Report on the Deliberation Results

December 7, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Emgality Subcutaneous Injection 120 mg Autoinjector
	Emgality Subcutaneous Injection 120 mg Syringe
Non-proprietary Name	Galcanezumab (Genetical Recombination) (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	January 24, 2020

Results of Deliberation

In its meeting held on December 2, 2020, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

November 6, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	(a) Emgality Subcutaneous Injection 120 mg Autoinjector (b) Emgality Subcutaneous Injection 120 mg Syringe
Non-proprietary Name	Galcanezumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	January 24, 2020
Dosage Form/Strength	(a) A kit (1 mL) containing 120 mg of Galcanezumab (Genetical Recombination) (b) A syringe (1 mL) containing 120 mg of Galcanezumab (Genetical Recombination)
Application Classification	Prescription drug, (1) Drugs with a new active ingredient
Definition	Galcanezumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human α- and β-calcitonin gene-related peptides (CGRP) monoclonal antibody, human framework regions and human IgG4 constant regions. In the H-chain, the amino acid residues at positions 227, 233 and 234 are substituted by Pro, Ala and Ala, respectively, and C-terminal Lys is deleted. Galcanezumab is produced in Chinese hamster ovary cells. Galcanezumab is a glycoprotein (molecular weight: ca.147,000) composed of 2 H-chains (γ4-chains), consisting of 445 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

Structure

L-chain

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DIQMTQSPSS LSASVGDRVT ITCRASKDIS KYLNWYQQKP GKAPKLLIYY
TSGYHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GDALPPTFGG
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC
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H-chain

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QVQLVQSGAE VKKPGSSVKV SCKASGYTFG NYWMQWVRQA PGQGLEWMGA
IYEGTGKTVY IQKFADRVTI TADKSTSTAY MELSSLRSED TAVYYCARLS
DYVSGFGYWG QGTTVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY
TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEAAGGPSVF LFPPKPKDTL
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD
GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLG
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Intrachain disulfide bonds: Solid lines

Interchain disulfide bonds: C214 in L-chain-C133 in H-chain, C225 in H-chain-C225 in H-chain, C228 in H-chain-C228 in H-chain

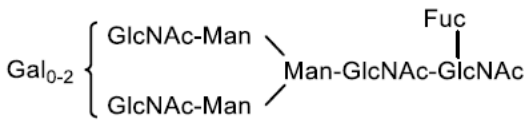
Pyroglutamate formation (partial): Q1 in H-chain

Glycosylation site: N296 in H-chain

Partial processing: G445 in H-chain

Amidation: L444 in H-chain

Putative structure of main carbohydrate chain:



Molecular formula: $C_{6392}H_{9854}N_{1686}O_{2018}S_{46}$ (protein portion)

Molecular weight: Approx. 147,000

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of migraine attacks, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The occurrences of serious hypersensitivity and serious cardiovascular events, safety in pregnant women, and long-term safety should be further investigated.

Indication

Prevention of migraine attacks

Dosage and Administration

The usual adult dosage is 240 mg of Galcanezumab (Genetical Recombination) administered subcutaneously as the first dose, followed by monthly doses of 120 mg injected subcutaneously.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

September 3, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	(a) Emgality Subcutaneous Injection 120 mg ATEOS EM (to be changed to Emgality Subcutaneous Injection 120 mg Autoinjector) (b) Emgality Subcutaneous Injection 120 mg Syringe
Non-proprietary Name	Galcanezumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	January 24, 2020
Dosage Form/Strength	(a) A kit (1 mL) containing 120 mg of Galcanezumab (Genetical Recombination) (b) A syringe (1 mL) containing 120 mg of Galcanezumab (Genetical Recombination)

Proposed Indication

Prevention of migraine attacks

Proposed Dosage and Administration

The usual adult dosage is 240 mg of Galcanezumab (Genetical Recombination) administered subcutaneously as the first dose, followed by monthly doses of 120 mg injected subcutaneously.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Galcanezumab (INN, galcanezumab), discovered by Eli Lilly and Company in the US, is a humanized recombinant immunoglobulin G (IgG) 4 monoclonal antibody against calcitonin gene-related peptide (CGRP). CGRP is a neuropeptide highly expressed in trigeminal ganglion neurons and trigeminal nerve terminals including dura mater during a migraine attack. An increased plasma or serum CGRP concentration induces pain syndrome such as migraine and cluster headache (*Cephalalgia.* 1994;14:320-7). Galcanezumab is expected to prevent migraine attacks by binding to CGRP, thereby inhibiting its physiological activity.

The clinical development of galcanezumab was initiated in 20[redacted] by Eli Lilly and Company. As of July 2020, galcanezumab has been approved for the indication "the prophylactic treatment of migraine" in ≥40 countries or regions including the US and Europe, and for the indication "treatment of episodic cluster headache" in 5 countries including the US.

In Japan, the clinical development of galcanezumab was started from 2016 by the applicant and a marketing application for galcanezumab with the proposed indication of "the prevention of migraine attacks" has recently been submitted, based on the results of Japanese and foreign clinical studies, etc.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

[redacted] library was prepared from [redacted] derived from [redacted] cells immunized with [redacted] CGRP fragment bound to [redacted]. [redacted] were selected from the library by screening based on [redacted], which were then optimized and humanized. Plasmids encoding the full length of H- and L-chains were obtained from the gene fragments encoding the variable region of H- and L-chains obtained from the above [redacted] and from the plasmids encoding the constant region of H- and L-chains of human IgG4. The expression construct of galcanezumab gene was obtained from H- and L-chain plasmids after the introduction of mutations in [redacted] of H-chain to suppress [redacted] formation, reduce effector function, and remove C-terminal lysine. The thus-obtained gene expression construct was introduced into CHO cells, and master cell bank (MCB) and working cell bank (WCB) were prepared from the clone optimal for the manufacture of galcanezumab.

The characterization and purity test of MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) were performed according to ICH Q5A (R1), Q5B, and Q5D Guidelines. Results confirmed their genetic stability during the manufacturing of galcanezumab. Except for endogenous retroviruses-like particles commonly observed in rodent-derived cell lines, viral or nonviral adventitious agents were not detected within the range of tests performed.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. A new MCB will be not prepared, while new WCB will be prepared as necessary.

2.1.2 Manufacturing process

The drug substance is manufactured by a process comprising seed culture, production culture, primary harvesting, viral inactivation by [redacted] treatment, [redacted] chromatography, viral inactivation and clarification by [redacted] treatment, [redacted] chromatography, [redacted] filtration, [redacted] filtration, and dispensing/freezing/storage.

Critical steps include production culture, viral inactivation by [redacted] treatment, [redacted] chromatography, viral inactivation and clarification by [redacted] treatment, [redacted] chromatography, and [redacted] filtration.

The process validation of the manufacturing process for the drug substance was conducted on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin except for CHO cells, the host cells, are used in the manufacturing process of the drug substance.

Purity tests were performed on the MCB, WCB, and CAL [see Section "2.1.1 Generation and control of cell substrate"]. The unprocessed bulk obtained by the commercial-scale manufacture was subjected to bioburden test, mycoplasma test, *in vitro* virus test, and mouse minute virus test. No contamination with either viral or nonviral adventitious agents was detected within the range of the tests performed. These tests on the unprocessed bulk are included in in-process controls.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Viral reduction factor (log_{10})			
	Murine leukemia virus	Porcine parvovirus	Pseudorabies virus	Reovirus type 3
Virus inactivation by [redacted] treatment	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Virus inactivation and clarification by [redacted] treatment	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] filtration	[redacted]	[redacted]	[redacted]	[redacted]
Total viral reduction factor	≥17.10	6.48	≥10.17	≥8.89

2.1.4 Manufacturing process development

Main changes in the manufacturing process during the development of the drug substance are shown below (each process is referred to as Processes A, B, C, D, E, and the proposed process). The formulations produced from the drug substances manufactured by Processes D, E, and the proposed process were used in the Japanese phase II and III studies.

1. From Process A to Process B: Introduction of [redacted], and changes in the production scale, cultivation step, purification step, and [redacted]
2. From Process B to Process C: Changes in production scale, cultivation step, purification step, [redacted], and [redacted]

3. From Process C to Process D: Introduction of [redacted] and changes in production scale, purification step, and [redacted]
4. From Process D to Process E: Change in purification step
5. From Process E to proposed process: Changes in [redacted], production scale, and purification step

With these changes in the manufacturing process, comparability of the quality attributes and pharmacokinetics (PK) was evaluated. The results confirmed the comparability of pre- and post-change drug substance [see Section "6.1 Summary of biopharmaceutic studies and associated analytical methods].

The quality by design (QbD) approach was used in the development of the manufacturing process [see Section "2.3 QbD"].

2.1.5 Characterization

2.1.5.1 Structure and characteristics

The drug substance was subjected to characterization tests described in Table 2.

Table 2. Parameters for characterization

Primary structure/higher order structure	Amino acid sequence, posttranslational modification (pyroglutamation, glycosylation, deamidation, isomerization, oxidation, hydroxylation, glycosylation, N- and C-terminal heterogeneity), disulfide bonds, free sulfhydryl groups, secondary structure, tertiary structure, quaternary structure, thermal stability
Physicochemical properties	Molecular weight/molecular size, charge variants, absorbance index, size variants, IgG subclass analysis
Carbohydrate structure	Glycosylation rate, oligosaccharide profile, carbohydrate structure analysis, monosaccharide-binding analysis
Biological properties	CGRP-inhibitory activity
	Fcγ receptor (I, IIa, and IIIa)-binding activity, complement-component (C1q)-binding activity, fetal Fc receptor-binding activity

CGRP-inhibitory activity was evaluated by homogeneous time resolved fluorescence (HTRF) assay using SK-N-MC cell lines derived from human neuroblastoma expressing CGRP receptors. The binding activity to fragment crystallizable (Fc) γ receptors and to the complement component was investigated by enzyme-linked immunosorbent assay (ELISA). Results confirmed that galcanezumab binds to neither Fcγ receptors nor the complement component [see Sections "3.1.1.2 Inhibitory effect of galcanezumab against human αCGRP and βCGRP" and "3.1.1.7 Binding capacity to Fcγ receptors I, IIa, and IIIa and to complement component C1q"].

2.1.5.2 Product-related impurities

Based on the results of the characterization, Related Substances A, B, and C were identified as product-related substances. Aggregates, fragments, and Impurity A were identified as product-related impurities. The aggregates and fragments are controlled by specifications established for the drug substance and for the drug product. Impurity A is not controlled by any specification because it is present only at a low level and is controllable by the manufacturing process.

2.1.5.3 Process-related impurities

Host cell deoxyribonucleic acid (DNA), Impurity B, host cell protein (HCP), Impurity C, elemental impurities, Impurities D, E, and F were identified as process-related impurities. It has been confirmed that host cell DNA, Impurity B, HCP, Impurity C, and elemental impurities are adequately removed in the manufacturing process. The applicant explained that Impurities D, E, and F are used in cell culture, and even if they are not removed in the purification step, the maximum amount of these impurities in the clinical use of galcanezumab predicted from the yield is below the acceptable daily exposure.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (cation exchange chromatography [CEX], CGRP-inhibitory activity, peptide mapping), osmotic pressure, pH, purity (size exclusion chromatography [SEC], capillary electrophoresis-sodium dodecyl sulfate [CE-SDS] [[redacted] and [redacted]]), charge heterogeneity (CEX), bacterial endotoxin, microbial limits, potency (CGRP-inhibitory activity), and assay (ultraviolet-visible spectrophotometry [UV/VIS]).

2.1.7 Stability of drug substance

Table 3 shows main stability studies conducted on the drug substance.

Table 3. Summary of main stability studies on drug substance

		Manufacturing process	Number of batches	Storage condition	Study period	Storage form
Long-term testing		Process [redacted]	3	≤−65°C	36 months	High-density polyethylene container with polypropylene stopper
		[redacted] process	4			
Accelerated testing		Process [redacted]	3	5 ± 3°C	6 months	
		[redacted] process	4			
Stress testing	Temperature	Process [redacted]	1	40 ± 2°C	4 weeks	Glass container
	Light	Process [redacted]		20°C, overall illumination of ≥1.2 million lux•h, an integrated near ultraviolet energy of ≥200 W•h/m^2		High-density polyethylene container, glass container

Long-term testing and accelerated testing showed no clear changes in the quality attributes throughout the study period.

Stress testing (temperature) showed increased aggregates in SEC, increased fragments in CE-SDS ([redacted]), increased fragments in CE-SDS ([redacted]), tendency of a decrease in [redacted] peak and tendency of increase in [redacted] variant in CEX, and increases in [redacted], [redacted], [redacted], and [redacted] in liquid chromatography-mass spectrometry (LC-MS) peptide mapping.

Stress testing (light) showed that the drug substance is unstable to light.

Based on the above, a shelf life of 36 months was proposed for the drug substance when stored in a high-density polyethylene container with a polypropylene stopper at ≤−65°C.

2.2 Drug products

2.2.1 Description and composition of drug products and formulation development

The drug products are aqueous injections containing 120 mg of galcanezumab per syringe (1 mL). The proposed drug products are a prefilled syringe (PFS) formulation in a needled glass syringe containing the drug solution and an autoinjector (AI) formulation in a syringe containing the drug solution with a pen-injector attached. Both are combination products. The excipients in drug product are L-histidine, L-histidine hydrochloride, sodium chloride, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of excipient buffer preparation, drug solution preparation, sterile filtration, filling/capping, assembling, labeling/packaging/testing, and storage.

Critical steps are drug solution preparation, sterile filtration, and filling/capping.

The process validation of manufacturing process was conducted on a commercial scale.

2.2.3 Manufacturing process development

[redacted], [redacted], [redacted], and [redacted] were changed during the process of drug product development. The phase III study was conducted using the formulation manufactured by the proposed process.

The comparability of quality attributes was evaluated between before and after the change of each manufacturing process for the drug product. The results confirmed the comparability between pre- and post-change drug product.

In the development of the manufacturing process of the drug product, a QbD approach was used [see Section “2.3 QbD”].

2.2.4 Control of drug product

The specifications for the drug product include content, description, identification (CEX, CGRP-inhibitory activity), pH, purity (SEC, CE-SDS [[redacted] and [redacted]]), charge heterogeneity (CEX), foreign insoluble matter, insoluble particulate matters, sterility, potency (CGRP-inhibitory activity), and assay (UV/VIS).

2.2.5 Stability of drug product

Table 4 shows the main stability studies of the drug product. Also, preliminary stability studies (long-term testing and accelerated testing) were performed on the PFS and AI formulations, which confirmed that their stability profiles are identical as those of the primary batch.

Table 4. Summary of the main stability studies of the drug product

	Number of batches[a]	Storage condition	Study period	Storage form[b]
Long-term testing	3	5 ± 3°C	24 months	Glass syringe with a stainless steel needle and a bromobutyl rubber plunger
Accelerated testing	3	30 ± 2°C/65 ± 5%RH	6 months	
Photostability testing	1	20°C, overall illumination of ≥1.2 million lux•h, an integrated near ultraviolet energy of ≥200 W•h/m^2		

a, The drug product manufactured by the proposed process using the drug substance manufactured by the proposed process
b, Intermediate product without plunger rod, AI components, etc.

Long-term storage testing showed no clear changes in quality attributes throughout the study period.

Accelerated testing showed increased aggregates in SEC, decreased sum of H- and L-chains in CE-SDS ([redacted]), decreased main peak area in CE-SDS ([redacted]), and decreased [redacted] peak area and increased [redacted] variants in CEX.

Photostability testing showed that the drug product is unstable to light.

Based on the above, a shelf life of 24 months was proposed for the drug product when stored in a glass syringe with a stainless-steel needle and a bromobutyl rubber plunger (primary container) at 2°C to 8°C, protected from light.

2.3 QbD

A QbD approach was used in the development of the drug substance and the drug product, and the strategy for quality control was developed by the following investigations.

- Identification of critical quality attributes (CQAs):
  The following CQAs were found to affect the quality attributes including the product-related impurities, process-related impurities [see Sections "2.1.5.2 Product-related impurities" and "2.1.5.3 Process-related impurities"], and product attributes, based on the information obtained in the development of galcanezumab and on the related findings.
  - Potency, aggregates, fragments, [redacted], host cell DNA, HCP, [redacted], [redacted], elemental impurities, microbiological safety, viral safety/adventitious agents, particulate matters, identity, appearance, protein content, pH, osmotic pressure, and dose (extractable volume, [redacted], and [redacted]).

- Process characterization:
  The processes affecting CQAs were identified and, in these processes, process control parameters significantly affecting CQAs and process performance were identified by means of risk assessment, etc. The acceptable range was confirmed.

- Establishment of the control methods:
  Based on the knowledge on the process including the above "process characterization," results of batch analysis, stability studies, etc., the methods for controlling the quality attributes of the drug substance and the drug product were established by the combination of the process parameters, in-process control, specifications, etc. [for the control of product-related impurities and process-related

impurities, see Sections "2.1.5.2 Product-related impurities" and "2.1.5.3 Process-related impurities"].

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is controlled appropriately.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Evaluation of the binding of galcanezumab to human and rat αCGRP (CTD 4.2.1.1.1)

The binding capacity of galcanezumab to human and rat αCGRP was investigated by surface plasmon resonance assay. When human or rat αCGRP was added to the galcanezumab-immobilized censor chip, equilibrium dissociation constant (K_D) (mean ± standard deviation [SD]) of galcanezumab for human and rat αCGRP was 31 ± 19 pmol/L and 250 ± 64 pmol/L, respectively.

3.1.1.2 Inhibitory effect of galcanezumab against human αCGRP and βCGRP (CTD 4.2.1.1.2 and 4.2.1.1.3)

Using SK-N-MC cells engineered to express calcitonin receptor-like receptor (CRLR) and receptor activity modifying protein (RAMP) which constitute a CGRP receptor, cyclic adenosine monophosphate (cAMP) concentration was measured by HTRF assay. Based on the results, the inhibitory effect of galcanezumab (0.00254-50 nmol/L) against the binding to human αCGRP and βCGRP was evaluated. IC_{50} (mean ± SD) of galcanezumab against cAMP production by human αCGRP and βCGRP was 0.35 ± 0.07 nmol/L and 0.18 ± 0.02 nmol/L, respectively.

3.1.1.3 Inhibitory effect of galcanezumab against cAMP production induced by human and rabbit αCGRP (CTD 4.2.1.1.4)

Galcanezumab was added to SK-N-MC cells engineered to express human CGRP receptors, to which human or rabbit αCGRP was added 30 minutes later, to measure cAMP concentration by HTRF assay. Galcanezumab concentration tested was 0.5 to 10000 pmol/L for human αCGRP and 2.5 to 50000 pmol/L for rabbit CGRP.

The dissociation rate constant (K_b) (mean ± SD) of galcanezumab against human and rabbit αCGRP was 44.2 ± 1.8 pmol/L and 4.1 ± 0.2 pmol/L, respectively. IC_{50} of galcanezumab against cAMP production by human and rabbit αCGRP was 0.23 nmol/L and 0.06 nmol/L, respectively.

3.1.1.4 Inhibitory effect of cAMP production induced by human αCGRP or by human amylin (CTD 4.2.1.1.4)

Using CHO cells engineered to express human AMY1 receptors, which is activated by CGRP and by human amylin, a calcitonin peptide family, the inhibitory effect of galcanezumab (0.01-20000 pmol/L) against the binding of human αCGRP (0.8 nmol/L) and human amylin (0.8 nmol/L) was investigated.

Galcanezumab inhibited human αCGRP-induced cAMP production with IC_{50} of 0.9 nmol/L but did not inhibit human amylin-induced cAMP production at any concentration tested.

3.1.1.5 Binding capacity to calcitonin family peptides (CTD 4.2.1.1.5)

The binding capacity of galcanezumab to human calcitonin family peptides, amylin, calcitonin, adrenomedullin, and intermedin was investigated by surface plasmon resonance assay, using human αCGRP as the positive control.

When each peptide (56, 167, or 500 nmol/L) was added to a galcanezumab-immobilized sensor chip, galcanezumab bound to human αCGRP, the positive control, at any concentration tested (0.56, 1.67, or 5 nmol/L), with the maximum change in signal obtained in cCGRP being approximately 14 units. In contrast, galcanezumab did not bind to amylin, calcitonin, or intermedin at any concentration tested, showing no change in the signal. With adrenomedullin, signal change was observed at all concentrations but the lowest, with the maximum change in signal being approximately 8 units.

3.1.1.6 Binding capacity to human CGRP receptors (CTD 4.2.1.1.6)

Using HEK293 cells engineered to express CGRP receptors, the binding capacity of galcanezumab to CGRP receptors was investigated. The anti-CGRP receptor antibody was used as the positive control, and the human IgG4 antibody as the negative control. Galcanezumab or each control (1-100 nmol/L) was added to HEK293 cells, the cells were stained with Hoechst33342, the nucleus-staining dye, and the reactivity was evaluated by using Mean Object Spot Total Intensity as the index. Galcanezumab did not bind to CGRP receptors at any concentration tested. The positive control at ≥3 nmol/L bound to CGRP receptors, whereas the negative control did not bind to the receptors at any concentration tested.

3.1.1.7 Binding capacity to Fcγ receptors I, IIa, and IIIa and to complement component C1q (CTD 4.2.1.1.7)

In order to investigate the immunostimulatory effect of galcanezumab mediated by binding to Fcγ receptors, the binding of galcanezumab to human Fcγ receptors and to complement components was evaluated. Galcanezumab (6.25-200 μg/mL) was added to plates coated with CD16a, CD32a, CD64, or complement component 1, q subcomponent (C1q), followed by the addition of horseradish peroxidase (HRP)-labeled anti human IgG F(ab')2 antibody and, after the addition of 3, 3', 5, 5'-tetramethylbenzidine (TMB) reagent, absorbance was measured by a colorimetric microplate reader. Human IgG1 antibody was used as the positive control, and human IgG4 antibody as the negative control. Human IgG1 antibody, the positive control, bound to all molecules tested, whereas neither galcanezumab nor human IgG4 antibody, the negative control, bound to any molecule tested.

3.1.2 *In vivo* studies

3.1.2.1 Inhibition of capsaicin-induced DBF increase in rats (CTD 4.2.1.1.8)

Galcanezumab (4 mg/kg) was administered subcutaneously to male Lewis rats and, after 5 days, capsaicin solution (2 mg/8 μL) was applied to the abdominal skin. After 25 minutes, the percent change from baseline in a capsaicin-induced dermal blood flow (DBF) was evaluated (n = 8/group). Human IgG4 antibody (4 mg/kg) was used as the control.

The rate of an increase in DBF from baseline was 138.7% in the control group and 27.0% in the galcanezumab group, demonstrating the inhibitory effect of galcanezumab against the increase in DBF.

3.1.2.2 Inhibition of capsaicin-induced DBF increase in monkeys (CTD 4.2.1.1.9)

Galcanezumab (5 mg/kg) was administered intravenously to cynomolgus monkeys and, after 1, 15, and 29 days, capsaicin solution (2 mg/20 μL) was applied to the forearm skin. The percent change from baseline in capsaicin-induced DBF in each measurement day was evaluated (n = 4-6/group). The rate of a galcanezumab-induced increase in DBF from baseline was 13.7%, 30.5%, and 38.9%, respectively, at Day 1, 15, and 29, demonstrating the inhibitory effect of galcanezumab against the increase in DBF.

3.2 Safety pharmacology

Table 5 shows the results of safety pharmacology studies.

Table 5. Summary of safety pharmacology studies

Organ	Test system	Endpoints and method	Dosage regimen	Route of administration	Finding	CTD
Central nervous system	Cynomolgus monkeys (n = 4/sex/group)	Monitoring of clinical signs	0, 2, 100 mg/kg Once weekly for 26 weeks	Subcutaneous	No effect on the central nervous system	4.2.3.2.6
Cardiovascular system	Cynomolgus monkeys (n = 3-6/sex/group)	Electrocardiogram	0, 1.5, 15, 100 mg/kg Once weekly for 6 weeks	Subcutaneous	No effect on the cardiovascular system	4.2.3.2.4
	Cynomolgus monkeys (n = 4/sex/group)	Electrocardiogram	0, 2, 100 mg/kg Once weekly for 26 weeks	Subcutaneous	No effect on the cardiovascular system	4.2.3.2.6
Respiratory system	Cynomolgus monkeys (n = 3-6/sex/group)	Respiratory rate, respiratory status	0, 1.5, 15, 100 mg/kg Once weekly for 6 weeks	Subcutaneous	No effect on the respiratory system	4.2.3.2.4
	Cynomolgus monkeys (n = 4/sex/group)	Respiratory rate, respiratory depth	0, 2, 100 mg/kg Once weekly for 26 weeks	Subcutaneous	No effect on the respiratory system	4.2.3.2.6

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics

The applicant's explanation about the action of CGRP and its involvement in migraine attack:

CGRP is a neuropeptide belonging to the calcitonin peptide family and is expressed as 2 isoforms, αCGRP and βCGRP. The former is expressed mainly in peripheral and central nervous systems, and the latter mainly in the enteric nervous system (*Neuroscience.* 1988;25:195-205).

CGRP dilates blood vessels (*Nature.* 1985;313:54-6) and is involved in neurogenic inflammation and nociception (*Pain.* 2013;154:700-7). CGRP also promotes the production and secretion of proinflammatory mediators (*Mol Pain.* 2011;7:94) and enhances the excitability of dorsal root ganglion neurons in culture by lowering the activation threshold (*Pain.* 2005;116:194-204). Increased plasma or serum CGRP concentration is associated with pain syndrome such as migraine and cluster headache (*Cephalalgia.* 1994;14:320-7), and continuous administration of CGRP triggers migraine-like headache attacks in patients with migraine (*Cephalalgia.* 2002;22:54-61, *Cephalalgia.* 2010;30:1179-86).

In the primary pharmacodynamic studies, galcanezumab bound to rat and human CGRP at high binding affinity and inhibited CGRP-induced cAMP production in *in vitro* studies. In the investigation on the binding of galcanezumab to human αCGRP, human amylin, and other peptides of calcitonin family, galcanezumab did not inhibit cAMP production induced by human amylin and, in surface plasmon resonance assay, did not bind to peptides of the calcitonin family except for adrenomedullin. The K_D of galcanezumab to human αCGRP was 31 pM, whereas the K_D of galcanezumab to adrenomedullin was estimated to be ≥500 nM.

Because of no established pathological animal model that allows the investigation of galcanezumab's preventive effect against migraine attacks, no study with *in vivo* pathological animal model was conducted. However, studies in rats and monkeys demonstrated that galcanezumab inhibits the increase in capsaicin-induced DBF, which is considered reflective of CGRP-induced vasodilation. It has been confirmed that the amino acid sequence of monkey CGRP is identical with that of human CGRP, suggesting that monkey is an appropriate animal species for investigating the effect of galcanezumab in humans.

The above results and the distribution of galcanezumab observed in the dura mater and the trigeminal ganglia [see Section "4.2.1 Distribution in central nervous system"] suggest the possibility that galcanezumab suppresses migraine attacks by binding to human αCGRP, thereby inhibiting the excitatory effect of αCGRP on nociceptive neurons, which activates pain pathway in peripheral nerves.

PMDA's view:
In vitro studies showed that galcanezumab binds to CGRP selectively and inhibits the binding of CGRP to CGRP receptors. *In vivo* studies demonstrated that an increase in capsaicin-induced DBF, which is mediated by the pharmacological action of CGRP, was inhibited by galcanezumab, suggesting that galcanezumab inhibits CGRP *in vivo* as well. Taking account of these findings and the applicant's explanation about the involvement of αCGRP in migraine attacks, galcanezumab is expected to suppress migraine attacks.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Serum galcanezumab concentration was measured by ELISA. The lower limit of quantitation was 0.020 μg/mL in rats and rabbits and 0.020 or 0.010 μg/mL in monkeys.

PK parameter values are expressed in mean or mean ± SD, unless specified otherwise.

4.1 Absorption

4.1.1 Single-dose study (CTD 4.2.2.2.1)

Following a single intravenous administration of galcanezumab 2 mg/kg to male monkeys (n = 2), $t_{1/2}$ of galcanezumab was 7.6 days, V_{ss} was 52.2 mL/kg (0.14 L), and CL was 0.24 mL/h/kg (0.015 L/day).

4.1.2 Repeated-dose studies (CTD 4.2.3.2.3, 4.2.3.2.6, 4.2.3.5.2.5, and 4.2.3.5.4.1)

Galcanezumab was administered subcutaneously once weekly for 26 weeks to male and female rats and to male and female monkeys. Table 6 shows PK parameter values of galcanezumab.

Table 6. PK parameters of galcanezumab following subcutaneous once-weekly doses

Animal species	Dose (mg/kg)	Sex	Number of animals	Time point of measurement (Day)	C_{max} (μg/mL)	$AUC_{0\text{-}7d}$ (μg·day/mL)
Rats	20	M	3/time point	1	164	800
			3/time point	176	173, 193[a]	1220
		F	3/time point	1	168	838
			3/time point	176	242	1280
	250	M	3/time point	1	990	5250
			3/time point	176	441	2440
		F	3/time point	1	1160	6500
			3/time point	176	1030	3430
Monkeys	2	M	4	1	27 ± 2	158 ± 12
			3	176	75 ± 31	446 ± 211
		F	4	1	26 ± 5	143 ± 31
			3	176	34 ± 45	192 ± 291
	100	M	4	1	1300 ± 68	7250 ± 658
			4	176	4540 ± 1930	23800 ± 5170
		F	4	1	1120 ± 147	5920 ± 613
			3	176	4440 ± 363	24500 ± 3290

a, Individual values of 2 animals

Galcanezumab was administered subcutaneously to pregnant rabbits on Gestation Day 7, 12, 16, and 20. Table 7 shows PK parameter values of galcanezumab.

Table 7. PK parameters of galcanezumab in pregnant rabbits following repeated subcutaneous doses

Dose (mg/kg)	Number of animals	Time point of measurement	C_{max} (μg/mL)	$AUC_{0\text{-}3d}$ (μg·day/mL)
30	5	Gestation Day 7	240 ± 27	467 ± 68
	5	Gestation Day 12	355 ± 74	904 ± 181
	5	Gestation Day 16	211 ± 104	417 ± 250
	5	Gestation Day 20	69 ± 47	103 ± 103
100	5	Gestation Day 7	1020 ± 224	1960 ± 344
	5	Gestation Day 12	1430 ± 115	3810 ± 357
	5	Gestation Day 16	1760 ± 228	4880 ± 604
	5	Gestation Day 20	1660 ± 255	4250 ± 563

Galcanezumab was administered to juvenile rats subcutaneously once every 3 days from 21 through 90 days after birth. Table 8 shows PK parameter values of galcanezumab.

Table 8. PK parameters galcanezumab in juvenile rats following repeated subcutaneous doses

Dose (mg/kg)	Sex	Number of animals	Time point of measurement	C_{max} (μg/mL)	$AUC_{0\text{-}7d}$ (μg·day/mL)
30	M	3/time point	Day 21 after birth	136	729
		3/time point	Day 90 after birth	692	4250
	F	3/time point	Day 21 after birth	129	725
		3/time point	Day 90 after birth	1430	5880
250	M	3/time point	Day 21 after birth	1250	6880
		3/time point	Day 90 after birth	2360	12040
	F	3/time point	Day 21 after birth	1470	7170
		3/time point	Day 90 after birth	3320	17200

4.2 Distribution

4.2.1 Distribution in central nervous system (CTD 4.2.2.3.1)

Following a single subcutaneous administration of ^{125}I-labeled galcanezumab or the control antibody (^{125}I-labeled IgG4) at 4 mg/kg to male rats, the distribution of galcanezumab in the central nervous system was investigated. In the ^{125}I-labeled galcanezumab group, the percentage of radioactivity concentration in each tissue relative to radioactivity concentration in plasma on Day 7 was only 0.10% to 0.35% in the central nervous system tissues (hypothalamus, prefrontal cortex, cerebellum, spinal cord, etc.) and 0.10% to 0.13% in cerebrospinal fluid, whereas in the peripheral tissues (dura mater, spleen, and trigeminal ganglia), the percentage was 5% to 11%. No significant difference was observed in the distribution of radioactivity between the ^{125}I-labeled galcanezumab group and the control antibody group.

The applicant explained that other tissue distribution studies were not conducted because galcanezumab is an IgG antibody that is distributed mainly within vascular systems and the distribution volume in monkeys [0.14 L, see Section "4.1.1 Single-dose study"] was almost the same as the estimated total plasma volume (0.224 L in a monkey weighing 5 kg, *Pharmaceut Res.* 1993;10:1093-5).

4.2.2 Placental transfer (CTD 4.2.3.5.2.2 and 4.2.3.5.2.5)

Galcanezumab 100 mg/kg was administered subcutaneously to rats once every week from 14 days before mating through Gestation Day 13. Galcanezumab concentration in fetal serum on Gestation Day 20 was 25% to 39% relative to the concentration in the serum of the maternal animal.

Galcanezumab 100 mg/kg was administered subcutaneously to rabbits on Gestation Days 7, 12, 16, and 20. Galcanezumab concentration in fetal serum on Gestation Day 29 was 110% to 441% relative to the concentration in the serum of the maternal animal.

4.3 Metabolism and excretion

Studies on the metabolism and excretion of galcanezumab were not conducted for this application.

The applicant's explanation about the metabolism and excretion of galcanezumab:
Galcanezumab is an IgG antibody and is presumably be eliminated from the body by the catabolism of protein into peptides and amino acids. IgG antibodies have shown to be excreted in human milk (*J Hum Lact.* 2005;21:439-43), the possibility cannot be excluded that galcanezumab is also excreted in milk, for being an IgG antibody. Whether to continue or discontinue breastfeeding should be determined by taking into account the clinical benefit of galcanezumab and the nutritional benefit of breast milk, and this will be advised via the package insert.

4.R Outline of the review conducted by PMDA

PMDA's view:
Although no nonclinical studies were conducted on the metabolism and excretion of galcanezumab, it is possible to deduce the metabolism and excretion of galcanezumab from the information so far available. The applicant's evaluation of nonclinical pharmacokinetics of galcanezumab is appropriate, judging from the submitted data and the applicant's explanation. Taking account of the possible excretion of galcanezumab in milk, the applicant intends to urge careful consideration of whether

breastfeeding needs to be continued in the use of galcanezumab for lactating patients via the package insert [see Section "4.3 Metabolism and excretion"], which is appropriate.

5. Toxicity and Outline of the Review Conducted by PMDA

As toxicology studies of galcanezumab, the applicant submitted the data from repeated-dose toxicity studies, reproductive and developmental toxicity studies, and toxicity studies in juvenile animals.

5.1 Single-dose toxicity

No single-dose toxicity study was conducted on galcanezumab. The acute toxicity of galcanezumab was evaluated based on the results of the initial dose in the 26-week repeated-dose toxicity studies in rats and monkeys (Table 9).

Table 9. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (SD)	Subcutaneous	0,[a] 20, 250	Acute toxicity evaluated in 26-week repeated dose toxicity study: No acute toxicity	>250	4.2.3.2.3
Male and female cynomolgus monkeys	Subcutaneous	0,[a] 2, 100	Acute toxicity evaluated in 26-week repeated dose toxicity study: No acute toxicity	>100	4.2.3.2.6

a, Water for injection containing 10 mmol/L sodium citrate buffer, 150 mmol/L sodium chloride, and 0.02% polysorbate 80

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in rats (6, 12, and 26 weeks) and in monkeys (6, 12, and 26 weeks) (Table 10). As changes associated with galcanezumab, inflammation at the administration site, etc. were observed in multiple studies. The applicant, however, explained that they were mild in severity and are of low toxicological significance [see Section "5.6 Local tolerance"]. In the repeated-dose toxicity studies in rats (26 weeks) and monkeys (26 weeks), the exposure ($AUC_{0\text{-}7d}$) at the no observed adverse effect level (NOAEL) (250 mg/kg in rats, 100 mg/kg in monkeys) was 2935 and 24150 μg·day/mL, respectively. The mean serum concentration calculated at steady state was 16 times (rats) and 130 times (monkeys) the mean serum concentration (26.5 μg/mL) at steady state in humans following the administration at the clinical dose (120 mg).

Table 10. Repeat-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	Attached document CTD
Male and female rats (SD)	Subcutaneous	6 weeks (once weekly) + 9-week withdrawal	0,[a] 1.5, 15, 100	≥15: Inflammation at administration site, etc.	100	4.2.3.2.1
Male and female rats (SD)	Subcutaneous	12 weeks (once weekly) + 6-week withdrawal	0,[a] 15, 100	No toxic finding	100	4.2.3.2.2
Male and female rats (SD)	Subcutaneous	26 weeks (once weekly)	0,[a] 20, 250	≥20: Inflammation at administration site, etc.	250	4.2.3.2.3
Male and female cynomolgus monkeys	Subcutaneous	6 weeks (once weekly) + 9-week withdrawal	0,[a] 1.5, 15, 100	≥1.5: Inflammation at administration site, etc.	100	4.2.3.2.4
Male and female cynomolgus monkeys	Subcutaneous	12 weeks (once weekly) + 6-week withdrawal	0,[a] 15, 100	≥15: Inflammation at administration site, etc.	100	4.2.3.2.5
Male and female cynomolgus monkeys	Subcutaneous	26 weeks (once weekly)	0,[a] 2, 100	≥2: Inflammation at administration site, etc. (females)	100	4.2.3.2.6

a, Water for injection containing 10 mmol/L sodium citrate buffer, 150 mmol/L sodium chloride, and 0.02% polysorbate 80

5.3 Genotoxicity

Because galcanezumab is an antibody and is not considered to directly interact with DNA or other chromosomal components, no genotoxicity study was conducted.

5.4 Carcinogenicity

Because galcanezumab is an antibody, its carcinogenicity was evaluated in accordance with ICH S6 (R1) Guideline without conducting any standard carcinogenicity study. The applicant determined that the carcinogenic risk of galcanezumab is low, judging from the following findings:

- In the repeated-dose toxicity studies conducted for up to 26 weeks in rats and monkeys, there were no findings suggestive of the carcinogenicity of galcanezumab.
- Carcinogenicity due to the CGRP-inhibitory action of galcanezumab is not suggested from the action of CGRP (e.g., proangiogenic effect, etc.).

5.5 Reproductive and developmental toxicity

Studies were conducted on fertility in male rats, fertility and embryo-fetal development in female rats, fertility and embryo-fetal development in rabbits, and the effects on pre- and post-natal development, including maternal function in rats (Table 11).

Table 11. Reproductive and developmental toxicity studies

Study	Test system	Rout of administration	Treatment duration	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	Attached document CTD
Fertility study	Male rats (SD)	Subcutaneous.	28 days before mating to 1 day before necropsy (once weekly)	0,[a] 30, 250	Parental animals: None Fertility: None	250	4.2.3.5.1.1
Study of fertility and embryo-fetal development	Female rats (SD)	Subcutaneous	14 days before mating to Gestation Day 13 (once weekly)	0,[a] 30, 100	Parental animals: None Fertility: None Fetuses: None	Parental animals (general toxicity): 100 (fertility): 100 Embryos/fetuses: 100	4.2.3.5.2.2
	Female rats (SD)	Subcutaneous	14 days before mating to Gestation Day 18 (twice weekly)	0,[b] 250	Parental animals: None Fertility: None Fetuses: 250: Increased rate of short ribs[c]	Parental animals (general toxicity): 250 (fertility): 250 Embryos/fetuses: 250	4.2.3.5.2.3
Study of embryo-fetal development	Female rabbits (NZW)	Subcutaneous	Gestation Day 7, 12, 16, 20	0,[a] 30, 100	Maternal animals: None Fetuses: None	Maternal animals: 100 Embryos/fetuses: 100	4.2.3.5.2.5
Study for effects on pre- and postnatal development, including maternal function	Female rats (SD)	Subcutaneous	Maternal animals: Gestation Day 6, 9, 12, 15, 18, 21, Lactation Day 2, 5, 8, 11, 14, 17, 20	0,[b] 30, 250	Maternal animals: Death: 250 (1/26[d]) F1 offspring: None	Maternal animals: 250 F1 offspring (general toxicity): 250 (development): 250	4.2.3.5.3.1

a, Water for injection containing 10 mmol/L sodium citrate buffer, 150 mmol/L sodium chloride, and 0.02% polysorbate 80
b, Water for injection containing 10 mmol/L L-histidine buffer, 150 mmol/L sodium chloride, and 0.02% polysorbate 80
c, For being a mutation-associated change, the applicant determined that it be of low toxicological significance based on the incidence among littermates within the range of the historical data of the study facility.
d, The cause of the death is unclear. The applicant however determined that the death was unrelated to the study drug for the following reason: no death was observed in the 250 mg/kg group in the rat study of fertility and embryo-fetal development which was conducted under a similar administration condition.

5.6 Local tolerance

Local tolerance was evaluated in repeated subcutaneous dose toxicity studies in rats and monkeys. Both rats and monkeys showed inflammatory change at the administration site, but it was a mild change accompanied no change in clinical signs and was reversible. The applicant determined that the change was of little toxicological significance and that galcanezumab has little local irritant effect.

5.7 Other toxicity studies

5.7.1 Study on juvenile animals

A study on juvenile rats was conducted (Table 12).

Table 12. Study on juvenile animals

Test system	Route of administration	Treatment duration	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	Attached document CTD
Male and female rats (SD)	Subcutaneous	21 to 90 days after birth (twice weekly)	0,[a] 30, 250	≥30: Inflammation-related findings[b] (mononuclear cell infiltration at the administration site, increased levels of fibrinogen and globulin), increased level of creatine kinase[b] 250: Changes in bone parameter values[c] (decreased mineral content at the femoral metaphysis/decreased mineral content in the trabecular bone/decreased bone density in the trabecular bone/decreased sectional area of the trabecular bone, decreased outer circumference of the periosteum of femoral shaft) Reversible	250	4.2.3.5.4.1

a, Water for injection containing 10 mmol/L L-histidine buffer, 150 mmol/L sodium chloride, and 0.02% polysorbate 80
b, The applicant determined that the findings were of low toxicological significance because they were mild and reversible.
c, The applicant determined that the findings were of low toxicological significance because no change was observed in the bone length or cortex and the findings were reversible.

5.R Outline of the review conducted by PMDA

Based on the documents submitted, PMDA concluded that the nonclinical toxicity studies did not raise any concern in the clinical use of galcanezumab.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

During the development process of galcanezumab, changes were made in the manufacturing process and manufacturing site of the drug substance and in the dosage form, formulation, and manufacturing site of the drug product [see Sections "2.1.4 Manufacturing process development" and "2.2.3 Manufacturing process development"]. The proposed formulations are PFS and AI formulations which are identical with those used in the Japanese and foreign phase III studies.

Serum galcanezumab concentration was measured by ELISA. The lower limit of quantitation was 0.00075 μg/mL. Total CGRP concentration in plasma was measured by electrochemiluminescence (ECL) method. The lower limit of quantitation was 0.06 ng/mL.

Serum anti-drug antibody (ADA) concentration was measured by ELISA. The detection limit was 7.5 ng/mL. Anti-galcanezumab neutralizing antibody in serum was assumed to be positive if optical density (OD) decreased by ≥19.9% in the presence of an excess amount of CGRP in the ADA assay system of ELISA.

6.1.1 Comparison between lyophilized formulation and liquid formulation (Study CGAO; CTD 5.3.3.1.3 [Reference data]; October 2015 to September 2016)

The lyophilized galcanezumab formulation (Process B) or the liquid galcanezumab formulation (Process D) was administered at 300 mg each subcutaneously as a single dose to 160 non-Japanese healthy

subjects (80/group). The least squares geometric mean ratio [90% confidence interval (CI)] of AUC_{last} and C_{max} of galcanezumab in the liquid formulation group to that in the lyophilized formulation group was 0.885 [0.817, 0.960] and 0.896 [0.831,0.966], respectively. Over-time changes in plasma total CGRP concentration were similar between the lyophilized formulation group and the liquid formulation group.

ADA was positive in 57.5% (92 of 160) of subjects, and neutralizing antibody was positive in all of these subjects. Treatment emergent anti-drug antibody (TE-ADA) was positive[1)] in 25.6% (41 of 160) of subjects.

6.1.2 Comparisons between administration sites and between PFS and AI formulations (Study CGAQ; CTD 5.3.3.4.1 [Reference data]; July 2016 to ■ 2017)

Galcanezumab 240 mg in the PFS or AI formulation was administered subcutaneously as a single dose in the upper arm, abdomen, or thigh of 160 non-Japanese healthy subjects (80/group). The least squares geometric mean ratio [90% CI] of AUC_{last} and C_{max} of galcanezumab in the AI group to that in the PFS group was 0.977 [0.885, 1.08] and 1.03 [0.933, 1.13], respectively.

Table 13 shows the PK parameter values of galcanezumab by administration site. The PK of galcanezumab was not significantly affected by the administration site.

Table 13. PK parameters of galcanezumab following a single subcutaneous dose of 240 mg by administration site

Administration site	Number of subjects	AUC_{last} (μg·day/mL)	C_{max} (μg/mL)
Upper arm	51	1090[a] (37.0)	30.5 (34.1)
Abdomen	52	1170[a] (31.8)	32.5 (36.9)
Thigh	46	1120[b] (32.8)	32.8 (38.0)

Geometric mean (coefficient of variation [%])
a, n = 44; b, n = 40

Over-time changes in total plasma CGRP concentration after galcanezumab administration were similar regardless of the formulation or administration site.

During this study, ADA was positive in 19.4% (31 of 160) of subjects and neutralizing antibody was positive in 15.6% (25 of 160) of subjects. At baseline, ADA was positive in 12 subjects, and neutralizing antibody was positive in 7 of them. During the 20-week follow-up period, 8 subjects turned positive for TE-ADA.[1)]

6.2 Clinical pharmacology

The PK and pharmacodynamic (PD) parameter values are expressed in mean or mean ± SD, unless specified otherwise.

1) Patients who tested positive for ADA at baseline and had a post-baseline antibody titer increasing ≥4 times the baseline value at least once or those who tested negative for ADA at baseline and had a post- baseline antibody titer of ≥20 at least once

6.2.1 Study in healthy subjects

6.2.1.1 Single and multiple subcutaneous administration study in Japanese and Caucasian subjects (Study CGAE; CTD 5.3.3.1.1; June 2014 to January 2015)

A single dose of galcanezumab 5, 50, 120, 300 mg or placebo was administered subcutaneously to 35 healthy subjects (19 Japanese, 16 Caucasians). Tables 14 and 15 show the PK parameter values of galcanezumab and total plasma CGRP concentration, respectively.

Table 14. PK parameters of galcanezumab following a single subcutaneous dose of galcanezumab

Dose (mg)	Subjects	N	AUC_{inf} (μg·day/mL)	C_{max} (μg/mL)	t_{max}[a] (day)	$t_{1/2}$ (day)	CL/F (L/day)	Vz/F (L)
5	Japanese	3	27.9 (19)	0.914 (11)	6.26	22.8 (28)	0.179 (19)	5.89 (12)
	Caucasians	3	28.8 (36)	0.657 (28)	7.00	27.0 (11)	0.174 (36)	6.75 (25)
50	Japanese	3	180 (48)	4.48 (63)	9.00	22.6 (20)	0.277 (48)	9.02 (28)
	Caucasians	2	103, 288[b]	2.46, 6.47[b]	5.00, 9.00[b]	23.2, 23.5[c]	0.174, 0.486[b]	5.83, 16.5[b]
120	Japanese	4	829 (4)[c]	19.5 (9)	4.62	28.7 (14)[c]	0.145 (4)[c]	5.99 (12)[c]
	Caucasians	3	700 (65)	16.2 (31)	7.00	26.8 (21)	0.171 (65)	6.62 (40)
300	Japanese	5	1870 (28)	44.4 (19)	5.00	29.5 (32)	0.160 (28)	6.81 (20)
	Caucasians	3	1440 (5)	36.8 (7)	5.00	24.0 (18)	0.209 (5)	7.22 (14)

Geometric mean (coefficient of variation [%])
a, Median; b, Individual values of 2 subjects; c, n = 3

Table 15. Total plasma CGRP concentration (ng/mL) following a single subcutaneous dose of galcanezumab

Time point of measurement	Placebo		5 mg		50 mg		120 mg		300 mg	
	Japanese (n = 4)	Caucasians (n = 4)	Japanese (n = 3)	Caucasians (n = 3)	Japanese (n = 3)	Caucasians (n = 3)	Japanese (n = 4)	Caucasians (n = 3)	Japanese (n = 5)	Caucasians (n = 3)
Baseline	0.13	0.08	0.03	0.03	0.03	0.03	0.03	0.03	0.04	0.03
After administration										
After 8 hours	0.15	0.11	0.03	0.03	0.03	0.03	0.05	0.03	0.03	0.06
After 1 day	0.17	0.11	0.03	0.03	0.03	0.03	0.10	0.06	0.07	0.09
After 2 days	0.15	0.11	0.05	0.03	0.06	0.11	0.22	0.19	0.20	0.22
After 4 days	0.17	0.09	0.09	0.06	0.14	0.31	0.38	0.33	0.47	0.46
After 5 days	0.19	0.11	0.09	0.11	0.19	0.41	0.48	0.43	0.63	0.62
After 7 days	0.18	0.12	0.16	0.16	0.30	0.62	0.68	0.59	1.12	0.82
After 14 days	0.16	0.11	0.18	0.18	0.56	0.52, 2.26[a]	0.89[b]	0.97	1.66	1.34
After 28 days	0.16	0.58	0.20	0.19	0.64	0.58, 1.86[a]	1.23[b]	1.38	2.19	2.01
After 56 days	0.17	0.42	0.07	0.09	0.45	0.52, 1.19[a]	1.16[b]	1.31	2.21	1.37, 2.47[a]
After 84 days	0.09	0.19	0.03	0.05	0.23	0.30, 0.55[a]	0.91[b]	0.96	1.55	0.77, 1.85[a]
After 112 days	0.09	0.16	0.03	0.03	0.12	0.18, 0.28[a]	0.51[b]	0.64	1.00	0.38, 1.02[a]
After 140 days	0.06	0.15	0.03	0.03	0.05	0.11, 0.14[a]	0.29[b]	0.38	0.74	0.25, 0.43[a]

a, Individual values in 2 subjects; b, n = 3

Galcanezumab 300 mg was administered subcutaneously 3 times 4 weeks apart to 8 healthy subjects (5 Japanese, 3 Caucasians). Table 16 shows the PK parameter values of galcanezumab.

Table 16. PK parameters of galcanezumab following multiple subcutaneous doses of galcanezumab

Time point of measurement	Subjects	N	AUC_{τ} (μg·day/mL)	C_{max} (μg/mL)	t_{max}[a] (day)	$t_{1/2}$ (day)	Cumulative index
Day 1	Japanese	5	808 (44)	38.0 (49)	5.00	-	-
	Caucasians	3	679 (42)	33.7 (38)	4.00	-	-
Day 29	Japanese	5	1310 (59)	64.1 (58)	9.00	-	-
	Caucasians	3	785, 725[b]	54.0 (70)	4.00	-	-
Day 57	Japanese	5	1410 (54)	67.1 (66)	4.00	34.7 (33)	1.74 (10)
	Caucasians	2	1080, 955[b]	51.8, 46.2[b]	5.00, 5.00[b]	24.9, 29.6[b]	1.71, 2.01[b]

Geometric mean (coefficient of variation [%])
a, Median; b, Individual values of 2 subjects; -, Not calculated

TE-ADA[1)] was positive in 1 Japanese subject receiving a single subcutaneous dose of galcanezumab 5 mg, and in 1 each of Japanese and Caucasian subject receiving multiple subcutaneous doses of galcanezumab 300 mg.

6.2.2 Studies in patients

6.2.2.1 Phase II study in Japanese patients with EM (Study CGAN; CTD 5.3.5.1.1: November 2016 to January 2019)

Galcanezumab 120, 240 mg or placebo was administered subcutaneously once monthly for 6 months to 459 Japanese patients with episodic migraine (EM). In the galcanezumab 120 mg group, the starting dose was 240 mg and each succeeding dose was 120 mg.

Serum galcanezumab concentration reached steady state faster in the 120 mg group than in the 240 mg group, whereas serum galcanezumab concentration at steady state in the 240 mg group was approximately 2 times that in the 120 mg group. Serum galcanezumab concentration decreased after the end of the treatment.

Total plasma CGRP concentration started to increase after galcanezumab treatment and decreased to near baseline after the end of the treatment. The concentration was slightly high in the 240 mg group as compared to the 120 mg group.

6.2.2.2 Long-term treatment study in Japanese patients with EM or CM (Study CGAP; CTD 5.3.5.2.1; [redacted] 2017 to August 2019)

Galcanezumab 120 or 240 mg was administered subcutaneously once monthly for 12 months to 246 Japanese patients with EM who had completed the double-blind phase in Study CGAN and 65 Japanese patients with chronic migraine (CM) newly enrolled in this study. Patients with EM in the 120 mg group who had been treated with placebo in Study CGAN and patients with CM assigned to the 120 mg group received the starting dose of 240 mg, followed by each succeeding dose of 120 mg.

Patients with EM who had been treated with galcanezumab in Study CGAN showed serum galcanezumab concentration being maintained at steady state. Patients with EM previously treated with placebo in Study CGAN and patients with CM newly enrolled in this study showed over-time change in serum galcanezumab concentration similar to that observed in Study CGAN.

Patients with EM who had been treated with galcanezumab in Study CGAN showed the total plasma CGRP concentration being maintained at steady state, which decreased after the end of the treatment.

Patients with EM who had been treated with placebo in Study CGAN and patients with CM newly enrolled in this study showed over-time change in total plasma CGRP concentration similar to that observed in Study CGAN.

6.2.2.3 Phase III study and long-term treatment study in non-Japanese patients with EM or CM

In the following phase III studies and long-term treatment study in non-Japanese patients with EM or CM, galcanezumab 120, 240 mg or placebo was administered once monthly for 3 to 12 months (in the galcanezumab 120 mg group, the starting dose was 240 mg). In both studies, over-time changes in serum galcanezumab concentration and in total plasma CGRP concentration were similar to those observed in Study CGAN.

- Phase III study in patients with EM (n = 862) (Study CGAG; CTD 5.3.5.1.3; January 2016 to [redacted] 2017)
- Phase III study in patients with EM (n = 922) (Study CGAH; CTD 5.3.5.1.4; January 2016 to [redacted] 2017)
- Phase III study in patients with CM (n = 1117) (Study CGAI; CTD 5.3.5.1.5; January 2016 to [redacted])
- Long-term treatment study in patients with EM or CM (n = 270) (Study CGAJ; CTD 5.3.5.2.2; December 2015 to September 2017)

6.2.3 PPK analysis

6.2.3.1 PPK analysis on data of clinical studies in non-Japanese subjects (CTD 5.3.3.5.1)

A population pharmacokinetic (PPK) analysis was conducted using the data of serum galcanezumab concentration at 15770 time points in 1889 subjects, obtained from the phase I foreign studies in Japanese and Caucasian healthy subjects and non-Japanese healthy subjects, respectively (Study CGAE and Study CGAO), the foreign phase II study (Study CGAB) and foreign phase III studies (Studies CGAG and CGAH) in non-Japanese patients with EM, and the foreign phase III study in non-Japanese patients with CM (Study CGAI). The PK of galcanezumab was described by a 1-compartment model with the first order absorption and linear elimination.

Candidate covariates for the PK parameters (CL/F, V/F, and absorption rate constant [k_a]) were age, dose, body weight, race,[2)] subrace,[3)] ethnicity,[4)] sex, healthy subjects, ADA titer, ADA-positive, TE-ADA-positive,[1)] creatinine clearance (CL_{cr}) based on Cockcroft-Gault equation, bilirubin, and administration site. Among these, body weight was selected as the covariate significantly affecting CL/F.

The population mean parameter values (inter-individual variability) of the final model were as follows: CL/F, 0.00785 L/h (34%); V/F, 7.33 L (34%); and k_a, 0.0199 h^{-1} (92%).

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2) Caucasians, blacks, Asians, mixed, native Americans

3) Japanese, blacks, Europeans, Chinese, Filipino, native Hawaiians, Koreans, Samoans, Thais, Vietnamese, native Americans, Pakistanis, Indians, Alaskan natives, Taiwanese, African Americans, Africans, Bahamians, Dominicans, Haitians, Jamaicans, West Indians, Middle East or North Africans, and Arabs

4) Non-Hispanics, Hispanics

The PK parameter values of galcanezumab were estimated separately for each administration site (upper arm, abdomen, thigh, or buttock), using the final model. The PK of galcanezumab did not show any significant difference depending on the administration site including the buttock, the site not used in Study CGAQ.

6.2.3.2 PPK analysis based on clinical studies in non-Japanese and Japanese subjects (CTD 5.3.3.5.2)

A PPK analysis was conducted using serum galcanezumab concentration data obtained from 2309 subjects at 19876 measuring time points in 6 foreign clinical studies used in Section "6.2.3.1 PPK analysis on data of clinical studies in non-Japanese subjects," Japanese phase II study in Japanese patients with EM (Study CGAN), and Japanese long-term treatment study in Japanese patients with EM or CM (Study CGAP). In this analysis, the final model constructed in Section "6.2.3.1 PPK analysis on data of clinical studies in non-Japanese subjects" was used as the basic model. The evaluation of the effect of ethnicity (Japanese or non-Japanese) on PK parameters (CL/F, V/F, and k_a) identified no significant effect of ethnicity on any of the PK parameters.

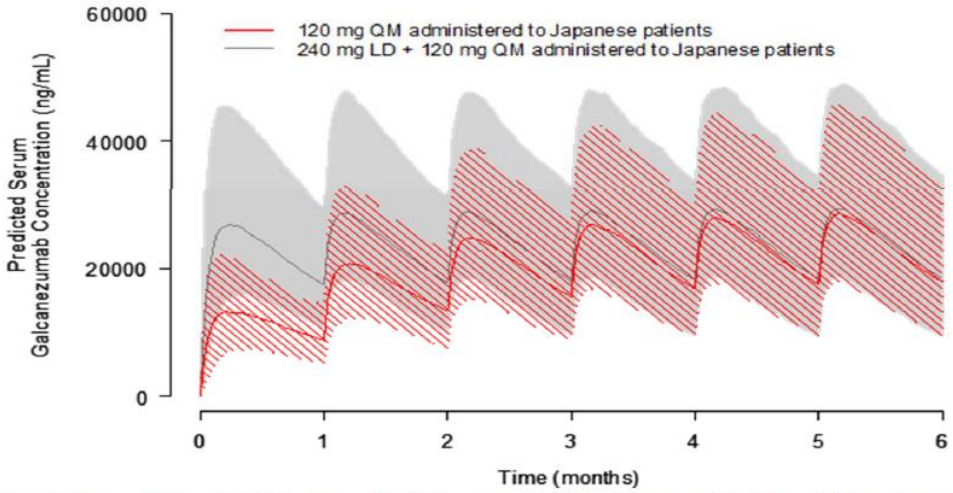
The population mean parameter values (inter-individual variability) of the final model were as follows: CL/F, 0.00772 L/h (32%); V/F, 7.06 L (32%); and k_a, 0.0200 h^{-1} (95%). Table 17 shows estimated PK parameter values of galcanezumab 120 mg (starting dose 240 mg) and 240 mg administered subcutaneously once monthly for 6 months.

Table 17. PK parameters of galcanezumab estimated from PPK analysis

Dose		120 mg[a]		240 mg	
Time point of measurement	PK parameter	Japanese[b]	Non-Japanese[c]	Japanese[b]	Non-Japanese[c]
Month 6	$C_{max, ss}$ (μg/mL)	32.9 (23)	27.8 (35)	66.2 (22)	54.0 (30)
	$t_{max, ss}$ (h)[d]	124	124	124	121
	$C_{min, ss}$ (μg/mL)	19.0 (32)	15.4 (53)	38.4 (31)	29.0 (46)
	$AUC_{\tau, ss}$ (μg·h/mL)	19100 (26)	15900 (41)	38400 (26)	30500 (36)

Geometric mean (coefficient of variation [%])
a, 240 mg at the starting dose; b, Studies CGAN and CGAP; c, Studies CGAG, CGAH, and CGAI; d, median

Figure 1 shows over-time changes in serum galcanezumab concentration predicted by the PPK analysis in patients receiving galcanezumab 120 mg or the starting dose of 240 mg plus succeeding doses of 120 mg subcutaneously once monthly. Based on the results, the applicant explained that serum galcanezumab concentration would reach steady state rapidly after the start of treatment if the once-monthly 120 mg regimen is started with the starting dose of 240 mg.



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

Figure 1. Over-time changes in serum galcanezumab concentration estimated by PPK analysis

6.2.4 Intrinsic factor PK studies

6.2.4.1 Effect of hepatic or renal impairment on the PK of galcanezumab

No clinical pharmacology study was conducted to evaluate the PK of galcanezumab in patients with hepatic or renal impairment.

The applicant's explanation:

Decreased hepatic or renal function is unlikely to affect the PK of galcanezumab, given the following observations:

- For being an IgG antibody, galcanezumab is thought to be eliminated from the body by the catabolism of protein into peptides and amino acids.
- In Section "6.2.3.1 PPK analysis on data of clinical studies in non-Japanese subjects," neither CL_{cr} calculated by Cockcroft-Gault equation (range, 24-308 mL/min) nor bilirubin (range, 2-46 μmol/L) was identified as a covariate significantly affecting the CL/F of galcanezumab.

6.R Outline of the review conducted by PMDA

6.R.1 Difference in the PK and PD of galcanezumab between Japanese and non-Japanese subjects and between patients with EM and patients with CM

The applicant's explanation:

In Study CGAE administering a single dose of galcanezumab 5 to 300 mg subcutaneously, no significant difference was observed in the PK or PD of galcanezumab between Japanese and Caucasian healthy subjects [see Section "6.2.1.1 Single and multiple subcutaneous administration study in Japanese and Caucasian subjects"]. Table 18 shows serum galcanezumab concentration in multiple subcutaneous administration of galcanezumab in the Japanese and foreign phase II, phase III, and long-term treatment studies. Both in patients with EM and in patients with CM, the mean serum galcanezumab concentration tended to be high in the Japanese population as compared to the non-Japanese population, but the distribution range of the individual values in the Japanese and non-Japanese population considerably overlapped each other. Total plasma CGRP concentration in multiple subcutaneous administration of

galcanezumab did not show any significant difference between Japanese and non-Japanese subjects, in patients with EM or in patients with CM.

Table 18. Comparison of serum galcanezumab concentration following multiple subcutaneous doses of galcanezumab (μg/mL)

Dose	Time point of measurement	EM		CM	
		Japanese (CGAN)	Non-Japanese (CGAG/CGAH)	Japanese (CGAP)	Non-Japanese (CGAI/CGAJ)
120 mg	Month 0.5	28.9 ± 7.6 (n = 115)	25.2 ± 9.2 (n = 430)	32.1 ± 8.8 (n = 32)	24.9 ± 8.3 (n = 292)
	Month 1	20.3 ± 5.1 (n = 115)	17.5 ± 6.9 (n = 430)	21.3 ± 7.7 (n = 32)	17.5 ± 6.2 (n = 295)
	Month 2	19.6 ± 6.8 (n = 115)	16.7 ± 7.5 (n = 421)	22.1 ± 9.3 (n = 32)	16.8 ± 7.2 (n = 288)
	Month 3	20.6 ± 7.4 (n = 113)	16.8 ± 7.6 (n = 408)	22.0 ± 9.0 (n = 32)	17.0 ± 7.3 (n = 281)
	Month 6	20.4 ± 7.5 (n = 104)	16.4 ± 8.5 (n = 381)	21.0 ± 8.3 (n = 30)	17.3 ± 8.8 (n = 22)
	Month 12	-	-	20.1 ± 8.6 (n = 28)	15.8 ± 6.6 (n = 18)
240 mg	Month 0.5	30.1 ± 9.1 (n = 114)	24.8 ± 8.6 (n = 409)	32.9 ± 8.4 (n = 33)	25.4 ± 8.9 (n = 304)
	Month 1	20.8 ± 6.8 (n = 114)	17.0 ± 6.9 (n = 422)	21.2 ± 7.6 (n = 32)	17.7 ± 6.4 (n = 300)
	Month 2	32.5 ± 11.4 (n = 113)	24.3 ± 9.6 (n = 414)	31.7 ± 10.8 (n = 30)	26.9 ± 10.9 (n = 298)
	Month 3	37.7 ± 13.3 (n = 113)	29.0 ± 11.7 (n = 400)	37.0 ± 13.3 (n = 30)	29.8 ± 11.7 (n = 294)
	Month 6	40.6 ± 18.4 (n = 111)	30.6 ± 12.5 (n = 369)	39.4 ± 13.5 (n = 29)	39.5 ± 16.6 (n = 28)
	Month 12	-	-	39.6 ± 13.6 (n = 27)	35.4 ± 16.0 (n = 26)

-, Not determined

In the PPK analysis using the clinical study data of non-Japanese and Japanese subjects [see Section "6.2.3.2 PPK analysis based on clinical studies in non-Japanese and Japanese subjects"], ethnicity (Japanese or non-Japanese) did not significantly affect the PK parameters (CL/F, V/F, and k_a) of galcanezumab, and the 90% prediction range of serum galcanezumab concentration in Japanese and non-Japanese subjects estimated by the final model mostly overlapped each other.

As for the PK and PD in patients with EM and in patients with CM, the results of the Japanese phase II study, foreign phase III study, and Japanese and non-Japanese long-term treatment studies did not show any significant difference either in serum galcanezumab concentration or total plasma CGRP concentration between patients with EM and patients with CM (Table 18).

The above results suggest that there is no significant difference in the PK or PD of galcanezumab between Japanese and non-Japanese subjects or between patients with EM and patients with CM.

PMDA's view:
Judging from the data submitted, the applicant's explanation about no significant difference in the PK or PD of galcanezumab between Japanese and non-Japanese subjects or between patients with EM and patients with CM is acceptable.

6.R.2 ADA

The applicant's explanation about the occurrence of ADA and neutralizing antibodies in clinical studies: Table 19 shows the percentage of ADA-positive or neutralizing antibody-positive subjects at baseline in the Japanese phase II study and in the Japanese and foreign long-term treatment studies. ADA and neutralizing antibody were positive in a certain percentage of subjects, which is possibly due to the exclusion of outliners in determining the cut points in the analyses of ADA and neutralizing antibody for galcanezumab.

Table 19. Percentage of ADA-positive or neutralizing antibody-positive subjects at baseline

Study	Treatment group	ADA-positive	Neutralizing antibody-positive
CGAN (double-blind period)	Placebo	6.5 (15/230)	3.0 (7/230)
	Galcanezumab	8.3 (19/229)	4.8 (11/229)
CGAP (open-label period)	Galcanezumab	7.7 (24/311)	4.5 (14/311)
CGAN (double-blind period) + CGAP (open-label period)	Galcanezumab	8.3 (10/120)	5.0 (6/120)
CGAJ (open-label period)	Galcanezumab	7.5 (20/266)	5.3 (14/266)

% (Number of patients)

Table 20 shows the percentage of subjects positive for TE-ADA[1)] or neutralizing antibody during the treatment period of Japanese and foreign long-term treatment studies. Most of the TE-ADA-positive[1)] subjects were also positive for neutralizing antibody. The percentage of patients became TE-ADA-positive for the first time during the 5-month follow-up period after the completion of galcanezumab administration period was 8% (25 of 299) in Study CGAP and in 9% (19 of 210) in Study CGAJ. The percentages of TE-ADA-positive[1)] and neutralizing antibody-positive subjects during the administration period and the follow-up period in the foreign phase III study were similar to those observed in the Japanese and foreign long-term treatment studies.

In most TE-ADA-positive[1)] subjects, the maximum antibody titer was <320. In studies administering galcanezumab for 12 months (Studies CGAP, CGAI, and CGAJ), most of the subjects who turned TE-ADA-positive[1)] during the administration period were found to have become TE-ADA-positive[1)] for the first time within 6 months after the start of administration.

Table 20. Percentage of subjects who became positive for TE-ADA[1)] or neutralizing antibody during the galcanezumab administration period of long-term treatment studies

Study	Patients	Treatment group	Duration of galcanezumab administration (months)	Incidence during galcanezumab administration	
				TE-ADA-positive	Neutralizing antibody-positive
CGAP	EM[a]	Placebo/galcanezumab 120 mg	12	16.1 (10/62)	16.1 (10/62)
		Placebo/galcanezumab 240 mg	12	10.9 (7/64)	9.4 (6/64)
		Galcanezumab 120 mg/ galcanezumab 120 mg	18	15.5 (9/58)	13.8 (8/58)
		Galcanezumab 240 mg/ galcanezumab 240 mg	18	9.7 (6/62)	8.1 (5/62)
	CM	Galcanezumab 120 mg	12	12.5 (4/32)	12.5 (4/32)
		Galcanezumab 240 mg	12	18.2 (6/33)	18.2 (6/33)
CGAJ	EM, CM	Galcanezumab 120 mg	12	12.4 (16/129)	12.4 (16/129)
		Galcanezumab 240 mg	12	7.3 (10/137)	7.3 (10/137)

% (Number of patients)

a, Proceeded to Study CGAP after completing the double-blind treatment phase of Study CGAN

The applicant's explanation about the effect of ADA on the PK, PD, efficacy, and safety of galcanezumab, based on the data from the Japanese and foreign phase I studies, phase II studies, phase III studies, and long-term treatment studies:

- During the treatment period and the follow-up period, serum galcanezumab concentration in subjects with a high ADA titer (≥640) was within the range observed in subjects with negative ADA or the lowest ADA titer (10-40).
- The results of Section "6.2.3.1 PPK analysis on data of clinical studies in non-Japanese subjects" showed that ADA titer, ADA positive, and TE-ADA positive[1)] were not identified as covariates significantly affecting the PK of galcanezumab.
- During the treatment period and the follow-up period, total plasma CGRP concentration in subjects with a high ADA titer (≥640) was within the range observed in subjects with negative ADA or the lowest ADA titer (10-40).
- Change from baseline in migraine headache days (MHD) per month was similar between TE-ADA-positive[1)] and -negative subjects [see Section "7.R.3.5 Efficacy in long-term administration"].
- No clear correlation was observed between the incidence or severity of injection site-related events or hypersensitivity-related events and TE-ADA positive[1)] or negative.

The above results suggest that ADA does not affect the PK, PD, efficacy, or safety of galcanezumab and therefore that ADA does not pose any clinical problems.

PMDA's view:

In Japanese and foreign clinical studies, ADA and neutralizing antibody were observed in a certain percentage of subjects, but they did not affect the PK, PD, or ADA of galcanezumab, and ADA did not tend to attenuate the efficacy of galcanezumab or cause more adverse events such as injection site-related events or hypersensitivity. Thus, regular measurement of ADA is not essential in clinical practice, and cautionary advice against ADA in clinical use of galcanezumab need not be provided. However, because of the possibly inadequate investigation on ADA, the occurrence of ADA and neutralizing antibody in the clinical studies should be communicated to healthcare professionals. If a serious allergic reaction or decreased efficacy of galcanezumab is observed during the treatment with galcanezumab, ADA should be determined and the relationship between ADA and efficacy or safety should be re-investigated as necessary.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted main efficacy and safety evaluation data from 9 studies shown in Table 21.

Table 21. Main evaluation data on efficacy and safety

Category	Region	Study	Phase	Study population	Number of subjects treated[a]	Outline of dosage regimen	Main endpoints
Evaluation	Foreign	CGAE	I	Healthy adults	45 (25)	Single-dose cohort: Placebo or galcanezumab 5, 50, 120, or 300 mg was administered subcutaneously as a single dose. Multiple-dose cohort: Placebo or galcanezumab 300 mg was administered subcutaneously for a total of 3 times 4 weeks apart.	Safety PK
	Foreign	CGAB	II	Patients with EM	410	Placebo or galcanezumab 5, 50, 120, or 300 mg was administered subcutaneously for a total of 3 times 1 month apart.	Efficacy Safety
	Japan	CGAN	II	Patients with EM	459	Placebo or galcanezumab 120 mg (starting dose, 240 mg) or 240 mg was administered subcutaneously for a total of 6 times 1 month apart.	Efficacy Safety
	Foreign	CGAG	III		858		Efficacy Safety
	Foreign	CGAH	III		915		Efficacy Safety
	Foreign	CGAI	III	Patients with CM	1113	Placebo or galcanezumab 120 mg (starting dose, 240 mg) or 240 mg was administered subcutaneously for a total of 12 times 1 month apart.	Efficacy Safety
	Global	CGAW	III	Patients with EM or CM who have an inadequate response to other drugs	462 (42)	Placebo or galcanezumab 120 mg (starting dose, 240 mg) was administered subcutaneously for a total of 6 times 1 month apart.	Efficacy Safety
	Japan	CGAP	III	Patients with EM or CM	311	EM: Galcanezumab 120 mg (starting dose, 240 mg in subjects who had been in the placebo group in Study CGAN) or 240 mg was administered subcutaneously for a total of 12 times 1 month apart. CM: Galcanezumab 120 mg (starting dose, 240 mg) or 240 mg was administered subcutaneously for a total of 12 times 1 month apart.	Efficacy Safety
	Foreign	CGAJ	III	Patients with EM or CM	270	Galcanezumab 120 mg (starting dose, 240 mg) or 240 mg was administered subcutaneously for a total of 12 times 1 month apart.	Efficacy Safety

a, The number in the parentheses indicates the number of Japanese subjects.

7.1 Phase I study (Study CGAE; CTD 5.3.3.1.1; June 2014 to January 2015)

A randomized, subject- and evaluator-blinded study in Japanese and Caucasian healthy subjects (target sample size, 44 subjects) was conducted to investigate the safety, tolerability, PK, and PD following single or multiple subcutaneous administration of galcanezumab at a single study site outside Japan.

In the single-dose cohort, a single dose of placebo or galcanezumab 5, 50, 120, or 300 mg was administered. In the multiple-dose cohort, placebo or galcanezumab 300 mg was administered 3 times 4 weeks apart. The study drug was administered subcutaneously in the abdomen.

A total of 45 enrolled subjects received the study drug (Table 22 for breakdown) and all of them were included in the safety analysis population. Treatment discontinuation occurred in 4 subjects (single-dose

cohort, 1 Caucasian in the galcanezumab 50 mg group, 1 Japanese in the 120 mg group, 1 Caucasian in the 300 mg group; multiple-dose cohort, 1 Caucasian in the galcanezumab 300 mg group). The main reason for the discontinuation was the request of the subject.

Table 22. Breakdown of enrolled subjects

	Single-dose cohort					Multiple-dose cohort	
	Placebo	Galcanezumab				Placebo	Galcanezumab
		5 mg	50 mg	120 mg	300 mg		300 mg/4 weeks
Japanese	n = 4	n = 3	n = 3	n = 4	n = 5	n = 1	n = 5
Caucasians	n = 4	n = 3	n = 3	n = 3	n = 3	n = 1	n = 3

Table 23 shows the incidences of adverse events and events reported in ≥2 subjects in any group. There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

Table 23. Incidences of adverse events (safety analysis population)

Single-dose cohort	Japanese				
	Placebo	Galcanezumab			
	(n = 4)	5 mg (n = 3)	50 mg (n = 3)	120 mg (n = 4)	300 mg (n = 5)
Incidence	75.0 (3)	66.7 (2)	66.7 (2)	100.0 (4)	100.0 (5)
Main events					
Injection site erythema	25.0 (1)	66.7 (2)	33.3 (1)	25.0 (1)	80.0 (4)
Injection site reaction	25.0 (1)	0 (0)	33.3 (1)	25.0 (1)	20.0 (1)
Neck pain	0 (0)	0 (0)	0 (0)	50.0 (2)	0 (0)
Injection site haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	20.0 (1)
Dermatitis contact	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

% (Number of subjects)

Single-dose cohort	Caucasians				
	Placebo	Galcanezumab			
	(n = 4)	5 mg (n = 3)	50 mg (n = 3)	120 mg (n = 3)	300 mg (n = 3)
Incidence	75.0 (3)	100.0 (3)	100.0 (3)	66.7 (2)	100.0 (3)
Main events					
Injection site erythema	50.0 (2)	100.0 (3)	100.0 (3)	33.3 (1)	66.7 (2)
Injection site reaction	25.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Neck pain	25.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dermatitis contact	0 (0)	0 (0)	0 (0)	33.3 (1)	0 (0)

% (Number of subjects)

Multiple-dose cohort	Japanese		Caucasians	
	Placebo	Galcanezumab	Placebo	Galcanezumab
		300 mg/4 weeks		300 mg/4 weeks
	(n = 1)	(n = 5)	(n = 1)	(n = 3)
Incidence	100.0 (1)	80.0 (4)	100.0 (1)	100.0 (3)
Main events				
Injection site erythema	100.0 (1)	80.0 (4)	100.0 (1)	66.7 (2)
Injection site reaction	0 (0)	80.0 (4)	0 (0)	33.3 (1)
Neck pain	0 (0)	0 (0)	0 (0)	0 (0)
Injection site haemorrhage	100.0 (1)	60.0 (3)	100.0 (1)	33.3 (1)
Dermatitis contact	0 (0)	60.0 (3)	0 (0)	66.7 (2)

% (Number of subjects)

7.2 Phase II studies

7.2.1 Foreign phase II study (Study CGAB; CTD 5.3.5.1.6; July 2014 to August 2015)

A randomized, double-blind study was conducted in non-Japanese patients with EM to investigate the efficacy, safety, and dose-response relationship of galcanezumab at 37 study sites outside Japan (target sample size, 402 subjects [134 in the placebo group, 67 in the galcanezumab group]).

The study consisted of the baseline measurement period of approximately 1 month, a 12-week double-blind treatment phase and a 12-week follow-up phase. During the study period, subjects were required to call Electronic Patient-Reported Outcomes (ePRO) interactive voice response system (IVRS) every day and answer questions about headache episodes they had experienced, etc. Before the start of the double-blind treatment phase, subjects were randomized to receive placebo or galcanezumab 5, 50, 120, or 300 mg at the ratio of 2:1:1:1:1 according to the minimization method with MHD (≥4 and <8 days, ≥8 and <11 days, ≥11 and ≤14 days, excluding suspected migraine headache) during the 28-day baseline measurement period and study site as adjustment factors. During the double-blind treatment phase, placebo or galcanezumab 5, 50, 120, or 300 mg was administered subcutaneously in the upper arm, abdomen, thigh, or buttock at a total of 3 office visits 4 weeks apart. The study sites and the subjects were blinded to the assignment during the double-blind treatment phase and throughout the follow-up phase.

The main inclusion criteria were patients aged 18 to 65 years who met the following conditions:

- Past history of migraine with or without aura according to International Classification of Headache Disorders (ICHD) version 3 beta (1.1 or 1.2) of International Headache Society (IHS) from ≥1 year before screening, and the first onset before age 50
- MHD (excluding suspected migraine) of 4 to 14 during the 28-day baseline measurement period, with migraine attacks of ≥2 times

The use of an antimigraine prophylactic drug was prohibited from ≥30 days before the baseline measurement period until the end of the double-blind treatment phase. The injection of botulinum A or B toxin into the head or neck was prohibited from ≥4 months before the baseline measurement period until the end of the double-blind treatment phase. The use of drugs for treating acute phase was permitted under certain conditions.[5)]

Of 414 subjects randomized, 410 received the study drug (137 in the placebo group, 68 in the galcanezumab 5 mg group, 68 in the 50 mg group, 70 in the 120 mg group, and 67 in the 300 mg group) and were included in Intent to treat (ITT). The ITT was used as the primary efficacy analysis population. During the double-blind treatment phase, 35 subjects (11, 9, 2, 8, and 5) discontinued the study. The main reason for the discontinuation was the subject's request in 16 subjects (6, 4, 1, 4, and 1).

As for change from baseline in MHD (except for suspected migraine) during the last 28 days in the 12-week double-blind treatment phase, the primary efficacy endpoint, the posterior probability of

5) Use of triptan and ergotamine was permitted for up to 9 days/month, and use of acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) for up to 14 days/month. Opioids and barbiturates were prohibited except for short-term, acute phase treatment (e.g., dental therapy).

improvement over placebo group (99.6%) exceeded the pre-defined value (95%) only in the galcanezumab 120 mg group (Bayesian time course hierarchical longitudinal model). Table 24 shows the change from baseline in MHD (including suspected migraine) during the last 28 days in the 12-week double-blind treatment phase.

Table 24. Change from baseline in MHD (days) during the last 28 days in the 12-week double-blind treatment phase (ITT [a])

	Placebo	Galcanezumab			
		5 mg	50 mg	120 mg	300 mg
Baseline Mean ± SD	(n = 134) 7.97 ± 3.08	(n = 65) 8.61 ± 3.30	(n = 68) 8.33 ± 3.21	(n = 69) 8.72 ± 3.47	(n = 66) 8.05 ± 2.79
Week 12 of double-blind treatment phase Mean ± SD	(n = 126) 4.03 ± 3.66	(n = 59) 3.78 ± 3.74	(n = 65) 3.88 ± 3.83	(n = 62) 2.64 ± 2.78	(n = 61) 3.26 ± 3.63
Change from baseline Mean ± SD	(n = 126) -3.84 ± 3.63	(n = 59) -4.76 ± 4.24	(n = 65) -4.52 ± 3.80	(n = 62) -5.85 ± 3.50	(n = 61) -4.62 ± 4.11

a, Subjects in ITT with both baseline and post-baseline data

Table 25 shows the incidences of adverse events during the double-blind treatment phase and events reported by ≥5% of subjects in any group.

Table 25. Incidences of adverse events during the double-blind treatment phase (ITT)

	Placebo	Galcanezumab			
	(n = 137)	5 mg (n = 68)	50 mg (n = 68)	120 mg (n = 70)	300 mg (n = 67)
Incidence	51.1 (70)	60.3 (41)	45.6 (31)	51.4 (36)	47.8 (32)
Main events					
Injection site pain	2.9 (4)	8.8 (6)	8.8 (6)	14.3 (10)	13.4 (9)
Upper respiratory tract infection	8.8 (12)	10.3 (7)	11.8 (8)	11.4 (8)	6.0 (4)
Nausea	2.9 (4)	1.5 (1)	2.9 (2)	0 (0)	6.0 (4)
Nasopharyngitis	2.2 (3)	11.8 (8)	4.4 (3)	8.6 (6)	3.0 (2)
Dysmenorrhoea[a]	0 (0)	1.8 (1)	6.6 (4)	0 (0)	3.6 (2)

% (Number of patients)

a, Incidence in female subjects (109 in the placebo group, 55 in the 5 mg group, 61 in the 50 mg group, 59 in the 120 mg group, and 56 in the 300 mg group)

No death occurred throughout the study period. During the double-blind treatment phase, other serious adverse events were observed in 1 subject (appendicectomy) in the galcanezumab 120 mg group. A causal relationship to the study drug was ruled out. An adverse event leading to discontinuation of the study drug was observed in 1 subject (visual impairment) in the galcanezumab 5 mg group and in 1 subject (abdominal pain) in the galcanezumab 300 mg group.

The incidence of adverse events during the follow-up phase was 28.0% (35 of 125 of subjects) in the placebo group and 29.0% (74 of 255 of subjects) in the galcanezumab group. The main events were back pain (5 subjects, 6 subjects) and sinusitis (3 subjects, 6 subjects). During the follow-up phase, serious adverse events were observed in 1 subject (Crohn's disease) in the galcanezumab 5 mg group and in 1 subject (suicidal ideation) in the 300 mg group. A causal relationship to the study drug was ruled out for both events.

7.2.2 Japanese phase II study (Study CGAN; CTD 5.3.5.1.1; December 2016 to January 2019)

A randomized, double-blind study in Japanese patients with EM was conducted to investigate the efficacy, safety, and dose-response relationship of galcanezumab at 40 study sites in Japan (target sample size, 451 subjects [225 in the placebo group, 113 in the galcanezumab group]).

The study consisted of a baseline measurement period of approximately 1 month, a 6-month double-blind treatment phase, and a 4-month follow-up phase. During the study period, subjects were required to log in to the ePRO diary every day and answer questions about headache episodes they had experienced, etc. At the start of the double-blind treatment phase, subjects were stratified by MHD during the 1-month baseline period (<8 days, ≥8 days) and randomized to the placebo group, the galcanezumab 120 mg group, or the galcanezumab 240 mg group at the ratio of 2:1:1. During the double-blind treatment phase, placebo, galcanezumab 120 mg (starting dose, 240 mg), or galcanezumab 240 mg was administered subcutaneously using the PFS formulation to the upper arm, abdomen, thigh, or buttock at a total of 6 office visits 1 month apart. The study sites and the subjects were blinded to the assignment during the double-blind treatment phase and throughout the follow-up phase. Subjects who completed the double-blind treatment phase had an option to proceed to Study CGAP, an open-label extension study. No follow-up was conducted for subjects who had proceeded to Study CGAP.

The main inclusion criteria were patients aged 18 to 65 years who met the following conditions:

- Past history of migraine with or without aura according to ICHD version 3 beta (1.1 or 1.2) of IHS from ≥1 year before screening, and the first onset before age 50
- Mean MHD of 4 to 14/month and migraine attacks occurring an average of ≥2 times per month both during the 3-month pre-screening and during the baseline measurement periods

The use of antimigraine prophylactic drug was prohibited from ≥30 days before the baseline measurement period until 1 month after the start of the follow-up phase. From 1 month after the start of the follow-up phase, the use of antimigraine prophylactic drug was permitted only for subjects with worsening symptom when the investigator considered clinically necessary. The injection of botulinum A or B toxin into the head or neck was prohibited from ≥4 months before the baseline measurement period throughout the study period. The use of drugs for treating acute phase was permitted under certain conditions.[6)]

A total of 459 randomized subjects (230 in the placebo group, 115 in the galcanezumab 120 mg group, 114 in the 240 mg group) received the study drug and were included in the safety analysis population and ITT, and the ITT was used as the primary efficacy analysis population. During the double-blind treatment phase, treatment discontinuation occurred in 19 subjects (5, 11, 3). Main reasons for the discontinuation were subject's request in 10 subjects (5, 5, 0) and adverse events in 7 subjects (0, 5, 2).

Table 26 shows the change from baseline in MHD per month during the 6-month double-blind treatment phase, the primary efficacy endpoint. A significant difference was observed between the placebo group

6) The use of opioids and barbiturates was permitted for up to 3 days/month and corticosteroid for emergency intravenous administration only for once.

and the galcanezumab 120 mg group and between the placebo group and the galcanezumab 240 mg group.

Table 26. Change from baseline in MHD (days) per month during the 6-month double-blind treatment phase (ITT[a])

	Placebo	Galcanezumab	
		120 mg	240 mg
Baseline Mean ± SD	(n = 230) 8.63 ± 2.95	(n = 115) 8.60 ± 2.80	(n = 114) 8.99 ± 2.99
Month 6 of double-blind treatment phase Mean ± SD	(n = 225) 8.25 ± 5.14	(n = 104) 5.56 ± 4.38	(n = 111) 5.21 ± 4.54
Change from baseline[b] Least squares mean ± SE	(n = 230) -0.59 ± 0.23	(n = 115) -3.60 ± 0.33	(n = 114) -3.36 ± 0.33
Difference from placebo group[b] Least squares mean [95% CI] *P* value	-	-3.01 [-3.80, -2.22] *P* < 0.001	-2.77 [-3.56, -1.98] *P* < 0.001

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point
b, Mixed models repeated measures (MMRM) with treatment group, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)
Step-down Dunnett procedure was used to adjust for multiplicity of test.

Table 27 shows the incidences of adverse events during the double-blind treatment phase and events reported by ≥5% of subjects in any group.

Table 27. Incidences of adverse events during the double-blind treatment phase (safety analysis population)

	Placebo	Galcanezumab	
		120 mg	240 mg
	(n = 230)	(n = 115)	(n = 114)
Incidence	64.8 (149)	85.2 (98)	81.6 (93)
Main events			
Injection site erythema	2.2 (5)	14.8 (17)	27.2 (31)
Nasopharyngitis	33.0 (76)	27.0 (31)	24.6 (28)
Gastroenteritis	2.2 (5)	6.1 (7)	2.6 (3)
Influenza	1.3 (3)	7.8 (9)	0.9 (1)
Injection site pruritus	0 (0)	8.7 (10)	20.2 (23)
Injection site swelling	1.3 (3)	10.4 (12)	10.5 (12)
Injection site pain	1.3 (3)	6.1 (7)	7.0 (8)
Dental caries	2.2 (5)	6.1 (7)	4.4 (5)
Urticaria	0 (0)	1.7 (2)	6.1 (7)
Back pain	1.3 (3)	1.7 (2)	5.3 (6)

% (Number of patients)

No death occurred throughout the study period. During the double-blind treatment phase, other serious adverse events were observed in 3 subjects in the galcanezumab 120 mg group (meniscus injury, sudden hearing loss, impacted tooth) and in 1 subject in the 240 mg group (nasal septum deviation). A causal relationship to the study drug could not be ruled out for sudden hearing loss in 1 subject in the galcanezumab 120 mg group. Adverse events leading to discontinuation of the study drug were observed in 5 patients in the galcanezumab 120 mg group (attention deficit hyperactivity disorder, cardiac function test abnormal, sudden hearing loss, tinnitus, ventricular extrasystoles) and in 2 subjects in the 240 mg group (injection site erythema, urticaria).

During the follow-up phase, adverse events were observed in 30.0% (30 of 100) of patients in the placebo group and in 39.4% (41 of 104) of patients in the galcanezumab group. The main event was

nasopharyngitis (4 patients, 8 patients). During the follow-up phase, a serious adverse event was observed in 1 patient (pneumonia) in the placebo group, but a causal relationship to the study drug was ruled out for the event.

7.3 Phase III studies

7.3.1 Foreign phase III study (a) (Study CGAG; CTD 5.3.5.1.3; January 2016 to [redacted] 2017)

A randomized, double-blind study was conducted in non-Japanese patients with EM to investigate the efficacy and safety of galcanezumab at 90 study sites outside Japan (target sample size, 825 subjects [413 in the placebo group, 206 in the galcanezumab group]). Subjects were stratified by region and MHD per month at baseline (<8 days, ≥8 days) and randomized to the placebo group, the galcanezumab 120 mg group, or the galcanezumab 240 mg group at the ratio of 2:1:1.

The study period, dosage regimen, main inclusion criteria, and restrictions of concomitant drugs were the same as those in Study CGAN [see Section "7.2.2 Japanese phase II study"] (except for transition to Study CGAP).

Of 862 subjects randomized, 858 (433 in the placebo group, 213 in the galcanezumab 120 mg group, 212 in the 240 mg group) received the study drug and were included in the safety analysis population and in ITT. The ITT was used as the primary efficacy analysis population. During the double-blind treatment phase, treatment was discontinued in 155 subjects (82, 36, 37). Main reasons for the discontinuation were subject's request in 60 subjects (33, 11, 16), lost to follow-up in 32 subjects (18, 9, 5), and adverse events in 26 subjects (10, 9, 7).

Table 28 shows the change from baseline in MHD per month during 6-month double-blind treatment phase, the primary efficacy endpoint. A significant difference was observed both between the placebo group and the galcanezumab 120 mg group and between the placebo group and the galcanezumab 240 mg group.

Table 28. Change from baseline in MHD (days) per month during 6-month double-blind treatment phase (ITT[a])

	Placebo	Galcanezumab	
		120 mg	240 mg
Baseline Mean ± SD	(n = 425) 9.09 ± 2.97	(n = 210) 9.16 ± 3.04	(n = 208) 9.09 ± 2.90
Month 6 of double-blind treatment phase Mean ± SD	(n = 342) 5.38 ± 4.43	(n = 177) 3.81 ± 4.42	(n = 171) 3.42 ± 3.90
Change from baseline[b] Least squares mean ± SE	(n = 425) -2.81 ± 0.24	(n = 210) -4.73 ± 0.29	(n = 208) -4.57 ± 0.29
Difference from placebo[b] Least squares mean [95% CI] *P* value	-	-1.92 [-2.48, -1.37] *P* < 0.001	-1.76 [-2.31, -1.20] *P* < 0.001

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point

b, MMRM with treatment group, region, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)

Comparisons of the primary endpoint between the galcanezumab 120 mg group and the placebo group and between the galcanezumab 240 mg group and the placebo group were performed using Dunnett test. For the evaluation of the primary endpoint and main secondary endpoints (50% response rate, 75% response rate, change in MHD per month requiring acute phase medication, change in the score limiting the daily social and work-related activities in Migraine Specific Quality of Life Questionnaire (MSQ), 100% response rate, change in Patient Global Impression of Severity [PGI-S]), the probability of type I error of the entire study was controlled to 5% (two-sided) using the superchain multiple testing procedure (*Stat Med*. 2013;32:486-508).

Table 29 shows the incidences of adverse events during the double-blind treatment phase and events reported by ≥5% of subjects in any group.

Table 29. Incidences of adverse events during the double-blind treatment phase (safety analysis population)

	Placebo	Galcanezumab	
	(n = 432)	120 mg (n = 206)	240 mg (n = 220)
Incidence	60.4 (261)	65.5 (135)	67.7 (149)
Main events			
Injection site pain	17.4 (75)	16.0 (33)	20.5 (45)
Injection site reaction	0.9 (4)	3.4 (7)	5.5 (12)
Upper respiratory tract infection	7.2 (31)	4.4 (9)	6.8 (15)
Nasopharyngitis	6.3 (27)	7.8 (16)	2.7 (6)
Urinary tract infection	3.5 (15)	3.9 (8)	5.9 (13)

% (Number of patients)

No death occurred throughout the study period. During the double-blind treatment phase, other serious adverse events were observed in 5 subjects in the placebo group (cholelithiasis in 2 subjects, deep vein thrombosis, pulmonary embolism, vertebral osteophyte) and in 6 subjects in the galcanezumab 120 mg group (incarcerated incisional hernia/seroma, ligament rupture, pancreatitis acute, small intestinal obstruction, tendonitis, tubular breast carcinoma). A causal relationship to the study drug was ruled out for all of them. Adverse events resulted in treatment discontinuation in 10 subjects in the placebo group, 7 in the galcanezumab 120 mg group, and 9 in the galcanezumab 240 mg group. The event observed in multiple subjects was migraine (1 in the placebo group, 1 in the galcanezumab 120 mg group, 4 in the 240 mg group).

During the follow-up phase, adverse events were observed in 26.1% (97 of 372) of subjects in the placebo group and 28.3% (104 of 368) in the galcanezumab group. The main event was upper respiratory tract infection (12 subjects in the placebo group, 11 subjects in the galcanezumab group). During the follow-up phase, serious adverse events were observed in 2 subjects in the placebo group (asthenia, ureterolithiasis) and 8 subjects in the galcanezumab group (pre-eclampsia, uterine leiomyoma, tonsil

cancer, vomiting, abortion missed, adjustment disorder with mixed anxiety and depressed mood, cardiac failure congestive/cardiomyopathy, inner ear disorder). A causal relationship to the study drug was ruled out for all of them.

7.3.2 Foreign phase III study (b) (Study CGAH; CTD 5.3.5.1.4; January 2016 to [redacted] 2017)

A randomized, double-blind study was conducted in non-Japanese patients with EM to investigate the efficacy and safety of galcanezumab at 109 study sites outside Japan (target sample size, 825 subjects [413 in the placebo group, 206 each in the galcanezumab groups]). Subjects were stratified by country and MHD per month during the baseline period (<8 days, ≥8 days) and randomized to the placebo group, the galcanezumab 120 mg group, or the galcanezumab 240 mg group at the ratio of 2:1:1.

The study period, dosage regimen, main inclusion criteria, and restrictions of concomitant drugs were the same as those in Study CGAN [see Section "7.2.2 Japanese phase II study"] (except for transition to Study CGAP).

Of 922 subjects randomized, 915 (461 in the placebo group, 231 in the galcanezumab 120 mg group, 223 in the galcanezumab 240 mg group) received the study drug and were included in the safety evaluation population and ITT. The ITT was used as the primary efficacy analysis population. During the double-blind treatment phase, treatment was discontinued in 129 subjects (74 in the placebo group, 28 in the galcanezumab 120 mg group, 27 in the galcanezumab 240 mg group). Main reasons for the discontinuation were subject's request in 64 subjects (39, 11, 14), adverse events in 22 subjects (8, 5, 9), and lost to follow-up in 17 subjects (10, 7, 0).

Table 30 shows the change from baseline in MHD per month during the 6-month double-blind treatment phase, the primary efficacy endpoint. A significant difference was observed both between the placebo group and the galcanezumab 120 mg group and between the placebo group and the galcanezumab 240 mg group.

Table 30. Change from baseline in MHD (days) per month during 6-month double-blind treatment phase (ITT[a])

	Placebo	Galcanezumab	
		120 mg	240 mg
Baseline Mean ± SD	(n = 450) 9.19 ± 2.98	(n = 226) 9.05 ± 2.88	(n = 220) 9.05 ± 2.94
Month 6 of double-blind treatment phase Mean ± SD	(n = 382) 5.81 ± 4.40	(n = 196) 4.21 ± 4.41	(n = 192) 3.99 ± 3.95
Change from baseline[b] Least squares mean ± SE	(n = 450) -2.28 ± 0.20	(n = 226) -4.29 ± 0.25	(n = 220) -4.18 ± 0.26
Difference from placebo[b] Least squares mean [95% CI] *P* value	-	-2.02 [-2.55, -1.48] *P* < 0.001	-1.90 [-2.44, -1.36] *P* < 0.001

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point

b, MMRM with treatment group, region, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)

Comparisons of the primary endpoint between the galcanezumab 120 mg group and the placebo group, and between the galcanezumab 240 mg group and the placebo group, was performed using Dunnett test. For the evaluation of the primary endpoint and main secondary endpoints (50% response rate, 75% response rate, change in MHD per month requiring acute phase medication, change in the score limiting the daily social and work-related activities in MSQ, 100% response rate, change in PGI-S), the probability of type I error of the entire study was controlled to 5% (two-sided) using the superchain multiple testing procedure *(Stat Med.* 2013;32:486-508).

Table 31 shows the incidences of adverse events during the double-blind treatment phase and events reported by ≥5% of subjects in any group.

Table 31. Incidences of adverse events during the double-blind treatment phase (safety analysis population)

	Placebo (n = 461)	Galcanezumab 120 mg (n = 226)	Galcanezumab 240 mg (n = 228)
Incidence	62.3 (287)	65.0 (147)	71.5 (163)
Main events			
Injection site pain	8.5 (39)	9.3 (21)	8.8 (20)
Injection site reaction	0.0 (0)	3.1 (7)	7.9 (18)
Nasopharyngitis	8.9 (41)	8.4 (19)	7.0 (16)
Upper respiratory tract infection	3.5 (16)	5.8 (13)	5.3 (12)

% (Number of patients)

No death occurred throughout the study period. During the double-blind treatment phase, other serious adverse events were observed in 5 subjects in the placebo group (gallbladder polyp, haemorrhoids, migraine, foot fracture/rib fracture/road traffic accident, suicide attempt), 5 subjects in the galcanezumab 120 mg group (adenocarcinoma of the cervix, bladder dysfunction, gastritis, pharyngitis bacterial, rectal polyp) and 7 subjects in the galcanezumab 240 mg group (acute myocardial infarction, cholelithiasis, disorientation/pyrexia, generalised tonic-clonic seizure, influenza, meniscus injury, transient ischaemic attack). A causal relationship to the study drug could not be ruled out for suicide attempt in 1 subject in the placebo group and disorientation/pyrexia in 1 subject in the galcanezumab 240 mg group. Adverse events leading to discontinuation of the study drug were observed in 8 subjects in the placebo group, 5 subjects in the galcanezumab 120 mg group, and 9 subjects in the galcanezumab 240 mg group. The event observed in multiple subjects was injection site reaction (1 subject in the galcanezumab 120 mg group, 3 subjects in the 240 mg group).

During the follow-up phase, adverse events were observed in 23.9% (98 of 410) of subjects in the placebo group and 19.5% (82 of 420) of subjects in the galcanezumab group. The main adverse event was viral upper respiratory tract infection (17 subjects, 9 subjects). During the follow-up phase, serious adverse events were observed in 3 subjects in the placebo group (appendicitis, goitre, pyelonephritis/urosepsis) and 4 subjects in the galcanezumab group (uterine leiomyoma, panic attack, patellofemoral pain syndrome, post-traumatic stress disorder). A causal relationship to the study drug was ruled out for all of them.

7.3.3 Foreign phase III study (c) (Study CGAI; CTD 5.3.5.1.5; January 2016 to [redacted] 20[redacted])

A randomized, double-blind study was conducted in non-Japanese patients with CM to investigate the efficacy and safety of galcanezumab at 116 study sites outside Japan (target sample size, 1140 subjects [570 in the placebo group, 285 in the galcanezumab group]).

The study consisted of a baseline measurement period of approximately 1 month, a 3-month double-blind treatment phase, a 9-month open-label treatment phase, and a 4-month follow-up phase. During the study period, subjects were required to log in to the ePRO diary every day and answer questions about headache episodes they had experienced. At the start of the double-blind treatment phase, subjects were stratified by country, overuse/no overuse of acute phase drugs, and use/no use of antimigraine

prophylactic drug, and were randomized to the placebo group, the galcanezumab 120 mg group, or the galcanezumab 240 mg group at the ratio of 2:1:1. During the double-blind treatment phase, placebo or galcanezumab 120 mg (starting dose, 240 mg), or galcanezumab 240 mg was administered subcutaneously for 3 times 1 month apart. During the open-label treatment phase, galcanezumab was administered subcutaneously for 9 times 1 month apart. The first dose of 240 mg and the second dose of 120 mg were followed by succeeding doses of either 120 or 240 mg selected at the discretion of the investigator. At each visit, the study drug was administered using the PFS formulation in the upper arm, abdomen, thigh, or buttock. The study site and subjects were blinded to the treatment assignment for the double-blind administration, and the blindness was maintained throughout the open-label treatment phase and the follow-up phase as well.

The main inclusion criteria were patients aged 18 to 65 years who met the following conditions:

- Being diagnosed with CM according to ICHD version 3 beta (1.3) of IHS, and the first onset before age 50
- An average of ≥15 days/month with headache both during the 3 months before screening and during the baseline measurement period (of these, ≥8 days/month with headache of migraine-like characteristics), and ≥1 day/month with no headache

The use of antimigraine prophylactic drugs (except for topiramate and propranolol) was prohibited from ≥30 days before the start of the baseline measurement period until 1 month after the start of the follow-up phase. Continued use of either topiramate or propranolol, but not both, for migraine prevention was permitted during the double-blind treatment phase if the dose had been stabilized ≥2 months before the start of the baseline measurement period. The use of other antimigraine prophylactic drugs was permitted from 1 month after the follow-up phase only for subjects with worsening symptom when considered clinically necessary by the investigator. The injection of botulinum A or B toxin into the head or neck was prohibited from ≥4 months before the baseline measurement period throughout the study period. The use of drugs for treating acute phase was permitted under certain conditions.[7)]

(a) Double-blind treatment phase

Of 1117 subjects randomized, 1113 (558 in the placebo group, 278 in the galcanezumab 120 mg group, 277 in the galcanezumab 240 mg group) received the study drug and were included in the safety evaluation population and ITT. The ITT was use as the primary efficacy analysis population. The treatment was discontinued in 75 subjects (49 subjects in the placebo group, 15 subjects in the galcanezumab 120 mg group, 11 subjects in the galcanezumab 240 mg group). Main reasons for the discontinuation were subject's request in 30 subjects (19, 4, 7), lost to follow-up in 15 subjects (10, 4, 1) and adverse events in 11 subjects (6, 3, 2).

Table 32 shows the change from baseline in MHD per month during the 3-month double-blind treatment phase, the primary efficacy endpoint. A significant difference was observed both between the placebo group and the galcanezumab 120 mg group and between the placebo group and the galcanezumab 240 mg group.

7) Use of opioids and barbiturates were permitted for ≤3 days/month, and use of corticosteroid was permitted for emergency intravenous administration only for once.

Table 32. Change from baseline in MHD (days) per month during the 3-month double-blind treatment phase (ITT[a])

	Placebo	Galcanezumab	
		120 mg	240 mg
Baseline Mean ± SD	(n = 538) 19.57 ± 4.61	(n = 273) 19.34 ± 4.25	(n = 274) 19.18 ± 4.62
Month 3 of double-blind treatment phase Mean ± SD	(n = 498) 15.24 ± 7.92	(n = 256) 12.81 ± 7.17	(n = 262) 13.29 ± 8.43
Change from baseline[b] Least squares mean ± SE	(n = 538) -2.74 ± 0.36	(n = 273) -4.83 ± 0.44	(n = 274) -4.62 ± 0.43
Difference from placebo[b] Least squares mean [95% CI] *P* value	-	-2.09 [-2.92, -1.26] *P* < 0.001	-1.88 [-2.71, -1.05] *P* < 0.001

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point

b, MMRM with treatment group, region, office visit (month), excess use/no excess use of baseline medications, use/no use of concomitant prophylactic drugs, and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

Comparison of the primary endpoint between the galcanezumab 120 mg group and the placebo group, and between the galcanezumab 240 mg group and the placebo group, was performed using Dunnett test. For the evaluation of the primary endpoint and main secondary endpoints (50% response rate, 75% response rate, change in MHD per month requiring acute phase medication, change in the score limiting the daily social and work-related activities in MSQ, 100% response rate, change in PGI-S), the probability of type I error of the entire study was controlled to 5% (two-sided) using the superchain multiple testing procedure (*Stat Med.* 2013;32:486-508).

Table 33 shows the incidences of adverse events and events reported by ≥5% of subjects in any group.

Table 33. Incidences of adverse events during the double-blind treatment phase (safety analysis population).

	Placebo	Galcanezumab	
	(n = 558)	120 mg (n = 273)	240 mg (n = 282)
Incidence	50.0 (279)	58.2 (63)	56.7 (160)
Main events			
Injection site pain	4.3 (24)	6.2 (17)	7.1 (20)
Injection site reaction	1.8 (10)	2.9 (8)	5.3 (15)
Nasopharyngitis	4.7 (26)	6.2 (17)	3.2 (9)

% (Number of patients)

No death occurred. Other serious adverse events were observed in 4 subjects in the placebo group (alcoholic pancreatitis, epistaxis, gastritis, myocardial infarction), 1 subject in the galcanezumab 120 mg group (colon cancer), and 4 subjects in the galcanezumab 240 mg group (hypokalaemia/nephrolithiasis, pancreatitis acute, pulmonary embolism, renal colic). A causal relationship to the study drug was ruled out for all events except for acute pancreatitis in the galcanezumab 240 mg group. Adverse events leading to discontinuation of the study drug were observed in 6 subjects in the placebo group, 1 subject in the galcanezumab 120 mg group, and 4 subjects in the galcanezumab 240 mg group. The event observed in multiple subjects was migraine (2 subjects in the placebo group).

(b) Open-label period

A total of 1022 subjects proceeded to the open-label period and received the study drug, and were included in the safety analysis population and ITT. The ITT was used as the primary efficacy analysis population. The treatment was discontinued in 197 subjects. Main reasons for the discontinuation were subject's request in 66 subjects, adverse events in 46 subjects, and lack of efficacy in 40 subjects.

Table 34 shows the change from baseline in MHD per month during the 9-month open-label treatment phase.

Table 34. Change from baseline in MHD (days) per month during the 9-month open-label treatment phase (ITT[a])

	Treatment group in double-blind period		
	Placebo	Galcanezumab	
		120 mg	240 mg
Month 9 of open-label treatment phase Mean ± SD	(n = 385) 9.23 ± 8.15	(n = 197) 8.39 ± 7.01	(n = 199) 9.92 ± 8.52
Change from baseline in double-blind period[b] Least squares mean ± SE	(n = 385) -8.46 ± 0.43	(n = 197) -9.03 ± 0.55	(n = 199) -7.98 ± 0.55

a, Subjects in ITT with baseline data and with data at Month 9 of the open-label treatment phase
b, MMRM with treatment group, region, office visit (month), excess use/no excess use of baseline medications, use/no use of concomitant prophylactic drugs, and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured)

Adverse events were observed in 70.4% (719 of 1022) of subjects. Main events were nasopharyngitis (98 subjects), upper respiratory tract infection (63 subjects), and injection site reaction (60 subjects).

No death occurred. Other serious adverse events were observed in 33 subjects (appendicitis, migraine, seizure, and urinary tract infection in 2 subjects each, etc.). A causal relationship to the study drug was ruled out for all events except for urticaria, seizure, migraine, and diverticulitis/abdominal pain upper. Adverse events leading to discontinuation of the study drug were observed in 46 subjects. The events observed in multiple subjects were urticaria (7 subjects) and back pain, dyspnoea, headache, hepatic enzyme increased, and rash (2 subjects each).

During the follow-up phase, no death occurred. The incidence of adverse events was 25.8% (231 of 897) in subjects who received ≥1 dose of galcanezumab. Main events were urinary tract infection in 15 subjects, nasopharyngitis in 14 subjects, and influenza in 11 subjects. Among subjects who received ≥1 dose of galcanezumab, 9 subjects had serious adverse events during the follow-up phase (abdominal pain lower, abdominal pain upper/haematemesis/nausea, foot fracture, pneumonia, pulmonary embolism, rash, urinary retention, urticaria, ventricular extrasystoles). A causal relationship to the study drug was ruled out for all events except for rash.

7.3.4 Global phase III study (Study CGAW; CTD 5.3.5.1.2; September 2018 to September 2019)

A randomized, double-blind study was conducted in patients with EM or CM who have an inadequate response to other drugs to investigate the efficacy and safety of galcanezumab at 64 study sites in Japan and foreign countries (target sample size, 420 subjects [250 patients with CM]).

The study consisted of a baseline measurement period of approximately 1 month, a 3-month double-blind treatment phase, and a 3-month open-label treatment phase. During the study period, subjects were required to log in to the ePRO diary every day and answer questions about headache episodes they had experienced. At the start of the double-blind treatment phase, subjects were stratified by country and frequency of headache during baseline period (EM with MHD of ≥4 and <8 days per month, EM or CM with MHD of ≥8 days per month) and were randomized to treatment groups. During the double-blind

treatment phase, placebo or galcanezumab 120 mg (240 mg starting dose) was administered subcutaneously for 3 times 1 month apart. During the open-label treatment phase, galcanezumab 120 mg (240 mg starting dose in subjects who received placebo during the double-blind treatment phase) was administered subcutaneously for 3 times 1 month apart. At each visit, the study drug was administered using the PFS formulation in the upper arm, abdomen, thigh, or buttock. Healthcare providers at the study sites were encouraged to treat subjects to reduce various injection site reactions (with cold compress, ice bag, topical anesthetic cream, etc.) before and after administration based on a clinical judgment or as needed. The study site and subjects continued to be blinded to the treatment assignment for the double-blind treatment phase during the open-label treatment phase as well.

The main inclusion criteria were patients aged 18 to 75 years who met the following conditions:

- Being diagnosed with migraine according to ICHD version 3 (1.1, 1.2, or 1.3) of IHS since ≥1 year before screening, and the first onset before age 50
- Mean MHD of ≥4/month and an average of ≥1 day/month with no headache both during the 3 months before screening and during the baseline measurement period
- Documented treatment history for the past 10 years before screening with 2 to 4 types of the following antimigraine prophylactic drugs that failed to show adequate efficacy (with the maximum tolerated doses in ≥2 months) or had safety problems: "propranolol or metoprolol," "topiramate," "valproic acid or divalproex," "amitriptyline," "flunarizine," "candesartan," "botulinum A or B toxin," and "other drugs approved in Japanese or foreign countries as antimigraine prophylactic drugs."

All of the following procedures were prohibited: the use of antimigraine prophylactic drugs from ≥5 days before the start of the baseline measurement period, the injection of botulinum A or B toxin into the head or neck from ≥3 months before the start of the baseline measurement period, and the use of cranial or cervical nerve block or the use of devices such as transcranial magnetic stimulator from ≥30 days before the start of the baseline measurement period. The prohibition lasted until the end of the study period. The use of drugs for treating acute phase was permitted under certain conditions.[8)]

(a) Double-blind treatment phase

[Entire population]

Of 463 subjects randomized, 462 (230 in the placebo group, 232 in the galcanezumab 120 mg group) received the study drug and were included in the safety analysis population and ITT. The ITT was used as the primary efficacy analysis population. A total of 11 subjects (4 in the placebo group, 7 in the galcanezumab 120 mg group) discontinued the study. Main reasons for the discontinuation were protocol deviation (1, 4) and subject's request in 3 subjects (2, 1).

Table 35 shows the change from baseline in MHD per month during the 3-month double-blind treatment phase, the primary efficacy endpoint. A significant difference was observed between the placebo group and the galcanezumab 120 mg group.

8) The use of opioids and barbiturates were permitted for ≤4 days/month, and the use of corticosteroid was permitted for emergency intravenous administration only for once.

Table 35. Change from baseline in MHD (days) per month during the 3-month double-blind treatment phase (ITTa, entire population)

	Placebo	Galcanezumab 120 mg
Baseline Mean ± SD	(n = 228) 12.94 ± 5.67	(n = 230) 13.39 ± 6.08
Month 3 of double-blind treatment phase Mean ± SD	(n = 224) 11.37 ± 6.68	(n = 224) 8.44 ± 6.42
Change from baseline[b] Least squares mean ± SE	(n = 228) -1.02 ± 0.32	(n = 230) -4.14 ± 0.32
Difference from placebo[b] Least squares mean [95% CI] *P* value	-	-3.12 [-3.92, -2.32] *P* < 0.0001

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point
b, MMRM with treatment group, region or country, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

Table 36 shows the results of the primary efficacy endpoint in subpopulations EM and CM.

Table 36. Change from baseline in MHD (days) per month during the 3-month double-blind treatment phase, in patients with EM and in patients with CM (ITT,[a] entire population)

	Patients with EM		Patients with CM	
	Placebo	Galcanezumab 120 mg	Placebo	Galcanezumab 120 mg
Baseline Mean ± SD	(n = 132) 9.20 ± 2.65	(n = 137) 9.47 ± 2.98	(n = 96) 18.08 ± 4.58	(n = 93) 19.17 ± 4.73
Month 3 of double-blind treatment phase Mean ± SD	(n = 129) 8.04 ± 4.77	(n = 136) 5.91 ± 4.21	(n = 95) 15.89 ± 6.26	(n = 88) 12.34 ± 7.28
Change from baseline[b] Least squares mean ± SE	(n = 132) -0.31 ± 0.34	(n = 137) -2.88 ± 0.34	(n = 96) -2.21 ± 0.64	(n = 93) -5.91 ± 0.65

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point
b, MMRM with treatment group, region or country, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

Adverse events were observed in 53.0% (122 of 230) of subjects in the placebo group and in 51.3% (119 of 232) of subjects in the galcanezumab 120 mg group. Main adverse events were nasopharyngitis (21 subjects, 16 subjects) and injection site pain (13, 5).

No death occurred. Other serious adverse events were observed in 2 subjects in the placebo group (Behcet's syndrome, lower limb fracture) and in 2 subjects in the galcanezumab 120 mg group (haemorrhoids, tonsillitis). A causal relationship to the study drug was ruled out for all events. An adverse event leading to discontinuation of the study drug was observed in 1 subject in the galcanezumab 120 mg group (rash generalized).

[Japanese population]

All of the 42 randomized subjects (20 in the placebo group, 22 in the galcanezumab 120 mg group) received the study drug and were included in the safety analysis population and ITT. Table 37 shows the results of the primary efficacy endpoint in the Japanese population.

Table 37. Change from baseline in MHD (days) per month during the 3-month double-blind treatment phase (ITT, Japanese population)

	Placebo (n = 20)	Galcanezumab 120 mg (n = 22)
Baseline Mean ± SD	13.34 ± 6.04	14.43 ± 7.15
Month 3 of double-blind treatment phase Mean ± SD	12.94 ± 6.08	10.93 ± 8.20
Change from baseline[a] Least squares mean ± SE	0.58 ± 0.99	-3.51 ± 0.95

a, MMRM with treatment group, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

Table 38 shows the results of the primary efficacy endpoint in subpopulations of EM and CM.

Table 38. Change from baseline in MHD (days) per month during the 3-month double-blind treatment phase, in patients with EM and in patients with CM (ITT, Japanese population)

	Patients with EM		Patients with CM	
	Placebo (n = 7)	Galcanezumab 120 mg (n = 9)	Placebo (n = 13)	Galcanezumab 120 mg (n = 13)
Baseline Mean ± SD	7.29 ± 2.29	8.81 ± 4.70	16.60 ± 4.71	18.33 ± 5.90
Month 3 of double-blind treatment phase Mean ± SD	11.33 ± 7.39	4.73 ± 4.05	13.81 ± 5.36	15.22 ± 7.61
Change from baseline[a] Least squares mean ± SE	3.19 ± 1.82	-3.75 ± 1.60	-1.02 ± 1.15	-3.16 ± 1.15

a, MMRM with treatment group, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

Adverse events were observed in 60.0% (12 of 20) of subjects in the placebo group and in 50.0% (11 of 22) of subjects in the galcanezumab 120 mg group. Main events were nasopharyngitis (4 subjects, 2 subjects) and influenza (2, 1). There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

(c) Open-label treatment phase

A total of 449 subjects (including 42 Japanese) proceeded to the open-label treatment phase and received the study drug, and were included in the safety analysis population and ITT. The ITT was used as the primary efficacy analysis population. A total of 17 subjects (including 2 Japanese) discontinued the study. Main reasons for the discontinuation were adverse events and lack of efficacy (5 subjects each) (adverse events in Japanese subjects).

Table 39 shows the change from baseline in MHD per month during the 3-month open-label treatment phase (6 months from the start of the double-blind treatment phase) (results in Japanese population are shown in Table 40).

Table 39. Change from baseline in MHD (days) per month during the 3-month open-label treatment phase (ITT,[a] entire population)

Treatment group during the double-blind treatment phase	Placebo (n = 211)	Galcanezumab (n = 215)
Month 3 of open-label treatment phase Mean ± SD	7.43 ± 6.90	7.15 ± 6.65
Change from baseline in the double-blind period[b] Least squares mean ± SE	-5.24 ± 0.40	-5.60 ± 0.40

a, Subjects in ITT with baseline data and with data at Month 3 of the open-label treatment phase
b, MMRM with treatment group, region or country, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured)

Table 40. Change from baseline in MHD (days) per month during the 3-month open-label treatment phase (ITT,[a] Japanese population)

Treatment group during the double-blind treatment phase	Placebo (n = 19)	Galcanezumab (n = 21)
Month 3 of open-label treatment phase Mean ± SD	10.71 ± 7.50	9.07 ± 8.38
Change from baseline in the double-blind period[b] Least squares mean ± SE	-2.55 ± 1.37	-4.80 ± 1.30

a, Subjects in ITT with baseline data and with data at Month 3 of the open-label treatment phase
b, MMRM with treatment group, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured)

Adverse events were observed in 43.0% (193 of 449) of subjects (54.8% [23 of 42] in Japanese population) during the open-label administration. The most common adverse event was nasopharyngitis in 19 subjects (nasopharyngitis and stomatitis in 3 subjects each in Japanese population).

No death occurred. Other serious adverse events were ovarian cyst ruptured, arthropod bite, asthenia, hemiplegia, inguinal hernia, injury, pain, pneumonia, and pulmonary embolism in 1 subject each (hemiplegia in a Japanese subject). Adverse events leading to discontinuation of the study drug were observed in 5 subjects (gastric bypass, injection site erythema, induration, attention deficit hyperactivity disorder, rash [attention deficit hyperactivity disorder and rash in Japanese subjects]).

7.3.5 Japanese phase III long-term treatment study (Study CGAP; CTD 5.3.5.2.1; ■ 2017 to August 2019)

An open-label, uncontrolled study was conducted in Japanese patients with EM who had completed the double-blind treatment phase of Study CGAN and newly enrolled Japanese patients with CM in order to investigate the safety, tolerability, and efficacy in long-term administration of galcanezumab at 44 study sites in Japan (target sample size, 300 subjects [150 each in the galcanezumab 120 and 240 mg groups; 240 patients with EM, 60 patients with CM]).

The study consisted of a 1-month baseline measurement period, a 12-month open-label treatment phase, and a 4-month follow-up phase. Patients with EM started the study from the open-label treatment phase. During the study period, subjects were required to record the frequency of headache, etc. in the headache diary. At the start of the open-label treatment phase, patients with EM who had been treated with galcanezumab in Study CGAN were assigned to treatment groups to continue with the same dose (galcanezumab 120 mg or 240 mg), and patients with EM who had received placebo in Study CGAN and newly enrolled patients with CM were randomized to the galcanezumab 120 mg or 240 mg group. During the open-label treatment phase, galcanezumab 120 mg (starting dose, 240 mg in patients with

EM from the placebo group of CGAN group and in newly enrolled patients with CM) or 240 mg were administered subcutaneously for a total of 12 times 1 month apart, in the upper arm, abdomen, thigh, or buttock, using the PFS formulation. At-home self-injection was allowed for the last 6 doses, only when considered permissible by the investigator.

The main inclusion criteria were patients with EM who had completed the double-blind treatment phase of Study CGAN or patients aged 18 to 65 years with CM who met the following conditions:

- Being diagnosed with CM according to ICHD version 3 beta (1.3) of IHS, and the first onset before age 50
- An average of ≥15 days/month with headache and ≥8 days/month with headache of migraine-like characteristics both during the ≥3 months before screening and during the baseline measurement period
- ≥1 day/month with no migraine both during the 3 months before screening and during the baseline measurement period

The use of antimigraine prophylactic drugs was prohibited from ≥30 days before the start of the baseline measurement period and throughout the study period. The injection of botulinum A or B toxin into the head or neck was prohibited from ≥4 months before the start of the baseline measurement period and throughout the study period. The use of drugs for treating acute phase was permitted under certain conditions.[9)]

A total of 311 subjects (patients with EM; 120 in the galcanezumab 120 mg group, 126 in the 240 mg group: patients with CM; 32 in the 120 mg group, 33 in the 240 mg group) received the study drug. All of them were included in the safety analysis population and ITT, and the ITT was used as the primary efficacy analysis population. During the open-label treatment phase, treatment was discontinued in 33 subjects (7, 16, 4, 6). Main reasons for the discontinuation were adverse events (5, 7, 3, 4) and subject's request (2, 8, 0, 0). Self-injection was performed by 41 subjects (19, 14, 5, 3).

Table 41 shows the change from baseline in MHD per month during the 12-month open-label treatment phase (at the start of the open-label treatment phase).

Table 41. Change from baseline in MHD (days) per month during the 12-month open-label treatment phase (ITT)

	Patients with EM			Patients with CM		
	120 mg/120 mg	240 mg/240 mg	Placebo/ 120 mg	Placebo/ 240 mg	120 mg	240 mg
Baseline Mean ± SD	(n = 58) 5.53 ± 4.21	(n = 62) 5.62 ± 4.56	(n = 62) 8.12 ± 5.20	(n = 64) 8.35 ± 5.37	(n = 32) 20.21 ± 4.40	(n = 33) 18.68 ± 5.69
Month 12 of open-label treatment phase Mean ± SD	(n =56) 3.54 ± 3.46	(n = 53) 4.19 ± 3.99	(n = 58) 4.06 ± 3.85	(n = 57) 5.05 ± 5.08	(n = 28) 10.71 ± 4.61	(n = 27) 10.62 ± 7.33
Change from baseline Mean ± SD	(n = 56) -1.82 ± 2.96	(n = 53) -1.49 ± 4.11	(n = 58) -4.29 ± 4.07	(n = 57) -3.23 ± 5.81	(n = 28) -9.44 ± 6.16	(n = 27) -8.97 ± 8.06

9) The use of opioids and barbiturates were permitted for ≤3 days/month, and use of corticosteroid was permitted for emergency intravenous administration only for once.

Table 42 shows the incidences of adverse events during the open-label treatment phase and events reported by ≥10% of subjects in any group.

Table 42. Incidences of adverse events during the open-label treatment phase (safety analysis population)

	Patients with EM		Patients with CM	
	120 mg (n = 120)	240 mg (n = 126)	120 mg (n = 32)	240 mg (n = 33)
Incidence	90.0 (108)	92.9 (117)	96.9 (31)	87.9 (29)
Main events				
Nasopharyngitis	43.3 (52)	48.4 (61)	40.6 (13)	48.5 (16)
Influenza	10.8 (13)	12.7 (16)	12.5 (4)	6.1 (2)
Cystitis	3.3 (4)	3.2 (4)	6.3 (2)	12.1 (4)
Injection site erythema	18.3 (22)	24.6 (31)	9.4 (3)	9.1 (3)
Injection site pruritus	14.2 (17)	20.6 (26)	15.6 (5)	12.1 (4)
Injection site pain	4.2 (5)	11.1 (14)	6.3 (2)	9.1 (3)
Diarrhoea	3.3 (4)	3.2 (4)	12.5 (4)	0 (0)

% (Number of patients)

No death occurred throughout the study period. During the open-label treatment phase, other serious adverse events were observed in 9 subjects (4 in the galcanezumab 120 mg group of patients with EM [uterine polyp, breast cancer, cholangitis acute, ligament rupture], 2 in the galcanezumab 240 mg group of patients with EM [fracture malunion, pneumonia], 1 in the galcanezumab 120 mg group of patients with CM [stress cardiomyopathy], 2 in the galcanezumab 240 mg group of patients with CM [appendicitis, intervertebral disc protrusion]). A causal relationship to the study drug was ruled out for all of them except for stress cardiomyopathy in the patient with CM in the galcanezumab 240 mg group. Adverse events leading to discontinuation of the study drug were observed in 19 subjects (5 [anxiety disorder in 2, uterine leiomyoma, asthenia, renal dysfunction], 7 [injection site pruritus, amnesia, genital herpes, hepatic function abnormal, injection site swelling, ligament injury, rash pruritic], 3 [injection site pruritus in 2, stress cardiomyopathy], 4 [anxiety, injection site urticaria, intervertebral disc protrusion, urticaria]).

During the follow-up phase, adverse events were observed in 33.2% (100 of 301) of subjects. The main event was nasopharyngitis in 21 subjects. During the follow-up phase, serious adverse events were observed in 2 subjects (intervertebral disc protrusion, pelvic inflammatory disease). A causal relationship to the study drug was ruled out for both of them.

7.3.6 Foreign phase III long-term treatment study (Study CGAJ; CTD 5.3.5.2.2; December 2015 to September 2017)

An open-label, uncontrolled study in non-Japanese patients with EM or CM was conducted to investigate the safety, tolerability, and efficacy of long-term administration of galcanezumab at 28 study sites outside Japan (target sample size, 250 subjects).

The study consisted of a 12-month open-label treatment phase and a 4-month follow-up phase. During the study period, subjects were required to report days with headache, etc. during the past 30 days at each monthly office visit or by phone. At the start of the open-label treatment phase, subjects were randomized to the galcanezumab 120 mg or 240 mg group. During the open-label treatment phase, galcanezumab 120 mg (starting dose 240 mg) or 240 mg was administered subcutaneously for a total of

12 times 1 month apart, in the upper arm, abdomen, thigh, or buttock, using the PFS or AI formulation. The second and all succeeding doses were required to be self-injected by the subject or administered by his/her caregiver, and 6 out of 12 doses were to be administered at home.

The main inclusion criteria were patients aged 18 to 65 years who met the following conditions:

- Being diagnosed with migraine according to ICHD version 3 beta (1.1, 1.2, or 1.3) of IHS and a history of migraine since ≥1 year before screening, with the first onset before age 50
- Mean MHD of ≥4/month and ≥1 day/month with no headache during the 3 months before screening

The use of antimigraine prophylactic drugs was prohibited from ≥30 days before the start of the open-label treatment phase until 1 month after the start of the follow-up phase. The injection of botulinum A or B toxin into the head or neck was prohibited from ≥4 months before the start of the open-label treatment phase and throughout the study period. From 1 month after the start of the follow-up phase, antimigraine prophylactic drug was permitted when the investigator considered clinically necessary because of worsening symptoms. The use of drugs for treating acute phase was permitted under certain conditions.[10)]

A total of 270 subjects randomized (135 in the galcanezumab 120 mg group, 135 in the galcanezumab 240 mg group) received the study drug, and all of them were included in the safety analysis population and ITT. The ITT was used as the primary efficacy analysis population. During the open-label treatment phase, treatment was discontinued in 60 subjects (38 in the 120 mg group, 22 in the 240 mg group). Main reasons for the discontinuation were lack of efficacy (13, 5), subject's request (10, 7), and adverse events (7, 6).

Table 43 shows the change from baseline in MHD per month during the 12-month open-label treatment phase (at the start of the open-label treatment phase).

Table 43. Change from baseline in MHD (days) per month during the 12-month open-label treatment phase (ITT[a])

	Galcanezumab	
	120 mg	240 mg
Baseline Mean ± SD	(n = 132) 9.65 ± 5.85	(n = 135) 11.40 ± 6.69
Month 12 of open-label treatment phase Mean ± SD	(n = 95) 3.33 ± 3.72	(n = 112) 4.00 ± 5.41
Change from baseline[b] Least squares mean ± SE	(n = 95) -6.35 ± 0.43	(n = 112) -6.54 ± 0.41

a, Subjects in ITT with baseline data and with data at Month 12 of the open-label treatment phase
b, MMRM with treatment group, study site, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured)

Table 44 shows the incidences of adverse events during the open-label treatment phase and events reported by ≥10% of subjects in either group.

10) The use of opioids and barbiturates were permitted for ≤3 days/month, and use of corticosteroid was permitted for emergency intravenous administration only for twice.

Table 44. Incidences of adverse events during the open-label treatment phase (safety analysis population)

	Galcanezumab	
	120 mg (n = 129)	240 mg (n = 141)
Incidence	82.2 (106)	85.8 (121)
Main events		
Injection site pain	17.1 (22)	19.9 (28)
Upper respiratory inflammation	7.0 (9)	14.9 (21)
Nasopharyngitis	17.8 (23)	12.8 (18)
Injection site reaction	11.6 (15)	9.2 (13)
Sinusitis	10.9 (14)	9.2 (13)

% (Number of patients)

No death occurred throughout the study period. During the open-label treatment phase, other serious adverse events were observed in 10 subjects (3 in the galcanezumab 120 mg group [lumbar radiculopathy, migraine, osteoarthritis], 7 in the galcanezumab 240 mg group [uterine leiomyoma embolisation, cholecystitis, diverticulum intestinal, intervertebral disc protrusion, non-cardiac chest pain, pain in extremity, pneumonia]). A causal relationship to the study drug was ruled out for all these events. Adverse events leading to discontinuation of the study drug were observed in 13 subjects (6 in the galcanezumab 120 mg group, 7 in the galcanezumab 240 mg group). The adverse event leading to treatment discontinuation in ≥2 subjects in either group was injection site reaction, which occurred in 4 subjects (2, 2).

During the follow-up phase, adverse events were observed in 33.5% (79 of 236) of subjects. Main events were back pain and urinary tract infection in 5 subjects each. During the follow-up phase, serious adverse events were observed in 5 subjects (haemorrhagic ovarian cyst, endocarditis/infective aneurysm/subarachnoid haemorrhage, lung neoplasm malignant, malignant melanoma, pineal gland cyst). A causal relationship to the study drug was ruled out for all these events except for lung neoplasm malignant.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about the clinical positioning of galcanezumab in the treatment of migraine: Migraine is a headache disorder characterized by repeated moderate to severe unilateral throbbing headache attacks that persist 4 to 72 hours. The headache is often accompanied by nausea, vomiting, photosensitivity, sound sensitivity, etc., severely interfering with activities of daily living. Patients who have experienced headache in ≥15 days per month over 3 months (including headache with migraine symptoms in ≥8 days) are diagnosed as CM, and those who have experienced headache in <15 days per month are diagnosed as EM (migraine with or without aura).

Migraine treatment is generally classified into acute-phase treatment aiming at reducing/eliminating headache symptoms and prophylactic therapy aiming at the prevention of migraine attacks. Nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans are used for acute treatment of migraine attacks. Prophylactic therapy is given if frequent headache attacks interfere with activity of daily living (Clinical Practice Guideline for Chronic Headache 2013). In Japan, oral sodium valproate, propranolol hydrochloride, and lomerizine hydrochloride have been approved. However, there are a certain number

of patients who had an inadequate response to these conventional drugs, which can also cause adverse drug reactions such as sleepiness. Thus, these drugs do not adequately meet the medical needs (*J Headache Pain*. 2019;20:68).

Galcanezumab is administered once a month and is expected to be effective from 1 month after the start of treatment [see Section "7.R.6.1 Starting dose"]. Therefore, galcanezumab is advantageous for patients having difficulty adhering to an oral regimen due to their lifestyles, patients suffering frequent migraine attacks with nausea/vomiting that make daily oral drug taking difficult, and those who cannot wait until the conventional drugs begin to work 2 to 3 months later (Clinical Practice Guideline for Chronic Headache 2013). Galcanezumab is expected to serve as a novel treatment option in prophylactic therapy of migraine attacks in patients with EM and CM, for the following reasons: (1) galcanezumab has a novel mechanism of action targeting at CGRP, and its efficacy has been demonstrated in the once-monthly regimen in patients with EM and CM, including those with migraine who had an inadequate response to other drugs; (2) there is no significant problem in its safety profile; and (3) clinical practice guidelines in the US and Europe (*Headache.* 2019;59:1-18, *J Headache Pain.* 2019;20:6) point out the advantages of galcanezumab in terms of efficacy, safety, and tolerability.

PMDA's view:
The majority of patients with migraine are in their 20s to 50s. Migraine attacks significantly affect daily and social activities. Therapy for migraine attack prevention has a clinical significance for patients who suffer interference with activities of daily living despite the acute phase treatment given. It is of a clinical significance to provide galcanezumab to clinical settings as a novel option for the prophylactic treatment against migraine attacks, in light of the clinically significant efficacy of galcanezumab with acceptable safety demonstrated in Japanese and foreign clinical studies, and promising benefits of galcanezumab for both EM and CM as well as its promising efficacy in patients who have not adequately responded to conventional drugs [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"]. For being an antibody preparation for monthly subcutaneous administration, galcanezumab has a risk of causing adverse drug reactions such as hypersensitivity (including anaphylaxis) and erythema at the injection site. Healthcare professionals and patients should be cautioned against these risks. Healthcare professionals should also be informed of the characteristics of galcanezumab so that each patient is treated with most suitable drug among the several options including galcanezumab [see Sections "7.R.4.1 Hypersensitivity-related adverse events" and "7.R.4.2 Injection site-related adverse events"]. The clinical positioning of galcanezumab in patients without prior treatment with conventional drugs is discussed further in Section "7.R.5 Intended population and indication of galcanezumab."

7.R.2 Appropriateness of clinical data package

(a) Difference in intrinsic and extrinsic ethnic factors between Japanese and non-Japanese people

The applicant's explanation about the intrinsic and extrinsic ethnic factors:
In terms of intrinsic ethnic factors, an epidemiological survey using ICHD shows the prevalence of migraine among Japanese people of 8.4% with sex ratio of approximately 3.6 (women/men) (*Cephalalgia.* 1997;17:15-22), which is not significantly different from the prevalence in the US and Europe (11%-12% [6%-7% in men, 16%-18% in women]) (*N Engl J Med.* 2002;346:257-70, *Neurology.* 2007;68:343-9). In light of hereditary factor(s), migraine is suggested to be a polygenic disease in a

pedigree analysis (*BMJ.* 1995;311:541-4) and a twin study (*Ann Neurol.* 1999;45:242-6), but no evident causative gene or disease-susceptibility gene has been identified. Therefore, genes are unlikely to cause ethnic difference in migraine at present. Also, no significant difference was observed in the PK or PD of galcanezumab between Japanese and non-Japanese subjects [see Section "6.R.1 Difference in PK and PD of galcanezumab between Japanese and non-Japanese subjects and between patients with EM and patients with CM"].

Extrinsic ethnic factors are as follows: ICHD is used for migraine diagnosis both in Japan and in the US and Europe; drugs used for acute phase therapy and for prophylactic treatment are largely comparable among these regions albeit slight differences in their approval statuses; stress and insufficient sleep are the main environmental factors affecting the frequency of migraine attacks common in Japan and the US/Europe. Thus there seems to be no significant difference in environmental factors among these regions.

(b) Background of conducting global phase III study (Study CGAW) and its appropriateness

The applicant's explanation:

In Japan, the phase I study in healthy subject (Study CGAE) demonstrated the similarity between Japanese and Caucasian subjects in the PK and PD of galcanezumab. The applicant therefore planned to construct a clinical data package that include results of the following studies: for EM; Japanese phase II study (Study CGAN) as a bridging study, to which the foreign phase III studies (Studies CGAG and CGAH) to be bridged; for CM, the Japanese long-term treatment study (Study CGAP) including patients with CM and the foreign phase III study (Study CGAI). However, the results of Studies CGAG and CGAH, which became available while Study CGAN was underway, did not show a dose-response relationship with superior efficacy of galcanezumab 240 mg to 120 mg, [redacted]. Based on these results and the results of Study CGAI, the optimal dose of galcanezumab was therefore considered to be 120 mg. Regarding Study CGAN as a Japanese dose-finding study, to verify the efficacy of galcanezumab 120 mg, Japan participated in Study CGAW, which was being planned to be conducted outside Japan involving patients with migraine (EM and CM) who had an inadequate response to other drugs.

Patients with EM or CM who had an inadequate response to other drugs was considered the appropriate target population for Study CGAW for the following reasons:

- Inclusion of EM and CM in the same study:
  EM and CM differ by the frequency of attacks but share a common pathology and are categorized in migraine in a single disease spectrum (*Curr Pain Headache rep*. 2012;16:86-92, *Headache.* 2017;57:109-25). The efficacy of galcanezumab did not significantly differ between EM and CM, based on the change from baseline in MHD per month in Studies CGAG and CGAH on EM and in Study CGAI on CM (difference between the galcanezumab 120 mg group and the placebo group; −1.92 days, −2.02 days, and −2.09 days, respectively). The safety data showed similar incidences of adverse events in the galcanezumab 120 mg groups during the double-blind treatment phase, i.e., 65.5%, 65.0%, and 58.2%, respectively, with the majority of the observed events being injection site reaction in all these studies [see Sections "7.3.1 Foreign phase III study (a)," "7.3.2 Foreign phase III study (b)," and "7.3.3 Foreign phase III study (c)"]. These results suggest that the efficacy, safety,

and recommended dosage regimen are the same for both EM and CM and that it is appropriate to include patients with EM and those with CM in 1 study.

- Inclusion of patients who had an inadequate response to other drugs:
  Studies CGAG, CGAH, and CGAI demonstrated the efficacy of galcanezumab regardless of the degree of inadequacy of response to other drugs [see Section "7.R.3.4 Factors affecting the efficacy"], suggesting that galcanezumab would preferentially be used in clinical settings for patients who had an inadequate response to conventional drugs. Therefore, the design of Study CGAW to verify the efficacy of galcanezumab in patients who had an inadequate response to multiple antimigraine prophylactic drugs was appropriate.

PMDA's view:
It is appropriate that Study CGAN, which was conducted as a bridging study, was regarded as a dose-finding study based on the results of the foreign studies (Studies CGAG, CGAH, and CGAI). It is also appropriate that Study CGAW, the study regarded as the confirmatory study in the approval application in Japan, was conducted as a global study and that the study targeted both EM and CM, in light of the following:

- The comparison of intrinsic and extrinsic ethnic factors did not reveal any regional difference that could be an obstacle to conducting the global study.
- The applicant's claim that EM and CM are diseases within the same disease spectrum is reasonable, and the objective of treatment is the reduction of frequency of migraine attacks in both of these patient groups.
- In the preceding foreign studies, the efficacy, safety, and tolerability of galcanezumab were the same between EM and CM, suggesting that the recommended dosage regimen was the same for EM and CM.

In Study CGAW, patients who had an inadequate response to other drugs were investigated. Patient eligibility for galcanezumab are discussed further in Section "7.R.5 Intended population and indication of galcanezumab."

7.R.3 Efficacy

7.R.3.1 Efficacy against EM

The applicant's explanation:
Studies CGAN, CGAG, and CGAH were conducted on patients with EM, using similar designs. Patients eligible for these 3 studies were those diagnosed with migraine according to the definition of ICHD version 3 beta of IHS, with the mean MHD per month of the past 3 months of 4 to 14 days and 2 or more episodes of migraine attacks per month. The use of change from baseline in MHD per month as the primary efficacy endpoint is recommended by the IHS's Guideline for controlled studies of antimigraine prophylactic drugs in adult patients with CM (*Cephalalgia.* 2008;28:484-95), and the endpoint was considered appropriate for patients with EM because of the common objective of treatment between EM and CM. In all these studies, a significant improvement was observed in the primary endpoint during the 6-month double-blind treatment phase in both the galcanezumab 120 and 240 mg groups as compared to the placebo group. [see Sections "7.2.2 Japanese phase II study," "7.3.1 Foreign

phase III study (a)," and "7.3.2 Foreign phase III study (b)"]. Also, the EM subpopulation in Study CGAW showed a tendency of improvement in the primary endpoint during the 3-month double blind treatment phase in the galcanezumab 120 mg group as compared to the placebo group [see Section "7.3.4 Global phase III study"]. Furthermore, as shown in Tables 45 and 46, each galcanezumab group obtained favorable results of main secondary endpoints, i.e., 50% response rate, 75% response rate, and 100% response rate,[11] and MHD requiring acute phase treatment as compared to the placebo group.

Table 45. Response rates[a] during the double-blind treatment phase (ITT[b])

		Placebo	Galcanezumab	
			120 mg	240 mg
Study CGAN	Number of patients evaluated	n = 230	n = 115	n = 114
	50% response rate	20.3 ± 2.0	49.8 ± 3.4	48.2 ± 3.5
	75% response rate	9.6 ± 1.3	25.5 ± 2.8	25.0 ± 2.8
	100% response rate	2.8 ± 0.6	9.0 ± 1.5	8.1 ± 1.5
Study CGAG	No. of patients evaluated	n = 425	n = 210	n = 208
	50% response rate	38.6 ± 1.7	62.3 ± 2.4	60.9 ± 2.5
	75% response rate	19.3 ± 1.4	38.8 ± 2.4	38.5 ± 2.4
	100% response rate	6.2 ± 0.8	15.6 ± 1.6	14.6 ± 1.6
Study CGAH	No. of patients evaluated	n = 450	n = 226	n = 220
	50% response rate	36.0 ± 1.7	59.3 ± 2.4	56.5 ± 2.5
	75% response rate	17.8 ± 1.3	33.5 ± 2.3	34.3 ± 2.3
	100% response rate	5.7 ± 0.7	11.5 ± 1.4	13.8 ± 1.5
Study CGAW (EM subpopulation)	No. of patients evaluated	n = 132	n = 137	
	50% response rate	17.1 ± 2.5	41.8 ± 3.2	
	75% response rate	3.7 ± 1.5	18.4 ± 2.5	
	100% response rate	0	7.7 ± 1.9	

Least squares mean ± SE

a, Generalized linear mixed-effects model with treatment group, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline as covariate

b, Subjects in ITT with baseline data and post-baseline data of ≥1 time point

[11] Percentage of subjects who achieved a ≥50%, ≥75%, and 100% decrease in MHD (mean MHD during the double-blind treatment phase)

Table 46. Change from baseline in MHD (days) requiring acute phase treatment per month during the double-blind treatment phase (ITT[a])

		Placebo	Galcanezumab	
			120 mg	240 mg
Study CGAN	Baseline Mean ± SD	(n = 230) 7.35 ± 2.97	(n = 115) 7.33 ± 2.91	(n = 114) 7.78 ± 2.96
	Month 6 of double-blind treatment phase Mean ± SD	(n = 225) 7.42 ± 5.00	(n = 104) 4.74 ± 3.88	(n = 111) 4.69 ± 4.24
	Change from baseline[b] Least squares mean ± SE	(n = 230) -0.12 ± 0.21	(n = 115) -3.02 ± 0.30	(n = 114) -2.81 ± 0.30
	Difference from placebo[b] Least squares mean [95% CI]	-	-2.90 [-3.61, -2.19]	-2.70 [-3.41, -1.99]
Study CGAG	Baseline Mean ± SD	(n = 425) 7.41 ± 3.48	(n = 210) 7.34 ± 3.65	(n = 208) 7.26 ± 3.27
	Month 6 of double-blind treatment phase Mean ± SD	(n = 342) 4.51 ± 4.30	(n = 177) 2.69 ± 3.39	(n = 171) 2.58 ± 3.31
	Change from baseline[c] Least squares mean ± SE	(n = 425) -2.15 ± 0.21	(n = 210) -3.96 ± 0.25	(n = 208) -3.76 ± 0.26
	Difference from placebo[c] Least squares mean [95% CI]	-	-1.81 [-2.28, -1.33]	-1.61 [-2.09, -1.14]
Study CGAH	Baseline Mean ± SD	(n = 450) 7.63 ± 3.41	(n = 226) 7.51 ± 3.35	(n = 220) 7.49 ± 3.23
	Month 6 of double-blind treatment phase Mean ± SD	(n = 382) 4.82 ± 3.99	(n = 196) 3.55 ± 4.15	(n = 192) 3.20 ± 3.69
	Change from baseline[c] Least squares mean ± SE	(n = 450) -1.85 ± 0.18	(n = 226) -3.67 ± 0.22	(n = 220) -3.63 ± 0.23
	Difference from placebo[c] Least squares mean [95% CI]	-	-1.82 [-2.29, -1.36]	-1.78 [-2.25, -1.31]
Study CGAW (EM subpopulation)	Baseline Mean ± SD	(n = 132) 8.10 ± 2.87	(n = 137) 8.47 ± 3.13	
	Month 3 of double-blind treatment phase Mean ± SD	(n = 129) 7.21 ± 4.74	(n = 136) 4.80 ± 3.81	
	Change from baseline[d] Least squares mean ± SE	(n = 132) -0.24 ± 0.32	(n = 137) -2.96 ± 0.31	
	Difference from placebo[d] Least squares mean [95% CI]	-	-2.71 [-3.49, -1.94]	

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point

b, MMRM with treatment group, office visit (month), interaction between treatment group and office visit (month), and MHD during 1-month baseline (<8 days vs. ≥8 days) as fixed effects, and with MHD requiring acute phase treatment during 1-month baseline, and interaction between MHD requiring acute phase treatment during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)

c, MMRM with treatment group, region or country, office visit (month), interaction between treatment group and office visit (month), and MHD during 1-month baseline (<8 days vs. ≥8 days) as fixed effects, and with MHD requiring acute phase treatment during 1-month baseline, and interaction between MHD requiring acute phase treatment during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)

d, MMRM with treatment group, region or country, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD requiring acute phase treatment during 1-month baseline, and interaction between MHD requiring acute phase treatment during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

Accordingly, the clinical studies in patients with EM demonstrated a significant decrease in MHD in the galcanezumab 120 mg group as compared to the placebo group. In addition, galcanezumab 120 mg obtained favorable results as compared to placebo in the percentage of subjects achieving ≥50% reduction in MHD, which is considered clinically significant (*Cephalalgia.* 2000;20:756-86), and MHD requiring acute phase treatment. These results indicate that galcanezumab has shown to have clinically significant efficacy in patients with EM.

PMDA's view:

Patients with migraine have problems with impaired daily living resulting from migraine attacks, and the objective of prophylactic therapy is to prevent migraine attacks. It is therefore appropriate that change from baseline in MHD was used as the primary efficacy endpoint of galcanezumab for patients

with EM. Studies CGAN, CGAG, CGAH, and CGAW in patients with EM demonstrated a significant difference in the decrease in MHD, the primary endpoint, between galcanezumab 120 mg and placebo. In addition, the efficacy of galcanezumab was shown in the response rates and MHD requiring acute phase treatment, indicating that the galcanezumab-induced decrease in MHD observed in the clinical studies contributes to the reduction of migraine-related interference in daily living, which is clinically significant. Galcanezumab thus has demonstrated efficacy in preventing migraine attacks in patients with EM.

7.R.3.2 Efficacy against CM

The applicant's explanation:

Study CGAI was conducted in patients who had been diagnosed with CM according to the definition of ICHD version 3 beta of IHS, with ≥1 migraine-free days in the past 3 months. In this study, the double-blind treatment phase was 3 months in order to minimize the period of exposure to placebo for subjects with CM, who present with severer symptoms. The primary efficacy endpoint was change from baseline in MHD per month, for the same reason as in clinical studies in subjects with EM [see Section "7.R.3.1 Efficacy against EM"]. A significant improvement was observed in the primary endpoint during the 3-month double-blind treatment phase in the galcanezumab 120 and 240 mg groups as compared to the placebo group [see Section "7.3.3 Foreign phase III Study (c)"]. Also, in the CM subpopulation of Study CGAW, a tendency of improvement was observed in the primary endpoint during the 3-month double-blind treatment phase in the galcanezumab 120 mg group as compared to the placebo group [see Section "7.3.4 Global phase III Study"]. Furthermore, as shown in Tables 47 and 48, the galcanezumab groups obtained favorable results as compared to the placebo group, in the main secondary endpoints, i.e., 50% response rate, 75% response rate, and 100% response rate,[11] and MHD requiring acute phase treatment.

Table 47. Response rates during the double-blind treatment phase (ITT[a])

		Placebo	Galcanezumab	
			120 mg	240 mg
Study CGAI	Number of patients evaluated	n = 538	n = 273	n = 274
	50% response rate[b]	15.4 ± 1.6	27.6 ± 2.7	27.5 ± 2.6
	75% response rate[b]	4.5 ± 0.9	7.0 ± 1.4	8.8 ± 1.7
	100% response rate[b]	0.5 ± 0.3	0.7 ± 0.4	1.3 ± 0.6
Study CGAW (CM subpopulation)	No. of patients evaluated	n = 96	n = 93	
	50% response rate[c]	8.9 ± 2.4	32.0 ± 4.0	
	75% response rate[c]	2.1 ± 1.2	8.8 ± 2.4	
	100% response rate[d]	0	3.0	

Least squares mean ± SE

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point

b, Generalized linear mixed-effects model with treatment group, office visit (month), excess use/no excess use of baseline medications, use/no use of concomitant prophylactic drugs, and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline as covariate

c, Generalized linear mixed-effects model with treatment group, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline as covariate

d, Mean

Table 48. Change from baseline in MHD (days) requiring acute phase treatment per month during the 3-month double-blind treatment phase (ITT[a])

		Placebo	Galcanezumab	
			120 mg	240 mg
Study CGAI	Baseline Mean ± SD	(n = 538) 15.65 ± 6.48	(n = 273) 15.26 ± 6.19	(n = 274) 14.50 ± 6.27
	Month 3 of double-blind treatment phase Mean ± SD	(n = 498) 11.95 ± 7.73	(n = 256) 9.31 ± 6.72	(n = 262) 9.67 ± 7.98
	Change from baseline[b] Least squares mean ± SE	(n = 538) -2.23 ± 0.33	(n = 273) -4.74 ± 0.40	(n = 274) -4.25 ± 0.40
	Difference from placebo[b] Least squares mean [95% CI]	-	-2.51 [-3.27, -1.76]	-2.01 [-2.77, -1.26]
Study CGAW (CM subpopulation)	Baseline Mean ± SD	(n = 96) 15.28 ± 5.88	(n = 93) 15.03 ± 6.30	
	Month 3 of double-blind treatment phase Mean ± SD	(n = 95) 13.46 ± 7.07	(n = 88) 8.95 ± 6.91	
	Change from baseline[c] Least squares mean ± SE	(n = 96) -1.38 ± 0.59	(n = 93) -5.40 ± 0.61	
	Difference from placebo[c] Least squares mean [95% CI]	-	-4.02 [-5.44, -2.61]	

a, Subjects in ITT with both baseline and post-baseline data
b, MMRM with treatment group, region or country, office visit (month), excess use/no excess use of baseline medications, use/no use of concomitant prophylactic drugs, and interaction between treatment group and office visit (month) as fixed effects, and with MHD requiring acute phase treatment during 1-month baseline, and interaction between MHD requiring acute phase treatment during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)
c, MMRM with treatment group, region or country, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD requiring acute phase treatment during 1-month baseline, and interaction between MHD requiring acute phase treatment during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

Accordingly, the clinical study in patients with CM demonstrated a significant decrease in MHD in the galcanezumab 120 mg group as compared to the placebo group. In addition, the galcanezumab 120 mg obtained favorable results as compared to the placebo in the percentage of subjects achieving ≥30% reduction in MHD, which is considered clinically significant (*Cephalalgia.* 2008;28:484-95), and MHD requiring acute phase treatment. These results indicate that galcanezumab has shown to have clinically significant efficacy in patients with CM.

PMDA's view:

Because of the common objective of the prophylactic treatment of migraine attacks, it is appropriate that the change from baseline in MHD was defined as the efficacy endpoint for galcanezumab in patients with CM, as was the case with patients with EM. Studies CGAI and CGAW in patients with CM demonstrated a significant decrease in MHD, the primary endpoint, in the galcanezumab 120 mg group as compared to the placebo group. In addition, galcanezumab exhibited efficacy in response rates and in MHD requiring acute phase treatment, indicating that the galcanezumab-induced decrease in MHD shown in the clinical studies contributes to the reduction of migraine-related difficulties in daily living, which is clinically significant. Thus, galcanezumab has demonstrated efficacy in preventing migraine attacks in patients with CM.

7.R.3.3 Efficacy in Japanese patients

The applicant's explanation:

In Study CGAW in patients with migraine who had an inadequate response to other drugs, the difference between the galcanezumab 120 mg and the placebo in change from baseline in MHD per month, the primary endpoint, was similar between the Japanese population with EM or those with CM and the

entire population with EM or those with CM, respectively, showing consistency. [see Figure 2 and Section "7.3.4 Global phase III Study"]. In the Japanese population with EM, MHD tended to worsen in the placebo group, presumably due to the number of subjects in the group of as small as 7, of which 1 reported an extreme increase in MHD. On the other hand, in the Japanese population with CM, MHD in the placebo group tended to decrease 3 months after the start of treatment. This is presumed to be due to the limited number of Japanese subjects (13), including 3 subjects experiencing decreased MHD in ≥7 days after 3 months of treatment. Thus, the different tendencies observed between the placebo group of the Japanese population with EM or CM and the placebo group in the entire population was unlikely to be attributable to ethnic factors.

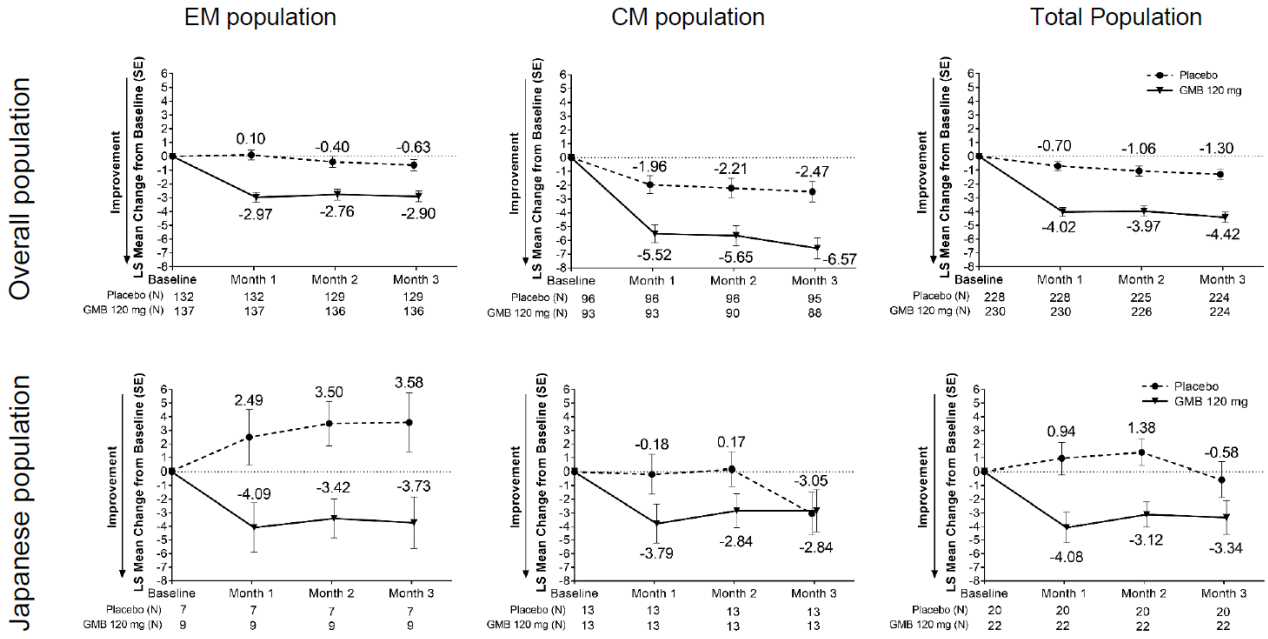


Figure 2. Over-time change from baseline in MHD (days) per month during the double-blind treatment phase in Study CGAW (ITT)

In the entire population, the secondary endpoints of 50% response rate, 75% response rate, and 100% response rate [see Sections "7.R.3.1 Efficacy against EM" and "7.R.3.2 Efficacy against CM"] were 13.3% in the placebo group and 37.7% in the galcanezumab 120 mg group for 50% response rate, 3.3% and 14.5% for 75% response rate, and 0% and 4.9% for 100% response rate, whereas, in the Japanese population, the rates were 1.7% and 33.3%, 0% and 15.2%, and 0% and 13.6%, respectively, showing similar tendencies.

For the following reasons, galcanezumab is also expected to be equally effective in Japanese patients with migraine including but not limited to those who have inadequately responded to other drugs:

- Study CGAN involving Japanese patients with EM including but not limited to those who had inadequately responded to other drugs showed a significant improvement in change from baseline in MHD per month in the galcanezumab 120 mg group as compared to the placebo group, with a tendency similar to that observed in the foreign phase III studies (Studies CGAG and CGAH).
- Study CGAI involving patients with CM including but not limited to those who had inadequately responded to other drugs demonstrated the efficacy of galcanezumab 120 mg. No significant ethnic

difference was observed in the Japanese and foreign clinical studies conducted. In addition, a similar decrease in MHD as in Study CGAI was observed in Study CGAP in Japanese patients with EM or CM including but not limited to those who had inadequately responded to other drugs, although not in placebo-controlled investigation.

PMDA's view:
Study CGAW showed a consistency in the results of the primary endpoint between the entire population and the Japanese population, which indicates that both EM and CM subpopulations of the Japanese population have a similar tendency to that observed in these subpopulations of the entire population. Also, the results of the secondary endpoints are similar between the entire population and the Japanese population, supporting the consistency of the primary endpoint between the entire population and the Japanese population. These indicate that the efficacy of galcanezumab demonstrated in patients inadequately responding to other drugs in the entire population is expected to be equally obtained in Japanese patients. Although no confirmatory study has been conducted in Japanese patients with migraine other than those with inadequate response to other drugs, galcanezumab is expected to be effective in this patient population, in light of the following:

- Foreign phase III studies (Studies CGAG, CGAH, and CGAI) demonstrated efficacy in non-Japanese patients with migraine including but not limited to those who had inadequately responded to other drugs.
- Study CGAN demonstrated efficacy in Japanese patients with EM including but not limited to those who had inadequately responded to other drugs.
- Japanese and foreign clinical studies showed neither tendency of significant difference in the efficacy between EM and CM nor clinically significant regional difference in the efficacy.

7.R.3.4 Factors affecting efficacy

The applicant's explanation:
Interactive factors observed in ≥2 studies among Studies CGAN, CGAG, CGAH, CGAI, and CGAW were the degree of inadequacy of the response to other drugs at baseline (adequate or inadequate response to ≥2 types of prophylactic drugs), the presence or absence of aura at baseline, and region. Table 49 shows the change from baseline in MHD in patients with adequate or inadequate response to other drugs at baseline. The interactions were observed in Studies CGAN and CGAG that included few subjects in the subgroup of poor responders, but not in Study CGAH, which included a relatively larger number of patients in the subgroup of poor responders, suggesting that the baseline degree of inadequacy of the response to other drugs does not significantly affect the efficacy of galcanezumab.

Table 49. Change from baseline in MHD (days) during the double-blind treatment phase by degree of inadequacy of response to other drugs at baseline (ITT[a])

Study	Inadequate response to other drugs at baseline	Placebo	Galcanezumab	
			120 mg	240 mg
Study CGAN[b]	Yes	(n = 41) -0.74 ± 0.63	(n = 19) -1.96 ± 0.93	(n = 14) -4.85 ± 1.10
	No	(n = 189) -0.57 ± 0.25	(n = 96) -3.92 ± 0.35	(n = 100) -3.14 ± 0.34
Study CGAG[c]	Yes	(n = 22) 0.47 ± 1.27	(n = 10) -0.65 ± 1.66	(n = 10) -3.00 ± 1.80
	No	(n = 403) -2.97 ± 0.25	(n = 200) -4.95 ± 0.30	(n = 198) -4.62 ± 0.30
Study CGAH[c]	Yes	(n = 63) -1.96 ± 0.62	(n = 33) -5.16 ± 0.72	(n = 34) -4.90 ± 0.77
	No	(n = 387) -2.35 ± 0.23	(n = 193) -4.25 ± 0.28	(n = 186) -4.07 ± 0.29
Study CGAI[d]	Yes	(n = 161) -1.44 ± 0.62	(n = 66) -5.91 ± 0.79	(n = 96) -3.30 ± 0.71
	No	(n = 377) -3.69 ± 0.43	(n = 207) -4.82 ± 0.48	(n = 178) -5.77 ± 0.53

Least squares mean ± SE

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point

b, MMRM with treatment group, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline, adequate/inadequate response to other drugs at baseline, interaction between MHD during 1-month baseline and office visit (month), interaction between adequate/inadequate response to other drugs at baseline and treatment group, interaction between adequate/inadequate response to other drugs at baseline and office visit (month), and interactions among adequate/inadequate response to other drugs at baseline, treatment group, and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)

c, MMRM with treatment group, region or country, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline, adequate/inadequate response to other drugs at baseline, interaction between MHD during 1-month baseline and office visit (month), interaction between adequate/inadequate response to other drugs at baseline and treatment group, interaction between adequate/inadequate response to other drugs at baseline and office visit (month), and interactions among adequate/inadequate response to other drugs at baseline, treatment group, and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)

d, MMRM with treatment group, region or country, office visit (month), excess use/no excess use of baseline medications, use/no use of concomitant prophylactic drugs, and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline, adequate/inadequate response to other drugs at baseline, interaction between MHD during 1-month baseline and office visit (month), interaction between adequate/inadequate response to other drugs at baseline and treatment group, interaction between adequate/inadequate response to other drugs at baseline and office visit (month), and interactions among adequate/inadequate response to other drugs at baseline, treatment group, and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

Table 50 shows change from baseline in MHD in patients with or without aura at baseline. In the galcanezumab 120 mg and 240 mg groups of Study CGAH and in the galcanezumab 120 mg of Study CGAI, the difference in change from baseline in MHD between the galcanezumab group and the placebo group was large in the subgroup without baseline aura as compared to the subgroup with baseline aura. However, the difference was likely attributable to a high response in the subgroup with baseline aura in the placebo group, the presence or absence of baseline aura is thus unlikely to affect the efficacy of galcanezumab.

Table 50. Change from baseline in MHD (days) during the double-blind treatment phase in patients with or without aura at baseline (ITT[a])

	Baseline aura	Placebo	Galcanezumab	
			120 mg	240 mg
Study CGAN[b]	Yes	(n = 139) -0.73 ± 0.30	(n = 64) -3.55 ± 0.45	(n = 77) -3.49 ± 0.41
	No	(n = 91) -0.35 ± 0.36	(n = 51) -3.67 ± 0.49	(n = 37) -3.20 ± 0.57
Study CGAG[c]	Yes	(n = 211) -3.35 ± 0.35	(n = 109) -4.96 ± 0.42	(n = 105) -4.85 ± 0.43
	No	(n = 214) -2.30 ± 0.33	(n = 101) -4.56 ± 0.41	(n = 103) -4.30 ± 0.40
Study CGAH[c]	Yes	(n = 249) -2.71 ± 0.34	(n = 119) -4.22 ± 0.40	(n = 122) -4.06 ± 0.40
	No	(n = 201) -1.47 ± 0.30	(n = 107) -4.13 ± 0.38	(n = 98) -4.07 ± 0.37
Study CGAI[d]	Yes	(n = 294) -3.66 ± 0.53	(n = 150) -4.82 ± 0.63	(n = 140) -5.69 ± 0.64
	No	(n = 244) -1.44 ± 0.53	(n = 123) -4.69 ± 0.63	(n = 134) -3.19 ± 0.63

Least squares mean ± SE

a, Subjects in ITT with baseline data and post-baseline data of ≥1 time point

b, MMRM with treatment group, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline, presence/absence of baseline aura, interaction between MHD during 1-month baseline and office visit (month), interaction between presence/absence of baseline aura and treatment group, interaction between presence/absence of baseline aura and office visit (month), and interaction among presence/absence of baseline aura, treatment group, and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)

c, MMRM with treatment group, region or country, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline, presence/absence of baseline aura, interaction between MHD during 1-month baseline and office visit (month), interaction between presence/absence of baseline aura and treatment group, interaction between presence/absence of baseline aura and office visit (month), and interaction among presence/absence of baseline aura, treatment group, and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 6-month administration period)

d, MMRM with treatment group, region or country, office visit (month), excess use/no excess use of baseline medications, use/no use of concomitant prophylactic drugs, and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline, presence/absence of baseline aura, interaction between MHD during 1-month baseline and office visit (month), interaction between presence/absence of baseline aura and treatment group, interaction between presence/absence of baseline aura and office visit (month), and interaction among presence/absence of baseline aura, treatment group, and office visit (month) as covariates (covariance structure: unstructured, estimated by the main effect in the treatment group during the 3-month administration period)

The region-based subgroup analysis showed that, in Study CGAH, the difference in change from baseline in MHD between the galcanezumab 240 mg and the placebo was greater in the European subgroup (-3.4 days) than in the North American subgroup (-1.2 days) and in the other region subgroup (-1.7 days), and that, in Study CGAI, the difference in change from baseline in MHD between the galcanezumab 120 mg and the placebo was smaller in the North American subgroup (-1.1 days) than in the European subgroup (-3.4 days) and the other regional subgroups (-3.2 days). These differences were likely attributable to the response in the placebo groups that varied by regional subgroups.

As described, multiple interacting factors were identified in the clinical studies, but none of them are considered to have significantly affected the efficacy.

PMDA's view:

Galcanezumab is effective in preventing migraine attacks in Japanese patients regardless of the degree of inadequacy of the response to other drugs or whether to have aura. The intended population for treatment with galcanezumab is further discussed in Section "7.R.5 Intended population and indication of galcanezumab."

7.R.3.5 Efficacy in long-term administration

The applicant's explanation:

Long-term efficacy of galcanezumab was evaluated in patients with EM or CM in Studies CGAN, CGAP, and CGAI. Galcanezumab 120 or 240 mg was administered to Japanese patients with EM who underwent the double-blind treatment phase of Study CGAN and the subsequent Study CGAP. The efficacy observed during the double-blind treatment phase of Study CGAN was maintained throughout the 12-month open-label treatment phase (Figure 3). In Study CGAI in non-Japanese patients with CM, the efficacy of galcanezumab 120 and 240 mg was maintained throughout the 3-month double-blind treatment phase and the 9-month open-label treatment phase (Figure 4). The effect of ADA on treatment efficacy was investigated by a comparison of change from baseline in MHD per month between ADA-positive subjects and ADA–negative subjects. As shown in Table 51, the change was similar between ADA-positive and -negative subjects, showing no effect of ADA on treatment efficacy.

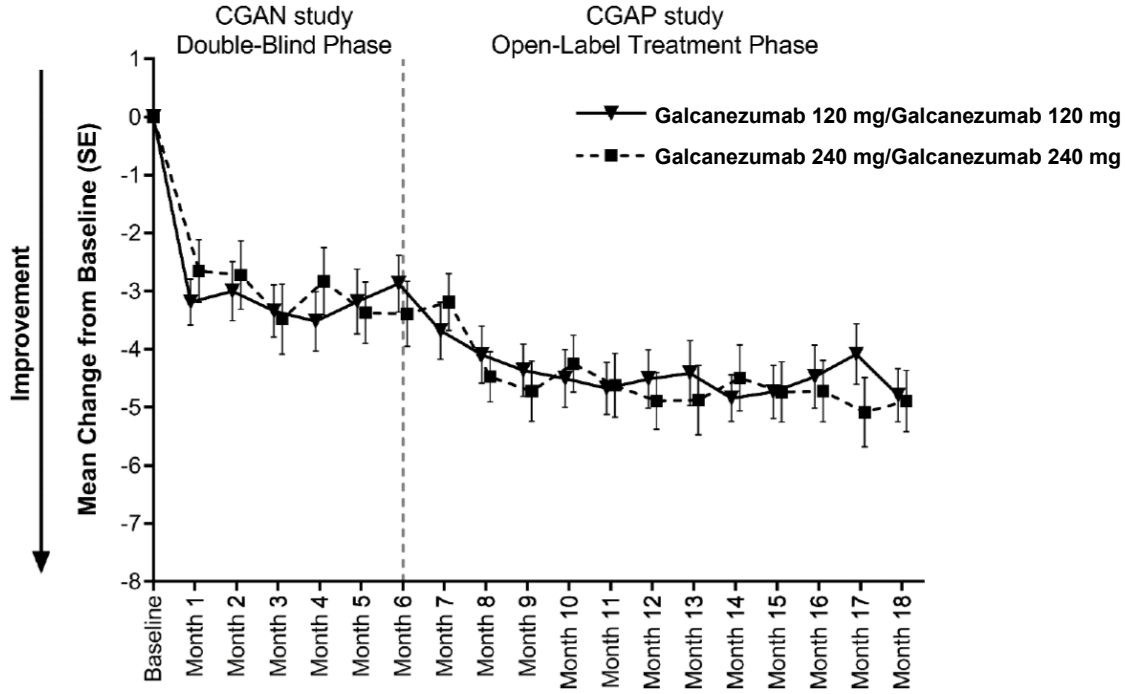
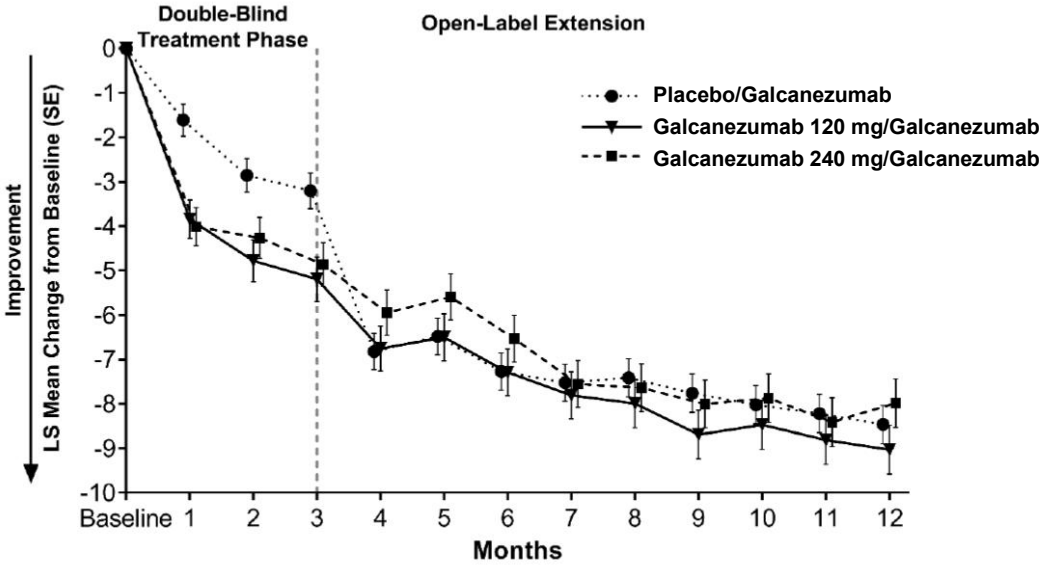


Figure 3. Over-time change from baseline in MHD (days) per month in patients with EM in Study CGAN/Study CGAP (ITT)



MMRM with treatment group, region or country, office visit (month), excess use/no excess use of baseline medications, use/no use of concomitant prophylactic drugs, and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline, and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured)

Figure 4. Over-time change from baseline in MHD (days) per month in patients with CM in Study CGAI (ITT)

Table 51. Change from baseline in MHD (days) during galcanezumab administration period in ADA-positive and -negative subjects

	TE-ADA negative[a]	TE-ADA positive[b]
Study CGAG	(n = 388) -4.67 ± 3.81	(n = 20) -4.29 ± 2.60
Study CGAH	(n = 402) -4.54 ± 3.46	(n = 32) -3.40 ± 4.20
Study CGAI	(n = 469) -7.44 ± 6.21	(n = 65) -7.51 ± 6.52
Study CGAJ	(n = 237) -5.98 ± 5.72	(n = 26) -4.56 ± 3.48
Study CGAN	(n = 206) -3.50 ± 3.47	(n = 23) -3.53 ± 3.57
Study CGAP	(n = 163) -4.85 ± 5.25	(n = 27) -4.69 ± 5.10

Mean ± SD

a, Patients not positive for TE-ADA

b, Patients with positive baseline ADA who showed a ≥4-fold increase in antibody titer from the baseline level at least once, and patients with negative baseline ADA who showed antibody titer of ≥20 at least once after baseline

PMDA's view:

Based on the study data submitted, galcanezumab is expected to suppress migraine attacks in both patients with EM and patients with CM in long-term treatment as well. Whether to continue galcanezumab treatment is discussed further in Section "7.R.6 Dosage and administration."

7.R.4 Safety

PMDA's view:

Based on the occurrence of adverse events in Japanese and foreign clinical studies, the reviews in the following subsections, and foreign post-marketing safety information on galcanezumab, there are no problems that can compromise the clinical benefits of galcanezumab. Thus, given the efficacy of

galcanezumab demonstrated in Section "7.R.3 Efficacy," galcanezumab has a clinically acceptable safety in patients with migraine.

Also, based on the results of the foreign phase III studies (Studies CGAG, CGAH, and CGAI) and the global phase III study (Study CGAW), there is no significant difference in the safety profiles of galcanezumab between patients with EM and patients with CM. The safety review in this section is based on the results of the pooled data set of Studies CGAW and CGAN, and the foreign phase III studies (Studies CGAG, CGAH, and CGAI combined).

7.R.4.1 Hypersensitivity-related adverse events

The applicant's explanation:

Table 52 shows the incidences of hypersensitivity-related events[12)] during the double-blind treatment phase in the Japanese and foreign clinical studies. No serious events were observed. Most of the hypersensitivity-related events were mild or moderate in severity. In Study CGAI, 2 cases of serious urticaria were observed during the open-label treatment phase and the follow-up phase. A causal relationship to the study drug could not be ruled out for the 1 case in the open-label treatment phase, but its outcome was reported as "recovered." Adverse events leading to treatment discontinuation were observed in 14 of 1022 subjects. In the long-term treatment studies (Studies CGAP and CGAJ), no serious hypersensitivity-related event was observed, and adverse events leading to treatment discontinuation were observed in 4 subjects (3 of 311 in Study CGAP, 1 of 270 in Study CGAJ).

Table 52. Incidences[a] of hypersensitivity-related events in Japanese and foreign clinical studies (safety analysis population)

	Study CGAW		Study CGAN			Pooled data set of foreign phase III studies		
				Galcanezumab			Galcanezumab	
	Placebo (n = 230)	Galcanezumab (n = 232)	Placebo (n = 230)	120 mg (n = 115)	240 mg (n = 114)	Placebo (n = 1451)	120 mg (n = 705)	240 mg (n = 730)
Hypersensitivity-related events	5.2 (12)	4.3 (10)	4.8 (11)	3.5 (4)	13.2 (15)	4.1 (59)	5.8 (41)	6.3 (46)
Urticaria	0.4 (1)	0	0 (0)	1.7 (2)	6.1 (7)	0.3 (5)	0.3 (2)	0.1 (1)
Asthma	0	0.4 (1)	0.9 (2)	2.6 (3)	1.8 (2)	0.3 (4)	0.3 (2)	0.3 (2)
Rhinitis allergic	0.9 (2)	0.4 (1)	0.9 (2)	0	1.8 (2)	0.2 (3)	0.4 (3)	0.5 (4)
Eczema	0.4 (1)	0	0.9 (2)	0.9 (1)	1.8 (2)	0.2 (3)	0.1 (1)	0.3 (2)
Conjunctivitis allergic	0	0	0.9 (2)	0.9 (1)	1.8 (2)	0.1 (1)	0	0
Rash	1.3 (3)	1.3 (3)	1.3 (3)	0	0	1.0 (15)	0.7 (5)	1.0 (7)
Cough	0.4 (1)	0.4 (1)	0.9 (2)	0.9 (1)	0	0.1 (2)	0.1 (1)	0
Serious adverse events	0	0	0	0	0	0	0	0
Adverse events leading to discontinuation of the study drug	0	0.4 (1)	0	0	0.9 (1)	0.1 (1)	0.3 (2)	0.3 (2)

% (Number of patients)

a, Among adverse events that were observed during the double-blind treatment phase and judged as hypersensitivity-related events by the applicant based on medical assessment under blinded conditions, events observed in any galcanezumab group with an incidence of ≥1.5% and that was higher than in the placebo group

According to the foreign post-marketing safety information,[13)] there were 1639 events of spontaneous reports related to hypersensitivity (1.94 events per 100 person-years, of which 157 were serious). Main

[12)] Adverse events classified in "Anaphylactic reaction," "Anaphylaxis/anaphylactoid shock conditions," "Hypersensitivity," or "Angioedema" in MedDRA SMQ

[13)] September 27, 2018 to March 31, 2020, estimated exposure period: 84300 person-years

serious events were dyspnoea (111 events, of which 29 were serious), anaphylactic reaction (20 events, of which 20 were serious), and hypersensitivity (140 events, of which 18 were serious).

Among TE-ADA-positive[1)] subjects, hypersensitivity-related events occurred in 2 of 23 subjects in Study CGAN, 7 of 80 subjects in Study CGAG, 10 of 97 subjects in Study CGAH, 34 of 207 subjects in Study CGAI, 14 of 65 subjects in Study CGAP, and 4 of 41 subjects in Study CGAJ. No serious events were observed. All hypersensitivity-related events were mild or moderate in severity.

Based on the above, the "Clinically Significant Adverse Reactions" section of the package insert will urge caution against reported serious hypersensitivity such as anaphylaxis, angioedema, and urticaria. Also, informative materials for healthcare professionals will be prepared and distributed.

PMDA's view:
Judging from the study data submitted, it is appropriate to urge caution against serious hypersensitivity in the "Clinically Significant Adverse Reactions" section of the package insert and to provide informative materials to healthcare professionals. Informative materials should also be made available for patients to provide information appropriately.

7.R.4.2 Injection site-related adverse events

The applicant's explanation:
Table 53 shows the incidences of injection site-related events[14)] during the double-blind treatment phase of Japanese and foreign clinical studies. The incidence was high in the galcanezumab 120 mg and 240 mg groups as compared to the placebo group. Injection site erythema was most common in Study CGAN, whereas injection site pain was most predominant in the pooled data set of foreign phase III studies. The majority of injection site-related events occurred on the day of study drug administration and resolved in several days, and they were mild to moderate in severity. No serious injection site-related event was observed during the open-label treatment phase. In the long-term treatment studies (Studies CGAP and CGAJ), no serious injection site-related event was observed, but adverse events leading to treatment discontinuation were observed in 10 subjects (5 of 311 subjects in Study CGAP, 5 of 270 subjects in Study CGAJ). In Study CGAW, pain relief measures at the injection site were permitted at the discretion of the physician, and performed measures were required to be documented. The protocols of other Japanese or foreign clinical studies did not clearly required the documentation of relief measures, and relief measures were not as strongly encouraged as in Study CGAW. In Study CGAW, approximately 5% of subjects in the respective treatment groups received relief measures before or after injection, using either a cool compress or ice bag. This indicates that the low incidence of injection site-related events in Study CGAW as compared to Study CGAN and in the pooled data set of the foreign phase III studies is unlikely to be due to the difference in the relief measure specification. The limited number of patients receiving relief measures in the clinical studies precluded both the evaluation of whether the pain-relief measures given before or after administration had helped reduce injection site-related events and the identification of priority relief measures to be taken.

14) Adverse events classified in "Injection site reactions" in MedDRA HLT

Table 53. Incidences[a)] of injection site-related events in Japanese and foreign clinical studies (safety analysis population)

	Study CGAW		Study CGAN			Pooled data set of foreign phase III studies		
	Placebo (n = 230)	Galcanezumab (n = 232)	Placebo (n = 230)	Galcanezumab		Placebo (n =1451)	Galcanezumab	
				120 mg (n = 115)	240 mg (n = 114)		120 mg (n = 705)	240 mg (n = 730)
Injection site-related events	10.0 (23)	6.9 (16)	5.7 (13)	26.1 (30)	39.5 (45)	12.6 (183)	18.2 (128)	22.7 (166)
Injection site erythema	2.6 (6)	3.4 (8)	2.2 (5)	14.8 (17)	27.2 (31)	1.4 (20)	2.8 (20)	4.0 (29)
Injection site pruritus	0	1.3 (3)	0	8.7 (10)	20.2 (23)	0.1 (2)	2.1 (15)	3.3 (24)
Injection site pain	5.7 (13)	2.2 (5)	1.3 (3)	6.1 (7)	7.0 (8)	9.5 (138)	10.1 (71)	11.6 (85)
Injection site swelling	0	0.4 (1)	1.3 (3)	10.4 (12)	10.5 (12)	0.1 (1)	1.1 (8)	0.6 (4)
Injection site reaction	2.6 (6)	0	0.4 (1)	0	0	1.0 (14)	3.1 (22)	6.2 (45)
Injection site induration	1.7 (4)	0.4 (1)	0.4 (1)	2.6 (3)	2.6 (3)	0.1 (1)	0.4 (3)	0.4 (3)
Injection site rash	0	0	0.9 (2)	0	2.6 (3)	0.1 (2)	0.9 (6)	0.6 (4)
Injection site inflammation	0	0	0	2.6 (3)	0	0	0.1 (1)	0.1 (1)
Injection site warmth	0	0	0	1.7 (2)	0.9 (1)	0.1 (1)	0	0
Serious adverse events	0	0	0	0	0	0	0	0
Adverse events leading to discontinuation of the study drug	0	0	0	0	0.9 (1)	0 (0)	0.3 (2)	0.7 (5)

% (Number of patients)

a, Among adverse events that were observed during the double-blind treatment phase, events observed in any galcanezumab group with an incidence of ≥1.5% and that was higher than in the placebo group

According to the foreign post-marketing safety information, [13)] there were 3653 cases of injection site-related spontaneous reports (4.33 per 100 person-years, of which 11 were serious). Main events were injection site pain (1265, of which 2 were serious), injection site erythema (384, of which 1 was serious), injection site reaction (301, of which 1 was serious), injection site pruritus (279, of which 1 was serious), and injection site swelling (256, of which 2 were serious).

Thus, there were no clinical data suggesting the necessity of any specific measures against injection-site related adverse events in galcanezumab administration. Injection site-related adverse events may be treated at the discretion of individual physicians as in usual care. Thus the package insert, etc. need not to specify the measures for persisting or aggravated injection site adverse events.

PMDA's view:

Injection site-related adverse events associated with galcanezumab are permissible, judging from the following observations: most of the injection site-related events observed in the Japanese and foreign clinical studies were mild to moderate and resolved in several days after administration; and the incidence of injection site-related adverse events leading to treatment discontinuation was not high in the double-blind treatment phase, i.e., 0 of 6 subjects in Study CGAW, 1 of 7 subjects in Study CGAN, and 7 of 35 subjects in the pooled data of foreign phase III studies. However, in contrast, the results of Study CGAN and the pooled data set of foreign phase III studies revealed frequent injection site-related events in the galcanezumab group as compared to the placebo group, with a tendency of high incidences of those events in Study CGAN than in the pooled data set of foreign phase III studies. Therefore, the possibility of injection site-related adverse events should be communicated appropriately to healthcare professionals and patients via the package insert and relevant informative materials.

7.R.4.3 Cardiovascular-related adverse events

The applicant's explanation:

The incidence of cardiovascular-related events[15)] during the double-blind treatment phase in Japanese and foreign clinical studies did not significantly differ between the galcanezumab groups and the placebo groups. Main events were hypertension, palpitations, and syncope. Hypertension was observed in 1.3% (3 of 230) of subjects in the placebo group and 0.4% (1 of 232) of subjects in the galcanezumab group in Study CGAW; 0.4% (1 of 230) of subjects in the placebo group, 0% (0 of 115) of subjects in the galcanezumab 120 mg group, and 0% (0 of 114) of subjects in the 240 mg group in Study CGAN; and 1.0% (15 of 1451) of subjects in the placebo group, 1.1% (8 of 705) of subjects in the galcanezumab 120 mg group, and 0.7% (5 of 730) of subjects in the 240 mg group in the pooled data set of foreign phase III studies. Palpitations were not observed in Study CGAW or CGAN but observed in 1.0% (5 of 1451) of subjects in the placebo group, 2.8% (2 of 705) of subjects in the galcanezumab 120 mg group, and 0.4% (3 of 730) of subjects in the 240 mg group in the pooled data set of foreign phase III studies. Syncope was not observed in Study CGAW or CGAN but observed in 0.4% (6 of 1451) of subjects in the placebo group, 0.1% (1 of 705) of subjects in the galcanezumab 120 mg group, and 0.3% (2 of 730) of subjects in the 240 mg group in the pooled data set of foreign phase III studies. Serious cardiovascular-related events were observed in 3 subjects in the placebo group (pulmonary embolism, deep vein thrombosis, myocardial infarction) and 3 subjects in the galcanezumab 240 mg group (acute myocardial infarction, pulmonary embolism, transient ischaemic attack) in the pooled data set of foreign phase III studies, but a causal relationship to the study drug was ruled out for all events. In the long-term treatment studies, a serious cardiovascular-related event was observed in 1 subject in the galcanezumab 120 mg group (stress cardiomyopathy) in Study CGAP but not in Study CGAJ.

According to the foreign post-marketing safety information,[13)] there were 494 cases of cardiovascular-related spontaneous reports (0.59 events per 100 person-years, of which 170 were serious). Main serious events were dyspnoea (111, of which 28 were serious), cerebrovascular accident (15 cases, of which 15 were serious), loss of consciousness (11 cases, of which 11 were serious), myocardial infarction (11 cases, of which 11 were serious), and hypertension (34 cases, of which 10 were serious). Post-marketing reports include cases with missing information about such as past history, concomitant drugs, and date of onset. More information needs to be collected to assess a causal relationship between cardiovascular events and galcanezumab.

As explained above, the available clinical study data or foreign post-marketing safety information do not indicate the cardiovascular or cerebrovascular risk of galcanezumab. Nevertheless, serious cardiovascular risk in elderly patients, patients with a serious cardiovascular disease or symptom, and patients with cardiovascular risk are to be included in the important missing information in the risk management plan for the following reasons:

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15) Among adverse events classified in "Cardiac arrhythmias", "Cardiac failure," "Cardiomyopathy," "Central nervous system vascular disorders," "Embolic and thrombotic events," "Hypertension," "Ischaemic heart disease," "Pulmonary hypertension," or "Torsade de pointes/QT prolongation" in MedDRA SMQ, those identified as cardiovascular-related events by the applicant based on medical evaluation under blinded conditions

- While CGRP dilates blood vessels [see Section "3.R.1 Primary pharmacodynamics"], CGRP antagonists inhibit the vasodilative effect of CGRP, possibly aggravating ischemic events (*Trends Pharmacol Sci.* 2016;37:779-88).
- Patients with migraine have a high prevalence of cardiovascular events (*JAMA.* 2006;296:283-91).
- In most of the clinical studies of galcanezumab, the administration period was ≤1 year. In addition, elderly patients (>65 years in Japanese studies and in foreign phase III studies, >75 years in Study CGAW) and patients with a serious cardiovascular disease or symptom or with a cardiovascular risk were excluded.

Outside Japan, post-marketing database surveys are currently underway or scheduled to be conducted, and the safety in long-term use of galcanezumab including serious cardiovascular events will be evaluated. Also in Japan, a post-marketing database survey is being planned to evaluate the risk of serious cardiovascular-related events and, based on the results obtained, the necessity of new risk minimization activities will be discussed [see Section "7.R.8 Post-marketing investigations"].

PMDA's view:
Information on serious cardiovascular-related events of galcanezumab should be collected in the post-marketing setting for the following reasons: although no evident cardiovascular-related risk has been indicated in either clinical studies or overseas post-marketing safety information, there is only limited information about long-term use of galcanezumab; cardiovascular risks remain unknown in patient populations that were excluded from the clinical studies, i.e., patients with cardiovascular risks and elderly patients; and the pharmacological effect of galcanezumab suggests a possible cardiovascular risk but currently there are no approved drugs with a similar mechanism of action. The appropriateness of this conclusion and the method of information collection will be finally determined taking account of comments raised in the Expert Discussion [see Section "7.R.8 Post-marketing investigations"].

7.R.4.4 Nerve disorder-related adverse events

The applicant's explanation:
Among the nerve disorder-related events[16)] observed during the double-blind treatment phase of Japanese and foreign clinical studies, relatively frequent events were dizziness and vertigo. Dizziness was observed in 0.4% (1 of 230) of subjects in the placebo group and 0.9% (2 of 232) of subjects in the galcanezumab group in Study CGAW; 0.9% (2 of 230) of subjects in the placebo group, 0% (0 of 115) of subjects in the galcanezumab 120 mg group, and 0.9% (2 of 114) of subjects in the 240 mg group in Study CGAN; and 2.9% (42 of 1451) of subjects in the placebo group, 2.8% (20 of 705) of subjects in the galcanezumab 120 mg group, and 2.9% (21 of 730) of subjects in the 240 mg group in the pooled data set of foreign phase III studies. The incidences were similar between the galcanezumab groups and the placebo groups. Vertigo was observed in 1.7% (4 of 230) of subjects in the placebo group and 0.4% (1 of 232) of subjects in the galcanezumab group in Study CGAW; 0.4% (1 of 230) of subjects in the placebo group, 0.9% (1 of 115) of subjects in the galcanezumab 120 mg group, and 0% (0 of 114) of subjects in the 240 mg group in Study CGAN; and 0.2% (3 of 1451) of subjects in the placebo group, 0.7% (5 of 705) of subjects in the galcanezumab 120 mg group, and 1.2% (9 of 730) of subjects in the

16) Adverse events classified in "Neurological disorders NEC" in MedDRA HLGT

240 mg group in the pooled data set of foreign phase III studies. The incidences tended to be higher in the galcanezumab group than in the placebo group in the pooled data set of foreign phase III studies. The only serious adverse event observed was disorientation in 1 subject in the galcanezumab 240 mg in the pooled data set of foreign phase III studies.

According to the foreign post-marketing safety information,[13] there were 810 cases of nerve disorder-related spontaneous reports (0.96 per 100 person-years, of which 67 were serious). Main serious events were loss of consciousness (11, of which 11 were serious), syncope (11, of which 8 were serious), and dizziness (202, of which 8 were serious).

Because its causal relationship to galcanezumab cannot be ruled out, vertigo will be listed in the "Other Adverse Reactions" section of the package insert to urge caution.

PMDA's view:
The foreign post-marketing safety information has revealed frequently reported serious adverse events including loss of consciousness, syncope, etc. Decreased regional blood flow in the cerebral cortex is thought to be involved in augural symptoms of migraine (visual symptoms, sensory symptoms, speech symptoms, etc.) (*Headache.* 2011;51:1289-96). Galcanezumab inhibits the vasodilative CGRP. Given these, the possibility cannot be denied that galcanezumab is involved in loss of consciousness, syncope, etc. However, nerve disorder-related adverse events did not tend to occur frequently in galcanezumab groups in the Japanese or foreign clinical studies, and thus it is appropriate to urge caution against vertigo in the "Other Adverse Reactions" section of the package insert as per the applicant's plan.

7.R.4.5 Psychiatric disorder-related adverse events

The applicant's explanation:
Among the psychiatric disorder-related adverse events[17] observed during the double-blind treatment phase in Japanese and foreign clinical studies, anxiety was relatively common. Anxiety occurred in 0.4% (1 of 230) of subjects in the placebo group and 0% (0 of 232) of subjects in the galcanezumab group in Study CGAW; none in Study CGAN; and 0.9% (13 of 1451) of subjects in the placebo group, 1.3% (9 of 705) of subjects in the galcanezumab 120 mg group, and 0.4% (3 of 730) of subjects in the 240 mg group in the pooled data set of foreign phase III studies. The serious adverse event observed was suicide attempt in 1 subject in the placebo group in the pooled data set of foreign phase III studies.

Patients with migraine are considered to have a high risk of suicidal ideation, suicidal behavior, and self-injurious behaviors without suicidal intent (*Headache.* 2012;52:723-31). The risk of these events after the study drug administration was evaluated in Study CGAN and foreign phase III studies using Columbia-Suicide Severity Rating Scale (C-SSRS), with recent history (past 1 month for suicidal ideation, past 1 year for suicidal behavior) as baseline. The occurrence of suicidal ideation, suicidal behavior, or self-injurious behaviors without suicidal intent, as compared to recent history, was as follows: During the double-blind treatment phase, suicidal ideation was observed in 0.9% (1 of 115) of subjects in the galcanezumab 120 mg group in Study CGAN; and 0.6% (9 of 1451) of subjects in the placebo group, 0.6% (4 of 705) of subjects in the galcanezumab 120 mg group, and 0.6% (4 of 730) of

[17] Adverse events classified in "Psychiatric disorders" in MedDRA SOC

subjects in the 240 mg group in the pooled data set of foreign phase III studies. Suicidal behavior was observed in 0.9% (1 of 1451) of subjects in the pooled data set of foreign phase III studies. Self-injurious behavior without suicidal intent was observed in 1.4% (2 of 1451) of subjects in the placebo group and 1.4% (1 of 730) of subjects in the galcanezumab 240 mg group in the pooled data set of foreign phase III studies. During the follow-up phase, suicidal ideation was observed in 0.5% (2 of 372) of subjects in the placebo group, 0.5% (1 of 183) of subjects in the galcanezumab 120 mg group, and 0.5% (1 of 185) of subjects in the 240 mg group in Study CGAG; 0.5% (1 of 212) of subjects in the galcanezumab 120 mg group and 0.5% (1 of 208) of subjects in the 240 mg group in Study CGAH. Suicidal behavior was observed in 0.5% (1 of 208) of subjects in the galcanezumab 240 mg group of Study CGAH, and self-injurious behavior without suicidal intent was observed in 0.5% (1 of 208) of subjects in the galcanezumab 240 mg group of Study CGAH. In the long-term treatment studies, suicidal ideation was observed in 0.6% (1 of 159) of subjects in the galcanezumab 240 mg in Study CGAP, and suicidal ideation was observed in 2.3% (3 of 129) of subjects in the galcanezumab 120 mg group and 0.7% (1 of 141) of subjects in the 240 mg group in Study CGAJ.

According to the foreign post-marketing safety information,[13)] there were 607 cases of psychiatric disorder-related spontaneous reports (0.72 per 100 person-years, of which 46 were serious) and 22 cases of suicide-related spontaneous reports (0.03 per 100 person-years, of which 20 were serious). Psychiatric disorder-related main serious events were depression (59, of which 6 were serious) and anxiety (97, of which 5 were serious), and the suicide-related main serious event was suicidal ideation (17, of which 17 were serious). However, currently there is no information that provides an indication of a causal relationship of these events to galcanezumab.

These results do not indicate any clear psychiatric disorder-related risk of galcanezumab currently. Thus there is no need to advise caution against a psychiatric disorder-related risk.

PMDA's view:
Psychological factors such as anxiety and depression are considered to be involved in the onset and clinical course of migraine (Clinical Practice Guidelines for Chronic Headache 2013). Psychiatric disorder-related adverse events could possibly result in a grave outcome such as complete suicide, it is thus clinically important to pay attention to these symptoms in deciding patient's eligibility and the continuation of the prophylactic treatment of migraine. Although suicidal ideation and suicide attempt were reported in the Japanese and foreign clinical studies and in the foreign post-marketing safety information, results of the evaluation using C-SSRS did not detect any significant difference in the incidence between the placebo group and the galcanezumab in the clinical studies; and serious adverse events related to suicidal ideation or suicidal attempt were observed only in 2 subjects in clinical studies including the follow-up phase, i.e., suicidal ideation in 1 subject (galcanezumab 300 mg group) during the follow-up phase of Study CGAB and suicidal attempt in 1 subject (placebo group) during the double-blind treatment phase in Study CGAH. Further, a causal relationship of the event observed in the galcanezumab group to the study drug was ruled out. Given these observations, the applicant's decision is acceptable that there is no current need to advise caution against suicide and other psychiatric disorder-related risks.

7.R.4.6 Liver disorder-related adverse events

The applicant's explanation about liver disorder-related adverse events:

Table 54 shows the incidences of liver function test abnormal during the double-blind treatment phase in the Japanese and foreign clinical studies. There were no subjects who met the criteria of Hy's law[18] in any study.

Table 54. Incidences of liver function test abnormal in Japanese and foreign clinical studies (safety analysis population)

	Study CGAW		Study CGAN			Pooled data set of foreign phase III studies		
	Placebo (n = 230)	Galcanezumab (n = 232)	Placebo (n = 230)	Galcanezumab 120 mg (n = 115)	Galcanezumab 240 mg (n = 114)	Placebo (n = 1451)	Galcanezumab 120 mg (n = 705)	Galcanezumab 240 mg (n = 730)
ALT ≥3 × ULN	0	0	0	0	0	0.5 (7)	0.6 (4)	0.8 (6)
AST ≥3 × ULN	0	0	0	0	0	0.1 (2)	0.2 (1)	0.4 (3)
ALP ≥2 × ULN	0	0.4 (1)	0	0	0	0	0.2 (1)	0
TBL ≥2 × ULN	0.4 (1)	0	0	0	0	0.1 (1)	0	0

% (Number of patients)
2 × ULN and 3 × ULN in the table indicate 2 and 3 times, respectively, the upper limit of the reference range.

According to the foreign post-marketing safety information,[13] there were 18 cases of liver disorder-related spontaneous reports (0.021 per 100 person-years, of which 6 were serious). Main events were alanine aminotransferase (ALT) increased (2, none of which was serious), aspartate aminotransferase (AST) increased (2, none of which was serious), hepatic enzyme increased (2, none of which was serious), and international normalised ratio increased (2 cases, none of which was serious).

These results do not indicate any liver disorder risk caused by galcanezumab currently. Thus there is no current need to advise caution against the liver disorder-related risk.

PMDA's view:

The applicant's decision is acceptable that there is no current need to advise caution against the liver disorder-related risk.

7.R.4.7 Gastrointestinal adverse events

The applicant's explanation:

CGRP receptors are distributed throughout the entire gastrointestinal system of humans. Toxicology studies in rodents showed that CGRP or CGRP receptor inhibitors suppress the motility of the gastrointestinal system and water secretion (*Neuropeptides.* 2017;64:95-99). Table 55 shows the incidences of gastrointestinal-related events[19] during the double-blind treatment phase in Japanese and foreign clinical studies. In the pooled data set of foreign phase III studies, the incidences of constipation and abdominal pain upper were high in the galcanezumab 120 and 240 mg groups as compared to the placebo group. The serious adverse event observed in ≥2 subjects was pancreatitis acute (1 subject each in the galcanezumab 120 and 240 mg groups). In the long-term treatment studies (Studies CGAP and CGAJ), a serious adverse event was observed in 1 subject (diverticulum intestinal), and an adverse event leading to treatment discontinuation occurred in 1 subject (1 of 270 subjects in Study CGAJ).

[18] Defined according to Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009.
[19] Adverse events classified in "Gastrointestinal disorders" in MedDRA SOC

Table 55. Incidences[a] of gastrointestinal-related events in Japanese and foreign clinical studies (safety analysis population)

	Study CGAW		Study CGAN			Pooled data set of foreign phase III studies		
	Placebo (n = 230)	Galcanezumab (n = 232)	Placebo (n = 230)	Galcanezumab 120 mg (n = 115)	Galcanezumab 240 mg (n = 114)	Placebo (n = 1451)	Galcanezumab 120 mg (n = 705)	Galcanezumab 240 mg (n = 730)
Gastrointestinal-related events	9.1 (21)	9.5 (22)	17.8 (41)	24.3 (28)	15.8 (18)	10.8 (156)	11.8 (83)	11.0 (80)
Dental caries	0.4 (1)	0.4 (1)	2.2 (5)	6.1 (7)	4.4 (5)	0.2 (3)	0	0.1 (1)
Toothache	0.4 (1)	0.9 (2)	1.7 (4)	4.3 (5)	0.9 (1)	0.6 (8)	0.7 (5)	1.0 (7)
Diarrhoea	0.9 (2)	0.4 (1)	3.0 (7)	3.5 (4)	2.6 (3)	2.1 (30)	2.0 (14)	1.5 (11)
Constipation	2.2 (5)	2.2 (5)	1.3 (3)	3.5 (4)	0.9 (1)	0.6 (8)	1.0 (7)	1.5 (11)
Abdominal pain upper	0	0.9 (2)	3.5 (8)	0	2.6 (3)	0.3 (5)	1.0 (7)	1.0 (7)
Abdominal pain	0.9 (2)	0.4 (1)	0.4 (1)	0	0	1.7 (24)	1.8 (13)	0.8 (6)
Gastritis	0.4 (1)	0.4 (1)	1.7 (4)	0.9 (1)	1.8 (2)	0.4 (6)	0.4 (3)	0.3 (2)
Abdominal discomfort	0	0.4 (1)	0.9 (2)	0.9 (1)	1.8 (2)	0.4 (6)	0.1 (1)	0.5 (4)
Serious adverse events	0	0.4 (1)	0	0.9 (1)	0	0.2 (3)	0.6 (4)	0.1 (1)
Adverse events leading to discontinuation of the study drug	0	0	0	0	0	0.1 (1)	0.1 (1)	0.3 (2)

% (Number of patients)

a, Among adverse events that were observed during the double-blind treatment phase, events observed in any galcanezumab group with an incidence of ≥1.5% and that was higher than in the placebo group

According to the foreign post-marketing safety information,[13)] there were 1017 cases of gastrointestinal-related spontaneous reports (1.21 per 100 person-years, of which 74 were serious). Main serious events were nausea (270, of which 7 were serious), swollen tongue (14, of which 7 were serious), constipation (179, of which 5 were serious), vomiting (94, of which 5 were serious), and intestinal obstruction (5, of which 5 were serious).

A causal relationship of constipation to galcanezumab cannot be ruled out. Constipation will be listed in the “Other Adverse Reactions” section of the package insert to raise cautions.

PMDA’s view:

The applicant’s decision to urge caution against gastrointestinal-related risks via the package insert, by including constipation in its “Other Adverse Reactions” section, is appropriate at present.

7.R.4.8 Effect on pregnancy

The applicant’s explanation:

The clinical studies of galcanezumab excluded pregnant or lactating women and required women with reproductive capacity to take contraceptive measures during the period of the clinical studies and for 5 months after the last dose of the study drug. However, pregnancy was reported in 22 participants of the clinical studies. The outcomes of pregnancy included normal outcome (9 subjects), premature baby (2), abortion spontaneous (2), abortion missed (1), elective termination (1), unknown or lost to follow-up (5), and indeterminate outcome (2). Pre-eclampsia was observed in 1 subject during the follow-up phase of Study CGAG. No particular problem was found in the reproductive and developmental toxicity studies of galcanezumab [see Section “5.5 Reproductive and developmental toxicity”].

The small number of pregnant women receiving galcanezumab precluded a definitive conclusion on the effect of exposure to galcanezumab in this population. The use of galcanezumab in pregnant women should be considered only if the expected therapeutic benefits outweigh the possible risks associated with treatment. Because the majority of patients with migraine are young women, safety in pregnant women is important in clinical practice and will be included in important missing information in the risk management plan. Every case of pregnant women reported during the usual pharmacovigilance activities will be followed up as closely as possible to monitor the condition of the mother and newborn, and additional safety activities will be considered as necessary based on the available information.

PMDA's view:
Although the effect of exposure to galcanezumab on pregnant women and on fetuses is currently unknown, no particular problems were observed in the clinical studies or reproductive and developmental toxicity studies of galcanezumab. Therefore, the applicant's explanation is appropriate that the use of galcanezumab in pregnant women should be considered only if the expected therapeutic benefits outweigh the possible risks associated with treatment. Given that the majority of patients with migraine are young women, pregnancy may occur during galcanezumab treatment in clinical settings as in the clinical studies, and the collection of such cases is important. While it is difficult to conduct a prospective survey on pregnancy events, there will be no major problems in collecting information through the usual pharmacovigilance activities. A final decision on the appropriateness of this conclusion will be made taking account of comments raised in the Expert Discussion.

7.R.5 Intended population and indication of galcanezumab

The applicant's explanation about the rationale for the proposed indication:
Japanese and foreign clinical studies demonstrated the inhibitory effect of galcanezumab against migraine attacks regardless of their frequency, response to other drugs, etc., with acceptable safety. According to Clinical Practice Guideline for Chronic Headache 2013, treatment of migraine is classified into "drugs for acute phase treatment" and "drugs for preventing migraine." In order to emphasize that galcanezumab does not prevent migraine itself but suppresses migraine attacks, the indication was proposed as "Prevention of migraine attacks."

PMDA asked the applicant to explain the necessity of limiting the use of galcanezumab only in patients who had an inadequate response to other drugs, taking account that Study CGAW, which is regarded as a confirmatory study for the approval application in Japan, enrolled patients who had an inadequate response to or are intolerant of 2 to 4 types of antimigraine prophylactic drugs; and in light of the recognition of galcanezumab in relevant foreign guidelines.

The applicant's explanation:
The efficacy and safety of galcanezumab were demonstrated in patients with migraine in foreign phase III studies (Studies CGAG, CGAH, and CGAI) and Japanese studies (Studies CGAN and CGAP) regardless of patients' response to other drugs, indicating that the degree of inadequacy of response to other drugs is not significantly related to the efficacy of galcanezumab [see Section "7.R.3.4 Factors affecting efficacy"]. Therefore, galcanezumab is expected to be safe and effective regardless of the inadequacy of response to other drugs.

Clinical practice guidelines of the US and Europe (*Headache.* 2019;59:1-18, *J Headache Pain.* 2019;20:6) point out that anti-CGRP monoclonal antibodies including galcanezumab have advantages in efficacy, safety, and tolerability but are more expensive than conventional prophylactic drugs, and that they should be administered to patients who had an inadequate response to or intolerant of ≥2 types of conventional treatments. In Japan, however, antimigraine prophylactic drugs approved in the US and Europe such as topiramate and botulinum toxin are not approved for the indication of migraine, and therefore Japanese patients have some different treatment options from those for non-Japanese patients. In addition, galcanezumab is expected to be effective in patients other than those who had an inadequate response to conventional drugs or unable to receive conventional drugs for a safety reason [see Section "7.R.1 Clinical positioning"]. It is thus unnecessary to limit eligible patients based on prior treatment history, etc.

PMDA asked the applicant to explain whether it is appropriate that the intended population includes patients with a history of myocardial infarction, angina unstable, percutaneous transluminal coronary angioplasty, coronary-artery bypass surgery, or ischemic stroke within 6 months before screening, and patients with a history of hemiplegic migraine, ophthalmoplegic migraine, or migraine with brainstem aura, who were excluded from the major Japanese and foreign clinical studies on the efficacy and safety of galcanezumab.

The applicant's explanation:
Cerebro- or cardiovascular event was considered to be a potential risk from the pharmacological action of galcanezumab [see Section "7.R.4.3 Cardiovascular-related adverse events"], patients with an acute cardiovascular event and/or serious cardiovascular risk or with a past history of cerebro- or cardiovascular event were excluded from the Japanese and foreign clinical studies. However, results of the clinical studies and the foreign post-marketing safety information[13)] do not suggest a cerebro- or cardiovascular risk of galcanezumab [see Section "7.R.4.3 Cardiovascular-related adverse events"]. Patients with atypical, rare-type migraine such as hemiplegic migraine were excluded to minimize the variation of symptoms from the standpoint of efficacy evaluation, but they are not considered to be a risk population associated with galcanezumab. For these reasons, it is unnecessary to actively exclude these patients from the intended population, although the exclusion of this patient population from the studies warrants attention.

PMDA's view:
The treatment with galcanezumab aims to reduce migraine attacks interfering with daily activities as with conventional drugs. Therefore its indication should be the same as that of conventional drugs which have been recognized as antimigraine prophylactic drugs.

The results of Japanese and foreign clinical studies indicate promising efficacy and safety of galcanezumab regardless of patients' prior treatment and, from the efficacy and safety viewpoints, there is no proven need to use conventional drugs in preference to galcanezumab. Also, given diverse lifestyles of patients, there is a certain validity in the applicant's explanation that galcanezumab may be more suitable than conventional oral drugs in some patients [see Section "7.R.1 Clinical positioning"].

Patients with a cerebro- or cardiovascular risk and those with a rare subtype such as hemiplegic migraine were excluded from the pivotal clinical studies for the present application. They are excluded from the intended populations for triptans, etc. because of the potential relationship of cerebrovascular contraction to the aura of migraine. However, no clear cardiovascular risk was observed in the clinical studies of galcanezumab or in the foreign post-marketing safety information [see Section "7.R.4.3 Cardiovascular-related adverse events"], and they can be included in the intended population of galcanezumab, as long as the exclusion of these patients from the clinical studies is appropriately communicated. Nevertheless, whether to administer galcanezumab should be carefully determined because galcanezumab is a drug with a novel action mechanism without sufficient long-term safety data, and galcanezumab is an injectable antibody preparation, which is unique from the conventional drugs, with a risk of adverse drug reactions such as hypersensitivity and injection site reaction [see Sections "7.R.4.1 Hypersensitivity-related adverse events" and "7.R.4.2 Injection site-related adverse events"]. Also, Clinical Practice Guideline for Chronic Headache 2013 states that migraine can be prevented from becoming chronic by giving advice on sleep and dietary habit or stress management to improve patient's lifestyle or by maintaining the optimal body weight, and that the prophylactic therapy is intended for patients who suffer interference with activities of daily living despite acute phase treatment of migraine attacks given. Taking into account these descriptions in the guidelines, the use of galcanezumab should be considered after appropriate treatments, such as non-drug therapies including measures against migraine induction/aggravating factors, and acute phase therapy are given.

Based on the above, PMDA concludes that the indication and related precautions in the package insert should be defined as below. The above conclusion will be finalized also taking account of comments from the Expert Discussion.

Indication
Prevention of migraine attacks

Precautions Concerning Indication
- The use of galcanezumab should be considered for patients who have been confirmed, by careful examination, to have multiple migraine attacks with or without aura per month or have chronic migraine.
- Galcanezumab should be used only for patients who continue to suffer interference with activities of daily living despite adequate non-drug therapy, acute-phase therapy against migraine attacks, etc. given according the latest guidelines.

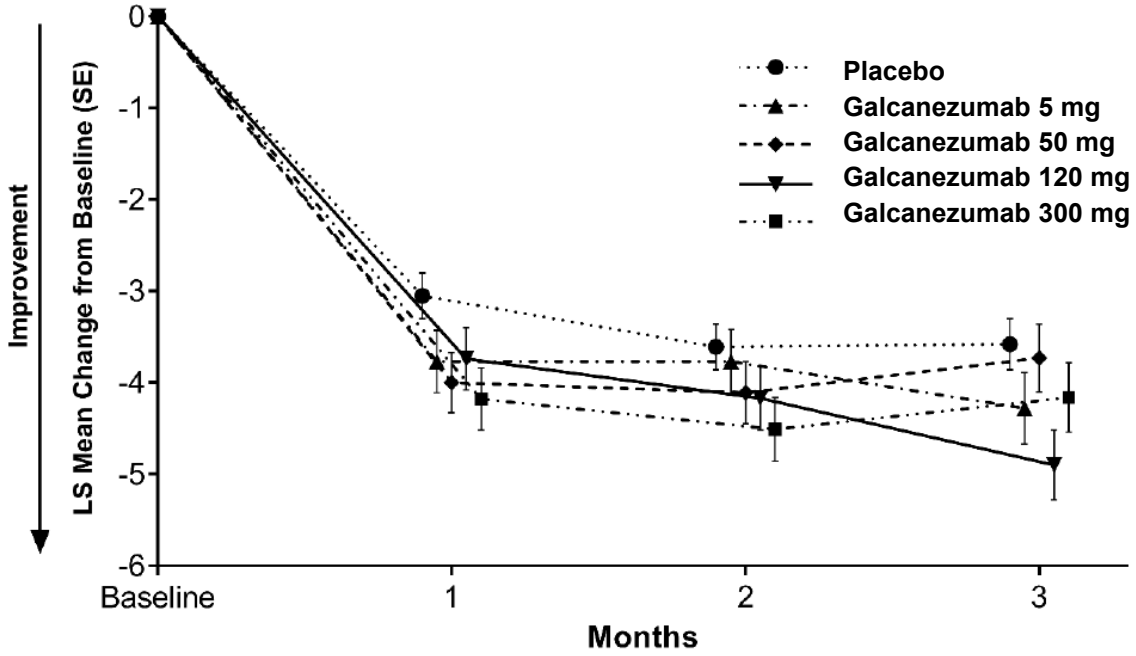
Important Precautions (excerpt)
- Galcanezumab should be administered under the supervision of a physician with adequate knowledge and experience in migraine treatment.
- Galcanezumab does not relieve ongoing migraine attacks. Patients should be instructed to take an antimigraine drug as needed once an attack develops during the treatment with galcanezumab. This should be thoroughly explained to the patient prior to the treatment.

7.R.6 Dosage and administration

7.R.6.1 Starting dose

The applicant's explanation about the justification for the starting dose of galcanezumab 240 mg:

In the foreign phase II study (Study CGAB), galcanezumab 5, 50, 120, 300 mg or placebo was administered to patients with EM once every month without specifying the starting dose. The difference in change from baseline in MHD from the placebo group became apparent from 1 month of treatment in the galcanezumab 300 mg group, while the difference was not apparent until 3 months of treatment in the 120 mg group (Figure 5). A simulation using a PPK model suggested that serum galcanezumab concentration would promptly reach steady state if the starting dose of 240 mg is administered in the galcanezumab 120 mg group. The foreign phase III studies (Studies CGAG, CGAH, and CGAI), therefore, was designed with the galcanezumab 120 mg group (starting dose 240 mg) and the 240 mg group. In all studies, galcanezumab 120 mg began to show its effect from Week 1 and the efficacy became evident from Month 1 in the group. In Japanese patients as well, galcanezumab 120 mg began to show its effect from Week 1 and the efficacy became evident from Month 1 in Study CGAN in patients with EM and Study CGAW in patients with EM or CM. It is therefore considered appropriate to start the treatment at 240 mg as was the case with the dosage regimen in foreign countries. It is clinically significant that the treatment effect becomes apparent from Month 1, in light of the conventional drugs requiring 2 to 3 months to show their efficacy.



MMRM with treatment group, study site, office visit (month), and interaction between treatment group and office visit (month) as fixed effects, and with MHD during 1-month baseline and interaction between MHD during 1-month baseline and office visit (month) as covariates (covariance structure: unstructured)

Figures 5. Over-time change from baseline in MHD (days) (excluding suspected migraine) per month in Study CGAB (ITT)

PMDA's view:

Prophylactic migraine treatment is essential for patients who suffer interference with activities of daily living even after the acute phase treatment of migraine attacks has been given and for patients ineligible for the acute phase medication. Therefore it is reasonable to use a dosage regimen that can exert its effect

soon after the administration begins, unless there are safety problems. In Japanese and foreign clinical studies that were conducted using the starting dose of 240 mg, galcanezumab exerted its efficacy without any significant safety problem as compared to the placebo group. Accordingly, the use of the starting dose of galcanezumab as 240 mg is reasonable.

7.R.6.2 Maintenance dose

The applicant's explanation about the justification for the maintenance dose of galcanezumab 120 mg:
In Studies CGAG and CGAH in patients with EM and in Study CGAI in patients with CM, galcanezumab 120 mg (starting dose, 240 mg) and 240 mg were investigated. A significant improvement in change from baseline in MHD per month, the primary endpoint, was observed in both galcanezumab 120 and 240 mg groups as compared to the placebo group, but the change was comparable between the 120 mg and 240 mg groups [see Sections "7.R.3.1 Efficacy against EM" and "7.R.3.2 Efficacy against CM"]. Similarly, in Study CGAN in Japanese patients with EM, the dose-response curve leveled off [see Section "7.R.3.1 Efficacy against EM"]. Accordingly, in Study CGAW, only the 120 mg dose was investigated as galcanezumab group, and results confirmed its efficacy in this group. In addition, there was no significant difference in the safety profiles between galcanezumab 120 mg and 240 mg in Japanese and foreign clinical studies.

Based on the above, it is considered appropriate to use the maintenance dose of 120 mg in Japan as well, as is the case with the approved dosage regimen in foreign countries.

PMDA's view:
Japanese and foreign clinical studies showed that galcanezumab 120 mg and 240 mg decreased MHD to a similar extent, with no significant difference in safety. In addition, the efficacy of galcanezumab 120 mg was confirmed in Study CGAW which is regarded as a confirmatory study in the approval application in Japan. Accordingly, the maintenance dose of galcanezumab 120 mg is acceptable.

7.R.6.3 Decision on treatment continuation/discontinuation

The applicant's explanation about the decision:
A decision making on whether to continue galcanezumab treatment is necessary not only when a safety-associated issue arises but also when (a) further treatment is unlikely to provide adequate efficacy or (b) the symptoms have improved and galcanezumab treatment seems to be no longer necessary.

To assess (a), a post hoc evaluation was performed on the efficacy, separately for subgroups classified by extent of decrease from baseline in MHD over 2 months after the start of galcanezumab treatment (Tables 56 and 57).

Table 56. Decrease in MHD (days) in patients with EM (ITT)

		MHD decrease after 2 months of treatment			
		Moderate[a]	Limited[b]	Minimum or no response[c]	Increased[d]
Number of patients who showed a ≥50% decrease in MHD after treatment for 3 to 6 months % (Number of patients)	Foreign phase III studies (Studies CGAG and CGAH)	50.0 (25/50)	40.8 (40/98)	17.9 (12/67)	9.3 (7/75)
	Japanese phase II study (Study CGAN)	18.2 (2/11)	27.3 (9/33)	31.6 (6/19)	0 (0/27)

a, Decrease by >30% to <50%; b, Decrease by >10% to ≤30%; c, Decrease by ≤10% or increase by ≤10%; d, Increase by >10%

Table 57. Decrease in MHD (days) in patients with CM (ITT)

		MHD decrease after 2 months of treatment		
		Moderate[a]	Minimum or no response[b]	Increased[c]
Number of patients who showed a ≥30% decrease in MHD after treatment for 3 months % (Number of patients)	Foreign phase III study (Study CGAI)	35.2 (25/71)	13.2 (16/121)	10.4 (5/48)
	CM population in Japanese long-term treatment study (Study CGAP)	50.0 (6/12)	15.4 (2/13)	0 (0/5)

a, Decrease by >10% to <30%; b, Decrease by ≤10% or increase by ≤10%; c, Increase by >10%

These results show the treatment effect observed at Month 2 and are suggestive of a certain extent of efficacy in subsequent months. The results also suggest the possibility that 10% to 30% of subjects may obtain moderate or greater efficacy in 3 to 6 months of treatment, even if the Month 2 efficacy is minimum or lower. Thus, it is difficult to judge the efficacy of galcanezumab in a short period. Whether to continue the treatment should be determined in light of the therapeutic benefit of galcanezumab after approximately 3 months, in accordance with the efficacy evaluation periods in the clinical studies.

In terms of the decision making in the case of (b), the efficacy and safety of long-term administration (up to 18 months) in Japanese patients with migraine were investigated in Studies CGAN and CGAP, which demonstrated long-term efficacy and acceptable safety over the treatment period investigated. Because of diverse lifestyles of patients involving activities which can be affected by migraine, such as schoolwork, job, household task, and childcare, treating physicians are expected to determine the need of prophylactic therapy with galcanezumab on a case-by-case basis. It is therefore difficult to specify the timing of decision making or provide criteria for discontinuation that accommodate various changes in disease conditions and lifestyles of patients. Rather, physicians should assess the need of further treatment on a regular basis according to the condition of individual patients.

Accordingly, the “Precautions Concerning Dosage and Administration” section will advise that the therapeutic benefits should be assessed after approximately 3 months of treatment with galcanezumab and the need of further treatment should be determined on a regular basis.

PMDA’s view:
Physicians should be advised not to continue galcanezumab treatment aimlessly in patients who are no longer likely to have good response to the treatment and those who no longer needs the treatment because of a favorable change in the occurrence of their migraine attacks or in their lifestyles. The applicant points out the difficulty in determining whether to continue the treatment in a short-term period. The primary efficacy evaluation period was 3 months in Study CGAW. The Clinical Practice Guideline for Chronic Headache 2013 advises that the efficacy of prophylactic therapies should be judged after

approximately 2 to 3 months. Given these, the applicant's view is acceptable that whether to continue the treatment with galcanezumab should be determined after approximately 3 months of treatment. On the other hand, the timing of treatment discontinuation depends on the situation of individual patients, precluding specifying the timing or criteria for discontinuation. Nevertheless, migraine generally tends to improve with age, and psychological and environmental factors, etc. contribute to the induction and aggravation of migraine (Clinical Practice Guideline for Chronic Headache 2013). Therefore, regardless of the availability of criteria, whether to continue galcanezumab treatment should be determined according to the condition of individual patients in whom migraine has once become well-controlled as a result of a drastic environmental change, etc. This should be advised in the package insert.

Thus, on the basis of the reviews in Sections "7.R.6.1 Starting dose" to "7.R.6.3 Decision on treatment continuation/discontinuation," PMDA concludes that the Dosage and Administration and the Precautions Concerning Dosage and Administration should be described as below. Details will be finalized taking account of comments raised in the Expert Discussion.

Dosage and Administration
The usual adult dosage is 240 mg of galcanezumab (genetical recombination) administered subcutaneously as the first dose, followed by monthly doses of 120 mg injected subcutaneously.

Precautions Concerning Dosage and Administration
During the treatment with galcanezumab, the clinical course of the patient should be closely monitored and the therapeutic benefit should be assessed after around 3 months of treatment. Galcanezumab should not be continued aimlessly. The discontinuation of galcanezumab should be considered in either of the following cases:

- There is no improvement in the symptoms.
- The patient no longer suffers interference with activities of daily living as a result of eliminated or reduced migraine attacks.

7.R.7 Self-injection

The applicant's explanation:
In the Japanese long-term treatment study (Study CGAP), 41 patients (patients with EM, 19 of 120 in the galcanezumab 120 mg group, 14 of 126 in the 240 mg group; patients with CM: 5 in the 120 mg group, 3 in the 240 mg group) underwent self-injection of galcanezumab using the PFS formulation from Month 6. The incidence of adverse events in these patients was 89.5% (17 of 19), 92.9% (13 of 14), 100% (5 of 5), and 100% (3 of 3), respectively, which was not significantly different from the incidence in the entire population (90.0%, 92.9%, 96.9%, and 87.9%, respectively). Main adverse events were nasopharyngitis, injection site erythema, injection site pain, influenza, and injection site pruritus, which were also observed in the entire population [see Section "7.3.5 Japanese phase III long-term treatment study"], with no adverse event associated with self-injection or device malfunction. No significant change was observed in efficacy between before and after the start of self-injection. In the foreign long-term treatment study (Study CGAJ), patients were required to perform self-injection using the PFS or AI formulation from the second dose, and 84 patients in the galcanezumab 120 mg group and 95 patients in the 240 mg group used both PFS and AI formulations. No significant difference was

observed in the tolerability of these patients between the PFS and AI formulations. No clinical data are available on Japanese patients treated with the AI formulation; instead, use-results are available on Taltz 80 mg Auto-injector for SC Injection, which uses almost the same AI as that of galcanezumab except for the color of the injection button, etc. From the use-results surveillance of Taltz 80 mg Auto-injector for SC Injection currently ongoing in Japan, 289 patients were confirmed to have performed a total of 2930 doses of galcanezumab self-injection, and there is no confirmed case of treatment discontinuation due to AI malfunction. Psoriasis, the main indication of Taltz 80 mg Auto-injector for SC Injection, primarily affects women in their 20s to 50s and men in their 50s (*J Dermatol.* 2011;38:1125-9), the age groups close to patients with migraine, for which galcanezumab is indicated. Thus, the self-injection of galcanezumab using the AI formulation in Japanese patients with migraine is unlikely to pose clinical problems. As one of the post-marketing risk-minimization activities, the applicant plans to provide relevant information to healthcare professionals via the package insert, operating instructions, and Drug Guide for Patients. Thus, it is possible for Japanese patients with migraine to safely perform the self-injection of galcanezumab using either PFS or AI formulation.

PMDA's view:
Taking account of the applicant's explanation, self-injection using either PFS or AI formulation is considered acceptable where patients have been instructed by physicians based on appropriate cautionary advice and information materials and have confirmed to be competent to perform the procedure smoothly.

7.R.8 Post-marketing investigations

The applicant's explanation:
For the purpose to investigate the risk of serious cardiovascular events in the clinical use of galcanezumab, the applicant plans to conduct post-marketing database surveillance. The occurrence of serious hypersensitivity, safety in pregnant women, and safety in long-term use will be investigated through the usual pharmacovigilance activities. In the US and Europe, database surveillance (5-year observation in approximately 5000 and 7000 patients, respectively, in the US and Europe) is planned to evaluate the use status of galcanezumab and long-term safety (serious cardiovascular events, serious hypersensitivity, malignant tumor, etc.).

PMDA's view:
For the serious cardiovascular events which are likely to occur due to the action mechanism of galcanezumab, it is considered beneficial to conduct post-marketing database surveillance in Japan by referring to the database surveillance to be implemented in foreign countries and thereby to evaluate the risk of these events in Japanese patients. Details of the post-marketing surveillance, etc. will be finalized taking account of comments raised in the Expert Discussion, including the identification of safety specifications and the appropriateness of risk classification, the pharmacovigilance activities, and risk minimization activities, according to "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2 dated April 11, 2012).

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that galcanezumab has efficacy in the prevention of migraine attacks and that galcanezumab has acceptable safety in view of its benefits. Galcanezumab is an injectable product targeting at CGRP to be administered once a month. It is of clinical significance to offer galcanezumab to the clinical settings as a novel treatment option for the prevention of migraine attacks. The indication, dosage and administration, cautionary statements in the package insert, and post-marketing investigations are subject to further discussion.

PMDA has concluded that galcanezumab may be approved if galcanezumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 2, 2020

Product Submitted for Approval

Brand Name	(a) Emgality Subcutaneous Injection 120 mg Autoinjector (b) Emgality Subcutaneous Injection 120 mg Syringe
Non-proprietary Name	Galcanezumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	January 24, 2020

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Safety

(a) Cardiovascular-related adverse events

The following comments were raised from the expert advisors:
Galcanezumab inhibits CGRP that has a vasodilating action. Because patients with cardiovascular risk and elderly patients were excluded from the clinical studies, cardiovascular risks of galcanezumab in these patient groups remain unknown. Patients with a cardiovascular risk for whom triptans are contraindicated may possibly be eligible for galcanezumab. Thus, it is important to collect information in the post-marketing setting about the occurrence of galcanezumab-associated serious cardiovascular-related events. Thus, the expert advisors supported the PMDA's conclusion stated in Section "7.R.4.3 Cardiovascular-related adverse events" of the Review Report (1).

(b) Effect on pregnancy

The following comments were raised from the expert advisors:
Generally, pregnancy alleviates migraine symptoms, but some patients suffer repeated severe migraine attacks even during pregnancy, and there are limited options of antimigraine prophylactic drugs and acute-phase medications that can be used in pregnant patients. In light of this situation, it is important to collect information about the effect of exposure to galcanezumab in pregnant women and fetuses. Thus, the expert advisors supported the PMDA's conclusion stated in Section "7.R.4.8 Effect on pregnancy" of the Review Report (1).

1.2 Intended population and indication for galcanezumab

The purpose to use galcanezumab is to alleviate migraine attacks that interfere with daily activities, similarly to the conventional antimigraine prophylactic drugs. Accordingly, the indication of galcanezumab should be the same as that of the approved and clinically recognized antimigraine prophylactic drugs. This conclusion of PMDA was supported by the expert advisors.

The following comment were raised from the expert advisors:
Galcanezumab should be used by physicians who are acquainted with diagnosis and treatment of headache, with competency in accurately diagnosing migraines, detecting complications of medication overuse headache, identifying aggravating factors of migraine, and providing lifestyle guidance. Thus, the expert advisors supported the PMDA's conclusion that the use of galcanezumab should be considered after appropriate non-drug therapy, acute-phase treatment, etc. are given. PMDA has also reached conclusions that patients with a cerebro- or cardiovascular risk and those with a rare subtype of migraine such as hemiplegic migraine may be included in the target population of galcanezumab, as long as healthcare professionals are appropriately informed of the exclusion of these patients from the clinical studies conducted, and that galcanezumab may be administered to patients regardless of prior treatment, based on the results of Japanese and foreign clinical studies. The expert advisors also supported these conclusions.

Taking account of the above comments from the Expert Discussion, PMDA has concluded that the indication and related precautions should be described in the package as follows:

Indication
Prevention of migraine attacks

Precautions Concerning Indication

- The use of galcanezumab should be considered for patients who have been confirmed, by careful examination, to have multiple migraine attacks with or without aura per month or chronic migraine.
- Galcanezumab should be used only for patients who continue to suffer interference with activities of daily living despite adequate non-drug therapy, acute-phase therapy against migraine attacks, etc. given according to the latest guidelines.

Important Precautions (excerpt)

- Galcanezumab should be administered under the supervision of a physician with adequate knowledge and experience in migraine treatment.
- Galcanezumab does not relieve ongoing migraine attacks. Patients should be instructed to take an antimigraine drug as needed once an attack develops during the treatment with galcanezumab. This should be thoroughly explained to the patient prior to the treatment.

1.3 Dosage and administration

PMDA's opinions in Section "7.R.6 Dosage and administration" of the Review Report (1), including the conclusion that the starting dose should be 240 mg and the maintenance dose 120 mg, was supported by the expert advisors. Meanwhile, the following comments were raised from the expert advisors:

- Many study participants responded to galcanezumab in 1 month of treatment. Given the efficacy assessment of conventional antimigraine prophylactic drugs being conducted in approximately 3 months of treatment, healthcare professionals should be advised not to continue galcanezumab treatment aimlessly for patients not responding to a >3-month long treatment.
- In the clinical studies, some subjects remained with reduced migraine symptoms even after treatment discontinuation, while others experienced the recurrence of worsening symptoms after discontinuation. Although a decision making is not easy on how much longer the treatment should be given to responders, physicians, whenever treating patients, should always keep the question in mind whether the patient really needs further prophylactic treatment.

Taking account of the above comments, PMDA has concluded that the Dosage and Administration and the Precautions Concerning Dosage and Administration sections should be described in the package insert as follows.

Dosage and Administration

The usual adult dosage is 240 mg of galcanezumab (genetical recombination) administered subcutaneously as the first dose, followed by monthly doses of 120 mg injected subcutaneously.

Precautions Concerning Dosage and Administration

During the treatment with galcanezumab, the clinical course of the patient should be closely monitored and the therapeutic benefit should be assessed after around 3 months of treatment. The discontinuation of galcanezumab should be considered when there is no improvement in the symptoms. Whether to continue the treatment should be assessed periodically thereafter, and the discontinuation of galcanezumab should be considered for patients who no longer suffer interference with activities of daily living as a result of eliminated or reduced migraine attacks.

1.4 Risk management plan (draft)

In view of the discussions presented in Section "7.R.8 Post-marketing investigations" in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for galcanezumab should include the safety specification presented in Table 58, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 59. The optimal method of pharmacovigilance activities using Medical Information Database should be further discussed from the viewpoint of feasibility.

Table 58. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity	• Not applicable	• Safety in pregnant women • Safety in long-term administration • Serious cardiovascular events
Efficacy specification		
Not applicable		

Table 59. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database surveillance (cardiovascular events)	• Disseminate data gathered through early post-marketing phase vigilance • Organize and disseminate informative materials for healthcare professionals • Organize and disseminate informative materials for patients

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. Overall, the collection of data and preparation of the application documents were conducted in accordance with the standards for the reliability of application documents, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. Meanwhile, the inspection revealed the following finding requiring a corrective action by the applicant, although it had no significant impact on the review of the overall clinical studies. PMDA notified the applicant of the problem.[20)]

Finding requiring corrective action

Sponsor

- Despite the advance agreement that data collected from patient diaries shall not be modified as a rule, a study site requested to modify data of 4 patients and the sponsor accepted the request. The modified data were used for the analyses of the primary efficacy endpoint and the secondary endpoints.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.2, CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

[20)] CTD 5.3.5.1.3, as in CTD 5.3.5.1.2, stipulates the principle that data collected from patient diaries shall not be modified. However, data from 2 patients were modified according to the request of the study site, and the secondary efficacy endpoints were analyzed using the modified data. PMDA confirmed that these changes did not significantly affect the overall evaluation of the study.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Prevention of migraine attacks

Dosage and Administration

The usual adult dosage is 240 mg of Galcanezumab (Genetical Recombination) administered subcutaneously as the first dose, followed by monthly doses of 120 mg injected subcutaneously.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ADA	Anti-drug antibodies
AI	Autoinjector
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
$AUC_{0\text{-}3d}$	AUC from Days 0 to 3 of administration
$AUC_{0\text{-}7d}$	AUC from Days 0 to 7 of administration
AUC_{inf}	AUC from 0 hour to infinity
AUC_{last}	AUC from 0 hour to the last measurable time point
AUC_{τ}	AUC in dosing interval
$AUC_{\tau,\ ss}$	AUC in dosing interval at steady state
C1q	Complement component 1, q subcomponent
CAL	Cells at the limit of in vitro cell age used for production
cAMP	Cyclic adenosine monophosphate
[redacted]	[redacted]
CE-SDS	Capillary electrophoresis- sodium dodecyl sulfate
CEX	Cation exchange chromatography
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CL	Total body clearance
CL/F	Apparent total body clearance
CL_{cr}	Creatinine clearance
CM	Chronic migraine
C_{max}	Maximum serum concentration
$C_{max,\ ss}$	Maximum serum concentration at steady state
$C_{min,\ ss}$	Minimum serum concentration at steady state
CQA	Critical quality attribute
CRLR	Calcitonin receptor-like receptor
DBF	Dermal blood flow
DNA	Deoxyribonucleic acid
ECL	Electrochemiluminescence
ELISA	Enzyme-linked immunosorbent assay
EM	Episodic migraine
Emgality	Emgality Subcutaneous Injection
ePRO	Electronic Patient-Reported Outcomes
[redacted]	[redacted]
Fc	Fragment crystallizable
Galcanezumab	Galcanezumab (genetical recombination)
HCP	Host cell protein
HRP	Horseradish peroxidase
HTRF	Homogeneous time resolved fluorescence
ICHD	International Classification of Headache Disorders
ICH Q5A (R1) Guideline	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000)

ICH Q5B Guideline	“Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products” (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH S6 (R1) Guideline	“Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals” (PFSB/ELD Notification No. 0323-1 dated March 23, 2012)
IgG	Immunoglobulin G
IHS	International Headache Society
ITT	Intent to treat
IVRS	Interactive voice response system
k_a	Absorption rate constant
K_b	Dissociation rate constant
KD	Equilibrium dissociation constant
LC-MS	Liquid chromatography - mass spectrometry
MCB	Master cell bank
MHD	Migraine headache days
MMRM	Mixed models repeated measures
MSQ	Migraine Specific Quality of Life Questionnaire
NSAIDs	Nonsteroidal anti-inflammatory drugs
NZW	New Zealand White
OD	Optical density
PD	Pharmacodynamics
PFS	Prefilled syringe
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QbD	Quality by design
RAMP	Receptor activity modifying protein
RNA	Ribonucleic acid
SD	Sprague-Dawley
SEC	Size exclusion chromatography
$t_{1/2}$	Elimination half-life
TBL	Total-bilirubin
TE-ADA	Treatment emergent anti-drug antibodies
t_{max}	Time of maximum serum concentration
$t_{max, ss}$	Time of maximum serum concentration at steady state
TMB	3, 3’, 5, 5’-Tetramethylbenzidine
UV/VIS	Ultraviolet-visible spectrophotometry
V/F	Apparent volume of distribution
V_{ss}	Volume of distribution at steady state
Vz/F	Apparent volume of distribution during the terminal phase
WCB	Working cell bank