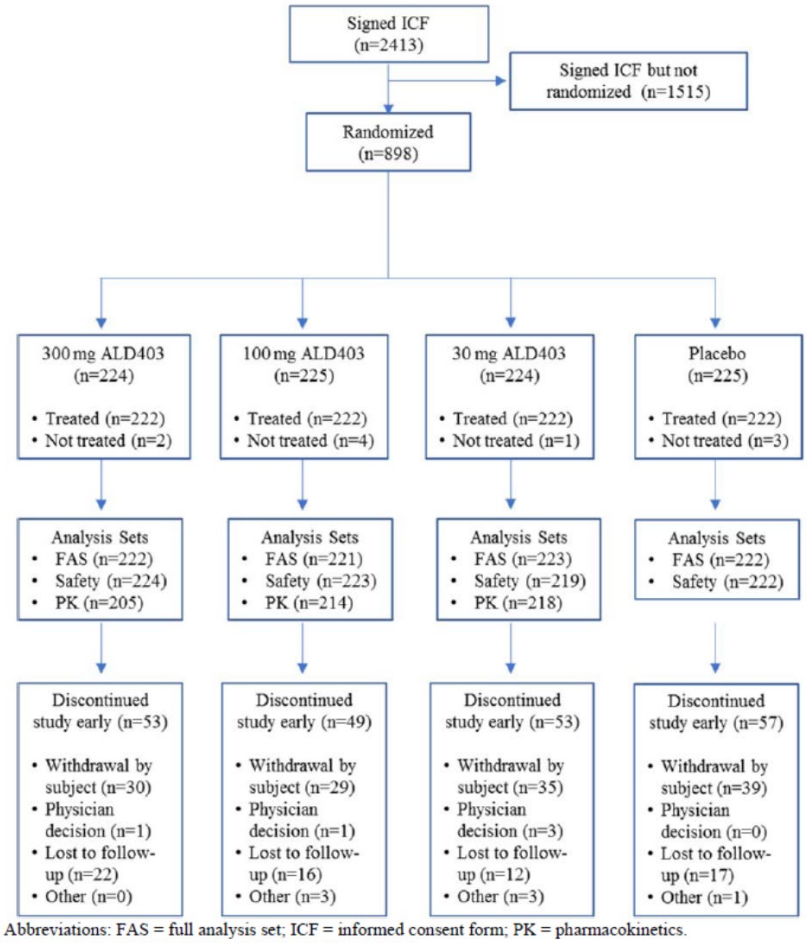
Missing values

Subjects who do not complete the eDiary daily were expected to have missing data. It was expected that most missing diary data would be sporadic. If the diary has been completed at least 21 days in a 28 day interval, then normalization was planned to be used. The results were planned to be normalized to 28 days by multiplying the observed results by the inverse of the completion rate. If the diary has been completed on less than 21 days in the 28 day interval then the results for the 28 day interval were planned to be a weighted function of the observed data for the current four week interval and the results from the previous interval. The weights were planned to be proportional to how many days the diary was completed. Specifically, the results were planned to be derived as $28 \cdot (W \cdot X_C + (1-W) \cdot X_P)$ where W is the days the diary was completed divided by 20, Xc is the available average daily results for the current interval and Xp are the average daily results for the previous interval.

Results

Participant flow

Figure 2: Subject Disposition



Abbreviations: FAS = full analysis set; ICF = informed consent form; PK = pharmacokinetics.
Sources: Table 14.1.1.1, Table 14.1.1.2a, Table 14.1.1.2b

The treatment arms were generally similar in numbers of patients who were randomized and treated and who completed the study, or discontinued early. Overall, a proportion of >20% of study participants discontinued the study prematurely. The number of patients who discontinued due to adverse events was slightly

increased in patients treated with eptinezumab 300 mg and 100 mg (1.4% each), compared to placebo-treated patients (<1%). The number of patients who withdrew due to study burden or lack of efficacy was greater in patients treated with placebo (9.5%/ 3.6 %) than withdrawals due these reasons among patients treated with placebo in the 300 mg (4.5%/ <1%), 100 mg (6.8 %/1.4%) and 30 mg (5.4%/ <1%) treatment groups.

Baseline data

Subject demographics across treatment groups were generally well balanced and any minor differences observed were not considered to be clinically relevant. The mean age was 39.8 years and most subjects (545 [61.4%]) were in the >35-year age group. The majority of the subjects were females (84.3% versus 15.7%), the majority were not of Hispanic or Latino ethnicity (727 subjects [81.9%]) and the majority were racially identified as white (744 subjects [83.8%]).

Table 11: Demographics and Baseline Characteristics (Safety Population)

Status	ALD403 300 mg N = 224	ALD403 100 mg N = 223	ALD403 30 mg N = 219	Placebo N = 222	Overall N = 888
Age (years)					
n	224	223	219	222	888
Mean (SD)	40.2 (11.72)	40.0 (10.66)	39.1 (11.54)	39.9 (11.67)	39.8 (11.39)
Median	40.0	40.0	37.0	39.5	39.0
Min, Max	18, 71	18, 68	18, 69	20, 68	18, 71
Age Group, n (%)					
≤35 years	89 (39.7)	73 (32.7)	93 (42.5)	88 (39.6)	343 (38.6)
>35 years	135 (60.3)	150 (67.3)	126 (57.5)	134 (60.4)	545 (61.4)
Sex, n (%)					
Male	25 (11.2)	44 (19.7)	34 (15.5)	36 (16.2)	139 (15.7)
Female	199 (88.8)	179 (80.3)	185 (84.5)	186 (83.8)	749 (84.3)
Ethnicity, n (%)					
Hispanic or Latino	40 (17.9)	42 (18.8)	45 (20.5)	34 (15.3)	161 (18.1)
Not Hispanic or Latino	184 (82.1)	181 (81.2)	174 (79.5)	188 (84.7)	727 (81.9)
Race, n (%)					
White	187 (83.5)	196 (87.9)	180 (82.2)	181 (81.5)	744 (83.8)
Black or African American	27 (12.1)	17 (7.6)	31 (14.2)	30 (13.5)	105 (11.8)
Asian	1 (<1)	1 (<1)	1 (<1)	2 (<1)	5 (<1)
American Indian or Alaska Native	2 (<1)	0	0	1 (<1)	3 (<1)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)	0	1 (<1)	3 (<1)
Multiple Races	5 (2.2)	7 (3.1)	5 (2.3)	5 (2.3)	22 (2.5)
Other	1 (<1)	1 (<1)	2 (<1)	2 (<1)	6 (<1)
Weight (kg)					
n	224	223	219	222	888
Mean (SD)	80.17 (20.883)	82.43 (23.378)	82.03 (23.269)	82.39 (21.726)	81.75 (22.315)
Median	76.25	79.10	78.00	79.00	78.00
Min, Max	40.2, 139.5	46.2, 190.1	45.2, 174.0	47.1, 160.9	40.2, 190.1
Height (cm)					
n	224	223	219	222	888
Mean (SD)	166.4 (8.09)	167.3 (9.13)	165.6 (8.40)	166.7 (9.16)	166.5 (8.72)
Median	165.0	167.0	165.0	165.0	165.0
Min, Max	148, 193	145, 199	150, 188	138, 196	138, 199
BMI (kg/m^2)[a]					
n	224	223	219	222	888
Mean (SD)	28.91 (7.137)	29.38 (7.656)	29.91 (8.324)	29.60 (7.279)	29.45 (7.605)
Median	27.20	27.80	28.20	27.95	27.80
Min, Max	16.2, 49.8	15.6, 59.3	17.8, 67.5	17.7, 52.6	15.6, 67.5

Abbreviations: BMI = body mass index; Max = maximum; Min = minimum.
[a] BMI = Body mass index calculated as weight (kg) / height $(m)^2$.
Source: Table 14.1.3.1

Table 13: eDiary-Reported Baseline Migraine and Headache Characteristics (Full Analysis Population)

eDiary-Reported Characteristic [a]	ALD403 300 mg N = 222	ALD403 100 mg N = 221	ALD403 30 mg N = 223	Placebo N = 222
Baseline migraine days				
Mean (SD)	8.6 (2.87)	8.7 (2.85)	8.7 (3.05)	8.4 (2.68)
Baseline headache days				
Mean (SD)	10.1 (3.06)	10.0 (3.02)	10.2 (3.35)	9.9 (2.83)
Baseline migraine attacks				
Mean (SD)	6.2 (2.26)	6.4 (2.19)	6.4 (2.53)	6.4 (2.27)
Baseline headache episodes				
Mean (SD)	7.6 (2.81)	7.7 (2.68)	8.0 (3.16)	8.0 (2.67)
Baseline migraine hours				
Mean (SD)	84.5 (55.42)	80.8 (51.76)	80.7 (54.24)	76.0 (44.64)
Baseline headache hours				
Mean (SD)	92.7 (58.62)	86.8 (53.44)	88.5 (57.19)	83.6 (46.91)
Baseline percent of migraines with severe intensity				
Mean (SD)	28.21 (25.410)	33.89 (28.635)	35.70 (30.332)	33.61 (28.478)
Baseline average length in hours of migraine attack				
Mean (SD)	15.34 (12.486)	13.83 (11.846)	14.05 (13.057)	12.87 (9.961)

Abbreviations: Max = maximum; Min = minimum.
[a] eDiary-reported migraine and headache characteristics at baseline.
Sources: Table 14.2.1.2.1, Table 14.2.1.2.1a, Table 14.2.2.5.2, Table 14.2.2.5.2a, Table 14.2.2.6.2, Table 14.2.2.6.2a, Table 14.2.2.7.2, Table 14.2.2.7.2a, Table 14.2.2.9.1, Table 14.2.2.9.1a.

Numbers analysed

All efficacy analyses were performed on the Full Analysis Population (FAP). The FAP included all randomized subjects who received investigational product/placebo. Subjects were summarized within the treatment group to which they were randomized.

A total of 898 subjects were randomized. A total of 888 subjects (98.9%) received treatment and were included in the safety population and full analysis population. A total of 10 subjects (1.1%) were randomized but not dosed.

Table 10: Summary of Analysis Populations (All Randomized Subjects)

	ALD403 300 mg n (%)	ALD403 100 mg n (%)	ALD403 30 mg n (%)	Placebo n (%)	Overall n (%)
All randomized subjects	224	225	224	225	898
Safety population	224 (100)	223 (99.1)	219 (97.8)	222 (98.7)	888 (98.9)
Full analysis population	222 (99.1)	221 (98.2)	223 (99.6)	222 (98.7)	888 (98.9)

Outcomes and estimation

Primary efficacy analyses

For the study's primary efficacy endpoint, the change in frequency of migraine days from Weeks 1-12 was measured in ALD403 treatment groups at 30, 100, and 300 mg, compared to placebo. This primary efficacy endpoint was calculated as the number of migraine days within 4-week intervals that were then averaged up to Week 12. The difference of this estimate from baseline was calculated as the change from baseline in the frequency of migraine days over Weeks 1-12.

Table 16: Analysis of Migraine Days by 12-Week Interval and Treatment (Full Analysis Population)

Interval	**ALD403 300 mg N = 222**	**ALD403 100 mg N = 221**	**ALD403 30 mg N = 223**	**Placebo N = 222**
Weeks 1-12				
Actual				
Estimated mean	4.3	4.7	4.6	5.4
Mean difference from placebo	-1.11	-0.69	-0.82	
95% CI	(-1.68, -0.54)	(-1.25, -0.12)	(-1.39, -0.25)	
Change from baseline				
Estimated mean	-4.3	-3.9	-4.0	-3.2
Mean difference from placebo	-1.11	-0.69	-0.82	
95% CI	(-1.68, -0.54)	(-1.25, -0.12)	(-1.39, -0.25)	
p-value	0.0001	0.0182	0.0046	

Key secondary efficacy analyses

75% Migraine Responder Rate (Weeks 1-4)

The 75% migraine responder rate over Weeks 1-4 demonstrated a statistically significant improvement for the ALD403 300 mg with an estimated difference of 11.3% (95% CI: 3.2, 19.3) vs. placebo. For the ALD403 100-mg group, the 75% migraine responder rate over Weeks 1-4 also demonstrated statistically significant improvement (P=0.0112) with an estimated difference of 10.5% (95% CI: 2.4, 18.6) vs. placebo. For the ALD403 30-mg group, the 75% migraine responder rate over Weeks 1-4 was also nominally statistically significant (P=0.0170) with an estimated difference of 9.8% (95% CI: 1.8, 17.8%) vs. placebo.

Table 17: Summary of 75% Migraine Responder Rate by 4-Week Interval and Treatment - Weeks 1-4 (Full Analysis Population)

Interval Assessment	ALD403 300 mg N = 222	ALD403 100 mg N = 221	ALD403 30 mg N = 223	Placebo N = 222
Weeks 1-4				
75% Responder - n (%)	70 (31.5)	68 (30.8)	67 (30.0)	45 (20.3)
Difference from placebo	11.3	10.5	9.8	
95% CI[a]	(3.2, 19.3)	(2.4, 18.6)	(1.8, 17.8)	
p-value[b]	0.0066	0.0112	0.0170	
Odds ratio relative to placebo[c]	1.817	1.752	1.694	
95 % CI[c]	(1.179, 2.802)	(1.134, 2.705)	(1.096, 2.618)	

Abbreviations: CI = confidence interval; SAP = statistical analysis plan.
Note: A 75% migraine responder was a subject who achieved a ≥75% reduction in migraine days. Missing eDiary data were handled using the rules provided in the SAP (Appendix 16.1.9).
Note: Unadjusted p-value was estimated for the 30-mg treatment arm while multiplicity adjusted p-values were estimated for the 300-mg and 100-mg groups as described in Table 15.
[a] 95% confidence intervals were calculated based upon normal approximation for 2 independent proportions. Stratification was not used.
[b] p-values for the key secondary endpoint 75% migraine responder rate for Weeks 1-4 were obtained from the Cochran-Mantel-Haenszel test stratified by randomized baseline migraine days (≤9 days, >9 days). Significant p-values were determined by the decision rule outlined by the SAP (Appendix 16.1.9).
[c] The common odds ratio and 95% confidence intervals were obtained from the Mantel-Haenszel test stratified by randomized baseline migraine days (≤9 days, >9 days).
Sources: Table 14.2.1.2.4 and Table 14.2.1.2.5

75% Migraine Responder Rate (Weeks 1-12)

The 75% migraine responder rate over Weeks 1-12 demonstrated a statistically significant improvement (P=0.0007) for ALD403 300 mg with an estimated difference of 13.5% (95% CI: 5.8, 21.2) vs. placebo. The 75% migraine responder rates for ALD403 300 mg across Weeks 1-4 and Weeks 1-12 were 31.5% and 29.7%, respectively, demonstrating sustained monthly responder rates over the 12-week interval. For the ALD403 100-mg group, the 75% migraine responder rate over Weeks 1-12 was not statistically significant (P=0.1126) with a difference of 6% (95% CI: -1.4, 13.3) vs. placebo. The treatment effect for the ALD403 30-mg group was nominally significant (P=0.0272) vs. placebo.

Table 18: Summary of 75% Migraine Responder Rate - Weeks 1-12 (Full Analysis Population)

Interval Assessment	ALD403 300 mg N=222	ALD403 100 mg N=221	ALD403 30 mg N=223	Placebo N=222
Weeks 1-12				
75% Responder - n (%)	66 (29.7)	49 (22.2)	55 (24.7)	36 (16.2)
Difference from placebo	13.5	6.0	8.4	
95% CI[a]	(5.8, 21.2)	(-1.4, 13.3)	(1.0, 15.9)	
p-value[b]	0.0007	0.1126	0.0272	
Odds ratio relative to placebo[c]	2.179	1.470	1.686	
95 % CI[c]	(1.379, 3.443)	(0.912, 2.368)	(1.057, 2.689)	

Abbreviations: CI = confidence interval; SAP = statistical analysis plan.
Note: A 75% migraine responder was a subject who achieved a ≥75% reduction in migraine days. Missing eDiary data were handled using the rules provided in the SAP (Appendix 16.1.9).
Note: Unadjusted p-value was estimated for the 30-mg treatment arm while multiplicity adjusted p-values were estimated for the 300-mg and 100-mg groups as described in Table 15.
[a] 95% confidence intervals were calculated based upon normal approximation for 2 independent proportions. Stratification was not used.
[b] P-values for the key secondary endpoint 75% migraine responder rate for Weeks 1-12 were obtained from the Cochran-Mantel-Haenszel test stratified by randomized baseline migraine days (≤9 days, >9 days). Significant p-values were determined by the decision rule outlined by the SAP (Appendix 16.1.9).
[c] The common odds ratio and 95% confidence intervals were obtained from the Mantel-Haenszel test stratified by randomized baseline migraine days (≤9 days, >9 days).
Sources: Table 14.2.1.2.3 and Table 14.2.1.2.5

50% Migraine Responder Rate (Weeks 1-12)

With a mean difference of 18.9 (95% CI: 9.8, 28.0), the ALD403 300-mg group with a 50% migraine responder rate of 56.3% demonstrated a statistically significant improvement (P=0.0001) vs. placebo. The ALD403 100-mg dose, with a mean difference of 12.4 (95% CI: 3.2, 21.5), was nominally significant (P=0.0085) for this endpoint vs. placebo. ALD403 30-mg dose with a mean difference of 12.8 (95% CI: 3.7, 22.0) was also nominally significant (P=0.0064) for this endpoint vs. placebo.

Table 19: Summary of 50% Migraine Responder Rate by 12-Week Interval and Treatment (Full Analysis Population)

Interval Assessment	ALD403 300 mg N=222	ALD403 100 mg N=221	ALD403 30 mg N=223	Placebo N=222
Weeks 1-12				
50% responder - n (%)	125 (56.3)	110 (49.8)	112 (50.2)	83 (37.4)
Difference from placebo	18.9	12.4	12.8	
95% CI[a]	(9.8, 28.0)	(3.2, 21.5)	(3.7, 22.0)	
p-value[b]	0.0001	0.0085	0.0064	
Odds ratio relative to placebo[c]	2.158	1.662	1.691	
95 % CI[c]	(1.476, 3.155)	(1.138, 2.427)	(1.159, 2.468)	

Abbreviations: CI = confidence interval; SAP = statistical analysis plan.
Note: A 50% migraine responder was a subject who achieved a ≥50% reduction in migraine days averaged over each of the 4-week intervals. Missing eDiary data were handled using the rules provided in the SAP (Appendix 16.1.9).
Note: Unadjusted p-value was estimated for the 30-mg treatment arm while multiplicity adjusted p-values were estimated for the 300-mg and 100-mg groups as described in Table 15.
[a] 95% confidence intervals were calculated based upon normal approximation for 2 independent proportions. Stratification was not used.
[b] p-values for the key secondary endpoint 50% migraine responder rate for Weeks 1-12 were obtained from the Cochran-Mantel-Haenszel test stratified by randomized baseline migraine days (≤9 days, >9 days). Significant p-values were determined by the decision rule outlined by the SAP (Appendix 16.1.9).
[c] The common odds ratio and 95% confidence intervals were obtained from the Mantel-Haenszel test stratified by randomized baseline migraine days (≤9 days, >9 days).
Sources: Table 14.2.2.1.2 and Table 14.2.1.2.5

Percentage of Subjects with Migraine on the Day After Dosing

For the baseline value, on average approximately 31% of subjects had a migraine on any given day during the 28-day screening period (daily migraine prevalence) based on migraine data captured by daily eDiary entries.

The percentage of subjects with a migraine on the day after dosing (Day 1) decreased to 14% and 15% in the ALD403 300-mg and 100-mg groups, respectively. When compared with placebo, the percentage of subjects with a migraine on the day after dosing (Day 1) in the ALD403 300-mg and 100-mg groups were both nominally significantly lower (P=0.0159 and 0.0312, respectively) than the 23% observed in the placebo group.

Table 20: Summary of Percentages of Subjects With a Migraine From Baseline to Day 7 (Full Analysis Population)

Assessment	ALD403 300 mg N=222	ALD403 100 mg N=221	ALD403 30 mg N=223	Placebo N=222
Percentage of Subjects with a Migraine				
Baseline[a]	30.8	31.0	31.0	29.8
Day 0[b]	18.5	19.4	19.9	20.5
Day 1	13.9	14.8	17.3	22.5
p-value[c]	0.0159	0.0312	0.1539	
Day 2	12.7	13.6	12.4	19.7
Day 3	13.1	11.4	16.1	16.6
Day 4	13.7	16.3	11.8	19.6
Day 5	15.0	20.6	14.1	21.0
Day 6	14.4	16.0	16.3	20.5
Day 7	20.4	15.6	19.5	18.6

[a] Baseline is the daily average over the 28-day screening period prior to receiving treatment.
[b] Day 0 is the first study treatment day.
[c] Unadjusted p-values for the key secondary endpoint percentage of subjects with a migraine on the day after dosing (Day 1) are obtained from an extended Cochran-Mantel-Haenszel test stratified by randomized baseline migraine days (<9 days, ≥9 days). The unadjusted p-values are deemed not significant per the decision rule outlined in the statistical analysis plan.
Source: Table 14.2.2.4.2

Secondary endpoint analyses

Reduction in Average Daily Migraine Prevalence from Baseline to Week 4

There were nominally significant and clinically meaningful improvements for the ALD403 groups compared with placebo in the reductions from baseline in average daily migraine prevalence over Weeks 1-4 with p-values of <0.0001, 0.0004 and <0.0001 for the 300-mg, 100-mg and 30-mg groups, respectively. The rates of average daily migraine prevalence, as measured each week over the first month, were similar to the Day 1 migraine prevalence rates shown in Table 20 (e.g., for ALD403 300 mg the Day 1 rate was 13.9% and the Week 1 rate was 14.4%).

Change in Frequency of Migraine Days Between Baseline and Time Periods Other Than Weeks 1-12

Results showed consistently reduced average migraine days in all the ALD403 treatment groups compared with placebo. The therapeutic effect was most consistently maintained in the ALD403 300-mg group across all dosing intervals, while increases in average monthly migraine days were observed in the ALD403 100-mg and ALD403 30-mg groups prior to the second, third and fourth dose.

Overall, the number (%) of subjects with a 50% or greater reduction in migraines from Weeks 1-48 was consistently higher in the ALD403 treatment groups than in the placebo group. The proportions of subjects with 50% or greater reduction in migraines were balanced across the ALD403 treatment groups. Results were similar for 50% headache responder rates.

Overall, the number (%) of subjects with a 75% or greater reduction in migraines from Weeks 1-48 was consistently higher in the ALD403 treatment groups than in the placebo group. The proportion of subjects with 75% or greater reduction in migraines was numerically greater in the 300-mg group as compared to the 100-mg and 30-mg groups in 10 of the twelve 4-week intervals. Results were similar for 75% headache responder rates.

100% Migraine Responder Rates (Weeks 1-48)

The ALD403 300-mg group was associated with greater 100% migraine responder rates during each 4-week interval compared with placebo over Weeks 1-12. Results for the ALD403 30-mg and 100-mg group were less consistent over the same 12-week period. The percent of 100% migraine responders in the ALD403 300-mg group was consistently higher than the other ALD403 dose groups from shortly after dosing and that result was maintained in all but one 4-week interval through Week 48.

Change in Acute Migraine Medication Days (Weeks 1-12)

An acute migraine medication day was a day with any triptan or ergotamine use as recorded in the eDiary. Mean acute migraine medication days was low at baseline and was reduced over Weeks 1-12 in all treatment groups. The reductions in acute migraine medication days from baseline were numerically greater in the ALD403 treatment groups with nominally statistically significant reductions in the ALD403 300-mg and ALD403 100-mg groups compared to the placebo group.

Change in acute migraine medication days (weeks 1-12)

An acute migraine medication day was a day with any triptan or ergotamine use as recorded in the eDiary. Mean acute migraine medication days was low at baseline and was reduced over Weeks 1-12 in all treatment groups. The reductions in acute migraine medication days from baseline were numerically greater in the ALD403 treatment groups with nominally statistically significant reductions in the ALD403 300-mg and ALD403 100-mg groups compared to the placebo group.

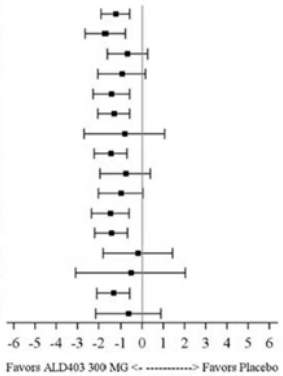
Ancillary analyses

Subgroup analyses

The following figures present forest plots of difference from placebo for ALD403 300 mg and ALD403 100 mg, respectively, in migraine days change from baseline over Weeks 1-12 by subgroup.

Figure 8: Forest Plot of Difference From Placebo in Monthly Migraine Days Change From Baseline Over Weeks 1-12 by Subgroup - ALD403 300 mg Versus Placebo (Full Analysis Population)

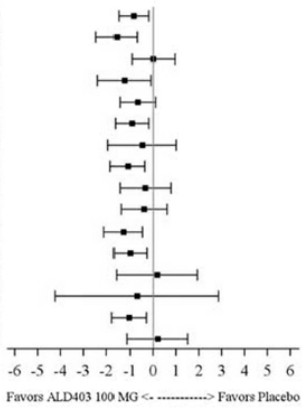
Variable	Subgroups	Change from Baseline ALD403 300 MG	Change from Baseline Placebo	Mean Difference from Placebo	95% CI
All Subjects	All	-4.32	-3.07	-1.3	(-1.91, -0.59)
Age Group at Diagnosis	<=21 years	-4.59	-2.86	-1.7	(-2.66, -0.80)
	>21 years	-3.99	-3.29	-0.7	(-1.65, 0.25)
Age (years)	<=35	-4.13	-3.17	-1.0	(-2.06, 0.14)
	>35	-4.45	-3.01	-1.4	(-2.28, -0.61)
Sex	F	-4.33	-3.01	-1.3	(-2.04, -0.61)
	M	-4.21	-3.39	-0.8	(-2.70, 1.05)
Baseline Migraine Days	<=9	-3.61	-2.13	-1.5	(-2.22, -0.73)
	>9	-5.58	-4.80	-0.8	(-1.94, 0.37)
Duration of Migraines (years)	<=15 years	-4.20	-3.20	-1.0	(-2.03, 0.03)
	>15 years	-4.41	-2.93	-1.5	(-2.36, -0.62)
Race	White	-4.43	-2.99	-1.4	(-2.20, -0.69)
	Black	-3.77	-3.58	-0.2	(-1.81, 1.42)
	Other	-3.53	-3.00	-0.5	(-3.09, 2.02)
Ethnic	Not Hispanic	-4.25	-2.90	-1.4	(-2.09, -0.61)
	Hispanic	-4.66	-4.02	-0.6	(-2.15, 0.87)



Note: Change from baseline is the difference in migraine days between baseline and Weeks 1-12. The mean difference from placebo and 95% confidence interval are from an analysis of covariance (ANCOVA) model with treatment as a factor and baseline migraine days as a covariate.
Source: Figure 14.5.2.3 (Panel 1)

Figure 9: Forest Plot of Difference From Placebo in Monthly Migraine Days Change From Baseline Over Weeks 1-12 by Subgroup - ALD403 100 mg Versus Placebo (Full Analysis Population)

Variable	Subgroups	Change from Baseline ALD403 100 MG	Change from Baseline Placebo	Mean Difference from Placebo	95% CI
All Subjects	All	-3.92	-3.07	-0.9	(-1.50, -0.20)
Age Group at Diagnosis	<=21 years	-4.44	-2.86	-1.6	(-2.47, -0.69)
	>21 years	-3.28	-3.29	0.0	(-0.92, 0.95)
Age (years)	<=35	-4.42	-3.17	-1.2	(-2.40, -0.10)
	>35	-3.68	-3.01	-0.7	(-1.46, 0.11)
Sex	F	-3.94	-3.01	-0.9	(-1.65, -0.20)
	M	-3.86	-3.39	-0.5	(-1.96, 1.01)
Baseline Migraine Days	<=9	-3.25	-2.13	-1.1	(-1.85, -0.38)
	>9	-5.14	-4.80	-0.3	(-1.45, 0.78)
Duration of Migraines (years)	<=15 years	-3.60	-3.20	-0.4	(-1.40, 0.61)
	>15 years	-4.22	-2.93	-1.3	(-2.12, -0.47)
Race	White	-3.98	-2.99	-1.0	(-1.71, -0.28)
	Black	-3.41	-3.58	0.2	(-1.59, 1.93)
	Other	-3.70	-3.00	-0.7	(-4.24, 2.84)
Ethnic	Not Hispanic	-3.94	-2.90	-1.0	(-1.78, -0.31)
	Hispanic	-3.83	-4.02	0.2	(-1.14, 1.51)



Note: Change from baseline is the difference in migraine days between baseline and Weeks 1-12. The mean difference from placebo and 95% confidence interval are from an analysis of covariance (ANCOVA) model with treatment as a factor and baseline migraine days as a covariate.
Source: Figure 14.5.2.3 (Panel 2)

Subgroup analyses raised concerns that there could be heterogeneity associated with race. In particular, black patients seemed to have a point estimate close to zero, suggesting that these patients did not benefit from treatment. Lack of efficacy for patients of colour was found replicated in study 011. This issue was raised and discussed in the day 180 LoOI. The applicant provided some reassurance that other variables may interact with treatment despite adjustment for race. This suggests that other variables than race may be associated with a larger or smaller effect of treatment. This includes the acute use of medication with more extreme positioning in US (either no medication or fixed combinations and opiates) as compared to EU. Although the extent of this cannot be evaluated, as the respective estimates are missing, this at least provides some reassurance, as it is not considered plausible that black patients would have a smaller treatment benefit than white patients.

Overall, the effect of 100 mg seems to be less robust than the effect of 300 mg. Several subgroups show point estimates close to zero, including subjects with age at diagnosis >21 years, male sex, >9 monthly days of migraine at baseline, ≤15 years of migraine history, black race and Hispanic ethnicity. Therefore, some uncertainty regarding heterogeneity of the treatment effect remains.

Missing data and study compliance

The majority of subjects remained in the study through Week 12 with fewer than 10 subjects (<5%) in the 300-mg and 100-mg groups not attending the Week 12 visits and 17 placebo subjects not attending the Week 12 visit (Table 7). The incidence of missing data increased with time during the study.

The dropouts and the missing eDiary reports were generally balanced across the treatment groups until Week 24, where a slightly higher rate was observed for the placebo group compared to the ALD403 treatment groups.

Study ALD403-CLIN-011: Chronic Migraine

Methods

Study Participants

The study included anti CGRP mAb-naïve, male and female patients between 18 and 65 years of age with a diagnosis of chronic migraine (defined as ≥15 to ≤26 headache days, of which ≥8 days were assessed as migraine days in the 28-day screening period). Subjects were allowed to concomitantly use non-mAb prophylactic headache medication, provided that this was stable for at least 3 months prior to screening. Patients with a history of complicated migraine, chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic, and familial hemiplegic migraine, as well as subjects with cardiovascular disease, neurological disease, cerebrovascular disease, diabetes, or Raynaud's disease were excluded from study participation.

Study 011 was conducted at approximately 150 centers in 13 countries with the majority of sites (53%) in the United States. Approximately 1050 subjects were to be randomly assigned in equal ratios to one of the 3 treatment groups (100 mg ALD403, 300 mg ALD403, or placebo).

Treatments

The eptinezumab doses of (100 mg or 300 mg) or placebo were prepared by the unblinded pharmacist or designee and were administered via IV over a period of 30 (+15) minutes on Day 0 and at the Week 12 (Day 84 ±3 days) visit by the blinded investigator or designee.

Subjects were randomly assigned to 1 of three treatment arms, 1 of 2 eptinezumab dose levels (100 mg or 300 mg) or placebo in a 1:1:1 ratio. Randomization occurred 28-30 days after the screening visit, after eligibility assessments were completed.

There were no pre-specified dose modifications or dose reductions allowed.

Stable concomitant (non-anti CGRP) prophylactic headache medication was allowed. Concomitant barbiturate and opioid medication, as well as codeine was restricted, but not prohibited. It is not clear, to which extend these medications were actually used across treatment groups and whether endpoint analyses might have been affected

Objectives

<u>Primary objective</u>

The primary objective of the study was to evaluate the efficacy of repeat doses of ALD403 administered IV compared to placebo in subjects with chronic migraine.

<u>Secondary objectives</u>

The secondary objectives of this study were:

• To evaluate the safety of repeat doses of ALD403 administered IV compared to placebo in subjects with chronic migraine.

• To evaluate the PK and immunogenicity of repeat doses of ALD403 administered IV to subjects with chronic migraine.

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the change in frequency of migraine days (Weeks 1-12).

Key Secondary Efficacy Endpoints

The key secondary endpoints were as follows:

- 75% migraine responder rate (Weeks 1-4)
- 75% migraine responder rate (Weeks 1-12)
- 50% migraine responder rate (Weeks 1-12)
- Percentage of subjects with a migraine on the day after dosing
- Reduction in migraine prevalence from baseline to Week 4
- Headache Impact Test (HIT-6)[a, b]
- Acute migraine medication usage[a, b]

[a] Applies only to the ALD403 300 mg dose.

[b] Please see Section 9.8.2 for further description of the planned analyses.

Randomisation and blinding (masking)

Approximately 1050 subjects were to be randomly assigned in equal ratios to one of the 3 treatment groups (100 mg ALD403, 300 mg ALD403, or placebo).

Randomization occurred 28 to 30 days after the screening visit, after eligibility assessments approved by the medical monitor and eligibility, including eDiary criteria, were reconfirmed by the investigator. As study drug was shipped upon confirmation of subject randomization, subjects were not always treated on the day of randomization. Every effort was made to conduct an on-site randomization visit; however, a phone visit was acceptable in cases where the subject's schedule did not permit an on-site visit. Sites completed randomization in IWRS, and the randomization assignment was obtained by the clinical study site's unblinded pharmacist or designee. Subjects were randomly assigned in equal to one of two ALD403 dose levels (100 mg or 300 mg) or placebo in a 1:1:1 ratio.

Subjects who withdrew from the clinical study after randomization were not replaced (i.e., their randomization numbers were not reused), including subjects who withdrew between randomization and treatment; these subjects retained their randomization assignment and subject number.

The study remained blinded until the last subject completed the Week 12 visit. A limited number of sponsor representatives were unblinded as per the Blinding Plan and outputs were generated for the primary endpoint assessment at Week 12. Operational members of the study team and clinical site staff remained blinded to subject level data and treatment assignment through the end of the study. The details of any unblinding events were recorded in the ALD403-CLIN-011 Unblinding Log and maintained in the trial master file. During the conduct of the study there were no cases where subject unblinding was required.

Statistical methods

Primary analysis populations

The Full Analysis Population was planned to be used for efficacy analyses. This set was planned to include all randomized subjects who received Investigational Product/placebo. Subjects were planned to be summarized within the treatment group to which they were randomized.

Outcome variable

The primary outcome was defined as the change from baseline to week 12 in monthly migraine days, where the baseline monthly migraine days were planned to be measured over a 28 days period after screening (i.e. before randomization) and the monthly migraine days up to week 12 were planned to be the average of the monthly migraine days in each 4 week period up to week 12 (i.e. the average of the migraine days in week 1-4, 5-8 and 9-12).

Initially, 75% response on week 1-12 was defined as primary outcome measure. A responder was planned to be defined as a subject who achieves a ≥75% reduction in migraine headache days when response rates for each of the four week intervals (1-4, 5-8, 9-12) are averaged.

Primary analysis model

An ANCOVA model was planned to be used to test for a difference between treatment arms. This model was planned to include the change from baseline measure as the response variable. Treatment and the stratification variables: baseline migraine days (continuous predictor) and prophylactic medication use (use vs. no use) were planned be the independent variables.

For the key secondary endpoints (including the initially planned primary 75% responder rate) a CMH test was planned. The tests was planned to be stratified by the randomization stratification factors.

Significance level and multiplicity

The significance level was planned to be 5% two-sided. Multiplicity due to different dose-levels and several key secondary endpoints was planned to be addressed by a hierarchical testing procedure, as follows:

The procedure was planned to start with the 300 mg vs placebo comparison for the primary endpoint. If this is significant, testing was planned to continue to key secondary endpoints for 300 mg. The procedure was planned to then move on to the 100 mg group for the primary endpoint and subsequently the secondary endpoints. The order of key secondary endpoints is not specified.

Of note, the hierarchy was different in the initial protocol and was amended. Initially, it was planned to test the primary endpoint for the 300 mg vs placebo comparison first, and then hierarchically continue with key secondary endpoints in the 300 mg group and the primary endpoint in the 100 mg group in parallel. In amendment 1, this was changed. The primary analysis was changed to be for change form baseline in MMDs, (Weeks 1-12), and a hierarchy was introduced to key secondary endpoints and dose level testing, specifying that key secondary endpoints for 300 mg would be tested before moving on to the 100 mg dose level. The order of key-secondary endpoints was specified as first the Weeks 1-4, 75% responder endpoint and then the Weeks 1-12 75% responder endpoint). In amendment 3, the order of key-secondary endpoints was updated.

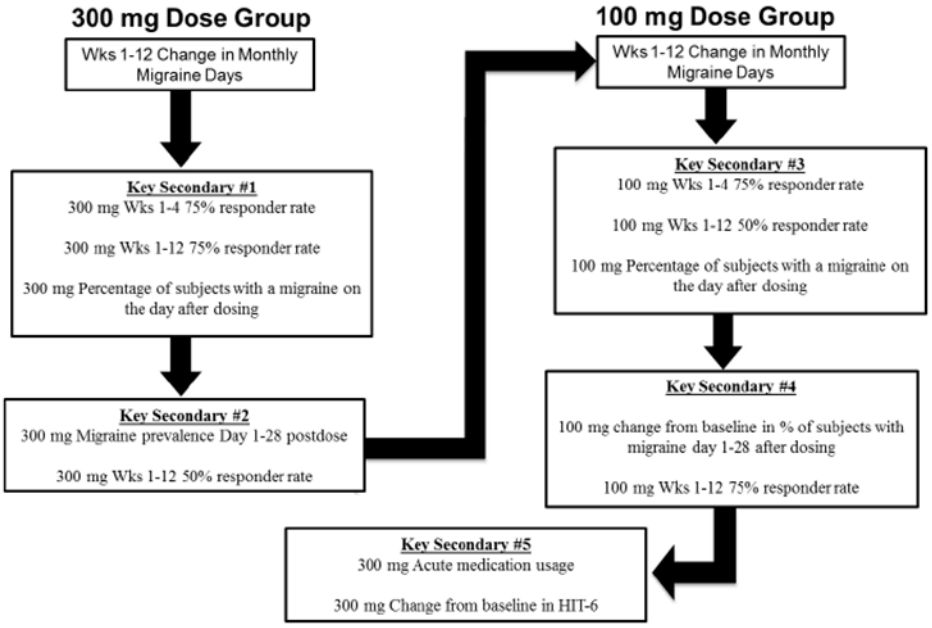
In the statistical analysis plan, dated 08 November 2017, it was specified differently that key secondary endpoints would be tested using Holm's procedure, i.e. overall a combination of gatekeeping and Holm's would be applied, rather than hierarchical testing, as follows:

"At a high level this procedure will start with the 300 mg vs placebo comparison for the primary endpoint. If this is significant, testing will continue to the first group of key secondary endpoints for 300 mg where Holm's multiplicity procedure will be used. Testing will then continue to the second group of key secondary endpoints and then move on to the 100 mg group for the primary endpoint and subsequently the key secondary endpoints using the same methodology (Holm's within each group)." The ordering as specified in the SAP is displayed in the following table, where key secondary #1 would be tested upon rejection of the null hypothesis regarding change from baseline (week 1-12) in the 300 mg vs placebo comparison (primary endpoint) and between key secondary # 2 and key secondary # 3 the same outcome would be tested in the 100 mg vs placebo comparison (primary outcome in lower dose level). Within one tier of key-secondary endpoints, all comparisons would need to be significant before continuation to the next tier.

Table 2: Key Efficacy Analyses and Multiplicity Adjustment

Testing Sequence	Endpoint	Population	Declare Significant
Key Secondary #1	300 mg Wk1-4 75% responder rate	FAP	$p_{(1)} < 0.0167$ $p_{(2)} < 0.025$ $p_{(3)} < 0.05$
	300 mg Wk1-12 75% responder rate	FAP	
	300 mg % subjects with migraine on the day after dosing	FAP	
Key Secondary #2	300 mg migraine prevalence Day 1-28 Post dose	FAP	$p_{(1)} < 0.025$ $p_{(2)} < 0.05$
	300 mg wk 1-12 50% responder rate	FAP	
Key Secondary #3	100 mg Wk1-4 75% responder rate	FAP	$p_{(1)} < 0.0167$ $p_{(2)} < 0.025$ $p_{(3)} < 0.05$
	100 mg Wk1-12 50% responder rate	FAP	
	100 mg % subjects with migraine on the day after dosing	FAP	
Key Secondary #4	100 mg migraine prevalence Day 1-28 Post dose	FAP	$p_{(1)} < 0.025$ $p_{(2)} < 0.05$
	100 mg wk 1-12 75% responder rate	FAP	
Key Secondary #5	300 mg Acute medication usage	FAP	$p_{(1)} < 0.025$ $p_{(2)} < 0.05$
	300 mg Change from baseline in HIT-6	FAP	

Figure 1: Decision Rule for Dose Levels (Primary and Secondary Endpoints)



Abbreviations: HIT-6 = Headache Impact Test; Wks = weeks
Note: All testing was performed on the full analysis population. For each step, if the endpoint(s) was/were statistically significant, testing could proceed to the next endpoint in the sequence; otherwise, testing was stopped.

Missing values

Subjects who do not complete the eDiary daily were expected to have missing data. It was expected that most missing diary data would be sporadic. If the diary has been completed at least 21 days in a 28 day interval, then normalization was planned to be used. The results were planned to be normalized to 28 days by multiplying the observed results by the inverse of the completion rate. If the diary has been completed on less than 21 days in the 28 day interval then the results for the 28 day interval were planned to be a weighted function of the observed data for the current four week interval and the results from the previous interval. The weights were planned to be proportional to how many days the diary was completed. Specifically, the results were planned to be derived as $28 \cdot (W \cdot X_C + (1-W) \cdot X_P)$ where W is the days the diary was completed divided by 20, Xc is the available average daily results for the current interval and Xp are the average daily results for the previous interval.

Results

Participant flow

A total of 1142 subjects were screened but not randomized, the majority as they did not meet all inclusion criteria.

Of the 1121 subjects who were randomized, 49 subjects (4.4%) were not treated, due to a variety of reasons, including subject withdrew from the study (19 subjects), due to AE (2 subjects), study burden (8 subjects), and other reasons (9 subjects). 27 subjects were randomized and but not treated due to other reasons. Overall, these reasons were not related to study drug (never received dosing).

55 subjects (5.1%) discontinued treatment early; the incidence of subjects who discontinued treatment early was generally balanced across the groups.

Table 7: Subject Disposition by Treatment Sequence (All Randomized Subjects)

Status	ALD403 300 mg n (%)	ALD403 100 mg n (%)	Placebo n (%)	Overall n (%)
Randomized subjects	374	372	375	1121
Subjects randomized but not treated	24 (6.4)	16 (4.3)	9 (2.4)	49 (4.4)
Discontinued treatment early a	15 (4.3)	16 (4.5)	24 (6.6)	55 (5.1)
Discontinued study early a	28 (8.0)	32 (9.0)	41 (11.2)	101 (9.4)
Reason for early treatment discontinuation				
Adverse event	8 (2.3)	3 (< 1)	3 (< 1)	14 (1.3)
Subject withdrew informed consent	5 (1.4)	7 (2.0)	14 (3.8)	26 (2.4)
Investigator decision	0	0	0	0
Termination of study by Sponsor	0	0	0	0
Lost to follow-up	2 (< 1)	3 (< 1)	5 (1.4)	10 (< 1)
Other	0	3 (< 1)	2 (< 1)	5 (< 1)
Reason for early study discontinuation a				
Withdrawal by subject	20 (5.7)	20 (5.6)	23 (6.3)	63 (5.9)
Adverse event	4 (1.1)	0	1 (< 1)	5 (< 1)
Study burden	3 (< 1)	4 (1.1)	3 (< 1)	10 (< 1)
Lack of efficacy	6 (1.7)	5 (1.4)	10 (2.7)	21 (2.0)
Worsening of study indication	0	0	0	0
Other	7 (2.0)	11 (3.1)	9 (2.5)	27 (2.5)
Randomization capped	0	0	0	0
Physician decision	0	2 (< 1)	1 (< 1)	3 (< 1)
Lost to follow-up	8 (2.3)	9 (2.5)	16 (4.4)	33 (3.1)
Death	0	0	0	0
Study terminated by Sponsor	0	0	0	0
Other	0	1 (< 1)	1 (< 1)	2 (< 1)

Reason randomized but not treated b				
Withdrawal by subject	9 (37.5)	8 (50.0)	2 (22.2)	19 (38.8)
Adverse event	2 (8.3)	0	0	2 (4.1)
Study burden	5 (20.8)	3 (18.8)	0	8 (16.3)

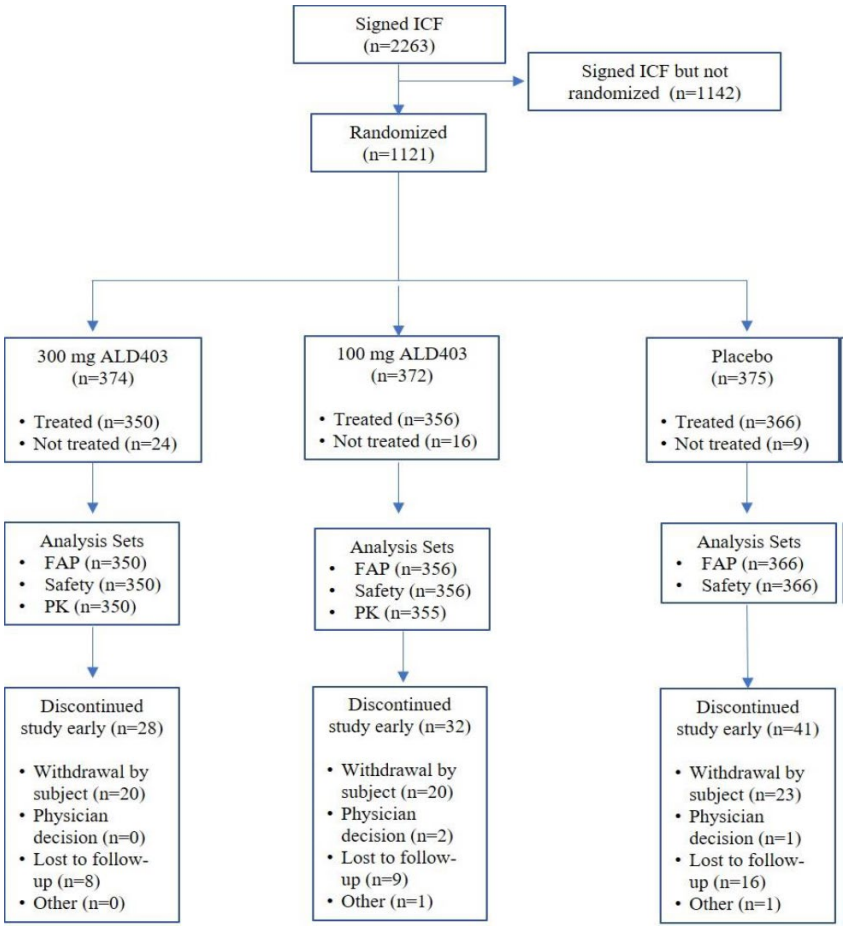
Status	**ALD403 300 mg n (%)**	**ALD403 100 mg n (%)**	**Placebo n (%)**	**Overall n (%)**
Lack of efficacy	0	0	0	0
Worsening of study indication	0	0	0	0
Other	2 (8.3)	5 (31.3)	2 (22.2)	9 (18.4)
Randomization capped	0	0	0	0
Physician decision	0	0	0	0
Lost to follow-up	1 (4.2)	1 (6.3)	1 (11.1)	3 (6.1)
Death	0	0	0	0
Study terminated by Sponsor	0	0	0	0
Other	14 (58.3)	7 (43.8)	6 (66.7)	27 (55.1)
Subjects by visit c				
Day 0	350 (93.6)	356 (95.7)	366 (97.6)	1072 (95.6)
Week 4	348 (93.0)	355 (95.4)	364 (97.1)	1067 (95.2)
Week 12	344 (92.0)	349 (93.8)	356 (94.9)	1049 (93.6)
Week 24	331 (88.5)	333 (89.5)	336 (89.6)	1000 (89.2)
Week 32	291 (77.8)	293 (78.8)	289 (77.1)	873 (77.9)

Abbreviations: n = number of subjects in a group

a Percentages based upon number of subjects in the full analysis population.

b Percentages based upon number of subjects randomized but had not received treatment. These subjects were not included in the full analysis population

c Subjects who attended each visit.



Baseline data

Demographics across groups were generally well balanced and any minor differences observed were not considered to be clinically relevant. The mean age was 40.5 years and most subjects (704 [65.7%]) were in the > 35-years age group. The majority of subjects were females (88.2%), most were not of Hispanic or Latino ethnicity (986 subjects [92.0%]), and most were racially identified as white (975 subjects [91.0%]). At baseline, 397 subjects (37.0%) reported prophylactic medication use.

Table 11: Demographics and Baseline Characteristics (Safety Population)

Status	**ALD403 300 mg N=350**	**ALD403 100 mg N=356**	**Placebo N=366**	**Overall N=1072**
Age (years)				
n	350	356	366	1072
Mean (SD)	41.0 (10.36)	41.0 (11.72)	39.6 (11.28)	40.5 (11.15)
Median	40.5	41.0	40.0	41.0
Min, max	18, 65	18, 65	18, 65	18, 65

Age Group, n (%)				
≤ 35 years	114 (32.6)	113 (31.7)	141 (38.5)	368 (34.3)
> 35 years	236 (67.4)	243 (68.3)	225 (61.5)	704 (65.7)
Sex, n (%)				
Male	36 (10.3)	49 (13.8)	41 (11.2)	126 (11.8)
Female	314 (89.7)	307 (86.2)	325 (88.8)	946 (88.2)
Ethnicity, n (%)				
Hispanic or Latino	18 (5.1)	33 (9.3)	35 (9.6)	86 (8.0)
Not Hispanic or Latino	332 (94.9)	323 (90.7)	331 (90.4)	986 (92.0)
Race, n (%)				
White	322 (92.0)	332 (93.3)	321 (87.7)	975 (91.0)
Black or African American	23 (6.6)	21 (5.9)	38 (10.4)	82 (7.6)
Asian	1 (< 1)	1 (< 1)	1 (< 1)	3 (< 1)
American Indian or Alaska Native	1 (< 1)	1 (< 1)	1 (< 1)	3 (< 1)
Native Hawaiian or other Pacific Islander	1 (< 1)	0	0	1 (< 1)
Multiple Races	2 (< 1)	1 (< 1)	4 (1.1)	7 (< 1)
Other	0	0	1 (< 1)	1 (< 1)
Region, n (%)				
European Union	53 (15.1)	50 (14.0)	51 (13.9)	154 (14.4)
North America	195 (55.7)	198 (55.6)	232 (63.4)	625 (58.3)
Other	102 (29.1)	108 (30.3)	83 (22.7)	293 (27.3)

Status	**ALD403 300 mg N=350**	**ALD403 100 mg N=356**	**Placebo N=366**	**Overall N=1072**
Weight (kg)				
n	350	356	366	1072
Mean (SD)	72.71 (15.340)	73.32 (15.655)	74.85 (16.259)	73.64 (15.774)
Median	70.30	71.95	73.00	72.00
Min, max	45.8, 117.9	39.2, 134.2	40.7, 126.8	39.2, 134.2

Height (cm)				
n	350	356	366	1072
Mean (SD)	166.1 (7.89)	166.2 (8.24)	166.3 (7.90)	166.2 (8.00)
Median	165.0	166.0	166.0	165.0
Min, max	144, 203	147, 194	142, 198	142, 203
BMI (kg/m2)a				
n	350	356	366	1072
Mean (SD)	26.25 (5.038)	26.42 (4.979)	27.02 (5.558)	26.57 (5.208)
Median	25.20	25.90	26.15	25.80
Min, max	15.9, 38.9	16.7, 38.8	17.3, 39.0	15.9, 39.0
Baseline migraine days, n (%)b				
< 17 days	193 (55.1)	192 (53.9)	204 (55.7)	589 (54.9)
≥ 17 days	157 (44.9)	164 (46.1)	162 (44.3)	483 (45.1)
Reported prophylactic medication use, n (%)c				
Yes	130 (37.1)	132 (37.1)	135 (36.9)	397 (37.0)
No	220 (62.9)	224 (62.9)	231 (63.1)	675 (63.0)
Calculated baseline migraine days, n (%)d				
< 17 days	197 (56.3)	199 (55.9)	206 (56.3)	602 (56.2)
≥ 17 days	153 (43.7)	157 (44.1)	160 (43.7)	470 (43.8)
Prior prophylactic medication use, n (%)e				
Yes	62 (17.7)	51 (14.3)	46 (12.6)	159 (14.8)
No	288 (82.3)	305 (85.7)	320 (87.4)	913 (85.2)

Status	**ALD403 300 mg N=350**	**ALD403 100 mg N=356**	**Placebo N=366**	**Overall N=1072**
Concomitant prophylactic medication use, n (%)f				
Yes	155 (44.3)	161 (45.2)	163 (44.5)	479 (44.7)
No	195 (55.7)	195 (54.8)	203 (55.5)	593 (55.3)

Abbreviations: BMI = body mass index; max = maximum; min = minimum, N = total number of subjects in a

group, n = total number of subjects with the event.

a Body mass index was calculated as weight (kg) / height (m)2.

b Baseline migraine days entered at randomization by the site.

c Prophylactic medication use entered at randomization by the site.

d Baseline migraine days calculated from the eDiary.

e Prior prophylactic medication use based on clinical review of the coded prior medication.

f Concomitant prophylactic medication use based on clinical review of the coded concomitant medications. Sources: Table 14.1.3.1.

Numbers analysed

All efficacy analyses were performed on the FAP and all safety analyses were performed on the safety population.

A total of 1121 subjects were randomized. A total of 1072 subjects (95.6%) received treatment and were included in the safety population and FAP. A total of 49 subjects (4.4%) were randomized but not dosed.

Table 10: Summary of Analysis Sets (All Randomized Subjects)

Status	**ALD403 300 mg n (%)**	**ALD403 100 mg n (%)**	**Placebo n (%)**	**Overall n (%)**
All randomized subjects	374	372	375	1121
Safety populationa	350 (93.6)	356 (95.7)	366 (97.6)	1072 (95.6)
Full analysis populationb	350 (93.6)	356 (95.7)	366 (97.6)	1072 (95.6)

Abbreviations: n = total number of subjects with the event.

a The safety population included all subjects who received study drug/placebo. Subjects were summarized within the group for which they actually received treatment.

b The full analysis population included all randomized subjects who received study drug/placebo. Subjects were summarized within the group to which they were randomized.

Outcomes and estimation

Primary efficacy analyses

The primary endpoint was calculated as the number of monthly migraine days within 4-week intervals that were then averaged up to week 12.

Table 16: Analysis of Migraine Days by 12-Week Interval and Treatment (Full Analysis Population)

Interval	ALD403 300 mg N=350	ALD403 100 mg N=356	Placebo N=366
Weeks 1-12			
Actual			
Estimated mean	7.9	8.5	10.5
Mean difference from placebo	-2.60	-2.03	
95% CI	(-3.45, -1.74)	(-2.88, -1.18)	
Change from baseline[a]			
Estimated mean	-8.2	-7.7	-5.6
Mean difference from placebo	-2.60	-2.03	
95% CI	(-3.45, -1.74)	(-2.88, -1.18)	
p-value[b]	< 0.0001	< 0.0001	

Key secondary efficacy endpoints

75% Migraine Responder Rate (Weeks 1-4)

The 75% migraine responder rate over Weeks 1-4 demonstrated a statistically significant improvement (P<0.0001) for the ALD403 300 mg group with an estimated difference of 21.3% (95% CI: 15.0, 27.6) versus placebo. For the ALD403 100 mg group, the 75% migraine responder rate over Weeks 1-4 also demonstrated statistically significant improvement (P<0.0001) with an estimated difference of 15.3% (95% CI: 9.3, 21.4) versus placebo.

Table 17: Summary of 75% Migraine Responder Rate by 4-Week Interval and Treatment – Weeks 1-4 (Full Analysis Population)

Interval Assessment	ALD403 300 mg N=350	ALD403 100 mg N=356	Placebo N=366
Weeks 1-4			
75% responder - n (%)	129 (36.9)	110 (30.9)	57 (15.6)
Difference from placebo	21.3	15.3	
95% CIa	(15.0, 27.6)	(9.3, 21.4)	
p-valueb	< 0.0001	< 0.0001	

Odds ratio relative to placeboc	3.206	2.445
95% CIc	(2.242, 4.583)	(1.705, 3.507)

Abbreviations: CI = confidence interval; N = total number of subjects in the group; n = number of subjects with the event; SAP = statistical analysis plan.

75% Migraine Responder Rate (Weeks 1-12)

The 75% migraine responder rate over Weeks 1-12 demonstrated a statistically significant improvement (P<0.0001) for ALD403 300 mg with an estimated difference of 18.1% (95% CI: 12.0, 24.3) versus placebo.

For the ALD403 100 mg group, the 75% migraine responder rate over Weeks 1-12 was also statistically significant (P=0.0001) with a difference of 11.7 (95% CI: 5.8, 17.5) versus placebo.

Table 18: Summary of 75% Migraine Responder Rate – Weeks 1-12 (Full Analysis Population)

Interval Assessment	**ALD403 300 mg N=350**	**ALD403 100 mg N=356**	**Placebo N=366**
Weeks 1-12			
75% Responder - n (%)	116 (33.1)	95 (26.7)	55 (15.0)
Difference from placebo	18.1	11.7	
95% CI a	(12.0, 24.3)	(5.8, 17.5)	
p-value b	< 0.0001	0.0001	
Odds ratio relative to placebo c	2.780	2.052	
95% CIc	(1.938, 3.987)	(1.419, 2.968)	

Abbreviations: CI = confidence interval; N = total number of subjects in the group; n = number of subjects with the event; SAP = statistical analysis plan.

50% Migraine Responder Rate (Weeks 1-12)

The ALD403 300 mg group with a 50% migraine responder rate of 61.4% and a mean difference of 22.1 (95% CI: 14.9, 29.2) versus placebo demonstrated a statistically significant improvement (P<0.0001) for this endpoint. The ALD403 100 mg dose with a 50% migraine responder rate of 57.6% and a mean difference of 18.2 (95% CI: 11.1, 25.4) versus placebo was also statistically significant (P<0.0001).

Table 19: Summary of 50% Migraine Responder Rate by 12-Week Interval and Treatment (Full Analysis Population)

Interval Assessment	ALD403 300 mg N=350	ALD403 100 mg N=356	Placebo N=366
Weeks 1-12			
50% responder - n (%)	215 (61.4)	205 (57.6)	144 (39.3)
Difference from placebo	22.1	18.2	
95% CIa	(14.9, 29.2)	(11.1, 25.4)	
p-valueb	< 0.0001	< 0.0001	
Odds ratio relative to placeboc	2.446	2.098	
95% CIc	(1.812, 3.301)	(1.559, 2.824)	

Abbreviations: CI = confidence interval; N = total number of subjects in the group; n = number of subjects with the event; SAP = statistical analysis plan.

Percentage of Subjects with Migraine on Day after Dosing (Day 1)

On average approximately 58% of subjects had a migraine on any given day during the 28-day screening period (daily migraine prevalence) based on migraine data captured by daily eDiary entries. The percentages of subjects with a migraine on the day after dosing (Day 1) were 27.8% and 28.6% in the ALD403 300 mg and 100 mg groups, respectively, compared with 42.3% in the placebo group. The percentages of subjects with a migraine on the day after dosing for the ALD403 300 mg and 100 mg groups versus placebo were statistically significant (P<0.0001 for both dose groups).

Table 20: Summary of Percentages of Subjects with a Migraine from Baseline to Day 7 (Full Analysis Population)

Assessment	ALD403 300 mg N=350	ALD403 100 mg N=356	Placebo N=366
Percentage of subjects with a migraine			
Baselinea	57.4	57.5	58.0
Day 0b	33.1	40.0	45.3
Day 1	27.8	28.6	42.3
p-valuec	< 0.0001	< 0.0001	
Day 2	26.4	30.4	36.9
Day 3	29.1	27.5	35.3
Day 4	28.0	30.1	44.8
Day 5	27.4	28.7	39.6

Day 6	29.2	33.3	41.4
Day 7	28.3	28.9	40.2

Abbreviations: N = total number of subjects in the group.

a Baseline was the average over the 28-day screening period prior to receiving treatment.

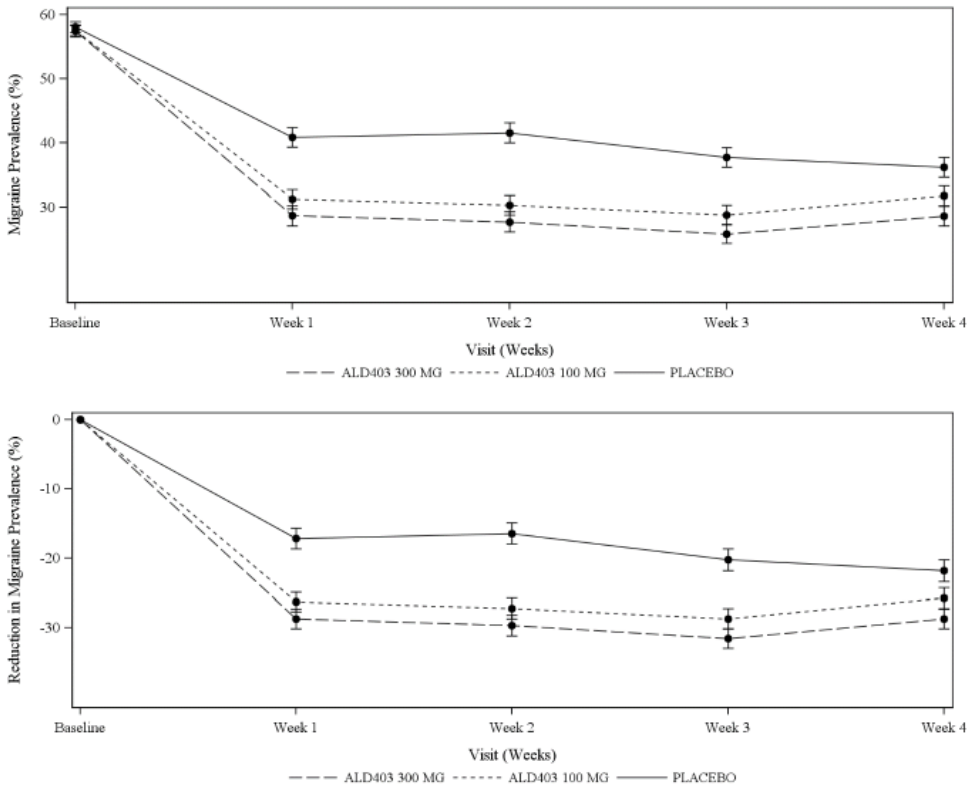
b Day 0 was the first study treatment day.

c p-values for the key secondary endpoint percentage of subjects with a migraine on the day after dosing (Day 1) were obtained from an extended Cochran-Mantel-Haenszel test stratified by randomized baseline migraine days (< 17 days, ≥ 17 days) and prophylactic medication use (yes vs. no). The p-values were deemed significant by the decision rule outlined in the statistical analysis plan.

Reduction in Migraine Prevalence from Baseline to Week 4

There was a nominally significant and clinically meaningful improvement for both ALD403 groups compared with placebo on reductions in average daily migraine prevalence for each of the 4 weeks. The mean difference of the change from baseline in average daily migraine prevalence over Weeks 1-4 was -11.0 (95% CI: -14.22, -7.77) for the ALD403 300 mg arm, while the difference was -8.26 (95% CI: -11.48, -5.05) for the ALD403 100 mg arm, both statistically significant versus placebo (P<0.0001).

Figure 5: Migraine Prevalence and Reduction in Migraine Prevalence by 1-Week Intervals



Headache Impact Test (HIT-6) - ALD403 300 mg

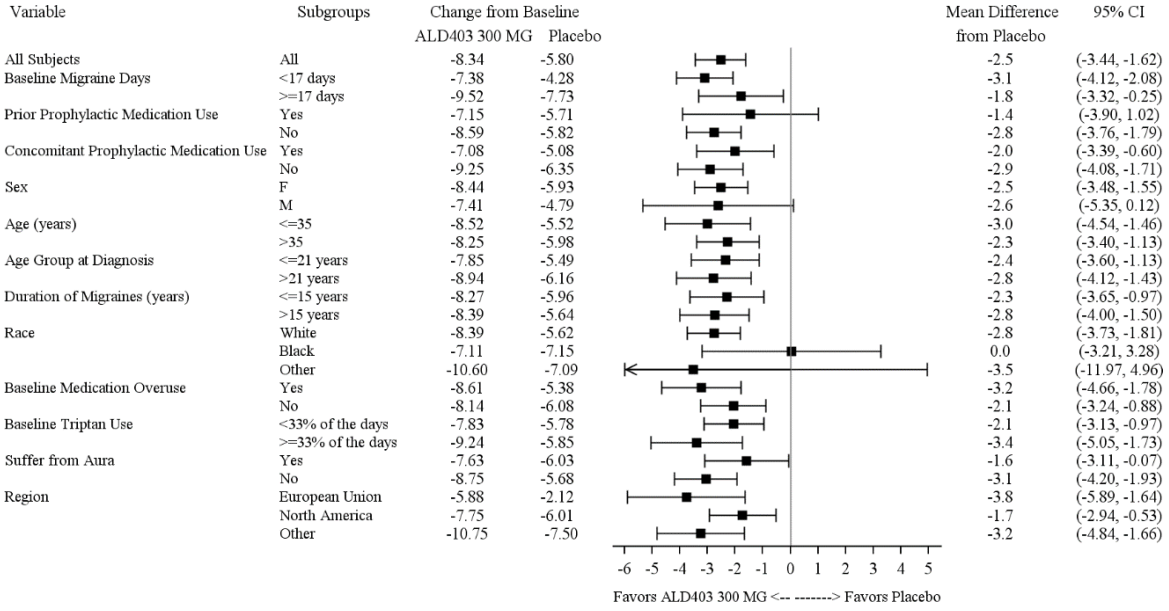
At baseline, the HIT-6 life impact scores were balanced among the groups. Most subjects in all groups had severe impact scores at baseline (310, 319, and 320 subjects [88.6%, 89.6%, and 87.4%] in the ALD403 300 mg, 100 mg, and placebo groups, respectively). The impact scores improved by Weeks 9-12 (assessed at Week 12) and 150, 183, and 220 subjects (42.9%, 51.4%, and 60.1%) had severe impact scores in the ALD403 300 mg, 100 mg, and placebo groups, respectively. The improvements were sustained through Week 32.

Ancillary analyses

Subgroup analyses

The following figures present forest plots of difference from placebo for ALD403 300 mg and ALD403 100 mg, respectively, in migraine days change from baseline over Weeks 1-12 by subgroup.

Figure 9: Forest Plot of Difference from Placebo in Migraine Days Change from Baseline over Weeks 1-12 by Subgroup - ALD403 300 mg Versus Placebo (Full Analysis Population)

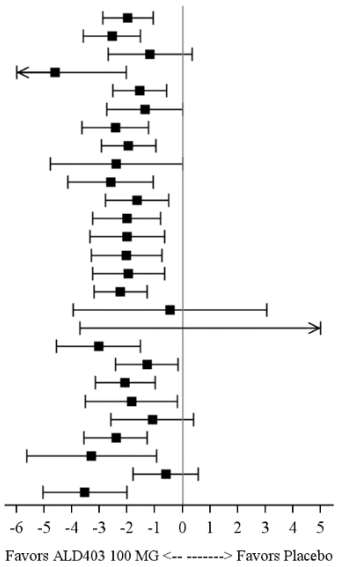


Note: Change from baseline was the difference in migraine days between baseline and Weeks 1-12. The 95% CIs were based on normal approximation.

Source: Figure 14.5.2.3 (Panel 1).

Figure 10: Forest Plot of Difference from Placebo in Migraine Days Change from Baseline over Weeks 1-12 by Subgroup - ALD403 100 mg Versus Placebo (Full Analysis Population)

Variable	Subgroups	Change from Baseline		Mean Difference from Placebo	95% CI
		ALD403 100 MG	Placebo		
All Subjects	All	-7.78	-5.80	-2.0	(-2.89, -1.07)
Baseline Migraine Days	<17 days	-6.83	-4.28	-2.6	(-3.58, -1.53)
	>=17 days	-8.90	-7.73	-1.2	(-2.70, 0.35)
Prior Prophylactic Medication Use	Yes	-10.33	-5.71	-4.6	(-7.19, -2.04)
	No	-7.36	-5.82	-1.5	(-2.51, -0.57)
Concomitant Prophylactic Medication Use	Yes	-6.44	-5.08	-1.4	(-2.73, 0.01)
	No	-8.78	-6.35	-2.4	(-3.63, -1.23)
Sex	F	-7.88	-5.93	-1.9	(-2.93, -0.96)
	M	-7.18	-4.79	-2.4	(-4.79, 0.01)
Age (years)	<=35	-8.12	-5.52	-2.6	(-4.14, -1.06)
	>35	-7.63	-5.98	-1.6	(-2.78, -0.51)
Age Group at Diagnosis	<=21 years	-7.51	-5.49	-2.0	(-3.26, -0.78)
	>21 years	-8.16	-6.16	-2.0	(-3.35, -0.64)
Duration of Migraines (years)	<=15 years	-7.99	-5.96	-2.0	(-3.31, -0.74)
	>15 years	-7.58	-5.64	-1.9	(-3.25, -0.65)
Race	White	-7.86	-5.62	-2.2	(-3.20, -1.29)
	Black	-7.60	-7.15	-0.5	(-3.96, 3.05)
	Other	-0.11	-7.09	7.0	(-3.70, 17.67)
Baseline Medication Overuse	Yes	-8.43	-5.38	-3.0	(-4.56, -1.52)
	No	-7.37	-6.08	-1.3	(-2.43, -0.16)
Baseline Triptan Use	<33% of the days	-7.85	-5.78	-2.1	(-3.16, -0.98)
	>=33% of the days	-7.69	-5.85	-1.8	(-3.51, -0.18)
Suffer from Aura	Yes	-7.13	-6.03	-1.1	(-2.59, 0.40)
	No	-8.10	-5.68	-2.4	(-3.56, -1.27)
Region	European Union	-5.41	-2.12	-3.3	(-5.64, -0.93)
	North America	-6.61	-6.01	-0.6	(-1.79, 0.58)
	Other	-11.03	-7.50	-3.5	(-5.05, -2.02)



Note: Change from baseline was the difference in migraine days between baseline and Weeks 1-12. The 95% CIs were based on normal approximation.

Consistent with study 006 heterogeneity associated with race is observed, suggesting that black patients may have a smaller or no treatment benefit. In the 431 (40%) patients diagnosed with medication-overuse headache (MOH) in PROMISE-2, the mean change from baseline in MMD (weeks 1-12) was for VYEPTI 100 mg -8.4 days, VYEPTI 300 mg -8.6 days, and placebo -5.4 days (mean difference to placebo of -3.0 days and -3.2 days for 100 mg and 300 mg, respectively).

Missing data and study compliance

Most subjects remained in the study through Week 12 with 13 subjects (< 5%) in the ALD403 300 mg and 100 mg groups not attending the Week 12 visits and 10 placebo subjects (< 5%) not attending the Week 12 visit (Table 7). Subjects who remained in the study and failed to interact with their eDiary each day, thereby resulting in sporadic missing data, are summarized in Table 14.2.1.1. The incidence of missing data increased with time during the study. The mean rate (average percent of days the subjects failed to report a headache or interact with the eDiary) during baseline was 2.12%, 2.03%, and 2.08%, and during Weeks 9-12 was 9.96%, 11.08%, and 12.32% for the ALD403 300 mg group, 100 mg group, and placebo group, respectively.

The dropouts and the missing eDiary reports were generally balanced across the groups until Week 24, where a slightly higher rate was observed for the placebo group compared with the ALD403 groups. The impact of missing eDiary reports was assessed through the sensitivity analyses of the primary efficacy endpoints. Results did not indicate substantial impact of the missing data on results of the primary efficacy endpoint, but this needs further evaluation through additional sensitivity analyses.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial 006

Title: A Parallel Group Double-Blind Randomized Placebo Controlled Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Frequent Episodic Migraines		
Study identifier	ALD403-CLIN-006,	
Design	Phase 3, multi-center, parallel group; double-blind; placebo controlled; subjects were randomly assigned into 1 of 3 ALD403 dose levels (30 mg, 100 mg, and 300 mg) or placebo in a 1:1:1:1 ratio. Randomization was stratified by migraine days during screening (≤9 days versus >9 days).	
	Duration:	60 weeks, hereof, 4 weeks for confirmation of eligibility, 36-weeks treatment period, 20-weeks follow-up period.
Hypothesis	Superiority	
Treatments groups	placebo	4 total infusions (day 0, week 12, 24, 36), n = 222
	30 mg	4 total infusions (day 0, week 12, 24, 36), n = 223
	100 mg	4 total infusions (day 0, week 12, 24, 36), n = 221
	300 mg	4 total infusions (day 0, week 12, 24, 36), n = 222
Endpoints and definitions	Primary endpoint: Change in frequency of monthly migraine days (weeks 1-12)	The primary efficacy endpoint was calculated as the number of migraine days within 4-week intervals that were then averaged up to Week 12. The difference of this estimate from baseline was calculated as the change from baseline in the frequency of migraine days over Weeks 1-12.
	Key secondary Endpoints: • 75% Responder rate (weeks 1-4) • 75% Responder rate (weeks 1-12) • 50% Responder rate (weeks 1-12)	75% responder rate was calculated Weeks 1-4 and Weeks 1-12 while 50% responder rate only was calculated Weeks 1-12

	• Percentage of subjects with a migraine on the day of dosing				
	Selected secondary Endpoints: Change in frequency of monthly migraine days (weeks 1-12, weeks 13-24, weeks 25-36, weeks 37-48) • 50%, 75%, 100% responder rates (weeks 1-12, weeks 13-24, weeks 25-36, weeks 37-48) • Change in acute migraine medication days (weeks 1-12) • 100% Responder rate (weeks 1-12) • Short-Form Health Survey (SF-36) • Health-Related Quality of Life (EQ-5D-5L)		Change in frequency of migraine as well as migraine responder rates for ALD403 were analysed across different intervals. Change in acute migraine medication days was limited to triptans and ergotamines.		
Database lock	14 Dec 2017				
<u>Results and Analysis</u>					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Full analysis Population Weeks 1-12				
Descriptive statistics and estimate variability	Treatment group	Placebo	30 mg	100 mg	*300 mg*
	Number subjects	222	223	221	222

	Baseline MMDs Change from baseline Mean difference from placebo	8.4 -3.2 -	8.7 -4.0 -0.82	8.7 -3.9 -0.69	8.6 -4.3 -1.11
	95% CI p-value		0.0046	0.0182	0.0001

Effect estimate per comparison	Key secondary endpoint: 75% responder rate (weeks 1-4)	Comparison groups	30 – 100 – 300 mg (vs. placebo)
		Difference from placebo (%)	9.8 – 10.5 – 11.3
		95% CI	(1.8, 17.8) - (2.4, 18.6) - (3.2, 19.3)
		P-value (Cochran-Mantel-Haenszel test)	0.0170 – 0.0112 – 0.0066
	Key secondary endpoint: 75% responder rate (weeks 1-12)	Comparison groups	30 – 100 – 300 mg (vs. placebo)
		Difference from placebo (%)	8.4 – 6.0 – 13.5
		95% CI	(1.0, 15.9)-(-1.4, 13.3)-(5.8, 21.2)
		P-value (Cochran-Mantel-Haenszel test)	0.0272 - 0.1126 - 0.0007
	Key secondary endpoint:	Comparison groups	30 – 100 – 300 mg (vs. placebo)

	50% responder rate (weeks 1-12)	Difference from placebo (%)	12.8 – 12.4 – 18.9
		95% CI	(3.7, 22.0)- (3.2, 21.5)- (9.8, 28.0)
		P-value (Cochran-Mantel-Haenszel test)	0.0064 - 0.0085 - 0.0001
	Key secondary endpoint: Percentage of subject with migraine on the day after dosing	Comparison groups	Placebo - 30 – 100 – 300 mg
		Baseline	29.8 – 31.0 – 31.0 – 30.8
		Day 1	22.5 – 17.3 - 14.8 – 13.9
		p-value (Cochran-Mantel-Haenszel test)	- 0.1539 – 0.0312 – 0.0159
Notes	Based on the decision rule (Section 11.4.1), the results for the study's primary efficacy endpoint was statistically significant in the ALD403 300-mg and 100-mg groups compared to placebo. The ALD403 30-mg group was nominally significant (P=0.0046) from placebo with a mean difference of -0.82 days (95% CI: -1.39, -0.25. *The initially planned primary outcome (75% responder rate (week 1-12)) was not significant in the 100 mg vs placebo comparison.*		

Summary of efficacy for trial 011

Title: A parallel group, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of ALD403 administered intravenously in subjects with chronic migraine		
Study identifier	ALD403-CLIN-011	
Design	This was a multinational Phase 3, parallel group, double-blind, randomized, placebo-controlled study enrolling subjects with chronic migraine.	
	Duration of main phase:	Total study duration36 weeks, including a 4-week screening phase, a 12 week treatment phase , and 20 weeks of follow-up after the final dose
Hypothesis	Superiority	
Treatments groups	placebo	2 total infusions (day 0, week 12), n = 366
	100 mg	2 total infusions (day 0, week 12), n = 356
	300 mg	2 total infusions (day 0, week 12), n = 350

Endpoints and definitions	Primary endpoint: Change in frequency of monthly migraine days (weeks 1-12)	The primary efficacy endpoint was calculated as the number of migraine days within 4-week intervals that were then averaged up to Week 12. The difference of this estimate from baseline was calculated as the change from baseline in the frequency of migraine days over Weeks 1-12.		
	Key Secondary endpoints: Key secondary Endpoints: • 75% Responder rate (weeks 1-4) • 75% Responder rate (weeks 1-12) • 50% Responder rate (weeks 1-12) • Percentage of subjects with a migraine on the day of dosing • Reduction in migraine prevalence from baseline to Week 4 • Headache Impact Test (HIT-6)a, b • Acute migraine medication usage	75% responder rate were calculated Weeks 1-4 and Weeks 1-12 while 50% responder rate only was calculated Weeks 1-12		
Database lock	20 April 2018			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis Population Weeks 1-12			
Descriptive statistics and	Treatment group	Placebo	100 mg	300 mg

estimate variability	Number of subject	375	372	374
	Primary endpoint: change in frequency of migraine days from Weeks 1-12(mean) Mean difference from placebo	-5.6	-7.7 -2.03	-8.2 -2.60
	95% CI p-value		(-2.88, -1.18) < 0.0001	(-3.45, -1.74) < 0.0001
Effect estimate per comparison	Key secondary endpoint: 75% responder rate (weeks 1-4)	Comparison groups	100 – 300 mg (vs. placebo)	
		Difference from placebo	15.3 – 21.3	
		95% CI	(9.3, 21.4) - (15.0, 27.6)	
		P-value (Cochran-Mantel-Haenszel test)	<0.0001 - <0.0001	
	Key secondary endpoint: 75% responder rate (weeks 1-12)	Comparison groups	100 – 300 mg (vs. placebo)	
		Difference from placebo	11.7 – 18.1	
		95% CI	(5.8, 17.5)-(12.0, 24.3)-(5.8, 21.2)	
		P-value (Cochran-Mantel-Haenszel test)	0.0001 - <0.0001	

	Key secondary endpoint: 50% responder rate (weeks 1-12)	Comparison groups	100 – 300 mg (vs. placebo)
		Difference from placebo	18.2 – 22.1
		95% CI	(11.1, 25.4) - (14.9, 29.2)
		P-value (Cochran-Mantel-Haenszel test)	< 0.0001 - < 0.0001
	Key secondary endpoint: Percentage of subject with migraine on the day after dosing	Comparison groups	Placebo – 100 – 300 mg
		Baseline	58.0– 57.5– 57.4
		Day 1	42.3– 28.6– 27.8
		p-value ((Cochran-Mantel-Haenszel test)	< 0.0001 - < 0.0001

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

No specific studies in special populations have been conducted. Patients > 65 years of age have been included in the pivotal trials, however, their absolute number was quite low [28 patients across pivotal studies (1.2%)]. Hence, only limited efficacy data are available for patients >65 years [28 patients across pivotal studies (1.2%)].

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy profile of eptinezumab was established in 2 pivotal Phase 3, randomized, double-blind, placebo-controlled studies. Study ALD403-CLIN-006 included patients with frequent episodic migraine, while study ALD403-CLIN-011 included patients with chronic migraine. The key inclusion criteria in the 2 pivotal studies were generally similar across both studies, with minor differences due to the disease state (EM or CM). Since episodic and chronic migraine are not considered different disease entities, but rather represent a continuum of severity of the same disease condition, the approach of only one pivotal trial in each migraine subtype is considered adequate (and was also agreed for other recently approved anti CGRF-therapies). The study designs followed the recommendation gained during EMA Scientific Advice and are also agreed. The dose regimens tested in the two phase 3 studies were based on preliminary efficacy and PK results from phase 2 clinical trials.

Study 006 was primarily conducted in the USA (79 sites), and in few study sites (5 sites) in the Republic of Georgia. No EU sites were included. Study 011 was conducted at approximately 150 centers in 13 countries with the majority of sites (53%) in the United States. Although this per se is not a matter of concern (as neither the disease characteristics, nor the underlying pathophysiology of migraine, nor eptinezumab's mode of action are expected to differ between the US and the European population), it might have impacted some patient characteristics, e.g. patient BMI. Overall, the body-mass-index (BMI) of approximately 30 across treatment groups (which corresponds to grade 1 adipositas) appears relatively high. In line with current guidance (ICH guideline E17 on general principles for planning and design of multi-regional clinical trials, EMA/CHMP/ICH/453276/2016, and Guideline on adjustment for baseline covariates in clinical trials, EMA/CHMP/295050/2013) it would have been expected that randomization was stratified by region or study site. Some uncertainty remains with regard to extrapolation from North America to other regions, also in light of results from study 011. However, there is currently no reason to expect that the effect of treatment would be smaller in Europe and it is not expected that further insight can be gained from study 006. The analysed patient populations were overall representative, although patients with certain subtypes of migraine (e.g., complicated migraine, migraine with brainstem aura, sporadic, and familial hemiplegic migraine) as well as patients with specific concomitant diseases, such as cardiovascular disease (hypertension, ischemic heart disease), neurological disease, cerebrovascular disease, diabetes, or Raynaud's disease, were excluded from study participation. Only few patients > 65 years of age took part in the clinical studies. Information on concomitant medication intake during Study 006 was tabulated and reviewed by a medical expert to identify if the medication in question were barbiturates, opioids, or codeine. Based on the classification, the patients with concomitant use of barbiturates, opioids, and codeine during the treatment period were further analysed. It was found that use during the treatment period was limited, and similar across treatment groups (13%, 14%, and 11% for eptinezumab 100 mg, eptinezumab 300mg, and placebo, respectively). A sensitivity analysis was conducted in order to assess the impact of the use of the concomitant barbiturates, opioids, and codeine medications, on the primary endpoint. The use was seen to be relatively stable over time. The primary analysis, change from baseline in MMDs Weeks 1-12, was repeated excluding the group of patients using these concomitant medications. The treatment effect was close to the results for the full study population, within <0.1 MMD, confirming that the impact from concomitant use of barbiturates, opioids, and codeine was low.

The treatment arms were generally balanced in terms of baseline characteristics and similar in numbers of patients who were randomized and treated and who completed the studyor discontinued early. Overall, a proportion of >20% of study participants in study 006 and > 9% of participants in study 011 discontinued the study prematurely. The number of patients who discontinued due to adverse events was slightly increased in patients treated with eptinezumab 300 mg and 100 mg, compared to placebo-treated patients. The number of patients who withdrew due to study burden or lack of efficacy was greater in patients treated with placebo. This might be considered indicative for a beneficial effect of eptinezumab treatment.

Efficacy data and additional analyses

With regard to the statistical analyses, for both studies (006 and 011), the estimand approach to withdrawal from treatment is not entirely understood. The strategy described by the applicant depends on whether data is missing after the intercurrent event or not, rather than on the intercurrent event. It seems that a treatment policy approach for withdrawal from treatment, but a hypothetical approach for withdrawal from study would better characterize the analysis. The applicant was asked to either confirm or to provide clarity. In addition, a justification why the hypothetical approach should be preferred over a treatment policy approach was requested. The definition of the primary outcome variable is complex. Change from baseline is defined as the difference between baseline and the monthly average over the first 12 weeks after

randomization. The provided descriptive statistics provide reassurance of the general approach to missing values taken by the applicant, and provide further clarity that the methods are overall appropriate. The analyses provided by the applicant provide some reassurance on the primary conclusions. The applicant conducted a multiple imputation approach using the placebo distribution as a basis for multiple imputation of missing diary entries. Treatment effect estimates were affected, but remained in favour of eptinezumab treatment. In particular, for the 300 mg dose, point estimates were smaller for the difference in mean change from baseline MMDs (-1.00 for multiple imputation vs. -1.11 in the original analysis) as well as for the risk difference for ≥75% responders (12.7% with multiple imputation vs. 13.5% in the original analysis). These changes do not raise any strong concern. However, as differences were observed with regard to missing data, in particular with regard to discontinuation from study, the assumptions underlying this imputation approach may be questionable. The applicant conducted a tipping point analysis, using the delta method, by artificially changing the probability for a migraine day in the multiple imputation approach using linear increments corresponding to 10% of the difference in observed migraine day proportions between the treatment groups. As discussed by the applicant in response to question 80, there may be issues with overdispersion in a binomial approach, but nonetheless this exercise is very much endorsed, as it may provide insight into the robustness towards assumptions on missing values. It is noted that the tipping point analysis was not carried out until detection of a tipping point and rather small steps were used in the delta method, without discussion on the plausibility or relevance of the increments. The increments ranged from 10% to 120% where 100% corresponds to a random draw using the mean proportion of observed migraine days in the placebo group. While the results from the exercise are reassuring, there remains some uncertainty, as it is not yet clear under which assumptions a different conclusion might have been made and whether such assumptions would be plausible. Thus, the robustness towards violations of the assumptions cannot be sufficiently assessed. Based on the linearity of the tipping point approach it seems that a delta of approximately 400% might be the tipping point, at which the difference in change in MMDs of the 300 mg arm vs the placebo arm comparison would no longer be statistically significant at the nominal level of $\alpha=0.05$. The applicant was therefore asked to confirm or correct this impression in the D180 LoOI, and to discuss the plausibility of the respective delta by discussing the plausibility of the assumed migraine day probabilities corresponding (e.g. discussing the corresponding percentile in the baseline distribution of MMDs). The applicant provided the requested information. The tipping point at which the results would no longer be statistically significant corresponds to an average daily migraine frequency of 0.336 (averaged across the 4-week periods; Weeks 1-4, Weeks 5-8, and Weeks 9-12) for eptinezumab 300 mg, which translates into a theoretical number of 9.4 MMDs for Weeks 1-12. Although a theoretical number of 9.4 MMD in a four week period is not impossible, this assumption appears rather pessimistic. Despite some uncertainty remains, this issue will not be further pursued.

The primary efficacy endpoint for this study was the change from baseline in monthly migraine days over weeks 1-12, calculated as the number of migraine days within 4-week intervals that were averaged up to week 12. The primary endpoint was statistically significant for the 300 mg and 100 mg treatment groups. Despite this statistical significance, the mean difference from placebo was only modest (300 mg: - 1.11/ 100 mg: - 0.69). Key secondary and secondary endpoints were supportive for the primary endpoint analysis. However, the initially planned primary outcome (75% responder rate (week 1-12)) was not significant for the 100 mg group. The 30 mg group was found to be nominal significant for the primary and all secondary endpoints, but not statistically significant in a confirmatory sense, as the 75% responder rate over week 1-12 was not significantly different between 100 mg and placebo, and this analysis was higher in hierarchy. The overall migraine prevalence on day 1 after treatment was lower in all treatment arms compared to placebo. Baseline prevalence across arms was hereby highly comparable between groups, arguing for a true treatment effect. Acute migraine medication (triptans and ergotamines) days across weeks 1-12 were lower for all

treatment groups compared to placebo, as was the mean change from baseline. However, only use of triptans and ergotamines was reported and analysed. Other medications, e.g. over-the-counter analgesics, might have been used by patients, but were not evaluated. HIT-6, and SF-36, were supportive for the primary and key secondary endpoints. The persistence of efficacy was in addition demonstrated by the change in frequency of migraine days (Weeks 13-24), which was greater in eptinezumab groups compared with placebo.

Although the difference on the primary efficacy endpoint was found to be rather modest, the size of treatment effect is in a range comparable to other anti-CGRP therapies recently authorised for the prevention of migraine in adults. Key secondary endpoints, especially the 75% responder rate, argue for a substantial treatment benefit of the 300 mg dosing regimen. However, clinical efficacy was not consistently robust for the 100 mg dose, especially in episodic migraine.

However, as discussed above, the robustness of these findings requires further investigation in light of a substantial amount of missing data and heterogeneity across subjects. The Applicant was therefore requested to provide reassurance that other variables than region or race may be responsible for a reduced treatment effect by investigating through appropriate multivariable analyses the role of relevant patient characteristics as well as previous and concomitant medication observed in study 011 (instead of referring to literature only). In this regard, the Applicant discussed results from multivariable ANCOVA models to investigate potential interactions with treatment that might be underlying observed heterogeneity of the treatment effect between black and white patients. Overall, the statistical approach is considered reasonable. Although the applicant did not provide any point or confidence interval estimates from the respective models, and the clinical relevance of potential interactions thus cannot be judged, the applicant provided some reassurance that other variables may interact with treatment despite adjustment for race. This suggests that other variables than race may be associated with a larger or smaller effect of treatment. This includes the acute use of medication with more extreme positioning in US (either no medication or fixed combinations and opiates) as compared to EU. Although the extent of this cannot be evaluated, as the respective estimates are missing, this at least provides some reassurance, as it is not considered plausible that black patients would have a smaller treatment benefit than white patients. Although some uncertainty remains, as it is not expected that this issue can be resolved, this point is not further pursued.

It is agreed that both treatment regimens, 100 mg and 300 mg, demonstrated to be efficacious in the treatment of EM and CM. Differences in response of some subgroups remain not completely understood, but might – at least in some cases – be chance findings and attributed to low patient numbers or non-medical factors. While 300 mg seems to have a more pronounced treatment effect across all treatment groups, the number of hypersensitivity reactions is remarkably higher in the 300 mg group compared to the 100 mg group (1.4% vs. 0.2%). Weighing the benefits and risks of treatment, the proposed posology with a recommended starting dose of 100 mg, with the option to increase to the 300 mg dose for patients who do not have a sufficient response after at least 12 weeks of treatment, seems acceptable. The amended wording in section 4.2 of the SmPC is considered adequate, since it clarifies the need for assessing treatment benefit 12 weeks after treatment initiation, and the need for a re-assessment 6 months after treatment initiation. The efficacy of such a dose escalation strategy in non-responders or partial-responders has not been formally tested in the context of clinical trials. However, the approach seems to be justified and sufficiently pragmatic and will also fit in a real-world therapeutic setting.

2.6.7. Conclusions on clinical efficacy

Overall, the data submitted could provide evidence for the efficacy of eptinezumab, administered as a 3-monthly 300 mg or 100 mg IV infusion, for the preventive treatment of episodic and chronic migraine in adults. Statistically significant and robust superiority over placebo was seen across the primary and most secondary endpoints for both dosing regimens. Although the difference to placebo on the primary efficacy endpoint was rather modest, the magnitude of treatment effect could be in line with what has been seen with recently authorized anti-CGRP therapies for subcutaneous administration. Eptinezumab is the first anti-CGRP treatment developed for the intravenous route of administration. The IV route and the less-than–monthly treatment regimen might be preferred by specific patient groups. Eptinezumab for IV administration may therefore complement the therapeutic landscape of anti-CGRP treatments for the prevention of migraine. Compared to "older" preventive treatments for migraine, that in part require long titration periods with a delayed onset of efficacy, daily drug intake, and an often poor tolerability, the rapid onset of treatment effect and the less frequent administration scheme are considered meaningful advances.

Both treatment regimens, 100 mg and 300 mg, demonstrated to be efficacious in the treatment of EM and CM. Differences in response of some subgroups remain not completely understood, but might be chance findings and attributed to low patient numbers or confounding factors. While 300 mg seems to have a more pronounced treatment effect across all treatment groups, the number of hypersensitivity reactions is remarkably higher in the 300 mg group compared to the 100 mg group (1.4% vs. 0.2%). Weighing the benefits and risks of treatment, the proposed posology with a recommended starting dose of 100 mg, with the option to increase to the 300 mg dose for patients who do not have a sufficient response after at least 12 weeks of treatment, seems acceptable. It is considered adequate to assess the treatment benefit 12 weeks after treatment initiation, and to re-assess 6 months after treatment initiation. The efficacy of such a dose escalation strategy in non-responders or partial-responders has not been formally tested in the context of clinical trials. However, the approach seems to be justified and sufficiently pragmatic and will also fit in a real-world therapeutic setting.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Eptinezumab has been evaluated in 12 clinical studies. Five studies were conducted in subjects with chronic migraines (CM) or episodic migraines (EM) and seven studies were clinical pharmacology studies conducted in subjects without migraine, with the exception of a few subjects with migraines that participated in both, Part B of clinical pharmacology study ALD403-CLIN-001 and in one of the migraine studies.

The integrated safety database included data from the pivotal studies ALD403-CLIN-006 (study 006) and ALD403-CLIN-011 (study 011) with the other three studies ALD403-CLIN-002 (study 002), ALD403-CLIN-005 (study 005) and ALD403-CLIN-013 (study 013) providing supportive data.

Study 013 is a long-term safety study and was ongoing at the time of the safety data integration. Thus, only data of the primary treatment phase of study 013 (the first 4 eptinezumab infusions, up to week 36) has been integrated in the SCS. A 120-day safety update presenting new and updated data from study 013 (data cutoff of 01 Feb 2019) and including an updated OE pool and the final study report (data cutoff 09 Apr 2019) were submitted.

Clinical Studies Included in the Summary of Clinical Safety (data cutoff 31 May 2018)

Study	Phase	Number of Subjects Treated	Study Design	Study Drugs / Administration / Frequency	Scheduled Post-dose Visits
Pivotal Studies					
ALD403-CLIN-006 (EM)	3	888 (hereof 222 placebo subjects)	Double-blind, randomized, placebo-controlled, parallel group	Eptinezumab 30, 100, or 300 mg or placebo IV infusion Day 0 and every 12 weeks through week 36 (4 doses)	Weeks 4, 8, 12, 16, 20, 24, 28, 36, 48, and 56
ALD403-CLIN-011 (CM)	3	1072 (hereof 366 placebo subjects)	Double-blind, randomized, placebo-controlled, parallel group	Eptinezumab 100 or 300 mg of placebo IV infusion Day 0 and week 12 (2 doses)	Weeks 2, 4, 8, 12, 16, 20, 24, and 32
Supportive Studies					
ALD403-CLIN-002 (EM)	1b	163 (hereof 82 placebo subjects)	Double-blind, randomized, placebo-controlled, parallel group	Eptinezumab 1000 mg or placebo IV infusion Single dose (day 0)	Weeks 2, 4, 8, 12, and 24
ALD403-CLIN-005 (CM)	2	616 (hereof 121 placebo subjects)	Double-blind, randomized, placebo-controlled, parallel group	Eptinezumab 10, 30, 100, or 300 mg or placebo IV infusion Single dose (day 0)	Weeks 4, 8, 12, 24, 36, and 49
ALD403-CLIN-013 [a] (CM)	3	128 (no placebo subjects)	Open-label, uncontrolled	Eptinezumab 300 mg IV infusion Day 0 and every 12 weeks through week 84 (8 doses)	Weeks 2, 4, 8, 12, 24, 36, (48, 60, 72, 84, and 104)

CM = chronic migraine; CSR = clinical study report; EM = episodic migraine; IV = intravenous

[a] This study was ongoing at the time of the safety data integration. Data from the primary treatment phase (up to, but not including, dosing at week 48) are included in the integrated safety database. Further/final data reported separately.

The overall safety population (N=2867) included all patients who received at least 1 dose of study drug (eptinezumab (N=2076) or placebo (N=791)) in any of the 5 studies included in the integrated safety database. The safety population included 1960 patients in the placebo-controlled pivotal phase 3 studies 006 (EM, N=888) and 011 (CM, N=1072), 128 patients in open-label long-term phase 3 safety study 013 (CM), 616 patients in phase 2 study 005 (CM) and 163 patients in phase 1b study 002 (EM).

Three different pools were defined for the analysis of the safety data:

PS pool: all patients in the pivotal studies (N=1960). Including patients in the placebo-controlled phase 3 studies 006 (EM) and 011 (CM). The treatment groups summarized include placebo, 30 mg Q12W (EM), 100 mg Q12W (EM+CM), 300 mg Q12W (EM+CM) and all eptinezumab.

OE pool: all eptinezumab-treated patients (N=2739). Including all eptinezumab-treated patients with migraine (CM, EM): in the placebo-controlled phase 3 studies 006 (EM) and 011 (CM), open-label long-term phase 3 safety study 013 (CM), phase 2 study 005 (CM) and phase 1b study 002 (EM). The treatment groups summarized include placebo, 10 mg SD (CM), 30 mg SD (CM), 30 mg Q12W (EM), 100 mg SD (CM), 100 mg Q12W (EM), 300 mg SD (CM), 300 mg Q12W (EM), 1000 mg SD (EM) and all eptinezumab.

PC pool: all patients in the placebo-controlled studies (N=2867). Including patients in the placebo-controlled phase 3 studies 006 (EM) and 011 (CM), phase 2 study 005 (CM) and phase 1b study 002 (EM). The treatment

groups summarized include placebo, 10 mg SD (CM), 30 mg SD (CM), 30 mg Q12W (EM), 100 mg SD (CM), 100 mg Q12W (EM), 300 mg SD (CM), 300 mg Q12W (EM), 1000 mg SD (EM) and all eptinezumab.

Numbers of Subjects Included in the Integrated Safety Database (Safety Population)

Study	Epti 1000 mg n (%)	Epti 300 mg n (%)	Epti 100 mg n (%)	Epti 30 mg n (%)	Epti 10 mg n (%)	Placebo n (%)	All Epti n (%)
ALD403-CLIN-002 (N=163)	81 (49.7)	NA	NA	NA	NA	82 (50.3)	81 (49.7)
ALD403-CLIN-005 (N=616)	NA	121 (19.6)	122 (19.8)	122 (19.8)	130 (21.1)	121 (19.6)	495 (80.4)
ALD403-CLIN-006 (N=888)	NA	224 (25.2)	223 (25.1)	219 (24.7)	NA	222 (25.0)	666 (75.0)
ALD403-CLIN-011 (N=1072)	NA	350 (32.6)	356 (33.2)	NA	NA	366 (34.1)	706 (65.9)
ALD403-CLIN-013 (N=128)	NA	128 (100)	NA	NA	NA	NA	128 (100)

Note: Denominator for percentages is the total number of subjects in the study.
Epti = eptinezumab; NA = not applicable.
Pivotal Study (PS) pool includes Studies 006 and 011.
Overall Eptinezumab (OE) pool includes Studies 002, 005, 006, 011, and 013.
Placebo-controlled (PC) pool includes Studies 002, 005, 006, and 011.
Source: Table 14.1.1.2.1, Integrated Summary of Safety (ISS) Tables, Figures, and Listings (TFLs) (Module 5.3.5.3)

Patient exposure

Patient Disposition (PS pool)

A total of 1,372 subjects received eptinezumab. 574 of these subjects received eptinezumab 300 mg, 579 subjects received eptinezumab 100 mg and 219 subjects received eptinezumab 30 mg. A total of 588 subjects received placebo.

Most subjects completed the study drug regimen and completed study participation. The proportions of subjects who discontinued the study drug were similar for all PS eptinezumab subjects (12.4%) and placebo subjects (13.3%). The most frequent reason for discontinuing the study drug in each of these groups was subject withdrawal of informed consent. Proportions of subjects who discontinued study drug due to AEs were similar in all PS eptinezumab subjects (2.3%) and placebo subjects (1.5%).

The proportions of subjects who discontinued the study were similar for all PS eptinezumab subjects (15.7%) and placebo subjects (16.7%). The most frequent reason for discontinuing the study was withdrawal by the subject (9.8% of all PS eptinezumab subjects and 10.5% of placebo subjects, respectively), mostly due to study burden, followed by "lost to follow-up" (4.9% of all PS eptinezumab subjects and 5.6% of placebo subjects, respectively).

Patient Disposition (OE pool)

A total of 2,076 subjects in the OE pool received eptinezumab. 81 of these subjects received eptinezumab 1000 mg, 823 of these subjects received eptinezumab 300 mg, 701 subjects received eptinezumab 100 mg, 341 subjects received eptinezumab 30 mg, and 130 subjects received eptinezumab 10 mg. A total of 791 subjects received placebo.

Most subjects completed the study drug regimen and completed study participation. The proportions of subjects who discontinued the study drug were similar for all OE subjects (8.7%) and subjects who received placebo (9.9%). The most frequent reason for discontinuing the study drug in each of these groups was subject withdrawal of informed consent. Proportions of subjects who discontinued study treatment due to AEs were similar in OE subjects (1.7%) and placebo subjects (1.1%).

The proportions of subjects who discontinued the study were similar for OE subjects (18.2%) and placebo subjects (17.3%), with the most frequent reason for discontinuing was withdrawal by the subject in 10.1% of OE subjects and 10.6% of placebo subjects, respectively, with study burden and "other" were the most frequent reasons given. The second most frequent reason for discontinuing the study in each of these groups was lost to follow-up (6.2% of all eptinezumab subjects and 5.4% of placebo subjects).

Subject Exposure by Treatment Group (PS pool)

	EM+CM		**EM**	**EM+CM**		
	Epti 300 mg N=574	**Epti 100 mg N=579**	**Epti 30 mg N=219**	**Placebo N=588**	**All Epti Pivotal N=1372**	**All Epti All Studies N=2076**
Day 0 Dose Received Treatment, n/m (%) [a]	574/574 (100)	579/579 (100)	219/219 (100)	588/588 (100)	1372/1372 (100)	2076/2076 (100)
Dose Interruption, n/m (%) [b]	9/574 (1.6)	8/579 (1.4)	6/219 (2.7)	6/588 (1.0)	23/1372 (1.7)	45/2076 (2.2)
Received Full Dose, n/m (%) [c]	8/9 (88.9)	7/8 (87.5)	4/6 (66.7)	4/6 (66.7)	19/23 (82.6)	37/45 (82.2)
Week 12 Dose Received Treatment, n/m (%) [a]	548/574 (95.5)	546/579 (94.3)	194/219 (88.6)	540/588 (91.8)	1288/1372 (93.9)	1408/1500 (93.9)
Dose Interruption, n/m (%) [b]	8/548 (1.5)	2/546 (0.4)	1/194 (0.5)	3/540 (0.6)	11/1288 (0.9)	15/1408 (1.1)
Received Full Dose, n/m (%) [c]	4/8 (50.0)	2/2 (100)	0/1	3/3 (100)	6/11 (54.5)	9/15 (60.0)
Week 24 Dose Received Treatment, n/m (%)[a]	190/224 (84.8)	188/223 (84.3)	182/219 (83.1)	177/222 (79.7)	560/666 (84.1)	675/794 (85.0)
Dose Interruption, n/m (%)[b]	2/190 (1.1)	0/188	2/182 (1.1)	0/177	4/560 (0.7)	5/675 (0.7)

	EM+CM		**EM**	**EM+CM**		
	Epti 300 mg N=574	**Epti 100 mg N=579**	**Epti 30 mg N=219**	**Placebo N=588**	**All Epti Pivotal N=1372**	**All Epti All Studies N=2076**
Received Full Dose, n/m (%) [c]	0/2	NA	1/2 (50.0)	NA	1/4 (25.0)	2/5 (40.0)
Week 36 Dose Received Treatment, n/m (%)[a]	180/224 (80.4)	177/223 (79.4)	169/219 (77.2)	167/222 (75.2)	526/666 (79.0)	638/794 (80.4)
Dose Interruption, n/m (%)[b]	1/180 (0.6)	2/177 (1.1)	2/169 (1.2)	2/167 (1.2)	5/526 (1.0)	6/638 (0.9)
Received Full Dose, n/m (%) [c]	1/1 (100)	2/2 (100)	2/2 (100)	2/2 (100)	5/5 (100)	5/6 (83.3)
Total Number of Doses Received, n (%) [d]						
1	26 (4.5)	33 (5.7)	25 (11.4)	47 (8.0)	84 (6.1)	668 (32.2)
2	358 (62.4)	358 (61.8)	10 (4.6)	365 (62.1)	726 (52.9)	731 (35.2)
3	10 (1.7)	11 (1.9)	17 (7.8)	9 (1.5)	38 (2.8)	41 (2.0)
4	180 (31.4)	177 (30.6)	167 (76.3)	167 (28.4)	524 (38.2)	636 (30.6)
Received the Protocol-Specified Number of Doses	518 (90.2)	517 (89.3)	167 (76.3)	509 (86.6)	1202 (87.6)	1890 (91.0)
Total Exposure Time (Days) [e]						
n	574	579	219	588	1372	2076

	EM+CM		EM	EM+CM		
	Epti 300 mg N=574	**Epti 100 mg N=579**	**Epti 30 mg N=219**	**Placebo N=588**	**All Epti Pivotal N=1372**	**All Epti All Studies N=2076**
Mean (SD)	272.1 (90.61)	267.9 (92.94)	346.5 (103.43)	262.3 (94.70)	282.2 (97.79)	284.1 (96.16)
Median	229.0	229.0	393.0	227.0	231.0	272.0
Min, Max	14, 472	14, 442	15, 460	16, 472	14, 472	13, 472
Categories of Total Exposure Time, n (%)[e]						
> 0 Day	574 (100)	579 (100)	219 (100)	588 (100)	1372 (100)	2076 (100)
>= 12 Weeks	562 (97.9)	562 (97.1)	210 (95.9)	569 (96.8)	1334 (97.2)	2008 (96.7)
>= 24 Weeks	537 (93.6)	531 (91.7)	196 (89.5)	531 (90.3)	1264 (92.1)	1872 (90.2)
>= 36 Weeks	197 (34.3)	191 (33.0)	183 (83.6)	185 (31.5)	571 (41.6)	1072 (51.6)
>= 48 Weeks	184 (32.1)	178 (30.7)	176 (80.4)	172 (29.3)	538 (39.2)	991 (47.7)

[a] The denominator is the number of subjects in these studies where the dose was planned to be administered at each visit.
[b] The denominator is the number of subjects who received treatment at each visit.
[c] A full dose is defined as having received an infusion volume of >= 100 mL. The denominator is the number of subjects who had dose interrupted at each visit.
[d] A subject could have received a maximum of 1 dose in Studies ALD403-CLIN-002 and -005, 2 doses in Study -011, and 4 doses in Studies -006 and-013. Percentages are based on safety population.
[e] Total Exposure Time = Last day on study (or Last day up to end of the primary treatment phase for Study ALD403-CLIN-013) - first dose date + 1. Percentages are based on safety population.
CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; Min = minimum; Max = maximum; NA = not applicable; SD = standard deviation.
Treatment/Dose level: Placebo (studies ALD403-CLIN-006 and -011), Epti 30 mg (study ALD403-CLIN-006), Epti 100 mg, Epti 300 mg and All Epti Pivotal (studies ALD403-CLIN-006 and -011), All Epti All Studies (all doses from all studies ALD403-CLIN-002, -005, -006, -011 and -013).
Study drug data from study ALD403-CLIN-013 are presented up to end of the primary treatment phase.
Source: Table 14.1.4.4.1 (ISS TFLs)

Subject Exposure by Treatment Group (OE pool)

	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81	**Epti 300 mg N=823**	**Epti 100 mg N=701**	**Epti 30 mg N=341**	**Epti 10 mg N=130**	**Placebo N=791**	**All Epti N=2076**
Day 0 Dose Received Treatment, n/m (%)[a]	81/81 (100)	823/823 (100)	701/701 (100)	341/341 (100)	130/130 (100)	791/791 (100)	2076/2076 (100)
Dose Interruption, n/m (%)[b]	1/81 (1.2)	17/823 (2.1)	11/701 (1.6)	12/341 (3.5)	4/130 (3.1)	8/791 (1.0)	45/2076 (2.2)
Received Full Dose, n/m (%)[c]	1/1 (100)	14/17 (82.4)	9/11 (81.8)	9/12 (75.0)	4/4 (100)	5/8 (62.5)	37/45 (82.2)
Week 12 Dose Received Treatment, n/m (%)[a]	NA	668/702 (95.2)	546/579 (94.3)	194/219 (88.6)	NA	540/588 (91.8)	1408/1500 (93.9)
Dose Interruption, n/m (%)[b]	NA	12/668 (1.8)	2/546 (0.4)	1/194 (0.5)	NA	3/540 (0.6)	15/1408 (1.1)
Received Full Dose, n/m (%)[c]	NA	7/12 (58.3)	2/2 (100)	0/1	NA	3/3 (100)	9/15 (60.0)
Week 24 Dose Received Treatment, n/m (%)[a]	NA	305/352 (86.6)	188/223 (84.3)	182/219 (83.1)	NA	177/222 (79.7)	675/794 (85.0)
Dose Interruption, n/m (%)[b]	NA	3/305 (1.0)	0/188	2/182 (1.1)	NA	0/177	5/675 (0.7)
Received Full Dose, n/m (%)[c]	NA	1/3 (33.3)	NA	1/2 (50.0)	NA	NA	2/5 (40.0)
Week 36 Dose Received Treatment, n/m (%)[a]	NA	292/352 (83.0)	177/223 (79.4)	169/219 (77.2)	NA	167/222 (75.2)	638/794 (80.4)
Dose Interruption, n/m (%)[b]	NA	2/292 (0.7)	2/177 (1.1)	2/169 (1.2)	NA	2/167 (1.2)	6/638 (0.9)

	EM	**EM+CM**			**CM**	**EM+CM**	
	Epti 1000 mg N=81	**Epti 300 mg N=823**	**Epti 100 mg N=701**	**Epti 30 mg N=341**	**Epti 10 mg N=130**	**Placebo N=791**	**All Epti N=2076**
Received Full Dose, n/m (%)[c]	NA	1/2 (50.0)	2/2 (100)	2/2 (100)	NA	2/2 (100)	5/6 (83.3)
Total Number of Doses Received, n (%)[d]							
1	81 (100)	155 (18.8)	155 (22.1)	147 (43.1)	130 (100)	250 (31.6)	668 (32.2)
2	NA	363 (44.1)	358 (51.1)	10 (2.9)	NA	365 (46.1)	731 (35.2)
3	NA	13 (1.6)	11 (1.6)	17 (5.0)	NA	9 (1.1)	41 (2.0)
4	NA	292 (35.5)	177 (25.2)	167 (49.0)	NA	167 (21.1)	636 (30.6)
Received the Protocol- Specified Number of Doses	81 (100)	751 (91.3)	639 (91.2)	289 (84.8)	130 (100)	712 (90.0)	1890 (91.0)
Total Exposure Time (Days)[e]							
n	81	823	701	341	130	791	2076
Mean (SD)	162.4 (26.32)	285.8 (87.68)	274.1 (92.23)	324.3 (107.40)	298.0 (91.92)	258.1 (95.40)	284.1 (96.16)
Median	168.0	252.0	231.0	374.0	344.0	226.0	272.0
Min, Max	13, 231	14, 472	14, 448	15, 469	26, 380	1, 484	13, 472
Categories of Total Exposure Time, n (%)[e]							
> 0 Day	81 (100)	823 (100)	701 (100)	341 (100)	130 (100)	791 (100)	2076 (100)
>= 12 Weeks	78 (96.3)	806 (97.9)	680 (97.0)	322 (94.4)	122 (93.8)	766 (96.8)	2008 (96.7)
>= 24 Weeks	46 (56.8)	771 (93.7)	642 (91.6)	298 (87.4)	115 (88.5)	692 (87.5)	1872 (90.2)
>= 36 Weeks	0	412 (50.1)	288 (41.1)	271 (79.5)	101 (77.7)	280 (35.4)	1072 (51.6)

	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81	Epti 300 mg N=823	Epti 100 mg N=701	Epti 30 mg N=341	Epti 10 mg N=130	Placebo N=791	All Epti N=2076
>= 48 Weeks	0	377 (45.8)	263 (37.5)	253 (74.2)	98 (75.4)	256 (32.4)	991 (47.7)

[a] The denominator is the number of subjects in these studies where the dose was planned to be administered at each visit.
[b] The denominator is the number of subjects who received treatment at each visit.
[c] A full dose is defined as having received an infusion volume of >= 100 mL. the denominator is the number of subjects who had dose interrupted at each visit.
[d] A subject could have received a maximum of 1 dose in Studies ALD403-CLIN-002 and -005, 2 doses in Study -011, and 4 doses in Studies -006 and -013. Percentages are based on safety population.
[e] Total Exposure Time = Last day on study (or Last day up to end of the primary treatment phase for Study ALD403-CLIN-013) - first dose date + 1. Percentages are based on safety population.
CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; Min = minimum; Max = maximum; NA = not applicable; SD = standard deviation.
Study drug data from study ALD403-CLIN-013 are presented up to end of the primary treatment phase.
Treatment/Dose level: Placebo (Studies ALD403-CLIN-002, -005, -006 and -011), Epti 10 mg (Study ALD403-CLIN-005), Epti 30 mg (Studies ALD403-CLIN-005 and -006), Epti 100 mg (Studies ALD403-CLIN-005, -006 and -011), Epti 300 mg (Studies ALD403-CLIN-005, -006, -011 and -013), Epti 1000 mg (Study ALD403-CLIN-002).
Source: Table 14.1.4.4.3 (ISS TFLs)

Demographic and Baseline Characteristics (PS pool)

	EM+CM		EM	EM+CM		
	Epti 300 mg N=574	Epti 100 mg N=579	Epti 30 mg N=219	Placebo N=588	All Epti Pivotal N=1372	All Epti All Studies N=2076
Age (years)						
n	574	579	219	588	1372	2076
Mean (SD)	40.7 (10.91)	40.6 (11.33)	39.1 (11.54)	39.7 (11.42)	40.4 (11.19)	39.5 (11.00)
Median	40.0	41.0	37.0	40.0	40.0	39.0
Min, Max	18, 71	18, 68	18, 69	18, 68	18, 71	18, 71
Age Group, n (%)						
< 65 years	567 (98.8)	576 (99.5)	215 (98.2)	579 (98.5)	1358 (99.0)	2061 (99.3)
>= 65 to < 75 years	7 (1.2)	3 (0.5)	4 (1.8)	9 (1.5)	14 (1.0)	15 (0.7)
>= 75 years	0	0	0	0	0	0
Sex, n (%)						
Male	61 (10.6)	93 (16.1)	34 (15.5)	77 (13.1)	188 (13.7)	290 (14.0)

	EM+CM		EM	EM+CM		
	Epti 300 mg N=574	**Epti 100 mg N=579**	**Epti 30 mg N=219**	**Placebo N=588**	**All Epti Pivotal N=1372**	**All Epti All Studies N=2076**
Female	513 (89.4)	486 (83.9)	185 (84.5)	511 (86.9)	1184 (86.3)	1786 (86.0)
Ethnicity, n (%)						
Hispanic or Latino	58 (10.1)	75 (13.0)	45 (20.5)	69 (11.7)	178 (13.0)	317 (15.3)
Not Hispanic or Latino	516 (89.9)	504 (87.0)	174 (79.5)	519 (88.3)	1194 (87.0)	1759 (84.7)
Race, n (%)						
White	509 (88.7)	528 (91.2)	180 (82.2)	502 (85.4)	1217 (88.7)	1843 (88.8)
Black or African American	50 (8.7)	38 (6.6)	31 (14.2)	68 (11.6)	119 (8.7)	175 (8.4)
Asian	2 (0.3)	2 (0.3)	1 (0.5)	3 (0.5)	5 (0.4)	12 (0.6)
American Indian or Alaska Native	3 (0.5)	1 (0.2)	0	2 (0.3)	4 (0.3)	7 (0.3)
Native Hawaiian or Other Pacific Islander	2 (0.3)	1 (0.2)	0	1 (0.2)	3 (0.2)	4 (0.2)
Multiple Races	7 (1.2)	8 (1.4)	5 (2.3)	9 (1.5)	20 (1.5)	24 (1.2)
Other	1 (0.2)	1 (0.2)	2 (0.9)	3 (0.5)	4 (0.3)	10 (0.5)
Not Reported	0	0	0	0	0	1 (<0.1)
Weight (kg)						
n	574	579	219	588	1372	2076
Mean (SD)	75.62 (18.065)	76.83 (19.497)	82.03 (23.269)	77.70 (18.854)	77.15 (19.687)	76.91 (18.743)
Median	73.00	74.00	78.00	75.65	74.00	74.15

	EM+CM		EM	EM+CM		
	Epti 300 mg N=574	**Epti 100 mg N=579**	**Epti 30 mg N=219**	**Placebo N=588**	**All Epti Pivotal N=1372**	**All Epti All Studies N=2076**
Min, Max	40.2, 139.5	39.2, 190.1	45.2, 174.0	40.7, 160.9	39.2, 190.1	39.2, 190.1
BMI (kg/m^2)[a]						
n	574	579	219	588	1372	2076
Mean (SD)	27.29 (6.080)	27.56 (6.309)	29.91 (8.324)	27.99 (6.381)	27.82 (6.641)	27.73 (6.206)
Median	26.00	26.50	28.20	27.00	26.40	26.70
Min, Max	15.9, 49.8	15.6, 59.3	17.8, 67.5	17.3, 52.6	15.6, 67.5	15.6, 67.5
Region, n (%)						
United States	381 (66.4)	382 (66.0)	194 (88.6)	417 (70.9)	957 (69.8)	1595 (76.8)
European Union	53 (9.2)	50 (8.6)	NA	51 (8.7)	103 (7.5)	103 (5.0)
Rest of World	140 (24.4)	147 (25.4)	25 (11.4)	120 (20.4)	312 (22.7)	378 (18.2)

[a] BMI = Body mass index, and it is calculated as weight (kg) / height (m^2).

CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation

Treatment/Dose level: Placebo (Studies ALD403-CLIN-006 and -011), Epti 30 mg (Study ALD403-CLIN-006), Epti 100 mg, Epti 300 mg and All Epti Pivotal (Studies ALD403-CLIN-006 and -011), All Epti All Studies (all doses from all Studies ALD403-CLIN-002, -005, -006, -011, and -013).

Percentages are based on safety population.

Demographic and Baseline Characteristics (OE pool)

	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81	**Epti 300 mg N=823**	**Epti 100 mg N=701**	**Epti 30 mg N=341**	**Epti 10 mg N=130**	**Placebo N=791**	**All Epti N=2076**
Age (years)							
n	81	823	701	341	130	791	2076

	EM	**EM+CM**			**CM**	**EM+CM**	
	Epti 1000 mg N=81	**Epti 300 mg N=823**	**Epti 100 mg N=701**	**Epti 30 mg N=341**	**Epti 10 mg N=130**	**Placebo N=791**	**All Epti N=2076**
Mean (SD)	38.6 (10.81)	40.3 (10.92)	39.9 (11.11)	37.9 (10.94)	36.4 (10.31)	39.3 (10.96)	39.5 (11.00)
Median	38.0	40.0	40.0	37.0	35.0	40.0	39.0
Min, Max	18, 55	18, 71	18, 68	18, 69	18, 55	18, 68	18, 71
Age Group, n (%)							
< 65 years	81 (100)	815 (99.0)	698 (99.6)	337 (98.8)	130 (100)	782 (98.9)	2061 (99.3)
>= 65 to < 75 years	0	8 (1.0)	3 (0.4)	4 (1.2)	0	9 (1.1)	15 (0.7)
>= 75 years	0	0	0	0	0	0	0
Sex, n (%)							
Male	14 (17.3)	103 (12.5)	111 (15.8)	45 (13.2)	17 (13.1)	105 (13.3)	290 (14.0)
Female	67 (82.7)	720 (87.5)	590 (84.2)	296 (86.8)	113 (86.9)	686 (86.7)	1786 (86.0)
Ethnicity, n (%)							
Hispanic or Latino	28 (34.6)	102 (12.4)	98 (14.0)	62 (18.2)	27 (20.8)	111 (14.0)	317 (15.3)
Not Hispanic or Latino	53 (65.4)	721 (87.6)	603 (86.0)	279 (81.8)	103 (79.2)	680 (86.0)	1759 (84.7)
Race, n (%)							
White	66 (81.5)	745 (90.5)	636 (90.7)	283 (83.0)	113 (86.9)	677 (85.6)	1843 (88.8)
Black or African American	10 (12.3)	58 (7.0)	50 (7.1)	45 (13.2)	12 (9.2)	84 (10.6)	175 (8.4)
Asian	4 (4.9)	4 (0.5)	2 (0.3)	1 (0.3)	1 (0.8)	7 (0.9)	12 (0.6)

	EM	**EM+CM**			**CM**	**EM+CM**	
	Epti 1000 mg N=81	**Epti 300 mg N=823**	**Epti 100 mg N=701**	**Epti 30 mg N=341**	**Epti 10 mg N=130**	**Placebo N=791**	**All Epti N=2076**
American Indian or Alaska Native	0	3 (0.4)	1 (0.1)	1 (0.3)	2 (1.5)	3 (0.4)	7 (0.3)
Native Hawaiian or Other Pacific Islander	0	2 (0.2)	1 (0.1)	1 (0.3)	0	2 (0.3)	4 (0.2)
Multiple Races	1 (1.2)	9 (1.1)	9 (1.3)	5 (1.5)	0	13 (1.6)	24 (1.2)
Other	0	1 (0.1)	2 (0.3)	5 (1.5)	2 (1.5)	5 (0.6)	10 (0.5)
Not Reported	0	1 (0.1)	0	0	0	0	1 (<0.1)
Weight (kg)							
n	81	823	701	341	130	791	2076
Mean (SD)	74.82 (16.545)	76.22 (17.688)	76.91 (19.149)	79.52 (21.660)	75.81 (15.360)	77.36 (18.305)	76.91 (18.743)
Median	72.50	73.40	74.30	76.60	74.75	75.50	74.15
Min, Max	46.1, 127.4	40.2, 139.5	39.2, 190.1	45.2, 174.0	45.1, 110.5	40.7, 160.9	39.2, 190.1
BMI (kg/m2)[a]							
n	81	823	701	341	130	791	2076
Mean (SD)	27.47 (5.166)	27.40 (5.789)	27.63 (6.149)	28.92 (7.552)	27.36 (5.402)	27.89 (6.142)	27.73 (6.206)
Median	26.10	26.30	26.70	27.40	26.90	27.00	26.70
Min, Max	17.2, 38.9	15.9, 49.8	15.6, 59.3	15.8, 67.5	18.0, 38.8	16.0, 52.6	15.6, 67.5
Region, n (%)							
United States	81 (100)	610 (74.1)	488 (69.6)	301 (88.3)	115 (88.5)	598 (75.6)	1595 (76.8)

	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81	**Epti 300 mg N=823**	**Epti 100 mg N=701**	**Epti 30 mg N=341**	**Epti 10 mg N=130**	**Placebo N=791**	**All Epti N=2076**
European Union	NA	53 (6.4)	50 (7.1)	NA	NA	51 (6.4)	103 (5.0)
Rest of World	NA	160 (19.4)	163 (23.3)	40 (11.7)	15 (11.5)	142 (18.0)	378 (18.2)

[a] BMI = Body mass index, and it is calculated as weight (kg) / height (m^2).
CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation.
Treatment/Dose level: Placebo (Studies ALD403-CLIN-002, -005, -006, and -011), Epti 10mg (Study ALD403-CLIN-005), Epti 30 mg (Studies ALD403-CLIN-005 and -006), Epti 100 mg (Studies ALD403-CLIN-005, -006, and -011), Epti 300 mg (Studies ALD403-CLIN-005, -006, -011, and -013), Epti 1000 mg (Study ALD403-CLIN-002).
Percentages are based on safety population.
Source: Table 14.1.3.1.3 (ISS TFLs)

Baseline Cardiovascular Risk Factors by Treatment Group (PS pool only)

	EM+CM		EM		EM+CM	
Baseline Risk Factors	**Epti 300 mg N = 574 n (%)**	**Epti 100 mg N = 579 n (%)**	**Epti 30 mg N = 219 n (%)**	**Placebo N = 588 n (%)**	**All Epti Pivotal N = 1372 n (%)**	**All Epti All Studies N = 2076 n (%)**
Hypertension-related[a]	24 (4.2%)	34 (5.9%)	1 (0.5%)	24 (4.1%)	59 (4.3%)	71 (3.4%)
Hyperlipidemia-related[b]	35 (6.1%)	43 (7.4%)	8 (3.7%)	36 (6.1%)	86 (6.3%)	129 (6.2%)
Diabetes-related[c]	0	3 (0.5%)	2 (0.9%)	5 (0.9%)	5 (0.4%)	7 (0.3%)
Prior history of ischemic CV events or procedures[d]	3 (0.5%)	4 (0.7%)	0	1 (0.2%)	7 (0.5%)	10 (0.5%)
Obesity - BMI ≥ 30 kg/m^2	165 (28.7%)	181 (31.3%)	85 (38.8%)	196 (33.3%)	431 (31.4%)	664 (32.0%)
Male and ≥ 45 years old	19 (3.3%)	36 (6.2%)	10 (4.6%)	27 (4.6%)	65 (4.7%)	99 (4.8%)
Female and ≥ 55 years old	54 (9.4%)	62 (10.7%)	21 (9.6%)	49 (8.3%)	137 (10.0%)	160 (7.7%)
Race: Black or African-American	50 (8.7%)	38 (6.6%)	31 (14.2%)	68 (11.6%)	119 (8.7%)	175 (8.4%)

	EM+CM		EM		EM+CM	
Baseline Risk Factors	**Epti 300 mg N = 574 n (%)**	**Epti 100 mg N = 579 n (%)**	**Epti 30 mg N = 219 n (%)**	**Placebo N = 588 n (%)**	**All Epti Pivotal N = 1372 n (%)**	**All Epti All Studies N = 2076 n (%)**
≥ 1 CV risk factors	268 (46.7%)	289 (49.9%)	130 (59.4%)	288 (49.0%)	687 (50.1%)	1016 (48.9%)
≥ 2 CV risk factors	75 (13.1%)	87 (15.0%)	26 (11.9%)	98 (16.7%)	188 (13.7%)	256 (12.3%)
Related demographic data:						
Subjects ≥ 40 years of age	299 (52.1%)	305 (52.7%)	100 (45.7%)	302 (51.4%)	704 (51.3%)	1008 (48.6%)
Males ≥ 40 years of age	25 (4.4%)	51 (8.8%)	13 (5.9%)	38 (6.5%)	89 (6.5%)	135 (6.5%)

[a] Includes essential hypertension, hypertension, prehypertension, or orthostatic hypertension
[b] Includes dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, or lipid metabolism disorder
[c] Includes glucose tolerance impaired, hyperglycemia, or impaired fasting glucose
[d] Includes angina pectoris, cardiomyopathy, cardiomegaly, chest pain, carotid artery bypass, arterial disorder, arteriosclerosis, or peripheral coldness
BMI = body mass index; CV = cardiovascular; CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab
Treatment/Dose level: Placebo (Studies ALD403-CLIN-006 and -011), Epti 30 mg (Study ALD403-CLIN-006), Epti 100 mg, Epti 300 mg and All Epti Pivotal (Studies ALD403-CLIN-006 and -011), All Epti All Studies (all doses from all Studies ALD403-CLIN-002, -005, -006, -011, and -013).
Percentages are based on safety population.

Adverse events

Common Adverse Events (PS pool)

The most frequent (≥ 2%) TEAEs that occurred with greater incidence in any eptinezumab dose group than in the placebo group (in descending order of frequency in PS eptinezumab subjects) were upper respiratory tract infection, nasopharyngitis, nausea, fatigue, dizziness, urinary tract infection, arthralgia, back pain, influenza, cough, pain in extremity, and pyrexia. These events generally occurred in similar proportions of all PS eptinezumab subjects, 300-mg eptinezumab subjects, 100-mg eptinezumab subjects, and placebo subjects. Upper respiratory tract infection and nasopharyngitis occurred in approximately 7% to 8% of PS eptinezumab subjects and approximately 6% of placebo subjects.

Grade 3 or higher TEAEs (PS pool)

The large majority of TEAEs in all treatment groups were mild or moderate in severity. TEAEs of grade 3 (severe) or higher severity occurred infrequently and in similar proportions of all PS eptinezumab subjects (2.2%), eptinezumab 300 mg subjects (2.6%), eptinezumab 100-mg subjects (1.7%), and placebo subjects (3.1%).

Two life-threatening (grade 4) TEAEs occurred in one placebo subject with multiple co-morbidities.

Grade 3 migraine occurred in 2 (0.1%) PS eptinezumab subjects (1 eptinezumab 300-mg subject and 1 eptinezumab 100-mg subject) and in 4 (0.7%) placebo subjects. One additional subject who received eptinezumab 300 mg had a grade 3 migraine with aura ("worsening migrainous visual phenomena") that was serious. Grade 3 ECG T wave inversion occurred in 2 PS eptinezumab subjects (both receiving 300 mg) and no placebo subjects. All other grade 3 TEAEs occurred in one subject in each treatment group.

Treatment-related Adverse Events (PS pool)

Treatment-related TEAEs, as determined by the investigator, were seen in 12.9% of PS eptinezumab subjects and 8.2% of placebo subjects. The incidence of treatment-related TEAEs increased with eptinezumab dose (11.0% in the 30-mg group, 11.7% in the 100 mg group, and 14.8% in the 300-mg group).

Overall Summary of Treatment-Emergent Adverse (PS pool)

Category	EM+CM		EM	EM+CM		
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)	All Epti All Studies N=2076 n (%)
Subjects with Any TEAE	311 (54.2)	296 (51.1)	128 (58.4)	303 (51.5)	735 (53.6)	1137 (54.8)
Number of TEAEs	756	699	313	717	1768	2938
Subjects with Any Study Drug Related TEAE	85 (14.8)	68 (11.7)	24 (11.0)	48 (8.2)	177 (12.9)	295 (14.2)
Number of Study Drug Related TEAEs	148	110	38	77	296	489
Subjects with Any Serious TEAE	7 (1.2)	7 (1.2)	4 (1.8)	9 (1.5)	18 (1.3)	35 (1.7)
Number of Serious TEAEs	11	13	5	11	29	53
Subjects with Any Grade 3 or Higher TEAE	15 (2.6)	10 (1.7)	5 (2.3)	18 (3.1)	30 (2.2)	54 (2.6)
Number of Grade 3 or Higher TEAEs	21	19	7	22	47	77
Subjects with Any TEAE of Special Interest	57 (9.9)	46 (7.9)	22 (10.0)	29 (4.9)	125 (9.1)	197 (9.5)
Number of TEAEs of Special Interest	65	71	28	34	164	255
Subjects with Any TEAE Leading to Study Drug Discontinuation[a]	13 (2.3)	9 (1.6)	12 (5.5)	8 (1.4)	34 (2.5)	40 (1.9)
Number of TEAEs Leading to Study Drug Discontinuation[a]	13	9	12	9	34	41
Subjects with Any TEAE Leading to Study Drug Infusion Interruption	9 (1.6)	9 (1.6)	6 (2.7)	6 (1.0)	24 (1.7)	40 (1.9)

Category	EM+CM		EM	EM+CM		
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)	All Epti All Studies N=2076 n (%)
Number of TEAEs Leading to Study Drug Infusion Interruption	9	11	7	8	27	46
Subjects with Any TEAE Resulting in Death	0	0	0	0	0	0
Number of TEAEs Resulting in Death	0	0	0	0	0	0

[a] The source of these data is from the Adverse Events CRF page.
CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; TEAE = treatment emergent adverse events.
Treatment/Dose level: Placebo (studies ALD403-CLIN-006 and -011), Epti 30 mg (study ALD403-CLIN-006), Epti 100 mg, Epti 300 mg and All Epti Pivotal (studies ALD403-CLIN-006 and -011), All Epti All Studies (all doses from all studies ALD403-CLIN-002, -005, -006, -011 and -013).
Adverse events from Study ALD403-CLIN-013 are presented up to end of the primary treatment phase.
Percentages are based on safety population.
Adverse events were coded using MedDRA version 20.1.

Treatment-Emergent Adverse Events Occurring in 2% or More Subjects in Any Eptinezumab Treatment Group and with Greater Incidence than in the Placebo Group by System Organ Class, Preferred Term and Treatment Group (PS pool)

System Organ Class Preferred Term	EM+CM		EM	EM+CM	
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)
Gastrointestinal disorders	64 (11.1)	41 (7.1)	30 (13.7)	51 (8.7)	135 (9.8)
Nausea	17 (3.0)	11 (1.9)	9 (4.1)	15 (2.6)	37 (2.7)
General disorders and administration site conditions	38 (6.6)	37 (6.4)	21 (9.6)	31 (5.3)	96 (7.0)
Fatigue	14 (2.4)	16 (2.8)	5 (2.3)	8 (1.4)	35 (2.6)
Pyrexia	4 (0.7)	2 (0.3)	5 (2.3)	3 (0.5)	11 (0.8)
Infections and infestations	165 (28.7)	152 (26.3)	72 (32.9)	159 (27.0)	389 (28.4)
Nasopharyngitis	47 (8.2)	36 (6.2)	14 (6.4)	34 (5.8)	97 (7.1)
Upper respiratory tract infection	42 (7.3)	37 (6.4)	25 (11.4)	36 (6.1)	104 (7.6)
Influenza	18 (3.1)	5 (0.9)	3 (1.4)	14 (2.4)	26 (1.9)
Urinary tract infection	16 (2.8)	11 (1.9)	4 (1.8)	9 (1.5)	31 (2.3)
Musculoskeletal and connective tissue disorders	41 (7.1)	45 (7.8)	25 (11.4)	47 (8.0)	111 (8.1)
Arthralgia	14 (2.4)	10 (1.7)	3 (1.4)	9 (1.5)	27 (2.0)
Back pain	9 (1.6)	14 (2.4)	4 (1.8)	13 (2.2)	27 (2.0)
Pain in extremity	4 (0.7)	3 (0.5)	5 (2.3)	2 (0.3)	12 (0.9)

System Organ Class Preferred Term	EM+CM		EM	EM+CM	
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)
Nervous system disorders	48 (8.4)	44 (7.6)	10 (4.6)	63 (10.7)	102 (7.4)
Dizziness	13 (2.3)	15 (2.6)	8 (3.7)	12 (2.0)	36 (2.6)
Respiratory, thoracic and mediastinal disorders	41 (7.1)	35 (6.0)	11 (5.0)	25 (4.3)	87 (6.3)
Cough	12 (2.1)	10 (1.7)	1 (0.5)	7 (1.2)	23 (1.7)

CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab.
Treatment/Dose level: Placebo (Studies ALD403-CLIN-006 and -011), Epti 30 mg (Study ALD403-CLIN-006), Epti 100 mg, Epti 300 mg, and All Epti Pivotal (Studies ALD403-CLIN-006 and -011).
Note: TEAEs shown in bold font indicate TEAEs that occurred in ≥ 2% of subjects in any PS eptinezumab group and with incidence that was at least 2% greater in the eptinezumab 100-mg or 300-mg groups than in the placebo group.
Percentages are based on safety population.
Adverse events were coded using MedDRA version 20.1. Subjects are counted only once per preferred term. Summary results are presented in decreasing order of preferred term frequency in 'Epti 300 mg' column.

Common Adverse Events (OE pool)

The most frequently occurring TEAEs (≥ 5%) in all OE subjects, the eptinezumab 300-mg and 100-mg groups, and the placebo group were nasopharyngitis and upper respiratory tract infection. Nasopharyngitis occurred in ≥ 2% of subjects in the eptinezumab 100-mg group (6.3%) or 300-mg group (8.7%) and with incidence that was at least 2% greater in either of these 2 groups than in the placebo group (5.2%). Upper respiratory tract infection occurred in similar proportions of OE subjects (7.6%), eptinezumab 300-mg subjects (7.8%), eptinezumab 100-mg subjects (6.4%), and placebo subjects (6.1%). No relationship between eptinezumab dose and the incidence of nasopharyngitis or upper respiratory tract infection was seen.

Grade 3 or higher TEAEs (OE pool)

The large majority of TEAEs in all treatment groups were mild or moderate in severity. As noted previously, TEAEs of grade 3 (severe) or higher severity occurred infrequently and in similar proportions of all OE (2.6%), eptinezumab 300-mg subjects (3.5%), eptinezumab 100-mg subjects (1.9%), and placebo subjects (2.4%).

As previously noted in the PS pool section, 1 placebo subject had two life-threatening (grade 4) TEAEs.

There were six grade 3 (severe) TEAEs that occurred in 2 or more OE eptinezumab subjects; these included migraine in 7 (0.3%) OE subjects and 5 (0.6%) placebo subjects, cholelithiasis in 3 (0.1%) OE subjects and no placebo subjects, uterine leiomyoma in 3 (0.1%) OE subjects and no placebo subjects, pneumonia in 2 (< 0.1%) OE and no placebo subjects, upper respiratory tract infection in 2 (< 0.2%) OE subjects and no placebo subjects and ECG T wave inversion in 2 (< 0.1%) OE subjects and no placebo subjects. All other grade 3 TEAEs occurred in 1 OE subject.

Treatment-related Adverse Events (OE pool)

Treatment-related TEAEs, as determined by the investigator, were seen in 14.2% of OE eptinezumab subjects and 9.4% of placebo subjects. The incidence of treatment-related TEAEs increased, with exception of the 10mg

dosing group, with eptinezumab dose (12.3% in the 30-mg group, 13.1% in the 100 mg group, 15.1% in the 300-mg group and 19.8% in the 1000-mg group).

Overall Summary of Treatment-Emergent Adverse (OE pool)

Category	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81 n (%)	Epti 300 mg N=823 n (%)	Epti 100 mg N=701 n (%)	Epti 30 mg N=341 n (%)	Epti 10 mg N=130 n (%)	Placebo N=791 n (%)	All Epti N=2076 n (%)
Subjects with Any TEAE	46 (56.8)	467 (56.7)	366 (52.2)	184 (54.0)	74 (56.9)	414 (52.3)	1137 (54.8)
Number of TEAEs	109	1212	942	454	221	1000	2938
Subjects with Any Study Drug Related TEAE	16 (19.8)	124 (15.1)	92 (13.1)	42 (12.3)	21 (16.2)	74 (9.4)	295 (14.2)
Number of Study Drug Related TEAEs	23	212	147	72	35	123	489
Subjects with Any Serious TEAE	2 (2.5)	17 (2.1)	11 (1.6)	4 (1.2)	1 (0.8)	11 (1.4)	35 (1.7)
Number of Serious TEAEs	5	24	18	5	1	13	53
Subjects with Any Grade 3 or Higher TEAE	3 (3.7)	29 (3.5)	13 (1.9)	8 (2.3)	1 (0.8)	19 (2.4)	54 (2.6)
Number of Grade 3 or Higher TEAEs	4	38	23	10	2	23	77
Subjects with Any TEAE of Special Interest	11 (13.6)	86 (10.4)	55 (7.8)	34 (10.0)	11 (8.5)	45 (5.7)	197 (9.5)
Number of TEAEs of Special Interest	14	98	86	44	13	53	255
Subjects with Any TEAE Leading to Study Drug Discontinuation[a]	0	19 (2.3)	9 (1.3)	12 (3.5)	0	8 (1.0)	40 (1.9)
Number of TEAEs Leading to Study Drug Discontinuation[a]	0	20	9	12	0	9	41
Subjects with Any TEAE Leading to Study Drug Infusion Interruption	0	19 (2.3)	11 (1.6)	10 (2.9)	0	6 (0.8)	40 (1.9)
Number of TEAEs Leading to Study Drug Infusion Interruption	0	20	15	11	0	8	46
Subjects with Any TEAE Resulting in Death	0	0	0	0	0	0	0
Number of TEAEs Resulting in Death	0	0	0	0	0	0	0

[a] The source of these data is from the Adverse Events CRF page.
CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; TEAE = treatment emergent adverse events
Adverse events from Study ALD403-CLIN-013 are presented up to the end of the primary treatment phase.
Adverse events were coded using MedDRA version 20.1
Percentages are based on safety population.
Treatment/Dose level: Placebo (Studies ALD403-CLIN-002, -005, -006, and -011), Epti 10 mg (Study ALD403-CLIN-005), Epti 30 mg (Studies ALD403-CLIN-005 and -006), Epti 100 mg (Studies ALD403-CLIN-005, -006, and -011), Epti 300 mg (Studies ALD403-CLIN-005, -006, -011, and -013), Epti 1000 mg (Study ALD403-CLIN-002).

Treatment-Emergent Adverse Events with Incidence of 2% or More in Subjects in the Overall, 300-mg, or 100-mg Eptinezumab Treatment Groups by Preferred Term and Treatment Group (OE pool)

Preferred Term	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81 n (%)	Epti 300 mg N=823 n (%)	Epti 100 mg N=701 n (%)	Epti 30 mg N=341 n (%)	Epti 10 mg N=130 n (%)	Placebo N=791 n (%)	All Epti N=2076 n (%)
Nasopharyngitis	1 (1.2)	72 (8.7)	44 (6.3)	17 (5.0)	6 (4.6)	41 (5.2)	140 (6.7)
Upper respiratory tract infection	7 (8.6)	64 (7.8)	45 (6.4)	32 (9.4)	9 (6.9)	48 (6.1)	157 (7.6)
Sinusitis	0	35 (4.3)	16 (2.3)	13 (3.8)	8 (6.2)	35 (4.4)	72 (3.5)
Nausea	1 (1.2)	29 (3.5)	20 (2.9)	13 (3.8)	6 (4.6)	26 (3.3)	69 (3.3)
Influenza	0	25 (3.0)	9 (1.3)	5 (1.5)	1 (0.8)	18 (2.3)	40 (1.9)
Fatigue	3 (3.7)	24 (2.9)	20 (2.9)	9 (2.6)	2 (1.5)	13 (1.6)	58 (2.8)
Urinary tract infection	1 (1.2)	23 (2.8)	14 (2.0)	5 (1.5)	4 (3.1)	18 (2.3)	47 (2.3)
Arthralgia	1 (1.2)	21 (2.6)	13 (1.9)	3 (0.9)	0	14 (1.8)	38 (1.8)
Bronchitis	0	21 (2.6)	17 (2.4)	9 (2.6)	4 (3.1)	25 (3.2)	51 (2.5)
Migraine	1 (1.2)	18 (2.2)	14 (2.0)	3 (0.9)	3 (2.3)	23 (2.9)	39 (1.9)
Dizziness	3 (3.7)	16 (1.9)	27 (3.9)	11 (3.2)	11 (8.5)	21 (2.7)	68 (3.3)
Back pain	3 (3.7)	15 (1.8)	17 (2.4)	4 (1.2)	4 (3.1)	19 (2.4)	43 (2.1)

CM = chronic migraine; EM = episodic migraine; EM + CM = episodic and chronic migraine; Epti = eptinezumab; TEAE = treatment emergent adverse events

Treatment/Dose level: Placebo (Studies ALD403-CLIN-002, -005, -006, and -011), Epti 10 mg (Study ALD403-CLIN-005), Epti 30 mg (Studies ALD403-CLIN-005 and -006), Epti 100 mg (Studies ALD403-CLIN-005, -006, and -011), Epti 300 mg (Studies ALD403-CLIN-005, -006, -011, and -013), Epti 1000 mg (Study ALD403-CLIN-002).

Note: TEAEs shown in bold font indicate TEAEs that occurred in ≥ 2% of subjects in the eptinezumab 100-mg or 300-mg groups and with incidence that was at least 2% greater in either of these 2 groups than in the placebo group.

Adverse events from Study ALD403-CLIN-013 are presented up to end of the primary treatment phase.

Percentages are based on safety population.

Adverse events were coded using MedDRA version 20.1. Subjects are counted only once per preferred term. Summary results are presented in decreasing order of preferred term frequency in 'Epti 300 mg' column.

Serious adverse events and deaths

Deaths and life threatening events

There were no subject deaths in any of the 5 clinical studies included in the integrated safety database or in any of the 7 clinical pharmacology studies. No life-threatening AEs occurred in any eptinezumab-treated subject. Two life-threatening (grade 4) TEAEs occurred in one subject with multiple comorbidities treated with placebo.

Other serious adverse events (PS pool)

SAEs occurred infrequently within the PS pool with 1.3% of all PS eptinezumab subjects and 1.5% of PS placebo subjects. The proportions of subjects with SAEs were similar in each eptinezumab dose group and the placebo group, and no relationship to eptinezumab dose was observed.

Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group (PS pool)

System Organ Class Preferred Term	EM+CM		EM	EM+CM		
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)	All Epti All Studies N=2076 n (%)
Subjects with Any Serious TEAE	7 (1.2)	7 (1.2)	4 (1.8)	9 (1.5)	18 (1.3)	35 (1.7)
Ear and labyrinth disorders	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Vertigo	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Gastrointestinal disorders	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Gastric ulcer	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Haematemesis	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Hepatobiliary disorders	0	1 (0.2)	1 (0.5)	0	2 (0.1)	3 (0.1)
Cholecystitis	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Hepatitis cholestatic	0	0	1 (0.5)	0	1 (<0.1)	1 (<0.1)
Infections and infestations	1 (0.2)	0	0	1 (0.2)	1 (<0.1)	5 (0.2)
Gastroenteritis	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Cellulitis	0	0	0	1 (0.2)	0	0
Injury, poisoning and procedural complications	2 (0.3)	2 (0.3)	1 (0.5)	0	5 (0.4)	6 (0.3)
Abdominal wound dehiscence	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Fall	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Post procedural complication	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Spinal compression fracture	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Post procedural constipation	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Procedural pain	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Stomal hernia	0	0	1 (0.5)	0	1 (<0.1)	1 (<0.1)
Tibia fracture	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Musculoskeletal and connective tissue disorders	0	0	1 (0.5)	1 (0.2)	1 (<0.1)	1 (<0.1)
Intervertebral disc protrusion	0	0	0	1 (0.2)	0	0
Rhabdomyolysis	0	0	1 (0.5)	0	1 (<0.1)	1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.3)	0	0	1 (0.2)	2 (0.1)	5 (0.2)
Benign breast neoplasm	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Breast cancer	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Breast cancer stage II	0	0	0	1 (0.2)	0	0
Nervous system disorders	2 (0.3)	2 (0.3)	0	2 (0.3)	4 (0.3)	8 (0.4)
Migraine with aura	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Seizure	1 (0.2)	0	0	0	1 (<0.1)	2 (<0.1)
Migraine	0	1 (0.2)	0	1 (0.2)	1 (<0.1)	1 (<0.1)

System Organ Class Preferred Term	EM+CM		EM	EM+CM		
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)	All Epti All Studies N=2076 n (%)
Syncope	0	1 (0.2)	0	2 (0.3)	1 (<0.1)	1 (<0.1)
Psychiatric disorders	1 (0.2)	3 (0.5)	0	0	4 (0.3)	8 (0.4)
Suicide attempt	1 (0.2)	1 (0.2)	0	0	2 (0.1)	2 (<0.1)
Depression suicidal	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Panic attack	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Suicidal ideation	0	1 (0.2)	0	0	1 (<0.1)	2 (<0.1)
Renal and urinary disorders	0	0	2 (0.9)	1 (0.2)	2 (0.1)	2 (<0.1)
Acute kidney injury	0	0	1 (0.5)	0	1 (<0.1)	1 (<0.1)
Nephrolithiasis	0	0	1 (0.5)	1 (0.2)	1 (<0.1)	1 (<0.1)
Reproductive system and breast disorders	0	0	0	2 (0.3)	0	2 (<0.1)
Menometrorrhagia	0	0	0	1 (0.2)	0	0
Uterine prolapse	0	0	0	1 (0.2)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (0.2)	0	2 (<0.1)
Apnoea	0	0	0	1 (0.2)	0	0
Chronic obstructive pulmonary disease	0	0	0	1 (0.2)	0	0

CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; TEAE = treatment emergent adverse events
Treatment/Dose level: Placebo (Studies ALD403-CLIN-006 and -011), Epti 30 mg (Study ALD403-CLIN-006), Epti 100 mg, Epti 300 mg and All Epti Pivotal (Studies ALD403-CLIN-006 and -011), All Epti All studies (all doses from all Studies ALD403-CLIN-002, -005, -006, -011, and -013).
Adverse events from Study ALD403-CLIN-013 are presented up to end of the primary treatment phase.
Percentages are based on safety population.
Adverse events were coded using MedDRA version 20.1. Subjects are counted only once per system organ class and per preferred term. Summary results are presented in alphabetic order of system organ class, and within each system organ class, TEAEs are sorted in decreasing order of preferred term frequency in "Epti 300 mg' column.
Source: Table 14.3.2.3.1.1 (ISS TFLs)

Other serious adverse events (OE pool)

Serious adverse events occurred infrequently in the OE pool: 1.7% of all OE eptinezumab subjects and 1.4% of OE placebo subjects. The occurrence of SAEs increased slightly with eptinezumab dose: 0.8% of 10-mg subjects, 1.2% of 30-mg subjects, 1.6% of 100-mg subjects, 2.1% of 300-mg subjects, and 2.5% of 1000-mg subjects. However, the proportion of placebo subjects with SAEs (1.4%) was greater than the proportions of subjects with SAEs in the 2 lowest eptinezumab doses and similar to the proportion of subjects with SAEs in the eptinezumab 100-mg group (1.6%).

Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group (OE pool)

System Organ Class Preferred Term	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81 n (%)	Epti 300 mg N=823 n (%)	Epti 100 mg N=701 n (%)	Epti 30 mg N=341 n (%)	Epti 10 mg N=130 n (%)	Placebo N=791 n (%)	All Epti N=2076 n (%)
Subjects with Any Serious TEAE	2 (2.5)	17 (2.1)	11 (1.6)	4 (1.2)	1 (0.8)	11 (1.4)	35 (1.7)
Ear and labyrinth disorders	0	1 (0.1)	0	0	0	0	1 (<0.1)

System Organ Class Preferred Term	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81 n (%)	Epti 300 mg N=823 n (%)	Epti 100 mg N=701 n (%)	Epti 30 mg N=341 n (%)	Epti 10 mg N=130 n (%)	Placebo N=791 n (%)	All Epti N=2076 n (%)
Vertigo	0	1 (0.1)	0	0	0	0	1 (<0.1)
Gastrointestinal disorders	0	0	1 (0.1)	0	0	0	1 (<0.1)
Gastric ulcer	0	0	1 (0.1)	0	0	0	1 (<0.1)
Haematemesis	0	0	1 (0.1)	0	0	0	1 (<0.1)
General disorders and administration site conditions	1 (1.2)	0	0	0	0	0	1 (<0.1)
Chest pain	1 (1.2)	0	0	0	0	0	1 (<0.1)
Hepatobiliary disorders	0	0	2 (0.3)	1 (0.3)	0	0	3 (0.1)
Cholecystitis	0	0	1 (0.1)	0	0	0	1 (<0.1)
Cholelithiasis	0	0	1 (0.1)	0	0	0	1 (<0.1)
Hepatitis cholestatic	0	0	0	1 (0.3)	0	0	1 (<0.1)
Immune system disorders	0	1 (0.1)	0	0	0	0	1 (<0.1)
Anaphylactic reaction	0	1 (0.1)	0	0	0	0	1 (<0.1)
Infections and infestations	1 (1.2)	4 (0.5)	0	0	0	2 (0.3)	5 (0.2)
Gastroenteritis	0	1 (0.1)	0	0	0	0	1 (<0.1)
Gastroenteritis viral	0	1 (0.1)	0	0	0	0	1 (<0.1)
Pneumonia	0	1 (0.1)	0	0	0	0	1 (<0.1)
Vaginal abscess	0	1 (0.1)	0	0	0	0	1 (<0.1)
Cellulitis	0	0	0	0	0	1 (0.1)	0
Kidney infection	1 (1.2)	0	0	0	0	0	1 (<0.1)
Wound infection	0	0	0	0	0	1 (0.1)	0
Injury, poisoning and procedural complications	0	3 (0.4)	2 (0.3)	1 (0.3)	0	0	6 (0.3)
Abdominal wound dehiscence	0	1 (0.1)	0	0	0	0	1 (<0.1)
Concussion	0	1 (0.1)	0	0	0	0	1 (<0.1)
Fall	0	1 (0.1)	0	0	0	0	1 (<0.1)
Head injury	0	1 (0.1)	0	0	0	0	1 (<0.1)
Post procedural complication	0	1 (0.1)	0	0	0	0	1 (<0.1)
Spinal compression fracture	0	1 (0.1)	0	0	0	0	1 (<0.1)
Post procedural constipation	0	0	1 (0.1)	0	0	0	1 (<0.1)
Procedural pain	0	0	1 (0.1)	0	0	0	1 (<0.1)
Stomal hernia	0	0	0	1 (0.3)	0	0	1 (<0.1)
Tibia fracture	0	0	1 (0.1)	0	0	0	1 (<0.1)
Musculoskeletal and connective tissue disorders	0	0	0	1 (0.3)	0	1 (0.1)	1 (<0.1)
Intervertebral disc protrusion	0	0	0	0	0	1 (0.1)	0
Rhabdomyolysis	0	0	0	1 (0.3)	0	0	1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (0.5)	1 (0.1)	0	0	1 (0.1)	5 (0.2)
Uterine leiomyoma	0	2 (0.2)	1 (0.1)	0	0	0	3 (0.1)
Benign breast neoplasm	0	1 (0.1)	0	0	0	0	1 (<0.1)
Breast cancer	0	1 (0.1)	0	0	0	0	1 (<0.1)

System Organ Class Preferred Term	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81 n (%)	Epti 300 mg N=823 n (%)	Epti 100 mg N=701 n (%)	Epti 30 mg N=341 n (%)	Epti 10 mg N=130 n (%)	Placebo N=791 n (%)	All Epti N=2076 n (%)
Breast cancer stage II	0	0	0	0	0	1 (0.1)	0
Nervous system disorders	1 (1.2)	4 (0.5)	3 (0.4)	0	0	2 (0.3)	8 (0.4)
Seizure	0	2 (0.2)	0	0	0	0	2 (<0.1)
Migraine with aura	0	1 (0.1)	0	0	0	0	1 (<0.1)
Serotonin syndrome	0	1 (0.1)	0	0	0	0	1 (<0.1)
Medication overuse headache	0	0	1 (0.1)	0	0	0	1 (<0.1)
Migraine	0	0	1 (0.1)	0	0	1 (0.1)	1 (<0.1)
Syncope	0	0	1 (0.1)	0	0	2 (0.3)	1 (<0.1)
Transient ischaemic attack	1 (1.2)	0	0	0	0	0	1 (<0.1)
Psychiatric disorders	1 (1.2)	2 (0.2)	4 (0.6)	0	1 (0.8)	1 (0.1)	8 (0.4)
Conversion disorder	1 (1.2)	1 (0.1)	0	0	0	0	2 (<0.1)
Suicide attempt	0	1 (0.1)	1 (0.1)	0	0	0	2 (<0.1)
Affective disorder	0	0	1 (0.1)	0	0	0	1 (<0.1)
Depression suicidal	0	0	1 (0.1)	0	0	0	1 (<0.1)
Panic attack	0	0	1 (0.1)	0	0	0	1 (<0.1)
Suicidal ideation	0	0	1 (0.1)	0	1 (0.8)	1 (0.1)	2 (<0.1)
Renal and urinary disorders	0	0	0	2 (0.6)	0	1 (0.1)	2 (<0.1)
Acute kidney injury	0	0	0	1 (0.3)	0	0	1 (<0.1)
Nephrolithiasis	0	0	0	1 (0.3)	0	1 (0.1)	1 (<0.1)
Reproductive system and breast disorders	0	1 (0.1)	1 (0.1)	0	0	2 (0.3)	2 (<0.1)
Pelvic pain	0	1 (0.1)	0	0	0	0	1 (<0.1)
Menometrorrhagia	0	0	0	0	0	1 (0.1)	0
Menorrhagia	0	0	1 (0.1)	0	0	0	1 (<0.1)
Uterine prolapse	0	0	0	0	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	1 (1.2)	1 (0.1)	0	0	0	1 (0.1)	2 (<0.1)
Respiratory distress	0	1 (0.1)	0	0	0	0	1 (<0.1)
Apnoea	0	0	0	0	0	1 (0.1)	0
Chronic obstructive pulmonary disease	0	0	0	0	0	1 (0.1)	0
Dyspnoea	1 (1.2)	0	0	0	0	0	1 (<0.1)

CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; TEAE = treatment emergent adverse events
Treatment/Dose level: Placebo (Studies ALD403-CLIN-002, -005, -006, and -011), Epti 10 mg (Study ALD403-CLIN-005), Epti 30 mg (Studies ALD403-CLIN-005 and -006), Epti 100 mg (Studies ALD403-CLIN-005, -006, and -011), Epti 300 mg (Studies ALD403-CLIN-005, -006, -011, and -013), Epti 1000 mg (Study ALD403-CLIN-002).
Adverse events from Study ALD403-CLIN-013 are presented up to end of the primary treatment phase.
Percentages are based on safety population.
Adverse events were coded using MedDRA version 20.1. Subjects are counted only once per system organ class and per preferred term. Summary results are presented in alphabetic order of system organ class, and within each system organ class, TEAEs are sorted in decreasing order of preferred term frequency in 'Epti 300 mg' column.
Source: Table 14.3.2.3.1.3 (ISS TFLs)

Adverse events of special interest (AESIs)

For the eptinezumab clinical development, the following adverse events are defined AESIs:

- Hypersensitivity and Anaphylactic Events
- Events Associated with Suicide

- Cardiovascular Events
- Nervous System Events
- Hepatic Events
- Events Associated with Study Drug Infusion

Treatment-Emergent Adverse Events of Special Interest (PS pool)

The proportion of subjects having an AESI was higher in the PS eptinezumab group (9.1%) than in the placebo group (4.9%). Across eptinezumab dose groups, these proportions did not appear to be related to dose. The large majority of AESIs were mild or moderate in severity; there were no life-threatening or fatal AESIs. Events coded to hypersensitivity, the most frequently occurring AESI, occurred in 0.9% PS eptinezumab subjects and no placebo subjects.

Treatment-Emergent Adverse Events of Special Interest by System Organ Class, Preferred Term, and Treatment Group (PS pool)

System Organ Class Preferred Term	EM+CM		EM	EM+CM		
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)	All Epti All Studies N=2076 n (%)
Subjects with Any TEAE of Special Interest	57 (9.9)	46 (7.9)	22 (10.0)	29 (4.9)	125 (9.1)	197 (9.5)
Cardiac disorders	4 (0.7)	3 (0.5)	6 (2.7)	2 (0.3)	13 (0.9)	20 (1.0)
Tachycardia	2 (0.3)	1 (0.2)	2 (0.9)	1 (0.2)	5 (0.4)	7 (0.3)
Bradycardia	1 (0.2)	0	0	0	1 (<0.1)	2 (<0.1)
Palpitations	1 (0.2)	1 (0.2)	3 (1.4)	1 (0.2)	5 (0.4)	8 (0.4)
Sinus tachycardia	0	1 (0.2)	1 (0.5)	0	2 (0.1)	2 (<0.1)
General disorders and administration site conditions[a]	7 (1.2)	9 (1.6)	5 (2.3)	7 (1.2)	21 (1.5)	31 (1.5)
Infusion site extravasation	5 (0.9)	4 (0.7)	3 (1.4)	5 (0.9)	12 (0.9)	16 (0.8)
Infusion site nerve damage	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Infusion site rash	1 (0.2)	1 (0.2)	1 (0.5)	0	3 (0.2)	3 (0.1)
Infusion site discomfort	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Infusion site eczema	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Infusion site erythema	0	1 (0.2)	0	1 (0.2)	1 (<0.1)	1 (<0.1)
Infusion site pain	0	2 (0.3)	1 (0.5)	1 (0.2)	3 (0.2)	4 (0.2)
Infusion site pruritus	0	1 (0.2)	1 (0.5)	0	2 (0.1)	2 (<0.1)
Immune system disorders	8 (1.4)	1 (0.2)	4 (1.8)	0	13 (0.9)	24 (1.2)
Hypersensitivity	8 (1.4)	1 (0.2)	4 (1.8)	0	13 (0.9)	23 (1.1)
Investigations	11 (1.9)	12 (2.1)	3 (1.4)	10 (1.7)	26 (1.9)	39 (1.9)
Blood pressure increased	3 (0.5)	6 (1.0)	1 (0.5)	4 (0.7)	10 (0.7)	14 (0.7)

System Organ Class Preferred Term	EM+CM		EM	EM+CM		
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)	All Epti All Studies N=2076 n (%)
Alanine aminotransferase increased	2 (0.3)	1 (0.2)	2 (0.9)	4 (0.7)	5 (0.4)	7 (0.3)
Aspartate aminotransferase increased	2 (0.3)	0	0	1 (0.2)	2 (0.1)	3 (0.1)
Hepatic enzyme increased	2 (0.3)	1 (0.2)	0	1 (0.2)	3 (0.2)	4 (0.2)
Heart rate increased	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Liver function test increased	1 (0.2)	1 (0.2)	0	1 (0.2)	2 (0.1)	3 (0.1)
Transaminases increased	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Blood bilirubin increased	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Blood pressure systolic increased	0	1 (0.2)	0	0	1 (<0.1)	2 (<0.1)
Electrocardiogram Q wave abnormal	0	1 (0.2)	0	0	1 (<0.1)	2 (<0.1)
Nervous system disorders	5 (0.9)	3 (0.5)	0	3 (0.5)	8 (0.6)	10 (0.5)
Syncope	4 (0.7)	3 (0.5)	0	3 (0.5)	7 (0.5)	8 (0.4)
Seizure	1 (0.2)	0	0	0	1 (<0.1)	2 (<0.1)
Psychiatric disorders	1 (0.2)	5 (0.9)	0	1 (0.2)	6 (0.4)	11 (0.5)
Suicide attempt	1 (0.2)	1 (0.2)	0	0	2 (0.1)	2 (<0.1)
Depression suicidal	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Suicidal ideation	0	4 (0.7)	0	1 (0.2)	4 (0.3)	9 (0.4)
Respiratory, thoracic and mediastinal disorders[b]	11 (1.9)	8 (1.4)	2 (0.9)	0	21 (1.5)	30 (1.4)
Rhinorrhoea	4 (0.7)	4 (0.7)	0	0	8 (0.6)	8 (0.4)
Cough	2 (0.3)	1 (0.2)	0	0	3 (0.2)	4 (0.2)
Dyspnoea	2 (0.3)	0	0	0	2 (0.1)	2 (<0.1)
Nasal congestion	2 (0.3)	2 (0.3)	1 (0.5)	0	5 (0.4)	9 (0.4)
Throat irritation	2 (0.3)	1 (0.2)	0	0	3 (0.2)	3 (0.1)
Sneezing	1 (0.2)	1 (0.2)	0	0	2 (0.1)	4 (0.2)
Choking sensation	0	0	1 (0.5)	0	1 (<0.1)	1 (<0.1)
Sinus congestion	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Wheezing	0	0	1 (0.5)	0	1 (<0.1)	1 (<0.1)
Skin and subcutaneous tissue disorders[a]	6 (1.0)	6 (1.0)	1 (0.5)	2 (0.3)	13 (0.9)	23 (1.1)
Rash	5 (0.9)	1 (0.2)	0	1 (0.2)	6 (0.4)	9 (0.4)
Pruritus	1 (0.2)	4 (0.7)	1 (0.5)	0	6 (0.4)	12 (0.6)
Pruritus generalised	0	1 (0.2)	0	0	1 (<0.1)	2 (<0.1)
Swelling face	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)
Urticaria	0	0	0	1 (0.2)	0	0
Vascular disorders	6 (1.0)	6 (1.0)	3 (1.4)	5 (0.9)	15 (1.1)	26 (1.3)

System Organ Class Preferred Term	EM+CM		EM	EM+CM		
	Epti 300 mg N=574 n (%)	Epti 100 mg N=579 n (%)	Epti 30 mg N=219 n (%)	Placebo N=588 n (%)	All Epti Pivotal N=1372 n (%)	All Epti All Studies N=2076 n (%)
Hot flush	3 (0.5)	2 (0.3)	1 (0.5)	0	6 (0.4)	8 (0.4)
Hypertension	2 (0.3)	3 (0.5)	1 (0.5)	5 (0.9)	6 (0.4)	11 (0.5)
Flushing	1 (0.2)	1 (0.2)	1 (0.5)	0	3 (0.2)	4 (0.2)

[a] By definition, these events occurred within 7 days of infusion.
[b] By definition, these events occurred on the infusion day.
CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; TEAE = treatment-emergent adverse events
Adverse events from Study ALD403-CLIN-013 are presented up to end of the primary treatment phase.
Adverse events were coded using MedDRA version 20.1. Subjects are counted only once per system organ class (SOC) and per preferred term. Summary results are presented in alphabetic order of SOC, and within each SOC, AEs are sorted in decreasing order of preferred term frequency in 'Epti 300 mg' column.
Percentages are based on safety population.
Treatment Dose level: Placebo (Studies ALD403-CLIN-006 and -011), Epti 30 mg (Study ALD403-CLIN-006), Epti 100 mg, Epti 300 mg and All Epti Pivotal (Studies ALD403-CLIN-006 and -011), All Epti All Studies (all doses from all Studies ALD403-CLIN-002, -005, -006, -011, and -013).
Source: Table 14.3.2.4.1.1 (ISS TFLs)

Treatment-Emergent Adverse Events of Special Interest (OE pool)

AESIs occurred more frequently in OE subjects (9.5%) than in placebo subjects (5.7%) (table 27). The occurrence of any AESI did not appear to be dose related. The large majority of AESIs were mild or moderate in severity; there were no life-threatening or fatal AESIs. Events coded to hypersensitivity, the most frequently occurring AESI, occurred in 1.1% of OE subjects and no placebo subjects.

Treatment-Emergent Adverse Events of Special Interest by System Organ Class, Preferred Term, and Treatment Group (OE pool)

System Organ Class Preferred Term	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81 n (%)	Epti 300 mg N=823 n (%)	Epti 100 mg N=701 n (%)	Epti 30 mg N=341 n (%)	Epti 10 mg N=130 n (%)	Placebo N=791 n (%)	All Epti N=2076 n (%)
Subjects with Any TEAE of Special Interest	11 (13.6)	86 (10.4)	55 (7.8)	34 (10.0)	11 (8.5)	45 (5.7)	197 (9.5)
Cardiac disorders	0	9 (1.1)	3 (0.4)	6 (1.8)	2 (1.5)	6 (0.8)	20 (1.0)
Palpitations	0	3 (0.4)	1 (0.1)	3 (0.9)	1 (0.8)	3 (0.4)	8 (0.4)
Tachycardia	0	3 (0.4)	1 (0.1)	2 (0.6)	1 (0.8)	1 (0.1)	7 (0.3)
Bradycardia	0	2 (0.2)	0	0	0	0	2 (<0.1)
Atrial fibrillation	0	1 (0.1)	0	0	0	1 (0.1)	1 (<0.1)
Sinus bradycardia	0	0	0	0	0	1 (0.1)	0
Sinus tachycardia	0	0	1 (0.1)	1 (0.3)	0	0	2 (<0.1)
Gastrointestinal disorders	0	0	0	1 (0.3)	0	1 (0.1)	1 (<0.1)
Oral pruritus	0	0	0	1 (0.3)	0	0	1 (<0.1)
Paraesthesia oral	0	0	0	0	0	1 (0.1)	0
General disorders and administration site conditions[a]	1 (1.2)	10 (1.2)	9 (1.3)	8 (2.3)	3 (2.3)	9 (1.1)	31 (1.5)
Infusion site extravasation	0	8 (1.0)	4 (0.6)	4 (1.2)	0	5 (0.6)	16 (0.8)
Infusion site nerve damage	0	1 (0.1)	0	0	0	0	1 (<0.1)

System Organ Class Preferred Term	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81 n (%)	Epti 300 mg N=823 n (%)	Epti 100 mg N=701 n (%)	Epti 30 mg N=341 n (%)	Epti 10 mg N=130 n (%)	Placebo N=791 n (%)	All Epti N=2076 n (%)
Infusion site rash	0	1 (0.1)	1 (0.1)	1 (0.3)	0	0	3 (0.1)
Chest pain	1 (1.2)	0	0	0	1 (0.8)	1 (0.1)	2 (<0.1)
Feeling hot	0	0	0	1 (0.3)	1 (0.8)	1 (0.1)	2 (<0.1)
Infusion site discomfort	0	0	1 (0.1)	0	0	0	1 (<0.1)
Infusion site eczema	0	0	1 (0.1)	0	0	0	1 (<0.1)
Infusion site erythema	0	0	1 (0.1)	0	0	1 (0.1)	1 (<0.1)
Infusion site pain	0	0	2 (0.3)	2 (0.6)	0	1 (0.1)	4 (0.2)
Infusion site pruritus	0	0	1 (0.1)	1 (0.3)	0	0	2 (<0.1)
Injection site paraesthesia	0	0	0	0	1 (0.8)	0	1 (<0.1)
Immune system disorders	0	16 (1.9)	2 (0.3)	6 (1.8)	0	0	24 (1.2)
Hypersensitivity	0	15 (1.8)	2 (0.3)	6 (1.8)	0	0	23 (1.1)
Anaphylactic reaction	0	1 (0.1)	0	0	0	0	1 (<0.1)
Investigations	6 (7.4)	12 (1.5)	14 (2.0)	5 (1.5)	2 (1.5)	14 (1.8)	39 (1.9)
Blood pressure increased	1 (1.2)	3 (0.4)	7 (1.0)	3 (0.9)	0	5 (0.6)	14 (0.7)
Alanine aminotransferase increased	1 (1.2)	2 (0.2)	2 (0.3)	2 (0.6)	0	5 (0.6)	7 (0.3)
Aspartate aminotransferase increased	0	2 (0.2)	1 (0.1)	0	0	2 (0.3)	3 (0.1)
Hepatic enzyme increased	0	2 (0.2)	1 (0.1)	0	1 (0.8)	1 (0.1)	4 (0.2)
Blood pressure systolic increased	0	1 (0.1)	1 (0.1)	0	0	0	2 (<0.1)
Heart rate increased	0	1 (0.1)	0	0	0	0	1 (<0.1)
Liver function test increased	0	1 (0.1)	1 (0.1)	0	1 (0.8)	1 (0.1)	3 (0.1)
Transaminases increased	0	1 (0.1)	0	0	0	1 (0.1)	1 (<0.1)
Blood bilirubin increased	0	0	1 (0.1)	0	0	0	1 (<0.1)
Electrocardiogram Q wave abnormal	1 (1.2)	0	1 (0.1)	0	0	0	2 (<0.1)
Electrocardiogram QT prolonged	3 (3.7)	0	0	0	0	1 (0.1)	3 (0.1)
Nervous system disorders	0	6 (0.7)	3 (0.4)	1 (0.3)	0	4 (0.5)	10 (0.5)
Syncope	0	4 (0.5)	3 (0.4)	1 (0.3)	0	4 (0.5)	8 (0.4)
Seizure	0	2 (0.2)	0	0	0	0	2 (<0.1)
Psychiatric disorders	0	3 (0.4)	7 (1.0)	0	1 (0.8)	3 (0.4)	11 (0.5)
Suicidal ideation	0	2 (0.2)	6 (0.9)	0	1 (0.8)	3 (0.4)	9 (0.4)
Suicide attempt	0	1 (0.1)	1 (0.1)	0	0	0	2 (<0.1)
Depression suicidal	0	0	1 (0.1)	0	0	0	1 (<0.1)
Intentional self-injury	0	0	1 (0.1)	0	0	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders[b]	1 (1.2)	14 (1.7)	9 (1.3)	6 (1.8)	0	1 (0.1)	30 (1.4)
Rhinorrhoea	0	4 (0.5)	4 (0.6)	0	0	0	8 (0.4)
Cough	0	3 (0.4)	1 (0.1)	0	0	0	4 (0.2)
Nasal congestion	0	3 (0.4)	3 (0.4)	3 (0.9)	0	0	9 (0.4)
Dyspnoea	0	2 (0.2)	0	0	0	0	2 (<0.1)
Sneezing	1 (1.2)	2 (0.2)	1 (0.1)	0	0	1 (0.1)	4 (0.2)

System Organ Class Preferred Term	EM	EM+CM			CM	EM+CM	
	Epti 1000 mg N=81 n (%)	Epti 300 mg N=823 n (%)	Epti 100 mg N=701 n (%)	Epti 30 mg N=341 n (%)	Epti 10 mg N=130 n (%)	Placebo N=791 n (%)	All Epti N=2076 n (%)
Throat irritation	0	2 (0.2)	1 (0.1)	0	0	0	3 (0.1)
Choking sensation	0	0	0	1 (0.3)	0	0	1 (<0.1)
Oropharyngeal pain	0	0	0	2 (0.6)	0	0	2 (<0.1)
Sinus congestion	0	0	1 (0.1)	0	0	0	1 (<0.1)
Wheezing	0	0	0	1 (0.3)	0	0	1 (<0.1)
Skin and subcutaneous tissue disorders[a]	3 (3.7)	8 (1.0)	7 (1.0)	3 (0.9)	2 (1.5)	2 (0.3)	23 (1.1)
Rash	1 (1.2)	6 (0.7)	2 (0.3)	0	0	1 (0.1)	9 (0.4)
Pruritus	1 (1.2)	2 (0.2)	4 (0.6)	3 (0.9)	2 (1.5)	0	12 (0.6)
Pruritus generalised	0	0	1 (0.1)	1 (0.3)	0	0	2 (<0.1)
Rash pruritic	1 (1.2)	0	0	0	0	0	1 (<0.1)
Swelling face	0	0	1 (0.1)	0	0	0	1 (<0.1)
Urticaria	0	0	0	0	0	1 (0.1)	0
Vascular disorders	1 (1.2)	12 (1.5)	8 (1.1)	3 (0.9)	2 (1.5)	8 (1.0)	26 (1.3)
Hot flush	1 (1.2)	4 (0.5)	2 (0.3)	1 (0.3)	0	0	8 (0.4)
Hypertension	0	4 (0.5)	4 (0.6)	1 (0.3)	2 (1.5)	6 (0.8)	11 (0.5)
Flushing	0	2 (0.2)	1 (0.1)	1 (0.3)	0	1 (0.1)	4 (0.2)
Hypotension	0	2 (0.2)	1 (0.1)	0	0	0	3 (0.1)
Prehypertension	0	0	0	0	0	1 (0.1)	0

[a] By definition, these events occurred within 7 days of infusion.
[b] By definition, these events occurred on infusion day.
CM = chronic migraine; EM = episodic migraine; Epti = eptinezumab; TEAE = treatment-emergent adverse events
Adverse events from Study ALD403-CLIN-013 are presented up to end of the primary treatment phase.
Adverse events were coded using MedDRA version 20.1. Subjects are counted only once per system organ class (SOC) and per preferred term. Summary results are presented in alphabetic order of SOC, and within each SOC, AEs are sorted in decreasing order of preferred term frequency in 'Epti 300 mg' column.
Percentages are based on safety population.
Treatment Dose level: Placebo (Studies ALD403-CLIN-002, -005, -006, and -011), Epti 10 mg (Study ALD403-CLIN-005), Epti 30 mg (Studies ALD403-CLIN-005 and -006) Epti 100 mg (Studies ALD403-CLIN-005, -006, -011), Epti 300 mg (Studies ALD403-CLIN-005, -006, -011, and -013), Epti 1000 mg (Study ALD403-CLIN-002).
Source: Table 14.3.2.4.1.3 (ISS TFLs)

Hypersensitivity and Anaphylactic Events

Including adverse events with a MedDRA coded SOC of Immune System Disorders and preferred terms of hypersensitivity, anaphylactic reaction, and anaphylactoid reaction.

By convention, AEs that occurred during the study drug infusion, led to a specific clinical action by the investigator and were determined by the investigator to be possible allergic response or infusion reaction were coded to the SOC of Immune System Disorders and the preferred term of hypersensitivity, hereafter referred as "events coded to hypersensitivity".

A medical assessment framework was used, considering the nature of symptoms reported by the investigator and any medical action taken by the investigator, including study drug interruption or standard medical treatment to manage the symptoms. This eased the investigators to determine if these TEAEs could be aggregated into a unifying diagnosis of hypersensitivity. This process allowed for a pragmatic clinical context for risk assessment and consistent medical evaluation across events.

Hypersensitivity and Anaphylactic Events (PS pool)

Events coded to hypersensitivity occurred in 13 (0.9%) PS eptinezumab subjects and no placebo subject. They occurred in all dose groups but did not appear to be dose related. Study drug was discontinued in all 13 (0.9%) PS study subjects with events coded to hypersensitivity.

There were no serious TEAEs of anaphylactic reaction and no events coded to hypersensitivity were serious in the PS pool.

Hypersensitivity and Anaphylactic Events (OE pool)

Events coded to hypersensitivity were the most frequent AESIs, occurring in 23 (1.1%) of OE subjects and no placebo subject. One of those subjects had 2 events coded to hypersensitivity, 1 during the first infusion and 1 during the second infusion, all other had one event (all hypersensitivity-coded events: 24). No association between the occurrence of these events and eptinezumab dose was seen.

Clinical presentation of these events was most commonly reported as being nonspecific allergic-type reactions with symptoms (verbatim terms) including nasal congestion, throat symptoms (scratchiness, tightness), itching, rash, hives, watery eyes, flushing, dizziness, nausea, vomiting, rapid heartbeat, localized swelling or burning sensation, sneezing, coughing, and wheezing. Other symptoms or physical signs characteristic of true immediate-type hypersensitivity reactions (e.g., IgE-mediated), such as urticaria, angioedema, and documented respiratory manifestations were rare. All but 1 of these events lasted 1 day or less. One event (rash) lasted 1.9 days. The majority of subjects received standard medical treatment for these events (or observation only) and all events resolved. Notably, 13 of the 23 OE subjects with events coded to hypersensitivity also had medical histories of allergies to environmental agents or medicines, or atopic diseases such as asthma and allergic rhinitis.

No events coded to hypersensitivity in the OE pool were serious. All of these events were mild (nine grade 1 events) or moderate (fifteen grade 2 events) in severity; none were severe (grade 3).

Events coded to hypersensitivity occurred mostly and in similar proportion either at the first or second infusion. Among the 17 subjects who had events coded to hypersensitivity in multiple dose studies, study drug infusion was interrupted in 16 (0.8%) and discontinued in 15 (0.7%) of the subjects.

One subject had an AESI of anaphylactic reaction of moderate (grade 2) severity during the first infusion of eptinezumab 300 mg. The event was considered by the investigator to be medically important and was therefore classified as serious.

The subject developed erythema, pruritus, nasal congestion, and hives across his entire body, with first symptoms starting 7 minutes after the start of the initial infusion of 300 mg eptinezumab (day 0). There were no symptoms referable to cardiovascular and/or respiratory compromise.

The subject was administered epinephrine 0.3 mg with no discernible effect within 10 minutes. Intravenous diphenhydramine 50 mg was then administered, and an almost immediate response was noted. The subject was withdrawn from additional study drug dosing due to this.

Due to the lack of respiratory or cardiovascular manifestations and no response to epinephrine but an immediate response to IV diphenhydramine, the MAA assessed the event differently as allergic reaction and infusion day reaction under the larger classification of immune system disorders. Nevertheless, the event is maintained as an (serious) anaphylactic reaction in the integrated safety database.

Hypersensitivity reactions including multiple TEAE terms related to hypersensitivity (AESIs)

Besides events coded to hypersensitivity, other TEAE preferred terms potentially related to hypersensitivity reactions have been considered. These included events coded to multiple preferred terms of urticaria, flushing/hot flushes, rash and pruritus. Hypersensitivity reactions (including multiple TEAE terms related to hypersensitivity) occurred in the PS pool at an incidence of 3.8% in the eptinezumab 300 mg group, 2.6% in the eptinezumab 100 mg group, and 1.2% in the placebo group.

Events Associated with Suicide (AESIs)

Adverse events of special interest in the psychiatric disorders SOC occurred with similar frequency in OE subjects (0.5%) and placebo subjects (0.4%), with no apparent relationship to eptinezumab dose. The most frequently occurring AESI in this SOC was suicidal ideation which occurred in similar proportions of OE and placebo subjects (0.4% in each).

Cardiovascular Events (AESIs)

Cardiovascular AESIs occurred infrequent and with similar frequency in eptinezumab treated and in placebo treated subjects of the PS and OE pool.

Nervous System Events (AESIs)

Nervous system AESIs occurred infrequent in the PS and OE pool. The only PT of seizure occurred in 2 subjects treated with 300 mg eptinezumab (< 0.1% of the OE population, both events were serious and assessed as not related) and in none of the placebo subjects.

Hepatic Events (AESIs)

Hepatic AESIs occurred infrequently (≤ 7 [0.3%] OE subjects) and in similar proportions of eptinezumab and placebo subjects. The occurrence of hepatic AESIs did not appear to be dose related. None of the hepatic AESIs in the OE subjects were serious and none were severe. All of the hepatic AESIs were significantly confounded by an array of risk factors and concomitant medication usage.

Events Associated with Study Drug Infusion (AESIs)

Adverse events of special interest in the general disorders and administration site conditions SOC occurred with similar frequency in OE subjects (1.5%) and placebo subjects (1.1%). By definition, these AESIs occurred on an infusion day or within the first 7 days of infusion. The occurrence of AESIs in this SOC did not appear to be dose related; however, the low incidence precludes any definitive conclusion. The majority of these events were infusion site-related AESIs (most frequent: infusion site extravasation) which are accounted for by the route of administration.

Adverse events of special interest leading to study drug discontinuation (AESIs)

AESIs leading to study drug discontinuation occurred in 21 (1%) OE subjects and no placebo subjects. Events coded to hypersensitivity were the most frequent events (15 (0.7% of) subjects of the OE population) with the majority of subjects (10 of 15) received eptinezumab 300 mg. Three OE subjects had study drug discontinued due to hypertension or blood pressure increased. Other AESIs leading to study drug discontinuation occurred in 1 subject each.

Adverse events of special interest leading to interruption of study drug infusion (AESIs)

AESIs leading to interruption of study drug infusion occurred in 1.8% OE subjects and in 0.6% placebo subjects. The most frequent reasons were infusion site extravasation, events coded to hypersensitivity and infusion site pain. Overall, the occurrence of all those events did not appear to be dose related, but events coded to hypersensitivity only occurred in subjects treated with eptinezumab, none in subjected treated with placebo. Moreover, a serious AESI of anaphylactic reaction led to interruption of study drug infusion occurred in 1 OE subject.

Laboratory findings

Clinical laboratory tests, including hematology and serum chemistry, were obtained in all 5 studies at screening and/or baseline and at regular intervals throughout the treatment and follow-up phases.

In each of the 5 clinical studies, mean clinical laboratory values at baseline were comparable in the eptinezumab and placebo groups. Mean clinical laboratory values and mean changes from baseline at all post-baseline visits were generally similar in the eptinezumab groups and the placebo groups. No dose related trends and no trends over time were observed.

Liver function test elevations occurred infrequently and in similar proportions of placebo and eptinezumab subjects. The incidence of these elevations did not appear to be dose related. There were no data to suggest that treatment with eptinezumab was associated with any liver toxicity.

TEAEs related to abnormalities in hematology and biochemistry tests occurred infrequently (< 1% of subjects in any eptinezumab group for any particular clinical laboratory-related preferred term in the Investigations SOC) and in similar proportions of all PS eptinezumab dosing groups and in placebo subjects. There was no apparent relationship between eptinezumab dose and the occurrence of clinical laboratory-related AEs.

The most frequently occurring TEAEs related to clinical laboratory findings were ALT increased (0.4% of PS eptinezumab subjects and 0.7% of placebo subjects) and lipids increased (0.4% of PS eptinezumab subjects and 0.3% of placebo subjects). No clinical laboratory-related TEAE was serious and all laboratory-related TEAEs in eptinezumab-treated subjects were mild or moderate in severity. One subject who received placebo had a grade 3 AESI of ALT increased.

Overall, the mean vital signs (SBP, DBP, heart rate, weight, and BMI) at baseline were comparable for eptinezumab and placebo subjects. There were no notable differences in post-baseline mean values or in mean changes from baseline between eptinezumab and placebo subjects. Mean changes from baseline were small and were similar for each eptinezumab dose group and the placebo group. There were no obvious trends over time in mean vital signs values.

TEAEs related to vital signs assessments occurred in < 2% of eptinezumab and placebo subjects and in similar proportions of eptinezumab and placebo subjects with no apparent relationship to eptinezumab dose.

Means for ECG parameters were comparable across all eptinezumab groups and the placebo group at baseline and at all post-baseline visits. Mean changes from baseline were small and comparable across all treatment groups at all post-baseline visits. There were no notable trends over time in any of these parameters in any of the treatment groups.

Individual ECG-related TEAEs occurred infrequently (i.e., no more than 3 OE subjects each [< 0.1%]). Treatment-emergent AEs of QT prolongation occurred in 3 of 2,076 OE subjects (0.1%) and 1 of 791 (0.1%) placebo subjects, all of them participated in study 002 in which subjects received either a single dose of

eptinezumab 1000 mg or placebo. All of these events were considered mild, and none of these subjects had a QTcF interval > 500 msec. T wave inversions occurred in 3 of 2,076 OE subjects (0.1%) and no placebo subjects.

Safety in special populations

A total of 23 subjects (14 (1%) eptinezumab subjects and 9 placebo subjects) in the PS pool were between the ages of 65 and 74 years; no subjects were 75 years of age or older. Due to the small numbers of subjects in the older age groups, no meaningful statements can be made regarding the AE profiles of eptinezumab in these age groups.

No clinically meaningful difference in terms of adverse events was observed between males and females.

African-American/Black subjects comprised 8.7% of PS eptinezumab subjects (N = 119) and 11.6% of placebo subjects (N = 68) only. Overall, African-American/Black subjects tended to have higher rates of TEAEs, including those treated with placebo even though the pattern of TEAEs seen in both white and black subjects was generally similar to that seen in all subjects in the PS pool.

The incidence of TEAEs by preferred term for black and white subjects revealed some notable differences. For instance, the incidences of nausea, vomiting, events coded to hypersensitivity and dizziness, among others, were higher among black eptinezumab subjects than black placebo subjects, and the difference between black eptinezumab and black placebo subjects was greater than the difference between white eptinezumab subjects and white placebo subjects.

AESIs generally occurred more frequently among black subjects regardless of SOC or preferred term in both the eptinezumab and placebo groups and also the proportion of black eptinezumab subjects with TEAEs leading to study drug discontinuation was higher (5.0%) than the proportion of black placebo subjects (none) and higher than in white subjects (2.1% and 1.6%, respectively).

Presently, there is no evidence linking eptinezumab with any negative impact on human pregnancy. However, due to the paucity of available human pregnancy data at the present time point, no definitive conclusions about the risks, if any, of eptinezumab use during pregnancy currently can be drawn.

Immunological events

The overall incidence of treatment emergent ADA and NAb detected in studies 005, 006, 011 and 013 was 15.9 % and 6.2% respectively. In study 002, for which a different ADA assay method was used, treatment-boosted anti-eptinezumab immunoreactivity was detected in 13.6%.

The incidences of TEAEs and AESIs were evaluated by ADA/Nab status (positive versus negative), ADA titer category and ADA titer value observed from the sample taken prior to the dose associated with the TEAE/AESI and the next available sample after the dose.

In Studies 005, 006, 011, and 013, 23 (1.2%) of 1,995 eptinezumab-treated subjects had AESIs coded to hypersensitivity), all of them mild or moderate as graded by the investigators. Further, a single, serious AESI of anaphylactic reaction of grade 2 severity occurred during the day 0 infusion of eptinezumab 300 mg (differently assessed by the company).

There was no apparent relationship of any of these events to pre-existing or treatment-emergent ADA or NAb positive status, ADA titer category or eptinezumab dose. There was no evidence for a risk of immune complex-related hypersensitivity, consistent with the relatively low ADA titers observed for all eptinezumab dose.

Safety related to drug-drug interactions and other interactions

Eptinezumab like most therapeutic proteins is not expected to be metabolized by liver CYP450 enzymes. Non-specific mechanisms of clearance and proteolysis are the primary expected routes of elimination. For these reasons, administration of concomitant medications that are small molecules is not expected to alter the PK of eptinezumab.

This is supported by results of the population PK analysis, in which migraine preventive medications were no significant covariate in models of volume of distribution and total plasma clearance for eptinezumab. Moreover, the coadministration with sumatriptan did not alter the single dose PK of eptinezumab and vice versa.

In both the PS and OE pools, the percentages of subjects with a new or changed dose of a CV medication after the first administration of study drug were low and similar across the eptinezumab and placebo groups. Among these groups, the percentages of subjects with a new or increased dose of a CV medication for an indication of high blood pressure or hypertension were also low and generally similar across the eptinezumab and placebo groups.

Discontinuation due to AES

Treatment-emergent adverse events leading to study drug discontinuation occurred infrequently and in a slightly higher proportion of subjects treated with eptinezumab (2.5% (PS pool) and 1.9% (OE pool)) than in placebo subjects (1.4% and 1.0%, respectively). The differences between the eptinezumab-treated and the placebo-treated patients are for both pools almost entirely accounted for by the occurrence of hypersensitivity-coding AEs that did not occurred in any of the placebo-treated patients.

Further AE that led to treatment discontinuation included hypertension and anaphylactic reaction.

Post marketing experience

Eptinezumab is approved in the USA since February 2020 for the preventive treatment of migraine in adults. The first PBRER for eptinezumab, covering the time period of 21-Feb-2020 to 20-Aug-2020, was submitted with this application. During this first postmarketing reporting period, a total of 70 AEs of which 6 were serious, including one case of hypersensitivity and one case of anaphylactic reaction, were reported.

Per FDA request, cases of events for myocardial infarction, stroke, hypertension and severe constipation are being monitored. In the period covered by the submitted PBRER, no cases with these events were received, no significant safety issues have been identified and no safety-related changes were made to the RSI.

2.6.9. Discussion on clinical safety

The numbers of subjects exposed to eptinezumab in the PS pool and in the OE pool and the numbers of doses these subjects received provide sufficient exposures to evaluate the safety of eptinezumab for administration every 12 weeks by IV infusion. A total of 1,288 PS subjects received at least 2 doses of eptinezumab

approximately 12 weeks apart, and 526 PS subjects received 4 doses of eptinezumab approximately 12 weeks apart.

In the OE pool, a total of 2,076 subjects with migraine received at least 1 dose of eptinezumab, representing 1,615 patient years of exposure, 1,334 subjects had at least 6 months of exposure to eptinezumab (2 doses plus follow-up for at least 5 half-lives (130 days)) and a total of 490 subjects had 1 year of exposure to eptinezumab (4 doses and follow-up).

The large majority of all subjects received their complete study drug dose without interruption. In the small proportion of subjects for whom the dose was interrupted (< 2% of eptinezumab 300-mg and 100-mg subjects (PS), < 4% at any dose (OE)), most went on to receive their full dose. There was no apparent association between eptinezumab dose and the occurrence of dose interruption, and the proportions of subjects with a dose interruption were similar in the eptinezumab and placebo groups at each scheduled dose day.

The majority of all subjects were white (> 85%) and female (> 80%) with a mean of age of approximately 40 years, reflecting the demographic characteristics of people with migraine in the general population.

Hypertension, hyperlipidemia, diabetes, and circulation conditions were notably lower among subjects in the PS pool than has been reported in community-based surveys of people with migraine. This reflects the exclusion of subjects with clinically significant cardiovascular conditions from the clinical studies. The most frequently occurring cardiovascular risk factor was obesity. This is similar to proportions of subjects with EM and CM in community-based surveys.

Section 4.4 Special Warnings and Precautions for Use was adapted to include patients with a history of cardiovascular disease and cardiovascular risk factors. In addition, the wording of section 4.4 was amended to state that patients with a history of neurological diseases or patients with psychiatric conditions that were uncontrolled and/or untreated were excluded from the clinical studies and that therefore only limited safety data are available in these patients.

The proportions of subjects with 1 or more TEAEs were similar for all PS subjects who received eptinezumab (53.6%), eptinezumab 300 mg (54.2%), eptinezumab 100 mg (51.1%), and placebo (51.5%) and were similar to those of subjects in the OE pool (eptinezumab at any dose (54.8%), eptinezumab 300 mg (56.7%), eptinezumab 100 mg (52.2%) and placebo (52.3%). No relationship between eptinezumab dose and the occurrence of 1 or more TEAEs was seen.

Most frequent (≥ 2%) TEAEs that occurred with greater incidence in any eptinezumab dose group than in the placebo group (in descending order of frequency in PS eptinezumab subjects) were upper respiratory tract infection (URTI), nasopharyngitis, nausea, fatigue, dizziness, urinary tract infection, arthralgia, back pain, influenza, cough, pain in extremity, and pyrexia. Of those TEAEs listed, the applicant agreed to include fatigue in the List of Adverse Reactions in section 4.8, since its frequency is likely to be higher than 1.1% over placebo.

The large majority of TEAEs in all treatment groups were mild or moderate in severity. TEAEs of grade 3 (severe) or higher severity occurred infrequently and in similar proportions of all PS eptinezumab and placebo subjects (3.1%). Treatment-emergent adverse events leading to interruption of study drug infusion occurred infrequently and in a slightly higher proportion of subjects treated with eptinezumab (1.7% (PS pool) and 1.9% (OE pool)) than in placebo subjects (1.0% and 0.8%, respectively). The differences between the eptinezumab-treated and the placebo-treated patients are for both pools almost entirely accounted for by the occurrence of hypersensitivity-coding AEs (n= 8 and n= 16 in the PS and OE pool, respectively) that did not occurred in any of the placebo-treated patients. Further TEAEs that led to interruption of study drug infusion that occurred in more than 1 subject in any treatment group included infusion site extravasation and infusion site pain and

nausea. All other TEAEs that led to interruption of study drug infusion occurred in single eptinzumab subjects only, including an anaphylactic reaction (assessed differently by the company) in one 300 mg eptinezumab subject of the OE pool. The overall incidence of treatment-related TEAEs, as determined by the investigator, was 12.9% for subjects treated with eptinezumab and 8.2% of placebo subjects in the PS pool and 14.2% for subjects treated with eptinezumab and 9.4% of placebo subjects in the OE pool, respectively. The incidence of treatment-related TEAEs increased with eptinezumab dose. Nasopharyngitis and hypersensitivity reactions occurred in ≥ 2% of subjects in any eptinezumab group of the PS pool with an incidence that was at least 2% greater in the eptinezumab 300 mg or 100 mg groups than in the placebo group. They are considered adverse drug reactions to eptinezumab.

Long-term TEAEs were evaluated using pooled data from Studies 006 and 013. TEAEs with onset between week 24 and week 36 in 22.9% of eptinezumab subjects and 19.9% of placebo subjects. The most frequently occurring (⩾ 1.0% of eptinezumab subjects) of these TEAEs were nasopharyngitis, upper respiratory tract infection, nausea and sinusitis and occurred in similar proportions in eptinezumab and placebo subjects.

TEAEs with onset between week 36 and week 48 occurred in 15.3% of eptinezumab subjects and 10.2% of placebo subjects. The only TEAE that occurred in ⩾ 1% of eptinezumab subjects was nasopharyngitis, which occurred in 1.9% of eptinezumab subjects (including 2.7% of eptinezumab 300-mg subjects and 1.7% of eptinezumab 100-mg subjects) and no placebo subjects.

Although TEAEs occurred infrequently during the third and fourth dosing intervals, the types of TEAEs that did occur were similar to the types of TEAEs that occurred across the dosing intervals in the OE pool, and were similar to the types of TEAEs that occurred after the first dose in the OE pool.

As per 120-Days Safety update, the safety profile in the OE pool observed with longer-term exposure to eptinezumab (median [min, max] of 272 [13, 757] days) remained unchanged from that presented in the SCS. There was no new pattern of TEAEs identified during this period.

No AEs of overdose have been reported. No specific treatment for overdose with eptinezumab exists. The route and proposed posology of 100 mg (300 mg) Q12W does not enhance the risk of overdose. However, accidental overdosing can never be totally excluded. As per the SmPC, symptomatic treatment/supportive measures are required in the event of overdose.

Abuse potential for eptinezumab is not suspected based on its mode of action, the absence of any indicative preclinical findings and the absence of any TEAEs suggesting abuse potential in the PS and OE pool populations of the clinical development program.

There were no subject deaths in any of the 5 clinical studies included in the integrated safety database or in any of the 7 clinical pharmacology studies. No life-threatening AEs occurred in any eptinezumab-treated subject.

SAEs occurred infrequently within the PS pool with 1.3% of all PS eptinezumab subjects and 1.5% of PS placebo subjects. The proportions of subjects with SAEs were similar in each eptinezumab dose group and the placebo group, and no relationship to eptinezumab dose was observed. The frequency of SAEs was slightly higher in the OE pool: 1.7% of all OE eptinezumab subjects and 1.4% of OE placebo subjects.

Outside the safety pools of the SCS, two SAEs were reported in the clinical pharmacology studies, and two additional in study 013, all of them assessed as not related.

AESIs occurred more frequently in eptinezumab-treated subjects than in placebo-treated subjects. The large majority of AESIs were mild or moderate in severity. As of 31 May 2018 (120-Day safety update) the incidence

of AESIs in the 300 mg group has increased by < 1% from 10.4% in the original application to 11.3% in the safety update period. The majority of newly reported AESIs were infusion site extravasation and infusion site pain. Serious AESIs occurred infrequently ((0.4%) OE subjects and 3 (0.4%) placebo subjects)).

Overall, the incidence of events coded to hypersensitivity has been low (<1%) and events have been of mild to moderate intensity.

By convention, AEs that occurred during the study drug infusion, led to a specific clinical action by the investigator and were determined by the investigator to be possible allergic response or infusion reaction were coded to the SOC of Immune System Disorders and the preferred term of hypersensitivity, hereafter referred as "events coded to hypersensitivity". Serious hypersensitivity, including anaphylactic reactions, has been included in the SmPC in the Special Warnings and Precautions for Use section (4.4), and hypersensitivity to eptinezumab or to any of the excipients listed in SmPC section 6.1 have been defined as a contraindication. Moreover are hypersensitivity reactions and anaphylactic reaction included in SmPC section 4.8 Undesirable effects.

Besides events coded to hypersensitivity, other TEAE preferred terms potentially related to hypersensitivity reactions (e.g., multiple preferred terms of urticaria, flushing/hot flushes, rash and pruritus) have been considered, and altogether they were summarized as hypersensitivity reactions. Hypersensitivity reactions (including multiple TEAE terms related to hypersensitivity) occurred in the PS pool at an incidence of 3.8% in the eptinezumab 300 mg group, 2.6% in the eptinezumab 100 mg group, and 1.2% in the placebo group and are considered an adverse drug reaction to eptinezumab.

Adverse events of special interest in the psychiatric disorders SOC occurred with similar frequency in OE subjects (0.5%) and placebo subjects (0.4%), with no apparent relationship to eptinezumab dose. The most frequently occurring AESI in this SOC was suicidal ideation which occurred in similar proportions of OE and placebo subjects (0.4% in each).

Cardiovascular AESIs occurred infrequently and with similar frequency in eptinezumab treated and in placebo treated subjects of the PS and OE pool.

Nervous system AESIs occurred infrequent in the PS and OE pool. The only PT of seizure occurred in 2 subjects treated with 300 mg eptinezumab (< 0.1% of the OE population, both events were serious and assessed as not related) and in none of the placebo subjects.

Hepatic AESIs occurred infrequently (≤ 7 [0.3%] OE subjects) and in similar proportions of eptinezumab and placebo subjects. The occurrence of hepatic AESIs did not appear to be dose related. None of the hepatic AESIs in the OE subjects were serious and none were severe. All of the hepatic AESIs were significantly confounded by an array of risk factors and concomitant medication usage.

Adverse events of special interest in the general disorders and administration site conditions SOC occurred with similar frequency in OE subjects (1.5%) and placebo subjects (1.1%). By definition, these AESIs occurred on an infusion day or within the first 7 days of infusion. The occurrence of AESIs in this SOC did not appear to be dose related; however, the low incidence precludes any definitive conclusion. The majority of these events were infusion site-related AESIs (most frequent: infusion site extravasation) which are accounted for by the route of administration.

AESIs leading to study drug discontinuation occurred in 21 (1%) OE subjects and no placebo subjects. Events coded to hypersensitivity were the most frequent events (15 (0.7% of) subjects of the OE population) with the majority of subjects (10 of 15) received eptinezumab 300 mg. Three OE subjects had study drug discontinued

due to hypertension or blood pressure increased. Other AESIs leading to study drug discontinuation occurred in 1 subject each.

AESIs leading to interruption of study drug infusion occurred in 1.8% OE subjects and in 0.6% placebo subjects. The most frequent reasons were infusion site extravasation, events coded to hypersensitivity and infusion site pain. Overall, the occurrence of all those events did not appear to be dose related, but events coded to hypersensitivity only occurred in subjects treated with eptinezumab, none in subjects treated with placebo. Moreover, a serious AESI of anaphylactic reaction led to interruption of study drug infusion occurred in 1 OE subject.

In each of the 5 clinical studies in subjects with migraine, mean clinical laboratory values at baseline were comparable in the eptinezumab and placebo groups. Mean clinical laboratory values and mean changes from baseline at all post-baseline visits were generally similar in the eptinezumab groups and the placebo groups. No dose related trends and no trends over time were observed.

Liver function test elevations occurred infrequently and in similar proportions of placebo and eptinezumab subjects. The incidence of these elevations did not appear to be dose related. There were no data to suggest that treatment with eptinezumab was associated with any liver toxicity.

TEAEs related to abnormalities in hematology and biochemistry tests occurred infrequently (< 1% of subjects in any eptinezumab group for any particular clinical laboratory-related preferred term in the Investigations SOC) and in similar proportions of all PS eptinezumab dosing groups and in placebo subjects. There was no apparent relationship between eptinezumab dose and the occurrence of clinical laboratory-related AEs.

The most frequently occurring TEAEs related to clinical laboratory findings were ALT increased (0.4% of PS eptinezumab subjects and 0.7% of placebo subjects) and lipids increased (0.4% of PS eptinezumab subjects and 0.3% of placebo subjects). No clinical laboratory-related TEAE was serious and all laboratory-related TEAEs in eptinezumab-treated subjects were mild or moderate in severity. One subject who received placebo had a grade 3 AESI of ALT increased.

Overall, the mean vital signs (SBP, DBP, heart rate, weight, and BMI) at baseline were comparable for eptinezumab and placebo subjects. There were no notable differences in post-baseline mean values or in mean changes from baseline between eptinezumab and placebo subjects. Mean changes from baseline were small and were similar for each eptinezumab dose group and the placebo group. There were no obvious trends over time in mean vital signs values.

TEAEs related to vital signs assessments occurred in < 2% of eptinezumab and placebo subjects and in similar proportions of eptinezumab and placebo subjects with no apparent relationship to eptinezumab dose.

There were no new patterns or trends in vital signs observed during the safety update period of study 013. Mean changes from baseline were small and clinically insignificant.

Means for ECG parameters were comparable across all eptinezumab groups and the placebo group at baseline and at all post-baseline visits. Mean changes from baseline were small and comparable across all treatment groups at all post-baseline visits. There were no notable trends over time in any of these parameters in any of the treatment groups.

Individual ECG-related TEAEs occurred infrequently (i.e., no more than 3 OE subjects each [< 0.1%]). Treatment-emergent AEs of QT prolongation occurred in 3 of 2,076 OE subjects (0.1%) and 1 of 791 (0.1%) placebo subjects. All 3 subjects with TEAEs of QT prolongation participated in Study 002 in which subjects received a single dose of eptinezumab 1000 mg. One subject who received placebo in this study also had a

TEAE of QT prolongation. All of these events were considered mild, and none of these subjects had a QTcF interval > 500 msec.

T wave inversions occurred in 3 of 2,076 OE subjects (0.1%) and no placebo subjects.

ECG data from Study 002 were excluded from the pooled analyses as they were not centrally read.

At the baseline C-SSRS assessment, no OE subject reported any suicidal behaviours; 1 (0.1%) placebo subject reported an actual suicide attempt. During the post-baseline treatment period, 2 (< 0.1%) OE subjects (one eptinezumab 300-mg subject and one eptinezumab 100-mg subject) and no placebo subject reported an actual suicide attempt on the C-SSRS. Narratives for these events inform that both subjects had pertinent medical histories of psychological conditions and current stressors that confound the evaluation of possible causal relationship to eptinezumab.

Only a few subjects eptinezumab subjects (14 (1.0%) and 9 placebo subjects (9 (1.5%)) in the PS pool were between the ages of 65 and 74 years and none was 75 years of age or older, reflecting the eligibility criteria for the studies and the age distribution of patients with migraine in the general population. Due to the small numbers of subjects in the older age groups, no meaningful statements can be made regarding the AE profiles of eptinezumab in these age groups. However, for the age group of ≥ 65 to < 75 years, no grade 3 or higher TEAEs and no serious TEAS were reported.

Due to the small numbers of subjects in the older age groups (≥ 65 < 75 years, ≥ 75 years) included in the clinical trials, the knowledge on the AE profile for patients ≥ 65 years of age is still very limited. Moreover, due to a higher prevalence of cardiovascular, neurological or psychiatric comorbidities and/or the respective risk factors in patients ≥ 65 years of age, special attention should be payed to cardiovascular, neurological or psychiatric AEs.

No clinically meaningful difference in terms of adverse events was observed between males and females.

African-American/Black subjects comprised 8.7% of PS eptinezumab subjects (N = 119) and 11.6% of placebo subjects (N = 68) only, the majority of study subjects was white (88.7% and 85.4%, respectively). The proportion of black subjects was slightly higher in study 006, the 1-year study (4 doses), than in study 011, the 6 month study (2 doses) (11.8% and 7.6%, respectively).

Overall, African-American/Black subjects tended to have higher rates of TEAEs, including those treated with placebo even though the pattern of TEAEs seen in both white and black subjects was generally similar to that seen in all subjects in the PS pool.

The incidence of TEAEs by preferred term for black and white subjects revealed some notable differences. For instance, the incidences of nausea, vomiting, events coded to hypersensitivity and dizziness, among others, were higher among black eptinezumab subjects than black placebo subjects, and the difference between black eptinezumab and black placebo subjects was greater than the difference between white eptinezumab subjects and white placebo subjects.

AESIs generally occurred more frequently among black subjects regardless of SOC or preferred term in both the eptinezumab and placebo groups (19.3% (black eptinezumab subjects) vs. 10.3% (black placebo subjects) and 7.9% (white eptinezumab subjects) vs. 4.4% (white placebo subjects), respectively).

Also the proportion of black eptinezumab subjects with TEAEs leading to study drug discontinuation was higher (5.0%) than the proportion of black placebo subjects (none) and higher than in white subjects (2.1% and 1.6%, respectively).

While some of these findings may reflect possible differences between whites and blacks, such as genetics, others are likely to be artefacts of the small numbers of black subjects and the large numbers of TEAE preferred terms evaluated, which make differences in percentages difficult to interpret. Moreover, differences in baseline characteristics such as mean BMI and medical/surgical history could contribute to the differences in safety findings. Other factors such as regional, socioeconomic and environmental, may also contribute to the difference between black and white subjects in terms of TEAS. For instance, all black patients randomized in Studies 006 and 011 were recruited at sites in the US.

Although, TEAE and AESI incidences were higher in black patients on eptinezumab or placebo: TEAEs: 78 [66%] versus 42 [62%]; AESIs: 23 [19%] versus 7 [10%], as compared to White patients on eptinezumab or placebo: TEAEs: 632 [52%] versus 247 [49%]; AESIs: 96 [7.9%] versus 22 [4.4%], the differences are not striking and the most frequent SOC terms were equally reported between the two groups. At present time there is no known biological plausibility justifying the higher AESI frequency in black patients.

Considering the above mentioned justifications, it can be considered that for the moment available information does not justify addressing specifically this aspect in SmPC.

Presently, there is no evidence linking eptinezumab with any negative impact on human pregnancy. However, due to the paucity of available human pregnancy data at the present time point, no definitive conclusions about the risks, if any, of eptinezumab use during pregnancy currently can be drawn.

Use in pregnant woman is included in the RMP as (safety concern of) missing information and pre-eclampsia is included as (safety concern of) important potential risk. Moreover, a post-marketing pregnancy program is planned as additional pharmacovigilance activity.

Clinical withdrawal or rebound effects to eptinezumab have not been observed in the pivotal clinical studies pool.

The potential effects of eptinezumab on the ability to drive or operate machinery or on mental ability have not been explicitly studied. Dizziness and fatigue occurred in more than 2% and all other TEAEs relevant to these abilities occurred in < 0.5% of the OE subjects with similar proportions observed in placebo subjects. This is reflected in the SmPC as follows: VYEPTI has no or negligible influence on the ability to drive and use machines.

The incidence of treatment emergent ADA and NAb detected in the five clinical studies was up to 17.4 (range 11.2-17.4)% and 7.8 (range 3.7-7.8)%, respectively. There was neither an apparent relationship of events coded to hypersensitivity and one single event of anaphylactic reaction (differently assessed by the company) to pre-existing or treatment-emergent ADA or NAb positive status, ADA titer category or eptinezumab dose, nor any evidence for a risk of immune complex-related hypersensitivity. In Study 002, for which a different ADA assay method was used, 11 subjects (13.6%) had treatment-boosted anti-eptinezumab immunoreactivity results.

Eptinezumab like most therapeutic proteins is not expected to be metabolized by liver CYP450 enzymes. Non-specific mechanisms of clearance and proteolysis are the primary expected routes of elimination. For these reasons, administration of concomitant medications that are small molecules is not expected to alter the PK of eptinezumab.

This is supported by results of the population PK analysis, in which migraine preventive medications were no significant covariate in models of volume of distribution and total plasma clearance for eptinezumab. Moreover, the coadministration with sumatriptan did not alter the single dose PK of eptinezumab and vice versa.

In both the PS and OE pools, the percentages of subjects with a new or changed dose of a CV medication after the first administration of study drug were low and similar across the eptinezumab and placebo groups. Among these groups, the percentages of subjects with a new or increased dose of a CV medication for an indication of high blood pressure or hypertension were also low and generally similar across the eptinezumab and placebo groups.

Treatment-emergent adverse events leading to study drug discontinuation occurred infrequently and in a slightly higher proportion of subjects treated with eptinezumab (2.5% (PS pool) and 1.9% (OE pool)) than in placebo subjects (1.4% and 1.0%, respectively). The differences between the eptinezumab-treated and the placebo-treated patients are for both pools almost entirely accounted for by the occurrence of hypersensitivity-coding AEs (n= 13 and n= 15 in the PS and OE pool, respectively) that did not occurred in any of the placebo-treated patients.

The only further AE that led to treatment discontinuation that occurred in more than 1 eptinezumab-treated pool subjects and no placebo subject was hypertension. All other TEAEs leading to study drug discontinuation occurred in 1 eptinezumab and/or 1 placebo subject each, including an anaphylactic reaction (assessed differently by the company) in one 300 mg eptinezumab subject of the OE pool.

2.6.10. Conclusions on clinical safety

Eptinezumab at all doses tested was generally well tolerated in migraine patients.

Only few discontinuation due to AEs have been registered in clinical trials and most events have been judged as been manageable and being of mild to moderate intensity.

AESIs in the eptinezumab clinical development program included hypersensitivity and anaphylactic events, events associated with suicide, cardiovascular, nervous system and hepatic events as well as events associated with study drug infusion. They occurred more frequently in eptinezumab-treated subjects than in placebo-treated subjects with the large majority of AESIs were mild or moderate in severity.

Adverse events of special interest in the general disorders and administration site conditions SOC occurred with similar frequency in subjects treated with eptinezumab (1.5%) than in placebo subjects (1.1%). The majority of these events were infusion site-related AESIs (most frequent: infusion site extravasation) which are accounted for by the route of administration. Moreover, rash and pruritus occurred slightly more frequent in OE subjects than in placebo subjects.

The incidence of events coded to hypersensitivity has been low (<1%) and events have been of mild to moderate intensity. All events occurred in subjects treated with eptinezumab. One subject had a serious AESI of anaphylactic reaction of moderate severity, as determined by the investigator. This event was assessed differently by the company with the terms of allergic reaction and infusion day reaction based on the lack of respiratory or cardiovascular manifestations and the pattern of response to the medications used for acute management of the event. However, further cases of anaphylactic reactions and one case of serious hypersensitivity reaction were reported during the further clinical development program and from postmarketing sources, which led to the integration of anaphylactic reaction in the SmPC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

Important identified risks	None
Important potential risks	Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension Pre-eclampsia
Missing information	Use in pregnant women Long-term safety

2.7.2. Pharmacovigilance plan

Table of Ongoing and planned additional pharmacovigilance activities in the PV Plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones[1]**	**Due Dates[1]**
Category 3 – Required Additional Pharmacovigilance Activities				
Study 19756N Long-term cardiovascular safety and real-world use of eptinezumab. An observational, historical cohort study of patients initiating eptinezumab in routine clinical practice **Planned**	• To assess the long-term cardiovascular risk in patients treated with eptinezumab, in comparison to appropriate control cohorts of patients with migraine who were not treated with eptinezumab • To evaluate the impact of a known history of cardiovascular diseases on the long-term cardiovascular risk • To characterize the utilization of eptinezumab in routine clinical practice	*Important potential risks*: • Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension *Missing information*: • Long-term safety	• Launch date reached in all relevant countries: 01-Jan-2023 • Database specific study progress reports: 30-Jun-2026[2] • End of study period:31-Dec-2028[3] • Full data availability in all healthcare databases: 31-Dec-2029 • Database analyses finalized: 30-Jun-2030	The study protocol should be submitted for PRAC review / approval within 3 months from MA granting The final study report is estimated to be available by 31-Dec-2030

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones[1]	Due Dates[1]
			• Individual database study reports: 30-Sep-2030 • Final study report: 31-Dec-2030	
Study 19419N A prospective, comparative pregnancy exposure registry cohort analysis of maternal, fetal and infant safety in women exposed to eptinezumab as compared to two migraine control cohorts unexposed to eptinezumab in the United States. **Planned**	• To prospectively estimate the frequency of selected maternal, fetal and infant outcomes in women with migraine exposed to eptinezumab during pregnancy. These outcomes will be compared with two migraine control cohorts unexposed to eptinezumab	*Important potential risks*: • Pre-eclampsia *Missing information*: • Use in pregnant women	• Launch date in the US: 06-Apr-2020 • Begin of study period: 06-Apr-2020 • Interim report[4]: 31-Dec-2028 • End of study period: 30-Jun-2034 • Final study report: 31-Dec-2034	The final study report is estimated to be available by 31-Dec-2034
Study 19420N Pregnancy, fetal and infant outcomes of pregnancies exposed to eptinezumab compared to two migraine control cohorts unexposed to eptinezumab: a claims database study in the United States. **Planned**	• To assess the pregnancy, fetal and infant outcomes of women with migraine exposed to eptinezumab during pregnancy compared to two unexposed control populations.	*Important potential risks*: • Pre-eclampsia *Missing information*: • Use in pregnant women	• Launch date in the US: 06-Apr-2020 • Begin of study period: 06-Apr-2020 • End of study period: 30-Jun-2027 • Full data availability: 30-Jun-2028 • Final study report: 31-Dec-2028	The final study report is estimated to be available by 31-Dec-2028

[1]All milestone and timeline estimates are conditional to the actual marketing authorization date and market access issues

[2]Study progress reports after 2 years of data since the first recorded use of eptinezumab have been accumulated in the respective health care databases, and assuming a lag-time of data availability in the databases of 1 year. In databases with longer lag-times, the milestone date would be delayed by the additional lag-time.

[3]Assuming a lag-time of data availability in the databases of 1 year. In databases with a lag-time of up to 2 years, the study period would end up to one year earlier to ensure compliance with the milestone 'Database analyses finalized'.

[4]An interim report is planned at the time of the final study report for the retrospective pregnancy cohort study 19420N (planned for 31-Dec-2028). In case the final study report for 19420N is delayed, the interim report milestone if 19419N would be updated accordingly. An interim report will not be produced, if study 19420N is finalized less than 1 year prior to study 19419N

For the Real-World Use and Long-term Cardiovascular Safety Study, the full study protocol should be submitted for PRAC review and approval within 3 months after marketing authorisation (MA) granting.

Routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures (RMMs) put in place for Vyepti.

2.7.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	Routine risk minimisation measures: Section 4.4 (Special Warnings and Precaution for use) of the proposed SmPC includes information that patients with a history of cardiovascular disease were excluded from the clinical trials and no safety data are available for these patients. Section 4.4 of the proposed SmPC also includes information that limited data is available in patients with cardiovascular risk factors. No additional risk minimisation measures	Additional pharmacovigilance activities: Long-term Cardiovascular Safety and Real-World Use of Eptinezumab Study (Study 19756N) (The study protocol should be submitted for PRAC review / approval within 3 months from MA granting)
Important potential risk: Pre-eclampsia	Routine risk minimisation measures: Section 4.6 (Fertility, Pregnancy and Lactation) of the proposed SmPC describes states that limited data is available on use in pregnancy and includes advice that it is preferable to avoid the use of eptinezumab during pregnancy. No additional risk minimisation measures	Additional pharmacovigilance activities: Eptinezumab Post-marketing Pregnancy Program (Study 19419N and Study 19420N)
Missing information: Use in pregnant women	Routine risk minimisation measures: Section 4.6 (Fertility, Pregnancy and Lactation) of the proposed SmPC describes the (limited) data available on use in pregnancy and advice that it is preferable to avoid the use of eptinezumab during pregnancy. No additional risk minimisation measures	Additional pharmacovigilance activities: Eptinezumab Post-marketing Pregnancy Program (Study 19419N and Study 19420N)
Missing information: Long-term safety	No routine or additional risk minimisation measures	Additional pharmacovigilance activities: Long-term Cardiovascular Safety and Real-World Use of Eptinezumab Study (Study 19756N)

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20.02.2020. The new EURD list entry will therefore use the {EBD} {IBD} to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vyepti (eptinezumab) is included in the additional monitoring list as it contains new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Migraine is a chronic neurological disease characterized by severe headache attacks with associated hypersensitivity to environmental stimuli, as well as gastrointestinal, cognitive, and vestibular symptoms that can be severe and disabling (Buse et al. 2009). Typically, the headaches affect one half of the head, are pulsating in nature, and last from 4 to 72 hours without treatment. The disease is associated with higher frequencies of depression, anxiety disorders, sleep disturbances, cardiovascular risk, chronic pain syndromes, and suicide attempts.

The therapeutic goal is to reduce the frequency and severity of migraine attacks, as well as the need for acute headache medication use.

3.1.2. Available therapies and unmet medical need

In case of infrequent migraine attacks (less than 2 times per month), treatment is limited to acute medications that include: triptans, nonsteroidal anti-inflammatory drugs, combination of analgesics, opioids, and ergots.

In case of frequent migraine attacks (2-6 times or more per month) prophylactic drugs are introduced on a daily basis, including antihypertensive, anti-epileptic, or antidepressant drugs. Most of the commonly used prophylactic drugs have a registered indication, however others are used off-label with limited evidence of efficacy. The safety profile of these drugs is not optimal with neurological AEs including dizziness, vertigo, nausea, anorexia, fatigue, memory problems, paraesthesia; often requiring dose titration, and carrying contraindications and warnings.

As a new therapeutic class, 3 other anti-CGRP mAb therapies for SC administration have recently been authorised. The rapid onset of treatment effect and the less frequent administration scheme, in conjunction with a good tolerability and safety profile are meaningful advances of these new therapies.

Eptinezumab is the first anti-CGRP treatment developed for the intravenous route of administration. The IV route and the less-than–monthly treatment regimen might be preferred by specific patient groups. Eptinezumab for IV administration may therefore complement the therapeutic landscape of anti-CGRP treatments for the prevention of migraine.

3.1.3. Main clinical studies

The eptinezumab clinical program was comprised of 12 clinical studies, hereof 2 phase 3 studies, and 1 open-label safety in the intended indication “prophylaxis of migraine in adults”.

The 2 pivotal Phase 3 efficacy studies were both randomized, double-blind, placebo-controlled studies. Study **ALD403-CLIN-006** included patients with frequent episodic migraine, defined as 4 to 14 MHDs/month at baseline.

Study **ALD403-CLIN-011** included patients with chronic migraine, defined as ≥15 to ≤26 headache days of which at least 8 with features of migraine.

Up to six (Study 011) and 12 months (Study 006) of placebo-controlled data are available from the 2 pivotal studies.

Key inclusion criteria in the 2 pivotal studies specified that subjects be adults with a history of migraine with or without aura. Exclusion criteria were generally similar across both studies, with minor differences due to the disease state (EM or CM). 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) were included in Study 011.

The following dose regimes of IMP were evaluated, given once every 12 weeks as an intravenous infusion:

Study 006: 30 mg, 100 mg, 300 mg eptinezumab or placebo in a 1:1:1:1 ratio.

Study 011: 100 mg, 300 mg eptinezumab or placebo in a 1:1:1 ratio.

3.2. Favourable effects

For patients with episodic migraine (study 006), the superiority over placebo was demonstrated for both, the 300 mg and the 100 mg dosing regimen:

The primary endpoint was statistically significant for the 300 mg and 100 mg treatment groups. Despite this statistical significance, the mean difference from placebo was relatively modest (300 mg: - 1.11/ 100 mg: -0.69). Although the effect size of the 30 mg dose regimen was numerically greater than the 100 mg arm (-0.82), using the decision rule, the 30 mg arm was considered not statistically significant.

The key secondary endpoints were supportive for the primary endpoint analysis:

The 300 mg dosing regimen was significantly superior over placebo for the 75% responder rate over weeks 1-4, 1-12, and the 50% responder rate over weeks 1-12. Significant improvement was also demonstrated by the 100 mg dose for the 75% responder rate over weeks 1-4, but not over weeks 1-12 (p-value: 0.113, OR: 1.47). Consequently, subsequent endpoints in hierarchical testing are considered descriptive only. The 100 mg dose showed nominally significant differences over placebo in the 50% responder rate over weeks 1-12. The 30 mg dose was nominally significant for all 3 key secondary endpoints.

In addition, the proportion of patients with migraine on day 1 after treatment was lower in all treatment arms compared to placebo (300 mg: 13.9; 100 mg: 14.8; 30 mg: 17.3; placebo: 22.5) and compared to baseline prevalence (baseline 300 mg: 18.5; baseline 100 mg: 14.8; baseline 30 mg: 17.3; baseline placebo: 20.5). Subgroup analyses demonstrated that those patients who experienced a migraine attack at day 0 were more likely to have migraine at day 1 if they were in the placebo arm, compared to eptinezumab treatment arms.

Acute migraine medication days across weeks 1-12 were lower for all treatment groups (300 mg: 0.7; 100 mg: 0.6; 30 mg: 0.8; placebo: 1.1) compared to placebo. Due to the used account for multiplicity, this reduction of acute migraine medication was nominally significant, but cannot be regarded as statistically significant in a confirmatory sense.

Other secondary endpoints, including patient reported outcomes as HIT-6, SF-36, MIDAS, and PGIC, are also supportive for the superior treatment effect of eptinezumab compared to placebo.

The persistence of efficacy has been demonstrated by the sustained reduction in average daily migraine prevalence and is further supported by the open-label long-term treatment effect observed in study 013.

For patients with chronic migraine (study 011), the superiority over placebo was demonstrated for both, the 300 mg and the 100 mg dosing regimen:

The primary endpoint was statistically significant from placebo for both doses tested. For the 300 mg dose the mean difference from placebo was of -2.60 days (95% CI: -3.45, -1.74). For the 100 mg dosing regimen the mean difference from placebo was -2.03 days (95% CI: -2.88, -1.18) for weeks 1-12.

The key secondary endpoints were supportive for the primary endpoint analysis:

The 300 mg dosing regimen was significantly superior over placebo for the 75% responder rate over weeks 1-4, 1-12, and the 50% responder rate over weeks 1-12. Significant improvement was also demonstrated by the 100 mg dose for the 75% responder rate over both, weeks 1-4, and weeks 1-12.

There was also a nominally significant and clinically meaningful improvement for both ALD403 groups compared with placebo on reductions in average daily migraine prevalence for each of the 4 weeks.

In addition, the overall migraine prevalence on day 1 after treatment was lower in all treatment arms compared to placebo (300 mg: 27.8; 100 mg: 28.6; placebo: 42.3).

Acute migraine medication (triptans and ergotamines) days across weeks 1-12 were lower for all treatment groups compared to placebo (300 mg: 3.2; 100 mg: 3.3; placebo: 4.3), as was the mean change from baseline (300 mg: -3.2; 100 mg: -3.3; placebo: -1.9).

Other secondary endpoints, including the patient reported outcomes HIT-6, SF-36, were supportive for the primary and key secondary endpoints.

The persistence of efficacy was in addition demonstrated by the change in frequency of migraine days (Weeks 13-24), which was greater in eptinezumab groups compared with placebo (mean difference -2.65 days for 300 mg, and -1.68 for 100 mg).

Both pivotal studies (006 + 011):

Overall, a modest but consistent treatment effect in terms of reduction of migraine headache days, migraine responder rates, percentage of subjects with a migraine on the day after dosing, change in migraine medication days, and supportive endpoints was found for all eptinezumab treatment arms. The superiority of the 300 mg and 100 mg group vs. placebo was found to be consistently statistically significant.

Although the difference on the primary efficacy endpoint was found to be rather modest, the size of treatment effect is in a range comparable to other anti-CGRP therapies recently authorised for the prevention of migraine in adults. Moreover, key secondary endpoints, especially the 75% responder rate, argue for a substantial treatment benefit of the 300 mg dosing regimen.

In study 006 both treatment regimens, 100 mg and 300 mg, demonstrated to be efficacious in the treatment of EM and CM. Differences in response of some subgroups remain not completely understood, but might – at least in some cases – be chance findings and attributed to low patient numbers or non-medical factors. While 300 mg seems to have a more pronounced treatment effect across all treatment groups, the number of hypersensitivity reactions is remarkably higher in the 300 mg group compared to the 100 mg group (1.4% vs. 0.2%). Weighing the benefits and risks of treatment, the proposed posology with a recommended starting dose of 100 mg, with the option to increase to the 300 mg dose for patients who do not have a sufficient response after at least 12 weeks of treatment, seems acceptable. The amended wording in section 4.2 of the

SmPC is considered adequate, since it clarifies the need for assessing treatment benefit 12 weeks after treatment initiation, and the need for a re-assessment 6 months after treatment initiation. The efficacy of such a dose escalation strategy in non-responders or partial-responders has not been formally tested in the context of clinical trials. However, the approach seems to be justified and sufficiently pragmatic and will also fit in a real-world therapeutic setting.

3.3. Uncertainties and limitations about favourable effects

As discussed above, overall a modest but consistent treatment effect in terms of reduction of migraine headache days, migraine responder rates, percentage of subjects with a migraine on the day after dosing, change in migraine medication days, and supportive endpoints was found in both eptinezumab pivotal trials.

However, some uncertainties with regard to the true size of the treatment effect remain due to the (restricted) allowance of barbiturates and opioids as concomitant treatment and since acute migraine medication use might be underestimated due to the fact that only the frequency of use of triptans and ergotamines was analysed, but not the use of over-the-counter analgesics. Several amendments took place during conduct of both pivotal studies. Changes included also the primary endpoint in study 006. The changes might have impacted study result and therefore need further clarification. Moreover, several FDA inspections took place. Results of these inspections were not provided so far and should be presented.

Moreover, there was considerable heterogeneity of the study population due to several alternatives of previous prophylactic medication use with different mode of actions, concomitant medication, frequency of migraine/ headache days and an unbalanced geographic patient allocation. This might have influenced efficacy results. In this respect, it should also be questioned whether the high mean BMI in study 006 might have (negatively) influenced efficacy results, and how these could be translated to patients with a lower body weight. The low number of EU participants might be a matter of concern.

In both studies, subgroup analyses suggest heterogeneity associated with race. In particular, black patients had a point estimate close to zero, suggesting that these patients did not benefit from treatment**.**

Only few data exist for patients > 65 years of age [28 patients across pivotal studies (1.2%)]. Hence, only limited efficacy data are available for this group.

3.4. Unfavourable effects

Eptinezumab was generally well tolerated in migraine patients.

AESIs in the eptinezumab clinical development program included hypersensitivity and anaphylactic events, events associated with suicide, cardiovascular, nervous system and hepatic events as well as events associated with study drug infusion. They occurred more frequently in eptinezumab-treated subjects than in placebo-treated subjects with the large majority of AESIs were mild or moderate in severity.

Overall, the incidence of events coded to hypersensitivity has been low (<1%) and events have been of mild to moderate intensity. All events occurred in subjects treated with eptinezumab. One subject had a serious AESI of anaphylactic reaction of moderate severity, as determined by the investigator. This event was assessed differently by the company with the terms of allergic reaction and infusion day reaction based on the lack of respiratory or cardiovascular manifestations and the pattern of response to the medications used for acute

management of the event. However, further cases of anaphylactic reactions and one case of serious hypersensitivity reaction were reported during the further clinical development program and from postmarketing sources.

Adverse events of special interest in the general disorders and administration site conditions SOC occurred with similar frequency in subjects treated with eptinezumab (1.5%) than in placebo subjects (1.1%). The majority of these events were infusion site-related AESIs (most frequent: infusion site extravasation) which are accounted for by the route of administration.

Besides events coded to hypersensitivity, infusion site-related AESIs were one of the main reasons for leading to interruption of study drug, most frequently due to infusion site extravasation and infusion site pain.

3.5. Uncertainties and limitations about unfavourable effects

The current exposure of eptinezumab in elderly patients is still very limited. In the clinical trial program only 0.7% of patients were ≥65 years of age (n=15, including those treated with placebo), and no subject was 75 years of age or older. Thus, no meaningful statements currently can be made regarding the AE profile of eptinezumab in patients ≥ 65 years of age.

Hypertension, hyperlipidemia, diabetes, and circulation conditions were notably lower among subjects in the PS pool than has been reported in community-based surveys of people with migraine. This reflects the exclusion of subjects with clinically significant cardiovascular conditions from the clinical studies. The generalizability of the safety profile of eptinezumab to the target population of migraine patients with certain cardiovascular risk factors is limited. "Use in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension" is included in the updated RMP version 1.2 under the risk category of important potential risks.

526 subjects received 4 doses of eptinezumab approximately 12 weeks apart and further data were obtained from the open label long-term safety study 013, in which more than 100 subjects received up to 4 additional dosing of 300 mg eptinezumab, 12 weeks apart. Although eptinezumab was generally well tolerated in migraine patients, in the short-term, with some limitations as addressed above, it is difficult to establish the long-term side effects of CGRP antagonists, given the limited long-term data.

The theoretical side-effects of blocking CGRP may pose a risk in subjects with comorbidities such as cardiovascular diseases (ischemic events, hypertension), gastrointestinal conditions (ulcers, irritable bowel syndrome), and skin issues (erythema, inflammation, wound healing). Long-term safety is included in the RMP under the risk category of missing information.

Differences were observed between black and white subjects in terms of safety data. Differences in baseline characteristics such as mean BMI and medical/surgical history as well as other factors such as regional, socioeconomic and environmental could contribute to the differences between black and white subjects in terms of TEAEs.

Presently, there is no evidence linking eptinezumab with any negative impact on human pregnancy. However, due to the paucity of available human pregnancy data at the present time point (24 women treated with eptinezumab), no definitive conclusions about the risks of eptinezumab use during pregnancy currently can be drawn. Use in pregnant women is already included in the RMP as safety concern of missing information and a post-marketing pregnancy program is planned for additional pharmacovigilance activity. Additionally, "pre-

eclampsia" is listed as a separate safety concern of the category "important potential risk" since this safety concern arises from the CGRP blocking characteristics of eptinezumab.

3.6. Effects Table

Table X. Effects Table for VYEPTI (eptinezumab) for prophylaxis of migraine in adults.

Effect	Short Description	Unit	Treatment	Results	Uncertainties/ Strength of evidence	References
Favourable Effects in Chronic Migraine (study 011)						
Migraine headache days	Change from baseline (week 1-12)	days	PBO 100 300	-5.6 -7.7 -8.2	 p-value: < 0.0001 p-value: < 0.0001	011
Responder rate	≥75% (w1-4)	%	PBO 100 300	15.6 30.9 36.9	 p-value: < 0.0001 p-value: < 0.0001	011
	≥75% (w1-12)	%	PBO 100 300	15.0 26.7 33.1	 p-value: < 0.0001 p-value: < 0.0001	011
Favourable Effects in Episodic Migraine (study 006)						
Migraine headache days	Change from baseline (week 1-12)	days	PBO 100 300	-3.2 -3.9 -4.3	 p-value: 0.0182 p-value: 0.0001	006
Responder rate	≥75% (w1-4)	%	PBO 100 300	20.3 30.8 31.5	 p-value: 0.0112 p-value: 0.0066	006
	≥75% (w1-12)	%	PBO 100 300	16.2 22.2 29.7	 p-value: 0.1126 p-value: 0.0007	006
Unfavourable Effects						
Hypersensitivity/ anaphylactic reaction (AESI) [a]	SOC of Immune System Disorders and PT of hypersensitivity, anaphylactic reaction, and anaphylactoid reaction	%	PBO 10 30 100 300 1000 OE	0 0 1.8 0.3 1.8 0 1.1		ISS, OE pool
Infusion site disorders (AESI)[b]	SOC of Administration Site Conditions and PT of Infusion site extravation (cont'd)[c]	%	PBO 10 30 100 300 1000 OE	0.9 0.8 2.1 1.3 1.2 0 1.3		ISS, OE pool

Effect	Short Description	Unit	Treatment	Results	Uncertainties/ Strength of evidence	References
Infusion site disorders (AESI)[b]	SOC of Skin and subcutaneous tissue disorders and PT of Rash, pruritus, swelling face and urticaria	%	PBO 10 30 100 300 1000 OE	0.3 1.5 0.9 1.0 1.0 3.7 1.1		ISS, OE pool

Abbreviations: AESI Adverse Event of Special interes, PBO Plabebo, PT Preferred Term, SOC System Organ Class
Notes: [a]by convention, AEs that occurred during the study drug infusion, led to a specific clinical action by the investigator and were determined by the investigator to be possible allergic response or infusion reaction were coded to the SOC of Immune System Disorders and the preferred term of hypersensitivity, hereafter referred as events coded to hypersensitivity.
[b] by definition, these events occurred within 7 days of infusion
[c] complete list: Infusion site extravasation, Infusion site nerve damage, Infusion site rash, Infusion site discomfort, Infusion site eczema, Infusion site erythema, Infusion site pain, Infusion site pruritus, Injection site paraesthesia.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Superiority of eptinezumab compared to placebo in reducing the frequency of migraine days, as well in decreasing the burden of migraine episodes and symptoms in patients with episodic and chronic migraine is considered demonstrated. The onset of treatment effect was prompt, with a trend for a treatment effect starting as early as day one. Persistence of efficacy was also demonstrated.

The difference from placebo in mean reduction of migraine days was rather modest, especially in patients with EM. However, with regard to the secondary EP 75% responder rate W1-4, responder rates in CM patients were nearly doubled compared to placebo for the 100 mg dose, and more than doubled for the 300 mg dose (~30%/ 37%vs. ~15%). Similar results were found for the EP 75% responder rate W-12 in this population. The effect was slightly less pronounced in EM patients, but there was also clear superiority over placebo for the 75% responder rate W1-4 endpoint (~31%/30% vs. ~20%), as well as for the 75% responder rate W1-12 EP (22%/30% vs. 16%). These results were supported by all secondary endpoints.

It can therefore be concluded that approximately 1/3 of treated patients had a clear, clinically relevant and sustained treatment benefit, while others may also have benefitted, but to a lesser extent. It is not clear, which patients might have benefitted most. There are many co-variates that might have influenced efficacy results, and not all have yet been analysed in specific subgroup-analyses. Most importantly, no data on over-the-counter acute analgesic use, and on the potential influence of different types of concomitant prophylactic migraine treatment have been presented. Also the influence of patient body-weight on efficacy results remains to be clarified. Importantly, it seems as if black patients have not benefitted from eptinezumab treatment. This finding needs further investigation.

However, overall the treatment effect observed seems to be in a range comparable to other anti-CGRP therapies recently authorised for the prevention of migraine in adults.

Based on current study data the safety profile of eptinezumab in general is acceptable. Eptinezumab was generally well tolerated in migraine patients.

Only few discontinuation due to AEs have been registered in clinical trials and most events have been judged as been manageable and being of mild to moderate intensity.

Infusion site-related AESIs were one of the main reasons for leading to interruption of study drug, most frequently due to infusion site extravasation and infusion site pain. Moreover, rash and pruritus occurred slightly more frequent in OE subjects than in placebo subjects. Some of the events are considered inherent problems of the method of administration, for instance infusion site extravasation, where others seem to be related to the study drug.

The incidence of events coded to hypersensitivity has been low (<1%) and events have been of mild to moderate intensity. All events occurred in subjects treated with eptinezumab. One more subject had a serious AESI of anaphylactic reaction of moderate severity, as determined by the investigator. The event was assessed differently by the company with the terms of allergic reaction and infusion day reaction based on the lack of respiratory or cardiovascular manifestations and the pattern of response to the medications used for acute management of the event. Further cases of anaphylactic reactions and serious hypersensitivity reaction were reported during the further clinical development program and from postmarketing sources.

Of concern are further the limited data on long-term safety, in patients ≥65 years of age and in migraine patients with certain cardiovascular risk factors or comorbidities, which should be further explored.

3.7.2. Balance of benefits and risks

The balance of benefits and risks is considered to be positive in the agreed indication.

3.7.3. Additional considerations on the benefit-risk balance

The benefit of eptinezumab treatment in the claimed indication seems to outweigh the risks.

However, the magnitude of treatment effect is limited and the strength of the evidence hampered by several issues that need to be resolved. These issues include the efficacy in certain patient subgroups, regional heterogeneity, influence of concomitant migraine/headache medications, the imputation of missing data, as well as the potential influence of body weight.

Moreover, the effect of 100 mg seems to be less robust than the effect of 300 mg. Several subgroups in the EM population show point estimates close to zero in the 100 mg group, thus suggesting potential lack of efficacy in these groups. In addition, the 300 mg dose consistently demonstrated a trend for a higher efficacy across all endpoints in both efficacy studies. It is agreed that both treatment regimens, 100 mg and 300 mg, demonstrated to be efficacious in the treatment of EM and CM. Differences in response of some subgroups remain not completely understood, but might – at least in some cases – be chance findings and attributed to low patient numbers or non-medical factors. While 300 mg seems to have a more pronounced treatment effect across all treatment groups, the number of hypersensitivity reactions is remarkably higher in the 300 mg group compared to the 100 mg group (1.4% vs. 0.2%). Weighing the benefits and risks of treatment, the proposed posology with a recommended starting dose of 100 mg, with the option to increase to the 300 mg dose for patients who do not have a sufficient response after at least 12 weeks of treatment, seems acceptable. The amended wording in section 4.2 of the SmPC is considered adequate, since it clarifies the need for assessing treatment benefit 12 weeks after treatment initiation, and the need for a re-assessment 6 months after treatment initiation. The efficacy of such a dose escalation strategy in non-responders or partial-responders

has not been formally tested in the context of clinical trials. However, the approach seems to be justified and sufficiently pragmatic and will also fit in a real-world therapeutic setting.

With regard to safety, uncertainties on potential cardiovascular risks, especially in elderly patients (>65 years) and on long-term safety currently negatively impact the acceptability of the safety profile of a drug that is intended for a non-life threatening disease. The safety profile is currently compromised by the occurrence of hypersensitivity reactions, including one serious hypersensitivity reaction and cases of anaphylactic reaction. Moreover, the burden due to infusion, including infusion-site related reactions, should be taken into account.

3.8. Conclusions

The overall benefit/risk balance of Vyepti is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vyepti is favourable in the following indication(s):

Vyepti is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

  None

- **Obligation to conduct post-authorisation measures**

  None

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that eptinezumab is to be qualified as a

new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 11 November 2021