AERINEX®

Anti-Calcitonin Gene-Related Peptide Receptor (anti-CGRPR) monoclonal antibody

ATC code: N02CX07

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

70 mg erenumab in 1.0 mL (70 mg/mL) solution.

• 70 mg/mL solution for injection in a pre-filled syringe, subcutaneous use.

Not all dosage forms may be available in all countries.

Active substance

Erenumab.

Excipients

Sucrose, Glacial acetic acid, Polysorbate 80, Water for injection, Sodium hydroxide.

INDICATIONS

Aerinex is indicated for prophylaxis of migraine in adults.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage

The recommended dose of Aerinex is 70 mg administered once monthly.

Some patients may benefit from a dosage of 140 mg administered once monthly [see section CLINICAL STUDIES]

If Aerinex dose is missed, administer as soon as possible. Thereafter, Aerinex can be scheduled monthly from the date of the last dose.

Special populations

Pediatrics

The safety and effectiveness of Aerinex has not been studied in pediatric patients.

Geriatrics

Clinical studies of Aerinex did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. No dose adjustment is required as the pharmacokinetics of erenumab are not affected by age.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Population pharmacokinetic analysis of integrated data from the Aerinex clinical trials did not reveal a difference in the pharmacokinetics of erenumab in patients with mild or moderate renal impairment relative to those with normal renal function. Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) have not been studied.

Hepatic impairment

No clinical studies have been performed in patients with hepatic impairment. Erenumab, as a human monoclonal antibody, is not metabolised by cytochrome P450 enzymes and hepatic clearance is not a major clearance pathway for erenumab.

Effects on ability to drive and use machines

Aerinex is expected to have no influence on the ability to drive and use machines.

Method of administration

Aerinex is administered subcutaneously.

Aerinex is intended for patient self-administration.

Administration should be performed by an individual who has been trained to administer the product. To administer the 140 mg dose, give two consecutive subcutaneous injections of 70 mg each of Aerinex.

For detailed instructions on storage, handling and administration, follow the directions provided in the "Instructions for Use".

Important administration instructions

Visually inspect Aerinex for particles and discoloration. Aerinex is a clear to opalescent, colorless to light yellow solution. Do not use if the solution is cloudy or discolored or contains flakes or particles.

Administer Aerinex in the abdomen, thigh, or upper arm subcutaneously. If you want to use the same injection site, make sure it is not the same spot you used for a previous injection. Do not inject into areas where the skin is tender, bruised, red, or hard.

Prefilled syringes are single use and designed to deliver the entire contents with no residual content remaining.

The needle cap of the prefilled syringe cover contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

None.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Data from two phase 3 and two phase 2 clinical studies in migraine were pooled to evaluate the safety of Aerinex in comparison to placebo up to 12 weeks after treatment initiation.

There were a total of 2656 patients (1613 Aerinex and 1043 placebo) in these studies. Of these, 893 subjects received 70 mg dose of Aerinex and 507 subjects received 140 mg dose of Aerinex.

The overall safety population including ongoing open-label extension phases with Aerinex includes 2537 patients (2310.3 patient years) who received at least one dose of Aerinex: 2066 patients were exposed for at least 6 months and 1213 were exposed for at least 12 months.

Tabulated summary of adverse drug reactions

Table 1 summarises all adverse reactions that occurred in Aerinex -treated patients during the 12-week placebo-controlled period of the pooled trials. Most of the adverse drug reactions (ADR) were mild or moderate in severity.

Frequency is provided by CIOMS category (e.g., Very Common (≥ 10%), Common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%)).

Table 1 Adverse drug reactions with Aerinex

System Organ Class	Adverse Drug Reaction Preferred Term	Frequency Category	Overall subject incidence at 70 mg (N = 893) n (%)	Overall subject incidence at 140 mg (N=507) n (%)
General disorders and administration site condition	Injection site reactions[a]	Common	50 (5.6) [a]	23 (4.5)[a]
Gastrointestinal disorders	Constipation	Common	12 (1.3)	16 (3.2)
Musculoskeletal and connective tissue disorders	Muscle spasm	Common	1 (0.1)	10 (2.0)
Skin and subcutaneous tissue disorders	Pruritus[b]	Common	6 (0.7) [b]	9 (1.8)[b]

[a] Injection Site Reactions includes multiple preferred terms, such as injection site pain and injection site erythema.

[b] Pruritus includes preferred terms of generalised pruritus, pruritus, and pruritic rash.

Description of selected adverse reactions

Injection site reactions

In the integrated 12-week placebo-controlled period of studies, in subjects treated with Aerinex the most frequent injection site reactions were injection site pain, injection site erythema, and injection site pruritus. A majority of injection site reactions were mild and transient. Injection site pain typically subsided within 1 hour after administration. One subject treated with Aerinex 70 mg SC discontinued due to injection site rash and no subject treated with Aerinex 140 mg SC discontinued due to injection site reactions in the 12-week placebo-controlled period of studies.

Post-Marketing Experience

Hypersensitivity reactions including rash and swelling/oedema.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of Aerinex has been evaluated using an immunoassay for the detection of binding anti-erenumab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralising antibodies.

In the 4 migraine prophylaxis efficacy studies [20120178, 20120295, 20120296 and 20120297], the incidence of anti-erenumab antibody development during the double-blind treatment phase was 6.3% (56/884) among subjects receiving 70 mg dose of Aerinex (3 of whom had in-vitro neutralizing activity) and was 2.6% (13/504) among subjects receiving 140 mg dose of Aerinex (none of whom had in-vitro neutralizing activity). There was no impact of anti-erenumab antibody development on efficacy or safety of erenumab.

The incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including

neutralising antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to erenumab with the incidence of antibodies to other products may be misleading.

INTERACTIONS

In an open-label, pharmacokinetic drug interaction study of Aerinex and a combined oral contraceptive in healthy female subjects, erenumab (140 mg subcutaneous [SC], single- dose) did not affect the pharmacokinetics of a combined oral contraceptive containing ethinyl estradiol and norgestimate.

In a randomised, double-blind, placebo-controlled study in healthy volunteers, concomitant administration of erenumab (140 mg intravenous [IV], single-dose) with sumatriptan had no effect on resting blood pressure compared with sumatritpan alone. Aerinex had no effect on the pharmacokinetics of sumatriptan.

Erenumab is not metabolised by cytochrome P450 enzymes and is unlikely to cause marked changes in pro-inflammatory cytokines that may impact cytochrome P450 enzyme expression or activity. As a result, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Interference with laboratory and diagnostic tests

Interference of Aerinex with laboratory and/or diagnostic tests has not been studied.

PREGNANCY, LACTATION, FERTILITY

Pregnancy

There are no adequate and well controlled studies on the use of Aerinex in pregnant women. In a cynomolgus monkey reproduction study, there were no effects on pregnancy, embryo-fetal or post-natal development (up to 6 months age) when erenumab was dosed throughout pregnancy at exposure levels 40 or 17-fold higher than those achieved in patients receiving erenumab at the 70 or 140 mg once monthly dosing regimen, respectively based on area under the concentration curve (AUC). Measurable erenumab serum concentrations were observed in the infant monkeys at birth, confirming that erenumab, like other IgG antibodies, crosses the placental barrier.

Animal studies are not always predictive of human response and therefore, it is not known whether Aerinex can cause fetal harm when administered to a pregnant woman. Aerinex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether Aerinex is present in human milk. There are no data on the effects of Aerinex on the breastfed child or the effects of Aerinex on milk production. Because drugs are excreted in human milk and because of the potential for adverse effects in nursing infants from Aerinex, a decision should be made whether to discontinue nursing or discontinue Aerinex, taking into account the potential benefit of Aerinex to the mother and the potential benefit of breast feeding to the infant.

Fertility

No data are available on the effect of Aerinex on human fertility. There were no adverse effects on surrogate markers of fertility (anatomic pathology or histopathology changes in reproductive

organs) in sexually mature monkeys at systemic exposures up to 283 or 123-fold higher than the clinical dose of 70 or 140 mg once monthly, respectively based on serum AUC (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

There is no experience with overdose in clinical trials with Aerinex. Doses up to 280 mg SC have been administered in clinical trials with no evidence of dose limiting toxicity.

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

CLINICAL PHARMACOLOGY

Mechanism of action

Erenumab is a human monoclonal antagonist antibody against the CGRP receptor with no significant pharmacological activity at adrenomedulin, calcitonin, and amylin receptors and lacks agonist activity at the CGRP receptor.

CGRP is a neuropeptide that modulates nociceptive signaling and a vasodilator that has been associated with migraine pathophysiology. In contrast with other neuropeptides, CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief. Intravenous infusion of CGRP induces migraine-like headache in patients suggesting that CGRP may play a causal role in migraine.

CGRP receptor is located at sites that are relevant to migraine pathophysiology. Erenumab potently and specifically competes with the binding of CGRP and inhibits its function at the CGRP receptor.

Pharmacodynamic effect

In a randomised, double-blind, placebo-controlled study (20140254) to evaluate the effect of Aerinex (140 mg IV, single dose) in patients with stable angina, Aerinex did not decrease exercise duration during a treadmill test compared to placebo and did not aggravate myocardial ischaemia in these patients.

Pharmacokinetic properties

Erenumab exhibits non-linear kinetics as a result of binding to CGRP-R. Subcutaneous administration of a 70 mg and 140 mg dose in healthy volunteers resulted in a C_{max} mean (standard deviation [SD]) of 6.1 (2.1) mcg/mL and 15.8 (4.8) mcg/mL respectively, and AUC_{last} mean (SD) of 159 (58) day*mcg/mL and 505 (139) day*mcg/mL respectively.

Less than 2 fold accumulation was observed in trough serum concentrations (C_{min} [SD] 5.7 [3.1] and 6.2 [2.9] mcg/mL for episodic and chronic migraine subjects, respectively following 70 mg doses; C_{min} [SD] 12.8 [6.53] and 14.9 [6.45] mcg/mL for episodic and chronic migraine subjects, respectively following 140 mg doses) administered subcutaneously every 4 weeks and serum trough concentrations approached steady state by 12 weeks of dosing. The effective half-life of Aerinex is 28 days.

Absorption
Following a single subcutaneous dose of 70 mg or 140 mg Aerinex administered to healthy adults, median peak serum concentrations were attained in approximately 6 days, and estimated absolute bioavailability was 82%.

Distribution

Following a single 140 mg intravenous dose, the mean (SD) volume of distribution during the terminal phase (V_z) was estimated to be 3.86 (0.77) L.

Metabolism and excretion

Two elimination phases were observed for Aerinex. At low concentrations, the elimination is predominately through saturable binding to target (CGRP-R), while at higher concentrations the elimination of Aerinex is largely through a non-specific, non-saturable proteolytic pathway.

Specific populations

The pharmacokinetics of erenumab were not affected by age, gender, race, migraine subtype (episodic or chronic migraine), or creatinine clearance, across all approved populations based on population pharmacokinetics (PK) analysis.

CLINICAL STUDIES

Aerinex was evaluated for prophylaxis of migraine in two pivotal studies across the spectrum of episodic and chronic migraine. Studies enrolled patients with a history of migraine, with or without aura according to the International Classification of Headache Disorders (ICHD-III) diagnostic criteria.

Aerinex treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy outcomes.

Chronic Migraine

Study 1 (Study 20120295)

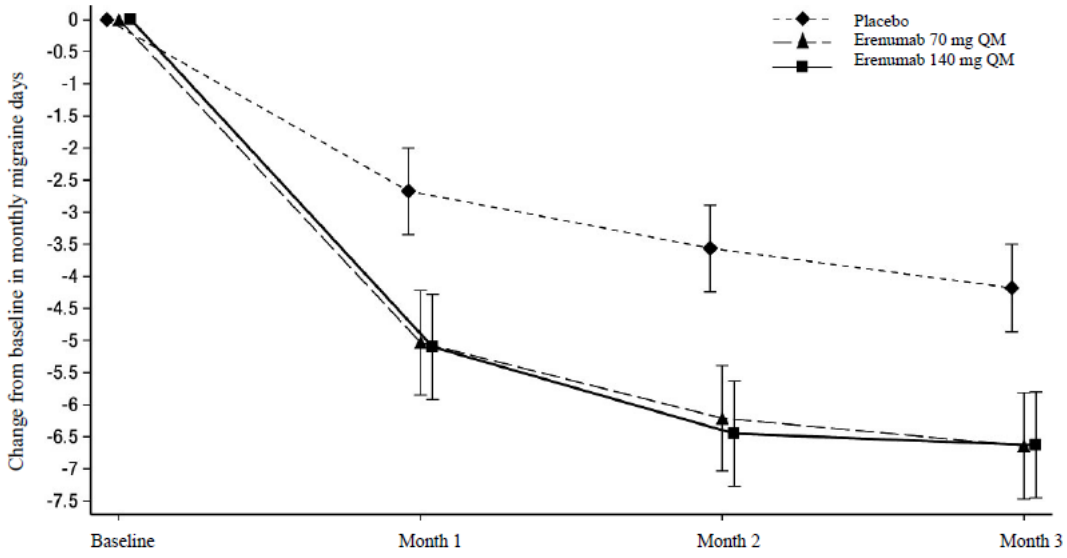
Aerinex was evaluated for prophylaxis of chronic migraine in a randomised, multi-center, 12 week, placebo-controlled, double-blind study. A total of 667 patients with a history of migraine with or without aura (≥15 headache days per month with ≥8 migraine days per month) were randomised to receive placebo (n = 286), Aerinex 70 mg (n = 191) or Aerinex 140 mg (n = 190) subcutaneous injections monthly for 12 weeks.

Randomisation was stratified by region (North America versus other) and the presence of acute medication overuse (present in 41% of overall patients) excluding patients with opioid overuse. The mean migraine frequency at baseline was approximately 18 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study.
Patients had a median age of 43 years (range: 18 to 66 years), 83% were female and 94% were white. Patients could have failed (i.e., no therapeutic response) up to 3 previous prophylactic treatment categories due to lack of efficacy, while there was no limit to the number of previous failures for poor tolerability. Overall in this study population, 68% had failed one or more previous prophylactic treatments due to lack of efficacy or poor tolerability, and 49% had failed two or more previous prophylactic treatments due to lack of efficacy or poor tolerability. In addition to excluding patients with opioid overuse, the study excluded patients with concurrent use of migraine prophylactic treatments. A total of 182 (96%) patients in the Aerinex 140 mg arm, 184 (96%) patients in the Aerinex 70 mg arm, and 265 (93%) patients in the placebo arm completed the study (i.e. completed Week 12 assessment). Of the 23 (3.4%) patients who discontinued treatment, 2 patients in the Aerinex 140 mg-treated group, no patients in the Aerinex 70 mg- treated group, and 2 patients in the placebo group discontinued due to adverse events.

The primary outcome measure was the change from baseline at Month 3 in monthly migraine days. Secondary outcome measures included the achievement of 50 to 100% reduction in monthly migraine days from baseline (≥50% responders), change from baseline in monthly acute migraine specific medication days, and change from baseline in cumulative monthly headache hours. Other than for cumulative monthly headache hours, Aerinex treatment demonstrated statistically significant and clinically meaningful improvements from baseline at Month 3 compared to placebo for efficacy outcomes as summarised in Figure 1 and Table 2.

Reduction in mean monthly migraine days from placebo were observed in a monthly analysis from Month 1 and in a follow up weekly analysis an onset of Aerinex effect was seen from the first week of administration.

Figure 1: Change from baseline in monthly migraine days in Study 1[a]



[a] Least-square means and 95% confidence intervals are presented.
The p-value for the difference in least-square means between erenumab and placebo assessed at Month 3 (primary outcome measure) were all< 0.001 for both Aerinex dose groups.

Table 2 Efficacy Outcomes in Study 1 at Month 3

	Aerinex 70 mg (n = 188)	Aerinex 140 mg (n = 187)	Placebo (n = 281)	Treatment difference /Odds ratio	p-value[a]
Efficacy outcomes					
Monthly migraine days (MMD)					
Mean change[b] 95% CI	-6.64 (-7.47; -5.81)	-6.63 (-7.45; -5.80)	-4.18 (-4.86; -3.50)	70 mg:-2.46 (-3.52; -1.39) 140 mg: -2.45 (-3.51; -1.38)	Both <0.00
≥50% MMD responders					
Percentage [%]	39.9%	41.2%	23.5%		
Odds ratio[c] 95% CI				70 mg: 2.18 (1.46; 3.27) 140 mg: 2.34 (1.56; 3.51)	Both < 0.00
≥ 75% MMD responders[d]					
%	17.0	20.9	7.8		n/a
Odds ratio 95% CI				70 mg: 2.43 (1.36; 4.33) 140 mg: 3.13 (1.78; 5.48)	
Monthly acute migraine specific medication days[e]					
Mean change[b] 95% CI	-3.45 (-4.02; -2.87)	-4.13 (-4.70; -3.56)	-1.58 (-2.05; -1.11)	70 mg: -1.86 (-2.60; -1.13) 140 mg: -2.55 (-3.28; -1.82)	Both <0.00
Cumulative headache hours					
Mean change[b] 95% CI	-64.76 (-78.34; -51.17)	-74.53 (-88.05; -61.01)	-55.22 (-66.38; -44.06)	70 mg: -9.54 (-26.98; 7.90) 140 mg: -19.31 (-36.71; -1.92)	ns
Patient-reported outcome measures					
HIT-6					
Mean change[f] 95% CI	-5.6 (-6.5; -4.6)	-5.6 (-6.5; -4.6)	-3.1 (-3.9; -2.3)	70 mg: -2.5 (-3.7; -1.2) 140 mg: -2.5 (-3.7; -1.2)	n/a
MIDAS total					
Mean change[f] 95% CI	-19.41 (-25.19; -13.62)	-19.76 (-25.56; -13.97)	-7.54 (-12.40; -2.69)	70 mg: -11.86 (-19.34; -4.39) 140 mg: -12.22 (-19.64; -4.75)	n/a

CI = confidence interval; MMD = monthly migraine days; ns = not significant; n/a = not applicable

[a] All p-values are reported as unadjusted p-values and are statistically significant after adjustment for multiple comparisons.

[b] Least-square mean (LSM) change from baseline at Month 3, treatment difference and p-value are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus Europe] and medication overuse [presence versus absence]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data.

[c] Odds ratio and p-value for ≥ 50% responders at month 3 are based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

[d] Post-hoc analysis; no hypothesis testing was performed.

[e] Migraine-specific medications include triptans and ergotamine derivatives.

[f] Change and reduction from baseline were evaluated at the last 4 weeks of the 12-week double-blind treatment phase.

Based on a pre-specified analysis, Aerinex 70 mg and 140 mg were efficacious in patients who had previously been treated with migraine prophylactics. Table 3 provides subgroup results of Study 1 based on prior prophylactic failure(s) due to lack of efficacy or intolerance, in a pre-specified analysis.

Table 3 Efficacy Outcomes in Study 1 at Month 3 in Subgroups Based on Prior Prophylactic Failure

	Aerinex 70 mg (patients never failed/failed ≥1 medication/ failed ≥2 medications, n=64/124/90)	**Aerinex 140 mg (patients never failed/failed ≥1 medication/ failed ≥2 medications, n=62/125/92)**	**Placebo (patients never failed/failed ≥1 medication/failed ≥2 medications, n=84/197/141))**	**Treatment difference / Odds ratio (95% CI)**
Monthly migraine days (MMD)[a] - Mean change[b] (95% CI)				TD
Never failed	-7.86 (-9.33; -6.39)	-6.14 (-7.61; -4.66)	-5.67 (-6.98; -4.36)	70 mg: -2.19 (-4.10; -0.28) 140 mg:-0.47 (-2.39; 1.46)
Failed ≥1 medication	-5.98 (-6.99; -4.97)	-6.84 (-7.84; -5.85)	-3.51 (-4.33; -2.70)	70 mg: -2.47 (-3.76; -1.18) 140 mg:-3.33 (-4.61; -2.06)
Failed ≥2 medications	-5.38 (-6.56; -4.20)	-6.96 (-8.10; -5.82)	-2.68 (-3.63; -1.72)	70 mg: -2.71 (-4.20; -1.21) 140 mg: -4.28 (-5.75; -2.80)
≥50% MMD responders[c]-%				OR[d]
Never failed	50%	41.9 %	38.1 %	70 mg: 1.75 (0.89; 3.43) 140 mg:1.33 (0.67; 2.66)
Failed ≥1 medication	34.7%	40.8 %	17.3 %	70 mg: 2.64 (1.56; 4.48) 140 mg: 3.30 (1.98; 5.51)
Failed ≥2 medications	35.6%	41.3 %	14.2 %	70 mg: 3.46 (1.81; 6.61) 140 mg: 4.18 (2.21; 7.91)
Monthly acute migraine-specific medication days[e] - Mean change[b] (95% CI)				TD
Never failed	-2.48 (-3.31; -1.64)	-2.48 (-3.31; -1.64)	-1.78 (-2.52; -1.05)	70 mg: -0.69 (-1.77; 0.38) 140 mg: -0.69 (-1.78; 0.39)
Failed ≥1 medication	-3.83 (-4.58; -3.08)	-4.90 (-5.64; -4.16)	-1.47 (-2.07; -0.87)	70 mg: -2.36 (-3.31; -1.41) 140 mg: -3.43 (-4.37; -2.49)
Failed ≥2 medications	-4.05 (-4.96; -3.15)	-5.39 (-6.27; -4.51)	-1.26 (-2.00; -0.53)	70 mg: -2.79 (-3.94; -1.65) 140 mg: -4.13 (-5.26; -3.00)

CI = confidence interval; MMD = monthly migraine days; TD = treatment difference; OR = odds ratio

[a] MMD at baseline was approximately 18 migraine days per month and similar across the above subgroups.

[b] Least-square mean (LSM) change from baseline at Month 3 and treatment difference are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus other and medication overuse [presence versus absence]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

[c] Responders are defined as patients who achieve ≥50% reduction on MMD from baseline

[d] Odds ratio for ≥50% responders at Month 3 based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

[e] Migraine-specific medications include triptans and ergotamine derivatives.

In patients with medication overuse (41% of the total population in Study 1), efficacy was observed with 70 mg and 140 mg Aerinex compared to placebo for monthly migraine days [LSM (95% Cl) 70 mg: -3.10 days (-4.83, -1.37)]; 140 mg: -3.10 days (-4.81, -1.39) 50% responders: 34.6% for 140 mg, 36.4% for 70 mg versus 17.7% for placebo), with odds ratio (95% CI) 70 mg: 2.67 (1.36, 5.22);140 mg: 2.51 (1.28, 4.94)) and in acute migraine-specific medication days (LSM (95% CI) 70 mg: -3.33 (-4.72, -1.94); 140 mg: -2.79 (-4.16, -1.42)).

Improvement in functional ability was assessed by the Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS) questionnaires. Mean change from baseline to Month 3 compared to placebo for the patient reported outcome measures are summarized in Table 2. The established between-group minimally important difference (MID) for the reduction in HIT-6 total score is 2.3.

Episodic Migraine

Study 2 (Study 20120296, STRIVE)

Study 2 was a randomized, multi-center, 24-week, placebo-controlled, double- blind study evaluating Aerinex for prophylaxis of episodic migraine. A total of 955 patients with history of migraine with or without aura for a duration of ≥ 12 months and 4-14 migraine days per month were randomized to receive either Aerinex 70 mg (n=317), Aerinex 140 mg (n = 319), or placebo (n = 319) by subcutaneous injection monthly for 6 months. Randomization was stratified by use of prophylactic medications (concomitant, prior use or no prior use) and region (North America vs. other). The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study.

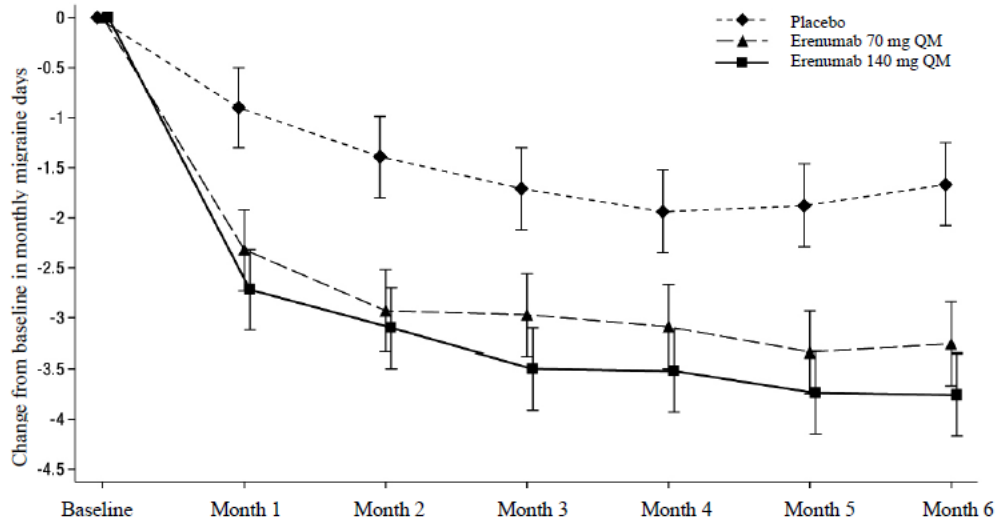
Patients had a median age of 42 years (range: 18 to 65 years), 85% were female and 89% were white. Patients could have failed to respond up to 2 previous prophylactic treatments. The study excluded patients with medication overuse. Overall, 865 (90.6%) patients completed the double-blind phase, including 287 (90.5%) in the 70 mg group, 294 (92.2%) in the 140 mg group, 284 (89.0%) in the placebo group. Of the 87 (9.1%) patients who discontinued treatment, 7 patients in the 70 mg Aerinex group, 6 patients in the 140 mg Aerinex group, and 7 patients in the placebo group discontinued due to adverse events.

The primary outcome measure was the change from baseline during months 4-6 in monthly migraine days. Secondary outcome measures included the achievement of a 50 to 100% reduction in mean monthly migraine days from baseline (≥50% responders), change from baseline in mean monthly acute migraine specific medication days and change from baseline in the two Migraine Physical Function Impact Diary (MPFID) domain scores: physical impairment (PI) and impact on everyday activities (EA).

The MPFID is a patient reported outcomes instrument that measures the impact of migraine on physical functioning. It contains 13 items evaluating the impact of migraine during the previous 24 hours on two physical functioning concepts of interest: “impact on everyday activities (EA)” (7 items, e.g. difficulty doing activities requiring concentration), “physical impairment (PI)” (5 items, e.g. difficulty doing activities requiring physical effort) and one global item assessing the overall impact on everyday activities. Patients rate the duration of impact or level of difficulty associated with migraine on a daily basis. Monthly MPFID scores are averaged over days with and without migraine; higher scores indicate worse impact on the EA and PI domains.

Aerinex treatment demonstrated statistically significant and clinically meaningful improvements from baseline during Months 4 to 6 compared to placebo for efficacy outcomes as summarized in Figure 2 and Table 4. Differences from placebo were observed as early as Month 1.
Based on a pre-specified analysis, Aerinex 70 mg and 140 mg were efficacious in patients who had previously been treated with migraine prophylactics. Table 5 provides subgroup results of Study 2 based on prior prophylactic failure due to lack of efficacy or intolerance, in a pre-specified analysis.

Figure 2: Change from baseline in monthly migraine days over time in Study 2[a]



[a] Least-square means and 95% confidence intervals are presented.
The p-value for the difference in least-square means between erenumab and placebo assessed as the average over months 4, 5 and 6 (primary outcome measure) was < 0.001 for both Aerinex dose groups.

Table 4: Efficacy Outcomes at Months 4-6 in Study 2

	Aerinex 70 mg (n = 312)	**Aerinex 140 mg** (n = 318)	**Placebo** (n = 316)	**Treatment difference / Odds ratio**	**p-value[a]**
Efficacy outcomes					
Monthly migraine days (MMD)					
Mean change[b] 95% CI	-3.23 (-3.58; -2.88)	-3.67 (-4.02; -3.33)	-1.83 (-2.18; -1.48)	70 mg: -1.40 (-1.88; -0.92) 140 mg: -1.85 (-2.33; -1.37)	Both <0.001
≥50% MMD responders					
Percentage [%]	43.3 %	50.0%	26.6%		
Odds ratio[c] 95% CI				70 mg: 2.13 (1.52; 2.98) 140 mg: 2.81 (2.01; 3.94)	Both < 0.001

≥ 75% MMD responders[d]					
%	20.8%	22.0 %	7.9 %		n/a
Odds ratio 95% CI				70 mg: 3.14 (1.91; 5.18) 140 mg: 3.35 (2.05; 5.49)	
Monthly acute migraine-specific medication days[e]					
Mean change[b] 95% CI	-1.13 (-1.34; -0.92)	-1.61 (-1.83; -1.40)	-0.20 (-0.41; 0.02)	70 mg: -0.94 (-1.23; -0.64) 140 mg: -1.42 (-1.71; -1.12)	Both <0.001
Patient-reported outcome measures					
MPFID physical impairment domain					
Mean change[b] 95% CI	-4.24 (-5.02; -3.45)	-4.81 (-5.59; -4.03)	-2.38 (-3.16; -1.59)	70 mg: -1.86 (-2.95; -0.77) 140 mg: -2.43 (-3.51; -1.35)	Both <0.001
MPFID impact on everyday activities domain					
Mean change[b] 95% CI	-5.52 (-6.28, -4.75)	-5.86 (-6.62; -5.10)	-3.30 (-4.06; -2.53)	70 mg: -2.22 (-3.28, -1.16) 140 mg: -2.57 (-3.62; -1.51)	Both <0.001
HIT-6					
Mean change 95% CI	-6.7 (-7.4; -6.0)	-6.9 (-7.6; -6.3)	-4.6 (-5.3; -4.0)	70 mg: -2.1 (-3.0; -1.1) 140 mg: -2.3 (-3.2; -1.3)	n/a
MIDAS (modified) total					
Mean change 95% CI	-6.7 (-7.6, -5.9)	-7.5 (-8.3; -6.6)	-4.6 (-5.5; -3.8)	70 mg: -2.1 (-3.3, -0.9) 140 mg: -2.8 (-4.0; -1.7)	n/a
Response on MPFID-physical impairment domain					
Percentage (%)[f]	39.1	42.5	30.1		
Odds Ratio 95% CI				70 mg: 1.49 (1.07; 2.08) 140 mg: 1.73 (1.24; 2.40)	
Response on MPFID-impact on everyday activities domain					
Percentage (%)[f]	49.0	50.3	34.5		
Odds Ratio 95% CI				70 mg: 1.83 (1.33; 2.52) 140 mg: 1.93 (1.40; 2.67)	

	Aerinex 70 mg (patients never failed/failed ≥1 medication, n=185/127)	Aerinex 140 mg (patients never failed/failed ≥1 medication, n=202/116)	Placebo (patients never failed/failed ≥1 medication, n=190/126)	Treatment difference (TD) / Odds ratio (OR) (95% CI)
Monthly migraine days (MMD)[a] - Mean change[b] (95% CI)				TD
Never failed	-3.26 (-3.83; -2.70)	-3.63 (-4.15; -3.10)	-2.32 (-2.87; -1.78)	70 mg: -0.94 (-1.54; -0.34) 140 mg: -1.30 (-1.89; -0.71)
Failed ≥1 medication	-2.64 (-3.34; -1.94)	-3.15 (-3.89; -2.42)	-0.62 (-1.32; 0.08)	70 mg: -2.02 (-2.81; -1.23) 140 mg: -2.54 (-3.35; -1.72)
≥50% MMD responders [c] -%				OR[d]
Never failed	46.5%	55.9%	32.6%	70 mg: 1.77(1.16; 2.69) 140 mg: 2.66 (1.76; 4.02)
Failed ≥1 medication	38.6%	39.7%	17.5%	70 mg: 2.93 (1.63; 5.27) 140 mg: 3.06 (1.70; 5.52)
Monthly acute migraine-specific medication days[e] - Mean change[b] (95% CI)				TD
Never failed	-0.91 (-1.20; -0.61)	-1.27 (-1.55; -0.99)	-0.33 (-0.62; -0.04)	70 mg: -0.57 (-0.89; -0.25) 140 mg: -0.94 (-1.25; -0.63)
Failed ≥1 medication	-1.51 (-2.00; -1.01)	-2.16 (-2.68; -1.65)	-0.05 (-0.54; 0.45)	70 mg: -1.46 (-2.02; -0.91) 140 mg: -2.12 (-2.69; -1.55)

CI = confidence interval; MMD = monthly migraine days; MPFID = Migraine Physical Function Impact Diary; TD = treatment difference; OR = odds ratio

[a] MMD at baseline was approximately 8 migraine days per month and similar across the above subgroups.

[b] Least-square mean change from baseline at Month 4-6 and treatment difference are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus other and medication overuse [presence versus absence]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

[c] Responders are defined as patients who achieve ≥50% reduction on MMD from baseline.

[d] Odds ratio for ≥50% responders at Month 4-6 based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

[e] Migraine-specific medications include triptans and ergotamine derivatives.

Table 5: Efficacy Outcomes at Months 4 to 6 in subgroups based on prior prophylactic failure in Study 2

NON-CLINICAL SAFETY DATA

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies have not been conducted with Aerinex. Aerinex is not pharmacologically active in rodents and has biologic activity in the cynomolgus monkeys, but this species is not an appropriate model for evaluation of tumorigenic risk. The mutagenic

potential of Aerinex has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.
There were no adverse effects on surrogate markers of fertility (anatomic pathology or histopathology changes in reproductive organs) in the chronic toxicology study in sexually mature monkeys subcutaneously administered Aerinex at dose levels up to 150 mg/kg twice weekly for 6 months, at systemic exposures up to 283 or 123-fold higher than the clinical dose of 70 mg or 140 mg once monthly, respectively based on serum AUC.

Animal toxicology

There were no adverse effects in monkeys dosed up to 150 mg/kg SC twice weekly for up to 6 months at systemic exposures up to 283 or 123-fold higher than the clinical dose of 70 or 140 mg once monthly, respectively, based on serum AUC.

INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

STORAGE

See folding box.

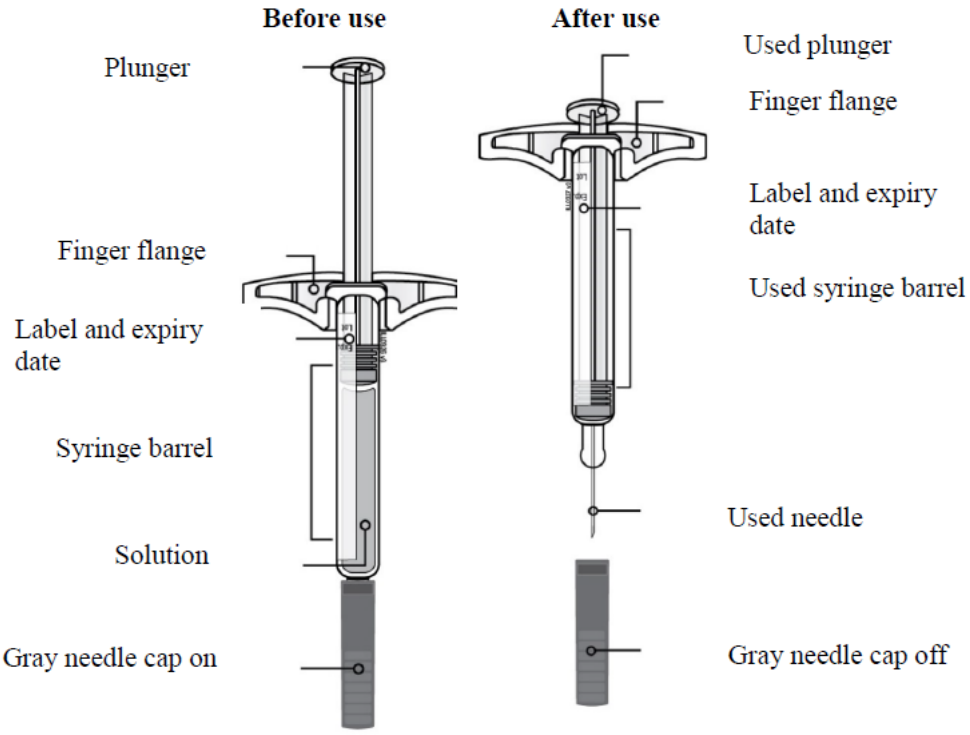
- Store refrigerated at 2° to 8° C (36° to 46° F) in the original carton to protect from light until time of use.
- If removed from the refrigerator, Aerinex should be kept at controlled room temperature (up to 25°C [77°F]) in the original carton and must be used within 14 days. Throw away Aerinex that has been left at room temperature for more than 14 days.
- Do not freeze.
- Do not shake.

Aerinex should not be used after the date marked "EXP" on the pack.
Aerinex must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Instruction for use of the 70 mg/mL Solution for injection in a Single-Use prefilled Syringe

Single-Use Prefilled Syringe



Important: Needle is inside

Important

Before you use an Aerinex prefilled syringe, read this important information:

Storing your Aerinex prefilled syringe

Keep the syringe out of the sight and reach of children.

Keep the syringe in the original carton to protect from light or physical damage.

The syringe should be kept in the refrigerator at 2˚C to 8˚C.

Throw away Aerinex that has been left at room temperature (up to 25°C) for more than 14 days.

Do not store the syringe in extreme heat or cold. For example, avoid storing in your car.

Do not freeze.

Using your Aerinex prefilled syringe

Do not try to inject Aerinex before receiving training from the doctor or nurse.

Do not use a syringe after the expiry date stated on the label.

Do not shake the syringe.

Do not remove the gray needle cap from the syringe until you are ready to inject.

Do not freeze or use the syringe if it has been frozen.

Do not use a syringe if it has been dropped on a hard surface. Part of the syringe may be broken even if you cannot see the break. Use a new syringe, and contact your healthcare provider (doctor, nurse or pharmacist).

This product contains natural rubber latex within the gray needle cap. The product may cause allergic responses in individuals who are sensitized to latex. Tell your healthcare provider if you are allergic to latex.

For more information or help contact your health care provider.

Step 1: Prepare

Read this before you inject.

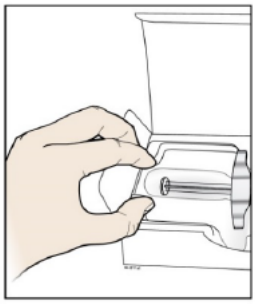
Check your prescription.

Your healthcare provider has prescribed a 70 mg or a 140 mg dose.

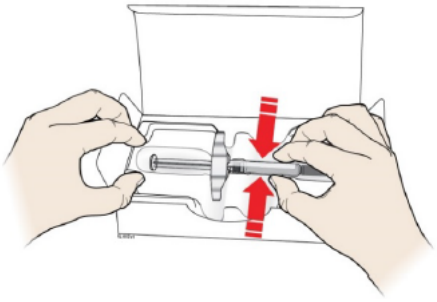
For a 70 mg dose, inject one syringe of 70 mg/mL.

For a 140 mg dose, inject two syringes of 70 mg/mL one after the other. To avoid discomfort at the site of injection, leave the syringes at room temperature for at least 30 minutes before injecting.

A) Remove the Aerinex prefilled syringe from the carton.
Grab the syringe barrel to remove the syringe from the tray.

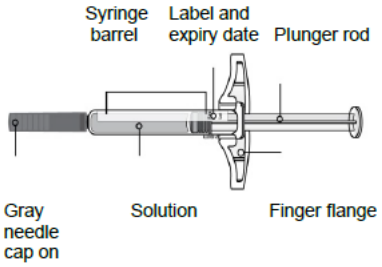


Place your finger and thumb on the edge of the tray to secure it while you remove the syringe.



Hold the syringe at the barrel (see arrows).

B) Inspect the Aerinex prefilled syringe.
Always hold the syringe by the syringe barrel.
Make sure the medicine in the syringe is clear and colorless to slightly yellow.
Leave the syringe(s) at room temperature for at least 30 minutes before injecting.
Do not use the syringe if the medicine is cloudy or discolored or contains flakes or particles.
Do not use the syringe if any part appears cracked or broken.
Do not use the syringe if the syringe has been dropped.
Do not use the syringe if the gray needle cap is missing or not securely attached.
Do not use the syringe if the expiry date printed on the label has passed.
In all cases, use a new syringe, and in case of doubts contact your health care provider.



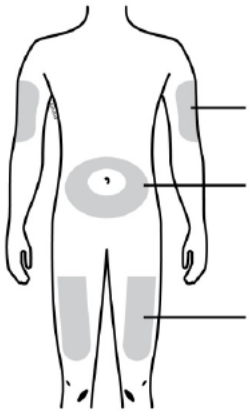
C) Gather all materials needed for the injections. Wash your hands thoroughly with soap and water.
On a clean, well-lit work surface, place the:

- One syringe
- Alcohol wipe
- Cotton ball(s) or gauze pad(s)
- Adhesive bandage
- Sharps disposal container


D) Prepare and clean the injection site(s).

D) Prepare and clean the injection site(s).
You can use:

- The thigh
- Stomach area (abdomen), except for a **five** cm area right around the navel
- Outer area of upper arm(if someone else is giving the injection)

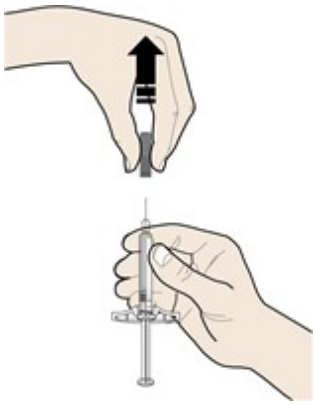


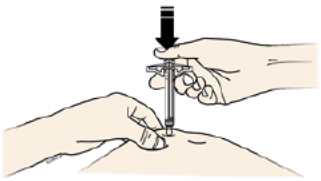
Clean your injection site with an alcohol wipe. Let your skin dry.

- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection if you need to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting directly into a raised, thick, red, or scaly skin patch or lesion, or areas with scars or stretch marks.

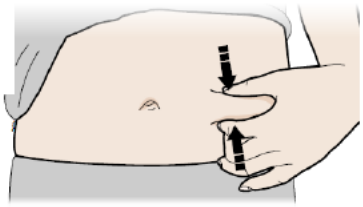
Step 2: Get ready

E) Pull the gray needle cap straight out and away from your body, only when you are ready to inject.
Do not leave the gray needle cap off for more than five minutes. This can dry out the medicine.
It is normal to see a drop of liquid at the end of the needle.
Do not twist or bend the gray needle cap.
Do not put the gray needle cap back onto the syringe.
Do not remove the gray needle cap from the syringe until you are ready to inject.



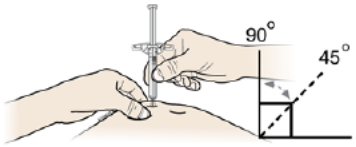


a firm surface.
mb and fingers, creating an area about **five** cm wide.
e injecting.



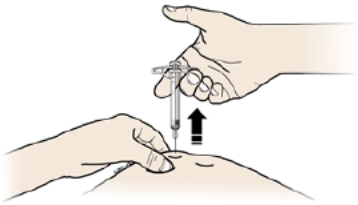
Step 3: Inject

G) While pinching, with the gray needle cap off, insert the syringe into the skin at an angle of 45 to 90 degrees.
Do not place your finger on the plunger rod while inserting the needle.



H) Using slow and constant pressure, push the plunger rod all the way down until it stops moving.

I) When done, release your thumb, and gently lift the syringe off of the skin.



Important: When you remove the syringe, if it looks like the solution is still in the syringe barrel, this means you have not received a full dose. Call your healthcare provider immediately.

Step 4: Finish

J) Discard the used syringe and the gray needle cap.
Put the used Aerinex syringe in a sharps disposal container right away after use**. Do not** throw away (dispose of) the syringe in your household trash.
Talk with your healthcare provider about proper disposal. There may be local regulations for disposal.
Do not reuse the syringe.
Do not recycle the syringe or sharps disposal container or throw them into household trash.
Important: Always keep the sharps disposal container out of the sight and reach of children.

K) Examine the injection site

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site.
Apply an adhesive bandage if needed.

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1.18 Batch number(s) of the FPPs used in *(Add as many rows as necessary)*

Clinical/bioequivalence studies	N/A		
Stability studies	**0010371979**	**0010370973**	**0010370975**
Validation/production scale batches	**0010291676**	**0010291678**	**0010291679**

Comments [e.g., batch size, explanation of NA (not applicable) answers] **105,000 units**

Composition of clinical, primary stability and validation/production FPP batches (kg)

Ingredients	Administration Unit		Bioequivalence <batch number>		Primary stability <batch number>		Production <batch number>	
	Mg	%*	Kg	%*	Kg	%*	kg	%*
Prefilled Syringe contents								
AMG 334	70		NA					
Sucrose	73		NA					
Polysorbate 80	0.10		NA					
Glacial acetic acid	1.5		NA					
Sodium hydroxide	Qs to target pH		NA					
Water for Injection	Qs to target volume		NA					

* Each ingredient is expressed as a percentage of the grand total.
** All components (……..) of the proprietary mixture are described in the compendia

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OVERALL QUERIES AND RECOMMENDATIONS FOR THIS MODULE
MODULE 2: CHEMICAL, PHARMACEUTICAL, NON-CLINICAL AND CLINICAL OVERVIEWS AND SUMMARIES

2.1

2.2	AMG334 (Erenumab) is a human monoclonal immunoglobulin G2 (IgG2) antibody subclass expressed in Chinese hamster ovary (CHO) cell line. AMG334 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 its corresponding receptor, CGRP-R. CGRP has been implicated in migraines and its levels are elevated in the blood during a migraine attack. The AMG334 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 of time. AMG334 consists of 2 heavy chains of the IgG2 class and 2 light chains of the human lambda subclass. AMG334 contains a total of 36 cysteine residues involved in both intrachain and interchain disulfide bonds. Each heavy chain contains 456 amino acids with 4 intrachain disulfide bonds. Each light chain contains 216 amino acids with 2 intrachain disulfide bonds. AMG334 contains 6 interchain disulfide bonds for a total of 18 intrachain and interchain disulfide bonds. As with all IgG2 antibodies studied, alternate disulfide linkages (IgG2-A/B and IgG2-B) between the Fab and hinge regions exist [Wypych et al., 2008]. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 306. As is typical with mammalian cell culture processes, C-terminal lysine 456 on the heavy chain is mostly removed due to the presence of carboxypeptidases during upstream production. The AMG334 drug substance manufacturing process consists of cell culture, harvest, and purification stages and was successfully implemented and validated at the commercial site and scale. Amgen Inc. (Amgen Thousand Oaks or ATO) was the former drug substance manufacturing site. The manufacturing operations for commercial drug substance were transferred to the Amgen Singapore Manufacturing Pte. Ltd. (ASM) site. The drug substance process description, process history, control strategy and stability for the drug substance manufactured at the ATO site are retained in the submission along with new data for the ASM site. The information contained in the QOS makes reference to ATO or ASM specific information (denoted with qualifier '-ATO' or '-ASM'). The details are summarized in [2.3.S Quality Overall Summary, Drug Substance] and [2.3.S Quality overall summary – Addendum] respectively and detailed in Module 3 Drug Substance. In addition, the product comparability for the drug substance manufactured at ATO and ASM has been demonstrated. The commercial drug product manufacturing site is Amgen Manufacturing Limited, located in Juncos, Puerto Rico (USA). The AMG334 drug product manufacturing process is comprised of buffer preparation, drug substance thaw, drug product formulation, bioburden reduction filtration, filtered formulated drug product hold, sterile filtration and aseptic filling, syringe plunger-stopper placement, inspection, and storage. AMG334 drug product is supplied as a sterile, single-use, preservative-free solution for subcutaneous (SC) injection in a prefilled syringe (PFS) or prefilled SureClick® autoinjector/pen (AI/Pen). The proposed commercial presentation for the AMG334 70 mg/1 mL in PFS and AI/Pen contains a 1.0 mL deliverable volume of 70 mg/mL AMG334 in 25 mM acetate, 7.3% (w/v) sucrose, 0.010% (w/v) polysorbate 80, pH 5.2 and proposed commercial presentation for the AMG334 140 mg/1 mL in PFS and AI/Pen contains a 1.0 mL deliverable volume of 140 mg/mL AMG334 in 34 mM acetate, 6.5% (w/v) sucrose, 0.010% 0, pH 5.2.

The formulation is optimized for stability of product quality attributes and is demonstrated as suitable for the product, container and its intended use throughout the registered shelf life. PFS and AI/Pen assembly and packaging occur at Amgen Europe B.V. (Amgen Breda or ABR), located in Breda, Netherlands and Amgen Technology (Ireland) Unlimited company (Amgen Dun Laoghaire or ADL). The drug product process description, process history, control strategy and stability are summarized in [2.3.P Quality Overall Summary, Drug Product].

The AMG334 drug substance and drug product comparability program evaluated throughout development, changes in process, manufacturing site, container, and delivery device including assessments of lot release and additional characterization data, and assessments of forced degradation or stressed stability conditions, as necessary. In compliance with ICH Harmonized Tripartite Guideline, *Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (Q5E)*, a risk based comparability strategy was employed to detect and evaluate any effects these changes may have on product quality. Overall, the combined lot release, characterization and stress stability results demonstrate that AMG334 drug substance and drug product manufactured throughout development and proposed for commercialization are comparable.

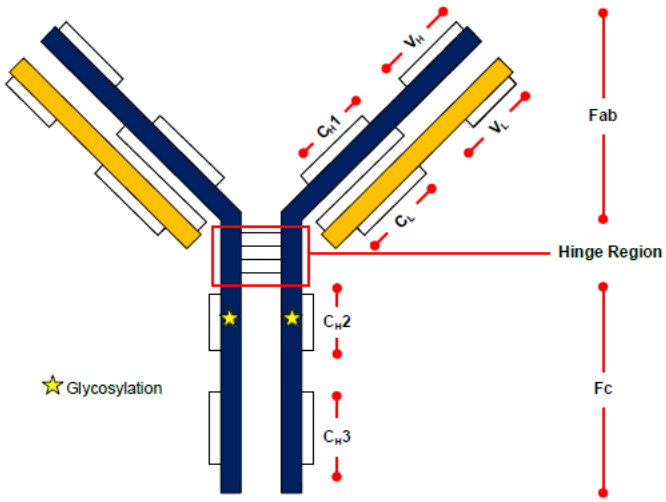
Establishment of the commercial control strategy for drug substance and drug product was based on knowledge obtained from development of the process, clinical and commercial scale runs, as well as risk and knowledge based product and process characterization studies. Small- scale studies were used to define the process, and the subsequent clinical and commercial scale runs demonstrated that the process, as designed, met requirements for product quality. Specifications and test methods were defined to assure product quality and patient safety. Data generated support the conclusion of successful validation of the drug substance and drug product manufacturing process at the commercial manufacturing sites. A continued process verification approach has been implemented which will ensure the continued capability of the process and controls to produce product that meets the desired quality throughout the lifecycle of the product.

Drug substance and drug product stability studies were performed in compliance with ICH Harmonized Tripartite Guidelines *Stability Testing of Biotechnological/Biological Products (Q5C)* and *Stability Testing of New Drug Substances and Products (Q1A)*. Data presented from primary lots support the proposed expiry period of 36 months for AMG334 drug substance and the requested 24 month shelf life for the 70 mg/mL and 140 mg/mL PFS and AI/Pen. The drug substance and drug product stability data will continue to be evaluated through the on-going stability program.

In compliance with the ICH Q5A guideline *Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* and CPMP/ BWP/268/95, *Note for Guidance on Virus Validation Studies: the Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses*, a comprehensive strategy has been implemented for reducing or preventing the introduction of adventitious agents, testing and evaluation of viral safety for the manufacture of AMG334.

The application includes all required Module 3 sections per ICH guidance, *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality M4Q (R1)*. Module 3 includes a single drug substance section (3.2.S) with data for drug substance

	pre-filled syringe, 70 mg/1mL pre-filled pen, 140 mg/1mL pre-filled syringe and 140 mg/1mL pre-filled pen, along with Appendices (3.2.A), and a regional section (3.2.R). Literature references are provided in 3.3 Literature References. Information on the delivery devices related specifically to the combination products are provided in 3.2.R Regional for each delivery device (PFS and AI/Pen) and contain information regarding the device description, device development, design verification, design validation, and risk management.

2.3	OVERALL QUALITY SUMMARY
For PPB use only	
2.3.1	**OVERVIEW OF ACTIVE PHARMACEUTICAL INGREDIENT(S) [API(S)]**
2.3.1.1	General Information of the API(S)
2.2.1.1.1	Nomenclature Recommended International non-proprietary name (INN) Erenumab Chemical Name Anti-human CGRP-R (calcitonin gene related peptide type 1 receptor) monoclonal antibody CAS Registry Number CAS: 1582205-90-0 United States Adopted Name Erenumab Company or Laboratory Code AMG334 Aerinex™
For PPB use only	
2.2.1.1.2	Structure **Figure 1-1 Schematic Structure of AMG334**  Heavy chains are shown in blue and light chains are shown in orange Disulfide linkages are indicated by solid black lines V_H is the variable domain of the heavy chain C_H1, C_H2, and C_H3 are the constant domains of the heavy chain V_L is the variable domain of the light chain C_L is the constant domain of the light chain
For PPB use only	

2.2.1.1.3 General Properties of the API(s)

Table 1-1 Physical and chemical properties of AMG334

Immunoglobulin subclass	IgG2
Sequence	Human sequence
Biological target	Specific binding to calcitonin gene-related peptide receptor (CGRP-R)
Molecular mass [a]	145,881 Da for deglycosylated molecule 148,767 Da including glycosylation
Cysteines	36
Number of intra and inter disulfide bonds	12 intrachain and 6 interchain (18 total)
Glycosylation	N-linked site: Asn^{306} on each heavy chain
Extinction coefficient	Theoretical: 1.5 mg^{-1} cm^{-1} mL at 280 nm Determined: 1.5 mg^{-1} cm^{-1} mL at 280 nm
Isoelectric point (pI)	Theoretical: 8.8 [b] Determined: 9.0
T_m (melting temperature)	73.8°C [d]

[a] Experimentally determined molecular mass
[b] Theoretical isoelectric point with C-terminal glycine on both heavy chains
[c] Experimentally determined melting temperature.
[d] Single transition observed. Thermal transitions of the C_H2 or C_H3 domains not resolved from the Fab domain.

AMG334 binds to both human and cynomolgus monkey CGRP-R with high affinity ([2.6.2], Pharmacology Written Summary). AMG334 causes a dose-dependent inhibition of CGRP signaling in *in-vitro* assays, confirming its potency in blocking this pathway. This dose-dependent inhibition of CGRP signaling is the basis of the cell-based bioassay used to measure potency of AMG334. Additional assays have been developed to support the biological characterization of AMG334 [3.2.S.3.1] Elucidation of Structure and Other Characteristics.

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2.3.1.2 Manufacture of the API(S)

2.3.1.2.1 Name and address of API(s) Manufacturer

Table 1. Drug Substance Facility Responsibilities

Manufacturer or Testing Facility	Address	Responsibility
Amgen Inc. (Amgen Thousand Oaks or ATO)	One Amgen Center Drive Thousand Oaks, CA 91320, USA	Drug substance lot release and stability testing
Amgen Manufacturing Limited (AML)	State Road 31 KM 24.6 Juncos, Puerto Rico 00777-4060, USA	Drug substance lot release and stability testing
Amgen Technology (Ireland) Unlimited Company (Referred to as Amgen Dun Laoghaire or ADL)	Pottery Road, Dun Laoghaire, Co Dublin, Ireland	Drug substance lot release and stability testing
Amgen Singapore Manufacturing Pte. Ltd. (ASM)	1 Tuas View Drive Singapore 637026 Singapore (SGP)	Drug substance manufacture Drug substance lot release testing

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2.3.1.2.2	Description of Manufacturing Process and Process Controls

2.2 Description of the manufacturing process and process controls

As part of the drug substance transfer to the ASM facility, minimal changes have been implemented in the manufacturing process in order to accommodate facility fit. A list of the process changes implemented at ASM compared to ATO is provided in Table 2-1. The impact of these changes has been characterized appropriately and the process has been validated ([3.2.S.2.5_ASM] Process Validation, [3.2.S.2.6_ASM] Process Characterization – Cell Culture and Harvest, [3.2.S.2.6_ASM] Process Characterization – Purification).

Table 2-1 Manufacturing Process Changes at ASM

Process Step	Manufacturing Process Changes at ASM
Cell Culture	Optional maintenance shake flask, revised final viable cell density (VCD) action limits
Harvest	Provision to reprocess harvest pool
Protein A Chromatography	Column diameter, cycles per lot, cycles per regeneration
Cation Exchange Chromatography	
Anion Exchange Chromatography	
Drug Substance Filtration, Fill, Storage and Reprocessing	
Pool hold temperature	Membrane volume, load factor
Drug substance container; provision to reprocess drug substance	

The changes to the cell culture process include optional use of a maintenance shake flask and updates to final VCD action limits based on additional data. A provision to reprocess the harvest pool was validated at ASM.

There are minor process changes to the purification, limited to scale and number of cycles of the protein A chromatography step, load factor and volume of the anion-exchange (AEX) membrane, and the drug substance container. The protein A chromatography column diameter is increased from 60 cm to 80 cm while keeping the bed height constant. The maximum number eased from 12 cycles to 8 cycles, enabled by the larger column volume and the number of cycles before denaturing cleaning is increased from 6 cycles to 8 cycles. There were no changes to the cation-exchange (CEX) chromatography step other than the pool being held at room temperature (15°C to 25°C) rather than 2°C to 8°C. The size of the AEX chromatography membrane is increased from 1.62 L to 2.5 L and the load factor increased from 6000 g/L to 8000 g/L.

A provision to reprocess drug substance by filtration was validated at ASM. The drug substance container is changed from a 10-L polycarbonate carboy used at ATO to a 12-L single use, triple layer-film bag (ethylene-vinyl acetate – product contact layer) used at ASM. The evaluation of extractables and leachables, suitability and appropriateness of the single-use system for use in commercial manufacturing are provided in [3.2.S.2.6_ASM] Process Characterization - Single- use Systems and [3.2.S.7.1] Stability Summary and Conclusions (ASM)). Due to the change to the drug substance container-closure type, thawing and pooling of drug substance in the drug product manufacturing process at Amgen Manufacturing Limited (AML), Juncos, Puerto Rico was re-validated for use with drug substance from ASM ([3.2.P.3.5_ASM] Process Validation).

The process descriptions are provided in:

- [3.2.S.2.2_ASM] Cell Culture and Harvest Process Flow Diagram
- [3.2.S.2.2_ASM] Cell Culture and Harvest Process Description
- [3.2.S.2.2_ASM] Purification Process Flow Diagram
- [3.2.S.2.2_ASM] Purification Process Description
- [3.2.S.2.2_ASM] Protein A Chromatography
- [3.2.S.2.2_ASM] Cation Exchange Chromatography
- [3.2.S.2.2_ASM] Anion Exchange Chromatography
- [3.2.S.2.2_ASM] Product Pool Hold Times
- [3.2.S.2.2_ASM] Polysorbate Addition, Filling and Storage
- [3.2.S.2.2_ASM] Transportation
- [3.2.S.2.2_ASM] Reprocessing

2.3.1.2.3	Control of Materials used in Manufacture of API **2.3.1 Raw materials** All manufacturing raw materials are received, identified, sampled, quarantined, tested, labeled, and released according to established written procedures. Materials used in the manufacture of the drug substance may be tested by Amgen or contract testing laboratories or accepted on the basis of a supplier's certification documentation. Identity testing is performed on all incoming raw materials. There are no materials of direct animal origin used in the manufacture of erenumab. Assessments of transmissible spongiform encephalopathy (TSE) and viral risk associated with the raw materials used in the erenumab process are provided in [3.2.A.2] (Adventitious Agents Safety Evaluation). Refer to [3.2.S.2.3_ASM] (Raw Materials) for a comprehensive list of raw materials used in the manufacture of erenumab.
2.3.1.2.4	Controls of Critical Steps and Intermediates **Control of critical steps and intermediates** Except for final viable cell density (VCD) action limits for the cell culture process, there are no changes to the in-process controls or their ranges due to the change from ATO to ASM. In- process controls parameters are summarized in [3.2.S.2.4_ASM] (Control of Critical Steps and Intermediates). The justification for selection of product quality IPCs and limits is presented in [3.2.S.2.6_ASM] (Process Characterization – Cell Culture and Harvest) and [3.2.S.2.6_ASM] (Process Characterization – Purification).
2.2.1.2.5	Process Validation and/or Evaluation the process, when executed within defined process parameter ranges, consistently produces drug substance that meets pre-defined acceptance criteria. Validation acceptance criteria for performance indicators were based on development data derived from process characterization, process understanding gained from prior knowledge, and data from pilot, clinical, and commercial manufacturing lots. Results obtained during process validation are described in [3.2.S.2.5_ASM] (Process Validation (ASM)) and provide evidence that the drug substance process is validated and consistently produces erenumab that meets pre-defined criteria. Drug substance process validation studies include: • Cell Culture and Harvest • Purification • In-process Pool Hold • Chromatography Resin Cleaning and Reuse • Membrane Cleaning and Reuse • Harvest Refiltration • Drug Substance Reprocessing Table 2-2 shows the ASM drug substance validation lots. A minimum of 3 consecutive, successful lots meeting acceptance criteria were required. A total of 5 lots were initiated as part of the process validation campaign. Cell culture lot 0010348174 was discarded upon detection of contamination. The root cause of this event was extrinsic to the process as contamination resulted from ingress of bacteria via a compromised single use connection on the bioreactor. Corrective action was implemented to improve the robustness of tubing connections. The requirement for three consecutive runs was fulfilled by cell culture lots 0010347873, 0010349872 and 0010351470. Cell culture lot 0010355389 was terminated upon completion of N-1 Expansion Bioreactor stage as all requirements for three consecutive process validation runs were met.

Table 2-2 Drug Substance Process Validation Lots

Vial Thaw Date	Date of Manufacture	Cell Culture Lot Number	Drug Substance Lot Number
23 Jul 2017	18 Sep 2017	0010347873	0010349865
06 Aug 2017	N/Aa	0010348174	N/Aa
20 Aug 2017	16 Oct 2017	0010349872	0010351717
03 Sep 2017	30 Oct 2017	0010351470	0010355401
01 Oct 2017	N/Ab	0010355389	N/Ab

a Lot 0010348174 was terminated at the Production bioreactor stage due to contamination event b Lot 0010355389 was terminated upon completion of N-1 Expansion Bioreactor stage due to completion of process validation

The erenumab purification process was successfully validated using data from 3 consecutive validation lots produced at commercial manufacturing scale. Results demonstrated acceptable and consistent performance based on pre-defined acceptance criteria. The purification process consists of protein A chromatography, viral inactivation, cation exchange chromatography, anion exchange chromatography, viral filtration, ultrafiltration/diafiltration, polysorbate 80 addition/final filtration, and drug substance fill. Results for the process parameters and performance indicators at each step are presented in the subsequent sections.

All process parameter results were within the acceptable ranges and all performance indicator results met the acceptance criteria. The results obtained during process validation demonstrate that cell culture, harvest, and purification processes are validated and consistently meet pre- defined acceptance criteria for process performance and product quality

2.3.1.3 Characterization of the API(S)

2.6.1 Process Characterization

Cell Culture and Harvest

Additional characterization was performed to support process changes to cell culture and harvest to the process parameters and their acceptable ranges. Changes made at ASM include optional maintenance (shake flask) culture to prolong the working cell bank by not thawing a new vial for each erenumab production lot or as a contingency plan to be able to expand the culture more quickly to the production stage compared to thawing a new vial, and revisions to the final viable cell density action limits.

Purification

The purification process characterization ([3.2.S.2.6_ASM] Process Characterization – Purification) for the following processing steps in the erenumab drug substance process include protein A chromatography, viral inactivation, CEX chromatography, AEX chromatography, viral filtration, ultrafiltration/diafiltration (UF/DF), polysorbate addition and drug substance
filling. Updates made to the purification process are highlighted below.

Minor updates were made to the DOE study for the CEX chromatography step resulting in no impact or changes to the critical process parameter. In addition, changes to the acceptable range for the AEX chromatography step (load factor) and inclusion of polysorbate addition and drug substance filling in bags and carboys for storage were included to support the manufacturing process.

Pool hold characterization studies were performed at the CEX chromatography process step. Changes to the pool hold times for the CEX step (temperature range, characterized hold time and acceptable hold times) were validated within the acceptable characterized hold times at commercial scale (2 kL production bioreactor) by demonstrating microbial control throughout the hold period.

2.6.2 Product Comparability

A comprehensive analytical comparability study was executed to support the comparison of drug substance manufactured in the ATO facility to drug substance manufactured in the ASM facility. Analytical comparability was assessed by routine batch analysis testing, additional characterization testing, and stressed stability as described in [3.2.S.2.6 Product Comparability
– ATO DS to ASM DS].

For evaluation of the batch analysis data, comparison was made to historical results using data comprised of sixteen (16) pre-change lots, except HIC-HPLC where the data comprised of twelve (12) pre-change lots. All results for the ASM drug substance lots met the batch analysis comparability assessment criteria, with the exception of isolated results related to charge variants (monitored by CEX-HPLC), Asp isomerization (monitored by HIC-HPLC) and HMW species (monitored by SE-UHPLC) that were outside the historical range. In each case, the results are well within the specifications and are just slightly outside of the historical ranges. Furthermore, additional characterization and forced degradation tests results for the ASM lots met the comparability assessment criteria for all tests. There is no impact to product quality or patient safety as a result of the slight decrease in basic peak (CEX-HPLC), slight increase in Asp isomerization (HIC-HPLC) and slight increase in HMW (SE-UHPLC) as detailed in [3.2.S.2.6 Product Comparability – ATO DS to ASM DS].

CEX-HPLC

A slight decrease in CEX-HPLC basic peaks was observed in the ASM lots. The results for CEX basic peaks while outside of the historical range are still within the product specification. The basic peak results were outside the historical range, as shown in Table 2-3.

Table 2-3 CEX-HPLC Results Outside of Historical Range

Specification Acceptance Criteria	Historical Range (min-max)	Lot Results % 0010351717	0010355785
Basic Peaks: 8.7% to 15.5%	Basic Peaks: 11.3% to 13.1%	Basic Peaks: 11.0	Basic Peaks: 10.9

	Forced degradation study demonstrates that the ASM and ATO drug substance degrade similarly with respect to CEX-HPLC. Attributes detected in the CEX-HPLC basic peaks are HMW species, Asp isomerization in the complementarity determining region (CDR), heavy chain (HC) and light chain (LC) N-terminal glutamine, HC C-terminal lysine, and HC C- terminal proline amide. HMW is a critical quality attribute detected by SE-UHPLC. Asp isomerization is a critical quality attribute detected by HIC-HPLC. Heavy chain and light chain N-terminal glutamine, HC C-terminal lysine, and HC C-terminal proline amide are non- critical quality attributes. Therefore, since critical quality attributes are detected by other methods and the remaining attributes in the basic peaks are non-critical, there is no impact to product quality or patient safety. The trend charts showing the ASM lot release results and historical drug substance data show the basic peak results to be within the inherent method variability (basic peaks standard deviation of 0.5%). The main and acidic peak species were consistent with historical data, which demonstrates that there was no concomitant change in the product-related impurities measured by this method.

2.3.1.4	Control of the API(S))

- **Specification**

[3.2.S.4.1], [2.3.S]

No changes are proposed to the current approved Specifications section.

- **Analytical procedures**

[3.2.S.4.2], [2.3.S]

No changes are proposed to the current approved Analytical procedures section.

- **Validation of analytical procedures**

[3.2.S.4.3], [2.3.S]

No changes are proposed to the current approved section for Validation of analytical procedures.

- **Batch analyses**

[3.2.S.4.4], [2.3.S]

This section includes batch analyses data for erenumab drug substance lots manufactured at ASM. All data meet the drug substance specifications provided in [3.2.S.4.1_ATO] (Specification) and demonstrate that the drug substance can be reproducibly manufactured. A summary of the manufacturing details for these drug substance lots is provided in [3.2.S.2.6_ASM] (Lot History).

Batch release data were also used in the comparability assessment for ASM drug substance compared to Amgen Thousand Oaks (ATO) drug substance. The analytical comparability results are detailed in [3.2.S.2.6 (Product Comparability – ATO Drug Substance to ASM Drug Substance)].

- **Justification of specification**

[3.2.S.4.5], [2.3.S]

No changes are proposed to the current approved section for Justification of specifications.

- **Reference standards or materials**

[3.2.S.5], [2.3.S]

No changes are proposed to the current approved section for Reference standards or materials.

2.3.1.5 Reference Standards or Materials of the API(S)

To date, 2 AMG334 reference standards were produced and the history of the reference standards is provided in Table 5-1. A comparison of release data for each of these standards is provided in Table 5-2 and [3.2.S.5] (Reference Standards or Material). The reference standard stability data is provided in [3.2.S.5] (Reference Standard Stability Data).

Table 5-1 History of AMG334 reference standards

Reference Standard Lot Number	Classification Date of Manufacture	Reference Standard Concentration (mg/mL)	Drug Substance Lot Number	Drug Substance Concentration (mg/mL)	Drug S Proce
0010081148	Interim Mar 2011	69.4	0010080560	68.8	Proces
0010245841	Primary Jun 2015	67.3	0010204578	138	Proces (Clinic

ATO = Amgen Thousand Oaks; AWA= Amgen Washington

2.3.1.6 Container Closure System of the API(S)

The container closure system for drug substance is a 10 L polycarbonate carboy sealed with a polypropylene screw cap closure containing a thermoplastic elastomer gasket. Specifications for the carboy and closure are listed in Table 6-1.

Table 6-1 Container closure specification

Parameter	Specification	Test Method
Carboy resin	Conforms to USP Class VI	Certificate of Conformance
Cap resin	Conforms to USP Class VI	Certificate of Conformance
Gasket resin	Conforms to USP Class VI	Certificate of Conformance
Dimensions	Wall thickness	Measurement
Visual	Free from visible contamination, damage or defects	Visual Inspection

USP = United States Pharmacopeia

The components of the drug substance container closure system are compliant with the respective United States Pharmacopeia (USP) and European Pharmacopoeia (PhEur) compendia. All container and closure system component materials passed the respective compendia testing ([3.2.S.6_ATO], Container Closure System).

Testing according to European Pharmacopoeia (PhEur) 3.2.2.1 (Plastic Containers for Aqueous Solutions for Infusion) was performed. Data in Table 6-2 demonstrate the physicochemical extraction characteristics of the container closure system. Carboy and closure component materials pass PhEur 3.2.2.1 testing.

2.3.1.7	Stability of the API(S) The stability studies described in this section were performed per the ICH Harmonized Tripartite Guide, *Stability Testing of Biotechnological/Biological Products* (Q5C) and *Stability Testing of New Drug Substances and Products (Q1A).* Stability studies are conducted at the recommended storage condition of -30□C □ 10□C and at elevated temperatures in order to assess the effect of these conditions on product quality. A description of the stability studies conducted and the analyses performed to establish drug substance expiry is provided in [3.2.S.7.1] (Stability Summary and Conclusions). Based on stability results collected to date, and as discussed and analyzed in the following sections, an expiry period of 36 months is proposed for AMG334 drug substance stored at the recommended storage condition of -30□C □ 10□C. **7.1 Stability Summary and Conclusions** The drug substance stability program currently consists of 7 lots stored at the recommended storage temperature of -30□C. The overall program includes four primary lots and three production lots. A summary of the drug substance lots in the stability program and the stability data currently available is provided in Table 7-1.
For PPB use only	
2.3.2	**OVERVIEW OF FINISHED PHARMACEUTICAL PRODUCT(S) [FPP(S)]**

2.3.2.1 Description and Composition of the FPP(S)

Description and composition of the drug product

The drug product is supplied as a sterile, single-use, preservative-free solution for SC injection in either a PFS or a prefilled AI/Pen. The AI/Pen is a disposable, handheld, mechanical (spring-based) delivery device that is provided ready-to-use, pre-assembled with the PFS.

Both presentations contain a 1.0 mL deliverable volume of 70 mg/mL AMG334 in 25 mM acetate, 7.3□ (w/v) sucrose, 0.010□ (w/v) polysorbate 80, pH 5.2. The primary container closure consists of a 1 mL Type I glass syringe with a staked-in-place stainless steel needle covered with an 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 dried natural rubber, protects the needle cannula, and may be supplemented with an outer plastic rigid cover (rigid needle shield or RNS). 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 closure system 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. The only difference between the RW needle used in the PFS and the STW needle used in the prefilled

AI/Pen configuration is that the STW needle has a larger needle inner diameter.

Table 1-1 Quantitative and qualitative composition of 1.0 mL of 70 mg/mL AMG334 drug product per prefilled syringe or auto-injector/pen

Component	Reference to Standard	Function	Concentration	Quantity (per dose)
AMG334	In house[a]	Active ingredient	70 mg/mL	70 mg
Sucrose	NF, PhEur, JP	Stabilizing agent and tonicity modifier	7.3% (w/v)	73 mg
Polysorbate 80	NF, PhEur, JP	Surfactant	0.010% (w/v)	0.10 mg
Glacial acetic acid	USP, PhEur, JP	Buffering agent	25 mM	1.5 mg
Sodium hydroxide	NF, PhEur, JP	pH adjusting agent	qs to target pH	qs to target pH
Water for injection	USP, PhEur, JP	Aqueous solvent	qs to target volume	qs to target volu

qs = quantum sufficit

[a] Tested to internal specifications (3.2.S.4.1, Specification).

2.3.2.2 Pharmaceutical Development of the FPP(S)

2.2.1 Formulation Development

Amgen focused on development of a liquid formulation with a high protein concentration, stable at 2□C to 8□C, and compatible with injection. The formulation development of the drug product is presented across three sections within the application, which are listed in Table 2-1.

Table 2-1 Summary of data presented within drug product formulation development

eCTD Section	Information Presented
3.2.P.2.2 (Formulation Development [70 mg/mL PFS])	Formulation Development History and Commercial Formulation Development. Robustness of the Formula in a PFS
3.2.P.2.2 (Overages [70 mg/mL PFS])	Confirmation that no overages are included in the PFS
3.2.P.2.2 (Physicochemical and Biological Properties [70 mg/mL PFS])	Physicochemical and biological properties of the commercial formulation in the PFS

Drug product developed for the initial clinical studies (Process 1 drug product) was supplied in a glass vial as a frozen liquid to minimize potential chemical and physical degradation. Both the Process 1 drug product, and the Process 1 drug substance from which it was produced, had the same formulation. The frozen liquid drug product consisted of 70 mg/mL AMG334 formulated with 10 mM sodium acetate, 9.0□ (w/v) sucrose, 0.004□ (w/v) polysorbate 20, pH 5.2 (Table 2-2). In order to provide the target dose for phase 3 clinical studies and in preparation for commercial use, Amgen developed both a revised drug substance formulation (Process 2 drug substance) and a revised drug product formulation, stable as a liquid at 2□C to 8□C. The drug product formulation is 70 mg/mL AMG334 formulated in 25 mM acetate, 7.3□ (w/v) sucrose,

0.010□ (w/v) polysorbate 80, pH 5.2. This formulation is intended to provide a sterile, preservative-free, dose of drug product for SC injection.

The commercial drug product presentation (Process 2 70 mg/mL drug product) consists of a liquid filled into a glass syringe. Both the PFS and AI/Pen presentations use 1 mL glass syringes that contain a 1.0 mL deliverable volume. The recommended drug product storage temperature is 2□C to 8□C.

A list of the drug product formulations and presentations used over the course of development is provided in Table 2-2.

Table 2-2 Comparison of drug product presentations

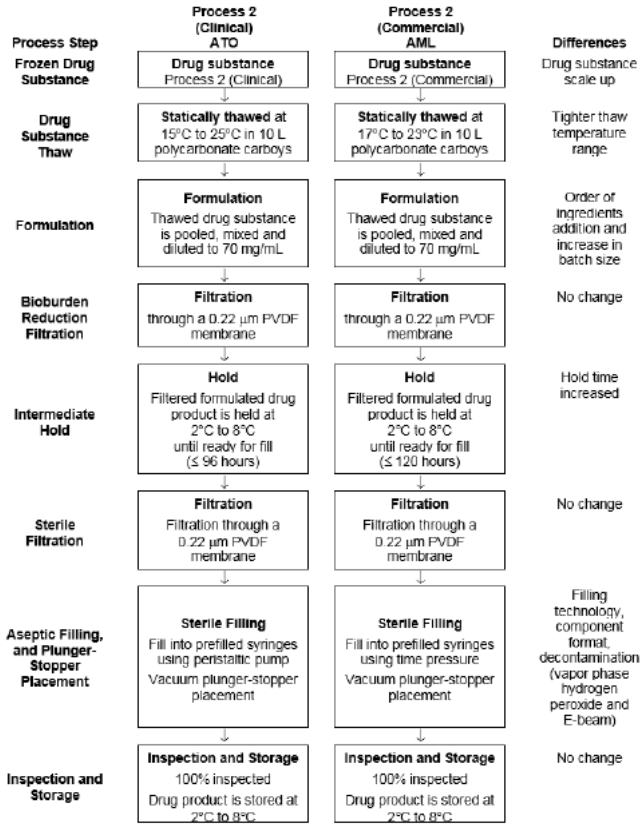
Parameter	Process 1 70 mg/mL DP	Process 2 70 mg/mL DP	
Drug substance	Process 1	Process 2	
Delivery method	IV, SC	SC	
Product presentation	70 mg glass vial	70 mg glass PFS, 70 mg AI/Pen	
Fill volume	1.0 mL	1.0 mL	
Protein concentration	70 mg/mL	70 mg/mL	
Buffer agent	10 mM sodium acetate[a]	15 mM sodium acetate[a]	25 mM acetate[b]
pH	5.2	5.2	
Tonicity agent viscosity modifier	9.0% (w/v) sucrose[a]	8.5% (w/v) sucrose[a]	7.3% (w/v) sucrose[b]
Surfactant	0.004% (w/v) polysorbate 20	0.010% (w/v) polysorbate 80	
Recommended storage temperature	−70°C to −20°C	2°C to 8°C	

[a] Excipient levels derived from process buffer targets – diafiltration buffer for Process 1, formulation buffer for Process 2.

2.3.2.3 Manufacture of the FPP(S)

The AMG334 drug product manufacturing process consists of the following unit operations: drug substance thaw, buffer formulation, drug product formulation, bioburden reduction filtration, filtered formulated drug product hold, sterile filtration, and filling into the final container closure system.

Figure 2-3 Clinical and commercial drug product manufacturing process flow comparison for prefilled syringes at ATO and AML



2.3.2.4 Control of Excipients for the FPP(S)

All excipients in the drug product formulation are specified in the current United States Pharmacopeia (USP), National Formulary (NF), European Pharmacopoeia (PhEur), or Japanese Pharmacopoeia (JP) as described in 3.2.P.4.1 (Specifications). The grades of excipients used in the drug product are provided in Table 4-1. Analytical procedures used to test the excipients are performed per current compendial methods (3.2.P.4.2, Analytical Procedures) and validation of the methods is therefore not required. There are no excipients of human or animal origin used in th manufacturing of AMG334 drug product. There are no
novel excipients in the drug product.

Table 4-1 AMG334 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

2.3.2.5 Control of the FPP(S)

5.1 Specifications

The specifications and test methods used to assure the quality of the prefilled syringe (PFS) drug product at release are listed in Table 5-1. The additional test methods and acceptance criteria used to assure the functionality of the AI/Pen at release are provided in Table 5-2.

Table 5-1 70 mg/mL prefilled syringe drug product specification

Parameter	Test Method	Method Type	Acceptance Criteria
Appearance	Appearance[a]	Visual	Liquid, practically free from particles
	Color[a]	Visual	≤ Y3 (colorless to light yellow)
	Clarity[a]	Spectrophotometric	≤ Reference III
Identity	ELISA	Immunoassay	Pass[b]
Purity and Impurities	CEX-HPLC	Chromatographic	26.5% to 33.6% acidic peaks
	SE-UHPLC	Chromatographic	≥ 98.6% main peak
			≤ 1.4% HMW species
	Reduced CE-SDS	Capillary electrophoresis	≥ 96.7% heavy chain + light chain
	HIC-HPLC	Chromatographic	≥ 96.3% main peak
			≤ 3.7% pre-peaks
Potency	Bioassay	Cell-based	70%to 130% relative potency
Quantity	Protein concentration[a]	UV Scan	63 to 77 mg/mL
	Deliverable volume[a]	Gravimetric	Pass (≥ 1.0 mL)
General	pH[a]	Potentiometric	4.9 to 5.5
	Osmolality[a]	Freezing point depression	250 to 350 mOsm/Kg
	Subvisible particles	Light obscuration	≤ 6000 particles ≥ 10 µm per container
			≤ 600 particles ≥ 25 µm per container
Adventitious Agents	Bacterial endotoxins[a]	LAL	≤ 0.25 EU/mg
	Sterility	Membrane filtration	Pass[c]

electrophoresis- sodium dodecyl sulfate; ELISA enzyme linked immunosorbent assay;
HIC-HPLC hydrophobic interaction chromatography high performance liquid chromatography; HMW
 high molecular weight; LAL limulus amebocyte lysate; SE-UHPLC size exclusion ultra high performance liquid chromatography; UV ultraviolet;
a Controlled by real time release testing (RTRT); complies, if tested
b "Pass" is defined as an optical absorbance signal to noise ratio for an individual sample replicate ≥ 10.0
c "Pass" is defined as no growth

Table 5-2 70 mg/mL AI/Pen drug product specification

Parameter	Test Method	Method Type	Acceptance Criteria
Device functionality	Injection time	Time measurement	≤ 15 seconds
	Deliverable volume	Gravimetric	Pass (≥ 1.0 mL)

5.2 Analytical Procedures

A summary of each analytical procedure is provided in 3.2.P.5.2 (Overview [70 mg/mL PFS]). Analytical procedures used to assess both drug substance and drug product are summarized in 3.2.S.4.2 (Analytical Procedures). Summaries of the analytical procedures used during development are provided in 3.2.P.5.4 (Analytical Methods Used During Development). Compendial methods are performed in accordance with current pharmacopoeia and were appropriately verified.

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. Method validation summaries for the analytical procedures specific to AMG334 drug product testing are provided in 3.2.P.5.3 (Overview [70 mg/mL PFS]) and 3.2.P.5.3 (Overview [70 mg/mL AI/Pen]). Validation of analytical procedures common to both drug substance and drug product lot release testing is summarized in 3.2.S.4.3 (Validation of Analytical Procedures). Validation summaries of analytical procedures used during development but not included on the commercial specification are provided in 3.2.S.4.4 (Validation of Analytical Procedures Used During Development) and 3.2.P.5.4 (Validation of Analytical Procedures Used During Development).

5.4 Batch Analyses

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

A summary of the sections and information provided is listed in Table 5-3. Validation lot provided in Table 5-4 and Table 5-5.

Table 5-3 Batch analyses summary

eCTD Section	Information Presented
3.2.P.5.4 (Batch Analyses [70 mg/mL PFS])	Batch analyses data for the 70 mg/mL PFS drug product lots manufactured from Process 2 (Clinical/Commercial) drug substance are provided. Lots were filled from Process 2 (Clinical) drug substance and used for process development, clinical and stability studies. Lots filled from Process 2 (Commercial) were used for validation (commercial), comparability, and stability studies.
3.2.P.5.4 (Batch Analyses [70 mg/mL AI/Pen])	Batch analyses data for the 70 mg/mL AI/Pen drug product lots manufactured from Process 2 (Clinical/Commercial) drug substance are provided. Lots were filled from Process 2 (Clinical) drug substance and used for clinical and stability studies. Lots were filled from Process 2 (Commercial) drug substance and used for validation (commercial lots), comparability and stability studies.
3.2.P.5.4 (Batch Analyses [140 mg/mL PFS])	Batch analyses data for the 140 mg/mL PFS drug product lots manufactured from Process 2 (Clinical) drug substance are provided. Lots were filled from Process 2 (Clinical) drug substance and the 140 mg/mL PFS was used for development, a single clinical study and stability studies.
3.2.P.5.4 (Batch Analyses [Process 1])	Batch analyses data from drug product lots manufactured from Process 1 drug substance are provided. Lots were used in nonclinical, clinical and stability studies as well as for an interim reference standard.

2.3.2.6	Reference Standards or Materials of the FPP(S) The same reference standard(s) are used for both AMG334 drug substance and drug product testing. Information regarding reference standard and suitability of a single reference standard for drug substance and drug product is included in 3.2.S.5 (Reference Standards or Materials).

2.3.2.7	Container Closure System of the FPP(S)

Primary Container Closure

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 barrel / plunger-stopper system is designed for minimal dead space to aid in a more consistent delivered dose. The stainless steel 27 gauge staked needle has two formats: 1) a regular wall (RW) needle and 2) a special thin wall (STW) needle, which has a larger inner diameter. The RW needle is used for the stand alone prefilled syringe (PFS) configuration, while the STW needle is used for the AI/Pen configuration. The elastomeric needle shield, which is formulated with dry natural rubber, protects the needle cannula and may be supplemented with an outer plastic rigid needle shield cover. The inner surface of the syringe barrel, the outer surface of needle and the plunger-stopper are coated with medical grade silicone oil to support the functionality of the syringe system. A plastic plunger rod is threaded into the plunger- stopper, and a flange extender is snapped onto the syringe for manual injection.

The syringe barrels, with staked needle and needle shield, are supplied pre-washed, siliconized, and ethylene oxide sterilized. The plunger-stopper is supplied pre-washed, siliconized, and sterilized by gamma radiation. The selection of the primary packaging components was based on results of various physical, chemical, and functional testing.

The syringe barrel and plunger-stopper comply with the requirements of the applicable USP, PhEur and JP monographs. Components are received, identified, sampled, quarantined, tested, and accepted or rejected according to written procedures

AI/Pen

The AMG334 70 mg/mL autoinjector/pen (AI/Pen) contains a Type 1 glass prefilled syringe (PFS). The PFS is the primary container closure system. The syringe system used for the 70 mg/mL prefilled AI/Pen assembly does not employ the additional outer rigid needle shield cover, the plunger rod or the flange extender.

The AI/Pen is a single-use, disposable, handheld, mechanical (spring-based) injection device which consists of a PFS contained within two subassemblies. The front subassembly is designed to hold the Type 1 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 2.2 kgf plunger spring. The components of the subassemblies do not come into contact with the AMG334 drug product.

The specifications for the syringe container closure components, which are contained within the AI/Pen, are located in 3.2.P.7 Container Closure System [70 mg/mL PFS]. Conformance of the AI/Pen to EN-ISO standards are provided in Device Design Verification [AI/Pen], summary of design validation and usability human factors studies (Device Design Validation [AI/Pen]).

7.2 Secondary Packaging

Plunger rods are assembled onto the PFS. The PFS are labeled and inspected for label presence, correct lot number, expiration date, and label material number. Upon completion of labeling, flange extenders are assembled onto 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.

The prefilled AI/Pens are assembled, labeled and inspected for label presence, correct lot number, expiration date, and label material number. The prefilled AI/Pens and inserts are placed into dispensing cartons. The carton protects the product from light as well as during shipping and storage.

2.3.2.8	Stability of the FPP(S) **Stability Summary and Conclusions** The stability studies were performed per the ICH Harmonized Tripartite Guidelines *Stability Testing of Biotechnological/Biological Products (Q5C)* and *Stability Testing of New Drug Substances and Products (Q1A)*. Based on stability data collected to date, an expiry period of 24 months is proposed for AMG334 drug product stored at the recommended storage temperature of 2□C to 8□C (referred to as 5□C). Additionally, to enhance convenience and facilitate dosing, storage for 14 days at up to 30□C is proposed. Three lots each of 70 mg/mL PFS and AI/Pen lots assembled with PFS drug product, lots filled from Amgen Singapore Manufacturing (ASM) drug substance were placed on stability at recommended storage condition of 2°C to 8°C and at elevated temperatures. A summary of the PFS and AI/Pen drug product lots in the stability program is provided in Table 8-1 and Table 8-2. The stability data is summarized below and further described in 3.2.P.8.1 (Stability Summary and Conclusion [70 mg/mL PFS]) and 3.2.P.8.1 Stability Summary and Conclusion [70 mg/mL AI/Pen]).
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For PPB use only	
For PPB use only	**OVERALL QUERIES AND RECOMMENDATIONS FOR THIS MODULE**
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DECLARATION BY AN APPLICANT

1. I, the undersigned certify that all the information in this application form and accompanying documentation is correct, complete and true to the best of my knowledge.
2. I further confirm that the information referred to in my application dossier is available for verification during current GMP inspection.
3. I agree that the undersigned has not marketed or advertised this product in Kenya and will follow the PPB requirements for advertisements of medicines
4. I also agree that the undersigned will implement a Pharmacovigilance plans for this product in accordance with PPB requirements
5. I also agree that I am obliged to follow the requirements of the Pharmacy and Poisons Act, which are related to pharmaceutical products.
6. I also consent to the processing of information provided by the Pharmacy and Poisons Board.

Name: **Dr. Alice Ngotho**
Position in the company: **Regulatory Affairs Manager**
Signature: ……
Date: **23/10/2019**
Official stamp:……..