5.01 ATOGEPANT, Tablet 60 mg, Aquipta®, Allergan Australia Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (STREAMLINED) listing for atogepant for the prophylaxis of adults with chronic or high frequency episodic migraine (HFEM) who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus galcanezumab.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients who have experienced at least 8 days of migraine headache days per month, over a period of at least 6 months, and have an inadequate response, intolerance, or a contraindication to at least three prophylactic migraine medications.
Intervention	Atogepant 60 mg once daily administered orally
Comparator	• Galcanezumab 240 mg loading dose followed by 120 mg monthly administered via subcutaneous injection and; • Fremanezumab 225 mg monthly administered via subcutaneous injection
Outcomes	Reduction in monthly migraine headache days, ≥50% reduction in monthly migraine headache days
Clinical claim	Atogepant is non-inferior in terms of efficacy and safety to galcanezumab and fremanezumab.

Source: Table 1-2, p5 of the submission.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. Atogepant was recommended for registration at the June ACM meeting for the following indication: 'prophylaxis of migraine in adults who have at least 4 migraine days per month'.

Previous PBAC consideration

2.2 Atogepant has not been previously considered by the PBAC.

2.3 Galcanezumab and fremanezumab are currently listed on the PBS as treatment for chronic migraine, defined as 'an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment', in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment.

2.4 In March 2022, the PBAC recommended that the chronic migraine indication for galcanezumab should be expanded to treatment-resistant migraine, which encompassed both chronic and HFEM in a single indication, with the clinical criteria for initiation amended to 'at least 8 days of migraine headache days per month, over a period of at least 6 months, prior to commencement of treatment' (paragraph 7.1, galcanezumab Public Summary Document (PSD), March 2022 PBAC meeting). The PBAC recommended that same changes to the restriction of fremanezumab in November 2022 (paragraph 7.1, fremanezumab PSD, November 2022 PBAC meeting). The ESC recalled the PBAC had previously considered galcanezumab and fremanezumab would be cost effective for the HFEM population at a price no higher than the effective price in chronic migraine (paragraph 7.1, fremanezumab PSD, November 2022 PBAC meeting). Neither galcanezumab nor fremanezumab were listed on the PBS for the expanded indication that includes HFEM at the time of the July 2023 PBAC meeting.

2.5 This submission sought reimbursement for atogepant under the amended clinical criteria (i.e., chronic and HFEM), on the assumption that galcanezumab and fremanezumab will be listed on the PBS for this broader population.

2.6 Rimegepant, an oral calcitonin gene-related peptide (CGRP) receptor antagonist, was also considered by the PBAC at the July 2023 meeting for the treatment of adults with acute migraine who have not responded adequately, are intolerant or contraindicated to treatment with at least two triptans.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ATOGEPANT					
Initial treatment					
atogepant 60 mg tablet, 28	$682.26 published price $[a] effective price	1	28	2	Aquipta
Continuing treatment					
atogepant 60 mg tablet, 28	$682.26 published price $[a] effective price	1	28	5	Aquipta

[a] The submission proposed that the effective price be calculated using the method outlined in Section 3 following a positive PBAC recommendation and sharing of the confidential effective price of the comparator (galcanezumab).

Category / Program: General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (STREAMLINED)
Severity: Treatment-resistant
Condition: Migraine
Indication: Treatment-resistant migraine
Treatment Phase: Initial treatment 1 (new patient)

Clinical criteria:
Patient must have experienced, at least 8 days of migraine headache days per month, over a period of at least 6 months, prior to commencement of treatment with this drug for this condition
AND
Clinical criteria:
Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with this drug for this condition
AND
Clinical criteria:
Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with this drug
Treatment criteria:
Must be treated by a neurologist
AND
Treatment criteria:
Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication
Population criteria:
Patient must be aged 18 years or older
Prescribing Instructions: Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate. AND Patient must have the number of migraine headache days per month documented in their medical records.

Category / Program: General Schedule
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required (STREAMLINED)
Severity: Treatment-resistant
Condition: Migraine
Indication: Treatment-resistant migraine
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine headache days per month
AND
Clinical criteria:
Patient must continue to be appropriately managed for medication overuse headache
Treatment criteria:
Must be treated by a neurologist
AND
Treatment criteria:
Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication
Population criteria:

Patient must be aged 18 years or older
Prescribing Instructions: Patient must have the number of migraine days per month documented in their medical records.

3.1 A Special Pricing Agreement (SPA) was requested for atogepant, with the effective approved ex-manufacturer price (AEMP) to be calculated using the proposed CMA and the effective price of galcanezumab.

3.2 The submission did not propose a grandfathering restriction, but it was noted that the proposed initial treatment restriction would allow patients receiving non-PBS subsidised atogepant to commence PBS-subsidised treatment.

3.3 The proposed restrictions were narrower than the draft TGA indication, which required patients to have at least four migraine days per month and did not require patients to have failed or be contraindicated to any prophylactic/preventive medications.

3.4 The proposed restrictions were not consistent with the clinical evidence, which included participants with episodic migraine who experience between four and seven migraine headache days and participants with chronic or episodic migraine who had failed less than three preventive medicines.

3.5 The ESC noted that the draft Product Information also included a 10 mg dose which was recommended for patients who use strong CYP3A4 or OATP inhibitors or have severe renal impairment.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 A migraine is characterised by moderate to severe attacks of unilateral pulsating head pain, associated with photophobia, phonophobia, nausea and/or vomiting, typically lasting four to 72 hours.[1] Classification of migraine disease activity is typically performed based on The International Classification of Headache Disorders 3rd Edition (ICHD-3).[3] Migraine is typically classified as occurring with or without aura.

4.2 Migraine can be further defined as chronic or episodic migraine. The ICHD-3 defined chronic migraine as 15 or more headache days per month with at least eight days meeting the criteria for migraine with or without aura. The ICHD-3 did not specifically define episodic migraine; however, other studies defined episodic migraine as those with migraine who have 14 or fewer headache days per month. Episodic migraine can be further defined as low-frequency episodic migraine and HFEM.

4.3 Migraine can be diagnosed by a general practitioner. Patients who have failed to respond to a therapeutic trial of multiple preventive medications and have a

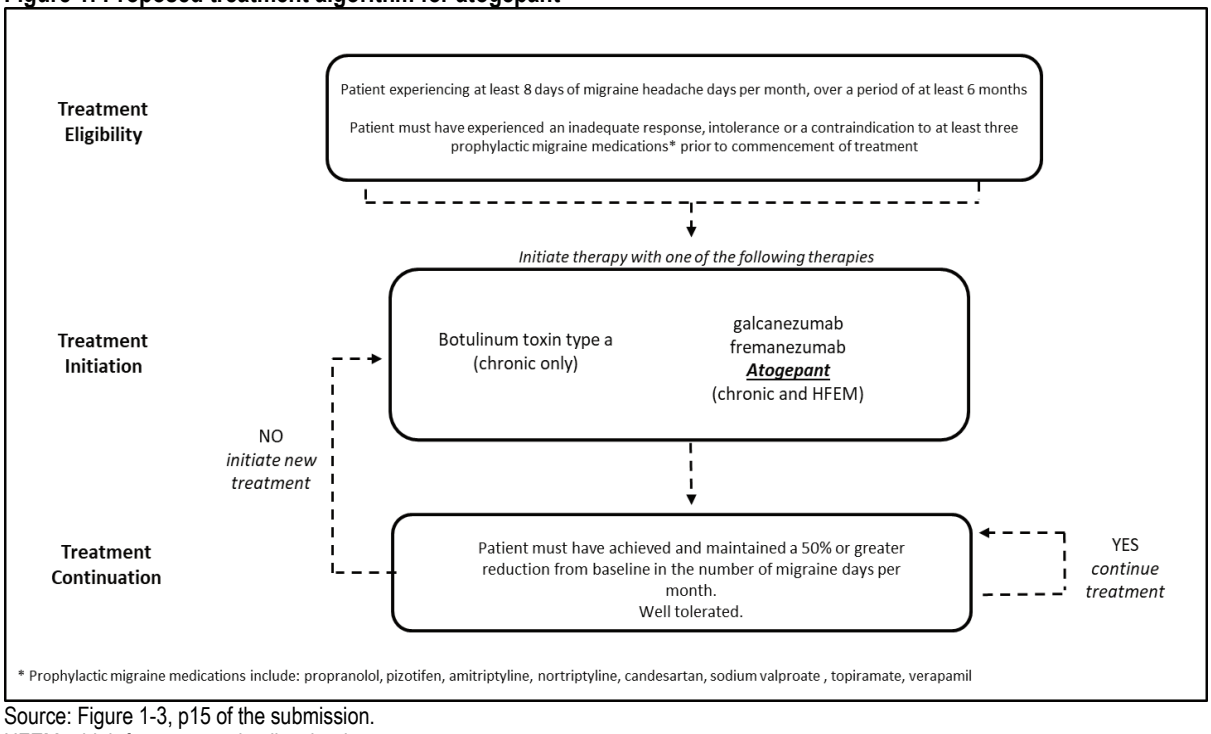
[1] International Headache Society from Headache Classification Committee of the International Headache Society (IHS) (2018) The International Classification of Headache Disorders, 3rd edition, Cephalalgia;38;1–211. https://journals.sagepub.com/doi/epub/10.1177/0333102413485658 [accessed 3 May 2023].

significant burden of symptoms or comorbid medication-overuse headaches, or patients for whom the diagnosis is uncertain, should be referred for shared management with a neurologist with expertise in headache or a tertiary headache clinic. Patients such as these are often managed collaboratively by their neurologists and general practitioners; however, only neurologists can prescribe PBS-subsidised botulinum toxin type A or CGRP inhibitors.

4.4 To be eligible for PBS-subsidised botulinum toxin type A or CGRP inhibitors, patients must have failed to achieve an adequate response to at least three prior preventive migraine medications (e.g., propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate). Once commenced on therapy, a patient must achieve and maintain a 50% or greater reduction from baseline in the number of migraine days per month after a specified period of time (12 weeks for CGRP inhibitors, 24 weeks for botulinum toxin type A) in order to be eligible for continuing PBS-subsidised treatment.

4.5 The submission proposed that atogepant be added as a therapy option for patients with chronic migraine and HFEM.

Figure 1: Proposed treatment algorithm for atogepant



Source: Figure 1-3, p15 of the submission.
HFEM = high frequency episodic migraine.

4.6 The submission noted that patients who do not meet the continuation criteria are currently able to initiate an alternative PBS treatment. The submission claimed that the availability of atogepant with its alternative mechanism of action and oral administration would lead to an increase in the amount of treatment sequencing that occurs compared with current practice. Additionally, the submission claimed that

eligible patients currently unsuitable for injections or needle phobic may seek treatment with atogepant if it listed on the PBS.

4.7 Atogepant is an orally administered, CGRP receptor antagonist. Atogepant competes with CGRP for occupancy at these receptors, preventing the actions of CGRP and its ability to induce and perpetuate migraine headache pain.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated galcanezumab and fremanezumab as the comparators for atogepant. The main arguments provided in support of this nomination were that they are the only PBS listed CGRP inhibitors for chronic migraine, with both recommended for PBS listing for the HFEM population. The submission noted that there is a difference in the mechanism of action with galcanezumab and fremanezumab molecules binding to the CGRP peptide and atogepant binding to the CGRP receptor. The ESC considered that the proposed comparators were appropriate.

5.2 The submission noted that eptinezumab was recommended for listing for the chronic migraine indication in July 2022 but is not currently listed on the PBS. The submission excluded eptinezumab as a comparator stating its uptake by general practitioners would be limited since it is administered as an intravenous infusion. Eptinezumab is an anti-CGRP antibody and was recommended on the basis of a cost-minimisation approach versus galcanezumab and fremanezumab. Eptinezumab could be considered a near market comparator for atogepant.

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is satisfied, it must make a statement to this effect.

5.4 For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: galcanezumab, fremanezumab in chronic migraine (and HFEM, should they be listed on the PBS for this indication and eptinezumab in chronic migraine should it be listed on the PBS).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (43), health care professionals and organisations (3) via the Consumer Comments facility on the PBS website. The comments from individuals and the consumer organisations, Migraine & Headache Australia and the Australian and New Zealand Headache Society, strongly supported the submission. They described the need for new and effective oral migraine treatments, the potential benefits of atogepant in preventing migraine pain and frequency and the decreased likelihood of side effects. The comments also described the effects of migraines on quality of life, including the debilitating effect of migraines and a decreased ability to work, study and socialise.

6.3 The PBAC noted the advice received from Migraine Australia which provided a detailed description of the impact of migraine and the available therapies. The advice also highlighted the importance of the availability of alternate and oral options for migraine prophylaxis and clarified the likely use of atogepant in clinical practice. The PBAC specifically noted the advice that the use of atogepant may improve the quality of life of migraine sufferers. The PBAC noted that this advice was supportive of the need for new migraine treatments

Clinical trials

6.4 No head-to-head trials were available comparing atogepant to galcanezumab or fremanezumab for chronic or episodic migraine. The submission was based on 14 clinical trials consisting of 16 trial populations (of which six were included for chronic migraine and ten for episodic migraine). An independent search using the submission's search terms located several potentially relevant trials. The atogepant ELEVATE trial (NCT04740827; available only as a conference abstract) may be of particular interest as it compared atogepant 60 mg to placebo in participants with episodic migraine who have previously failed two to four classes of oral preventive treatments. The Pre-Sub-Committee Response (PSCR) noted that the ELEVATE abstract was published after lodgement of the submission and stated that the data from the trial supported the efficacy and safety claims made in the submission.

6.5 The atogepant trials listed below compared atogepant 60 mg once daily to placebo, the galcanezumab trials compared galcanezumab 120 mg monthly to placebo, and the fremanezumab trials compared fremanezumab 675 mg every three months or 225 mg monthly to placebo. Many of the trials included additional arms that were not part of the application for PBS listing or not currently PBS listed (e.g., atogepant 30 mg once daily arm in the PROGRESS trial; galcanezumab 240 mg arm in the REGAIN trial). Results for medicine doses unrelated to this submission were not presented.

6.6 For the chronic migraine population (k=4,)):

- One randomised controlled trial of atogepant versus placebo in participants who had failed four or fewer preventive medications (two with different mechanisms of action (MoA)): PROGRESS.
- One randomised controlled trial of galcanezumab versus placebo in participants who had failed three or fewer preventive medication classes: REGAIN.
- Two randomised controlled trials of fremanezumab versus placebo in participants who had failed one or fewer preventive medication clusters: HALO-CM and NCT03303079.

6.7 For the episodic migraine population (k=8):

- One randomised controlled trial of atogepant versus placebo in participants who had failed three or fewer preventive medications (two with different MoA): ADVANCE.
- One randomised controlled trial of atogepant versus placebo in participants who had failed two or fewer preventive medications with different MoA: NCT02848326.
- Three randomised controlled trials of galcanezumab versus placebo in participants who had failed two or fewer preventive medication classes: EVOLVE-1, EVOLVE-2, PERSIST .
- One randomised controlled trial of galcanezumab versus placebo in participants who had failed two or fewer adequately dosed preventive treatments: NCT02959177.
- Two randomised controlled trials of fremanezumab versus placebo in participants who had failed one or fewer preventive medication clusters: HALO-EM and NCT03303092.

6.8 For both episodic and chronic migraine populations (k=2):

- One randomised controlled trial of galcanezumab versus placebo in participants who had failed two to four preventive medications: CONQUER.
- One randomised controlled trial of fremanezumab versus placebo in participants who had failed two to four preventive medications: FOCUS.

6.9 The trials differed in the number of prior preventive migraine treatments participants were required to have trialled. Additionally, there were differences between the trials in terms of how the number of prior treatments were considered i.e. mechanisms of action, class or clusters of treatments, which made it difficult to determine how many participants in each trial would be eligible or ineligible for treatment with atogepant under the proposed PBS listing.

6.10 The atogepant study 3101-302-002 (NCT03700320; not listed above) was not included in the efficacy analysis for episodic migraine as it did not measure comparative effectiveness; however, it was included as supporting evidence for safety.

6.11 The PBAC has not previously considered evidence from the atogepant trials, the galcanezumab PERSIST and NCT02959177 trials for episodic migraine, the fremanezumab NCT023303079 trial for chronic migraine or the HALO-EM and NCT03303092 trials for episodic migraine. Some of these trials were published after consideration of previous PBAC submissions, whereas others were excluded because the eligibility criteria (number of prior preventive treatments failed) did not align with the proposed PBS restriction.

6.12 When the CONQUER and FOCUS trials were presented for HFEM, subgroup analyses of participants with HFEM and participants with HFEM who had failed three or more prior therapies were presented as well as the whole trial populations (paragraph 6.24, galcanezumab (episodic migraine) PSD, November 2020 PBAC meeting; paragraphs 6.18 and 6.23, fremanezumab PSD, November 2022 PABC meeting)

6.13 The submission presented the results of pre-specified subgroup analyses from the atogepant PROGRESS trial for chronic migraine (age group, sex, race, body mass index (BMI), baseline migraine headache days, current and prior preventive migraine exposure). The submission presented limited results of subgroup analyses from the atogepant ADVANCE trial for episodic migraine (prior preventive migraine exposure). The clinical claim relied on these subgroup analyses to support the claims that patient characteristics and prior preventive migraine medication use were not treatment effect modifiers and thus, mitigate transitivity issues in the indirect treatment comparisons.

6.14 The submission stated that for the PROGRESS trial, the subgroup analysis for participants who had not responded to three or more preventive medications with different mechanisms of action was not presented as there were less than five participants within that subgroup. The submission did not provide subgroup analyses to align the atogepant trials with the proposed PBS listing (patients experiencing at least eight migraine headache days per month who have experienced an inadequate response, intolerance, or a contraindication to at least three preventive migraine medications prior to commencement of treatment with atogepant, galcanezumab, or fremanezumab).

6.15 The submission presented four indirect comparisons comparing atogepant with galcanezumab and fremanezumab for chronic and episodic migraine using the Bucher method and placebo as the common reference group. This evidence was presented to support the claim of non-inferior effectiveness.

6.16 The submission also presented the following meta-analyses of the primary and key secondary endpoints of the trials by CRGP inhibitor for both chronic and episodic migraine:

- Primary endpoint (change from baseline in mean monthly migraine days) for the whole trial populations.
- Primary endpoint (change from baseline in mean monthly migraine days) for the chronic migraine trial populations or subpopulations only, or episodic migraine trial populations or subpopulations only.
- Key secondary endpoint (≥50% reduction in monthly migraine) for the whole trial populations.

6.17 The results of the meta-analyses were presented to support a claim of a class effect across CGRP inhibitors. The presence of a class effect does not necessarily support a claim of non-inferiority (as discussed in paragraph 6.37).

6.18 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Atogepant versus placebo		
Chronic Migraine		
PROGRESS 3101-303-002 NCT03855137	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Atogepant for the Prevention of Chronic Migraine (PROGRESS).	April 2022
Episodic migraine		
ADVANCE 3101-301-002 NCT03777059	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine (ADVANCE). Ailani J, Lipton RB, Goadsby PJ et al. ADVANCE Study Group. Atogepant for the Preventive Treatment of Migraine Schwedt TJ, Lipton RB, Ailani J et al. Time course of efficacy of atogepant for the preventive treatment of migraine: Results from the randomized, double-blind ADVANCE trial Lipton RB, Pozo-Rosich P, Blumenfeld AM et al. Rates of Response to Atogepant for Migraine Prophylaxis Among Adults: A Secondary Analysis of a Randomized Clinical Trial	October 2020 *NEJM* 19 Aug 2021; 385(8): 695-706. *Cephalalgia* Jan 2022; 42(1): 3-11. *Journal of American Medical Association Network Open* Jun 2022; 5(6): e2215499.
NCT02848326	A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study To Evaluate The Efficacy, Safety, And Tolerability Of Multiple Dosing Regimens Of Oral AGN-241689 In Episodic Migraine Prevention Goadsby PJ, Dodick DW, Ailani J et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial	August 2019 *Lancet Neurology* Sep 2020; 19(9): 727-737.
Galcanezumab versus placebo		
Chronic migraine		
REGAIN NCT02614261	Detke HC, Goadsby PJ, Wang S et al. Galcanezumab in chronic migraine The randomized, double-blind, placebo-controlled REGAIN study	*Neurology* December 11 2018; 91(24): 2211-2221.

Trial ID	Protocol title/ Publication title	Publication citation
	Ruff DD, Ford JH, Tockhorn-Heidenreich A et al. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure	*Cephalalgia* July 2019; 39(8): 931-944.
	Ford J, Tassorelli C, Leroux E et al. Changes in patient functioning and disability: results from a phase 3, double-blind, randomized, placebo-controlled clinical trial evaluating galcanezumab for chronic migraine prevention (REGAIN)	*Quality of Life Research* Jan 2021; 30(1): 105-115.
	Tobin JA, Joshi S, Ford JH et al. Reductions in acute medication use and healthcare resource utilization in patients with chronic migraine: a secondary analysis of a phase 3, randomized, double-blind, placebo-controlled study of galcanezumab with open-label extension (REGAIN)	*Journal of Medical Economics* Jan-Dec 2022; 25(1): 1030-1038.
	Pozo-Rosich P, Detke HC, Wang S et al. Long-term treatment with galcanezumab in patients with chronic migraine: results from the open-label extension of the REGAIN study	*Current Medical Research Opinion* May 2022; 38(5): 731-742.
Episodic migraine		
EVOLVE-1 NCT02614183	Stauffer VL, Dodick DW, Zhang Q et al. Evaluation of Galcanezumab for the Prevention of Episodic Migraine The EVOLVE-1 Randomized Clinical Trial	*JAMA Neurology* 2018; 75(9): 1080-1088.
EVOLVE-2 NCT02614196	Skljarevski V, Matharu M, Millen BA et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial	*Cephalalgia An International Journal of Headache* 2018; 38(8): 1442-1454.
PERSIST NCT03963232	Hu B, Li G, Li X et al. Galcanezumab in episodic migraine: the phase 3, randomized, double-blind, placebo-controlled PERSIST study	*Journal of Headache and Pain* Jul 2022; 23(1): 90.
NCT02959177	Sakai F, Ozeki A, Skljarevski V. Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: A phase 2 randomized controlled clinical trial	*Cephalalgia Reports,* 2020; 3: 1-10.
	Igarashi H, Shibata M, Ozeki A et al. Early Onset and Maintenance Effect of Galcanezumab in Japanese Patients with Episodic Migraine	*Journal of Pain Research* Nov 2021; 14: 3555-3564.
Chronic and episodic migraine		
CONQUER NCT03559257	Mulleners WM, Kim B-K, Lainez MJA et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial	*Lancet Neurology* 2020; 19: 814-25.
	Kuruppu DK, Tobin J, Dong Y et al. Efficacy of galcanezumab in patients with migraine who did not benefit from commonly prescribed preventive treatments	*BMC Neurology* April 2021; 21(1): 175.
	Schwedt TJ, Kuruppu DK, Dong Y et al. Early onset of effect following galcanezumab treatment in patients with previous preventive medication failures	*Journal of Headache and Pain* March 2021; 22(1):15.
	Reuter U, Lucas C, Dolezil D et al. Galcanezumab in Patients with Multiple Previous Migraine Preventive Medication Category Failures: Results from the Open-Label Period of the CONQUER Trial	*Advanced Therapies* Nov 2021; 38(11): 5465-5483.
	Okonkwo R, Tockhorn-Heidenreich A, Stroud C et al. Efficacy of galcanezumab in patients with migraine and history of failure to 3-4 preventive medication categories: subgroup analysis from CONQUER study	*Journal of Headache and Pain* Sep 2021; 22(1): 113.

Trial ID	Protocol title/ Publication title	Publication citation
	Stauffer VL, Wang S, Voulgaropoulos M et al. Effect of Galcanezumab Following Treatment Cessation in Patients With Migraine: Results From 2 Randomized Phase 3 Trials	*Headache* Jun 2019; 59(6): 834-847.
	Tepper SJ, Ailani J, Ford JH et al. Effects of Galcanezumab on Health-Related Quality of Life and Disability in Patients with Previous Failure of 2-4 Migraine Preventive Medication Categories: Results from a Phase IIIb Randomized, Placebo-Controlled, Multicenter Clinical Trial (CONQUER)	*Clinical Drug Investigation* Mar 2022; 42(3): 263-275.
	Ambrosini A, Estemalik E, Pascual J et al. Changes in acute headache medication use and health care resource utilization: Results from a randomized, double-blind, placebo-controlled clinical trial evaluating galcanezumab in adults with treatment-resistant migraine (CONQUER)	*Journal of Managed Care and Specialty Pharmacy* Jun 2022; 28(6): 645-656.
Fremanezumab versus placebo		
Chronic migraine		
HALO-CM NCT02621931	Silberstein SD, Dodick DW, Marcelo EB et al. Fremanezumab for the Preventive Treatment of Chronic Migraine	*NEJM* 2017; 377: 2113-2122.
	Lipton RB, Cohen JM, Galic M et al. Effects of fremanezumab in patients with chronic migraine and comorbid depression: Subgroup analysis of the randomized HALO CM study	*Headache* Apr 2021; 61(4): 662-672.
	Lipton RB, Cohen JM, Gandhi SK et al. Effect of fremanezumab on quality of life and productivity in patients with chronic migraine	*Neurology* Aug 2020; 95(7): e878-e888.
	Goadsby PJ, Silberstein SD, Yeung PP et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study	*Neurology* Nov 2020; 95(18): e2487-e2499.
NCT03303079	Sakai F, Suzuki N, Kim BK et al. Efficacy and safety of fremanezumab for chronic migraine prevention: Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients	*Headache* Jul 2021; 61(7): 1092-1101.
Episodic migraine		
HALO-EM NCT02629861	Dodick DW, Silberstein SD, Bigal ME et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine A Randomized Clinical Trial	*JAMA* 2018; 319: 1999-2008.
	Brandes JL, Kudrow D, Yeung PP et al. Effects of fremanezumab on the use of acute headache medication and associated symptoms of migraine in patients with episodic migraine	*Cephalalgia* Apr 2020; 40(5): 470-477.
NCT03303092	Sakai F, Suzuki N, Kim BK et al. Efficacy and safety of fremanezumab for episodic migraine prevention: Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients	*Headache* Jul 2021; 61(7): 1102-1111.
Chronic and episodic migraine		
FOCUS NCT03308968	Ferrari MD, Diener HC, Xiaoping N et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial	*The Lancet* 2019; 394: 1030-40.
	Ashina M, Cohen JM, Galic M et al. Efficacy and safety of fremanezumab in patients with episodic and chronic migraine with documented inadequate response to 2 to 4 classes of migraine preventive medications over 6 months of treatment in the phase 3b FOCUS study	*Journal of Headache and Pain* 10 July 2022; 22: 68.

Trial ID	Protocol title/ Publication title	Publication citation
	Spierings ELH, Ning X, Ramirez Campos V et al. Improvements in quality of life and work productivity with up to 6 months of fremanezumab treatment in patients with episodic and chronic migraine and documented inadequate response to 2 to 4 classes of migraine-preventive medications in the phase 3b FOCUS study	*Headache* Oct 2021*; 61: 1376-1386.*
	Pazdera L, Cohen JM, Ning X et al. Fremanezumab for the Preventive Treatment of Migraine: Subgroup Analysis by Number of Prior Preventive Treatments with Inadequate Response	*Cephalalgia* Sep 2021; 41: 1075-1088.
	Spierings ELH, Kärppä M, Ning X et al. Efficacy and safety of fremanezumab in patients with migraine and inadequate response to prior preventive treatment: subgroup analyses by country of a randomized, placebo-controlled trial	*Journal of Headache and Pain* Apr 2021; 22(1): 26.
	MaassenVanDenBrink A, Terwindt GM, Cohen JM et al. Impact of age and sex on the efficacy of fremanezumab in patients with difficult-to-treat migraine: results of the randomized, placebo-controlled, phase 3b FOCUS study	*Journal of Headache and Pain* Dec 2021; 22(1): 152.
	Lampl C, Rapoport AM, Cohen JM et al. Efficacy and quality-of-life improvements with fremanezumab treatment in patients with difficult-to-treat migraine with associated neurological dysfunction	*European Journal of Neurology* Jul 2022; 29(7): 2129-2137.

Source: Tables 2-3 and 2-4, pp29-33 of the submission.

6.19 The key features of the included evidence for chronic migraine are summarised in the table below.

Table 3: Key features of the included evidence – indirect comparison (chronic migraine)

Trial	n[a]	Design/ duration	Risk of bias	Patient population	Outcomes
Atogepant vs. placebo					
PROGRESS	521	R, DB, MC 12 weeks	Low	Failed ≤4 preventive medications (2 with different MoA), no concomitant preventive medications	1˚: Change from baseline in mean monthly migraine days 2˚: ≥50% reduction from baseline in mean monthly migraine days; Other clinical assessments; QoL, Safety
Galcanezumab vs. placebo					
REGAIN	838	R, DB, MC 3 months	Low	Failed ≤3 preventive medication classes	Same as PROGRESS
CONQUER	463	R, DB, MC 3 months	Low	CM and EM, failed 2 to 4 preventive medications, no concomitant preventive medications	Same as PROGRESS
Meta-analysis	1,273	(1) Included REGAIN and CONQUER whole trial populations (2) included REGAIN and CONQUER and CM populations/subpopulations only			
Fremanezumab vs. placebo					
FOCUS	838	R, DB, MC 12 weeks	Low	CM and EM, failed 2 to 4 preventive medications, no concomitant triptans or ergots	Same as PROGRESS
HALO-CM	1,130	R, DB, MC 12 weeks	Low	Failed ≤1 preventive medication cluster, up to one concomitant preventive medication	1˚: Change from baseline in mean monthly headache days 2˚: Change from baseline in mean monthly migraine days; Other clinical assessments; QoL, Safety
NCT03303079	571	R, DB, MC 12 weeks	Low	Failed ≤1 preventive medication cluster, concomitant treatment not discussed in submission	
Meta-analysis	845	(1) Included FOCUS, HALO-CM and NCT03303079 whole trial populations (2) included FOCUS, HALO-CM and NCT03303079 and CM populations/subpopulation only; (3) sensitivity analyses removed the FOCUS trial to reduce heterogeneity.			

Source: Tables 2-6, 2-8 & 2-16, pp37, 39-43, 50-51 & 75 of the submission; Figure 2-7, p120 of the submission; Attachment 2.5 of the submission.

1˚ = primary; 2˚ = secondary; CM = chronic migraine; DB = double blind; EM = episodic migraine; MC = multi-centre; MoA = mechanism of action; QoL = quality of life; R = randomised

[a] number of participants in the trial arms relevant to the submission, not necessarily the total number of trial participants

6.20 The key features of the included evidence for episodic migraine are summarised in the table below. Episodic migraine was consistently defined as a migraine headache with or without aura occurring on 4-14 days per month in all trials.

Table 4: Key features of the included evidence – indirect comparison (episodic migraine)

Trial	n[a]	Design/ duration	Risk of bias	Patient population	Outcomes
Atogepant vs. placebo					
ADVANCE	458	R, DB, MC 12 weeks	Low	Failed ≤4 preventive medications (2 different MoA), no concomitant preventive medications	1˚: Change from baseline in mean monthly migraine days 2˚: ≥50% reduction from baseline in mean monthly migraine days; Other clinical assessments; QoL, Safety
NCT02848326	373	R, DB, MC 12 weeks	Low	Failed ≤2 preventive medications with different MoA, no concomitant preventive medications	Same as ADVANCE
Meta-analysis	700	(1) Included ADVANCE and NCT02848326 whole trial populations (2) included ADVANCE and NCT02848326 EM populations/subpopulations only			
Galcanezumab vs. placebo					
EVOLVE-1	648	R, DB, MC 6 months	Low	Failed ≤2 preventive medication classes, no concomitant preventive medications	Same as ADVANCE
EVOLVE-2	696	R, DB, MC 6 months	Low	Same as EVOLVE-1	Same as ADVANCE
CONQUER	463	R, DB, MC 3 months	Low	CM and EM, failed 2 to 4 preventive medications, no concomitant preventive medications	Same as ADVANCE
PERSIST	520	R, DB, MC 6 months	Low	Same as EVOLVE-1	Same as ADVANCE
NCT03959177	345	R, DB, MC 6 months	Low	Failed ≤2 preventive medications, concomitant treatment not discussed in submission	Same as ADVANCE
Meta-analysis	2,654	(1) Included EVOLVE-1, EVOLVE-2, CONQUER, PERSIST and NCT03959177 whole trial populations (2) included EVOLVE-1, EVOLVE-2, CONQUER, PERSIST and NCT03959177 EM populations/subpopulations only			
Fremanezumab vs. placebo					
HALO-EM	875	R, DB, MC 12 weeks	Low	Failed ≤1 preventive medication cluster, concomitant medications permitted	Same as ADVANCE
FOCUS	838	R, DB, MC 12 weeks	Low	CM and EM, failed 2 to 4 preventive medications, no concomitant triptans or ergots	Same as ADVANCE
NCT03303092	357	R, DB, MC 12 weeks	Low	Failed ≤1 preventive medication cluster, concomitant treatment not discussed in submission	Same as ADVANCE
Meta-analysis	1,384	(1) Included HALO-EM, FOCUS and NCT03303092 whole trial populations (2) included HALO-EM, FOCUS and NCT03303092 EM populations/subpopulations only; (3) sensitivity analyses removed the FOCUS trial to reduce heterogeneity.			

Source: Tables 2-7, 2-9 & 2-17, pp44-49, 52-54 & 78-79 of the submission; Figure 2-13, p129 of the submission; Attachment 2.5 of the submission.

1˚ = primary; 2˚ = secondary; CM = chronic migraine; DB = double blind; EM = episodic migraine; MC = multi-centre; MoA = mechanism of action; QoL = quality of life; R = randomised.

[a] number of participants in the trial arms relevant to the submission, not necessarily the total number of trial participants

6.21 All the episodic migraine trials included participants with less severe disease (four to 14 migraine days per month) than the proposed PBS population (at least eight days of migraine headache per month).

6.22 The key differences between the trials for chronic migraine were:

- The fremanezumab FOCUS trial included participants experiencing chronic and episodic migraine, with outcomes presented for the combined population based on published data.
- The number of prior prophylactic migraine treatments. The mean (SD) number of prior prophylactic medications failed in the atogepant PROGRESS trial ranged between 1.5 (1.0) and 1.6 (1.0), compared with between 3.8 (1.9) and 4.0 (2.2) in the galcanezumab CONQUER trial (chronic migraine subpopulation). Mean prior prophylactic medications failed was not reported for the other trials included for chronic migraine.
- Baseline monthly migraine headache days, with participants in the fremanezumab FOCUS trial modified intention to treat (mITT) population experiencing fewer migraine headache days. Mean (SD) monthly migraine headache days ranged between 14.1 (5.6) days and 14.3 (6.1) days in the FOCUS trial and 15.2 (5.0) days and 19.6 (4.6) days in the other trials included for chronic migraine.
- Baseline monthly headache days, with participants in the fremanezumab FOCUS trial mITT population experiencing fewer headache days. Mean (SD) monthly headache days ranged between 12.4 (5.8) days and 12.8 (5.9) days in the FOCUS trial and 13.1 (7.2) days and 21.6 (4.1) days in the other trials included for chronic migraine.
- Baseline acute medication use days, with participants in the fremanezumab FOCUS trial mITT population experiencing fewer acute medication use days. Mean (SD) monthly acute medication use days ranged between 12.2 (6.0) days and 12.8 (6.2) days in the FOCUS trial and 13.0 (6.9) days and 16.4 (6.0) days in the other trials included for chronic migraine. The fremanezumab NCT03303079 trial did not report monthly acute medication use days.
- Whether the TGA-approved dose was used, with participants in the fremanezumab 225 mg monthly arms of the HALO-CM, FOCUS and NCT03303079 trials receiving a loading dose.
- Concomitant preventive migraine medication use, with participants in the atogepant PROGRESS trial receiving less concomitant preventive treatment. Between 9% and 12% of participants in the atogepant PROGRESS trial received concomitant preventive treatment compared with between 13% and 15% in the galcanezumab REGAIN trial and 20% and 22% in the fremanezumab HALO-CM trial. The galcanezumab CONQUER trial did not permit concomitant preventive treatment and the fremanezumab FOCUS trial did not permit concomitant use of triptans/ergots as a preventive treatment for migraine.
- Definition of a migraine day based on duration of headache, ranging from 30 minutes or more in the galcanezumab REGAIN and CONQUER trials to two hours or more in the PROGRESS trial and four consecutive hours in the fremanezumab HALO-CM, FOCUS, and NCT03303079 trials.

6.23 The key differences across the trials for episodic migraine were:

- The fremanezumab FOCUS trial included participants experiencing chronic and episodic migraine, with outcomes presented for the combined population based on published data.
- The percentage of participants who had failed prior prophylactic migraine treatments. Fewer participants in the atogepant NCT02848326 trial and the fremanezumab HALO-EM trial had previously failed preventive migraine treatments (between 27% and 29% and between 18% and 22% respectively). This compared with between 70% and 72% in the atogepant ADVANCE trial, 43% to 46% in the galcanezumab PERSIST trial and 100% in the galcanezumab CONQUER and fremanezumab FOCUS trials. The NCT03303092 trial did not report the percentage of participants who had received prior preventive treatment.
- The mean migraine illness duration, with participants in the galcanezumab PERSIST trial had a shorter migraine illness duration. The mean (SD) migraine illness duration ranged from 12.4 (8.2) years to 12.8 (9.2) years in the PERSIST trial, compared with between 18.3 (11.4) years in of the fremanezumab NCT03303092 trial and 22.9 (13.1) years in the galcanezumab CONQUER trial (episodic migraine subpopulation).
- Baseline monthly migraine headache days, with participants in the fremanezumab FOCUS trial mITT population experiencing more migraine headache days. Mean (SD) monthly migraine headache days ranged between 14.1 (5.6) days and 14.3 (6.1) days in the FOCUS trial and 6.3 (3.2) days and 9.5 (3.0) days in the other trials included for episodic migraine.
- Concomitant preventive migraine medication use, with participants in the fremanezumab HALO-EM and NCT03303092 trials receiving more concomitant preventive treatment. Concomitant preventive medication use was not allowed in the atogepant ADVANCE and NCT02848326 trials, EVOLVE-1, CONQUER, PERSIST, and NCT02959177 trials, or the fremanezumab FOCUS trial but was permitted in the fremanezumab HALO-EM trial (used by between 20% and 21% of participants) and NCT03303092 trial (used by 19% to 20% of participants).

6.24 The submission stated that the PBAC had previously accepted a minimally clinically important difference (MCID) for a reduction in monthly migraine days of at least two days in the evaluation of fremanezumab for chronic migraine (paragraph 6.13, fremanezumab PSD, November 2019 PBAC meeting) and galcanezumab and fremanezumab as treatment for HFEM (paragraph 6.17, galcanezumab PSD, November 2020 PBAC meeting; paragraph 6.16, fremanezumab PSD, November 2022 PBAC meeting). Based on this MCID, the submission proposed a non-inferiority margin for a reduction in monthly migraine days in patients of two days for both chronic migraine and HFEM. The submission did not present a comparison of this outcome for the HFEM population.

6.25 The submission proposed different MCIDs for the patient relevant outcome of headache impact test-6 (HIT-6) for chronic and episodic migraine. For chronic migraine, the submission proposed a MCID of -2.3 based on a study by Coeytaux (2006). For episodic migraine, the submission proposed an MCID of -2.5 based on a trial by Smelt (2014). The PBAC has previously considered the MCID by Coeytaux (2006) (Section 8, Botulinum toxin type A PSD, July 2012 PBAC meeting).

Comparative effectiveness

Chronic migraine

6.26 Table 5 presents the results of the key primary and secondary continuous outcomes for chronic migraine in the atogepant PROGRESS trial.

Table 5: Summary of key primary and secondary outcome results at 12 weeks from the atogepant PROGRESS trial (MMRM analysis): continuous data with outcome presented as change from baseline

Trial ID	Treatment arms	Atogepant			Placebo			Mean difference	
		N	Mean baseline (SD)	Mean change, LSM [SE]	N	Mean baseline, (SD)	Mean change, LSM [SE]	LSMD (95%CI)	p-value
Change from baseline in mean monthly migraine days									
PROGRESS	ATOG 60 mg vs. PBO	256	19.16 (5.280)	-6.88 [0.406]	246	18.95 (4.775)	-5.05 [0.411]	**-1.82 (-2.89, -0.75)**	**0.0009**
Change from baseline in mean monthly headache days									
PROGRESS	ATOG 60 mg vs. PBO	256	21.52 *(4.319)*	-7.00 [0.401]	246	21.40 *(4.101)*	-5.13 [0.405]	**-1.87 (-2.93, -0.81)**	**0.0005** ***0.0009***
Change from baseline in mean monthly acute medication use days									
PROGRESS	ATOG 60 mg vs. PBO	256	15.46 *(7.377)*	-6.23 [0.386]	246	15.42 *(6.991)*	-4.10 [0.392]	**-2.13 (-3.13, -1.13)**	**<0.0001** ***0.0009***
Change from baseline in MSQ v2.1 RFR Score									
PROGRESS	ATOG 60 mg vs. PBO	256	43.56 (18.907)	23.33 [1.365]	246	43.55 (19.047)	17.18 [1.381]	**6.15 (2.51, 9.79)**	**0.0009**
Change from baseline in mean AIM-D (performance of daily activities)									
PROGRESS	ATOG 60 mg vs. PBO	256	31.18 (16.470)	-12.82 [0.718]	246	29.50 (13.733)	-9.44 [0.720]	**-3.38 (-5.27, -1.49)**	**0.0005** ***0.0009***
Change from baseline in mean AIM-D (physical impairment domain)									
PROGRESS	ATOG 60 mg vs. PBO	256	27.11 (16.630)	-10.63 [0.665]	246	25.24 (13.522)	-7.92 [0.667]	**-2.71 (-4.47, -0.96)**	**0.0025**
Change from baseline in mean HIT-6									
PROGRESS	ATOG 60 mg vs. PBO	256	64.26 (5.005)	-7.94 [0.513]	246	64.08 (4.768)	-5.17 [0.520]	**-2.77 (-4.14, -1.40)**	**<0.0001**

Source: Table 2-22, pp86-87 of the submission; Tables 14, 19 & 21 of the PROGRESS CSR. **Bold** indicates statistically significant results. *Italicised text (p-values with multiplicity adjustment) added during the evaluation. Change from baseline in mean HIT-6 was assessed without adjusting for multiplicity so is nominally significant.*

AIM-D = activity impairment in migraine diary; ATOG = Atogepant; CI = confidence interval; HIT-6 = headache impact test-6; LSM = least-squares mean; LSMD = least-squares mean difference; MMRM = mixed model for repeated measure; MSQ-RFR = Migraine-Specific Quality of Life Questionnaire version 2.1 – role function-restrictive domain score; N = total participants in group; PBO = placebo; SD = standard deviation; SE = standard error.

6.27 The whole trial analysis of the atogepant PROGRESS trial indicated that atogepant was superior to placebo in terms of the primary outcome (change of mean monthly migraine days) and the majority of secondary outcomes. The mean difference in

reduction in monthly migraine days (-1.87; 95% CI: -2.93, -0.81) did not meet the MCID of two days proposed by the submission.

6.28 The submission stated that the comparative improvement in the change from baseline in the HIT-6 score of -2.77 (95% CI: -4.14, -1.40) between atogepant and placebo was above the MCID of -2.3 for chronic migraine, demonstrating a clinically meaningful improvement in headache-specific quality of life with atogepant treatment. The upper 95% bound (-1.40) of the improvement in HIT-6 was less than the MCID of -2.3, suggesting that the improvement was potentially not clinically significant. The change from baseline in HIT-6 was not relied upon for the clinical claim.

6.29 The submission also presented results for response, defined as a ≥50% reduction in mean monthly migraine days as a dichotomous outcome for the PROGRESS trial (not presented above). A statistically significant higher proportion of participants achieved a ≥50% reduction in monthly migraine days with atogepant 60 mg once daily (105/256; 41.0%) compared with placebo (64/246; 29.2%) with an odds ratio of 2.04 (95% Confidence Interval [CI]: 1.38, 3.00; p=0.0003).

6.30 Table 6 presents results for change from baseline in mean monthly migraine days for the whole trial populations and subgroup analyses based on the number of current or prior migraine prevention medication failures.

Table 6: Results of change in mean monthly migraine days at 12 weeks/three months for participants with chronic migraine (whole trial and subgroup analyses): continuous data with outcome presented as change from baseline

Trial ID/ Subgroup	Treatment arms	CGRP inhibitor			Placebo			Mean difference[a] (95%CI)
		N	Mean baseline (SD)	Mean change [SE][a]	N	Mean baseline (SD)	Mean change [SE][a]	
Whole trial population								
PROGRESS	ATOG 60 mg vs. PBO	256	19.2 (5.3)	-6.9 [0.41]	246	19.0 (4.8)	-5.5 [0.4]	**-1.8 (-2.9, -0.8)**
REGAIN	GAL 120 mg vs. PBO	273	19.4 (4.3)	-4.8 [0.4]	538	19.6 (*4.6*)	-2.7 [0.4]	**-2.1 (-2.9, -1.3)**
CONQUER	GAL 120 mg vs. PBO	232	13.4 (6.1)	-4.1 [0.3]	230	13.0 (5.7)	-1.0 [0.3]	**-3.1 (-3.9, -2.3)**
HALO-CM	FREM 675 mg vs. PBO	375	16.2 (4.9)	-4.9 [0.4]	371	16.4 (5.2)	-3.2 [0.4]	**-1.7 (-2.5, -0.9)**
	FREM 225 mg vs. PBO[b]	375	16.0 (5.2)	-5.0 [0.4]	371	16.4 (5.2)	-3.2 [0.4]	**-1.8 (-2.6, -1.0)**
FOCUS	FREM 675 mg vs. PBO	276	14.1 (5.6)	-3.7 [0.3]	279	14.3 (6.1)	-0.6 [0.3]	**-3.1 (-3.8, -2.4)**
	FREM 225 mg vs. PBO[b]	283	14.1 (5.6)	-4.1 [0.3]	279	14.3 (6.1)	-0.6 [0.3]	**-3.5 (-4.2, -2.8)**
NCT03303079[c]	FREM 675 mg vs. PBO	189	15.2 (5.0)	-4.1 [0.4] *-4.1 [0.5]*	190	15.4 (5.0)	-2.4 [0.4] *-2.8 [0.5]*	**-1.7 (-2.6,-0.8)** ***-2.1 (-3.1,-1.1)***
	FREM 225 mg vs. PBO[b]	187	16.4 (5.3)	-4.1 [0.4] *-4.9 [0.5]*	190	15.4 (5.0)	-2.4 [0.4] *-2.8 [0.5]*	**-1.7 (-2.5,-0.8)** ***-1.3 (-2.3,-0.3)***
Subgroup of patients with 2-4 prior treatment failures								
PROGRESS[d]	ATOG 60 mg vs. PBO	88	20.3 (0.6) *20.3 (5.4)*	-6.4 [0.7]	76	19.4 (0.6) *19.4 (5.0)*	-4.5 [0.7]	**-1.9 (-3.8, -0.02)**
CONQUER (CM subgroup)	GAL 120 mg vs. PBO	95	19.2 (4.7)	-6.0 [6.8] *-6.0 [0.7]*	98	18.1 (4.7)	-2.2 [5.9] *-2.2 [0.6]*	**-3.7 (-5.2, -2.2)**
FOCUS (CM subgroup)	FREM 675 mg vs. PBO	169	NR	-3.9 [0.5]	167	NR	-0.7 [3.3]	**-3.2 (-4.2., -2.2)**
	FREM 225 mg vs. PBO[b]	173	NR	-4.5 [3.0] *-4.5 [0.2]*	167	NR	-0.7 [3.3] *-0.7 [0.3]*	**-3.8 (-4.8, -2.8)**
Subgroup of patients with ≥3 prior treatment failures								
REGAIN	GAL 120 mg vs. PBO	103	NR	-5.6 [5.8] *-5.6 [0.6]*	36	NR	-0.4 [7.7] *-0.4 [1.3]*	**-5.2 (-7.7, -2.8)**
CONQUER	GAL 120 mg vs. PBO	42	21.4 (4.7)	-6.7 [7.6] *-6.7 [1.2]*	42	20.6 (4.4)	-1.6 [7.3] *-1.6 [1.1]*	**-5.1 (-8.3, -1.9)**

Source: Tables 2-20, 2-23 & 2-35, pp83-84, 88 & 117 of the submission; Table 5, eptinezumab PSD, July 2022 PBAC meeting. **Bold** indicates statistically significant results. *Italicised text (data added from PROGRESS CSR, Sakai (2021a), conversions from SD to SE using SD/Sqrt(N)) added during the evaluation.*

ATOG = Atogepant; CGRP = Calcitonin gene-related peptide; CI = confidence interval; CM = chronic migraine; FREM = Fremanezumab; GAL = Galcanezumab; N = total participants in group; PBO = placebo; SD = standard deviation; SE = standard error.

[a] Mean change from baseline analysed as least-squares mean; mean difference analyses as least-squares mean difference.

[b] With a 675mg loading dose.

[c] Submission presented mean change and mean difference results for headache days, not migraine days.

[d] Based on past use only and 2-4 failures of preventive migraine medications with different mechanisms of action.

6.31 Table 7 presents the indirect comparison results for change from baseline in mean monthly migraine days for participants with chronic migraine (whole trial populations and chronic migraine populations/subpopulations). This was the primary outcome in the atogepant PROGRESS trial and relied upon for the clinical claim.

Table 7: Results of the indirect comparison for change from baseline in mean monthly migraine days for participants with chronic migraine (whole trial populations)

Trial	Treatment arms	Change from baseline, days, LSM [SE]			LSMD, days (95% CI)
		Atogepant	Placebo	GALC/FREM	
Whole trial populations					
Atogepant vs placebo					
PROGRESS	ATOG 60 mg vs. PBO	N = 256 -6.88 [0.406]	N = 246 -5.05 [0.411]	-	**-1.82 (-2.89, -0.75)**
Pooled atogepant (I^2 = N/A; p = N/A)					**-1.83 (-2.96, -0.70)**
Galcanezumab vs placebo					
REGAIN	GAL 120 mg vs. PBO	-	N = 538 -2.7 [0.4]	N = 273 -4.8 [0.4]	**-2.1 (-2.9, -1.3)** **-2.10 (-3.21, 0.99)** [a]
CONQUER [b]	GAL 120 mg vs. PBO	-	N = 230 -1.0 [0.3]	N = 232 -4.1 [0.3]	**-3.1 (-3.9, -2.3)**
Pooled galcanezumab (I^2 = 50%; p = 0.16)					**-2.67 (-3.64, -1.70)**
Fremanezumab vs placebo					
HALO-CM	FREM 225 mg vs. PBO	-	N = 371 -3.2 [0.4]	N = 375 -3.2 (SD: 7.7) -5.0 [0.4]	**-1.80 (-2.91, -0.69)**
FOCUS [b]	FREM 225 mg vs. PBO	-	N = 279 -0.6 [0.3]	N = 283 -4.1 (SD: 5.0) [0.3]	**-3.50 (-4.33, -2.67)**
NCT03303079	FREM 225 mg vs. PBO	-	N = 190 -2.4 [0.4] -2.8 [0.5] [c]	N = 187 -4.1 (SD: 5.5) -4.9 [0.5] [c]	**-1.70 (-2.81, -0.59)** **-2.1 (-3.48, -0.72)** [c]
Pooled fremanezumab (**I^2 = 78%; p = 0.01**)					**-2.38 (-3.62, -1.14)**
Pooled fremanezumab (excluding FOCUS due to heterogeneity) (I^2 = 0%; p = 0.90)					**-1.75 (-2.53, -0.97)**
Atogepant vs galcanezumab (95% CI)					0.84 (-0.65, 2.33)
Atogepant vs fremanezumab (95% CI)					0.55 (-1.13, 2.23)
Atogepant vs fremanezumab excluding FOCUS trial due to heterogeneity (95% CI)					-0.08 (-1.45, 1.29)
Chronic migraine population/subpopulations only					
Atogepant vs placebo					
PROGRESS (same as whole population analysis above)					**-1.82 (-2.89, -0.75)**
Pooled atogepant (I^2 = N/A; p = N/A)					**-1.83 (-2.96, -0.70)**
Galcanezumab vs placebo					
REGAIN (same as whole population analysis above)					**-2.1 (-2.9, -1.3)** **-2.10 (-3.21, 0.99)** [a]
CONQUER (CM subgroup)	GAL 120 mg vs. PBO	-	n = 98 -2.2 (SD: 5.9) [0.6]	n = 95 -6 (SD: 6.8) [0.7]	**-3.80 (-5.61, -1.99)**
Pooled galcanezumab CM populations/subpopulations (I^2 = 60%; p = 0.12)					**-2.80 (-4.44, -1.16)**
Fremanezumab vs placebo					
HALO-CM (same as whole population analysis above)					**-1.80 (-2.91, -0.69)**
FOCUS (CM subgroup)	FREM 225 mg vs. PBO	-	n = 167 -0.7 (SD: 3.3) [0.3]	n = 173 -4.5 (SD: 3) [0.2]	**-3.80 (-4.47, -3.13)**
NCT03303079 (same as whole population analysis above)					**-1.70 (-2.81, -0.59)** **-2.1 (-3.48, -0.72)** [c]
Pooled fremanezumab CM populations/subpopulations (I^2 = 87%; p = 0.0005)					**-2.49 (-4.00, -0.97)**
Pooled fremanezumab CM populations/subpopulations (excluding FOCUS due to heterogeneity) (I^2 = 0%; p = 0.90)					**-1.75 (-2.53, -0.97)**
Atogepant vs galcanezumab (95% CI)					0.97 (-1.02, 2.96)
Atogepant vs fremanezumab (95% CI)					0.66 (-1.23, 2.55)

Trial	Treatment arms	Change from baseline, days, LSM [SE]			LSMD, days (95% CI)
		Atogepant	Placebo	GALC/FREM	
Atogepant vs fremanezumab excluding FOCUS trial due to heterogeneity (95% CI)					-0.08 (-1.45, 1.29)

Source: Tables 2-20, 2-23, 2-43 & 2-47, pp83, 88, 139 & 145 of the submission, Figures 2-7-2-10, pp120, 122, 123 & 125 of the submission.
Bold indicates statistically significant results. LSMD from RevMan) added during the evaluation.
CI = confidence interval; CM = chronic migraine; FREM = Fremanezumab; GAL = Galcanezumab; LSM = least square mean; LSMD = least square mean difference; PBO = placebo; SD = standard deviation; SE = standard error.
[a] LSMD calculated in RevMan
[b] included participants with chronic and episodic migraine.
[c] Submission presented results for headache days, italicised text presents results for migraine days.
Note 1: Deviations in confidence intervals from Table 6 due to SEs were converted to SDs using SD=SE*Sqrt(N)
Note 2: pooled fremanezumab results and indirect comparisons comparing atogepant to fremanezumab with and without the FOCUS trial use headache days in the NCT03303079 trial, not migraine days.

6.32 The indirect comparison results demonstrated no statistical difference between atogepant and galcanezumab or fremanezumab in terms of the number of mean monthly migraine days in patients with chronic migraine. The ESC noted that the point estimates of the indirect comparison results suggest that galcanezumab and fremanezumab resulted in a greater reduction in monthly migraine days than atogepant. The ESC noted that the upper bound of the 95% confidence interval was greater than the non-inferiority margin of two days in the comparisons between atogepant and galcanezumab, suggesting that atogepant was potentially inferior to galcanezumab. The non-inferiority margin of 2 days was also exceeded for the comparisons between atogepant and fremanezumab when the FOCUS trial was included in the analyses; however, when the FOCUS trial was excluded the non-inferiority margin was met. The ESC noted that of the three fremanezumab trials, it was likely FOCUS was the most applicable to the PBS population (as patients had failed 2 to 4 prior prophylactic medications) and considered excluding the results for FOCUS from the ITC was not appropriate. Additionally, the ESC noted the indirect comparison used headache days (rather than migraine days) for fremanezumab which would favour atogepant in the ITC. There was a higher response with placebo in the atogepant trials compared to the galcanezumab and fremanezumab trials, suggesting there could be unobserved differences across the trials reducing transitivity. The PSCR stated that the higher placebo rates in the atogepant trials might have biased the results in favour of the comparators, further supporting the claim of non-inferiority. The ESC considered that differences in placebo response would be accounted for as part of the Bucher indirect comparison method.

6.33 The PBAC recommended the PBS listing of eptinezumab for the treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications based on a claim of non-inferiority to galcanezumab and fremanezumab (paragraphs 7.1 and 7.6, eptinezumab PSD, July 2022 PBAC meeting). The indirect comparisons between eptinezumab and galcanezumab and eptinezumab and fremanezumab focused on the subgroup of participants with chronic migraine with two to four and three or more preventive treatment failures. The atogepant submission stated that the subgroup analyses it presented for participants with two to four treatment failures should be interpreted with caution due to statistical heterogeneity and use of multiple

subgroups. The atogepant submission did not present a subgroup analysis for participants with three or more treatment failures.

- The least squares mean difference between eptinezumab and galcanezumab in participants with two to four preventive treatment failures was 0.6 days (95% CI: -2.05, 3.25; p = 0.658) (paragraph 6.20, eptinezumab PSD, July 2022 PBAC meeting). For atogepant versus galcanezumab this was 2.33 days (95% CI: -0.09, 4.75).
- The least squares mean difference between eptinezumab and fremanezumab in participants with two to four preventive treatment failures was 0.62 days (95% CI: -1.43, 2.67; p=0.554) (paragraph 6.20, eptinezumab PSD, July 2022 PBAC meeting). For atogepant versus fremanezumab this was 1.91 days (95% CI: -0.10, 3.92).

6.34 Table 8 presents the indirect comparison results for ≥50% reduction in monthly migraine days in the whole populations in chronic migraine. The submission did not present an indirect comparison for ≥50% reduction in monthly migraine days in the chronic migraine population/subpopulations. This outcome was relied upon for the clinical claim. This outcome also aligns with the proposed continuation criteria.

Table 8: Summary of results of the indirect comparison for ≥50% reduction in monthly migraine days for the whole populations in chronic migraine

Trial ID	Treatment arms	CGRP inhibitor n/N (%)	Placebo n /N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)	Risk Difference (95% CI)
Atogepant vs placebo						
PROGRESS	ATOG 60 mg vs. PBO	105/256 (41.0)	64/246 (26.0)	**1.98 (1.35, 2.89)**	**1.58 (1.22, 2.04)**	**0.15 (0.07, 0.23)**
Galcanezumab vs placebo						
REGAIN	GAL 120 mg vs. PBO	75/273 (27.6)	83/538 (15.4)	**3.92 (2.47, 6.23)**	**1.78 (1.35, 2.35)**	**0.12 (0.06, 0.18)**
CONQUER[a]	GAL 120 mg vs. PBO	88/232 (37.9)	31/230 (13.5)	**2.08 (1.46, 2.96)**	**2.81 (1.95, 4.06)**	**0.24 (0.17, 0.32)**
Pooled galcanezumab		163/505 (32.3)	114/768 (14.8)	**2.80 (1.50, 5.23)**	**2.20 (1.40, 3.45)**	**0.18 (0.06, 0.30)**
Fremanezumab vs placebo						
HALO-CM	FREM 225 mg vs. PBO	153/375 (40.8)	67/371 (18.1)	**5.52 (3.40, 8.97)**	**2.26 (1.76, 2.90)**	**0.23 (0.16, 0.29)**
FOCUS[a]	FREM 225 mg vs. PBO	97/283 (34.3)	24/278 (8.6)	**3.13 (2.24, 4.37)**	**3.97 (2.62, 6.01)**	**0.26 (0.19, 0.32)**
NCT03303079	FREM 225 mg vs. PBO	54/186 (29.0)	25/190 (13.2)	**2.70 (1.59, 4.57)**	**2.21 (1.44, 3.39)**	**0.16 (0.08, 0.24)**
Pooled fremanezumab		304/844 (36.0)	116/839 (13.8)	**3.57 (2.41, 5.31)**	**2.66 (1.87, 3.78)**	**0.22 (0.17, 0.27)**
Pooled fremanezumab (excluding FOCUS due to heterogeneity)		207/561 (36.7)	92/561 (16.4)	**3.00 (2.26, 3.98)**	**2.25 (1.81, 2.78)**	**0.20 (0.13, 0.26)**
Atogepant vs galcanezumab (95% CI)		–	–	0.71 (0.34, 1.47)	0.72 (0.43, 1.21)	-0.03, (-0.17, 0.11)
Atogepant vs fremanezumab (95% CI)		–	–	**0.56 (0.32, 0.96)**	**0.59 (0.38, 0.92)**	-0.07 (-0.16, 0.02)
Atogepant vs fremanezumab excluding FOCUS trial (95% CI)		–	–	0.66 (0.41, 1.06)	**0.70 (0.50, 0.98)**	-0.05 (-0.15, 0.05)

Source: Table 2-44, p140 of the submission; Figure 2-11, p126 of the submission. **Bold** indicates statistically significant results.
CGRP = Calcitonin gene-related peptide; CI = confidence interval; FREM = Fremanezumab; GAL = Galcanezumab; n = number of participants with the event; N = number of participants in the group; PBO = placebo.
[a] included participants with chronic and episodic migraine.

6.35 The indirect comparison results for the ≥50% reduction in monthly migraine days demonstrated no statistical difference between atogepant and galcanezumab measured using the odds ratio, relative risk or risk difference. The indirect comparison between atogepant fremanezumab (including FOCUS) measured using the risk difference was also not statistically significant but the results were statistically significant in favour of fremanezumab when measured using the odds ratio and relative risk. The point estimates of the indirect comparison results suggested that galcanezumab and fremanezumab resulted in a greater proportion of participants experiencing a ≥50% reduction in monthly migraine days than atogepant. No non-inferiority margin was proposed for this outcome.

6.36 The whole trial meta-analysis for the primary endpoint of change from baseline in mean monthly migraine days indicated that atogepant, galcanezumab and fremanezumab were superior to placebo in reducing the number of migraine days per month, with a total change from baseline (95% CI) across the treatments of -2.41 days

(-3.07, -1.75). The submission noted significant heterogeneity across the six chronic migraine trials (heterogeneity test; p=0.02, I^2=61%). The fremanezumab FOCUS trial was identified as an outlier, with the trials becoming more homogenous when the trial was removed from the meta-analysis (heterogeneity test; p=0.19, I^2=35%). When the FOCUS trial was removed, the meta-analysis showed that atogepant, galcanezumab and fremanezumab were superior to placebo in reducing the number of migraine days per month, with a total change from baseline (95% CI) across the treatments of -2.18 days (-2.77, -1.60). The submission reported a class effect across the three CGRP inhibitors with the test for subgroup differences between the three treatments being insignificant (with FOCUS: p=0.54, I^2=0%); without FOCUS: p=0.32, I^2=12.5%).

6.37 The ESC considered using the I^2 statistic and Cochran's Q test (i.e., p value in paragraph above) to conclude there were no significant differences between atogepant, galcanezumab and fremanezumab may not have been appropriate. The ESC noted the Cochran's Q test may not be accurate if the individual trials have a moderate sample size[2] and has a low power to detect differences if there are a small number of studies in the meta-analysis[3]. Additionally, the ESC noted a lack of significant difference does not necessarily support a claim of non-inferiority. The ESC also noted the issues raised in paragraph 6.32 regarding the meta-analysis.

Episodic migraine

6.38 Table 9 presents the results of the key outcomes in the atogepant ADVANCE and NCT028484326 trials for episodic migraine.

[2] Kulinskaya E, Dollinger M, Bjorkestol, K. Testing for homogeneity in meta-analysis I. The one-parameter case: standardised mean difference. Biometrics 2011 Mar: 67(1):203-212.

[3] Hardy R, Thompson S. Detecting and describing heterogeneity in meta-analysis. Statistics in Medicine 1998, 17(8): 841-856.

Table 9: Summary of key secondary outcome results at 12 weeks from the atogepant ADVANCE trial and primary outcome at 12 weeks for the NCT02848326 trial: continuous data with outcome presented as change from baseline

Trial ID	Treatment arms	Atogepant			Placebo			Mean difference	
		N	Mean baseline (SD)	Mean change, LSM [SE]	N	Mean baseline (SD)	Mean change, LSM [SE]	LSMD (95%CI))	p-value
Change from baseline in mean monthly migraine days									
ADVANCE	ATOG 60 mg vs. PBO	222	7.75 (2.31)	-4.20 [0.20]	214	7.51 (2.39)	-2.48 [0.20]	**-1.72 (-2.28, -1.15)**	**<0.0001**
NCT02848326	ATOG 60 mg vs. PBO	177	7.74 (2.6)	-3.55 [0.2]	278	7.81 (2.5)	-2.85 [0.2]	**-0.70 (-1.35, -0.06)**	***0.0390***
Change from baseline in mean monthly headache days									
ADVANCE	ATOG 60 mg vs. PBO	222	9.00 *(2.56)*	-4.23 [0.22]	214	8.43 *(2.55)*	-2.52 [0.23]	**-1.71 (-2.32, -1.10)**	**<0.0001**
Change from baseline in mean monthly acute medication use days									
ADVANCE	ATOG 60 mg vs. PBO	222	6.89 *(3.17)*	-3.85 [0.18]	214	6.48 *(3.15)*	-2.35 [0.18]	**-1.50 (-2.00, -1.01)**	**<0.0001**
Change from baseline in MSQ v2.1 RFR Score									
ADVANCE	ATOG 60 mg vs. PBO	222	47.48 (20.55)	31.25 [1.59]	214	46.78 (19.87)	20.45 [1.62]	**10.80 (6.42, 15.18)**	**<0.0001**
Change from baseline in mean AIM-D (performance of daily activities)									
ADVANCE	ATOG 60 mg vs. PBO	222	15.74 (8.34)	-9.41 [0.50]	214	15.06 (8.32)	-6.09 [0.50]	**-3.32 (-4.68, -1.96)**	**<0.0001**
Change from baseline in mean AIM-D (physical impairment domain)									
ADVANCE	ATOG 60 mg vs. PBO	222	11.48 (7.77)	-6.49 [0.44]	214	10.99 (8.03)	-4.03 [0.44]	**-2.46 (-3.65, -1.28)**	**<0.0001** ***0.0002***
Change from baseline in mean HIT-6									
ADVANCE	ATOG 60 mg vs. PBO	222	*NR*	-9.20 [0.53]	214	*NR*	-5.24 [0.54]	**-3.96 (-5.42, -2.50)**	**<0.0001**

Source: Table 2-27, pp94-95 of the submission; Tables 11-1, 11-7 & 11-8 of the ADVANCE CSR. **Bold** indicates statistically significant results. *Italicised text (values from the CSR and p-values with multiplicity adjustment) added during the evaluation. Change from baseline in mean HIT-6 was assessed without adjusting for multiplicity so is nominally significant.*

AIM-D = activity impairment in migraine diary; ATOG = Atogepant; CI = confidence interval; HIT-6 = headache impact test-6; LSM = least-squares mean; LSMD = least-squares mean difference; MMRM = mixed model for repeated measure; MSQ-RFR = Migraine-Specific Quality of Life Questionnaire version 2.1 – role function-restrictive domain score; N = total participants in group; PBO = placebo; SD = standard deviation; SE = standard error.

6.39 The whole trial analysis of the atogepant ADVANCE and NCT028484326 trials indicated that atogepant was superior to placebo in terms of the primary outcome (change of mean monthly migraine days) and the majority of secondary outcomes.

6.40 The submission stated that the comparative improvement in the change from baseline in the HIT-6 score of -3.96 (95% CI: -5.42, -2.50) between atogepant and placebo was above the MCID of -2.5 for episodic migraine, demonstrating a clinically meaningful improvement in headache-specific quality of life with atogepant treatment.

6.41 The submission also presented results for response defined as the proportion of patients achieving a ≥50% reduction in mean monthly migraine days as a dichotomous outcome for the ADVANCE trial (not presented below). A statistically significant higher proportion of participants achieved a ≥50% reduction in monthly migraine days with atogepant 60 mg once daily (134/222; 60.8%) compared with placebo (62/214; 29.0%) with an odds ratio of 3.82 (95% CI: 2.56, 5.71; p<0.0001).

6.42 Table 10 presents the subgroup analysis of the atogepant ADVANCE trial for the change from baseline in mean monthly migraine days based on the use of prior migraine prevention medication failures (yes/no). The submission stated that subgroup results based on the number of prior preventive migraine treatments in the ADVANCE trial was not presented as data for such an analysis were limited. No information was presented regarding prior preventive migraine medication use in the atogepant NCT02848326 trial. The submission's claim that differences in prior treatment was unlikely to have an effect was uncertain.

Table 10: Results of change in mean monthly migraine days at 12 weeks in the ADVANCE trial (whole trial and subgroup analysis): continuous data with outcome presented as change from baseline

Subgroup	Treatment arms	Atogepant			Placebo			Mean difference	
		N	Mean baseline (SD)	Mean change, LSM [SE]	N	Mean baseline, (SD)	Mean change, LSM [SE]	LSMD (95%CI)	p-value
Whole trial results									
Whole trial population	ATOG 60 mg vs. PBO	222	7.75 (2.307)	-4.20 [0.20]	214	7.51 (2.388)	-2.48 [0.201]	**-1.72 (-2.28, -1.15)**	**<0.0001**
Prior exposure to preventive migraine medication									
Yes	ATOG 60 mg vs. PBO	152	*7.95 (2.257)*	*-4.42 [0.247]*	152	*7.59 (2.414)*	*-2.26 [0.246]*	**-2.2 (-2.9, -1.5)**	-
No	ATOG 60 mg vs. PBO	70	*7.32 (2.370)*	*-3.58 [0.344]*	62	*7.32 (2.333)*	*-2.92 [0.364]*	-0.7 (-1.7, 0.3)	-

Source: Table 2-25, pp90-91 of the submission; p118 of the submission; Table 11-26 of the ADVANCE CSR. **Bold** indicates statistically significant results. *Italicised text (data from ADVANCE CSR) added during the evaluation.*
ATOG = Atogepant; CI = confidence interval; LSM = least-squares mean; LSMD = least-squares mean difference; N = total participants in group; PBO = placebo; SD = standard deviation; SE = standard error.

6.43 The submission stated that participants were naïve to preventive migraine treatment showed a smaller reduction in monthly migraine headache days, largely driven by a higher placebo response in the naïve subgroup. No conclusions could be drawn regarding the role of prior treatments as a treatment effect modifier since no statistical tests for treatment interaction were presented in the submission.

6.44 The mean number of migraine days at baseline in the ADVANCE trial whole population (7.75) and sub-populations with (7.95) and without (7.32) prior preventive treatment was less than the HFEM threshold defined by the PBS eligibility criteria as eight or more migraine headache days per month.

6.45 Table 11 presents the indirect comparison results for change from baseline in mean monthly migraine days for participants with episodic migraine (whole trial populations). This was the primary outcome in all the trials and relied upon for the clinical claim. The submission stated that the FOCUS trial was excluded from the fremanezumab meta-analysis as the episodic migraine subgroup data was not publicly available. The evaluation noted that FOCUS trial episodic migraine subgroup data for this outcome was available in Ferrari 2019 (not presented below). The ESC noted that of the three fremanezumab trials, it was likely FOCUS was the most applicable to the PBS population as patients had failed 2 to 4 prior prophylactic medications.

Table 11: Results of the indirect comparison for change from baseline in mean monthly migraine days for participants with episodic migraine (whole trial populations)

Trial	Treatment arms	Change from baseline, days, LSM [SE]			LSMD (95% CI)
		Atogepant	Placebo	GALC/FREM	
Whole trial populations					
Atogepant vs placebo					
ADVANCE	ATOG 60 mg vs. PBO	N = 222 -4.0 [0.2]	N = 214 -2.5 [0.2]	-	**-1.72 (-2.30, -1.14)**
NCT02848326	ATOG 60 mg vs. PBO	N = 177 -3.55 [0.2]	N = 178 -2.85 [0.2]	-	-0.70 (-1.49, 0.09)
Pooled atogepant **I^2 = 76%; p = 0.04**					**-1.25 (-2.24, -0.25)**
Galcanezumab vs placebo					
EVOLVE-1	GAL 120 mg vs. PBO	-	N = 425 -2.8 [NR]	N = 210 -4.7 [NR]	**-1.90 (-2.61, -1.19)**
EVOLVE-2	GAL 120 mg vs. PBO	-	N = 461 -2.3 [0.2]	N = 231 -4.3 [0.3]	**-2.00 (-2.71, -1.29)**
CONQUER[a]	GAL 120 mg vs. PBO	-	N = 230 -1.0 [0.3]	N = 232 -4.1 [0.3]	**-3.10 (-3.93, -2.27)**
PERSIST	GAL 120 mg vs. PBO	-	N = 259 -2.0 [0.2]	N = 261 -3.8 [0.2]	**-1.80 (-2.35, -1.25)**
NCT02959177	GAL 120 mg vs. PBO	-	N = 230 -0.6 [0.2]	N = 115 -3.6 [0.3]	**-3.01 (-3.80, -2.22)**
Pooled galcanezumab **I^2 = 65%; p = 0.02**					**-2.21 (-2.66, -1.77)** ***-2.32 (-2.85, -1.78)***
Fremanezumab vs placebo					
HALO-EM	FREM 225 mg vs. PBO	-	N = 294 -2.2 [0.2]	N = 290 -3.7 [0.2]	**-1.50 (-2.19, -0.81)**
FOCUS[a]	FREM 225 mg vs. PBO	-	N = 279 -0.6 [0.3]	N = 283 -4.1 [0.3]	**-3.50 (-4.33, -2.67)**
NCT03303092	FREM 225 mg vs. PBO	-	N = 117 -1.0 [0.4]	N = 121 -4.0 [0.4]	**-3.00 (-4.11, -1.89)**
Pooled fremanezumab (**I^2 = 86%; p = 0.0007)**					**-2.64 (-3.97, -1.30)**
Atogepant vs galcanezumab (95% CI)					1.07 (-0.06, 2.20)
Atogepant vs fremanezumab (95% CI)					1.39 (-0.28, 3.06)
Episodic migraine population/subpopulations only					
Atogepant vs placebo					
ADVANCE (same as whole population analysis above)					**-1.72 (-2.30, -1.14)**
NCT02848326 (same as whole population analysis above)					-0.70 (-1.49, 0.09)
Pooled atogepant (I^2 = 76%; p = 0.04)					-1.25 (-2.24, -0.25)
Galcanezumab vs placebo					
EVOLVE-1 (same as whole population analysis above)					**-1.90 (-2.61, -1.19)**
EVOLVE-2 (same as whole population analysis above)					**-2.00 (-2.71, -1.29)**
CONQUER (EM subgroup)	GAL 120 mg vs. PBO	-	N = 132 -0.3 (SD: 3.4) *[0.3]*	N = 137 -2.9 (SD: 3.5) *[0.3]*	**-3.10 (-3.93, -2.27)** ***-2.60 (-3.43, -1.77)***
PERSIST (same as whole population analysis above)					**-1.80 (-2.35, -1.25)**
NCT02959177 (same as whole population analysis above)					**3.01 (-3.80, -2.22)**
Pooled galcanezumab (I^2 = 49%; p = 0.10)					**-2.21 (-2.66, -1.77)**
Fremanezumab vs placebo					
HALO-EM (same as whole population analysis above)					**-1.50 (-2.19, -0.81)**
NCT03303092 (same as whole population analysis above)					**-3.00 (-4.11, -1.89)**
Pooled fremanezumab (**I^2 = 80%; p = 0.02)**					**-2.64 (-3.97, -1.30)** ***-2.18 (-3.65, -0.72)***
Atogepant vs galcanezumab (95% CI)					0.96 (-0.25, 2.17)

Trial	Treatment arms	Change from baseline, days, LSM [SE]			LSMD (95% CI)
		Atogepant	Placebo	GALC/FREM	
Atogepant vs fremanezumab excluding FOCUS trial (95% CI)					1.39 (-0.35, 3.13) *0.93 (-0.84, 2.70)*

Source: Tables 2-28, 2-45 & 2-49, pp96, 142 & 147 of the submission, Figures 2-13 & 2-14, pp129 & 131 of the submission. **Bold** indicates statistically significant results. *Italicised text based on corrected meta-analysis result added during the evaluation.*
CI = confidence interval; FREM = Fremanezumab; GAL = Galcanezumab; LSM = least square mean; LSMD = least square mean difference; PBO = placebo; SD = standard deviation; SE = standard error.
[a] included participants with chronic and episodic migraine.

6.46 The indirect comparison results demonstrated no statistical difference between atogepant and galcanezumab or fremanezumab, although the ESC noted that the point estimates of the indirect comparison results suggest that galcanezumab and fremanezumab (corrected) resulted in a greater reduction in monthly migraine days than atogepant. The ESC noted that the upper bounds of the 95% confidence intervals were greater than the non-inferiority margin of two days in the comparison between atogepant and galcanezumab and fremanezumab, suggesting that atogepant was potentially inferior to galcanezumab and fremanezumab. There was a higher response with placebo in the atogepant trials compared to the galcanezumab and fremanezumab trials, suggesting there could be unobserved differences across the trials reducing transitivity. The PSCR stated that the higher placebo rates in the atogepant trials might have biased the results in favour of the comparators, further supporting the claim of non-inferiority. The ESC considered that differences in placebo response would be accounted for as part of the Bucher indirect comparison method.

6.47 Table 12 presents the indirect comparison results for ≥50% reduction in monthly migraine in the whole populations in episodic migraine. The submission did not present an indirect comparison for ≥50% reduction in monthly migraine days in the episodic migraine population/subpopulations. This outcome was relied upon for the clinical claim. This outcome also aligns with the proposed continuation criteria.

Table 12: Summary of results of the indirect comparison for ≥50% reduction in monthly migraine days for the whole populations in episodic migraine

Trial ID	Treatment arms	CGRP inhibitor n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	Treatment effect (RR)	Treatment effect (RD)
Atogepant vs placebo						
ADVANCE	ATOG 60 mg vs. PBO	135/222 (60.8)	62/214 (29.0)	**3.80 (2.55, 5.67)**	**2.10 (1.66, 2.65)**	**0.32 (0.23, 0.41)**
NCT02848326	ATOG 60 mg vs. PBO	86/176 (48.9)	58/177 (32.8)	**1.96 (1.27, 3.02)**	**1.49 (1.15, 1.93)**	**0.16 (0.06, 0.26)**
Pooled atogepant				**2.74 (1.43, 5.26)**	**1.78 (1.27, 2.48)**	**0.24 (0.09, 0.40)**
Galcanezumab vs placebo						
EVOLVE-1	GAL 120 mg vs. PBO	131/210 (62.3)	164/425 (38.6)	**2.64 (1.88, 3.71)**	**1.62 (1.38, 1.90)**	**0.24 (0.16, 0.32)**
EVOLVE-2	GAL 120 mg vs. PBO	137/231 (59.3)	166/461 (36.0)	**2.59 (1.87, 3.58)**	**1.65 (1.40, 1.94)**	**0.23 (0.16, 0.31)**
CONQUER	GAL 120 mg vs. PBO	88/232 (37.9)	31/230 (13.5)	**3.92 (2.47, 6.23)**	**2.81 (1.95, 4.06)**	**0.24 (0.17, 0.32)**
PERSIST	GAL 120 mg vs. PBO	143/261 (54.8)	85/259 (32.8)	**3.83 (2.35, 6.22)**	**1.67 (1.36, 2.05)**	**0.22 (0.14, 0.30)**
NCT02959177	GAL 120 mg vs. PBO	57/115 (49.6)	47/230 (20.4)	**2.48 (1.74, 3.54)**	**2.43 (1.77, 3.32)**	**0.29 (0.14, 0.30)**
Pooled galcanezumab				**2.87 (2.40, 3.42)**	**1.87 (1.57, 2.24)**	**0.24 (0.20, 0.28)**
Fremanezumab vs placebo						
HALO-EM	FREM 225 mg vs. PBO	137/287 (47.7)	81/290 (27.9)	**2.36 (1.67, 3.33)**	**1.71 (1.37, 2.13)**	**0.20 (0.12, 0.28)**
FOCUS	FREM 225 mg vs. PBO	97/283 (34.3)	24/278 (8.6)	**5.52 (3.40, 8.97)**	**3.97 (2.62, 6.01)**	**0.26 (0.19, 0.32)**
NCT03303092	FREM 225 mg vs. PBO	50/121 (41.3)	13/116 (11.2)	**5.58 (2.82, 11.02)**	**3.69 (2.12, 6.42)**	**0.30 (0.20, 0.41)**
Pooled fremanezumab				**4.02 (2.12, 7.62)**	**2.85 (1.49, 5.43)**	**0.25 (0.19, 0.30)**
Atogepant vs galcanezumab (95% CI)		–	–	0.96 (0.49, 1.88)	0.95 (0.65, 1.39)	0.00 (-0.16, 0.16)
Atogepant vs fremanezumab (95% CI)		–	–	0.68 (0.27, 1.70)	0.63 (0.30, 1.29)	-0.01 (-0.17, 0.15)

Source: Table 2-46, p143 of the submission; Figure 2-15, p132 of the submission. **Bold** indicates statistically significant results.
CGRP = Calcitonin gene-related peptide; CI = confidence interval; FREM = Fremanezumab; GAL = Galcanezumab; n = number of participants with the event; N = number of participants in the group; PBO = placebo.

6.48 The indirect comparison results for the ≥50% reduction in monthly migraine days demonstrated no statistical difference between atogepant and galcanezumab or fremanezumab measured using the odds ratio, relative risk or risk difference. No non-inferiority margin was proposed for this outcome.

6.49 The whole trial meta-analysis for the primary endpoint of change from baseline in mean monthly migraine days showed indicated that atogepant, galcanezumab and fremanezumab were superior to placebo in reducing the number of migraine days per month, with a total change from baseline (95% CI) across the treatments of -2.18 days (-2.69, -1.68). The submission noted significant heterogeneity across the ten episodic migraine trials (heterogeneity test; p=0.00001, I2=79%); however, sensitivity analysis

did not identify any single trial that significantly contributed to the heterogeneity. The submission reported a class effect across the three CGRP inhibitors with the test for subgroup differences between the three treatments being insignificant (p=0.13, I^2=50.5%)

6.50 The ESC noted the issues discussed in paragraph 6.37 were also relevant for this meta-analysis.

Comparative harms

Chronic migraine

6.51 Table 13 presents the summary safety outcomes for the trials included in the chronic migraine analysis. The safety results for the chronic and episodic migraine subpopulations in the galcanezumab CONQUER and fremanezumab FOCUS trials were presented together in the table below.

Table 13: Summary of key adverse events in the randomised trials (chronic migraine)

Trial ID	Treatment arms	CGRP inhibitor, n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)
Any TEAE					
PROGRESS	ATOG 60 mg vs. PBO	165/261 (63.2)	126/255 (49.4)	1.3 (1.1, 1.5)	0.14 (0.05, 0.22)
REGAIN	GAL 120 mg vs. PBO	159/273 (58)	279/588 (50)	1.2 (1.1, 1.4)	0.11 (0.04, 0.18)
CONQUER[a]	GAL 120 mg vs. PBO	119/232 (51)	122/230 (53)	1.0 (0.8, 1.2)	-0.02 (-0.11, 0.07)
HALO-CM[b]	FREM 675 mg vs. PBO	265/376 (70)	240/375 (64)	1.1 (1.0, 1.2)	0.06 (-0.00, 0.13)
	FREM 225 mg vs. PBO	270/379 (71)	240/375 (64)	1.1 (1.0, 1.2)	0.07 (0.01, 0.14)
FOCUS[a,b]	FREM 675 mg vs. PBO	151/276 (55)	134/277(48)	1.1 (1.0, 1.3)	0.06 (-0.02, 0.15)
	FREM 225 mg vs. PBO	129/285 (45)	134/277 (48)	0.9 (0.8, 1.1)	-0.03 (-0.11, 0.05)
NCT03303079[b]	FREM 675 mg vs. PBO	116/190 (61.1)	118/191 (61.8)	1.0 (0.8, 1.2)	-0.01 (-0.11, 0.09)
	FREM 225 mg vs. PBO	116/188 (61.7)	118/191 (61.8)	1.0 (0.9, 1.2)	-0.00 (-0.10, 0.10)
Any serious AE					
PROGRESS	ATOG 60 mg vs. PBO	7/261 (2.7)	3/255 (1.2)	2.3 (0.6, 8.7)	0.02 (-0.01, 0.04)
REGAIN	GAL 120 mg vs. PBO	1/273 (<1)	4/588 (<1)	0.54 (0.1, 4.8)	-0.00 (-0.01, 0.01)
CONQUER[a]	GAL 120 mg vs. PBO	2/232 (1)	2/230 (1)	1.0 (0.1, 7.0)	-0.00 (-0.02, 0.02)
HALO-CM[b]	FREM 675 mg vs. PBO	3/376 (<1)	6/375 (2)	0.5 (0.1, 2.0)	-0.01 (-0.02, 0.01)
	FREM 225 mg vs. PBO	5/379 (1)	6/375 (2)	0.8 (0.3, 2.7)	-0.00 (-0.02, 0.01)
FOCUS[a,b]	FREM 675 mg vs. PBO	2/276 (<1)	4/277 (1)	0.5 (0.1, 2.7)	-0.01 (-0.02, 0.01)
	FREM 225 mg vs. PBO	4/285 (1)	4/277 (1)	1.0 (0.2, 3.8)	-0.00 (-0.02, 0.02)
NCT03303079[b]	FREM 675 mg vs. PBO	1/190 (<1)	1/191 (<1)	1.0 (0.1, 16.)	0.00 (-0.01, 0.01)
	FREM 225 mg vs. PBO	3/188 (1.6)	1/191 (<1)	3.0 (0.3, 29.0)	0.01 (-0.01, 0.03)
Any TEAE leading to discontinuation					
PROGRESS	ATOG 60 mg vs. PBO	9/261 (3.4)	10/255 (3.9)	0.9 (0.4, 2.1)	-0.00 (-0.04, 0.03)
REGAIN	GAL 120 mg vs. PBO	2/273 (<1)	6/588 (1)	0.7 (0.1, 3.5)	-0.00 (-0.02, 0.01)
CONQUER[a]	GAL 120 mg vs. PBO	1/232 (<1)	0*/230 (0)	1.0 (0.1, 15.8)	0.00 (-0.01, 0.02)
HALO-CM[b]	FREM 675 mg vs. PBO	5/376 (1)	8/375 (2)	0.5 (0.1, 2.0)	-0.01 (-0.03, 0.01)
	FREM 225 mg vs. PBO	7/379 (2)	8/375 (2)	0.9 (0.3, 2.4)	-0.00 (-0.02, 0.02)
FOCUS[a,b]	FREM 675 mg vs. PBO	1/276 (<1)	3/277 (1)	0.3 (0.01, 3.2)	-0.01 (-0.02, 0.01)
	FREM 225 mg vs. PBO	4/285 (1)	3/277 (1)	1.3 (0.3, 5.7)	0.00 (-0.02, 0.02)
NCT03303079[b]	FREM 675 mg vs. PBO	0[c]/190 (0)	2/191 (1.0)	0.5 (0.05, 5.5)	-0.01 (-0.03, 0.01)
	FREM 225 mg vs. PBO	0[c]/188 (0)	2/191 (1.0)	0.5 (0.05, 5.6)	-0.01 (-0.03, 0.01)

Source: Table 2-30, pp100-101 of the submission.

ATOG = Atogepant; CGRP = Calcitonin gene-related peptide; CI = confidence interval; FREM = Fremanezumab; GAL = Galcanezumab; n = number of participants experiencing event; N = total participants in group; PBO = placebo; RD = risk difference; RR = relative risk.

[a] Results for chronic migraine and episodic migraine subpopulations combined.

[b] The fremanezumab trials used a loading dose of fremanezumab 675mg followed by 4 weekly or monthly injections of fremanezumab 225 mg.

[c] An incidence of 1 was used in the submission for the relative risk calculation.

6.52 The submission stated that overall, atogepant appeared to be safe and well tolerated in participants with chronic migraine. Most treatment-emergent adverse events were mild or moderate in severity. There were seven reported serious treatment-emergent adverse events in the atogepant 60 mg once daily group, the incidence of which did not differ significantly from placebo; infection and infestations (n=2), COVID-19 (n=1), bronchitis (n=1), injury, poisoning and procedural complications (n=2) and fall (n=1). There were no deaths reported during the PROGRESS trial.

6.53 In comparison to galcanezumab and fremanezumab, atogepant had a similar safety profile apart from injection site AEs that arose from the subcutaneous administration of the two comparator treatments. Galcanezumab was associated with a higher

incidence of injection site related AEs compared to placebo such as injection site reactions (REGAIN; galcanezumab 5% vs placebo 2%) and erythema (REGAIN; galcanezumab 5% vs placebo 1%).

6.54 Atogepant had a higher incidence of gastrointestinal events compared to galcanezumab and fremanezumab, although as stated in the submission these were of mild or moderate severity.

Episodic migraine

6.55 Table 14 presents the summary safety outcomes for the trials included in the episodic migraine analysis. The safety results for the chronic and episodic migraine subpopulations in the CONQUER and FOCUS trials were presented together in Table 13 and are not duplicated in Table 14.

6.56 The submission stated that the majority of TEAEs were considered to be mild or moderate in severity. No serious treatment-emergent AEs were reported with atogepant 60 mg once daily arm of the atogepant ADVANCE trial. The submission stated that seven severe TEAEs were reported in NCT02848326 in the atogepant 60 mg once daily arm, the incidence of which did not differ significantly from the placebo group; nausea (n=1), anaemia (n=1), gastrointestinal disorders (n=3), blood and lymphatic disorders (n=1) and diarrhoea (n=1).

6.57 In comparison to galcanezumab and fremanezumab, atogepant had a similar safety profile apart from injection site AEs that arose from the subcutaneous administration of the two comparator treatments.

6.58 Atogepant had a higher incidence of gastrointestinal events compared to galcanezumab and fremanezumab, although as stated in the submission these were of mild or moderate severity. In the atogepant ADVANCE and NCT02848326 trials and 3101-302-002 study between 4.8% and 7.2% of participants receiving atogepant experienced constipation, whereas constipation was not reported as occurring in >2% of participants in any of the galcanezumab or fremanezumab trials. In the atogepant ADVANCE and NCT02848326 trials and 3101-302-002 study between 4.3% and 11.8% of participants receiving atogepant experienced nausea, compared with between <1% and 4.8% of patients receiving placebo. Less than 2% of participants receiving galcanezumab and 2.4% of participants receiving fremanezumab experienced nausea.

Table 14: Summary of key adverse events in the randomised trials (episodic migraine)

Trial ID	Treatment arms	CGRP inhibitor, n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)
Any TEAE					
ADVANCE	ATOG 60 mg vs. PBO	124/231 (53.7)	126/222 (56.8)	0.9 (0.8 – 1.1)	-0.1 (-0.2-0.1)
NCT02848326	ATOG 60 mg vs. PBO	107/186 (57.5)	92/186 (49.5)	1.2 (1.0 – 1.4)	-0.03 (-0.12,0.06)
3101-302-002	ATOG 60 mg vs. SoC[a]	364/543 (67.0)	154/196 (78.6)	0.9 (0.8 – 0.9)	0.08 (-0.02, 0.18)
EVOLVE-1	GAL 120 mg vs. PBO	135/206 (67.7)	261/432 (60.4)	1.1 (1.0 – 1.2)	0.05 (-0.03, 0.13)
EVOLVE-2	GAL 120 mg vs. PBO	147/226 (65.0)	287/461 (62.3)	1.0 (0.9 – 1.2)	0.03 (-0.05, 0.10)
PERSIST	GAL 120 mg vs. PBO	130/261 (49.8)	112/259 (43.2)	1.2 (1.0 – 1.4)	0.07 (-0.02, 0.15)
NCT02959177	GAL 120 mg vs. PBO	98/115 (85.2)	149/230 (64.8)	1.3 (1.2 – 1.5)	0.20 (0.11, 0.29)
HALO-EM	FREM 675 mg vs. PBO	193/291 (66.3)	171/293 (58.4)	1.1 (1.0 – 1.3)	0.08 (0.00, 0.16)
	FREM 225 mg vs. PBO	192/290 (66.2)	171/293 (58.4)	1.1 (1.0 – 1.3)	0.08 (0.00, 0.16)
NCT03303092	FREM 675 mg vs. PBO	74/118 (62.7)	77/117 (65.8)	1.0 (0.8 – 1.2)	-0.03 (-0.15, 0.09)
	FREM 225 mg vs. PBO	69/121 (57.0)	77/117 (65.8)	0.9 (0.7 – 1.1)	-0.09 (-0.21, 0.04)
Any serious AE					
ADVANCE	ATOG 60 mg vs. PBO	0[d]/231 (0.0)	2/222 (0.9)	0.5 (0.0 – 5.2)	-0.01 (-0.02, 0.01)
NCT02848326	ATOG 60 mg vs. PBO	2/186 (1.1)	2/186 (1.1)	1.0 (0.1 – 7.0)	0.00 (-0.02, 0.02)
3101-302-002	ATOG 60 mg vs. SoC[a]	24/543 (4.4)	7/196 (3.6)	1.2 (0.5 – 2.8)	0.01 (-0.02, 0.04)
EVOLVE-1	GAL 120 mg vs. PBO	6/206 (2.9)	5/432 (1.2)	2.52 (1.1, 5.6)	0.02 (-0.01, 0.04)
EVOLVE-2	GAL 120 mg vs. PBO	5/226 (2.2)	5/461 (1.1)	2.1 (0.6 – 7.0)	0.01 (-0.01, 0.03)
PERSIST	GAL 120 mg vs. PBO	NR	NR	NA	NA
NCT02959177	GAL 120 mg vs. PBO	3/115 (2.6)	0/230 (0.0)	6.0 (0.6 – 57)	0.03 (-0.01, 0.06)
HALO-EM	FREM 675 mg vs. PBO	3/291 (1.0)	7/293 (2.4)	0.4 (0.1 – 1.7)	-0.01 (-0.03, 0.01)
	FREM 225 mg vs. PBO	3/290 (1.0)	7/293 (2.4)	0.4 (0.1 – 1.7)	-0.01 (-0.03, 0.01)
NCT03303092	FREM 675 mg vs. PBO	0 (0.0)	0 (0.0)	NA	NA
	FREM 225 mg vs. PBO	0 (0.0)	0 (0.0)	NA	NA
Any TEAE leading to discontinuation					
ADVANCE	ATOG 60 mg vs. PBO	6/231 (2.6)	6/222 (2.7)	1.0 (0.3 – 2.9)	0.0 (-0.1-0.1)
NCT02848326	ATOG 60 mg vs. PBO	6/186 (3.2)	5/186 (2.7)	1.2 (0.4 – 3.9)	0.01 (-0.03, 0.04)
3101-302-002	ATOG 60 mg vs. SoC[a]	31/543 (5.7)	5/196 (2.6)	2.2 (0.9 – 5.7)	0.03 (0.00, 0.06)
EVOLVE-1	GAL 120 mg vs. PBO	2/206 (<1)	0/432 (0)	4.2 (0.4 – 46)	NA
EVOLVE-2	GAL 120 mg vs. PBO	5/226 (2.2)	8/461 (1.7)	1.3 (0.4 – 3.9)	0.00 (-0.02, 0.03)
PERSIST	GAL 120 mg vs. PBO	NR	NR	NA	NA
NCT02959177	GAL 120 mg vs. PBO	5/115 (4.4)	0[d]/230 (0.0)	10.0 (1.2 – 85)	0.04 (0.00, 0.08)
HALO-EM	FREM 675 mg vs. PBO	5/291 (1.7)	5/293 (1.7)	1.0 (0.3 – 3.4)	0.00 (-0.02, 0.02)
	FREM 225 mg vs. PBO	5/290 (1.7)	5/293 (1.7)	1.0 (0.3 – 3.5)	0.00 (-0.02, 0.02)
NCT03303092	FREM 675 mg vs. PBO	0[b]/118 (0.0)	1/117 (<1)	1.0 (0.1 – 16)	-0.01 (-0.03, 0.01)
	FREM 225 mg vs. PBO	1/121 (<1)	1/117 (<1)	1.0 (0.1 – 15)	-0.00 (-0.02, 0.02)

Source: Table 2-32, pp106-107 of the submission.

ATOG = Atogepant; CGRP = Calcitonin gene-related peptide; CI = confidence interval; FREM = Fremanezumab; GAL = Galcanezumab; n = number of participants experiencing event; N = total participants in group; NA = not applicable; NR = not reported; PBO = placebo; RD = risk difference; RR = relative risk; SoC = standard of care.

[a] SoC was any oral preventive migraine treatment that was not atogepant.

[b] An incidence of 1 was used in the submission for the relative risk calculation.

Benefits/harms

6.59 A benefits and harms table is not presented as the submission made a claim of non-inferiority**.**

Clinical claim

Chronic migraine

6.60 The submission described atogepant as non-inferior in terms of effectiveness and safety compared with galcanezumab and fremanezumab in patients with chronic migraine who meet the PBS criteria.

6.61 The ESC considered that the claim of non-inferior effectiveness was uncertain because:

- the point estimates of the indirect comparisons favoured galcanezumab and fremanezumab, and the upper bound of the 95% confidence interval for the change in monthly migraine days was greater than the non-inferiority margin of two days in the comparison between atogepant and galcanezumab, suggesting that atogepant was potentially inferior to galcanezumab. The non-inferiority margin of 2 days was also exceeded for the comparisons between atogepant and fremanezumab when the FOCUS trial was included in the analyses; and
- there were transitivity issues across the trials included in the indirect comparisons. In particular, there were differences across the trials in terms of prior preventive treatments. The subgroup analyses presented were insufficient to assess the impact of prior treatments on outcomes.

6.62 In comparison to galcanezumab and fremanezumab, the ESC considered that atogepant had a similar safety profile apart from injection site AEs that arose from the subcutaneous administration of the two comparator treatments. Atogepant had a higher incidence of gastrointestinal events compared to galcanezumab and fremanezumab, although these were of mild or moderate severity. Overall, atogepant appeared to be safe and well tolerated in participants with chronic migraine. The ESC noted that there were differences in the types of adverse events, due to the difference in the modes of administration of the agents.

6.63 The ESC noted that the applicability of the trial evidence to the proposed PBS population was uncertain as fewer than five participants in the atogepant PROGRESS trial had failed at least three preventive medications, and thus met the proposed PBS restriction criteria.

6.64 For CM, the PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.65 For CM, the PBAC considered that the claim of non-inferior comparative safety was reasonable.

Episodic migraine

6.66 The submission described atogepant as non-inferior in terms of effectiveness and safety compared with galcanezumab and fremanezumab in patients with HFEM who meet the PBS criteria.

6.67 The ESC considered that the claim of non-inferior effectiveness was uncertain because:

- the point estimates of the indirect comparisons favoured galcanezumab and fremanezumab, and the upper bounds of the 95% confidence intervals for the change in monthly migraine days were greater than the non-inferiority margin of two days in the comparisons between atogepant and galcanezumab and fremanezumab, suggesting that atogepant was potentially inferior to galcanezumab and fremanezumab; and
- there were transitivity issues across the trials included in the indirect comparison. In particular, there were differences across the trials in terms of prior preventive treatments. The subgroup analyses presented were insufficient to assess the impact of prior treatments on outcomes. The fremanezumab FOCUS trial was also included in the analysis, which included participants experiencing chronic and episodic migraine.

6.68 In comparison to galcanezumab and fremanezumab, the ESC considered that atogepant had a similar safety profile apart from injection site AEs that arose from the subcutaneous administration of the two comparator treatments. Atogepant had a higher incidence of gastrointestinal events compared to galcanezumab and fremanezumab, although these were of mild or moderate severity. Overall, atogepant appeared to be safe and well tolerated in participants with episodic migraine. The ESC noted that there were differences in the type of adverse events, due to the difference in the modes of administration of the agents.

6.69 The ESC noted that the applicability of the trial evidence to the proposed PBS population was highly uncertain as no evidence was presented specifically for the HFEM population who had failed at least three preventive medications. The atogepant ADVANCE and NCT02848326 trials included participants with less severe disease (four to 14 migraine days per month) than the proposed PBS population (at least eight days of migraine headache per month). No subgroup analyses for participants with HFEM were presented. Further, no data was presented on participants in the ADVANCE and NCT02848326 trials who had three or more prior preventive treatment failures.

6.70 For EM, the PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.71 For EM, the PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.72 The submission presented a CMA based on the claim of non-inferior effectiveness and safety for atogepant compared to galcanezumab. As noted in paragraph 5.3, fremanezumab may be considered an alternative therapy.

6.73 Table 15 presents the elements used to calculate equi-effective doses.

Table 15: Elements used to calculate the equi-effective dose

Treatment	Dose	Pack size	Days per pack	Treatment regimen
Atogepant	60 mg tablet once daily	28 tablets	28	Ongoing
Galcanezumab	Loading dose: 2 x 120 mg SC injections	2 injections	30	
	Maintenance dose: 1 x 120 mg SC injection	1 injection	30	

Source: Tables 3-2, 3-3 & 3-4, pp156-157 of the submission.
SC = subcutaneous.

6.74 The dosing regimens were consistent with the draft TGA Product Information for atogepant and approved Product Information for galcanezumab.

6.75 On 1 April 2023, the published AEMP of galcanezumab was reduced from $498.59 to $463.00. The published AEMP of fremanezumab in March and April 2023 was $488.89.

6.76 The submission assumed that 10% of patients receiving galcanezumab would require medical assistance to use a pre-filled pen or auto-injector and cited vedolizumab as treatment for moderate to severe ulcerative colitis and Crohn's disease as the PBAC precedent for this assumption. The PBAC had previously accepted that 10% of patients would require assistance with injections involving 'a visit to a doctor' and considered that it was reasonable to assume 10% of patients receiving subcutaneous vedolizumab would require assistance (paragraph 6.48, vedolizumab PSD, November 2020 PBAC meeting). The ESC considered that the assumption that 10% of patients would require assistance with galcanezumab administration was likely overestimated and would decrease over the duration of treatment with galcanezumab. The pre-PBAC response reiterated that the assumption was reasonable.

6.77 Table 16 presents the results of the cost minimisation approach presented in the submission. This table also includes additional comparisons with the galcanezumab and fremanezumab April 2023 published prices conducted during the evaluation using the submission's CMA method.

Table 16: Results of the cost-minimisation approach

Component	Atogepant	Galcanezumab (March 2023)	*Galcanezumab (April 2023)*	*Fremanezumab (April 2023)*
Medicine costs (AEMP)				
Cost per dose (pack/injection)	$488.18	$498.59	*$463.00*	*$488.89*
Dose duration (pack/injection)	28 days	30 days	30 days	30 days
Units over 24 months	26.07[a]	25.33[b]	25.33[b]	24.33[c]
Total cost – medicine	$12,727.67	$12,630.95	$11,729.33	$11,896.32
Administration costs over 2 years				
Injections with medical assistance (10%)	0	2.43	2.43	2.43
Unit cost of medical assistance	$0	$39.75	$39.75	$39.75
Total cost – administration	$0	$96.73	$96.73	$96.73
TOTAL COST over 2 years	**$12,727.67**	**$12,727.67**	**$11,826.06**	**$11,993.05**
Difference in cost/2 years	**-**	**$0**	**-$901.61**	**-$734.62**
AEMP of atogepant	**-**	**$488.18**	**$453.60**	**$460.00**

Source: Table 3-4, p157 of the submission; calculated during evaluation.
AEMP = approved ex-manufacturer price.
[a] Calculation not presented in the submission but assumed in the evaluation to be = (365*2)/28
[b] Calculation not presented in the submission but assumed in the evaluation to be = (365*2)/30+1
[c] (365*2)/30

Drug cost/patient/2 years

6.78 The cost of atogepant over two years at the proposed published DPMQ and assuming 100% compliance was $17,787 compared with $14,149 for the comparator, galcanezumab (using March 2023 published prices and including loading dose).

Estimated PBS usage & financial implications

6.79 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial impacts associated with the PBS listing of atogepant for chronic migraine and HFEM. The key inputs used in the financial estimates are presented in the table below.

Table 17: Key inputs for financial estimates

Data	Value applied and source	Comment
Market size		
Scripts in current market (chronic migraine, 2022)	105,502 (Jan-Nov 22 PBS Item reports for galcanezumab (12478R & 12469G) and fremanezumab (12611R, 12603H, 13115G & 13129B) + 11,821 (linear extrapolation to estimate Dec)	The approach was reasonable, however actual data for Dec 22 were available at the time of the evaluation (12,212 scripts).
Market growth (chronic + HFEM)	78% in Year 1 with growth decreasing annually to 4% in Year 6. Based on logarithmic growth trend line fitted to historic PBS services 2019-2022. Assumed market was established, linear growth tested in sensitivity analyses	The ESC considered the assumptions regarding market growth were highly uncertain.
Treatment utilisation		
Uptake rate	5% in Year 1 with uptake increasing 5% annually to 30% in year 6. Based on assumptions.	No justification was provided for these assumptions.
Costs		
MBS costs	$39.75 (MBS item 23). Assumed 10% of patients receiving galcanezumab/ fremanezumab require medical assistance for injections	This was consistent with the cost-minimised price. However, the PBAC agreed with the ESC that the assumption that 10% of patients require injection assistance was uncertain.

Source: Tables 4-1, 4-3 & 4-5, pp162, 165 & 169 of the submission; Figure 4-1, p166 of the submission; Sheets 3a & 4b, Section 4 workbook.
DPMQ = dispensed price for maximum quantity; HFEM = high frequency episodic migraine; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

6.80 Table 18 presents the estimated financial implications for the listing of atogepant based on the proposed published price of atogepant (DPMQ = $682.26) (rather than the price calculated in Table 16) and the published price of galcanezumab in March 2023 (DPMQs = $1,111.02 initial and $559.08 continuing).

Table 18: Estimated use and financial implications (March 2023 published prices for comparators)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	[1]	[2]	[3]	[4]	[5]	[6]
Number of patients years	[7]	[7]	[7]	[7]	[8]	[8]
Estimated financial implications of atogepant						
Cost to PBS/RPBS less copayments ($)	[9]	[10]	[11]	[12]	[13]	[14]
Estimated financial implications for galcanezumab and fremanezumab						
Cost to PBS/RPBS less copayments ($)	[15]	[15]	[15]	[15]	[15]	[15]
Net financial implications						
Net cost to PBS/RPBS ($)	[9]	[9]	[9]	[9]	[10]	[10]
Net cost to MBS[a] ($)	[15]	[15]	[15]	[15]	[15]	[15]
Net cost to the Australian Government ($)	[9]	[9]	[9]	[9]	[10]	[10]

Source: Tables 4-6, 4-7, 4-8 & 4-10, pp169, 171, 173 & 175 of the submission.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
[a] The submission used the 80% benefit.
The redacted values correspond to the following ranges:
[1] *10,000 to < 20,000*
[2] *20,000 to < 30,000*
[3] *40,000 to < 50,000*
[4] *60,000 to < 70,000*
[5] *80,000 to < 90,000*
[6] *100,000 to < 200,000*
[7] *500 to < 5,000*
[8] *5,000 to < 10,000*
[9] *$0 to < $10 million*
[10] *$10 million to < $20 million*
[11] *$20 million to < $30 million*
[12] *$40 million to < $50 million*
[13] *$50 million to < $60 million*
[14] *$60 million to < $70 million*
[15] *net cost saving*

6.81 The submission expected that the net implications of substitution would be nil once the effective price of atogepant was derived and used with the effective prices of galcanezumab and fremanezumab.

6.82 The submission did not include sequential use and treatment of patients who are unsuitable for injections or needle phobic in the financial estimates in Table 18. However, the submission considered the impact of sequential use and uptake of atogepant in patients unsuitable for CGRP injections as part of the proposed risk sharing arrangement (RSA) (see Financial Management – Risk Sharing Arrangements section below). The ESC considered it would have been appropriate to include sequential use and use in patients unsuitable for CGRP injections in the financial model to estimate any potential additional cost to the PBS/ RPBS.

6.83 The submission noted that there would be 300 grandfathered patients from the atogepant patient familiarisation programme. The submission stated that grandfathered patients would be captured through the market share approach as these patients would have otherwise initiated and utilised galcanezumab or fremanezumab.

Quality Use of Medicines

6.84 The submission referred to the TGA risk management plan and stated that support would be provided to prescribers and patients.

6.85 That evaluation considered that given that CGRPs are a relatively new class of medicines with high potential for drug-drug interactions and the resulting potential need to reduce doses as a result of these interactions, further detail regarding the proposed support for prescribers and patients should have been provided. In particular, the quality use of medicines plan should provide guidance on dose reduction given the availability of a 10 mg dose, but that the submission is for the 60 mg strength only and dose reductions are required for some drug interactions.

Financial Management – Risk Sharing Arrangements

6.86 The submission noted the RSA currently in place for galcanezumab and fremanezumab. The submission proposed a separate RSA for atogepant as treatment for CM and HFEM to account for sequential treatment and patients who are eligible but unsuitable for CGRP injections. The submissions for galcanezumab and fremanezumab proposed increasing the existing CM RSA caps to include treatment for HFEM (paragraph 6.70, galcanezumab PSD, March 2022 PBAC meeting; paragraph 6.55, fremanezumab PSD, November 2022 PBAC meeting).

6.87 The submission proposed an RSA using three steps:

1. Calculate the magnitude of sequential treatment. Using March 2023 published prices for fremanezumab and galcanezumab, this was estimated to be an additional $10 million to < $20 million in Year 2, increasing to $40 million to < $50 million in Year 6, totalling $100 million to < $200 million over six years. No evidence was provided in the submission regarding the effectiveness or cost-effectiveness of sequential treatment of CGRP inhibitors.
2. Calculate the magnitude of patients unsuitable for injections or needle phobic. The submission estimated that 16% of patients were unsuitable for injections or needle phobic, based on a systematic review and meta-analysis of patients avoiding the influenza vaccination.
3. Account for substitution of current CGRPs. Based on March 2023 published prices for fremanezumab and galcanezumab, these savings were $0 to < $10 million in Year 1 increasing to $50 million to < $60 million in Year 6 and $100 million to < $200 million over six years (Table 18).

6.88 The ESC considered that the proposed RSA was not appropriate. The ESC noted that it was not appropriate to transfer the predicted cost offsets from the substitution of galcanezumab and fremanezumab to the proposed atogepant RSA. The ESC considered that, if recommended, atogepant should join the current CGRP RSA which should be expanded to include the HFEM population; however, the ESC noted this could not be determined from the information provided in the submission.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend atogepant for use as prophylaxis in adult patients with chronic migraine (CM) or high frequency episodic migraine (HFEM) who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications. The PBAC acknowledged that there was a need for an oral prophylactic migraine treatment but considered that the indirect treatment comparisons presented did not establish that atogepant was non-inferior in terms of effectiveness compared to the nominated comparators, galcanezumab and fremanezumab. The PBAC considered that the utilisation estimates were not adequately supported and that the structure of the Risk Sharing Arrangement (RSA) as proposed in the submission was poorly justified.

7.2 The key reason for this outcome was due to the comparative clinical evidence.

7.3 The PBAC acknowledged the consumer comments that highlighted the clinical need for an oral prophylactic migraine treatment and supported the submission.

7.4 The PBAC recalled that in March 2022, it had recommended that the currently listed CM indication for galcanezumab should be expanded to treatment-resistant migraine, which encompassed both CM and HFEM in a single indication. Fremanezumab received a similar recommendation in November 2022. The PBAC noted galcanezumab and fremanezumab were currently only listed for CM and the expansion to treatment-resistant migraine had not progressed.

7.5 The PBAC accepted the proposed place in therapy as a fourth line prophylactic treatment for CM and HFEM.

7.6 The PBAC considered that the nomination of galcanezumab and fremanezumab as comparators was appropriate (although both agents are currently PBS listed for CM only).

7.7 The PBAC noted that the proposed PBS restriction for atogepant was consistent with the restriction recommended for treatment-resistant migraine recommended for galcanezumab and fremanezumab (see paragraph 7.4).

7.8 The PBAC noted that as there were no head-to-head trials comparing atogepant with either galcanezumab or fremanezumab, the submission was based on a number of indirect treatment comparisons (ITCs).

7.9 The PBAC noted that for the CM indication, the evidence consisted of one randomised trial (PROGRESS) comparing atogepant with placebo and five trials comparing either galcanezumab (REGAINE and CONQUER) or fremanezumab (HALO-CM, NCT03303079 and FOCUS) with placebo. The PBAC noted that there were substantial differences between the trials, as outlined in paragraph 6.22, including the mean number of prior prophylactic medications trialled (1.5 to 1.6 in the atogepant trial compared to 3.8 to

4.0 in the galcanezumab and fremanezumab trials). The PBAC noted that there were applicability issues with the PROGRESS trial as only five enrolled patients met the proposed PBS restriction criteria and had received three or more prior prophylactic treatments.

7.10 The PBAC noted that for the HFEM indication, the evidence consisted of two randomised trials comparing atogepant with placebo (ADVANCE and NCT02848326) and eight trials comparing either galcanezumab (EVOLVE-1, EVOLVE-2, PERSIST, NCT02959177 and CONQUER) or fremanezumab (HALO-EM, NCT03303092 and FOCUS) with placebo. The PBAC noted that there were substantial differences between the trials, as outlined in paragraph 6.23, including differences in the proportions of patients who had failed prior prophylactic treatments and the mean number of migraine days per month. Further, the PBAC noted that no evidence was presented for the HFEM population.

7.11 For CM, the PBAC noted that the indirect comparison results between atogepant and galcanezumab demonstrated no statistical differences in terms of change in the mean number of monthly migraine days and proportion of patients with a ≥ 50% reduction in monthly migraine days. For the comparisons with fremanezumab, the PBAC noted that although the results for change in the mean number of monthly migraine days were not statistically different, the results for the proportion of patients with a ≥ 50% reduction in monthly migraine days statistically favoured fremanezumab. For HFEM, the PBAC noted that the indirect comparison results demonstrated no statistical differences between atogepant and galcanezumab or fremanezumab in terms of change in the mean number of monthly migraine days and the proportion of patients with a ≥ 50% reduction in monthly migraine days. The PBAC noted that the point estimates for both outcomes consistently favoured the comparators. The PBAC noted that the upper 95% confidence interval exceeded the proposed non-inferiority margin of 2 days for the change from baseline in the mean number of monthly migraine days for the atogepant vs galcanezumab and fremanezumab comparisons for CM and HFEM, further suggesting that atogepant was potentially inferior.

7.12 The PBAC considered that based on the issues outlined above, the claim that atogepant was non-inferior in terms of efficacy compared to galcanezumab and fremanezumab was not adequately supported.

7.13 In terms of safety, the PBAC noted that atogepant was associated with mild to moderate gastrointestinal events and galcanezumab and fremanezumab were associated with injection site reactions and erythema. On balance, the PBAC considered that atogepant had a similar safety profile to galcanezumab and fremanezumab.

7.14 The PBAC noted that the submission presented a CMA that compared atogepant to galcanezumab. The PBAC considered the structure of the CMA was reasonable but agreed with ESC that the assumption that 10% of patients would require assistance with galcanezumab administration was poorly justified, likely overestimated and

would decrease over the duration of treatment.

7.15 The PBAC considered that the utilisation estimates presented in Table 18 were not adequately supported. The PBAC noted that the assumptions regarding market growth were highly uncertain and that the uptake rates given oral administration were likely underestimated. Further, the PBAC noted that the estimates presented in Table 18 did not include the potential additional use associated with sequential use or treatment of patients who were needle phobic or unsuitable for injections; however, these patients were included in the proposed RSA (see paragraph 7.17).

7.16 The PBAC noted no evidence was provided supporting the clinical effectiveness or cost-effectiveness of sequential use of CGRP inhibitors. The PBAC considered the extent of use of atogepant in patients who were needle phobic or unsuitable for injections was poorly supported in the submission.

7.17 The PBAC noted that the submission proposed an RSA which was separate from the current CGRP inhibitor RSA for CM. Further, the PBAC noted that the submission proposed that the predicted cost offsets from the substitution of galcanezumab and fremanezumab would be transferred to the atogepant RSA and that the atogepant RSA would account for sequential use and use in patients who were need phobic or unsuitable for injections. The PBAC considered that, if recommended, atogepant should join the current CGRP inhibitor RSA, ensuring effective management of Commonwealth expenditure across all CGRP inhibitors. The PBAC further noted that the RSA should be expanded to include the HFEM population (if fremanezumab and galcanezumab do not progress recommendations for this population). The PBAC recalled it had previously provided advice regarding the size of the HFEM population (paragraph 7.9, fremanezumab PSD, November 2022 PBAC meeting). Further proposed additional costs to the Commonwealth, including those attributed to sequential use and use in needle phobic patients would need to be appropriately justified (see paragraph 7.16).

7.18 In terms of quality use of medicines, the PBAC noted that a 10 mg dose was included in the draft Product Information for use in patients with severe renal impairment or who receive strong CYP3A4 or OATP inhibitors. The PBAC considered that, if the 10 mg dose was not included in a future submission, details should be provided as to how dose reductions should be managed.

7.19 The PBAC considered a resubmission for atogepant should address the following issues:

- The outstanding uncertainty in the non-inferiority efficacy claim by providing any additional available data for atogepant in the CM and HFEM populations;
- Present a revised CMA removing the assumption that 10% of galcanezumab patients would require administration assistance (see paragraph 7.14);
- Provide revised utilisation and financial impact estimates and propose an RSA that addresses the issues outlined in paragraphs 7.15, 7.16 and 7.17.

The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

AbbVie is disappointed with this outcome.