Calcitonin gene-related peptide (CGRP)-targeting antibodies as a first-line option for the prevention of migraine in adults: A Japanese Headache Society position statement.

The Board of Directors, the Japanese Headache Society in collaboration with the Clinical Practice Guideline Committee, the Japanese Headache Society

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<Recommendations>

Calcitonin gene-related peptide (CGRP)-targeting monoclonal antibodies should be considered as a first-line therapy for migraine prevention in adults along with the other preventive medications approved in Japan, including CGRP receptor antagonists.

<Commentary and Evidence>

Role of CGRP in the pathophysiology of migraine

CGRP was first discovered in 1982 as a novel 37-amino-acid neuropeptide derived from a splice variant of the calcitonin gene [1]. Subsequently, a distinct isoform produced from a separate gene was discovered. The original calcitonin-gene-derived form is termed α-CGRP, and the later-identified isoform is called ß-CGRP [2]. In migraine pathogenesis, α-CGRP plays a principal role and predominates—by more than tenfold—in the trigeminal system. Hereafter, the term "CGRP" is used to refer to this isoform.
CGRP is abundantly expressed in first-order trigeminal neurons closely associated with migraine pathophysiology [3]. Higher circulating CGRP levels in migraine patients have been reported compared to healthy controls [4, 5]. Moreover, intravenous administration of CGRP has been shown to trigger migraine attacks in individuals with migraine [6, 7]. These findings support the causative involvement of CGRP in migraine. CGRP was considered as a *bona fide* therapeutic target of migraine, which eventually led to the development of CGRP-receptor antagonists (gepants) and CGRP-targeting monoclonal antibodies.

Clinical trial data on CGRP-targeting monoclonal antibodies in Japanese Populations

Galcanezumab [8]

In a six-month randomized, placebo-controlled trial among Japanese patients with episodic migraine (EM), participants were randomized to receive galcanezumab 120 mg (with an initial dose of 240 mg; n = 115), galcanezumab 240 mg (n = 114), or placebo (n = 230), administered monthly. The primary outcome was the change from baseline in monthly migraine days. Compared to placebo (−0.59 days), both galcanezumab groups showed statistically significant reductions (−3.6 days for 120 mg, −3.36 days for 240 mg; $p < 0.001$). The most common treatment-emergent adverse event

(TEAE) was injection-site erythema, occurring in 2.2% of placebo recipients, 14.8% of the 120 mg group, and 27.2% of the 240 mg group.

Fremanezumab

In a three-month randomized controlled trial targeting EM patients, subjects were assigned to receive fremanezumab 225 mg (n = 121), a one-time 675 mg dose (n = 117), or placebo (n = 116), administered at 4-week intervals [9]. Monthly migraine days decreased by −4.0 days in both fremanezumab groups, compared to −1.0 day in the placebo group ($p < 0.0001$). Injection-site redness was the most frequent TEAE (placebo 12.8%, 225 mg 15.7%, 675 mg 11.9%).

In a separate three-month RCT enrolling chronic migraine (CM) patients, subjects received fremanezumab 225 mg (initial dose 675 mg; n = 189), a single 675 mg dose (n = 191), or placebo (n = 191), with dosing every four weeks [10]. The primary endpoint—change from baseline in monthly days with moderate-to-severe headache—decreased by −4.1 days in both treatment groups, compared to −2.4 days in the placebo group ($p < 0.001$). Injection-site erythema was reported in 11.0% (placebo), 15.4% (225 mg), and 12.1% (675 mg).

Erenumab [11]

In a six-month placebo-controlled RCT including both EM and CM patients, erenumab 70 mg (n = 130) versus placebo (n = 131) was administered monthly. Over months 4–6, monthly migraine days decreased by −3.60 days with erenumab versus −1.98 days with placebo ($p < 0.001$). The most common TEAE was nasopharyngitis, occurring in 28.2% of the treatment group and 26.9% of the placebo group.

Clinical Use Aligned with Optimal-Use Promotion Guidelines

Currently, the three CGRP-targeting monoclonal antibodies are administered in accordance with optimal-use promotion guidelines as outlined below:

<Patient Selection Criteria>

Prior to initiating therapy, patients must satisfy all of the following conditions:

1. A thorough clinical evaluation, guided by the *International Classification of Headache Disorders, 3rd edition (ICHD-3)*, confirms

the presence of multiple monthly episodes of migraine—with or without aura—or diagnosis of chronic migraine.

2. For at least three months before treatment, patients must have averaged ≥ 4 monthly migraine days.
3. Patients must have already engaged in non-pharmacological interventions—such as sleep hygiene, dietary guidance, maintenance of appropriate body weight, and stress management—along with acute-phase migraine treatments; despite these measures being adequately applied, patients continue to experience significant interference with daily life.
4. Among migraine prophylactic agents approved in Japan—such as propranolol hydrochloride, sodium valproate, and lomerizine hydrochloride—patients must be unable to use or continue at least one due to one or more of the following reasons:
    - Inadequate effectiveness
    - Poor tolerability
    - Contraindications or significant safety concerns

<Criteria for continuation or discontinuation of therapy>
Throughout treatment, patients should be closely monitored. Approximately three months (after three doses) following therapy initiation, the clinical benefit should be evaluated. If no symptom improvement is observed, discontinuation should be considered. Thereafter, the requirement for ongoing therapy should be periodically reassessed, particularly if migraine frequency or severity declines to the extent that daily life is no longer significantly impaired.

Real-world clinical use and its implications

Over more than four years of clinical exposure, multiple real-world data involving Japanese patients have been released (see **Table 1**) [12-23]. Although these real-world data lack the methodological rigor of RCTs, they demonstrate efficacy and safety consistent with RCT findings. Notably, while RCTs often impose stringent inclusion criteria, real-world practice encompasses patients with broader age ranges and comorbidities, thereby enhancing the clinical relevance of these outcomes.
However, the high cost of therapy—including drug expenses—remains a major consideration from a health-economic standpoint. Accordingly, both

patients and healthcare providers should discuss treatment goals and cost-effectiveness to build sustainable and realistic therapeutic plans when introducing CGRP-targeting monoclonal antibody therapies.

Global landscape of therapies targeting the CGRP pathway

The clinical adoption of CGRP-targeted therapies began earlier in the United States and European countries and has produced substantial real-world evidence—one study analyzing approximately 5,800 cases supports both efficacy and safety [24]. In 2022, the European Headache Federation (EHF) guidelines recommended incorporating CGRP-related antibodies among first-line preventive options for migraine [25]. The guidelines warned that delaying initiation of CGRP-based treatment—in favor of less optimal prophylactics—might delay patient benefit and potentially promote migraine chronification.

Subsequently, CGRP receptor antagonists (gepants) were approved for migraine therapy. In 2024, the American Headache Society (AHS) issued a position statement placing CGRP-related therapies alongside topiramate, valproate, and β-blockers as first-line prophylactic options—targeting chronic migraine patients and episodic migraine patients with moderate-to-severe disability (e.g., MIDAS ≥ 11 or HIT-6 > 50) [26].

In 2025, the International Headache Society (IHS) published evidence-based guidelines that strongly recommend CGRP-targeting agents ("Strong in favor") [27]. The IHS further advocates reducing monthly migraine or moderate-to-severe headache days to less than four for optimal headache control [28]. This threshold aligns closely with the Japanese 2021 Clinical Practice Guidelines' recommendation to consider prophylaxis for patients experiencing three or more disabling headache days per month **(CQII-3-1)[※]**.

Altogether, global trends are moving towards earlier introduction of CGRP-targeting therapies to strengthen migraine prevention.

Conclusion

Migraine is a very disabling disorder [29]. There is growing global consensus that CGRP-related medications should be recommended as first-line options for migraine prevention. Real-word evidence has been accumulating that CGRP-targeting antibodies are effective for migraine prevention with

favorable safety profiles in Japanese patients. Consequently, the Board of Directors, the Japanese Headache Society recommends that CGRP-targeting monoclonal antibodies be considered as a first-line therapy for migraine prevention in adults along with the other preventive medications approved in Japan, including CGRP receptor antagonists. However, prior to their use, it is essential to confirm the diagnosis of migraine, analyze the current headache status, provide lifestyle guidance as outlined in the Optimal Use Promotion Guidelines, and emphasize shared decision-making with the patient.

References

1. Amara SG, Jonas V, Rosenfeld MG, Ong ES, Evans RM (1982) Alternative RNA processing in calcitonin gene expression generates mRNAs encoding different polypeptide products. Nature 298(5871):240-244. https://doi.org/10.1038/298240a0.
2. Alevizaki M, Shiraishi A, Rassool FV, Ferrier GJ, MacIntyre I, Legon S (1986) The calcitonin-like sequence of the beta CGRP gene. FEBS Lett 206(1):47-52. https://doi.org/10.1016/0014-5793(86)81338-2.
3. Edvinsson L, Haanes KA, Warfvinge K, Krause DN (2018) CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol 14(6):338-350. https://doi.org/10.1038/s41582-018-0003-1.
4. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28(2):183-187. https://doi.org/10.1002/ana.410280213.
5. Garate G, Pascual J, Pascual-Mato M, Madera J, Martin MM, Gonzalez-Quintanilla V (2024) Untangling the mess of CGRP levels as a migraine biomarker: an in-depth literature review and analysis of our experimental experience. J Headache Pain 25(1):69. https://doi.org/10.1186/s10194-024-01769-4.
6. Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J (2002) CGRP may play a causative role in migraine. Cephalalgia 22(1):54-61. https://doi.org/10.1046/j.1468-2982.2002.00310.x.
7. Hansen JM, Hauge AW, Olesen J, Ashina M (2010) Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia 30(10):1179-1186. https://doi.org/10.1177/0333102410368444.
8. Sakai F, Ozeki, A., Skljarevski, V. (2020) Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: A

phase 2 randomized controlled clinical trial. Cephalalgia Rep 3:1-10.

9. Sakai F, Suzuki N, Kim BK, Tatsuoka Y, Imai N, Ning X, et al. (2021) Efficacy and safety of fremanezumab for episodic migraine prevention: Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. Headache 61(7):1102-1111. https://doi.org/10.1111/head.14178.
10. Sakai F, Suzuki N, Kim BK, Igarashi H, Hirata K, Takeshima T et al. (2021) Efficacy and safety of fremanezumab for chronic migraine prevention: Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. Headache 61(7):1092-1101. https://doi.org/10.1111/head.14169.
11. Takeshima T, Sakai F, Hirata K, Imai N, Matsumori Y, Yoshida R et al. (2021) Erenumab treatment for migraine prevention in Japanese patients: Efficacy and safety results from a Phase 3, randomized, double-blind, placebo-controlled study. Headache 61(6):927-935. https://doi.org/10.1111/head.14138.
12. Takizawa T, Ohtani S, Watanabe N, Miyazaki N, Ishizuchi K, Sekiguchi K et al. (2022) Real-world evidence of galcanezumab for migraine treatment in Japan: a retrospective analysis. BMC Neurol 22(1):512. https://doi.org/10.1186/s12883-022-03041-1.
13. Suzuki S, Suzuki K, Shiina T, Haruyama Y, Hirata K (2023) Real-world experience with monthly and quarterly dosing of fremanezumab for the treatment of patients with migraine in Japan. Front Neurol 14:1220285. https://doi.org/10.3389/fneur.2023.1220285.
14. Ito Y, Mitsufuji T, Okada M, Fujita S, Yokoyama R, Kawasaki H et al. (2023) Early Effect of Calcitonin Gene-related Peptide Monoclonal Antibodies in Migraine with Medication Overuse: A Single-center Retrospective Study. Intern Med 62(23):3455-3460. https://doi.org/10.2169/internalmedicine.1471-22.
15. Suzuki K, Suzuki S, Shiina T, Tatsumoto M, Fujita H, Haruyama Y et al. (2023) Effectiveness of three calcitonin gene-related peptide monoclonal antibodies for migraine: A 12-month, single-center, observational real-world study in Japan. Cephalalgia 43(5):3331024231177649. https://doi.org/10.1177/03331024231177649.
16. Ohtani S, Watanabe N, Ihara K, Takahashi N, Miyazaki N, Ishizuchi K et al. (2023) Real-world evidence of fremanezumab for treating migraine in Japan: a retrospective study. BMC Neurol 23(1):404. https://doi.org/10.1186/s12883-023-03449-3.
17. Sadamoto Y.(2023) Efficacy of erenumab on absenteeism and presenteeism in migraine patients using MIDAS. Japanese J Headache 50(1):140-147. https://doi.org/10.50860/jjho.50.1_140. (in Japanese, Abstract in English)
18. Tanei T, Fuse Y, Maesawa S, Nishimura Y, Ishizaki T, Nagashima Y et al. (2024) Real-

world clinical results of CGRP monoclonal antibody treatment for medication overuse headache of migraine without abrupt drug discontinuation and no hospitalization. Heliyon 10(22):e40190. https://doi.org/10.1016/j.heliyon.2024.e40190.

19. Shibata M, Fujita K, Hoshino E, Minami K, Koizumi K, Okada S et al. (2024) Real-world experience with calcitonin gene-related peptide-targeted antibodies for migraine prevention: a retrospective observational cohort study at two Japanese headache centers. BMC Neurol 24(1):32. https://doi.org/10.1186/s12883-023-03521-y.
20. Sanno N, Basugi A, Ohta M, Sakai F. (2023) Real-world evidence of prevention of migraine with CGRP related monoclonal antibodies – the characteristics of patients positive stopping - . Japanese J Headache 50(3):605-611. https://doi.org/10.50860/jjho.50.3_605. (in Japanese, Abstract in English)
21. Kikui S, Daisuke D, Miyahara J, Sugiyama H, Ota K, Murakata K et al. (2024) Effectiveness of fremanezumab treatment in patients with migraine headache. Pain Med 25(11):664-670. https://doi.org/10.1093/pm/pnae050.
22. Yamamoto M, Furukawa Y, Miyauchi A, Hara W, Monma K, Kaida K (2024) Effectiveness and safety of galcanezumab for prevention of chronic and episodic migraine. Neurological Therapeutics 41(3):442-446. https://doi.org/10.15082/jsnt.41.3_442.(in Japanese, Abstract in English)
23. Ihara K, Takahashi N, Ohtani S, Watanabe N, Ishizuchi K, Takemura R et al. (2025) Real-world Efficacy of Erenumab on Migraine-associated Symptoms and Patient-reported Satisfaction Levels: A Retrospective Study in Japan. Intern Med 64(6):825-831. https://doi.org/10.2169/internalmedicine.4037-24.
24. Caronna E, Gallardo VJ, Egeo G, Vazquez MM, Castellanos CN, Membrilla JA et al. (2024) Redefining migraine prevention: early treatment with anti-CGRP monoclonal antibodies enhances response in the real world. J Neurol Neurosurg Psychiatry 95(10):927-937. https://doi.org/10.1136/jnnp-2023-333295.
25. Sacco S, Amin FM, Ashina M, Bendtsen L, Deligianni CI, Gil-Gouveia R et al. (2022) European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. J Headache Pain 23(1):67. https://doi.org/10.1186/s10194-022-01431-x.
26. Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A, American Headache S (2024) Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. Headache 64(4):333-341. https://doi.org/10.1111/head.14692.
27. Ornello R, Caponnetto V, Ahmed F, Al-Khazali HM, Ambrosini A, Ashina S et al. (2025) Evidence-based guidelines for the pharmacological treatment of migraine.

Cephalalgia 45(4):3331024241305381. https://doi.org/10.1177/03331024241305381.

28. Sacco S, Ashina M, Diener HC, Haghdoost F, Lee MJ, Monteith TS et al. (2025) Setting higher standards for migraine prevention: A position statement of the International Headache Society. Cephalalgia 45(2):3331024251320608. https://doi.org/10.1177/03331024251320608.

29. Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Ozge A et al. (2021) Migraine: epidemiology and systems of care. Lancet 397(10283):1485-1495. https://doi.org/10.1016/S0140-6736(20)32160-7.

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Research Articles on Migraine Prevention with CGRP-related Monoclonal Antibodies in Japanese Patients

First Author	Year of Publication	Journal; Volume(Issue): First Page	Number of Cases					Efficacy	Adverse Events
			Overall	Galcanezumab	Fremanezumab (Monthly)	Fremanezumab (Quarterly)	Erenumab	50% RR	
Takizawa T, et al.	2022	BMC Neurology 22: 512	EM25/CM27	52				At 3M: Overall: 61.5% EM: 76.0% CM: 48.1%	No serious AEs; ISR 34.6%; constipation 4 (7.7%); fatigue 3 (5.8%); burning sensation 2 (3.8%); dizziness 2 (3.8%); urticaria, alopecia, limb stiffness, chills, eczema, hypertension, menstrual disorder, back pain, somnolence, headache 1 each (1.9%)
Suzuki S, et al.	2023	Frontiers in Neurology 14: 1220285	EM54/CM73		75	42		At 6M: Overall: 67.6% EM: 90.4% CM: 52.2%	No serious AEs; ISR 11 (8.6%); constipation 1 (0.8%); discontinuation 1 (due to ISR)
Ito Y, et al.	2023	Intern Med 62: 3455	EM with MOH6/CM with MOH28	16	10		8	At 1M (50% response rate not reported): Mean change -5.7 days	Not reported
Suzuki K, et al.	2023	Cephalalgia 43: 1	EM83/CM145	60	73	50	45	Overall: 1M 36.0%, 3M 48.2%, 6M 61.0%, 12M 73.7% EM: 1M 61.4%, 3M 66.3%, 6M 81.0%, 12M 91.7% CM: 1M 22.1%, 3M 39.3%, 6M 49.0%, 12M 62.9%	No serious AEs; ISR 22 (9.6%); constipation 6 (2.6%) [E 4, G 1, F 1]; mostly mild and transient, no additional treatment required
Ohtani S, et al	2023	BMC Neurology 23: 404	EM19/CM10		19	10 (M→Q)		At 4M: Overall 55.2%, Monthly 52.6%	ISR 16 (55.2%), mostly mild–moderate; severe in 2 (erythema, swelling); constipation, pruritus, rash, nausea, new-onset headache, back pain, scalp pain, palpitations, dizziness 1 each (3.4%)
Sadamoto Y	2023	Japanese J Headache 50: 140	EM53/CM22				75	At 6M (estimated from figure): Overall: 63.6%, EM: 65%, CM: 60%	No serious AEs; constipation 22.7% (mostly transient after initial dose, improved with laxatives); ISR pruritus 12%
Tanei T, et al.	2024	Heliyon 10:e40190	CM with MOH33	14	13		6	At 3M: 85.7%	None; 6 dropouts (non-AE related)
Shibata M, et al.	2024	BMC Neurology 24: 32	EM49/CM19	31	24		13	At 3M: Overall: 50.0% EM: 53.1% CM: 42.1%	No serious AEs; constipation 5 (7.4%); ISR 2 (2.9%); hypertension (SBP >20 mmHg), alopecia, diarrhea 1 each (1.5%); no discontinuation
Sanno N, et al.	2024	Japanese J Headache 50: 605	EM320/CM256	222	174 (no distinction between M and Q regimens)		180	At 6M: EM: G 63.0%, F 59.6%, E 66.7% CM: G 44.7%, F 39.1%, E 43.4%	No serious AEs; pain 82 (13.2%); erythema 60 (9.7%); pruritus 42 (6.8%); dizziness, fatigue, urticaria, constipation 2 each
Kikui S, et al.	2024	Pain Medicine 25: 664	EM38/CM55		93 (no distinction between M and Q regimens)			At 6M: EM 57.6%, CM 45.5% At 12M: EM 57.1%, CM 54.2%	No serious AEs; ISR 4; constipation, fatigue, rash, pruritus 1 each
Yamamoto M, et al.	2024	Neurological Therapeutics; 41: 442	EM17/CM18	35				At 6M: EM 88.2% At 3M: CM 27.8%	No serious AEs; 4 (11.4%): ISR, nausea, constipation, somnolence
Ihara K, et al.	2025	Intern Med 64: 825	EM8/CM11				19	At 3M: Overall 42%	ISR 6 (32%, mostly mild); constipation 4 (21%, all resolved spontaneously or with minimal treatment)
Yoshida S, et al.	2025	J Headache Pain 26: 51	EM13/CM14	27		27		At 3M: Overall: 70.4% EM: 83.3% CM: 46.7%	No serious AEs; ISR 1(3.7%)