Assessment report for pharmaceutical medicinal product

(AIMOVIG®) Erenumab 70 mg/ml Solution for Injection
Date of submission, held on the 3rd July 2018

Division of Health Product Enterprise Services

Name of product	Aimovig®
Active Substance(s) (ATC code)	INN :Erenumab (N02CD01)
Pharmaceutical form	Solution for injection
Strength	Erenumab 70 mg/ml
Routes of administration	Subcutaneous injection (SC)
Therapeutic indication)s(	Indication as stated in SmPC: Aimovig is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.
	Indications as stated in the patient information leaflet (PIL) ใช้ป้องกันอาการปวดหัวไมเกรนในผู้ใหญ่ ซึ่งแพทย์วินิจฉัยแล้วว่าจำเป็นต้องใช้ยานี้
Submitted number and date of submission	1C 15055/61 (NB) 3 July 2018
E-Identifier Number	E6100037

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Assessment report for AIMOVIG®

Submitted number : 1C 15055/61 (NB)

E-identifier : E6100037 (sequence 0000)

Submitted date : 3 July 2018

Part 1 :Introduction and summary review

Migraine is a multi-symptom chronic disease characterized by a moderate to severe unilateral throbbing headache lasting from 4 to 72 hours .The symptoms include nausea, vomiting, and sensitivity to light, sound, and head movements.(1) The severe pain and other associated symptoms have been shown to affect a patient's physical and social ability and reduce quality of life.(2, 3)

Migraine pathology involves sensitization and excitation of trigeminal ganglion nerves caused by many neuro-peptides such as substance P, and calcitonin gene-related peptide (CGRP).(1) Calcitonin gene-related peptide (CGRP), greatly expressed in trigeminal neurons, induces edema, increases blood flow, and recruits inflammatory cells, promoting neurogenic inflammation and leading to migraine pain at Peripheral Nervous System .Besides during migraine, CGRP is released centrally at synapses in the trigemino-cervical complex to sensitize neuronal circuits associated with diminution of the neuron activation threshold, leading to allodynia, nausea, photophobia, and phonophobia. CGRP levels are distinctively increased during the headache phase of both migraines with or without aura .(4, 5)

11% of an adult has migraine attack worldwide(6) Medical treatment for migraine is non-specific symptomatic agents such as non-steroidal anti-inflammatory drugs (NSAID) or migraine-specific medications such as triptans or ergotamine derivatives7.(7) As a result of epidemiologic studies, pharmacological prophylactic treatment is recommended to be part of the treatment for migraine patients who have high severity of disease characterized by frequent attacks or functional impact

Many of the commonly prescribed prophylaxis treatments were not intentionally developed for preventing migraine, such as antiepileptic drugs, β-blockers and antidepressant. After following the use of these drugs, the result has reviewed that it was lack of efficacy, tolerability and patient adherence.(8) Thus, effective prophylactic therapies for migraine are greatly needed. According to the pathophysiology of migraine, CGRP is a target for migraine preventive therapies. AMG-334 (Erenumab), a human monoclonal immunoglobulin G2, is a potent, selective, full antagonist of the CGRP receptor that consequently inhibits the action of CGRP (9) resulting in reducing the frequency of migraine days. Erenumab, commercially available as Aimovig®, is a recent developed migraine preventive agent for prophylaxis of migraine in adults .

Part 2 :Summary of the dossier

2.1 Type of marketing authorization application

- **Product type:** New Biological medicinal product
- **Application type :**Stand-alone application
- **Review method :**Full assessment. 2 experts for quality part and internal reviewer using un-redacted assessment report from EMA together with expert panel meeting for overall assessment

2.2 Administrative data

2.2.1 Product information

Name of Product :Invented name	Aimovig®
Active Substance (s)	INN :Erenumab
Strength	Erenumab 70 mg/ml

Therapeutic class (ATC Code)	Analgetics, antimigraine preparations ATC code : N02CD01
Pharmaceutical form	Solution for injection
Route of administration	Subcutaneous injection (SC)
Drug Characteristics	Colorless to slightly yellow solution for injection.
Packaging	Each Pre-filled syringe /pre-filled pen contains 1 mL solution .
Package size(s)	Each blister/tray comprises of 1, 2 syringe/pen in a carton box.

2.2.2 Source

- **Name and address of the applicant for importation**

  Novartis (Thailand) Ltd .689 Bhiraj Tower at Emquartier, 25th Floor, Sukhumvit Road, North Klongton, Vadhana, Bangkok 10110 Tel. 02-080-0999/ 02-028-9797

- **Name and address of the manufacturer(s) of the dosage form**

  Amgen Manufacturing Limited, State Road 31, Km 24.6 Juncos, Puerto Rico 00777-4060, United States of America

- **Name and address of and the primary packaging**
  Amgen Manufacturing Limited, State Roas 31, Km 24.6 Juncos, Puertto Rico 00777-4060, United States of America.

- **Name and address of and the secondary packaging**

  Amgen Europe B.V, Minervum 7061, 4817ZK Breda, Netherlands.

- **Name and address of the manufacture(s) which take responsibility on technical batch release**

  Amgen Europe B.V, Minervum 7061, 4817ZK Breda, Netherlands.

Evaluation results

The manufacturer was licensed as manufacturer for human medicine product .The manufacturer has been permitted both in sterile products and non-sterile product. The manufacturer has been certified GMP compliance of a manufacturer by Health Care Inspectorate- Pharmaceutical Affairs and Medical Technology, Netherlands; membered of EudraGMP and PIC/s and certified CPP from USFDA.

Marketing authorization holder, Novartis (Thailand) Ltd, also attached GMP clearance certificate approved by Bureau of drug control, Thai FDA.

Part 3 :Analytical Physico-Chemical, Biological and Microbiological Documentation

3.1 Drug subtance

3.1.1 General Information

3.1.1.1 Nomenclature

Recommended International Non-proprietary Name (INN)	Erenumab
Chemical name(s)	Anti-human CGRP-R (calcitonin gene-related

	peptide type 1 receptor monoclonal antibody)
Amgen laboratory code name	AMG 334

3.1.1.2 Structure

AMG 334 is a human monoclonal antibody of the immunoglobulin G2 (IgG2) subclass produced in Chinese hamster ovary cell (CHO) by using recombinant DNA technology, consisting of 2 heavy chains and 2 light chains of the human lambda subclass. AMG 334 contains 36 cysteine residues involved intrachain and interchain disulfide bonds .

3.1.1.3 General Properties

1 .Physical and Chemical Properties

Physical and chemical properties were provided adequately in dossier.

2 .Biological Properties

AMG 334 (IgG2) specifically binds to the extracellular domain of the calcitonin gene-related peptide receptor (CGRP-R) and prevents its interaction with the neuropeptide CGRP. CGRP is expressed in and released by sensory nerves and acts as a potent vasodilator upon binding to CGRP-R. CGRP has been implicated in migraines and its levels are elevated in the blood during a migraine attack . The AMG 334 mechanism of action in migraine prevention is through binding to the CGRP-R, thereby blocking the action of the CGRP ligand for a prolonged period.

3.1.2 Manufacture

3.1.2.1 Manufacturer(s)

The drug substance is manufactured in accordance with current Good Manufacturing Practices (cGMPs). The facilities involved in the manufacture and testing of AMG 334 drug substance, including contract laboratories were provided.

The review found that all relevant drug substance sites have valid manufacturing authorisations or valid GMP certificates as appropriate.

3.1.2.2 Description of Manufacturing Process and Process Controls

The manufacturing process and process controls were sufficiently described in dossier.

Evaluation result

Erenumab (AMG-334) was manufactured by the manufacturer which has valid GMP certified by Health Care Inspectorate- Pharmaceutical Affairs and Medical Technology, Netherlands; membered of EudraGMP and PIC/s. Manufacturing process and quality control is suitable, so all of documents confirm that drug substance manufacturing processes are reliable suitable and acceptable.

3.1.2.3 Control of Materials

The control of materials data were provided and sufficiently described in dossier.

The host cell history is sufficiently described. The overall approach for testing of the genetic stability is approvable. They are manufactured in compliance with cGMP, tested and characterised according to ICH Q5D. Cell bank test method descriptions are sufficient.

Descriptions of the adventitious agents test methods and results are provided.

3.1.2.4 Control of critical steps and intermediates

Justifications for selection of product quality IPCs and limits were provided.

Test methods for IPC testing are sufficiently described. The overall scientific approach and anonymised data was presented in response to a question. The approach regarding the PK modelling and the conclusion are supported.

3.1.2.5 Process Validation

AMG 334 process validation is appropriately described and the manufacturing process for drug substance can be considered validated. No concerns are raised as regards the transport qualification of AMG 334 drug substance.

3.1.2.6 Manufacturing Process Development

Three versions of the drug substance manufacturing process have been used during the clinical development. Based on the totality of data, the comparability exercise is approvable.

Process parameter and performance indicator definitions and their ranges and/or limits are provided.

Based on the knowledge derived from process characterisation and prior knowledge, acceptable ranges for the process parameters were established. When operated within the process parameter acceptable ranges, the process delivers acceptable quality and process performance. Approaches for establishing IPC limits are presented.

Attributes that may have a severe, major or moderate impact on the safety or efficacy profile of AMG 334 were identified as CQAs in alignment with ICH Q8 (R2). AMG 334 CQAs are summarised in the dossier. AMG 334 quality attributes are controlled using a diverse set of control elements.

The strategy to use multivariate understanding to increase process knowledge and establish ranges for process parameters is supported.

The proposed manufacturing description with the identified acceptable ranges and the definition of acceptable ranges are acceptable as it has been assured that any negative effects due to potential interactions between process parameters will be detected by the proposed control strategy. Attributes impacted by two-factor interactions are controlled as CQAs. The dossier is updated with information regarding identified interactions and the DoE models' goodness-of-prediction. This is acceptable.

Small-scale model qualification is approvable. Minor offsets are sufficiently justified.

The proposed IPCs, as based on process characterisation, process validation and experience from commercial scale runs are approvable.

Buffer parameter acceptable ranges were defined based on process characterisation. The parameters are verified to meet acceptance criteria prior to use in the process. This is acceptable.

In-process hold pools characterisation and chromatography resin and filter reuse are sufficiently described.

The AMG 334 manufacturing process includes single-use equipment for cell culture, mixing and purification pools. The information as regards the extensive single-use material characterisation and qualification is sufficient, no concerns are raised.

An extensive process characterisation was performed. This approach, and the outcome, is acceptable.

3.1.3 Characterisation

Biochemical, biophysical, and biological characterisation of AMG 334 was conducted to provide a comprehensive understanding of the structural and functional properties and to enable an assessment of the criticality of product quality attributes (PQAs). Forced degradation studies were performed to reveal potential degradation pathways. All methods are qualified as fit for purpose.

The active substance manufacturing process has been assessed for its potential to introduce process-related impurities. Impurities derived from the host cell and "potentially safety concern" (PSC) reagents were analysed for their clearance through the purification process.

An extensive product characterisation is presented and endorsed. The conclusions regarding primary, secondary and tertiary structures are supported.

Site and occupancy for the N-glycosylation was determined. No O-linked or non-human moieties were detected.

It is agreed that the described potency assay is a good representation of the AMG 334 mechanism of action.

There was no evidence of ADCC or CDC. These conclusions are supported.

No concerns are raised regarding conclusions on forced degradation studies.

The conclusion that product-related impurities are well-controlled by the manufacturing process, recommended storage conditions, and associated analytical monitoring is supported.

Reduction of residual amounts of process-related impurities was demonstrated in small scale challenge experiments and commercial scale process validation lots. The approach and the conclusions are supported.

The evaluation and conclusions for process reagents considered to have "potential safety concerns" are scientifically sound and acceptable.

3.1.4 Control of drug substance

3.1.4.1 Specification

The development of the AMG 334 drug substance specification was performed in accordance with ICH Q6B (Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products) and ICH Q8 (Pharmaceutical Development).

A tightening of the specifications limits was requested and undertaken by the Applicant, during the review.

The justifications for omitting analyses for certain process-related impurities from routine testing and specifications are acceptable. The proposed limits for protein concentration and bacterial endotoxins are acceptable. The proposed drug substance specification is acceptable.

3.1.4.2 Analytical procedures

The descriptions of the methods used in the release and stability testing of active substance are acceptable.

The non-compendial methods used in the release of active substance have been satisfactorily validated in accordance with recommendations as per ICH Q2 and is therefore deemed acceptable.

3.1.4.3 Validation of Analytical procedure

Analytical procedures had been validated in accordance with ICH Q2(R1) (ICH Harmonized Tripartite Guide Validation of Analytical Procedures :Text and Methodology). The validation demonstrates their use as appropriated for purpose for lot release and stability indicating attributes .Compendial methods are appropriately verified for their intended use also.

3.1.4.4 Batch analyses

Batch analyses data of AMG334 are demonstrated all of results passed acceptance criteria. Batch analysis data confirm consistency and uniformity of the DS.

3.1.4.5 Justification of specification

The development of the DS specification was performed in accordance with ICH guideline Q6B and Q8.The in-process limits and DS specification acceptance criteria are justified and appropriate based on product characterization, process characterization and capability, clinical experience, manufacturing process experience, relative amounts of product-related substances and impurities, impact of product quality attributes on safety and efficacy, manufacturing experience with similar monoclonal antibody processes, formulation development studies, analytical method performance, acceptable safety levels and WHO, USP, Ph.Eur, JP and ICH guideline. Test methods for DS release and justification of the acceptance criteria for each method are provided .Moreover, MAH provided the Justification of analytical procedures used during development also.

3.1.5 Reference standard or materials

The primary reference standard is qualified to be representative of the product produced from the commercial manufacturing process .Working reference standards are qualified to be representative of the primary standard which require a standard or control for execution .

Evaluation result

Specification, analytical method and validation method of drug substance was followed by USP, European Pharmacopeia and in-house methods were also evaluated by method validation on suitable parameters. Then all can summarized that manufacturing process, analytical method and process validation of drug substance was reliable, suitable and acceptable.

3.1.6 Container closure system

Drug substance contained in standard container is suitable, reliable, and acceptable.

3.1.7 Stability

The stability studies were performed comply with the ICH Harmonized Tripartite guide, Stability testing of Biotechnological/Biological products (Q5C) and Stability Testing of New Drug Substances and Products (Q1A). Studies are conducted at the recommended storage condition and elevated temperatures in other conditions for product quality test .From the results, an expiry period of 30 months is proposed for drug substance stored at the recommended storage condition.

No statistically significant or meaningful changes are observed acceptance criteria included in the post-approval stability program ensure that the quality of AMG 334 is appropriately measured and controlled throughout the shelf life.

Evaluation results

Number of batch, condition, duration and parameters followed by ICH guideline are suitable. The stability results indicate that the active substance manufactured by the proposed suppliers sufficiently stable in the proposed container.

3.2 Drug product

3.2.1 Pre-filled syringe (PFS)

3.2.1.1 Description and Composition of the Drug Product

The 70 mg/ml drug product is provided as a sterile, single-use, preservative-free solution for SC injection in prefilled syringe (PFS). The primary container is a Type I glass with a staked needle cover with elastomeric needle shield and a bromobutyl plunger-stopper laminated with a fluoropolymer film on the product contact surface .The elastomeric needle shield is made from natural rubber, protects the needle cannula, and is supplemented with an outer plastic rigid cover . A plastic plunger rod is threaded into the plunger-stopper.The qualitative composition of the finished product is provided.

Evaluation results

The formulation including active ingredient and excipients is complied with USP, NF, Ph.Eur and in-house specification that show formulation has standard and acceptable. Moreover they have no use novel excipients in the formulation.

3.2.1.2 Pharmaceutical Development

Overall, the description of pharmaceutical development is sufficiently comprehensive and justifies the development of formulation composition, manufacturing process and container closure system.

3.2.1.3 Manufacture

3.2.1.3.1 Manufacturer(s)

- **Manufacturing/ Primary packaging site**

  Amgen Manufacturing Limited, State Road 31, Km 24.6 Juncos, Puerto Rico 00777-4060, United States of America

- **Secondary packaging site**

  Amgen Europe B.V, Minervum 7061, 4817ZK Breda, Netherlands.

Evaluation result

The manufacturer is suitable and acceptable. They show valid certificate of GMP compliance of a manufacturer from Health Care Inspectorate- Pharmaceutical Affairs and Medical Technology, Netherlands and certified CPP from USFDA. The process is considered to be a standard manufacturing process. The in-process controls are adequate for controlling these steps. Major steps of the manufacturing process have been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

3.2.1.3.2 Controls of Critical Steps and Intermediates

Performance indicators allow direct assessment of product quality and/or process consistency. Performance indicators are evaluated against predetermined limits during process validation and a subset of performance indicators are designated as in-process control (IPC) parameters for routine manufacture. IPCs which should be controlled within a defined range to ensure final product quality are designated as critical. In addition to IPCs, some in-process tests may be designated as real time release testing (RTRT). IPCs are part of the comprehensive integrated control strategy.

3.2.1.3.3 Process Validation and/or Evaluation

The finished product process validation lifecycle strategy is designed to demonstrate that the manufacturing process is controlled, reproducible, and consistently yields finished product with the required product quality .The PFS used in the prefilled AI/Pen device uses an nRNS in the primary container .Both RNS and nRNS primary containers are the same, with the only difference being the inner diameter of the staked needle. Process validation included the filling of both the RNS and nRNS, hence both presentations have been validated.

The validation data presented demonstrate that the process is robust and performs as intended, giving a finished product which meets the quality requirements when conducted within the defined operating ranges. Three commercial-scale consecutive finished product lots were manufactured to validate the formulation and syringe filling process which covered the intended commercial batch size range. The validation was run at set points while the ranges of process parameters were challenged during the manufacturing process development. This is found acceptable.

The sterility assurance of the filling process was evaluated and assured through the aseptic process simulation validation (media fill) and sterilization validation programs. Media fill validation was successfully performed and completed at AML to support the finished product aseptic process conditions for AMG 334. Results and requirements for the media fill validation are in line with the current EU requirements. This is found acceptable.

3.2.1.4 Control of Excipients

All excipients in the DP formulation are specified in the USP, NF, Ph .Eur .or JP .The analytical procedures used to test the excipients are performed per current compendial methods .There is no excipient of human or animal origin used in the manufacturing process .There are no novel excipients in the drug product .

Table 28. AMG 334 Drug Product Formulation Excipients

Excipient	Grade
Sucrose	NF, PhEur, JP
Polysorbate 80	NF, PhEur, JP
Glacial acetic acid	USP, PhEur, JP
Sodium hydroxide	NF, PhEur, JP
Water for injection	USP, PhEur, JP

3.2.1.5 Control of Drug Product

3.2.1.5.1 Specification (s)

The specifications and test methods used to assure the quality of the finished product. The additional test methods and acceptance criteria used to assure the functionality of the AI/Pen at release are provided.

Relevant tests are included in the specifications for the finished product. As requested, test method number has been given to all analytical procedures used in the specifications for release and end-of shelf-life in the finished product specifications document.

Some parameters are tested as real time release testing (RTRT) controls at the process step of syringe filling. Many tests used for release testing and stability testing of finished product are also used for release testing and stability testing of the active substance. These methods and validation results cover both the active substance and finished product. The analytical procedures were validated in accordance with ICH Q2 and the compendial methods have been verified according to the appropriate compendia chapters and determined to be suitable for use.

3.2.1.5.2 Analytical Procedures

Analytical procedure used to assess drug substance, drug product and procedures used during development are provided in dossier. Compendial methods are performed in accordance with current pharmacopoeia and were appropriately verified .

3.2.1.5.3 Validation of Analytical Procedures

Analytical procedures were validated in accordance with ICH Harmonized Tripartite Guide *Validation of Analytical Procedures :Text and Methodology (Q2)R1*. Compendial methods are appropriately verified for their intended use.

Evaluation result

There are specification, analytical procedures and validation of analytical procedures. All of them conducted by acceptable standard. The specification and the analytical procedures of drug product follow USP, Ph.Eur and in-house verified by analytical validation. Moreover, Manufacturer identify in process control in each steps for consistency. Overall we can summarise that the control of drug product is suitable, reliable, consistent and acceptable.

3.2.1.5.4 Batch Analyses

Batch analyses data from AMG334 finished product lots manufactured during development through scale-up and transfer to the commercial manufacturing sites have been provided .Each lot was tested to the specification in place at the time of manufacture.

3.2.1.5.5 Characterization of Impurities

Although the product-related impurities could have a potential impact on patient safety or product efficacy, they are present only at a very low level in the DP and are controlled to acceptable levels by the manufacturing process .The risk assessment and over all control strategy for each of these product-related impurities is presented .

3.2.1.5.6 Justification of Specifications

Development of the DP specifications was performed in accordance with ICH Harmonized tripartite guideline, *Specifications :Test Procedures and Acceptance Criteria for Biotechnological/Biological Product (Q6B) and Pharmaceutical Development (Q8) .T*he specifications are intended to ensure safety and efficacy .Drug product in-process control)IPC (and specification testing were established to ensure the safety, identity, potency and purity of product .The specification acceptance criteria are justified.

To establish specification acceptance criteria for a subset of test methods, lot release and stability data were evaluated to estimate ranges.

3.2.1.6 Reference Standards or Materials

The same reference standard(s) are used for both AMG 334 drug substance and drug product testing.

3.2.1.7 Container Closure System

The primary container closure consists of a 1 mL Type I glass syringe with a stainless steel staked needle closed with an elastomeric needle shield and a bromobutyl elastomeric plunger-stopper laminated with a fluoropolymer film on the product contact surface. The syringe barrel and plunger-stopper comply with the requirements of the applicable USP, PhEur and JP monographs.

After plunger rods are assembled onto the PFS, the PFS are labelled and inspected for label presence, lot number, expiration date and material number. Upon completion of labelling, flange extenders are assembled on to the syringes. The assembled PFS and inserts are placed into dispensing cartons. The carton protects the product from light as well as during shipping and storage.

Evaluation result

Quality of container closure system of drug product complies with USP, Ph.Eur. MAH attached certificate of analysis data for considering, all results comply with the proposed specification. Then we can summarize that container closure of drug product is suitable and acceptable.

3.2.1.8 Stability

The stability studies were conducted per the ICH Q5C and Q1A. Based on results, an expiry period of 24 months is proposed for DP stored at the recommended storage temperature of 2-8°C. Moreover, to enhance convenience and facilitate dosing, storage for 14 days at up to 25°C is proposed.

The stability of primary and production lots was evaluated. The accelerated condition and the stressed condition were tested on all primary and production lots. To support the proposed storage for 14 days at up to 25°C, stability testing after storage at the recommended storage condition for 24 months was evaluated.
The stability of the drug product held at elevated temperatures are consistent across the primary and production lots. Stability of the drug product after exposure to light, temperature cycling, typical transport conditions, and room temperature has also been evaluated. These experimental stability studies show that the drug product is stable in the primary container, protected from light, under conditions that may be encounter during transport, storage, handling and use.

Evaluation result

Stability test of drug product including number of batch, condition, duration and parameter is suitable. Drug product stability protocol conforms to ASEAN Guideline. So, the proposed shelf-life of 24 months at the recommended storage temperature of 2-8°C and storage for 14 days at up to 25°C is acceptable.

3.2.2 Pre-filled pen (Auto-injector pen: AI/Pen)

3.2.2.1 Description and Composition of the Drug Product

The drug product of AI/Pen is provided as sterile, single-use, preservative-free solution for SC same as in PFS. The AI/Pen is disposable, handheld, mechanical (spring-based) delivery device provided ready-to-used, pre-assembled with the PFS. The PFS contained within the AI/Pen has a non-rigid needle shield (nRNS, a needle shield without an outer plastic rigid cover) and does not include a plastic plunger rod. The primary container for the PFS and AI/Pen is the same, except the PFS uses a regular wall (RW) needle and the AI/Pen uses a special thin wall (STW) needle which is larger needle inner diameter. The quantitative and qualitative composition is the same as PFS dosage form.

3.2.2.2 Pharmaceutical Development

The 70 mg/ml autoinjector/pen contains the same AMG 334 and excipient concentration as the 70 mg/ml prefilled syringe (PFS) The components of the AI/Pen do not contact with the DP.

The primary container closure system for the AI/Pen is the same as the PFS configuration except a special thin wall (STW) needle is assembled into the syringe instead of the regular wall (RW) needle. The STW needle has a larger needle inner diameter than RW. As the needle tip is fully embedded in the needle shield for both the STW and RW needle systems, there is no impact to

container closure integrity (CCI) which is a function of the quality of fit between the container closure components. The CCI was evaluated. Data showing CCI is maintained after transportation.

The drug product was tested for compatibility after extrusion of product through the syringe using the AI/Pen delivery device to identify any additional potential impact from shear stress extrusion. The analytical results support the conclusion that there is no impact on product quality as a result of extrusion by the AI/Pen. Therefore, data indicate that the quality of AMG 334 DP is not impacted by the delivery device (AI/Pen) and the components of the AI/Pen subassemblies coming in contact with the user have been shown to be biocompatible.

3.2.2.3 Manufacture

3.2.2.3.1 Manufacturer(s)

- **Manufacturing/ Primary packaging site**

  Amgen Manufacturing Limited, State Road 31, Km 24.6 Juncos, Puerto Rico 00777-4060, United States of America

- **Secondary packaging site**

  Amgen Europe B.V, Minervum 7061, 4817ZK Breda, Netherlands.

Evaluation result

The manufacturer is suitable and acceptable They show valid certificate of GMP compliance of a manufacturer from Health Care Inspectorate- Pharmaceutical Affairs and Medical Technology, Netherlands and certified CPP from USFDA. The process is considered to be a standard manufacturing process. The in-process controls are adequate for controlling these steps. Major steps of the manufacturing process have been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

3.2.2.3.2 Controls of Critical Steps and Intermediates

There are no critical steps identified during assembly of the PFS into the AI/Pen components since assembly has been confirmed to have no adverse impact to product quality.

3.2.2.3.3 Process Validation and/or Evaluation

The DP process evaluation for PFS also applies to the AI/Pen manufacturing including evaluation for primary containers and the process for filling the two primary containers, regular wall (RW) and the special thin wall (STW)

For all of process validation of AI/Pen manufacturing, every method are validated and provided the complete results in dossier.

3.2.2.4 Control of Excipients

For this section, data of control of excipients is the same as in PFS including the specification for excipients used in the manufacture of DP, the analytical procedures, methods validation and justification of specifications.

3.2.2.5 Control of Drug Product

3.2.2.5.1 Specification (s)

The AI/Pen contains a prefilled syringe (PFS), the PFS DP is tested and released. The results show drug product is in-range of the specification. The addition test methods and acceptance criteria are associated with the container and showed.

3.2.2.5.2 Analytical Procedures

Analytical procedure used to assess drug substance, drug product and procedures used during development are provided in dossier. Compendial methods are performed in accordance with current pharmacopoeia and were appropriately verified .

3.2.2.5.3 Validation of Analytical Procedures

The analytical procedures were validated in accordance with ICH Harmonized Tripatide Guide Validation of Analytical Procedures: Text and Methodology (Q2(R1))

The deliverable volume measurement is as descriped in compendial. This method had been appropriatedly verified. For the injection time method, the validation was conducted and the results demonstrates the suitability of this method for the routine assessment of the injection time under actual conditions of use.

Evaluation result

There are specification, analytical procedures and validation of analytical procedures. All of them conducted by acceptable standard. The specification and the analytical procedures of drug product follow Ph.Eur and in-house verified by analytical validation. Moreover, Manufacturer identify in process control in each steps for consistency. Overall we can summarise that the control of drug product is suitable, reliable, consistent and acceptable.

3.2.2.5.4 Batch Analyses

Batch analyses data from AMG334 finished product lots manufactured during development through scale-up and transfer to the commercial manufacturing sites have been provided. Each lot was tested to the specification in place at the time of manufacture.

3.2.2.5.5 Characterization of Impurities

For this section, the characterization of impurities data is the same as the PFS. Because of the drug product container closure system demonstated that there is no impact to product quality, the reference to PFS data is acceptable.

3.2.2.5.6 Justification of Specifications

Because of the AI/Pen is assembled with PFS, the justification for PFS is refered to this point. In addition, the device functionality specification for the AI/Pen includes testing of injection time and deliverable volume. The injection time specification is based on user needs and has been shown to be acceptable for products that are administered with an AI/Pen. The deliverable volume release specification is set to ensure the appropriated DP volume is delivered to meet the label claim and to ensure proper patient dosing.

3.2.2.6 Reference Standards or Materials

The same reference standard is used for both AMG 334 DS and DP product testing.

3.2.2.7 Container Closure System

The AI/Pen contains a Type 1 glass prefilled syringe (PFS). The PFS is the primary container closure system and decribed in Container closure systems of PFS. The PFS used for the AI/Pen will assemble with two subassemblies. The front subassemblies are designed to hold the type I glass PFS with staked needle and non-rigid needle shield and the rear subassembly contains a plunger rod and spring that drives dose delivery. The AI/Pen is assembled with a 27 gauge (G) special thin wall (STW) needle PFS and a plunger spring. The components of the subassemblies do not contact with the DP.

The specifications for the syringe container closure systems are located in Container closure systems of PFS. The conformance of the AI/Pen to EN-ISO standards Device design verification, summary of design validation and usability human factors studies Device design validation are provided.

For the secondary packaging, the AI/Pen are labelled and inspected for the label, lot number, expiration date, and label material number. The AI/Pen and inserts are placed into dispensing cartons. The carton protects the product from light as well as during transport and storage.

Evaluation result

Quality of container closure system of drug product complies with USP, Ph.Eur. MAHs attached certificate of analysis data for considering, all results comply with the proposed specification. Then we can summarize that container closure of drug product is suitable and acceptable.

3.2.2.8 Stability

The stability studies were conducted per the ICH Q5C and Q1A. Based on results, an expiry period of 24 months is proposed for DP stored at the recommended storage temperature of 2-8°C. Moreover, to enhance convenience and facilitate dosing, storage for 14 days at up to 25°C is proposed for PFS.

The proposed expiry for the AI/Pen is the same as PFS proposed based on the following consideration.

1. Both PFS and AI/Pen share the same primary container closure system.
2. Comparability data demonstrate that DP quality is not impacted by AI/Pen
3. Stability data in this section show that product quality in not impacted by the device.

Evaluation result

Stability test of drug product including number of batch, condition, duration and parameter is suitable. Drug product stability protocol conforms to ASEAN Guideline. So, the proposed shelf-life of 24 months at the recommended storage temperature of 2-8°C and storage for 14 days at up to 25°C is acceptable.

Assessor's conclusions on Quality

The evaluating result of un-redacted assessment report from EMA and analyzing in Thai-Asian environment and regulation can summarize that the critical points involving efficacy and safety had been clarify already. Moreover, the expert committee meeting on 27th June 2019 summarized in the similarly results. Then overall in the quality data on manufacturing and quality control of drug substances and drug product is acceptable.

Part 4 :Non-clinical documentation

4.1 Pharmacokinetics (ADME)

4.1.1 Absorption

Following SC administration in monkeys, the absolute bioavailability was approximately 60% and the absorption half-life was approximately 0.94 day. AUC accumulation ratios were approximately 2 following twice weekly SC administration of 25 to 225 mg/kg for 4 weeks, and approximately 1.5- 3 following twice weekly SC administration of 25 and 150 mg/kg for 3- and 6 months. There was no appreciable difference in exposure between sexes. In an IV dose range of 0.1 to 3 mg/kg IV, the Cmax and AUC was greater than dose-proportional; and in an IV dose range of 3 to 300 mg/kg exposure was approximately dose-proportional.

4.1.2 Distribution

IgG antibodies have limited diffusional distribution from serum to tissue due to their molecular size. The steady state volume of distribution of AMG 334 estimated from population model analysis was 250 mL which is consistent with being 2- to 5-times that of plasma volume.

4.1.3 Metabolism

No metabolism studies were conducted. Such studies are not considered relevant for a monoclonal antibody product because the expected consequence of metabolism is normal catabolic degradation to small peptides and individual amino acids.

4.1.4 Excretion

As a monoclonal antibody, no urinary excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion of AMG 334 were conducted.

4.2 Pharmacodynamics

4.2.1 Primary pharmacodynamics

For primary pharmacodynamics point, non-clinical studies have shown that AMG 334 binds to the CGRP receptor and inhibits signalling with CGRP. AMG 334 was not active on rat, dog or rabbit receptor but was activeat the cynomolgus receptor, with similar activity as in the human receptor. In vivo activity was shown in a cynomolgus model of capsaicin induced increase in dermal blood flow. Since there are no animal migraine models, all evidence for therapeutic effect is derived from clinical data.

4.2.2 Secondary pharmacodynamics

Since the widespread distribution of CGRP, the applicant has provided a comprehensive discussion on the identified potential targets

Cardiovascular: CGRP is a potent vasodilator. The exogenous CGRP has been shown to relate with vasodiation and systemic administration may cause hypotension in normotensive and hypertensive rats. The data from studies suggest that CGRP does not play a role in the control of systemic blood pressure in normal individuals.

A theoretical cardiovascular safety risk with CGRP receptor blockade is lack of compensatory vasodilation, especially in the context of the circulation during ischemic conditions. Infusion of CGRP at supraphysiological doses reduced MI size in a rat ischemia model. However, a CGRP receptor antagonist had no effect. It is believed that endogenous CGRP release is not sufficient to provide cardiovascular protection.

Bone: In rats, CGRP positive neurons are detectable in trabecular bone and differentiating osteoblasts express the CGRP receptor. Injection of CGRP in rats provides protection from gonadectomy-induced bone loss.

In the chronic repeat-dose study in cynomolgus monkey, there were no effects on biomarkers for bone formation and resorption, and no histopathological changes in the bone.

Gastric mucosa: CGRP has been postulated to have protective effects of gastric injury. In rat model, endogenous CGRP reduced gastric acid secretion and intravenous administration of CGRP antagonists prevented this inhibitory effect. Low doses of peripherally administered CGRP showed the ameliorated experimentally-induced gastric ulcers in rats and mice.

Pregnancy: It has been postulated that CGRP may be important for the increase in uteroplacental blood flow and decrease in uterine vascular resistance during pregnancy. In a rat model for preeclampsia, continuous infusion of CGRP resulted in decreased blood pressure and improved fetal growth and survival. In an enhanced pre- and postnatal developmental study in the cynomolgus monkey with AMG 334 there were no adverse findings.

Respiratory system: CGRP is present in sensory nerve fibers throughout the respiratory tract and has been implicated in the regulation of vascular tone in the lungs. In toxicology studies in cynomolgus mokeys there were no clinical signs of histopathological changes associated with respiratory distress.

Immune system: Sensory nerves containing CGRP are detected in primary and secondary lymphoid organs. During inflammatory response, levels of CGRP rapidly increase. CGRP is a negative regulator of innate and adaptive immunity, limits tissue damage in inflammatory disorders, and facilitates wound healing.

In vitro and in vivo models, CGRP was shown to down-regulated pro-inflammatory cytokines and chemokines, decrease antigen presentation, decrease NK cytolytic activity and decrease expression of the costimulatory receptor CD6 on dendritic cells and macrophages, and stimulate production of the anti-inflammatory cytokine IL-10. Additionally, CGRP may suppress Th1 responses and promote Th2 responses.

Safety pharmacology

The effects of AMG 334 on cardiovascular, respitation rate and neurovehavioral effects were assessed in a cynomolgus monkey study. There were no AMG 334 related arrhythmias or changes in ECG waveform, QRS duration or QTc interval. There were no biologically-significant changes in PR interval, HR, BP, body temperature, RR or neurological assessments. Exposure to AMG 334 was > 30-fold the clinical Cmax.

4.3 Toxicology

Repeat dose toxicity: There were no toxicological findings of importance for the safety assessment. One female monkey in the 1 month GLP study was euthanized on day 29 because of complications from immune complex-associated pathology secondary to the development of circulating anti-AMG 334 immune complexes. Since immunogenicity in an animal study is not predictive for clinical immunogenicity, this event is not suggestive of a clinical risk.

Genotoxicity: It is highly unlikely that AMG 334 would react with DNA or other chromosomal material because AMG 334 is a recombinant monoclonal antibody made up of amino acid and conbtains no inorganic or synthetic organic linkers or other non-protein portions.

Carcinogenicity: There were no non-clinical studies conducted to assess carcinogenic risk because of the limitation of the animal model. Nevertheless, a comprehensive assessment of carcinogenic potential was performed. CGRP acts to down-regulate inflammation and a CGRP receptor inhibitor would not be anticipated to impair immune surveillance of tumors. In vitro, CGRP increased cell proliferation by activating members of the mitogen-activated protein kinase family. Elevated CGRP expression has been observed in both plasma and tumors from specific cancers. The functional significance of the CGRP receptor and the ligand is unclear. However, functional inhibition of CGRP would not be associated with carcinogenic risk.

Reproduction toxicity: There were no AMG 334-related effects on pregnancy/postpartum outcomes. For foetuses, there were no AMG-334 related effects in the placenta or on body weight, or on teratologic external, visceral, heart, or on skeletal evaluations and neurobehavioral assessments, where applicable.

Local tolerance: From the repeated dose studies, there were no macroscopic changes suggestive of intolerance. Macroscopic changes and/or minimal to moderate microscopic changes at the subcutaneous/intravenous injection site was observed and were attributed to the injection procedure and not related to the pharmacological activity of AMG 334.

Evaluation result

Non-clinical data could summarize that study design were suitable and the results were reliable. Toxicity study followed good laboratory practice and not found unexpected toxicity. The expert committee meeting on 27th June 2019 summarized in the similarly results as un-redacted assessment report from EMA that overall in non-clinical data was suitable and acceptable.

Part 5 :Clinical Study Reports

The proposed indication of Aimovig 70 mg is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month. The clinical data can be summarized as below.

Table: Clinical study of phase 2/3 studies in migraine

<table>
<tr><th>No.</th><th>Trial No.</th><th>Design</th><th>Subjects/
Primary Objective(S)</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td>1</td><td>20120295 (Pivotal)</td><td>Phase 2, randomized, double-blind, placebo-controlled for 12 week</td><td><u>Subjects</u>

Subjects with chronic migraine; ≥ 15 headache days per month with

≥ 8 migraine days per month

Age: 18 to 65 years

<u>Primary Objective</u>

Monthly migraine days (MMD) reduction in weeks 9-12

<u>Secondary Objective</u>

≥50% reduction in MMD from (baseline to last 4 weeks of the 12-week DB treatment)

Change from baseline in monthly acute migraine-specific medication treatment days in last 4 weeks of the 12-week DB treatment.

Change from baseline in cumulative headache hours in last 4 weeks of the 12-week DB treatment</td><td>n=667

Placebo or Erenumab 70 or 140 mg QM SC</td><td>Primary objective
<table><tr><td>Group</td><td>Placebo</td><td>AMG-334 70 mg</td><td>AMG-334 140 mg</td></tr><tr><td>N</td><td>281</td><td>188</td><td>187</td></tr><tr><td>MMD (LSM estimate)</td><td>-4.18</td><td>-6.64</td><td>-6.63</td></tr><tr><td>95% CI</td><td>(-4.86, -3.50)</td><td>(-7.47, -5.81)</td><td>(-7.45, -5.80)</td></tr></table>
Effect of Estimate per comparison
<table><tr><td></td><td>Comparison group</td><td>70 mg VS Placebo</td><td>140 mg VS Placebo</td></tr><tr><td rowspan="3">MMD</td><td>Diff. in LSM</td><td>-2.46</td><td>-2.45</td></tr><tr><td>95% CI of diff.</td><td>(-3.52,-1.39)</td><td>(-3.51, -1.38)</td></tr><tr><td>P-value</td><td><0.001</td><td><0.001</td></tr><tr><td rowspan="2">Responder rate MMD</td><td>Adjusted odds ratio</td><td>2.18</td><td>2.34</td></tr><tr><td>95% CI</td><td>(1.46, 3.27)</td><td>(1.56, 3.51)</td></tr></table></td></tr>
</table>

<table>
<tr><th>No.</th><th>Trial No.</th><th>Design</th><th>Subjects/
Primary Objective(S)</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>P-value</td><td><0.001</td><td><0.001</td></tr>
<tr><td rowspan="3">Acute medication days</td><td>Difference in LSM</td><td>-1.86</td><td>-2.55</td></tr>
<tr><td>95% CI of difference</td><td>(-2.60, -1.13)</td><td>(-3.28, -1.82)</td></tr>
<tr><td>P-value</td><td><0.001</td><td><0.001</td></tr>
<tr><td rowspan="3">Cumulative headache hours</td><td>Difference in LSM</td><td>-9.54</td><td>-19.31</td></tr>
<tr><td>95% CI of difference</td><td>(-26.98, 7.90)</td><td>(-36.71, -1.92)</td></tr>
<tr><td>p-value</td><td>0.28</td><td>0.030</td></tr>
</table>
</td></tr>
<tr><td>2</td><td>20120296 (Pivotal)</td><td>Phase 3, randomized, double-blind, placebo-controlled for 24 week</td><td><u>Subjects</u>

Subjects with episodic migraine; 4 to < 15 migraine days/month with < 15 headache days/month

Age: 18- 65 years

<u>Primary Objective</u>

Monthly migraine days reduction in months 4, 5, and 6

<u>Secondary Objective</u>

50% reduction from baseline in mean monthly migraine days over the last 3 months (months 4, 5, and 6) of the double-blind treatment phase

Change from baseline in mean</td><td>n=955

Placebo or Erenumab 70 or 140 mg QM SC</td><td>Primary objective
<table>
<tr><td>Group</td><td>Placebo</td><td>AMG-334 70 mg</td><td>AMG-334 140 mg</td></tr>
<tr><td>N</td><td>289</td><td>296</td><td>302</td></tr>
<tr><td>MMD (LSM estimate)</td><td>-1.83</td><td>-.323</td><td>-3.67</td></tr>
<tr><td>95% CI</td><td>(-2.18, -1.48)</td><td>(-3.58, -2.88)</td><td>(-4.02, -3.33)</td></tr>
</table>
Effect of Estimate per comparison
<table>
<tr><td></td><td>Comparison group</td><td>70 mg VS Placebo</td><td>140 mg VS Placebo</td></tr>
<tr><td rowspan="2">MMD</td><td>Diff. in LSM</td><td>-1.40</td><td>-1.85</td></tr>
<tr><td>95% CI of diff.</td><td>(-1.88, 0.92)</td><td>(-2.33, 1-37)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>No.</th><th>Trial No.</th><th>Design</th><th>Subjects/
Primary Objective(S)</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td></td><td></td><td></td><td>monthly acute migraine-specific medication treatment days over the last 3 months (months 4, 5, and 6) of the double-blind treatment phase

Change from baseline in mean physical impairment domain scores as measured by the MPFID over the last 3 months (months 4, 5, and 6) of the double-blind treatment phase

Change from baseline in mean impact on everyday activities domain scores as measured by the MPFID over the last 3 months (months 4, 5, and 6) of the double-blind treatment phase</td><td></td><td>
<table>
<tr><td></td><td>P-value</td><td><0.001</td><td><0.001</td></tr>
<tr><td rowspan="3">Responder rate MMD</td><td>Common odds ratio</td><td>2.13</td><td>2.81</td></tr>
<tr><td>95% CI</td><td>(1.52, 2.98)</td><td>(2.01, 3.94)</td></tr>
<tr><td>P-value</td><td><0.001</td><td><0.001</td></tr>
<tr><td rowspan="3">Acute medication days</td><td>Difference in LSM</td><td>-0.94</td><td>-1.42</td></tr>
<tr><td>95% CI of difference</td><td>(-1.23, -0.64)</td><td>(-1.71, -1.12)</td></tr>
<tr><td>P-value</td><td><0.001</td><td><0.001</td></tr>
<tr><td rowspan="3">MPFID Physical impairment</td><td>Difference in LSM</td><td>-1.86</td><td>-2.43</td></tr>
<tr><td>95% CI of difference</td><td>(-2.95, -0.77)</td><td>(-3.51, -1.35)</td></tr>
<tr><td>p-value</td><td><0.001</td><td><0.001</td></tr>
<tr><td rowspan="3">MPFID Everyday activities</td><td>Difference in LSM</td><td>-2.22</td><td>-2.57</td></tr>
<tr><td>95% CI of difference</td><td>(-3.28, -1.16)</td><td>(-3.62, -1.51)</td></tr>
<tr><td>p-value</td><td><0.001</td><td><0.001</td></tr>
</table>
</td></tr>
</table>

Clinical studies are divided in 3 parts

The clinical trials were performed in accordance with GCP as climed by the applicant.

1. Clinical Pharmacokinetic

Absorption: The mean absorption time after sc administration was estimated to be 3.36 days and absorption phase was completed in 12 days.

The relative bioavailability for SC administration was 54% for AMG 334 after a single 140-mg dose. Based on the PopPK analysis the subcutaneous bioavailability of AMG 334 was estimated to be 81.8%.

Distribution: The estimated central volume of distribution was 4.350 L and volume of distribution at steady-state was 7.6 L.

Elimination: The linear clearance is independent of AMG 334 concentrations and estimated to be 198 mL/d, which is similar to the reported clearance for endogenous IgG, with a moderate IIV (27.6% CV). The nonlinear clearance is dependent on its concentrations and target density. The maximal nonlinear clearance of the AMG 334-CGRP receptor complex is approximately 3.09 L/day and 16 times faster than the linear clearance (0.198 L/d).

At the clinical dose of 140 mg SC QM, the target-mediated pathway is saturated (peripheral target binding is >99%) for the entire dosing QM interval at steady state. Therefore, total clearance is predominantly linear (ie, nonlinear clearance is negligible) at the clinical dose regimen, and the terminal halflife can be approximated using clearances and volumes of distribution, which is approximately 28 days.

2. Clinical efficacy

To support proposed indication, prophylaxis of migraine in adults who have at least 4 migraine days per month, 2 pivotal clinical efficacy studies are conducted.

2.1 Study in Chronic migraine 20120295

This study was a phase 2, randomized, double-blind, placebo-controlled study in subjects with CM. The study consisted of an up to 3 weeks' screening phase, a 4 weeks' baseline phase, a 12-week double-blind treatment phase that included AMG 334 at doses of 70 mg and 140 mg administered monthly by subcutaneous (SC) injection, and a 12 weeks' follow-up phase.

Objectives: To evaluate the effect of erenumab compared to placebo on the change from baseline in the number of monthly migraine days in adults with chronic migraine.

Outcomes/endpoints: The primary endpoint for this study is the change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase.

The results:

Table 11. Change From Baseline in Monthly Migraine Days, Observed, GLIMMIX Model (Efficacy Analysis Set)

		AMG 334	
	Placebo (N = 281)	70 mg (N = 188)	140 mg (N = 187)
Baseline			
Mean (SE)	18.24 (0.28)	17.94 (0.32)	17.78 (0.34)
Median	18.06	17.68	17.63
Q1, Q3	14.82, 21.78	15.00, 20.37	14.48, 21.00
Minimum, Maximum	5.6, 28.0	8.1, 28.0	8.1, 28.0
Change from baseline at week 12 (month 3)			
n	267	178	182
Mean (SE)	-4.24 (0.38)	-6.63 (0.45)	-6.53 (0.50)
Median	-3.75	-7.26	-6.52
Q1, Q3	-8.00, 0.07	-11.25, -2.00	-10.81, -1.14
Minimum, Maximum	-21.8, 9.0	-20.3, 10.6	-26.1, 7.0
Adjusted analysis[a]			
LSM estimate	-4.18	-6.64	-6.63
(95% CI of LSM)	(-4.86, -3.50)	(-7.47, -5.81)	(-7.45, -5.80)
Difference in LSM	–	-2.46	-2.45
(95% CI of difference)	–	(-3.52, -1.39)	(-3.51, -1.38)
p-value	–	< 0.001	< 0.001

CI – confidence interval; LSM – least squares mean; N – Number of subjects in the analysis set; Q1 – first quartile; Q3 = third quartile; SE = standard error.

Summary: The primary endpoint was significant at both doses tested (70 mg and 140 mg SC once monthly). The mean reduction of monthly migraine days was -6.53 days at the 140 mg dose (-6.63 at 70 mg) and -4.24 in the placebo group, yielding a numerical difference of -2.29 monthly migraine days compared to placebo at the 140 mg dose.

2.2 Study in Episodic migraine 20120296

This was a phase 3, randomized, double-blind, placebo-controlled study in subjects with EM. The study had a 24-week double-blind treatment phase that included AMG 334 at doses of 70 mg and 140 mg QM (every 4 weeks) SC. Subjects who completed the double-blind phase were then re-randomized to receive either AMG 334 70 mg or AMG 334 140 mg QM SC for an additional 28 weeks of treatment.

Objectives: To evaluate the effect of erenumab compared to placebo on the change from baseline in the number of monthly migraine days in adults with episodic migraine.

Outcomes/endpoints: Change from baseline in mean monthly migraine days. The mean monthly migraine days will be calculated using the monthly migraine days from each of the last 3 months (months 4, 5, and 6) of the double-blind treatment phase.

The results:

Table 15. Change From Baseline to the Last 3 Months (Months 4, 5, and 6) in Mean Monthly Migraine Days During the Double-blind Treatment Period, Observed, GLIMMIX Model (Efficacy Analysis Set)

		AMG 334	
	Placebo (N = 316)	70 mg (N = 312)	140 mg (N = 318)
Baseline			
n	316	312	318
Mean (SD)	8.25 (2.51)	8.31 (2.45)	8.33 (2.48)
Median	8.00	8.00	8.00
Q1, Q3	6.00, 10.00	6.40, 10.00	6.76, 10.00
Minimum, Maximum	3.0, 14.9	3.5, 14.5	3.2, 16.0
Mean over month 4, 5 and 6			
n	289	296	302
Mean (SE)	6.33 (0.22)	4.95 (0.21)	4.48 (0.18)
Median	5.71	4.31	3.82
Q1, Q3	3.59, 8.49	2.14, 7.13	2.08, 6.52
Minimum, Maximum	0.0, 20.7	0.0, 19.0	0.0, 15.6
Change from baseline in mean over month 4, 5 and 6			
n	289	296	302
Mean (SE)	-1.95 (0.22)	-3.36 (0.21)	-3.83 (0.18)
Median	-1.95	-3.65	-3.96
Q1, Q3	-4.26, 0.20	-5.66, -1.50	-6.09, -1.86
Minimum, Maximum	-12.0, 12.4	-13.4, 9.0	-13.0, 6.6
Adjusted analysis[a,b]			
LSM estimates	-1.83	-3.23	-3.67
(95% CI of LSM)	(-2.18, -1.48)	(-3.58, -2.88)	(-4.02, -3.33)
Difference in LSMs	--	-1.40	-1.85
(95% CI of difference)	--	(-1.88, -0.92)	(-2.33, -1.37)
p-value	--	< 0.001	< 0.001

CI = confidence interval; N = number of subjects in the analysis set; LSM = Least squares means; Min = minimum; Max = maximum; Q1 = first quartile; Q3 = third quartile. The pairwise comparisons compare each AMG 334 group vs. placebo (reference group).

Summary: The reduction in monthly migraine days was -3.83 at the 140 mg, -3.36 at the 70 mg dose, and -1.95 in the placebo group. The treatment difference was -1.88 for the 140 mg dose compared to placebo.

3. Clinical safety

Table 5-3 Treatment-emergent adverse events >= 1% patients in either AMG 334 70 mg or 140 mg group and >= 2 x the rate in the placebo group – Pool A (Integrated Safety Analysis Set)

		AMG 334			
Preferred Term	Placebo (N = 1043) n (%)	7 mg or 21 mg (N = 213) n (%)	70 mg (N = 893) n (%)	140 mg (N = 507) n (%)	All (N = 1613) n (%)
Any preferred term ≥ 1% patients in either AMG 334 70 mg or 140 mg group and ≥ 2x the rate in the placebo group	42 (4.0)	5 (2.3)	60 (6.7)	49 (9.7)	114 (7.1)
Injection site pain	18 (1.7)	2 (0.9)	33 (3.7)	8 (1.6)	43 (2.7)
Constipation	11 (1.1)	1 (0.5)	12 (1.3)	16 (3.2)	29 (1.8)
Injection site erythema	2 (0.2)	1 (0.5)	9 (1.0)	10 (2.0)	20 (1.2)
Bronchitis	6 (0.6)	0 (0.0)	9 (1.0)	7 (1.4)	16 (1.0)
Muscle spasms	4 (0.4)	0 (0.0)	1 (0.1)	10 (2.0)	11 (0.7)
Pruritus generalized	1 (0.1)	1 (0.5)	0 (0.0)	6 (1.2)	7 (0.4)

12-Week Placebo-controlled Pool: studies 20120178, 20120295, 20120296, and 20120297
N = Number of patients in the analysis set; n = Number of patients reporting ≥ AE; % = n/N * 100.
Preferred terms are sorted in descending frequency of the All AMG 334 column
Source: [SCS-Table 20]

AMG-334 was generally well tolerated, although a small increase in the incidence of injection site reactions, constipation, muscle spasms and pruritus were observed in the controlled studies. There is a theoretical concern that treatment with a CGRP receptor antagonism may aggravate ischemic events such as stroke, TIA and MI. Because of the clinical trial exclusion criteria, no data is available in migraine patients with major cardiovascular and cerebrovascular disease.

Due to no subject with major cardiovascular disease (MI, stroke, TIA and unstable angina) were included to phase 2 and 3 clinical trials, the concern of cardiovascular, cerebrovascular, and peripheral arterial disorder related to AMG-334 treatment in migraine patients is identified as missing information.

Evaluation result

The studies were mostly designed in agreement with recommendations in the international guidelines on clinical trials in migraine. All main efficacy endpoints were significant throughout the main clinical studies.

Assessor's conclusions on clinical

As the information of pharmacokinetic, efficacy and safety clinical data is acceptable. The study design, population and duration are suitable for proposed indication. The safety data show that no reported unexpected pattern of adverse event. The most common are injection site reactions, constipation, muscle spasms and pruritus.

There are some concerned points from Thai advisory expert committee on 27th June 2019. The theoretical side effect about vasodilation, cardiovascular side effects leads to the additional request for long-term safety data. The MAHs submitted the long-term safety data (the data consist of the population treated with Erenumab with at least 1 treament, continuous treatment ≥1 year and exposured ≥ 3 years) and provide the late breaking information (late May 2018) of study 20120178 in EM patient population (still ongoing) to prove the safety concerned. The results show the long period Erenumab was well tolerated and safe, with no new safety signals detected over the extended treatment period, no dose dependency of adverse events, and with infrequent discontinuation due to adverse events. There was no evidence that Erenumab is associated with adverse vascular effects.

So, the over all data from the evaluation, the un-redacted assessment report form EMA and the Thai advisory expert committee on 27th June 2019 can conclude that Aimovig 70 mg has enough efficacy and safety data that support the proposed indication for prophylaxis of migraine in adults who have at least 4 migraine day per month and the MAHs also conducted the proper RMP as an RMP from EMA to minimized the risk of usage this medication.

Part 6 :Risk Management Plan

There are some of concerns about Aimovig. For important potential risks, the cardiovascular outcomes in patients with pre-exising myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension are concern. For missing information, using in pregnant woment (including those at risk of pre-eclampsia) and longterm usage are concern. The applicant were conducted the RMP as an RMP from EMA.

Evaluation results

The information of RMP is valid and suitable due to the risk management had been conducted in summary of product characteristic and patient leaflet already.

Label evaluation

Registered label from Novartis (Thailand) Ltd. is Unit carton label and inner label following Thai FDA 2009 ANNEX 3 Package insert and labeling rule.

UNIT CARTON

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
10	Country's Registration Number	✓	✓
11	Name and address of Marketing Authorization Holder	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labeling	✓	✓
14	Recommended Daily Allowance (Vitamins and minerals)	n/a	n/a
15	Warning	n/a	n/a
16	Pack sizes	✓	✓

✓ Available or appropriate
n/a not available

INNER LABEL

No	Topic	Available	Appropiate
1	Product name	✓	✓
2	Dosage form*	X	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date*	X	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition*	X	✓
10	Country's Registration Number*	X	✓
11	Name and address of Marketing Authorization Holder*	X	✓

12	Name and address of manufacturer*	X	✓
13	Special labelling*	X	✓
14	Recommended Daily Allowance* (Vitamin and minerals)	n/a	n/a
15	Warning*	n/a	n/a
16	Pack sizes	✓	✓

✓ Available or appropriate
n/a not available
* exempted for small ampoule and vial

Patient information leaflet (PIL) evaluation

Patient information leaflet of Aimovig 70 mg is adapted from SmPC and the originator SmPC .The information in Patient information leaflet is accurate, complete, and consistency with SmPC, quality data, non-clinical data and clinical data .The important information for patient is summarized in this PIL, however, user testing in Thai is required 12 months after receiving registered paper.

Summary of product characteristics (SmPC) evaluation

Summary of product characteristics conform to quality, non-clinical and clinical supporting data. The important information for healthcare professional is summarized in this SmPC conformed to SmPC of Aimovig 70 mg solution for injection in pre-filled syringe and Aimovig 70 mg solution for injection in pre-filled pen approved in EMA.

Overall Benefit/risk assessment

As evaluation results, the reviewers evaluated the documents submitted to support the quality, efficacy and safety of Erenumab 70 mg. It concluded that quality of Erenumab is acceptable and pass the standard criteria, non-clinical and clinical data supported proposed indication and no serious adverse event reported during study through post-marketing. The evaluation results of un-redacted assessment report from EMA and Thai advisory expert committee on 27th June 2019 are consistency, overall benefit/risk assessment is positive, so all can summarized Aimovig 70 mg solution for injection in pre-filled syringe and Aimovig 70 mg Solution for injection in pre-filled syringe/pre-filled pen registered indication below is acceptable;

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

Erenumab registered in new biological product. MAHs have to follow up adverse event closely and comply with risk management plan. Then we should approve Erenumab in special control medicine and the overall benefit/risk assessment supports approval of Erenumab, under the following 4 requirements

1) This medicine will only be prescribed in hospitals and clinics.

2) Follow the adverse event in post-marketing conducted by SMP protocol submitted in eCTD.

3) Submit the complete version of PIL after the user testing passes the criteria (user testing result should be submitted to Thai FDA within 12 months after the marketing authorization approval).

4.) Submit data of ongoing trials to Thai FDA within 6 months after the final study reports available and submit data follow by proposed risk management plan in 1.8.2 Risk management system on eCTD, as attached file.

Internal reviewer

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(Kridiphol Janthranant)

Evaluator

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(Worasuda Yoongthong)

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Appendix