Health Technology Assessment (HTA)

HTA Report: Appendices

Title	Calcitonin gene-related peptide antagonists for the prevention of migraine
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Technology	Erenumab (Aimovig®) Fremanezumab (Ajovy®) Galcanezumab (Emgality®) Eptinezumab (Vyepti®)
Type of Technology	Pharmaceuticals
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Appendix A: Conditions for CGRP antagonist reimbursement in Switzerland

Overview of the coverage conditions of erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®) and eptinezumab (Vyepti®) according to the Spezialitätenliste[1]:

1. The treatment needs an approval of costs by the health insurer after prior consultation with the medical officer. The granted approval of costs must cover a period of 12 months.
2. A Foederatio Medicorum Helveticorum (FMH)/Swiss Medical Association-certified specialist in neurology must make the diagnosis, prescribe the CGRP antagonist and supervise the follow-up.
3. Adult patients have to suffer for at least 1 year from either chronic or episodic migraines and their attacks have to be documented for at least 3 months. Chronic migraine patients have to experience migraines with attacks that last at least 4 hours on at least 15 days per month. Episodic migraine patients have to experience migraines with attacks that last at least 4 hours on at least 8 days per month. Their attacks have to be characterised by an aura or strong pain intensity combined with severe nausea/vomiting or severely debilitating photo- or phonophobia.
4. Patients have to be pre-treated with at least 2 prophylactic therapies including beta blockers, calcium antagonists, anticonvulsants or amitriptyline[a] for at least 3 months each. Patients have to either respond insufficiently to the prophylactic therapies or the prophylactic therapies are contraindicated for the patient, or they had to be discontinued due to documented and clinically relevant side effects. (An insufficient treatment response is defined as a lack of reduction in migraine days by at least 50% after 3 months of treatment compared to before commencing treatment.)
5. In order for the treatment to be continued after 3 months, the average number of days per month with a migraine have to be reduced compared to the average value for the 3 months before commencing treatment and the reduction has to be documented in a migraine journal. This must be assessed by the FMH specialist in neurology.
6. In order for the treatment to be continued after 6 months, the average number of days with a migraine have to be reduced by at minimum 50% compared to the average value for the

[a] Amitriptyline is not listed as an approved prior prophylactic treatment needed for the prescription of erenumab (Aimovig®).

3 months before commencing treatment and the reduction has to be documented in a migraine journal. This must be assessed by the FMH specialist in neurology and reported in writing to the health insurer's medical officer.

7. In the case of an insufficient response to treatment with either erenumab, galcanezumab, fremanezumab or eptinezumab after 3 or 6 months, all further treatment attempts with the same CGRP antagonist or treatment with the other 3 CGRP antagonists is not reimbursed.
8. Treatment with erenumab, galcanezumab, fremanezumab or eptinezumab must be discontinued no later than 1 year after treatment initiation. In the case of a relapse within 6 months of discontinuation (i.e. at least 8 migraine days in a month), the resumption of treatment with a CGRP antagonist can be requested for an additional 12 months via a renewed approval of costs. If a relapse occurs after 6 months from discontinuation, the patient must meet the initial criteria for reimbursement as previously met for the first prescription.
9. Each subsequent year of treatment must meet the criteria listed above, where treatment must be discontinued and only recommenced upon relapse, with patients needing to meet the appropriate reimbursement criteria. This process may continue for as long as the treatment is still necessary and effective for the patient.
10. Upon request the following evidence must be submitted to the health insurer's medical officer:
    a. Documentation of the duration, and insufficient response to prior prophylactic treatment before commencing a CGRP antagonist (i.e. based on medical records or migraine diary)
    b. Before commencing treatment: A migraine diary recording 3 months prior to commencing CGRP antagonist treatment
    c. Post-initiation of treatment: A migraine diary recording 3, 6 and 12 months of CGRP antagonist treatment

NOTE 1: The pack of Ajovy® 3 pre-filled syringes is only reimbursed for the explicit prescription of the quarterly dosing schedule.

NOTE 2: If 2 Emgality® pre-filled pens are used in the first month of treatment, Eli Lilly (Suisse) SA will reimburse CHF449.36 for one pre-filled pen at the request of the health insurer with whom the insured person was insured at the respective reference point. Value added tax (i.e. Mehrwertsteuer) cannot be reclaimed in addition to this amount. The request for reimbursement should generally be made within 6 months of the invoice being issued.

NOTE 3: For patients who require 300 mg of Vyepti® per infusion (according to prescription information), a fixed proportion of the costs for the second and third administered pack of Vyepti® 100 mg will be reimbursed by Lundbeck (Switzerland) AG based on the ex-factory price at the request of the health insurer with whom the insured person was insured at the time of procurement of the medicine. Lundbeck (Switzerland) AG will notify the health insurer of the reimbursement amount. Value added tax (i.e. Mehrwertsteuer) cannot be reclaimed in addition to this amount. The health insurer requests for reimbursement from Lundbeck (Switzerland) AG. Reimbursement requests should be made from the time of administration.

Appendix B: Sources of literature (databases)

Literature sources

Table A1 Biomedical bibliographic databases

Source	Website
OVID—Medline & Embase (combined)	https://ovidsp.ovid.com/
The Cochrane Library	https://www.cochranelibrary.com/
EconLit	https://www.aeaweb.org/econlit/
INAHTA HTA Database	https://database.inahta.org/
Cost-Effectiveness Analysis (CEA) Registry hosted by Tufts Medical Centre	https://cevr.tuftsmedicalcenter.org/databases/cea-registry

Abbreviations
CEA Registry = Cost-Effectiveness Analysis Registry hosted by Tufts Medical Centre, **DARE** = Database of Abstracts of Reviews of Effects, **HTA** = Health Technology Assessment Database, **NHS EED** = National Health Service Economic Evaluation Database, **York CRD** = University of York Centre for Reviews and Dissemination.

Table A2 Clinical trial registries

Source	Website
ClinicalTrals.gov	https://clinicaltrials.gov/
EU Clinical Trials Registry	https://www.clinicaltrialsregister.eu/

Abbreviations
EU = European Union.

Table A3 HTA agency websites

Source	Website
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Austria	
Austrian Institute for Health Technology Assessment (AIHTA)	https://aihta.at/page/homepage/en
Gesundheit Österreich GmbH (GOG)	http://www.goeg.at
Argentina	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar
Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Brazil	
National Committee for Technology Incorporation (CONITEC)	http://conitec.gov.br/en/
Agência Nacional de Saúde Suplementar/ National Regulatory Agency for Private Health Insurance and Plans (ANS)	https://www.gov.br/ans/pt-br

Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Ontario Health (OH)	https://www.ontariohealth.ca/
Colombia	
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co
Denmark	
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/
Assistance Publique – Hôpitaux de Paris	http://cedit.aphp.fr
Germany	
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
Kazakhstan	
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development (RCHD)	http://www.rcrz.kz
Korea	
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng
Malaysia	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Norway	
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Peru	
Institute of Health Technology Assessment and Research (IETSI)	http://www.essalud.gob.pe/ietsi/

Poland	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Republic of China, Taiwan	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw
Russian Federation	
Center for Healthcare Quality Assessment and Control (CHQAC)	www.rosmedex.ru
Singapore	
Agency for Care Effectiveness (ACE)	Agency for Care Effectiveness (ACE) (ace-hta.gov.sg)
Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
Tunisia	
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr
United Kingdom	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html
Uruguay	
Health Assessment Division, Ministry of Public Health (HAD)	http://www.msp.gub.uy

Source:
Based on the INAHTA members list[2]

Table A4 Specialty websites

Source	Website
Australia	
Australian Pain Society	https://www.apsoc.org.au/Home
The Australian and New Zealand Headache Society	https://anzheadachesociety.org/
Australian and New Zealand Association of Neurologists	https://www.anzan.org.au/
Migraine and Headache Australia	https://headacheaustralia.org.au/#
Global	
International Association of the study of pain	https://www.iasp-pain.org/
International Headache Society	https://his-headache.org/en/resources/
World Federation of Neurology	https://wfneurology.org/
USA	
American Headache Society	https://americanheadachesociety.org/resources/
American Academy of Neurology	https://www.aan.com/
Canada	
Canadian Headache Society	https://headachesociety.ca/
United Kingdom	
Association of British Neurologists	https://www.theabn.org/
British Association for the Study of Headache	https://www.bash.org.uk/
Europe	
European Headache Federation	https://www.ehf-headache.com/
European Academy of Neurology	https://www.ean.org/
Danish Headache Society	https://dhos.dk/
Dutch Headache Society (NHV)	https://www.nederlandsehoofdpijnvereniging.nl/
French Headache Society	https://sfemc.fr/17-sfemc.html
German Society for Neurology (DGN)	https://dgn.org/
German Migraine and Headache Society (DMKG)	https://www.dmkg.de/german-migraine-and-headache-society
Portuguese Headache Society	http://www.cefaleias-spc.com/
Swiss Headache Society	https://headache.ch/DirectLinks/Home
South America	
Brazilian Headache Society	https://sbcefaleia.com.br/
Latin America	
Mexican Association of Headaches and Migraines	https://amcemig.com/

Search results

Systematic review search results

Table A5 Summary of biomedical bibliographic database search results

Database	Results
OVID—Medline & Embase (combined)	5852
Cochrane Library	1407
EconLit	41
INAHTA Database	9
CEA Registry	3
Total	**7,312**

Abbreviations
CEA Registry = Cost-Effectiveness Analysis Registry hosted by Tufts Medical Centre, **DARE** = Database of Abstracts of Reviews of Effects, **HTA** = Health Technology Assessment Database, **NHS EED** = National Health Service Economic Evaluation Database, **York CRD** = University of York Centre for Reviews and Dissemination.

Postface: Systematic review search results (updated search)

Table A6 Summary of biomedical bibliographic database search results (updated search)

Database	Results
OVID—Medline & Embase (combined)	924
Cochrane Library—CENTRAL	251
EconLit	0
INAHTA HTA Database	0
CEA Registry	0
Total	**1,175**

Abbreviations
CEA Registry = Cost-Effectiveness Analysis Registry hosted by Tufts Medical Centre, **DARE** = Database of Abstracts of Reviews of Effects, **HTA** = Health Technology Assessment Database, **NHS EED** = National Health Service Economic Evaluation Database, **York CRD** = University of York Centre for Reviews and Dissemination.

Efficacy, effectiveness, and safety search results

Table A7 Search strategy – Ovid (Medline and Embase) [09-03-2022]

Population	1.	Migraine*.mp	122,926
	2.	exp migraine/	101,330
	3.	'episodic migraine'.mp	5,039
	4.	'chronic migraine'.mp	8,825
Comparator	5.	'calcitonin gene related peptide'.mp	36,875
	6.	exp calcitonin gene related peptide/	28,105
	7.	'$CGRP$'.mp	25,239
	8.	Erenumab.mp	1,458
	9.	(AMG334 OR AMG 334 OR AMG-334).mp	140
	10.	Fremanezumab.mp	1,094
	11.	(TEV48125 OR TEV 48125 OR TEV-48125).mp	124
	12.	Galcanezumab.mp	1,043
	13.	LY2951742.mp	112
	14.	(Eptinezumab OR eptinezumab-jjmr).mp	468
	15.	**ALD403.mp**	61
Search string	16.	**Or/1-4**	**122,965**
	17.	**Or/5-15**	**40,393**
	18.	**16 and 17**	**7,468**
Search string (10-year filter)	19.	**Limit 18 to last 10 years**	**5,852**

Table A8 Search strategy – Cochrane Library [09-03-2022]

Population	1.	(Migraine):ti,ab,kw	8,757
	2.	MeSH descriptor: [Migraine Disorders] explode all trees	2,940
	3.	**#1 OR #2**	8,757
Comparator	4.	(calcitonin gene related peptide):ti,ab,kw	1,227
	5.	(CGRP):ti,ab,kw	992
	6.	MeSH descriptor: [calcitonin gene related peptide] explode all trees	354
	7.	(erenumab):ti,ab,kw	284
	8.	((AMG334):ti,ab,kw OR (AMG 334):ti,ab,kw OR (AMG-334):ti,ab,kw)	69
	9.	(fremanezumab):ti,ab,kw	401
	10.	((TEV48125):ti,ab,kw OR (TEV 48125):ti,ab,kw OR (TEV-48125):ti,ab,kw)	49
	11.	(Galcanezumab):ti,ab,kw	264
	12.	(LY2951742):ti,ab,kw	56
	13.	((Eptinezumab):ti,ab,kw OR (**eptinezumab-jjmr**):ti,ab,kw)	149
	14.	**(ALD403)**:ti,ab,kw	31
	15.	**#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14**	**1,970**
Search string	16.	**#3 AND #15**	**1,444**
Search string (10-year filter)	17.	**#17 with Cochrane Library publication date from Mar 2012 to Mar 2022**	**1,407**

Economic search results

Table A9 Search strategy – EconLit [09-03-2022]

Population	1.	Migraine	41
Comparator	2.	Calcitonin gene-related peptide	2
	3.	CGRP	0
	4.	Erenumab	0
	5.	Fremanezumab	0
	6.	Galcanezumab	0
	7.	Eptinezumab	0
Search string	8.	**#1 OR #2**	**41**

Abbreviations
CGRP = calcitonin gene-related peptide.

Table A10 Search strategy – INAHTA HTA Database [09-03-2022]

Population	1.	Migraine	72
Comparator	2.	Calcitonin gene-related peptide	0
	3.	CGRP	1
	4.	Erenumab	4
	5.	Fremanezumab	3
	6.	Galcanezumab	4
	7.	Eptinezumab	0
Search string	8.	**#1 AND #2 OR #3 OR #4 OR #5 OR #6 OR #7**	**9**

Abbreviations
CGRP = calcitonin gene-related peptide, **INAHTA** = International Network of Agencies for Health Technology Assessment.

Table A11 Search strategy – CEA Registry [09-03-2022]

Population	1.	Migraine	21
Comparator	2.	Calcitonin gene-related peptide	0
	3.	CGRP	0
	4.	Erenumab	3
	5.	Fremanezumab	0
	6.	Galcanezumab	0
	7.	Eptinezumab	0
Search string	8.	**#1 AND #4**	**3**

Abbreviations
CGRP = calcitonin gene-related peptide, **CEA Registry** = Cost-Effectiveness Analysis Registry hosted by Tufts Medical Centre.

Clinical trials search results

Table A12 Clinical trials search strategy [09-03-2022]

Database	Search strategy	Results
Clinicaltrials.gov	(CGRP AND Migraine) OR (Calcitonin gene-related peptide AND Migraine) OR Fremanezumab AND Migraine) OR (Galcanezumab AND Migraine) OR (Erenumab AND Migraine) OR (Eptinezumab AND Migraine)	CGRP AND Migraine: 38 Calcitonin gene-related peptide AND Migraine: 36 Fremanezumab AND Migraine: 11 Galcanezumab AND Migraine: 10 Erenumab AND Migraine: 25 Eptinezumab AND Migraine: 8 **Sub-total: 103**
EU Clinical Trials Registry	(CGRP AND Migraine) OR (Calcitonin gene-related peptide AND Migraine) OR Fremanezumab AND Migraine) OR (Galcanezumab AND Migraine) OR (Erenumab AND Migraine) OR (Eptinezumab AND Migraine)	CGRP AND Migraine: 6 Calcitonin gene-related peptide AND Migraine: 4 Fremanezumab AND Migraine: 6 Galcanezumab AND Migraine: 4 Erenumab AND Migraine: 9 Eptinezumab AND Migraine: 3 **Sub-total: 32**
	Total	**135**

Abbreviations
CGRP = calcitonin gene-related peptide, **EU** = European Union.

Postface: Efficacy, effectiveness, and safety search results (updated search)

Table A13 Search strategy for Ovid (Medline and Embase) – 27 January 2023

Population	20.	Migraine*.mp	133059
	21.	exp migraine/	110065
	22.	'episodic migraine'.mp	5661
	23.	'chronic migraine'.mp	9772
Comparator	24.	'calcitonin gene related peptide'.mp	38420
	25.	exp calcitonin gene related peptide/	29112
	26.	'$CGRP$'.mp	26601
	27.	Erenumab.mp	1867
	28.	(AMG334 OR AMG 334 OR AMG-334).mp	145
	29.	Fremanezumab.mp	1385
	30.	(TEV48125 OR TEV 48125 OR TEV-48125).mp	125
	31.	Galcanezumab.mp	1361
	32.	LY2951742.mp	116
	33.	(Eptinezumab OR eptinezumab-jjmr).mp	637
	34.	ALD403.mp	64
Search string	35.	**Or/1-4**	**133107**
	36.	**Or/5-15**	**42426**
	18.	**16 and 17**	**8718**
Search string (10 year filter)	19.	**Limit 18 to last 10 years**	**6935**
Search update	20.	**limit 19 to yr="2022 - 2024"**	**1358**
Deduplicated updated search	21.	**remove duplicates from 20**	**924**

Abbreviations:
CGRP = calcitonin gene-related peptide.
Notes:
‡ Duplicates removed via Ovid 'deduplicate' function. These duplicates have been captured in the PRISMA flow diagram.

Table A14 Search strategy for Cochrane Library – 9 February 2022

Population	18.	(Migraine):ti,ab,kw	9,199
	19.	MeSH descriptor: [Migraine Disorders] explode all trees	3,387
	20.	**#1 OR #2**	9,199
Comparator	21.	(calcitonin gene related peptide):ti,ab,kw	1,348
	22.	(CGRP):ti,ab,kw	1,066
	23.	MeSH descriptor: [calcitonin gene related peptide] explode all trees	400
	24.	(erenumab):ti,ab,kw	311
	25.	((AMG334):ti,ab,kw OR (AMG 334):ti,ab,kw OR (AMG-334):ti,ab,kw)	69
	26.	(fremanezumab):ti,ab,kw	420
	27.	((TEV48125):ti,ab,kw OR (TEV 48125):ti,ab,kw OR (TEV-48125):ti,ab,kw)	49
	28.	(Galcanezumab):ti,ab,kw	278
	29.	(LY2951742):ti,ab,kw	56
	30.	((Eptinezumab):ti,ab,kw OR (eptinezumab-jjmr):ti,ab,kw)	189
	31.	(ALD403):ti,ab,kw	35
	32.	**#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14**	**2,165**
Search string	33.	**#3 AND #15**	**1,597**
Search string (1 year filter)	34.	**#16 with Cochrane Library publication date in The last year**	**251**

Abbreviations:
CGRP = calcitonin gene-related peptide.

Table A15 Search strategy for EconLit – 9 February 2023

Population	9.	Migraine	41
Comparator	10.	Calcitonin gene-related peptide	2
	11.	CGRP	0
	12.	Erenumab	0
	13.	Fremanezumab	0
	14.	Galcanezumab	0
	15.	Eptinezumab	0
Search string	16.	**#1 AND #2**	**0**
Search string (1 year filter)	17.	**#8 publication date in the last year**	**0**

Abbreviations:
CGRP = calcitonin gene-related peptide.

Table A16 Search strategy INAHTA HTA Database – 9 February 2023

Population	9.	Migraine	72
Comparator	10.	Calcitonin gene-related peptide	0
	11.	CGRP	1
	12.	Erenumab	4
	13.	Fremanezumab	3
	14.	Galcanezumab	4
	15.	Eptinezumab	0
Search string	16.	**#1 AND #3 OR #4 OR #5 OR #6**	**9**
Search string (1 year filter)	17.	**#8 publication date in the last year**	**0**

Abbreviations
CGRP = calcitonin gene-related peptide, **INAHTA** = International Network of Agencies for Health Technology Assessment.

Table A17 Search strategy for CEA registry – 9 February 2023

Population	9.	Migraine	23
Comparator	10.	Calcitonin gene-related peptide	2
	11.	CGRP	1
	12.	Erenumab	4
	13.	Fremanezumab	0
	14.	Galcanezumab	0
	15.	Eptinezumab	0
Search string	16.	**#1 AND #2 OR #3 OR #4**	**1**
Search string (1 year filter)	17.	**#8 publication date in the last year**	**0**

Abbreviations:
CGRP = calcitonin gene-related peptide; **CEA registry** = cost-effectiveness analysis Registry hosted by Tufts Medical Centre.

Appendix C: Study inclusion and exclusion criteria

Table A18 Study inclusion and exclusion criteria

Population 1	Patients who suffer from episodic migraine (i.e. characterised by less than 15 headache days per month)[3] *Exclusion criteria: Paediatric patients‡*
Population 2	Patients who suffer from chronic migraine (i.e. characterised by 15 or more headache days per month, for 3 months or more, with at least 8 migraine days per month)[3] *Exclusion criteria: Paediatric patients‡*
Intervention(s)	• Erenumab (Aimovig®)—70 or 140 mg once monthly • Fremanezumab (Ajovy®)—225 mg once monthly or 675 mg quarterly • Galcanezumab (Emgality®)—120 mg once monthly (starting dose of 240 mg) • Eptinezumab (Vyepti®)—100 mg or 300 mg quarterly *Exclusion criteria: Other CGRP antagonists (e.g. gepants), combination therapy with more than one intervention/comparator*

Comparator(s)	• Placebo
	• standard of care for migraine prevention
	  ○ Beta blockers: propranolol, metoprolol
	  ○ Calcium antagonist: flunarizine
	  ○ Anticonvulsants: topiramate
	  ○ Antidepressants: amitriptyline
	• Other CGRP antagonists (i.e. comparing each of the interventions to each other)
	Exclusion criteria: Other beta blockers, calcium antagonists, anticonvulsants and antidepressants not listed here and/or not reimbursed in Switzerland

Outcome(s)	**Clinical outcomes:** • Monthly migraine days (MMDs) and monthly headache days (MHDs) • Health-related and migraine-specific quality of life (e.g. HIT-6, MSQ v2.1, MIDAS, EQ-5D, SF-36) • Migraine/headache pain intensity (e.g. VAS, NRS) • Number of days per month with a migraine that needs to be treated with acute pain relievers (i.e. MMDs with acute medication use) • Response rate (defined as a reduction of the average number of days with migraines of at least 50% after 6 months of treatment compared to prior to the treatment beginning) • Treatment adherence • Mortality • Treatment-related adverse events (AEs) • Serious adverse events (SAEs) • Adverse events leading to discontinuation • Adverse events upon discontinuation of CGRP antagonists (e.g. rebound effect) **Health-economic outcomes:** • Costs, utilities, ICER and budget impact
Design	**Studies will be selected based on the following hierarchy of study design, with preference given for the highest level of evidence.** **Effectiveness and safety outcomes:** • RCTs > non-randomised comparative studies > single-arm studies reporting pre- and post-treatment results Note: Inclusion of studies with ≥50 participants (all study designs) **Health-economics outcomes:** • RCTs > non-randomised comparative studies > single-arm studies reporting pre- and post-treatment results Note: Inclusion of studies with ≥50 participants (all study designs) *Exclusion criteria: case reports, conference abstracts, letter to the editors, expert opinions, editorials, review articles, non-human/laboratory studies, studies with <50 participants*
Country	No restriction
Year	RCTs: 10-year limit Non-RCTs: 5-year limit
Language	English, French, German and Italian

Abbreviations

AEs = adverse events, **CGRP** = calcitonin gene-related peptide, **EQ-5D** = EuroQol 5-dimension questionnaire, **HIT-6** = Headache Impact Test, **ICER** = incremental cost-effectiveness ratio, **MHDs** = monthly headache days, **MIDAS** = Migraine Disability Assessment Scale, **MMDs** = monthly migraine days, **MSQ** = Migraine-Specific Quality of Life questionnaire, **NRS** = numerical rating scale, **RCT** = randomised control trial, **SAEs** = serious adverse events, **SF-36** = 36-Item Short Form Health Survey, **UK** = United Kingdom, **USA** = United States of America, **VAS** = visual analogue scale, **WHO** = World Health Organisation.

Notes

‡ As per expert advice, CGRP antagonists are not authorised for use in paediatric patients.[4]

Appendix D: List of excluded publications at full text

Incorrect population (k=6)

1. Winner PK, McAllister P, Chakhava G, et al Effects of Intravenous Eptinezumab vs Placebo on Headache Pain and Most Bothersome Symptom When Initiated During a Migraine Attack: a Randomized Clinical Trial. JAMA 2021;325(23):2348-56.

2. Robblee J, Devick KL, Mendez N, et al Real-World Patient Experience With Erenumab for the Preventive Treatment of Migraine. Headache 2020;60:2014-25.

3. de Hoon J, Van Hecken A, ermeulen C, et al Phase I, Randomized, Double-blind, Placebo-controlled, Single-dose, and Multiple-dose Studies of Erenumab in Healthy Subjects and Patients With Migraine. Clinical pharmacology and therapeutics 2018;103(5):815-25.

4. De Icco R, Fiamingo G, Greco R, et al Neurophysiological and biomolecular effects of erenumab in chronic migraine: An open label study. Cephalalgia;40:1336-45.

5. Ashina H, Iljazi A, Al-Khazali HM, et al Efficacy, tolerability, and safety of erenumab for the preventive treatment of persistent post-traumatic headache attributed to mild traumatic brain injury: An open-label study. Journal of Headache and Pain;21

6. Alex A, Vaughn C, Rayhill M. Safety and Tolerability of 3 CGRP Monoclonal Antibodies in Practice: A Retrospective Cohort Study. Headache 2020;60:2454-62.

Incorrect intervention (k=13)

1. Dodick DW, Goadsby PJ, Silberstein SD, et al Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. *The lancet Neurology* 2014;13(11):1100-07.

2. Vo P, Wen S, Martel MJ, et al Benefit-risk assessment of erenumab and current migraine prophylactic treatments using the likelihood of being helped or harmed. *Cephalalgia* 2018;39:608-16.

3. Slof J. Cost-Effectiveness Analysis of Early versus Non-early Intervention in Acute Migraine Based on Evidence from the 'Act When Mild' Study. *Applied Health Economics and Health Policy* 2012;10(3):201-15.

4. Pak K, Kim J, Lee GH, et al Effectiveness of Calcitonin Gene-Related Peptide Receptor Antagonists for Migraine Treatment: A Meta-Analysis. *European Neurology* 2022

5. Hong P, Liu Y. Calcitonin gene-related peptide antagonism for acute treatment of migraine: a meta-analysis. *The International journal of neuroscience* 2017;127:20-27.

6. Gantenbein AR, Agosti R, Gobbi C, et al Impact on monthly migraine days of discontinuing anti-CGRP antibodies after one year of treatment - a real-life cohort study. *Cephalalgia* 2021;41:1181-86.

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8. Drellia K, Kokoti L, Deligianni CI, et al Anti-CGRP monoclonal antibodies for migraine prevention: A systematic review and likelihood to help or harm analysis. *Cephalalgia* 2021;41:851-64.

9. Citrome L, Sánchez Del Rio M, Dong Y, et al Benefit-Risk Assessment of Galcanezumab Versus Placebo for the Treatment of Episodic and Chronic Migraine Using the Metrics of Number Needed to Treat and Number Needed to Harm. *Advances in therapy* 2021;38(8):4442-60.

10. Caronna E, Jose Gallardo V, Alpuente A, et al Safety of anti-CGRP monoclonal antibodies in patients with migraine during the COVID-19 pandemic: Present and future implications. *Neurologia* 2021;36:611-17.

11. Breen ID, Brumfiel CM, Patel MH, et al Evaluation of the Safety of Calcitonin Gene-Related Peptide Antagonists for Migraine Treatment among Adults with Raynaud Phenomenon. *JAMA Network Open* 2021

12. Altamura C, Cevoli S, Aurilia C, et al Locking down the CGRP pathway during the COVID-19 pandemic lockdown: the PandeMig study. *Neurological Sciences* 2020;41:3385-89.

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Incorrect comparator (k=4)

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3. Siddiqui M, Shah PV, Balani P, et al Comparing the Efficacy, Safety, and Superiority of Calcitonin Gene-Related Peptide Monoclonal Antibodies and Botox in Preventing and Treating Migraines. *Cureus* 2021;13(1):e13002.

4. Popoff E, Johnston K, Croop R, et al Matching-adjusted indirect comparisons of oral rimegepant versus placebo, erenumab, and galcanezumab examining monthly migraine days and health-related quality of life in the treatment of migraine. *Headache* 2021

Incorrect outcome (k=7)

1. VanderPluym J, Dodick DW, Lipton RB, et al Fremanezumab for preventive treatment of migraine: functional status on headache-free days. *Neurology* 2018;91(12):E1152-E65.

2. Stauffer VL, Sides R, Lanteri-Minet M, et al Comparison between prefilled syringe and autoinjector devices on patient-reported experiences and pharmacokinetics in galcanezumab studies. *Patient Preference and Adherence* 2018;12:1785-95.

3. 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* 2021;22(1):1-12.

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7. Ailani J, Winner P, Hartry A, et al Patient preference for early onset of efficacy of preventive migraine treatments. *Headache* 2022;20

Incorrect publication type (k=184)

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6. Nagaraj K, enbussche N, Goadsby PJ. Role of Monoclonal Antibodies against Calcitonin Gene-Related Peptide (CGRP) in Episodic Migraine Prevention: Where Do We Stand Today? *Neurology India*;69:S59-S66.

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21. Dodick D, Ashina M, Kudrow D, et al A phase 3, randomised, double-blind, placebocontrolled study to evaluate the efficacy and safety of erenumab in migraine prevention: Primary results of the arise trial. *Journal of Neurology, Neurosurgery and Psychiatry*;88:e24.

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41. Scott LJ. Correction to: Galcanezumab: A Review in the Prevention of Migraine and Treatment of Episodic Cluster Headache (Drugs, (2020), 80, 9, (893-904), 10.1007/s40265-020-01329-5). *Drugs*;80:1379.

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45. Bottiroli S, De Icco R, Vaghi G, et al Correction to: Psychological predictors of negative treatment outcome with Erenumab in chronic migraine: data from an open label long-term prospective study (The Journal of Headache and Pain, (2021), 22, 1, (114), 10.1186/s10194-021-01333-4). *Journal of Headache and Pain*;22

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55. Anonymous. Erratum: Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy (Neurology (2020)). *Neurology*;94:900.

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64. Department of Error: 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(10203) (1030–1040), (S0140673619319464), (10.1016/S0140-6736(19)31946-4)). *Lancet* 2020

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Incorrect language (k=0)

Nil

Incorrect date limit (k=4)

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Unable to access (k=0)

Nil

Trial data not included in analyses (k=17)

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Postface: List of excluded publications at full text (updated search)

Incorrect population (k=1)

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NOTE: ***Non-randomised studies of interventions (NRSI) assessed for eligibility to answer the Additional Question(s) (see Section 6.1 of HTA Protocol) regarding 'switching of CGRP-antagonists'.***

Incorrect intervention (k=2)

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NOTE: ***NRSI assessed for eligibility to answer the Additional Question(s) (see Section 6.1 of HTA Protocol) regarding 'switching of CGRP-antagonists'.***

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Incorrect comparator (k=0)

Nil

Incorrect outcome (k=4)

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study of galcanezumab with open-label extension (REGAIN). Journal of Medical Economics, 2022. 25(1): p. 1030-1038.

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Incorrect publication type (k=0)

Nil

Incorrect study design (k=11)

1. Tepper, S.J., 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, 2022. 42(3): p. 263-275.

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NOTE: ***These publications that have been excluded as incorrect study design are related to RCTs which have already been included in the HTA report, however have been deemed to not add further value to the current data/results that have been reported.***

Incorrect language (k=0)

Nil

Incorrect date limit (k=0)

Nil

Duplicates (k=2)

1. Ferrari, M.D., et al, Two-year efficacy and safety of erenumab in participants with episodic migraine and 2-4 prior preventive treatment failures: results from the LIBERTY study. Journal of neurology, neurosurgery, and psychiatry, 2022. 93(3): p. 254-262.

2. Reuter, U., et al, Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia : an international journal of headache, 2022. 42(2): p. 108-118.

Note: Publications identified through original literature search (up to 9 March 2022).

Unable to access (i.e. embargo) (k=0)

Nil

Appendix E: Minimum clinically important differences and improvements for outcomes of interest

A non-systematic targeted search was conducted to identify minimum clinically important differences (MCIDs), minimum important change (MIC), minimal important differences (MIDs) and minimal clinically important improvement (MCII) related to the outcomes of interest (see ***Section 5.4.1***). It was planned to use the identified MCID, MICs and MIDs (***Table A19***) as a guide, not as a complete assessment of the literature. The MIDs, MICs and MCID generally relate to headache frequency (i.e. MHDs, response rate) and health-related and migraine-specific quality of life (i.e. HIT-6, MIDAS, MSQ v2.1, VAS). The applicability of these MIDs, MICs and MCID to the current HTA report is currently uncertain. There are differences in population demographics, diagnosis and interventions, so caution must be taken when extrapolating the MIDs, MICs and MCID to the outcomes reported.

Table A19 Minimal clinically important differences/improvements for outcomes of interest

Outcome measure	MIC/MID/MCII/MCID	Study type	Population demographics	Author, year
Headache frequency				
Headache days	Between-group difference: 1 day per month MID	Clinical study	Mixed headache conditions (incl. episodic and chronic migraine)	Silberstein et al 2010[5]
Response rate	50% reduction from baseline MID	Guidance document	Episodic migraine	Tfelt-Hansen et al 2000[6]
	30% reduction from baseline MID	Guidance document	Chronic migraine	Silberstein et al 2008[7]
HRQoL				
HIT-6	Within-group improvements: ≥5.0 points Between-group difference: ≥2.3 points MID	Guidance document Clinimetric assessment	Chronic migraine Chronic daily headache	Bayliss et al 2002[8] Coeytaux et al 2006[9]
	Within-group change: -2.5 points (mean change) -6 points (ROC curve) Between-group difference: -1.5 points MIC	Clinimetric assessment	Migraine	Smelt et al 2013[10]
MIDAS	4.5 points MIC	Clinical study	High frequency episodic migraine & chronic migraine	Carvalho et al 2022[11]

MSQ v2.1 Domain: RR	Between-group mean: 3.2 MID	Clinimetric assessment	Migraine	Cole et al 2009[12]
	Within-group mean: 10.9 MID	Clinical study (RCT)	Chronic migraine	Dodick et al 2007[13]
MSQ v2.1 Domain: RP	Between-group mean: 4.6 MID	Clinimetric assessment	Migraine	Cole et al 2009[12]
	Within-group mean: 8.3 MID	Clinical study (RCT)	Chronic migraine	Dodick et al 2007[13]
MSQ v2.1 Domain: EF	Between-group mean: 7.5 MID	Clinimetric assessment	Migraine	Cole et al 2009[12]
	Within-group mean: 12.2 MID	Clinical study (RCT)	Chronic migraine	Dodick et al 2007[13]
VAS	1.5-3.2 points (cm) 30% pain reduction MCID	Clinimetric assessment	Chronic pain	Calixtre et al 2020[14]

Abbreviations:
cm = centimeter, **EF** = emotional function, **HIT-6** = Headache Impact Test, **HRQoL** = health-related quality of life, **incl.** = including, **MCID** = minimum clinically important difference, **MCII** = minimal clinically important improvement, **MIC** = minimum important change, **MID** = minimal important differences, **MIDAS** = Migraine Disability Assessment Scale, **MSQ v2.1** = Migraine-Specific Quality of Life questionnaire version 2.1, **RCT** = randomised controlled trial, **ROC** = receiver operating characteristic; **RP** = role preventive, **RR** = role restrictive, **VAS** = visual analogue scale.

Appendix F: Additional Study Characteristics

Table A20 Study characteristics: Participant inclusion/exclusion criteria conditions for concomitant preventative migraine medication and previous migraine preventative treatment failure

Trial ID	Concomitant preventative migraine medications	Inclusion/exclusion criteria based on previous migraine preventative treatment failure
Erenumab		
ARISE 2018[15] NCT02483585[16]	Included (1 medication permitted; stable A dose within 2 months before the start of BL phase and throughout the study): - Divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin, beta blockers, tricyclic antidepressants, enlafaxine, desvenlafaxine, duloxetine, milnacipran, flunarizine, verapamil, lomerizine, lisinopril, candesartan, clonidine, guanfacine, cyproheptadine, methysergide, pizotifen, butterbur, feverfew, magnesium (≥600 mg/day), riboflavin (≥100 mg/day)	**Exclusion criteria**: No therapeutic response in migraine prevention after an adequate therapeutic trial of >2 of the following medication categories: Category 1: Divalproex sodium, sodium valproate; Category 2: Topiramate; Category 3: Beta blockers; Category 4: Tricyclic antidepressants; Category 5: Serotonin-norepinephrine reuptake inhibitors; Category 6: Flunarizine, verapamil
EMPOwER 2021[17] NCT03333109	No concomitant preventative medications allowed	**Exclusion criteria:** No therapeutic response with more than 2 of the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial: Category 1: Divalproex sodium, sodium valproate; Category 2: Topiramate; Category 3: Beta blockers (e.g. atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol); Category 4: Tricyclic antidepressants (e.g. amitriptyline, nortriptyline, protriptyline); Category 5: Serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine, desvenlafaxine, duloxetine, milnacipran); Category 6: Flunarizine, verapamil; Category 7: Lisinopril, candesartan.
LIBERTY 2018[18] NCT03096834[19-22]	No concomitant preventative medications allowed	**Inclusion criteria:** Failed 2-4 prior migraine prophylaxis treatments out of propranolol/ metoprolol, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, locally approved products (e.g. oxeterone or pizotifen) **OR** Failed one AND failed OR not suitable A for a second of the following: - Propranolol OR metoprolol - Topiramate - Flunarizine - Failed or not suitable A for valproate or divalproex

Trial ID	Concomitant preventative migraine medications	Inclusion/exclusion criteria based on previous migraine preventative treatment failure
		Exclusion criteria: Failed more than 4 prior migraine prophylaxis treatments out of propranolol/metoprolol, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, locally approved products (e.g. oxeterone or pizotifen)
Sakai et al 2019[23] NCT02630459[24,25]	Included (1 medication permitted; stable A dose within 2 months before the start of BL phase and throughout the study): - Divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin, beta blockers, tricyclic antidepressants, venlafaxine, desvenlafaxine, duloxetine, milnacipran, flunarizine, verapamil, lomerizine, lisinopril, candesartan, clonidine, guanfacine, cyproheptadine, methysergide, pizotifen, butterbur, feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)	**Exclusion criteria:** No therapeutic response in migraine prevention after an adequate therapeutic study of >2 of the following medication categories: Category 1: Divalproex sodium, sodium valproate; Category 2: Topiramate; Category 3: Beta blockers; Category 4: Tricyclic antidepressants; Category 5: Serotonin-norepinephrine reuptake inhibitors; Category 6: Flunarizine, verapamil, lomerizine; Category 7: Lisinopril, candesartan
STRIVE 2017[26] NCT02456740[27-34]	Included (1 medication permitted; stable A dose within 2 months before the start of BL phase and throughout the study): - Divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin, beta blockers, tricyclic antidepressants, venlafaxine, desvenlafaxine, duloxetine, milnacipran, flunarizine, verapamil, lomerizine, lisinopril, candesartan, clonidine, guanfacine	**Exclusion criteria:** No therapeutic response in migraine prevention after an adequate therapeutic trial of >2 of the following medication categories: Category 1: Divalproex sodium, sodium valproate; Category 2: Topiramate; Category 3: Beta blockers; Category 4: Tricyclic antidepressants; Category 5: Serotonin-norepinephrine reuptake inhibitors; Category 6: Flunarizine, verapamil; Category 7: Lisinopril, candesartan
Sun et al 2016[35] NCT01952574[36-39]	No concomitant preventative medications allowed.	**Exclusion criteria:** Patients were excluded if they had no response for at least 6 weeks to >2 of the following preventive treatment categories: 1) divalproex sodium, sodium valproate; 2) topiramate; 3) beta blockers; 4) tricyclic antidepressants; 5) venlafaxine, desvenlafaxine, duloxetine, milnacipran; 6) flunarizine, verapamil; 7) lisinopril, candesartan; 8) butterbur, feverfew, magnesium (≥600 mg/day), riboflavin (≥100 mg/day)
Tepper et al 2017[40] NCT02066415[41-48]	No concomitant preventative medications allowed.	**Exclusion criteria:** Patients were excluded if they had no therapeutic response in migraine prevention after an adequate therapeutic trial of >3 of the following medication categories: Category 1: Divalproex sodium, sodium valproate; Category 2: Topiramate; Category 3: Beta blockers; Category 4: Tricyclic antidepressants; Category 5: Flunarizine or verapamil; Category 6: Venlafaxine or desvenlafaxine, duloxetine or milnacipran; Category 7: Botulinum toxin; Category 8: Lisinopril or candesartan
HER-MES 2022[49] NCT03828539[50]	No concomitant preventative medications allowed.	**Inclusion criteria:** Patients were eligible if they had not received prior prophylactic migraine treatment (naive) or, due to lack of efficacy or tolerability, had failed or had not been suitable A for up to three previous prophylactic treatments from the following: - Metoprolol/propranolol, Amitriptyline, Flunarizine

Trial ID	Concomitant preventative migraine medications	Inclusion/exclusion criteria based on previous migraine preventative treatment failure
Takeshima et al 2021[51] NCT03812224[52,53]	Included (1 medication permitted; >2 months prior to BL and throughout the study): - Divalproex sodium, sodium valproate, topiramate, carbamazepine or gabapentin, all beta blockers (e.g. metoprolol, propranolol, timolol, atenolol, nadolol, nebivolol, pindolol, bisoprolol), all tricyclic antidepressants (e.g. amitriptyline, nortriptyline, protriptyline), venlafaxine, desvenlafaxine, duloxetine or milnacipran, flunarizine, verapamil, lomerizine, lisinopril, candesartan, clonidine or guanfacine, cyproheptadine, methysergide, pizotifen, butterbur, feverfew, magnesium (≥600 mg/day), riboflavin (≥100 mg/day) Excluded if used daily for migraine prevention (>2 months prior to BL): - Fluoxetine, fluvoxamine, acetazolamide, picotamide, cyclandelate, ergot-derivatives, steroids, triptans, nicardipine, nifedipine, nimodipine	**Exclusion criteria:** No therapeutic response with ≥3 of the following 8 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial: Category 1: Divalproex sodium, sodium valproate; Category 2: Topiramate; Category 3: Beta blockers (e.g. atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol); Category 4: Tricyclic antidepressants (e.g. amitriptyline, nortriptyline, protriptyline); Category 5: Serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine, desvenlafaxine, duloxetine, milnacipran); Category 6: Flunarizine, verapamil, lomerizine; Category 7: Lisinopril, candesartan; Category 8: Botulinum toxin
Eptinezumab		
PROMISE-1 2020[54] NCT02559895[55,56]	No concomitant preventative medications allowed.	NR
Dodick et al 2019[57] NCT02275117	No concomitant preventative medications allowed.	NR
PROMISE-2 2020[58] NCT02974153[59-64]	Included (stable A dose for at least 3 months prior to screening, with no alterations through week 24): - Divalproex sodium, sodium valproate, topiramate, gabapentin, metoprolol, propranolol, timolol, atenolol, nadolol, bisoprolol, amitriptyline, venlafaxine, cinnarizine, fluoxetine, lamotrigine, flunarizine, verapamil, pizotifen, butterbur, feverfew	NR
Fremanezumab		
Bigal et al 2015b[65] NCT02025556[66,67]	Included for 30% of population (1 medication; stable A dose for at least 2 months prior to beginning trial and throughout the study): - beta-blockers: atenolol, propranolol, metoprolol, nadolol, timolol - calcium channel blocker/benzocycloheptene: flunarizine, pizotifen - antidepressants: amitriptyline, venlafaxine, nortriptyline, duloxetine - anti-epileptic medications: topiramate, valproate, divalproate	**Exclusion criteria:** Previously failed (lack of efficacy) ≥2 of the following clusters for treatment of episodic migraine or chronic migraine after adequate therapeutic trial defined as use for at least 3 months at accepted migraine therapeutic doses: Cluster A: divalproex sodium, sodium valproate; Cluster B: flunarizine, pizotifen; Cluster C: amitriptyline, nortriptyline, venlafaxine, duloxetine; Cluster D: atenolol, nadolol, metoprolol, propranolol, timolol

Trial ID	Concomitant preventative migraine medications	Inclusion/exclusion criteria based on previous migraine preventative treatment failure
HALO EM 2018[68] NCT02629861[69,70]	Included for 30% of population (1 medication; stable A dose for at least 2 months prior to beginning trial and throughout the study): - beta-blockers: atenolol, propranolol, metoprolol, nadolol, timolol - calcium channel blocker/benzocycloheptene: flunarizine, pizotifen - antidepressants: amitriptyline, venlafaxine, nortriptyline, duloxetine - anti-epileptic medications: topiramate, valproate, divalproate	**Exclusion criteria:** Previously failed (lack of efficacy) ≥2 of the following clusters for treatment of episodic migraine or chronic migraine after adequate therapeutic trial defined as use for at least 3 months at accepted migraine therapeutic doses: Cluster A: divalproex sodium, sodium valproate; Cluster B: flunarizine, pizotifen; Cluster C: amitriptyline, nortriptyline, venlafaxine, duloxetine; Cluster D: atenolol, nadolol, metoprolol, propranolol, timolol
Sakai et al 2021b[71] NCT03303092[72]	Included for 30% of population (1 medication; stable A dose for at least 2 months prior to beginning trial and throughout the study): - beta-blockers: atenolol, propranolol, metoprolol, nadolol, timolol - calcium channel blocker/benzocycloheptene: flunarizine, pizotifen - antidepressants: amitriptyline, venlafaxine, nortriptyline, duloxetine - anti-epileptic medications: topiramate, valproate, divalproate	**Exclusion criteria**: Previously failed (lack of efficacy) ≥2 of the following clusters for treatment of episodic migraine or chronic migraine after use for at least 3 months at accepted migraine therapeutic doses: Cluster A: topiramate, divalproex sodium, sodium valproate; Cluster B: lomerizine, flunarizine, pizotifen; Cluster C: amitriptyline, nortriptyline, venlafaxine, duloxetine; Cluster D: atenolol, nadolol, metoprolol, propranolol, timolol
Bigal et al 2015a[73] NCT02021773[74,75]	Included (≤2 medications; stable A dose for at least 2 months prior to beginning trial and throughout the study): - E.g. topiramate, propranolol	**Exclusion criteria:** Failed >2 medication categories or >3 preventive medications (within two medication categories) due to lack of efficacy for prophylactic treatment of episodic migraine or chronic migraine after an adequate therapeutic trial.
HALO CM 2017[76] NCT02621931[77-82]	Included for 30% of population (1 medication; stable A dose for at least 2 months prior to beginning trial and throughout the study): - beta-blockers: atenolol, propranolol, metoprolol, nadolol, timolol - calcium channel blocker/benzocycloheptene: flunarizine, pizotifen - antidepressants: amitriptyline, venlafaxine, nortriptyline, duloxetine - anti-epileptic medications: topiramate, valproate, divalproate	**Exclusion criteria**: Previously failed (lack of efficacy) ≥2 of the following clusters for treatment of episodic migraine or chronic migraine after adequate therapeutic trial defined as use for at least 3 months at accepted migraine therapeutic doses: Cluster A: divalproex sodium, sodium valproate; Custer B: flunarizine, pizotifen; Cluster C: amitriptyline, nortriptyline, venlafaxine, duloxetine; Cluster D: atenolol, nadolol, metoprolol, propranolol, timolol
Sakai et al 2021a[83] NCT03303079[84]	Included in 30% of population (1 medication; stable A dose for at least 2 months prior to beginning trial and throughout the study): - beta-blockers: atenolol, propranolol, metoprolol, nadolol, timolol - calcium channel blocker/benzocycloheptene: flunarizine, pizotifen - antidepressants: amitriptyline, venlafaxine, nortriptyline, duloxetine - anti-epileptic medications: topiramate, valproate, divalproate	**Exclusion criteria**: Patients who have previously failed (lack of efficacy) ≥2 of the following clusters for treatment of episodic migraine or chronic migraine after use for at least 3 months at accepted migraine therapeutic doses: Cluster A: topiramate, divalproex sodium, sodium valproate; Cluster B: lomerizine, flunarizine, pizotifen; Cluster C: amitriptyline, nortriptyline, venlafaxine, duloxetine; Cluster D: atenolol, nadolol, metoprolol, propranolol, timolol
FOCUS 2019[85] NCT03308968[86,87]	Exclusion criteria: - At the time of screening visit, receiving any preventive migraine medications, regardless of the medical indication for >5 days and expects to continue with these medications.	**Inclusion criteria**: At the time of screening, documented inadequate response to 2-4 classes of prior preventive migraine medications within the past 10 years (in medical chart or by treating physician's confirmation)

Trial ID	Concomitant preventative migraine medications	Inclusion/exclusion criteria based on previous migraine preventative treatment failure
Galcanezumab		
Dodick et al 2014a[88] NCT01625988	No concomitant preventative medications allowed.	**Exclusion criteria**: Failure to respond to >2 adequately dosed (i.e. maximum tolerated dose by the patient for a sufficient duration) approved migraine prevention treatments.
EVOLVE-1 2018[89] NCT02614183[90]	No concomitant preventative medications allowed.	**Exclusion criteria**: Failure to respond to ≥3 adequately dosed migraine preventive treatments from different classes (i.e. maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure.
EVOLVE-2 2018[91] NCT02614196[92]	No concomitant preventative medications allowed.	**Exclusion criteria**: Failure to respond to ≥3 adequately dosed migraine preventive treatments from different classes (i.e. maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure.
Sakai et al 2020a[93] NCT02959177[94-97]	No concomitant preventative medications allowed.	**Exclusion criteria**: Failure to respond to ≥3 adequately dosed migraine preventive treatments from different classes (i.e. maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure.
Skljarevski et al 2018[98] NCT02163993[99-101]	No concomitant preventative medications allowed.	**Exclusion criteria**: Failure to respond to ≥2 effective migraine preventive treatments as defined by the American Academy of Neurology/American Headache Society treatment guidelines level A and B evidence.
REGAIN 2018[102] NCT02614261[103,104]	Included (stable A dose for at least 2 months prior to beginning trial and throughout the study): - Topiramate or propranolol	**Exclusion criteria**: Failure to respond to ≥3 adequately dosed migraine preventive treatments from different classes (i.e. maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure.
CGAJ 2018[105] NCT02614287[66,67]	No concomitant preventative medications allowed.	**Exclusion criteria**: Failure to respond to ≥3 adequately dosed migraine preventive treatments from different classes (i.e. maximum tolerated dose for at least 2 months). Failure to respond due to tolerability issues is not considered a treatment failure.
CONQUER 2020[106] NCT03559257[107,108]	No concomitant preventative medications allowed.	**Inclusion criteria:** Previous failure to 2-4 migraine preventive medication categories in the past 10 years from the following list due to inadequate efficacy (i.e. maximum tolerated dose for at least 2 months) and/or safety/tolerability reason: a) propranolol or metoprolol; b) topiramate; c) valproate or divalproex; d) amitriptyline; e) flunarizine; f) candesartan; g) botulinum toxin A or B (if documented that botulinum toxin was taken for chronic migraine); h) medication locally approved for prevention of migraine

Abbreviations:
BL = baseline, **ID** = identification.

Postface: Additional Study Characteristics (updated search)

Table A21 Study characteristics: Participant inclusion/exclusion criteria conditions for concomitant preventative migraine medication and previous migraine preventative treatment failure (updated search)

Trial ID	Concomitant preventative migraine medications	Inclusion/exclusion criteria based on previous migraine preventative treatment failure
Erenumab		
DRAGON 2022[109] NCT03867201	No concomitant preventative medications allowed	**Exclusion criteria:** Previously failed (lack of efficacy/tolerability) ≥3 of the following categories for treatment of episodic migraine or chronic migraine after adequate therapeutic trial, defined as use for ≥6 weeks at accepted migraine therapeutic doses: Category 1: divalproex sodium, sodium valproate; Category 2: topiramate; Category 3: beta blockers (e.g. atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol), Category 4: tricyclic antidepressants (e.g. amitriptyline, nortriptyline, protriptyline); Category 5: flunarizine, verapamil, cinnarizine; Category 6: serotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine, desvenlafaxine, duloxetine, milnacipran); Category 7: botulinum toxin; Category 8: lisinopril, candesartan; Category 9: pregabalin, gabapentin; Category 10: zonisamide; Category 11: memantine; Category 12: pizotifen.
Eptinezumab		
DELIVER 2022[110] NCT04418765[111]	No concomitant preventative medications allowed	**Inclusion criteria:** Previous failure in the past 10 years due to inadequate efficacy (i.e. maximum tolerated dose for at least 3 months) and/or safety/tolerability reasons of 2–4 migraine preventive medication categories from the following list: a) propranolol or metoprolol; b) topiramate; c) valproate or divalproex; d) amitriptyline; e) flunarizine; f) candesartan; g) botulinum toxin A or B (if documented that botulinum toxin was taken for chronic migraine).
Galcanezumab		
PERSIST 2022[112] NCT03963232	No concomitant preventative medications allowed	**Exclusion criteria**: Failure to respond to ≥3 adequately dosed migraine preventive treatments from different classes (i.e. maximum tolerated dose for at least 2 months). Medications defined as migraine preventive treatments are – tricyclic antidepressants: amitriptyline, serotonin-norepinephrine reuptake inhibitor: venlafaxine; anti-epileptic drugs: valproic acid and topiramate; beta-blockers: metoprolol, propranolol, timolol, atenolol, nadolol; calcium channel blocker: flunarizine; triptans: frovatriptan, naratriptan, and zolmitriptan; traditional Chinese medicine/herbal - medications may not be exhausted and more details refer to the medication

Trial ID	Concomitant preventative migraine medications	Inclusion/exclusion criteria based on previous migraine preventative treatment failure
		list: petasites/butterbur, toutongling, and duliang; others locally approved medications of preventive migraine).

Abbreviations:
ID = identification

Appendix G: Data Extraction Tables

Note: New data added to tables from updated search have been highlighted in purple.

Monthly migraine days (MMDs)

Table A22 MMDs in patients receiving erenumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Episodic migraine						
ARISE[15]	Low	3 months	ERU 70 mg	282	-2.9 (SE 0.2)	MD -1.0 (95% CI: -1.6, -0.5), p<0.001
			Placebo	288	-1.8 (SE 0.2)	
EMPOwER[17]	High	1 month	ERU 70 mg	325	-2.66 (SE 0.23)	MD -0.97 (95% CI: -1.59, -0.35), p=0.002
			ERU 140 mg	214	-3.12 (SE 0.28)	MD -1.44 (95% CI: -2.13, -0.74), p<0.001
			Placebo	324	-1.69 (SE 0.23)	NA
		2 months	ERU 70 mg	316	-3.68 (SE 0.24)	MD -1.20 (95% CI: -1.85, -0.55), p<0.001
			ERU 140 mg	205	-3.88 (SE 0.29)	MD -1.40 (95% CI: -2.13, -0.67), p<0.001
			Placebo	318	-2.48 (SE 0.24)	NA
		3 months	ERU 70 mg	306	-4.2 (SE 0.25)	MD -1.09 (95% CI: -1.77, -0.42), p=0.002
			ERU 140 mg	199	-4.79 (SE 0.30)	MD -1.69 (95% CI: -2.45, -0.93), p<0.001
			Placebo	310	-3.1 (SE 0.25)	NA
LIBERTY[18]	Low	1–4 weeks	ERU 140 mg	119	-1.8 (SE 0.4)	MD -1.8 (95% CI: -2.7, -0.9), p<0.001
			Placebo	124	0.1 (SE 0.3)	
		5–8 weeks	ERU 140 mg	119	-2.3 (SE 0.4)	MD -2.4 (95% CI: -3.4, -1.4), p<0.001
			Placebo	124	0.1 (SE 0.4)	
		9–12 weeks	ERU 140 mg	118	-1.8 (SE 0.4)	MD -1.6 (95% CI: -2.7, -0.5), p=0.004
			Placebo	120	-0.2 (SE 0.4)	
		3 months	ERU 140 mg	76	-1.8 (SE 0.6)	MD -1.3 (95% CI: -2.7, 0.1), p=0.07
			Placebo	69	-0.5 (SE 0.5)	
Sakai et al 2019[23]	Low	4–6 months	ERU 70 mg	135	-2.25 (95% CI: -2.78, -1.73)	MD -2.31 (95% CI: -3.00, -1.62), p<0.001
			ERU 140 mg	136	-1.83 (95% CI: -2.35, -1.31)	MD -1.89 (95% CI: -2.58, -1.20), p<0.001
			Placebo	136	0.06 (95% CI: -0.46, 0.58)	NA
STRIVE[26]	Low	1 month	ERU 70 mg	312	-2.32 (95% CI: -2.73, -1.92)	MD -1.42 (95% CI: -1.99, -0.85), p<0.00001

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
			ERU 140 mg	318	-2.72 (95% CI: -3.12, -2.32)	MD -1.89 (95% CI: -2.62, -1.16), p<0.00001
			Placebo	316	-0.90 (95% CI: -1.30, -0.50)	NA
		2 months	ERU 70 mg	312	-2.93 (95% CI: -3.34, -2.52)	MD -1.54 (95% CI: -2.12, -0.96), p<0.00001
			ERU 140 mg	318	-3.10 (95% CI: -3.50, -2.70)	MD -1.71 (95% CI: -2.28, -1.14), p<0.00001
			Placebo	316	-1.39 (95% CI: -1.80, -0.99)	NA
		3 months	ERU 70 mg	312	-2.97 (95% CI: -3.38, -2.56)	MD -1.26 (95% CI: -1.84, -0.68), p<0.0001
			ERU 140 mg	318	-3.50 (95% CI: -3.91, -3.10)	MD -1.79 (95% CI: -2.37, -1.21), p<0.00001
			Placebo	316	-1.71 (95% CI: -2.12, -1.30)	NA
		4 months	ERU 70 mg	312	-3.09 (95% CI: -3.50, -2.67)	MD -1.15 (95% CI: -1.73, -0.57), p<0.0001
			ERU 140 mg	318	-3.52 (95% CI: -3.93, -3.11)	MD 1.58 (95% CI: -2.16, -1.00), p<0.00001
			Placebo	316	-1.94 (95% CI: -2.35, -1.52)	NA
		5 months	ERU 70 mg	312	-3.34 (95% CI: -3.75, -2.93)	MD -1.46 (95% CI: -2.04, -0.88), p<0.00001
			ERU 140 mg	318	-3.74 95% CI: -4.15, -3.33)	MD -1.86 (95% CI: -2.44, -1.28), p<0.00001
			Placebo	316	-1.88 (95% CI: -2.29, -1.46)	NA
		6 months	ERU 70 mg	312	-3.26 (95% CI: -3.67, -2.84)	MD -1.59 (95% CI: -2.17, -1.01), p<0.00001
			ERU 140 mg	318	-3.76 (95% CI: -4.17, -3.35)	MD -2.09 (95% CI: -2.67, -1.51), p<0.00001
			Placebo	316	-1.67 (95% CI: -2.08, -1.25)	NA
		4–6 months	ERU 70 mg	312	-3.2 (SE 0.2)	MD -1.4 (95% CI: -1.9, -0.9), p<0.001
			ERU 140 mg	318	-3.7 (SE 0.2)	MD -1.9 (95% CI: -2.3, -1.4), p<0.001
			Placebo	316	-1.8 (SE 0.2)	NA
Sun et al 2016[35]	Low	12 weeks	ERU 70 mg	104	-3.4 (SE 0.4)	-1.1 (95% CI: -2.1, -0.2), p=0.021
			Placebo	153	-2.3 (SE 0.3)	
Chronic migraine						
Tepper et al 2017[40]	Low	3 months	ERU 70 mg	188	-6.6 (SE 0.4)	MD -2.5 (95% CI: -3.5, -1.4), p<0.0001
			ERU 140 mg	187	-6.6 (SE 0.4)	MD -2.5 (95% CI: -3.5, -1.4), p<0.0001
			Placebo	281	-4.2 (SE 0.4)	NA

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
DRAGON 2022[109]	Some concerns	Week 4	ERU 70 mg	277	-6 (SE 0.4)	MD -2.53 (95% CI: -3.54, -1.52), p<0.001
			Placebo	277	-3.4 (SE 0.4)	NA
		Week 8	ERU 70 mg	274	-7.4 (SE 0.4)	MD -1.96 (95% CI: -3.10, -0.82), p=0.001
			Placebo	274	-5.4 (SE 0.4)	NA
		Week 12	ERU 70 mg	270	-8.2 (SE 0.5)	MD -1.57 (95% CI: -2.83, -0.30), p=0.015
			Placebo	274	-6.6 (SE 0.5)	NA
Episodic and chronic migraine						
HER-MES[49*]	Low	4–6 months	ERU 70 or 140 mg	383	-5.86 (SE 0.24)	MD -1.84 (95% CI: -2.43, -1.25), p<0.001
			Topiramate 25–100 mg	385	-4.02 (SE 0.24)	
Takeshima et al 2021[51,53**]	Low	4–6 months	ERU 70 mg	129	-3.60 (SE 0.38)	MD -1.62 (95% CI: -2.52, -0.73), p<0.001
			Placebo	128	-1.98 (SE 0.38)	
Subgroups of patients with >2 prior treatment failures - Episodic migraine						
LIBERTY[18]	Low	3 months	ERU 140 mg	76	-1.8 (SE 0.6)	MD -1.3 (95% CI: -2.7, 0.1), p=0.07
			Placebo	69	-0.5 (SE 0.5)	
STRIVE[30]	Low	1 month	ERU 70 mg	49	-1.6 (SD NR)	NR†
			ERU 140 mg	58	-2.5 (SD NR)	NR
			Placebo	54	-0.3 (SD NR)	NR
		2 months	ERU 70 mg	49	-1.8 (SD NR)	NR
			ERU 140 mg	58	-3 (SD NR)	NR
			Placebo	54	-0.4 (SD NR)	NR
		3 months	ERU 70 mg	49	-1.8 (SD NR)	NR
			ERU 140 mg	58	-3.5 (SD NR)	NR
			Placebo	54	-0.9 (SD NR)	NR
		4 months	ERU 70 mg	49	-2 (SD NR)	NR
			ERU 140 mg	58	-2.7 (SD NR)	NR
			Placebo	54	0 (SD NR)	NR
		5 months	ERU 70 mg	49	-1.4 (SD NR)	NR
			ERU 140 mg	58	-3 (SD NR)	NR
			Placebo	54	-0.7 (SD NR)	NR
		6 months	ERU 70 mg	49	-1.2 (SD NR)	NR
			ERU 140 mg	58	-3.1 (SD NR)	NR
			Placebo	54	-0.1 (SD NR)	NR
		4–6 months	ERU 70 mg	49	Range from 4–6 mo	MD -1.3 (95% CI: -2.6, 0.0), p<0.05
			ERU 140 mg	58	Range from 4–6 mo	MD -2.7 (95% CI: -4.0, -1.4), p<0.001

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
			Placebo	54	Range from 4–6 mo	NA
Takeshima et al 2021[51]*	Low	4–6 months	ERU 70 mg	78	-2.92 (SE NR)	MD -1.67 (95% CI: -2.56, -0.78), p<0.001
			Placebo	81	-1.25 (SE NR)	
Subgroups of patients with >2 prior treatment failures - Chronic migraine						
Takeshima et al 2021[51]**	Low	4–6 months	ERU 70 mg	50	-5.11 (SE NR)	MD -1.57 (95% CI: -3.39, 0.24), p=0.089
			Placebo	52	-3.54 (SE NR)	
Tepper et al 2017[41]	Low	3 months	ERU 70 mg	93	-5.4 (SE NR)	MD -2.7 (95% CI: -4.2, -1.2), p<0.001
			ERU 140 mg	92	-7.0 (SE NR)	MD -4.3 (95% CI: -5.8, -2.8), p<0.001
			Placebo	142	-2.7 (SE NR)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **mo** = months, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SD** = standard deviation, **SE** = standard error.
Notes
Blue text indicates RACS calculated comparisons.
* In HER-MES, the following number of patients were included: For erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%). Chronic (≥15 MMDs) = 42 (10.8%).
** Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine.
† Mean differences were unable to be calculated by RACS because there was no measure of variance (SD or SE) reported.

Table A23 MMDs in patients receiving eptinezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Episodic migraine						
PROMISE-1[54,55]	High	1–12 weeks	EPT 100 mg	221	-3.9 (95% CI: -4.28, -3.47)	MD -0.69 (95% CI: -1.25, -0.12), p=0.0182
		1–12 weeks	EPT 300 mg	222	-4.3 (95% CI: -4.70, -3.90)	MD -1.11 (95% CI: -1.68, -0.54), p=0.0001
		1–12 weeks	Placebo	222	-3.2 (95% CI: -3.60, -2.79)	NA
		13–24 weeks	EPT 100 mg	221	-4.5 (NR)	MD -0.76 (95% CI: -1.40, -0.11), p=NR
		13–24 weeks	EPT 300 mg	222	-4.8 (NR)	MD -1.02 (95% CI: -1.66, -0.37), p=NR
		13–24 weeks	Placebo	222	-3.8 (NR)	NA
Chronic migraine						
Dodick et al 2019[57]	Some concerns	3 months	EPT 100 mg	118	-7.7 (SD 6.9)	MD -2.1 95% CI: -3.8, -0.4), p=0.0178
		3 months	EPT 300 mg	114	-8.2 (SD 7.0)	MD -2.7 (95% CI: -4.4, -0.9), p=0.0034
		3 months	Placebo	116	-5.6 (SD 6.6)	NA
PROMISE-2[58,63,64]	Low	1–12 weeks	EPT 100 mg	356	-7.7 (Range -22, 10), p<0.0001	MD -2.0 (95% CI: -2.9, -1.2), p<0.0001
		1–12 weeks	EPT 300 mg	350	-8.2 (Range -23, 11), p<0.0001	MD -2.6 (95% CI: -3.4, -1.7), p<0.0001

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
		1–12 weeks	Placebo	366	-5.6 (Range -25, 9)	NA
		13–24 weeks	EPT 100 mg	356	-8.3 (SD 7.03)	MD - 1.98 (95% CI: - 2.94, -1.01), p=0.0003
		13–24 weeks	EPT 300 mg	350	-9.0 (SD 6.72)	MD -2.65 (95% CI: - 3.62, -1.68), p<0.00001
		13–24 weeks	Placebo	366	-6.4 (SD 7.16)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
DELIVER 2022[110]	Low	1–12 weeks	EPT 100 mg	299	-4.8 (SE 0.4)	MD -2.7 (95% CI: -3.4, -2.0), p<0.0001
			EPT 300 mg	293	-5.3 (SE 0.4)	MD -3.2 (95% CI: -3.9, -2.5), p<0.0001
			Placebo	298	-2.1 (SE 0.4)	NA
		13–24 weeks	EPT 100 mg	287	-5.4 (SE 0.4)	MD -3.0 (95% CI: -3.8, -2.2), p<0.0001
			EPT 300 mg	286	-6.1 (SE 0.4)	MD -3.7 (95% CI: -4.5, -3.0), p<0.0001
			Placebo	295	-2.4 (SE 0.4)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS calculated comparisons.

Table A24 MMDs in patients receiving fremanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Episodic migraine						
Bigal et al 2015b[65]	Low	1–4 weeks	FRE 225 mg	96	NR	MD 2.13 (95% CI: -3.36, -0.90), p=0.0007
			FRE 675 mg	97	NR	MD -2.42 (95% CI: -3.65, -1.19), p=0.0001
			Placebo	104	NR	NA
		5–8 weeks	FRE 225 mg	96	NR	MD -2.49 (95% CI: -3.78, -1.20), p=0.0002
			FRE 675 mg	97	NR	MD -2.66 (95% CI: -3.95, -1.36), p<0.0001
			Placebo	104	NR	NA
		9–12 weeks	FRE 225 mg	96	NR	MD -2.81 (95% CI: -4.07, -1.55), p<0.0001
			FRE 675 mg	97	NR	MD -2.64 (95% CI: -3.90, -1.38), p<0.0001
			Placebo	104	NR	NA
HALO EM[68]	High	4 weeks	FRE 225 mg	287	-3.5 (95% CI: -4.05, -2.93)	MD -1.8 (95% CI: -2.43, -1.18), p<0.001
			FRE 675 mg	288	-3.3 (95% CI: -3.85, -	MD -1.6 (95% CI: -2.22, -

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
					2.71)	0.97), p<0.001
			Placebo	290	-1.7 (95% CI: -2.24, -1.13)	NA
		12 weeks	FRE 225 mg	287	-3.7 (95% CI: -4.15, -3.18)	MD -1.5 (95% CI: -2.01, -0.93), p<0.001
			FRE 675 mg	288	-3.4 (95% CI: -3.94, -2.96)	MD -1.3 (95% CI: -1.79, -0.72), p<0.001
			Placebo	290	-2.2 (95% CI: -2.68, -1.71)	NA
Sakai et al 2021b[71]	Low	1–12 weeks	FRE 225 mg	121	-4.0 (SE 0.4)	MD -3.0 (95% CI: -3.74, -2.23), p<0.0001
			FRE 675 mg	117	-4.0 (SE 0.4)	MD -3.0 (95% CI: -3.76, -2.24), p<0.0001
			Placebo	116	-1.0 (SE 0.4)	NA
Chronic migraine						
Bigal et al 2015a[73]	Low	1–4 weeks	FRE 675/225 mg*	88	NR	MD -2.07 (95% CI: -3.7, -0.5), p=0.012
			Placebo	89	NR	
		5–8 weeks	FRE 675/225 mg	88	NR	MD -1.64 (95% CI: -3.4, 0.13), p=0.069
			Placebo	89	NR	
		9–12 weeks	FRE 675/225 mg	88	NR	MD -1.72 (95% CI: -3.7, 0.2), p=0.08
			Placebo	89	NR	
HALO CM[76]	Low	3 months	FRE 225 mg	375	-5.0 (SE 0.4)	MD -1.8 (SE 0.4), p<0.001
			FRE 675 mg	375	-4.9 (SE 0.4)	MD -1.7 (SE 0.4), p<0.001
			Placebo	371	-3.2 (SE 0.4)	NA
Sakai et al 2021a[83]	Low	1–12 weeks	FRE 225 mg	187	-4.9 (SE 0.5)	MD -2.1 (95% CI: -3.10, -1.12), p<0.001
			FRE 675 mg	189	-4.1 (SE 0.5)	MD -1.3 (95% CI: -2.27, -0.29), p=0.011
			Placebo	190	-2.8 (SE 0.5)	NA
Episodic and chronic migraine						
FOCUS[85]**	Low	1 month	FRE quarterly	276	-4.1 (SE 0.4)	MD -3.6 (95% CI: -4.3, -2.8), p<0.0001
			FRE monthly	283	-4.1 (SE 0.4)	MD -3.5 (95% CI: -4.2, -2.8), p<0.0001
			Placebo	278	-0.6 (SE 0.4)	NA
		3 months	FRE quarterly	276	-3.7 (SE 0.3)	MD -3.1 (95% CI: -3.8, -2.4), p<0.0001
			FRE monthly	283	-4.1 (SE 0.3)	MD -3.5 (95% CI: -4.2, -2.8), p<0.0001
			Placebo	278	-0.6 (SE 0.3)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
FOCUS[85]**	Low	3 months	FRE	50	-3.6 (SE 0.7)	MD -3.4 (95% CI: -5.0, -1.8),

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
			quarterly			p<0.0001
			FRE monthly	60	-4.6 (SE 0.7)	MD -4.4 (95% CI: -6.0, -2.8), p<0.0001
			Placebo	54	-0.2 (SE 0.7)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error.
Notes
* In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles.
** In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A25 MMDs in patients receiving galcanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Episodic migraine						
CONQUER [106]	Low	3 months	GAL120 mg	137	-2.9 (SE 0.3)	MD -2.6 (95% CI: -3.4, -1.7), p<0.001
			Placebo	132	-0.3 (SE 0.3)	
EVOLVE-1 [89]	Low	1–6 months	GAL120 mg	210	-4.7 (SE 0.29)	MD -1.9 (95% CI: -2.5, -1.4), p<0.001
			GAL 240 mg	208	-4.6 (SE 0.29)	MD -1.8 (95% CI: -2.3, -1.2), p<0.001
			Placebo	425	-2.8 (SE 0.24)	NA
EVOLVE-2 [91]	Low	1–6 months	GAL 120 mg	226	-4.3 (SE 0.3)	MD -2.02 (SE 0.27), p<0.001
			GAL 240 mg	220	-4.2 (SE 0.3)	MD -1.90 (SE 0.27), p<0.001
			Placebo	450	-2.3 (SE 0.2)	NA
Sakai et al 2020a [93]	Low	1–6 months	GAL 120 mg	115	-3.60 (95% CI: -4.25, -2.96)	MD -3.01 (95% CI: -3.80, -2.22), p<0.001
			GAL 240 mg	114	-3.36 (95% CI: -4.01, -2.71)	MD -2.77 (95% CI: -3.56, -1.98), p<0.001
			Placebo	230	-0.59 (95% CI: -1.05, -0.14)	NA
Skljarevski et al 2018 [98]	Low	1–12 weeks	GAL 120 mg	69	-4.80 (SE 0.37)	MD -1.14 (95% CI: -2.02, -0.29), p=0.01
			Placebo	134	-3.66 (SE 0.28)	
PERSIST 2022 [112]	Low	Month 1	GAL 120 mg	260	-3.6 (SE NR)	NR
			Placebo	258	-1.6 (SE NR)	NA
		Month 2	GAL 120 mg	260	-3.8 (SE NR)	NR
			Placebo	258	-2.02 (SE NR)	NA
		Month 3	GAL 120 mg	260	-4.04 (SE NR)	NR
			Placebo	258	-2.35 (SE NR)	NA

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
		Months 1–3	GAL 120 mg	260	-3.81 (SE 0.23)	MD -1.82 (95% CI: -2.32, -1.32), p<0.0001
			Placebo	258	-1.99 (SE 0.23)	NA
Chronic migraine						
CONQUER [106]	Low	3 months	GAL 120 mg	95	-6.0 (SE 0.7)	MD -3.7 (95% CI: -5.2, -2.2), p<0.001
			Placebo	98	-2.2 (SE 0.6)	NA
REGAIN[102]	Low	1–3 months	GAL 120 mg	273	-4.8 (SE 0.4)	MD -2.1 (95% CI: -2.9, -1.3), p<0.001
			GAL 240 mg	274	-4.6 (SE 0.4)	MD -1.9 (95% CI: -2.7, -1.1), p<0.001
			Placebo	538	-2.7 (SE 0.4)	NA
Episodic and chronic migraine						
CGAJ[105*]	High	12 months	GAL 120 mg	135	-5.6 (SE 0.34)	MD 0.90 (95% CI: -0.03, 1.83), p=0.06
			GAL 240 mg	135	-6.5 (SE 0.33)	
Subgroups of patients with >2 prior treatment failures - chronic migraine						
REGAIN[103]	Low	1–3 months	GAL 120 mg	72	-5.35 (SE 0.71)	MD -4.35 (SE 0.07), p<0.001
			GAL 240 mg	104	-2.77 (SE 0.66)	MD 1.77 (SE 0.63), p<0.01
			Placebo	174	-1.01 (SE 0.54)	NA

Abbreviations

CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SD** = standard deviation, **SE** = standard error.

Notes

Blue text indicates RACS calculated comparisons.

* In the CGAJ trial there were two treatment groups; GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% of patients had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% of patients had chronic migraine.

Monthly headache days (MHDs)

Table A26 MHDs in patients receiving erenumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Change from baseline	Difference between treatments
Episodic migraine						
Sun et al 2016[35]	Low	12 weeks	ERU 70 mg	104	-3.5 (SE 0.4)	MD -1.2 (95% CI: -2.1, -0.2), p=0.022
		12 weeks	Placebo	153	-2.4 (SE 0.3)	
Episodic and chronic migraine						
Takeshima et al 2021[51*]	Low	4–6 months	ERU 70 mg	130	-3.85 (SE 0.41)	MD -1.28 (95% CI: -2.22, -0.33), p=0.008
		4–6 months	Placebo	131	-2.57 (SE 0.41)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **MD** = mean difference, **ROB** = risk of bias, **SE** = standard error.
Notes
* Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine.

Table A27 MHDs in patients receiving eptinezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
Episodic migraine						
PROMISE-1[54]	High	1–12 weeks	EPT 100 mg	221	-4.0 (SD 3.30)	MD -0.70 (95% CI: -1.33, -0.07), p=0.03
			EPT 300 mg	222	-4.5 (SD 3.96)	MD -1.20 (95% CI: -1.90, -0.50), p=0.0007
			Placebo	222	-3.3 (SD 3.51)	NA
Chronic migraine						
Dodick et al 2019[57]	Some concerns	3 months	EPT 300 mg	114	-9.6 (6.9)	MD -2.8 (95% CI: -4.5, -1.0), p=0.0022
			EPT 100 mg	118	-8.9 (6.8)	MD -2.0 (95% CI: -3.7, -0.3), p= 0.0224
			Placebo	116	-6.9 (6.4)	NA
PROMISE-2[58,63]	Low	1–12 weeks	EPT 100 mg	356	-8.2 (SD 5.78)	MD -1.7 (95% CI: -2.6, -0.9), p<0.0001
			EPT 300 mg	350	-8.8 (SD 6.1)	MD -2.3 (95% CI: -3.2, -1.4), p<0.00001
			Placebo	366	-6.4 (SD 5.99)	NA
		13–24 weeks	EPT 100 mg	356	-9.6 (SD 6.62)	-1.5 (95% CI: -2.44, -0.47), p=0.003
			EPT 300 mg	350	-10.6 (SD 6.83)	-2.4 (95% CI: -3.43, -1.42), p<0.00001
			Placebo	366	-8.1 (SD 6.90)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
DELIVER 2022[110]	Low	1–12 weeks	EPT 100 mg	299	-4.6 (SE 0·37)	MD -2.6 (95% CI: -3.3, -1.9), p<0.0001
			EPT 300 mg	293	-5.1 (SE 0.37)	MD -3.0 (95% CI: -3.7, -1.9), p<0.0001
			Placebo	298	-2.1 (SE 0.38)	NA
		13–24 weeks	EPT 100 mg	287	-5.6 (SE 0.39)	-3.0 (95% CI: -3.8, -2.3), p<0.0001
			EPT 300 mg	286	-6.2 (SE 0.39)	-3.6 (95% CI: -4.4, -2.9), p<0.0001
			Placebo	295	-2.6 (SE 0.39)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **MHDs** = monthly headache days, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS calculated comparisons.

Table A28 MHDs in patients receiving fremanezumab

	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
Episodic migraine						
Bigal et al 2015b[65]	Low	Weeks 1–4	FRE 225 mg	96	NR	-2.14 (95% CI: -3.33, -0.95), p=0.0005
			FRE 675 mg	97	NR	-2.05 (95% CI: -3.23, -0.86), p=0.0008
			Placebo	104	NR	NA
		Weeks 5–8	FRE 225 mg	96	NR	-2.62 (95% CI: -3.88, -1.36), p<0.0001
			FRE 675 mg	97	NR	-2.39 (95% CI: -3.65, -1.13), p=0.0002
			Placebo	104	NR	NA
		Weeks 9–12	FRE 225 mg	96	NR	-2.63 (95% CI: -3.91, -1.34), p<0.0001
			FRE 675 mg	97	NR	-2.58 (95% CI: -3.87, -1.30), p<0.0001
			Placebo	104	NR	NA
Chronic migraine						
Bigal et al 2015a[73]	Low	Weeks 1–4	FRE 675/225 mg*	88	NR	-2.13 (95% CI: -3.8, -0.5), p=0.012
			Placebo	89	NR	
		Weeks 5–8	FRE 675/225 mg	88	NR	-1.31 (95% CI: -3.1, 0.5), p=0.151
			Placebo	89	NR	
		Weeks 9–12	FRE 675/225 mg	88	NR	-1.74 (95% CI: -3.6, 0.1), p=0.069

	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
			Placebo	89	NR	
HALO CM[76]	Low	4 weeks	FRE 225 mg	375	-4.5 (SE 0.3)	-2.4 (95% CI: -3.23, -1.57), p<0.00001
			FRE 675 mg	375	-4.4 (SE 0.3)	-2.3 (95% CI: -3.13, -1.47), p<0.00001
			Placebo	371	-2.1 (SE 0.3)	NA
		12 weeks	FRE 225 mg	375	-4.6 (SE 0.3)	-2.1 (95% CI: -2.93, -1.27), p<0.00001
			FRE 675 mg	375	-4.3 (SE 0.3)	-1.8 (95% CI: -2.63, -0.97), p<0.0001
			Placebo	371	-2.5 (SE 0.3)	NA
Sakai et al 2021a[83]	Low	weeks 1–12	FRE 225 mg	187	-4.1 (SE 0.4)	-1.7 (95% CI: -2.54, -0.80), p<0.001
			FRE 675 mg	189	-4.1 (SE 0.4)	-1.7 (95% CI: -2.55, -0.82), p<0.001
			Placebo	190	-2.4 (SE 0.4)	NA
Episodic and chronic migraine						
FOCUS[85]**	Low	1 month	FRE quarterly	276	-4.2 (SE 0.4)	-3.7 (95% CI: -4.4, -3.0), p<0.0001
			FRE monthly	283	-4.5 (SE 0.3)	-3.9 (95% CI: -4.6, -3.2), p<0.0001
			Placebo	278	-0.5 (SE 0.3)	NA
		3 months	FRE quarterly	276	-3.9 (SE 0.3)	-3.2 (95% CI: -3.9, -2.5), p<0.0001
			FRE monthly	283	-4.2 (SE 0.3)	-3.6 (95% CI: -4.3, -2.9), p<0.0001
			Placebo	278	-0.6 (SE 0.3)	NA
Subgroup in episodic and chronic migraine patients						
FOCUS[86]	Low	1 month 2 Tx failures	FRE quarterly	140	-4.1 (0.43)	-3.2 (95% CI: -4.09, -2.21), p<0.0001
			FRE monthly	133	-4.7 (0.43)	-3.8 (95% CI: -4.71, -2.80), p<0.0001
			Placebo	141	-1.0 (0.43)	NA
		1 month 3 Tx failures	FRE quarterly	85	-4.1 (0.58)	-4.0 (95% CI: -5.34, -2.60), p<0.0001
			FRE monthly	98	-4.0 (0.58)	-3.8 (95% CI: -5.11, -2.49), p<0.0001
			Placebo	82	-0.2 (0.56)	NA
		1 month 4 Tx failures	FRE quarterly	49	-5.3 (1.03)	-6.0 (95% CI: -8.30, -3.78), p<0.0001
			FRE monthly	50	-5.2 (0.90)	-5.9 (95% CI: -8.02, -3.81), p<0.0001

	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
			Placebo	54	0.7 (1.03)	NA
		3 months 2 Tx failures	FRE quarterly	140	-3.9 (0.42)	-2.7 (95% CI: -3.64, -1.86), p<0.0001
			FRE monthly	133	-4.8 (0.42)	-3.6 (95% CI: -4.47, -2.65), p<0.0001
			Placebo	141	-1.2 (0.42)	NA
		3 months 3 Tx failures	FRE quarterly	85	-3.9 (0.59)	-3.6 (95% CI: -4.96, -2.21), p<0.0001
			FRE monthly	98	-3.5 (0.59)	-3.2 (95% CI: -4.56, -1.93), p<0.0001
			Placebo	82	-0.3 (0.57)	NA
		3 months 4 Tx failures	FRE quarterly	49	-4.7 (1.01)	-5.2 (95% CI: -7.42, -3.07), p<0.0001
			FRE monthly	50	-4.9 (0.88)	-5.4 (95% CI: -7.47, -3.42), p<0.0001
			Placebo	54	0.6 (1.02)	NA

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MHDs** = monthly headache days, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error, **Tx** = treatment.

Notes

Blue text indicates RACS calculated comparisons.

* In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles.

** In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A29 MHDs in patients receiving galcanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs	Difference between treatments
Episodic migraine						
Dodick et al 2014a[88]	Low	3 months	GAL 150 mg	107	-4.9 (4.1)	MD -1.3 (90%CI: -2.1, -0.5), p=0.012
			Placebo	110	-3.7 (4.2)	
Skljarevski et al 2018[99]	Low	3 months	GAL 120 mg	69	-3.11 (SE 0.31)	MD -0.64 (95% CI: -1.39, 0.11), p=0.09
			Placebo	134	-2.47 (SE 0.22)	
Chronic migraine						
REGAIN[102]	Low	Average across months 1–9	GAL 120 mg	273	-4.8 (SE 0.4)	MD -1.8 (95% CI: -2.7, -1.0), p<0.001
			GAL 240 mg	274	-4.6 (SE 0.4)	MD -1.6 (95% CI: -2.4, -0.8), p<0.001
			Placebo	538	-3.0 (SE 0.4)	NA
Episodic and chronic migraine						
CGAJ[105]*	High	12 months	GAL 120 mg	135	-2.2 (0.3)	MD -0.10 (95% CI: -0.93, 0.73), p=0.81
			GAL 240 mg	135	-2.1 (0.3)	

Abbreviations

CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHDs** = monthly headache days, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error.

Notes

Blue text indicates RACS calculated comparisons.

* In the CGAJ trial there were two treatment groups; GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% of patients had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% of patients had chronic migraine.

Migraine Headache days (MHDs) with acute medication usage

Table A30 MHDs with acute medication usage, erenumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Episodic migraine						
ARISE[15]	Low	3 months	ERU 70 mg	282	-1.2 (SE 0.1)	MD -0.6 (95% CI: -1.0, -0.2), p=NR
			Placebo	288	-0.6 (SE 0.1)	
EMPOwER[17]	High	1 month	ERU 70 mg	123	-1.63 (SE 0.22)	MD -1.33 (95% CI: -1.93, -0.73), p<0.001
			ERU 140 mg	80	-1.90 (SE 0.28)	MD -1.60 (95% CI: -2.28, -0.92), p<0.001
			Placebo	127	-0.30 (SE 0.22)	NA
		2 months	ERU 70 mg	123	-2.03 (SE 0.24)	MD -1.50 (95% CI: -2.14, -0.86), p<0.001
			ERU 140 mg	80	-2.28 (SE 0.29)	MD -1.75 (95% CI: -2.47, -1.02), p<0.001
			Placebo	127	-0.53 (SE 0.23)	NA
		3 months	ERU 70 mg	123	-1.84 (SE 0.26)	MD -1.36 (95% CI: -2.07, -0.64), p<0.001
			ERU 140 mg	80	-2.39 (SE 0.33)	MD -1.90 (95% CI: -2.71, -1.09), p<0.001
			Placebo	127	-0.49 (SE 0.26)	NA
LIBERTY[18]	Low	weeks 1–4	ERU 140 mg	119	-1.1 (SE 0.2)	MD -1.4 (95% CI: -2.0, -0.8), p<0.001
			Placebo	124	0.3 (SE 0.2)	
		weeks 5–8	ERU 140 mg	119	-1.3 (SE 0.2)	MD -1.9 (95% CI: -2.6, -1.2), p<0.001
			Placebo	124	0.6 (SE 0.3)	
		weeks 9–12	ERU 140 mg	118	-1.3 (SE 0.2)	MD -1.7 (95% CI: -2.4, -1.0), p<0.001
			Placebo	120	0.5 (SE 0.3)	
Sakai et al 2019[23]	Low	months 4–6	ERU 70 mg	135	-1.19 (95% CI: -1.64, -0.74)	MD -2.07 (95% CI: -2.66, -1.49), p<0.001
			ERU 140 mg	136	-1.16 (95% CI: -1.60, -0.71)	MD -2.04 (95% CI: -2.63, -1.45), p<0.001
			Placebo	136	0.88 (95% CI: 0.44, 1.33)	NA
STRIVE[26]	Low	1 month	ERU 70 mg	312	-0.78 (95% CI: -1.03, -0.53)	MD -0.75 (95% CI: -1.10, -0.40), p<0.0001
			ERU 140 mg	318	-1.40 (95% CI: -1.65, -1.15)	MD -1.37 (95% CI: -1.72, -1.02), p<0.0001
			Placebo	316	-0.03 (95% CI: -0.28, 0.22)	NA
		2 months	ERU 70 mg	312	-1.10 (95% CI: -1.35, -0.85)	MD -0.76 (95% CI: -1.11, -0.41), p<0.0001
			ERU 140 mg	318	-1.56 (95% CI: -1.81, -1.31)	MD -1.22 (95% CI: -1.57, -0.87), p<0.0001
			Placebo	316	-0.34 (95% CI: -0.59, -0.09)	NR
		3 months	ERU 70 mg	312	-1.12 (95% CI: -1.37, -	MD -0.79 (95% CI: -1.14,

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
					0.87)	-0.44), p<0.0001
			ERU 140 mg	318	-1.56 (95% CI: -1.81, -1.31)	MD -1.23 (95% CI: -1.58, -0.88), p<0.0001
			Placebo	316	-0.33 (95% CI: -0.58, -0.08)	NA
		4 months	ERU 70 mg	312	-1.08 (95% CI: -1.33, -0.82)	MD -0.89 (95% CI: -1.25, -0.53), p<0.0001
			ERU 140 mg	318	-1.56 (95% CI: -1.81, -1.31)	MD -1.37 (95% CI: -1.73, -1.01), p<0.0001
			Placebo	316	-0.19 (95% CI: -0.45, 0.06)	NA
		5 months	ERU 70 mg	312	-1.17 (95% CI: -1.43, -0.92)	MD -1.20 (95% CI: 0.84, 1.56), p<0.0001
			ERU 140 mg	318	-1.61 (95% CI: -1.87, -1.36)	MD 0.44 (95% CI: 0.07, 0.81), p=0.02
			Placebo	316	-0.40 (95% CI: -0.66, -0.14)	NA
		6 months	ERU 70 mg	312	-1.14 (95% CI: -1.40, -0.89)	MD -1.15 (95% CI: -1.52, -0.78), p<0.0001
			ERU 140 mg	318	-1.67 (95% CI: -1.92, -1.41)	MD -1.68 (95% CI: -2.04, -1.32), p<0.0001
			Placebo	316	0.01 (95% CI: -0.25, 0.26)	NA
		4–6 months	ERU 70 mg	312	-1.1 (SE 0.1)	MD -0.9 (95% CI: -1.2, -0.6), p<0.001
			ERU 140 mg	318	-1.6 (SE 0.1)	MD -1.4 (95% CI: -1.7, -1.1), p<0.001
			Placebo	316	-0.2 (SE 0.1)	NA
Sun et al 2016[35]	Low	12 weeks	ERU 70 mg	104	-2.5 (SE 0.3)	MD -1.2 (95% CI: -2, -0.3), p=0.006
			Placebo	153	-1.4 (SE 0.3)	
Chronic migraine						
Tepper et al 2017[40]	Low	3 months	ERU 70 mg	188	-3.5 (SE 0.3)	MD -1.9 (95% CI: -2.6, -1.1), p<0.0001
			ERU 140 mg	187	-4.1 (SE 0.3)	MD -2.6 (95% CI: -3.3, -1.8), p<0.0001
			Placebo	281	-1.6 (SE 0.2)	NA
DRAGON 2022[109]	Some concerns	Week 12	ERU 70 mg	270	-5.34 (SE 0.39)	-0.67 (95% CI: -1.76, 0.41), p=0.223
			Placebo	274	-4.66 (SE 0.39)	NA
Episodic and chronic migraine						
Takeshima et al 2021[51-53]	Low	4–6 months	ERU 70 mg	130	-2.57 (SE 0.32)	MD -1.47 (95% CI: -2.24, -0.71), p<0.001
			Placebo	131	-1.10 (SE 0.32)	
Subgroups of patients with >2 prior treatment failures - episodic migraine						
LIBERTY[18]	Low	Week 12	ERU 140 mg	76	-1.3 (SE 0.3)	MD -1.7 (95% CI: -2.6, -0.7), p<0.001
			Placebo	69	0.4 (SE 0.4)	
STRIVE[30]	Low	1 month	ERU 70 mg	49	-0.9 (SD NR)	NR

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
			ERU 140 mg	58	-2.2 (SD NR)	NR
			Placebo	54	-0.2 (SD NR)	NR
		2 months	ERU 70 mg	49	-1.4 (SD NR)	NR
			ERU 140 mg	58	-2.5 (SD NR)	NR
			Placebo	54	0 (SD NR)	NR
		3 months	ERU 70 mg	49	-1.1 (SD NR)	NR
			ERU 140 mg	58	-2.4 (SD NR)	NR
			Placebo	54	-1 (SD NR)	NR
		4 months	ERU 70 mg	49	-1.5 (SD NR)	NR
			ERU 140 mg	58	-2.4 (SD NR)	NR
			Placebo	54	0.3 (SD NR)	NR
		5 months	ERU 70 mg	49	-1 (SD NR)	NR
			ERU 140 mg	58	-2.2 (SD NR)	NR
			Placebo	54	-0.4 (SD NR)	NR
		6 months	ERU 70 mg	49	-0.7 (SD NR)	NR
			ERU 140 mg	58	-2.3 (SD NR)	NR
			Placebo	54	0.5 (SD NR)	NR
		4-6 months	ERU 70 mg	49	NR	MD -1.2 (95% CI: -2.2, -0.3), p=sig*
			ERU 140 mg	58	NR	MD -2.5 (95% CI: -3.4, -1.5), p=sig*
			Placebo	54	NR	NA
Subgroups of patients with >2 prior treatment failures - episodic migraine						
Tepper et al 2017[41]	Low	3 months	ERU 70 mg	93	-4.1 (SE NR)	MD -2.8 (95% CI: -3.9, -1.7), p<0.001
			ERU 140 mg	92	-5.4 (SE NR)	MD -4.1 (95% CI: -5.3, -3.0), p<0.001
			Placebo	142	-1.3 (SE NR)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MHDs** = monthly headache days, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SD** = standard deviation, **SE** = standard error, **sig** = significant.
Notes
Blue text indicates RACS calculated comparisons.

Table A31 MHDs with acute medication usage, eptinezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Episodic migraine						
PROMISE-1[54]	High	1–12 weeks	EPT 100 mg	221	-0.9 (SD 2.00)	MD -0.50 (95% CI: -0.81, -0.19), p=0.002
			EPT 300 mg	222	-0.8 (SD 1.77)	MD -0.40 (95% CI: -0.69, -0.11), p=0.006
			Placebo	222	-0.4 (SD 1.27)	NA
Chronic migraine						
PROMISE-2[58,63]	Low	1–12 weeks	EPT 100 mg	356	-3.3 (SD 4.89)	MD -1.2 (95% CI: -1.7, -0.6), p<0.0001
			EPT 300 mg	350	-3.5 (SD 4.62)	MD -1.4 (95% CI: -1.9, -0.9), p<0.0001
			Placebo	366	-1.9 (SD 4.18)	NA
		13–24 weeks	EPT 100 mg	356	-3.4 (SD 5.14)	MD -1.1 (95% CI: -1.86, -0.42), p=NR
			EPT 300 mg	350	-3.9 (SD 4.96)	MD -1.7 (95% CI: -2.44, -1.01), p=NR
			Placebo	366	-2.2 (SD 4.73)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
DELIVER 2022[110]	Low	1–12 weeks	EPT 100 mg	298	-4.1 (SE 0·33)	-2.5 (95% CI: -3.2, -1.9), p<0.0001
			EPT 300 mg	290	-4.6 (SE 0.34)	-3.0 (95% CI: -3.6, -2.4), p<0.0001
			Placebo	298	-1.6 (SE 0.34)	NA
		13–24 weeks	EPT 100 mg	287	-4.6 (SE 0.36)	-2.9 (95% CI: -3.6, -2.2), p<0.0001
			EPT 300 mg	285	-5.2 (SE 0.36)	-3.5 (95% CI: -4.2, -2.8), p<0.0001
			Placebo	294	-1.7 (SE 0.36)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **MHDs** = monthly headache days, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS calculated comparisons.

Table A32 MHDs with acute medication usage, fremanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Episodic migraine						
Bigal et al 2015b[65]	Low	Weeks 1–4	FRE 225 mg	NR	NR	MD -2.12 (95% CI: -3.15, -1.09), p<0.0001
			FRE 675 mg	NR	NR	MD -1.98 (95% CI: -3.01, -0.94), p=0.0002
			Placebo	NR	NR	NA
		Weeks 5–8	FRE 225 mg	NR	NR	MD -2.32 (95% CI: -3.44, -1.21), p<0.0001
			FRE 675 mg	NR	NR	MD -1.86 (95% CI: -2.97, -0.74), p=0.0012
			Placebo	NR	NR	NA
		Weeks 9–12	FRE 225 mg	NR	NR	MD -1.76 (95% CI: -2.86, -0.66), p=0.0018
			FRE 675 mg	NR	NR	MD -1.70 (95% CI: -2.80, -0.60), p=0.0026
			Placebo	NR	NR	NA
HALO EM[68] [69]	High	12 weeks	FRE 225 mg	287	-3.0 (95% CI: -3.41, -2.56)	MD -1.4 (95% CI: -1.84, -0.89), p<0.001
			FRE 675 mg	288	-2.9 (95% CI: -3.34, -2.48)	MD -1.3 (95% CI: -1.76, -0.82), p<0.001
			Placebo	290	-1.6 (95% CI: -2.04, -1.20)	NA
Sakai et al 2021b[71]	Low	weeks 1–12	FRE 225 mg	121	-3.3 (SE 0.3)	MD -2.8 (95% CI: -3.55, -2.14), p<0.0001
			FRE 675 mg	117	-3.3 (SE 0.4)	MD -2.8 (95% CI: -3.54, -2.12), p<0.0001
			Placebo	116	-0.5 (SE 0.4)	NA
Chronic migraine						
Bigal et al 2015a[73]	Low	Weeks 1–4	FRE 675/225 mg	NR	NR	MD -1.99 (95% CI: -3.6, -0.4), p=0.016
			Placebo	NR	NR	
		Weeks 5–8	FRE 675/225 mg	NR	NR	MD -2.16 (95% CI: -3.9, -0.5), p=0.014
			Placebo	NR	NR	
		Weeks 9–12	FRE 675/225 mg	NR	NR	MD -2.15 (95% CI: -4.0, 0.3), p=0.02
			Placebo	NR	NR	
HALO CM[76]	Low	12 weeks	FRE 225 mg	375	-4.2 (SE 0.3)	MD -2.3 (95% CI: -3.13, -1.47), p<0.00001
			FRE 675 mg	375	-3.7 (SE 0.3)	MD -1.8 (95% CI: -2.63, -0.97), p<0.0001
			Placebo	371	-1.9 (SE 0.3)	NA
Sakai et al 2021a[83]	Low	weeks 1–12	FRE 225 mg	187	-3.7 (SE 0.4)	MD -1.3 (95% CI: -2.18, -0.43), p=0.003
			FRE 675 mg	189	-3.9 (SE 0.4)	MD -1.4 (95% CI: -2.30, -0.56), p=0.001
			Placebo	190	-2.4 (SE 0.4)	NA

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Episodic and chronic migraine						
FOCUS[85]	Low	3 months	FRE quarterly	276	-3.7 (SE 0.3)	MD -3.1 (95% CI: -3.8, -2.4), p<0.0001
			FRE monthly	283	-3.9 (SE 0.3)	MD -3.4 (95% CI: -4.0, -2.7), p<0.0001
			Placebo	278	-0.6 (SE 0.3)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
FOCUS[86]	Low	1 month 2 Tx failures	FRE quarterly	140	-4.2 (0.44)	MD -3.2 (95% CI: -4.18, -2.27), p<0.0001
			FRE monthly	133	-4.4 (0.44)	MD -3.5 (95% CI: -4.42, -2.48), p<0.0001
			Placebo	141	-0.9 (0.43)	NA
		1 month 3 Tx failures	FRE quarterly	85	-4.0 (0.51)	MD -3.5 (95% CI: -4.66, -2.24), p<0.0001
			FRE monthly	98	-3.9 (0.51)	MD -3.3 (95% CI: -4.51, -2.19), p<0.0001
			Placebo	82	-0.5 (0.49)	NA
		1 month 4 Tx failures	FRE quarterly	49	-4.3 (0.91)	MD -5.4 (95% CI: -7.41, -3.41), p<0.0001
			FRE monthly	50	-4.2 (0.80)	MD -5.3 (95% CI: -7.19, -3.45), p<0.0001
			Placebo	54	1.1 (0.91)	NA
		3 months 2 Tx failures	FRE quarterly	140	-4.0 (0.44)	MD -2.9 (95% CI: -3.79, -1.94), p<0.0001
			FRE monthly	133	-4.3 (0.44)	MD -3.2 (95% CI: -4.12, -2.23), p<0.0001
			Placebo	141	-1.2 (0.43)	NA
		3 months 3 Tx failures	FRE quarterly	85	-3.7 (0.51)	MD -3.2 (95% CI: -4.44, -2.06), p<0.0001
			FRE monthly	98	-3.5 (0.51)	MD -3.0 (95% CI: -4.18, -1.89), p<0.0001
			Placebo	82	-0.4 (0.49)	NA
		3 months 4 Tx failures	FRE quarterly	49	-3.6 (0.93)	MD -4.8 (95% CI: -6.80, -2.81), p<0.0001
			FRE monthly	50	-4.0 (0.82)	MD -5.2 (95% CI: -7.05, -3.33), p<0.0001
			Placebo	54	1.2 (0.94)	NA

Abbreviations
CI = confidence interval, **FRE**= fremanezumab, **MD** = mean difference, **MHDs** = monthly headache days, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error, **Tx** = treatment.
Notes
Blue text indicates RACS calculated comparisons.

Table A33 MHDs with acute medication usage, galcanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
Episodic migraine						
CONQUER[106]	Low	3 months	GAL 120 mg	137	-3.0 (SE 0.3)	MD -2.7 (95% CI: -3.5, -1.9), p<0.0001
			Placebo	132	-0.2 (SE 0.3)	
EVOLVE-1[89]	Low	1–6 months	GAL 120 mg	210	-4 (SE 0.25)	MD -1.8 (95% CI: -2.3, -1.3), p<0.001
			GAL 240 mg	208	-3.8 (SE 0.26)	MD -1.6 (95% CI: -2.1, -1.1), p<0.001
			Placebo	425	-2.2 (SE 0.21)	NA
EVOLVE-2[91]	Low	1–6 months	GAL 120 mg	226	-3.7 (SE 0.2)	MD -1.80 (95% CI: -2.35, -1.25), p<0.00001
			GAL 240 mg	220	-3.6 (SE 0.2)	MD -1.70 (95% CI: -2.25, -1.15), p<0.00001
			Placebo	450	-1.9 (SE 0.2)	NA
Sakai et al 2020a[93]	Low	1–6 months	GAL 120 mg	115	-3.02 (95% CI: -3.60, -2.43)	MD -2.90 (95% CI: -3.61, -2.19), p<0.001
			GAL 240 mg	114	-2.81 (95% CI: -3.40, -2.23)	MD -2.70 (95% CI: -3.41, -1.99), p<0.001
			Placebo	230	-0.12 (95% CI: -0.53, 0.30)	NA
Skljarevski et al 2018[98]	Low	1–12 weeks	GAL 120 mg	69	-3.59 (SE 0.31)	MD -1.08 (95% CI: -1.84, -0.32), p=0.005
			Placebo	134	-2.51 (SE 0.23)	
PERSIST 2022[112]	Low	Months 1-3	GAL 120 mg	260	-2.49 (SE 0.22)	MD -1.78 (95% CI: -2.25, -1.31), p<0.0001
			Placebo	258	-0.71 (SE 0.22)	NA
Chronic migraine						
CONQUER[106]	Low	3 months	GAL 120 mg	95	-5.4 (SE 0.6)	MD -4.0 (95% CI: -5.4, -2.6), p<0.0001
			Placebo	98	-1.4 (SE 0.6)	
REGAIN[102]	Low	1–6 months	GAL 120 mg	273	-4.7 (SE 0.4)	MD -2.5 (95% CI: -3.3, -1.8), p<0.001
			GAL 240 mg	274	-4.3 (SE 0.4)	MD -2.0 (95% CI: -2.8, -1.3), p<0.001
			Placebo	538	-2.2 (SE 0.3)	NA
Episodic and chronic migraine						
CGAJ[105]	High	12 months	GAL 120 mg	135	-5.1 (SE 0.4)	MD 0.00 (99%CI: -1.11, 1.11), p=1.00
			GAL 240 mg	135	-5.1 (SE 0.4)	
Subgroups of patients with >2 prior treatment failures - episodic migraine						
CONQUER[107]	Low	3 months	GAL 120 mg	56	-3.5 (SE 0.7)	MD -2.8 (SE 0.8), p=0.0008
			Placebo	44	-0.7 (SE 0.8)	
Subgroups of patients with >2 prior treatment failures - chronic migraine						
CONQUER[107]	Low	3 months	GAL 120 mg	42	-7.0 (SE 1.1)	MD -6.2 (SE 1.8), p<0.0001
			Placebo	42	-0.8 (SE 1.0)	
REGAIN[103]	Low	1–3 months	GAL 120 mg	NR	-5.81 (SE 0.69)	MD -4.46 (SE 0.69), p<0.001
			GAL 240 mg	NR	-3.40 (SE 0.65)	MD -2.06 (SE 0.61),

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean number of MHDs with acute medication	Difference between treatments
						p<0.001
			Placebo	NR	-1.35 (SE 0.53)	NA

Abbreviations

CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MHDs** = monthly headache days, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error.

Notes

Blue text indicates RACS calculated comparisons.

Response rate (>50%)

Table A34 Response rate (>50%), erenumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
ARISE[15]	Low	3 months	ERU 70 mg	282	112 (39.7)	OR 1.59 (95% CI: 1.12, 2.27), p=0.010
			Placebo	288	85 (29.5)	
EMPOwER[17]	High	1 month	ERU 70 mg	329	128 (38.9)	OR 1.7 (95% CI: 1.2, 2.4), p=0.001
			ERU 140 mg	219	104 (47.5)	OR 2.5 (95% CI: 1.7, 3.5), p<0.001
			Placebo	330	89 (27)	NA
		2 months	ERU 70 mg	329	175 (53.2)	OR 1.9 (95% CI: 1.4, 2.7), p<0.001
			ERU 140 mg	219	116 (53)	OR 1.9 (95% CI: 1.4, 2.7), p<0.001
			Placebo	330	122 (37)	NA
		3 months	ERU 70 mg	329	182 (55.3)	OR 1.5 (95% CI: 1.1, 2.1), p=0.007
			ERU 140 mg	219	140 (63.9)	OR 2.2 (95% CI: 1.6, 3.2), p<0.001
			Placebo	330	148 (44.8)	NA
LIBERTY[18]	Low	1 month	ERU 140 mg	119	27 (23)	OR 5.9 (95% CI: 2.3, 14.9), p<0.001
			Placebo	124	6 (5)	
		2 months	ERU 140 mg	119	37 (31)	OR 3.3 (95% CI: 1.7, 6.4), p<0.001
			Placebo	124	15 (12)	
		3 months	ERU 140 mg	119	36 (30)	OR 2.7 (95% CI: 1.4, 5.2), p=0.002
			Placebo	124	17 (14)	
Sakai et al 2019[23]	Low	4–6 months	ERU 70 mg	135	39 (28.9)	OR 5.60 (95% CI: 2.60, 12.06), p<0.001
			ERU 140 mg	136	37 (27.2)	OR 4.73 (95% CI: 2.24, 9.99), p<0.001
			Placebo	136	10 (7.4)	NA
STRIVE[26]	Low	1 month	ERU 70 mg	312	102 (32.7)	OR 2.65 (95% CI: 1.80, 3.89), p=<0.00001
			ERU 140 mg	318	113 (35.5)	OR 3.00 (95% CI: 2.05, 4.40), p<0.00001
			Placebo	316	49 (15.5)	NA
		2 months	ERU 70 mg	312	124 (39.7)	OR 2.05 (95% CI: 1.45, 2.88), p<0.0001
			ERU 140 mg	318	143 (45.0)	OR 2.54 (95% CI: 1.81, 3.56), p<0.00001
			Placebo	316	77 (24.4)	NA
		3 months	ERU 70 mg	312	129 (41.3)	OR 1.98 (95% CI: 1.41, 2.77), p<0.0001

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
			ERU 140 mg	318	153 (48.1)	OR 2.60 (95% CI: 1.87, 3.63), p<0.00001
			Placebo	316	83 (26.3)	NA
		4 months	ERU 70 mg	312	128 (41.0)	OR 1.72 (95% CI: 1.23, 2.40), p=0.001
			ERU 140 mg	318	158 (49.7)	OR 2.44 (95% CI: 1.76, 3.39), p<0.00001
			Placebo	316	91 (28.8)	NA
		5 months	ERU 70 mg	312	147 (47.1)	OR 2.17 (95% CI: 1.56, 3.01), p<0.00001
			ERU 140 mg	318	153 (48.1)	OR 2.26 (95% CI: 1.63, 3.13), p<0.00001
			Placebo	316	92 (29.1)	NA
		6 months	ERU 70 mg	312	147 (47.1)	OR 2.14 (95% CI: 1.54, 2.97), p<0.00001
			ERU 140 mg	318	156 (49.1)	OR 2.31 (95% CI: 1.67, 3.20), p<0.00001
			Placebo	316	93 (29.4)	NR
		4–6 months	ERU 70 mg	312	135 (43.3)	OR 2.13 (95% CI: 1.52, 2.98), p<0.001
			ERU 140 mg	318	159 (50.0)	OR 2.81 (95% CI: 2.01, 3.94), p<0.001
			Placebo	316	84 (26.6)	NA
Sun et al 2016[35]	Low	12 weeks	ERU 70 mg	99	46 (46)	OR 2.0 (95% CI: 1.2, 3.4), p=0.011
			Placebo	144	43 (30)	
Chronic migraine						
Tepper et al 2017[40]	Low	3 months	ERU 70 mg	188	75 (40)	OR 2.2 (95% CI: 1.5, 3.3), p=0.0001
			ERU 140 mg	187	77 (41)	OR 2.3 (95% CI: 1.6, 3.5), p<0.0001
			Placebo	281	66 (23)	NA
DRAGON 2022[109]	Some concerns	Week 4	ERU 70 mg	279	92 (33)	OR 2.19 (95% CI: 1.48, 3.25), p<0.001
			Placebo	278	51 (18.3)	NA
		Week 8	ERU 70 mg	279	122 (43.7)	OR 1.72 (95% CI: 1.21, 2.45), p=0.002
			Placebo	278	87 (31.3)	NA
		Week 12	ERU 70 mg	279	131 (47)	OR 1.54 (95% CI: 1.09, 2.17), p=0.014
			Placebo	278	102 (36.7)	NA
Episodic and chronic migraine						
HER-MES[49]*	Low	24 weeks	ERU 70 or 140 mg	388	215 (55.4)	OR 2.76 (95% CI: 2.06, 3.71) RR 1.78 (95% CI: 1.50, 2.11), p<0.001
			Topiramate 25–100 mg	388	121 (31.2)	
Subgroups of patients with >2 prior treatment failures - episodic migraine						

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
LIBERTY[18]	Low	Week 12	ERU 140 mg	72	8 (11.1)	OR 2.9 (95% CI: 1.2, 7.0), p=0.019
			Placebo	76	20 (26.3)	
STRIVE[30]	Low	1 month	ERU 70 mg	49	9 (18.4)	OR 2.21 (95% CI: 0.68, 7.11), p=0.19
			ERU 140 mg	58	17 (29.3)	OR 4.06 (95% CI: 1.38, 11.97), p=0.01
			Placebo	54	5 (9.3)	NA
		2 months	ERU 70 mg	49	13 (26.5)	OR 2.08 (95% CI: 0.78, 5.55), p=0.15
			ERU 140 mg	58	24 (41.4)	OR 4.06 (95% CI: 1.63, 10.13), p=0.003
			Placebo	54	8 (14.8)	NA
		3 months	ERU 70 mg	49	13 (26.5)	OR 2.08 (95% CI: 0.78, 5.55), p=0.15
			ERU 140 mg	58	27 (46.6)	OR 5.01 (95% CI: 2.01, 12.45), p=0.0005
			Placebo	54	8 (14.8)	NA
		4–6 months	ERU 70 mg	49	13 (26.5)	OR 2.9 (95% CI: 1.0, 8.3), p=0.05
			ERU 140 mg	58	21 (36.2)	OR 4.5 (95% CI: 1.7, 12.4), p=0.003
			Placebo	54	6 (11.1)	NA
Subgroups of patients with >2 prior treatment failures - chronic migraine						
Tepper et al 2017[41]	Low	3 months	ERU 70 mg	93	33 (35.6)	OR 3.5 (95% CI: 1.8, 6.6), p<0.001
			ERU 140 mg	92	38 (41.3)	OR 4.2 (95% CI: 2.2, 7.9), p<0.001
			Placebo	142	20 (14.2)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
Takeshima et al 2021[51]**	Low	4–6 months	ERU 70 mg	130	41 (31.5)	OR 2.33 (95% CI: 1.29, 4.23), p=0.005
			Placebo	131	22 (16.8)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **RR** = relative risk.
Notes
Blue text indicates RACS calculated comparisons.
* In HER-MES, the following number of patients were included: For erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%). Chronic (≥15 MMDs) = 42 (10.8%).
** Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine.

Table A35 Response rate (>50%), eptinezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
PROMISE-1[54,55]	High	1–12 weeks	EPT 100 mg	221	110 (49.8)	OR 1.662 (95% CI NR), p=0.0085
			EPT 300 mg	222	125 (56.3)	OR 2.158 (95% CI NR), p=0.0001
			Placebo	222	83 (37.4)	NA
		13–24 weeks	EPT 100 mg	221	137 (62.0)	OR 1.55 (95% CI: 1.06, 2.26), p=0.02
			EPT 300 mg	222	145 (65.3)	OR 1.78 (95% CI: 1.22, 2.61), p=0.003
			Placebo	222	114 (51.4)	NA
Chronic migraine						
Dodick et al 2019[57]	Some concerns	Weeks 1–12	EPT 300 mg	114	65 (57)	OR 1.95 (95% CI: 1.15, 3.29), p=0.013
			EPT 100 mg	118	65 (55.1)	OR 1.80 (95% CI: 1.07, 3.02), p=0.029
			Placebo	116	47 (40.5)	NR
PROMISE-2[58,63]	Low	1–12 weeks	EPT 100 mg	356	205 (57.6)	OR 2.1 (95% CI: 1.6, 2.8), p<0.0001
			EPT 300 mg	350	215 (61.4)	OR 2.4 (95% CI: 1.8, 3.3), p<0.0001
			Placebo	366	144 (39.3)	NA
		13–24 weeks	EPT 100 mg	356	217 (61.0)	OR 1.99 (95% CI: 1.48, 2.67), p<0.00001
			EPT 300 mg	350	224 (64.0)	OR 2.66 (95% CI: 1.68, 3.06), p<0.00001
			Placebo	366	161 (44.0)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
DELIVER 2022[110]	Low	Weeks 1-12	EPT 100 mg	299	126 (42)	OR 4.9 (95% CI: 3.3, 7.5), p<0.0001
			EPT 300 mg	293	145 (49)	OR 6.6 (95% CI: 4.4, 10.0), p<0.0001
			Placebo	298	39 (13)	NA
		Weeks 13-24	EPT 100 mg	287	150 (52)	OR 3.56 (95% CI: 2.50, 5.10), p<0.0001
			EPT 300 mg	286	169 (59)	OR 4.69 (95% CI: 3.29, 6.75), p<0.0001
			Placebo	295	70 (24)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Table A36 Response rate (>50%), fremanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
Bigal et al 2015b[65]	Low	Weeks 1–4	FRE 225 mg	95	42 (44)	OR 3.33 (95% CI: 1.77, 6.27), p=0.0001
			FRE 675 mg	96	50 (52)	OR 4.57 (95% CI: 2.43, 8.58), p<0.0001
			Placebo	104	20 (19)	NA
		Weeks 5–8	FRE 225 mg	95	52 (55)	OR 2.28 (95% CI: 1.29, 4.04), p=0.0043
			FRE 675 mg	96	53 (55)	OR 2.33 (95% CI: 1.32, 4.12),

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
						p=0.0034
			Placebo	104	36 (35)	NA
		Weeks 9–12	FRE 225 mg	95	53 (56)	OR 2.38 (95% CI: 1.35, 4.22), p=0.0027
			FRE 675 mg	96	55 (57)	OR 2.53 (95% CI: 1.43, 4.49), p=0.0013
			Placebo	104	36 (35)	NA
HALO EM[68,70]	High	1–12 weeks	FRE 225 mg	287	137 (47.7)	Difference vs placebo 19.8 (95% CI: 12.0, 27.6), p<0.001
			FRE 675 mg	288	128 (44.4)	Difference vs placebo 16.5 (95% CI: 8.9, 24.1), p<0.001
			Placebo	290	81 (27.9)	NA
		12 weeks	FRE 225 mg	263	130 (51.2)	OR 1.64 (95% CI: 1.16, 2.32), p=0.005
			FRE 675 mg	269	132 (49)	OR 1.62 (95% CI: 1.15, 2.28), p=0.006
			Placebo	268	100 (37.2)	NA
Sakai et al 2021b[71]	Low	12 weeks	FRE 225 mg	121	50 (41.3)	Difference vs placebo 30.1 (95% CI: 19.6, 40.6), p<0.0001
			FRE 675 mg	117	53 (45.3)	Difference vs placebo 34.1 (95% CI: 23.4, 44.7), p<0.0001
			Placebo	116	13 (11.2)	NA
Chronic migraine						
Bigal et al 2015a[74]	Low	Weeks 1–4	FRE 675/225 mg	87	36 (41)	OR 2.2 (95% CI: 1.1, 4.1), p=0.019
			Placebo	89	22 (25)	
		Weeks 5–8	FRE 675/225 mg	87	42 (48)	OR 1.44 (95% CI: 0.79, 2.62), p=0.231
			Placebo	89	35 (39)	
		Weeks 9–12	FRE 675/225 mg	87	46 (53)	OR 2.44 (95% CI: 1.3, 4.5), p=0.004
			Placebo	89	28 (31)	
HALO CM[76,82]	Low	1–12 weeks	FRE 225 mg	375	153 (41)	OR 3.13 (95% CI: 2.24, 4.37), p<0.001
			FRE 675 mg	375	141 (38)	OR 2.73 (95% CI: 1.95, 3.83), p<0.001
			Placebo	371	67 (18)	NA
		12 weeks	FRE 225 mg	345	154 (44.5)	OR 3.64 (95% CI: 2.57, 5.15), p<0.001
			FRE 675 mg	350	142 (40.5)	OR 3.08 (95% CI: 2.18, 4.37), p<0.001
			Placebo	342	62 (18.1)	NA
Sakai et al 2021a[83]	Low	1–12 weeks	FRE 225 mg	186	54 (29.0)	Difference vs placebo 15.9 (95% CI: 7.8, 24.0), p<0.001
			FRE 675 mg	189	55 (29.1)	Difference vs placebo 15.9 (95% CI: 7.9, 24.0), p<0.001

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
			Placebo	190	25 (13.2)	NA
Episodic and chronic migraine						
FOCUS[85]*	Low	1 month	FRE quarterly	276	105 (38)	OR 5.8 (95% CI: 3.6, 9.3), p<0.0001
			FRE monthly	283	101 (36)	OR 5.3 (95% CI: 3.3, 8.4), p<0.0001
			Placebo	278	28 (10)	NA
		3 months	FRE quarterly	276	95 (34)	OR 5.8 (95% CI: 3.6, 9.6), p<0.0001
			FRE monthly	283	97 (34)	OR 5.8 (95% CI: 3.6, 9.5), p<0.0001
			Placebo	278	24 (9)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.
* In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A37 Response rate (>50%), galcanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
Dodick et al 2014a[88]	Low	3 months	GAL 150 mg	98	69 (70.4)	OR 2.88 (90% CI: 1.78-4.69), p=0.0003
			Placebo	104	47 (45.2)	
EVOLVE-1[89]	Low	6 months	GAL 120 mg	210	Mean 62.3% (SE 2.4)	OR 2.63 (95% CI: 2.05, 3.37), p<0.001
			GAL 240 mg	208	Mean 60.9% (SE 2.5)	OR 2.48 (95% CI: 1.94, 3.18), p<0.001
			Placebo	425	Mean 38.6% (SE 1.7)	NA
EVOLVE-2[91]	Low	1–6 months	GAL 120 mg	226	Mean 59.3% (SE 2.4)	NR, p<0.001
			GAL 240 mg	220	Mean 56.5% (SE 2.5)	NR, p<0.001
			Placebo	450	Mean 36% (SE 1.7)	NA

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Sakai et al 2020a[93]	Low	1–6 months	GAL 120 mg	115	57 (49.8)	OR 3.83 (95% CI: 2.35, 6.22), p<0.001
			GAL 240 mg	114	55 (48.2)	OR 3.63 (95% CI: 2.23, 5.91), p<0.001
			Placebo	230	47 (20.3)	NA
Skljarevski et al 2018[98]	Low	1–12 weeks	GAL 120 mg	69	53 (76.5)	OR 2.10 (95%CI: 1.09, 4.06), p=0.03
			Placebo	134	82 (60.9)	
PERSIST 2022[112]	Low	Months 1–3	GAL 120 mg	260	Mean 54.9% (SE 2.4)	OR 2.48 (95% CI: 1.87, 3.29), p< 0.0001
			Placebo	258	Mean 32.9% (SE 2.3)	NA
Chronic migraine						
REGAIN[102,104]	Low	1–3 months	GAL 120 mg	273	27.6 (2.7)	OR 2.1 (95% CI: 1.6, 2.8), p<0.001
			GAL 240 mg	274	27.5 (2.6)	OR 2.1 (95% CI: 1.6, 2.8), p<0.001
			Placebo	538	15.4 (1.6)	NA
Episodic and chronic migraine						
CGAJ[105]*	High	12 months	GAL 120 mg	135	89 (65.6)	OR 0.70 (95% CI: 0.42, 1.19), p=0.19
			GAL 240 mg	135	99 (73.7)	
Subgroups of patients with >2 prior treatment failures - chronic migraine						
REGAIN[103]	Low	1–3 months	GAL 120 mg	NR	29.6 (4.7)	OR 2.22 (95% CI: 1.26, 3.92)
			GAL 240 mg	NR	18.7 (3.3)	OR 4.05 (95% CI: 2.25, 7.31)
			Placebo	NR	9.4 (1.9)	NA

Abbreviations

CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.

Notes

Blue text indicates RACS calculated comparisons.

* In the CGAJ trial there were two treatment groups; GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% of patients had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% of patients had chronic migraine.

Response rate (>75%)

Table A38 Response rate (>75%), erenumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
EMPOwER[17]	High	1 month	ERU 70 mg	329	58 (17.6)	OR 1.2 (95% CI: 0.8, 1.8), p=0.386
			ERU 140 mg	219	58 (26.5)	OR 2.0 (95% CI: 1.3, 3.1), p=0.001
			Placebo	330	50 (15.2)	NA
		2 months	ERU 70 mg	329	101 (30.7)	OR 1.5 (95% CI: 1.1, 2.2), p=0.016
			ERU 140 mg	219	71 (32.4)	OR 1.7 (95% CI: 1.1, 2.5), p=0.009
			Placebo	330	74 (22.4)	NA
		3 months	ERU 70 mg	329	124 (37.7)	OR 1.7 (95% CI: 1.2, 2.4), p=0.001
			ERU 140 mg	219	94 (42.9)	OR 2.2 (95% CI: 1.5, 3.1), p<0.001
			Placebo	330	86 (26.1)	NA
LIBERTY[18]	Low	1 month	ERU 140 mg	119	11 (9)	OR 26.39 (95% CI: 1.54, 453.12), p=0.02
			Placebo	124	0	
		2 months	ERU 140 mg	119	9 (8)	OR 3.3 (95% CI: 0.9, 12.3), p=0.1
			Placebo	124	3 (2)	
		3 months	ERU 140 mg	119	14 (12)	OR 3.2 (95% CI: 1.1, 9.0), p=0.025
			Placebo	124	5 (4)	
STRIVE[30]	Low	1 month	ERU 70 mg	49	1 (2)	OR 3.37 (95% CI: 0.13, 84.70), p=0.46
			ERU 140 mg	58	5 (8.6)	OR 11.21 (95% CI: 0.60, 207.67), p=0.10
			Placebo	54	0 (0)	NA
		2 months	ERU 70 mg	49	3 (6.1)	OR 1.70 (95% CI: 0.27, 10.60), p=0.57
			ERU 140 mg	58	12 (20.7)	OR 6.78 (95% CI: 1.44, 31.91) 0=0.02
			Placebo	54	2 (3.7)	NA
		3 months	ERU 70 mg	49	7 (14.3)	OR 8.83 (95% CI: 1.05, 74.63), p=0.05
			ERU 140 mg	58	12 (20.7)	OR 13.83 (95% CI: 1.73, 110.44), p=0.01
			Placebo	54	1 (1.9)	NA
		4–6 months	ERU 70 mg	49	5 (10.2)	OR 13.47 (95% CI: 0.73, 250.29), p=0.08
			ERU 140 mg	58	5 (8.6)	OR 11.21 (95% CI: 0.60, 207.67), p=0.10

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
			Placebo	54	0 (0)	NA
Chronic migraine						
Tepper et al 2017[41]	Low	3 months	ERU 70 mg	93	10 (11.1)	OR 3.6 (95% CI: 1.2, 10.9), p<0.05
			ERU 140 mg	92	25 (21.7)	OR 8.0 (95% CI: 2.8, 23.0), p<0.001
			Placebo	142	5 (3.5)	NA
Subgroups of patients with >2 prior treatment failures - episodic migraine						
LIBERTY[18]	Low	Week 12	Placebo	76	9 (11.8)	OR 3.0 (95% CI: 0.8, 11.5), p=0.089
			ERU 140 mg	72	3 (4.2)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Table A39 Response rate (>75%), eptinezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
PROMISE-1[54,55]	High	1–4 weeks	EPT 100 mg	221	68 (30.8)	OR 1.752 (95% CI NR), p=0.0112
			EPT 300 mg	222	70 (31.5)	OR 1.817 (95% CI NR), p=0.0066
			Placebo	222	45 (20.3)	NA
		1–12 weeks	EPT 100 mg	221	49 (22.2)	OR 1.47 (95% CI NR), p=0.1126
			EPT 300 mg	222	66 (29.7)	OR 2.179 (95% CI NR), p=0.0007
			Placebo	222	36 (16.2)	NA
		13–24 weeks	EPT 100 mg	221	74 (33.5)	OR 1.53 (95% CI: 1.01, 2.31), p=0.04
			EPT 300 mg	222	89 (40.1)	OR 2.03 (95% CI: 1.35, 3.05), p=0.0006
			Placebo	222	55 (24.8)	NA
Chronic migraine						
Dodick et al 2019[57]	Some concerns	1–12 weeks	EPT 300 mg	114	38 (33.3)	OR 1.92 (95% CI: 1.06, 3.47), p=0.033
			EPT 100 mg	118	37 (31.4)	OR 1.75 (95% CI: 0.97, 3.17), p=0.072
			Placebo	116	24 (20.7)	NA
PROMISE-2[58,63]	Low	1–4 weeks	EPT 100 mg	356	110 (30.9)	OR 2.4 (95% CI: 1.7, 3.5), p<0.0001
			EPT 300 mg	350	129 (36.9)	OR 3.2 (95% CI: 2.2, 4.6), p<0.0001
			Placebo	366	57 (15.6)	NA
			EPT 100 mg	356	95 (26.7)	OR 2 (95% CI: 1.4,3.0), p=0.0001

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
		1–12 weeks	EPT 300 mg	350	116 (33.1)	OR 2.8 (95% CI: 1.9, 4.0), p<0.0001
			Placebo	366	55 (15.0)	NA
		13–24 weeks	EPT 100 mg	356	140 (39.3)	OR 2.08 (95% CI: 1.51, 2.87), p<0.00001
			EPT 300 mg	350	151 (43.1)	OR 2.43 (95% CI: 1.77, 3.35), p<0.00001
			Placebo	366	87 (23.8)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
DELIVER 2022[110]	Low	Weeks 1-12	EPT 100 mg	299	47 (16)	OR 9.2 (95% CI: 4.2, 24.4), p<0.0001
			EPT 300 mg	293	55 (19)	OR 11.4 (95% CI: 5.2, 30.2), p<0.0001
			Placebo	298	6 (2)	NA
		Weeks 13-24	EPT 100 mg	287	61 (21)	OR 3.8 (95% CI: 2.2, 6.6), p<0.0001
			EPT 300 mg	286	79 (28)	OR 5·3 (95% CI: 3.20, 9.20), p<0.0001
			Placebo	295	20 (7)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Table A40 Response rate (>75%), fremanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
Bigal et al 2015b[65]	Low	Weeks 1–4	FRE 225 mg	95	28 (29)	OR 5.01 (95% CI: 2.15, 11.68), p=0.0001
			FRE 675 mg	96	22 (23)	OR 3.57 (95% CI: 1.50, 8.47), p=0.0026
			Placebo	104	8 (8)	NA
		Weeks 5–8	FRE 225 mg	95	30 (32)	OR 2.74 (95% CI: 1.36, 5.50), p=0.0039
			FRE 675 mg	96	34 (35)	OR 3.25 (95% CI: 1.63, 6.48), p=0.0006
			Placebo	104	15 (14)	NA
		Weeks 9–12	FRE 225 mg	95	34 (36)	OR 2.34 (95% CI: 1.23, 4.45), p=0.0087
			FRE 675 mg	96	39 (41)	OR 2.87 (95% CI: 1.52, 5.42), p=0.0009
			Placebo	104	20 (19)	NA
Episodic and chronic migraine						

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
FOCUS[85]*	Low	3 months	FRE quarterly	276	23 (8)	OR 4.2 (95% CI: 1.7, 10.6), p=0.0021
			FRE monthly	283	35 (12)	OR 6.6 (95% CI: 2.7, 16.1), p<0.0001
			Placebo	278	6 (2)	NA

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.

Notes

Blue text indicates RACS calculated comparisons.

* In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A41 Response rate (>75%), galcanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
Dodick et al 2014[88]	Low	3 months	GAL150 mg	98	48 (49)	OR 2.54 (90% CI: 1.56-4.13)
			Placebo	104	28 (26.9)	
EVOLVE-1[89]	Low	6 months	GAL 120 mg	210	Mean 38.8% (SE 2.4)	OR 2.65 (95% CI: 2.04, 3.45), p<0.001
			GAL 240 mg	208	Mean 38.5% (SE 2.4)	OR 2.62 (95% CI: 2.01, 3.41), p<0.001
			Placebo	425	Mean 19.3% (SE 1.4)	NA
EVOLVE-2[91]	Low	1–6 months	GAL 120 mg	226	Mean 33.5% (SE 2.3)	p<0.001
			GAL 240 mg	220	Mean 34.3% (SE 2.3)	p<0.001
			Placebo	450	Mean 17.8% (SE 1.3)	NR
Sakai et al 2020a[93]	Low	1–6 months	GAL 120 mg	115	29 (25.5)	OR 3.19 (95% CI: 1.73, 5.86), p<0.001
			GAL 240 mg	114	28 (25)	OR 3.08 (95% CI: 1.67, 5.68), p<0.001
			Placebo	230	22 (9.6)	NA
PERSIST 2022[112]	Low	Months 1–3	GAL 120 mg	260	Mean 29.2% (SE 2.1)	OR 2.82 (95% CI: 2.01, 3.97), p< 0.0001
			Placebo	258	Mean 12.7% (SE 1.6)	NA
Chronic migraine						
REGAIN[102,104]	Low	Averages across	GAL 120 mg	273	7.0 (1.4)	OR 1.6 (95% CI: 1.0, 2.5), p=0.031

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
		months 1–3	GAL 240 mg	274	8.8 (1.7)	OR 2.0 (95% CI: 1.4, 3.1), p<0.001
			Placebo	538	4.5 (0.9)	NA
Episodic and chronic migraine						
CGAJ[105]*	High	12 months	GAL 120 mg	135	60 (44.5)	OR 0.72 (95% CI: 0.45, 1.16), p=0.18
			GAL 240 mg	135	71 (52.5)	
Subgroups of patients with >2 prior treatment failures - chronic migraine						
REGAIN[103]	Low	months 1–3	GAL 120 mg	NR	6.3 (2.2)	OR 2.27 (95% CI: 0.95, 5.42)
			GAL 240 mg	NR	5 (1.6)	OR 2.87 (95% CI: 1.11, 7.41)
			Placebo	NR	2.3 (0.8)	NA

Abbreviations

CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.

Notes

Blue text indicates RACS calculated comparisons.

* In the CGAJ trial there were two treatment groups; GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% of patients had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% of patients had chronic migraine.

Response rate (100%)

Table A42 Response rate (100%), erenumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
EMPOwER[17]	High	1 month	ERU 70 mg	329	22 (6.7)	OR 0.8 (95% CI: 0.5, 1.4), p = 0.467
			ERU 140 mg	219	26 (11.9)	OR 1.5 (95% CI: 0.9, 2.7), p = 0.151
			Placebo	330	27 (8.2)	NA
		2 months	ERU 70 mg	329	47 (14.3)	OR 1.2 (95% CI: 0.8, 1.9), p = 0.403
			ERU 140 mg	219	38 (17.4)	OR 1.5 (95% CI: 0.9, 2.5), p = 0.084
			Placebo	330	40 (12.1)	NA
		3 months	ERU 70 mg	329	73 (22.2)	OR 1.7 (95% CI: 1.2, 2.6), p = 0.008
			ERU 140 mg	219	50 (22.8)	OR 1.8 (95% CI: 1.2, 2.8), p = 0.009
			Placebo	330	47 (14.2)	NA
LIBERTY[18]	Low	1 month	ERU 140 mg	119	4 (3)	OR 9.70 (95% CI: 0.52, 182.17), p=0.13
			Placebo	124	0	
		2 months	ERU 140 mg	119	3 (3)	OR 7.48 (95% CI: 0.38, 146.39), p=0.18
			Placebo	124	0	
		3 months	ERU 140 mg	119	7 (6)	OR 16.60 (95% CI: 0.94, 293.96), p=0.06
			Placebo	124	0	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Table A43 Response rate (100%), eptinezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
PROMISE-1[55]	High	1–12 weeks	EPT 100 mg	221	25 (11.43)	OR 1.29 (95% CI: 0.69, 2.39), p=0.42
			EPT 300 mg	222	37 (16.79)	OR 2.02 (95% CI: 1.13, 3.61), p=0.02
			Placebo	222	20 (9.14)	NA
		13–24	EPT 100 mg	221	44 (19.71)	OR 1.48 (95% CI: 0.90, 2.43), p=0.13

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
		weeks	EPT 300 mg	222	54 (24.45)	OR 1.91 (95% CI: 1.18, 3.10), p=0.009
			Placebo	222	32 (14.26)	NA
Chronic migraine						
PROMISE-2[63,64]	Low	1–12 weeks	EPT 100 mg	356	38 (10.8)	OR 2.1 (95% CI: 1.23, 3.86), p<0.0001
			EPT 300 mg	350	53 (15.1)	OR 2.4 (95% CI: NR), p<0.0001
			Placebo	366	19 (5.1)	NA
		13–24 weeks	EPT 100 mg	356	63 (17.8)	OR 2.10 (95% CI: 1.34, 3.28), p=0.001
			EPT 300 mg	350	73 (20.8)	OR 2.57 (95% CI: 1.66, 3.98), p<0.0001
			Placebo	366	34 (9.3)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias.
Notes 1
Blue text indicates RACS calculated comparisons.

Table A44 Response rate (100%), fremanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic and chronic migraine						
FOCUS[85]	Low	3 months	FRE quarterly	276	0	Not estimable
			FRE monthly	283	4 (1)	OR 8.97 (95% CI: 0.48, 167.35), p=0.14
			Placebo	278	0	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Table A45 Response rate (100%), galcanezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Number of responses (%)	Difference between groups
Episodic migraine						
Dodick et al 2014a[88]	Low	3 months	GAL 150 mg	98	31 (31.6)	OR 2.16 (90% CI: 1.24-3.75), p=0.02
			Placebo	104	18 (17.3)	NR
EVOLVE-1[89]	Low	6 months	GAL 120 mg	210	Mean 15.6% (SE 1.6)	OR 2.80 (95% CI: 1.96, 4.01), p<0.001
			GAL 240 mg	208	Mean 14.6% (SE 1.6)	OR 2.61 (95% CI: 1.81, 3.75), p<0.001
			Placebo	425	Mean 6.2% (SE 0.8)	NA
EVOLVE-2[91]	Low	1–6 months	GAL 120 mg	226	Mean 11.5% (SE 1.4)	NR p<0.001
			GAL 240 mg	220	Mean 13.8% (SE 1.5)	NR p<0.001
			Placebo	450	Mean 5.7% (SE 0.7)	NR
Sakai et al 2020a[93]	Low	1–6 months	GAL 120 mg	115	10 (9)	OR 3.03 (95% CI: 1.12, 8.19), p<0.001
			GAL 240 mg	114	9 (8.1)	OR 2.73 (95% CI: 0.99, 7.53), p<0.001
			Placebo	230	7 (2.8)	NR
PERSIST 2022[112]	Low	Months 1–3	GAL 120 mg	260	Mean 11.9% (SE 1.4)	OR 3.31 (95% CI: 1.99, 5.50), p<0.0001
			Placebo	258	Mean 3.9% (SE 0.9)	NA
Chronic migraine						
REGAIN[102,104]	Low	1–3 months	GAL 120 mg	273	0.7 (0.4)	OR 1.4 (95% CI: 0.4, 4.4), p=0.597
			GAL 240 mg	274	1.3 (0.6)	OR 2.6 (95% CI: 1.0, 7.0), p=0.058
			Placebo	538	0.5 (0.3)	NA
Chronic and episodic migraine						
CGAJ[105]	High	12 months	GAL 120 mg	135	29 (21.4)	Not estimable
			GAL 240 mg	135	29 (21.4)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **NR** = not reported, **RoB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS calculated comparisons.

MSQ

Table A46 MSQ in patients receiving erenumab

Trial name	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
Episodic migraine							
ARISE[15]	Low	3 months	MSQ RFR	ERU 70 mg	282	15.2 (SE 1.0)	MD 5.5 (95% CI: 2.8, 8.2), p<0.001
				Placebo	288	9.7 (SE 1.0)	
			MSQ RFP	ERU 70 mg	282	12.0 (SE 0.9)	MD 3.6 (95% CI: 1.1, 6.0), p=0.005
				Placebo	288	8.4 (SE 0.9)	
			MSQ EF	ERU 70 mg	282	11.8 (SE 1.1)	MD 4.5 (95% CI: 1.6, 7.4), p=0.002
				Placebo	288	7.3 (SE 1.1)	
STRIVE[28]	Low	4–6 months	MSQ RFR	ERU 70 mg	312	16.8 (SE 0.85)	MD 5.1 (95% CI:2.8, 7.4), p<0.001
				ERU 140 mg	318	18.1 (SE 0.84)	MD 6.5 (95% CI:4.2, 8.8), p<0.001
				Placebo	316	11.7 (SE 0.85)	NA
			MSQ RFP	ERU 70 mg	312	12.7 (SE 0.76)	MD 4.2 (95% CI:2.2, 6.3), p<0.001
				ERU 140 mg	318	13.9 (SE 0.75)	MD 5.4 (95% CI:3.4, 7.5), p<0.001
				Placebo	316	8.5 (SE 0.76)	NA
			MSQ EF	ERU 70 mg	312	12.9 (SE 0.87)	MD 5.2 (95% CI:2.8, 7.6), p<0.001
				ERU 140 mg	318	14.4 (SE 0.87)	MD 6.7 (95% CI:4.4, 9.1), p<0.001
				Placebo	316	7.7 (SE 0.88)	NA
Sun et al 2016[35]	Low	4 weeks	MSQ RFR	ERU 70 mg	104	NR	MD 3.8 (95% CI: -0.4, 8.0), p=0.08
				Placebo	151	NR	
			MSQ RFP	ERU 70 mg	104	NR	MD 2.8 (95% CI: -1.0, 6.5), p=0.15
				Placebo	151	NR	
			MSQ EF	ERU 70 mg	104	NR	MD 3.4 (95% CI: -1.0, 7.7), p=0.13
				Placebo	151	NR	
		8 weeks	MSQ RFR	ERU 70 mg	104	NR	MD 3.9 (95% CI: -0.4, 8.1), p=0.076
				Placebo	151	NR	
			MSQ RFP	ERU 70 mg	104	NR	MD 1.9 (95% CI: -1.9, 5.6), p=0.33
				Placebo	151	NR	
			MSQ EF	ERU 70 mg	104	NR	MD 3.0 (95% CI: -1.3, 7.4), p=0.17
				Placebo	151	NR	
		12 weeks	MSQ	ERU 70 mg	104	NR	MD 1.8 (95% CI: -

Trial name	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
			RFR	Placebo	151	NR	2.5, 6.1), p=0.41
			MSQ RFP	ERU 70 mg	104	NR	MD 0.5 (95% CI: -3.3, 4.3), p=0.79
				Placebo	151	NR	
			MSQ EF	ERU 70 mg	104	NR	MD 1.9 (95% CI: -2.6, 6.3), p=0.41
				Placebo	151	NR	
Chronic migraine							
Tepper et al 2017[44]	Low	3 months	MSQ RFR	ERU 70 mg	188	17.7 (95% CI: 14.9, 20.6)	MD 6.0 (95% CI: 2.3, 9.6), p=0.002
				ERU 140 mg	187	19.1 (95% CI: 16.3, 22.0)	MD 7.4 (95% CI: 3.7, 11), p<0.001
				Placebo	281	11.8 (95% CI: 9.4, 14.1)	NA
			MSQ RFP	ERU 70 mg	188	13.0 (95% CI: 10.5, 15.6)	MD 4.1 (95% CI: 0.9, 7.4), p=0.013
				ERU 140 mg	187	13.8 (95% CI: 11.3, 16.4)	MD 4.9 (95% CI: 1.7, 8.2), p=0.003
				Placebo	281	8.9 (95% CI: 6.8, 11.0)	NA
			MSQ EF	ERU 70 mg	188	18.2 (95% CI: 15.0, 21.3)	MD 8.3 (95% CI: 4.3, 12.4), p=0.013
				ERU 140 mg	187	18.8 (95% CI: 15.6, 21.9)	MD 8.9 (95% CI: 4.9, 13), p<0.001
				Placebo	281	9.9 (95% CI: 7.3, 12.5)	NA

Abbreviations

CI = confidence interval, **EF** = Emotional Function, **ERU** = erenumab, **n** = number of patients, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **NA** = not applicable, **NR** = not reported, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

MSQ in patients receiving eptinezumab

Trial name	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine							
DELIVER 2022[111]	Low	Week 12	MSQ RFR	EPT 100 mg	271	25.0 (SE 1.8)	MD 11.3 (95% CI: 8.0, 14.7), p<0.0001
				EPT 300 mg	284	28.7 (SE 1.7)	MD 15.0 (95% CI: 11.6, 18.3), p<0.0001
				Placebo	288	13.7 (SE 1.8)	NA
			MSQ RFP	EPT 100 mg	271	22.7 (SE 1.6)	MD 11.1 (95% CI: 8.0, 14.3), p<0.0001
				EPT 300 mg	283	25.0 (SE 1.6)	MD 13.5 (95% CI: 10.4, 16.6), p<0.0001
				Placebo	288	11.6 (SE 1.6)	NA
			MSQ EF	EPT 100 mg	271	20.6 (SE 1.8)	MD 11.1 (95% CI: 7.5, 14.6), p<0.0001

Trial name	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
				EPT 300 mg	283	23.1 (SE 1.8)	MD 13.5 (95% CI: 10.0, 17.0), p<0.0001
				Placebo	288	9.6 (SE 1.8)	NA
		Week 24	MSQ RFR	EPT 100 mg	259	30.1 (SE 1.8)	MD 15.1 (95% CI: 11.7, 18.5), p<0.0001
				EPT 300 mg	275	30.0 (SE 1.7)	MD 15.0 (95% CI: 11.6, 18.4), p<0.0001
				Placebo	278	15.0 (SE 1.8)	NA
			MSQ RFP	EPT 100 mg	259	25.7 (SE 1.7)	MD 12.6 (95% CI: 9.4, 15.8), p<0.0001
				EPT 300 mg	275	26.3 (SE 1.6)	MD 13.2 (95% CI: 10.1, 16.4), p<0.0001
				Placebo	278	13.1 (SE 1.6)	NA
			MSQ EF	EPT 100 mg	259	24.1 (SE 1.9)	MD 14.1 (95% CI: 10.5, 17.7), p<0.0001
				EPT 300 mg	275	24.1 (SE 1.8)	MD 14.1 (95% CI: 10.6, 17.7), p<0.0001
				Placebo	278	9.9 (SE 1.8)	NA

Abbreviations
CI = confidence interval, **EF** = Emotional Function, **EPT** = eptinezumab, **n** = number of patients, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **NA** = not applicable, **NR** = not reported, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

Table A47 MSQ in patients receiving fremanezumab

Trial name	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
Chronic migraine							
HALO CM[79]	Low	4 weeks	MSQ RFR	FRE 225 mg	375	19.4 (SE NR)	7.4 (SE 1.43), p<0.0001
				FRE 675 mg	375	19.1 (SE NR)	7.1 (SE 1.35), p<0.0001
				Placebo	371	12 (SE NR)	NA
			MSQ RFP	FRE 225 mg	375	15.8 (SE NR)	6.3 (SE 1.15), p<0.0001
				FRE 675 mg	375	15.3 (SE NR)	5.9 (SE 1.14), p<0.0001
				Placebo	371	9.4 (SE NR)	NA
			MSQ EF	FRE 225 mg	375	19.5 (SE NR)	7.4 (SE 1.54), p<0.0001
				FRE 675 mg	375	19.1 (SE NR)	7.1 (SE 1.54), p<0.0001
				Placebo	371	12.1 (SE NR)	NA
		12 weeks	MSQ RFR	FRE 225 mg	375	21 (SE NR)	6.3 (SE 1.42), p<0.0001
				FRE 675 mg	375	20.3 (SE NR)	5.6 (SE 1.42), p<0.0001
				Placebo	371	14.7 (SE NR)	NA
			MSQ RFP	FRE 225 mg	375	15.5 (SE NR)	3.9 (SE 1.26), p=0.0017
				FRE 675 mg	375	15.9 (SE NR)	4.3 (SE 1.25), p=0.0007
				Placebo	371	11.6 (SE NR)	NA
			MSQ EF	FRE 225 mg	375	20.3 (SE NR)	3.3 (SE 1.55), p=0.0348
				FRE 675 mg	375	20.9 (SE NR)	3.9 (SE 1.55), p=0.0126
				Placebo	371	17 (SE NR)	NA

Trial name	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Change from baseline	Difference between treatments
Episodic and chronic migraine							
FOCUS[85]*	Low	4 months	MSQ total	FRE quarterly	276	15.7 (SE 1.5)	8.8 (95% CI: 5.7, 11.9), p<0.0001
				FRE monthly	283	17.5 (SE 1.5)	10.6 (95% CI: 7.5, 13.7), p<0.0001
				Placebo	278	6.9 (SE 1.5)	NA

Abbreviations

CI = confidence interval, **EF** = Emotional Function, **FRE** = fremanezumab, **n** = number of patients, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **NA** = not applicable, **NR** = not reported, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error.

Notes

* In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A48 MSQ in patients receiving galcanezumab

	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Mean chance in MSQ	Difference between interventions
Episodic migraine							
EVOLVE-1[89]	Low	4–6 months	MSQ RFR	GAL 120 mg	189	32.4 (SE 1.31)	MD 7.7 (95% CI: 5.2-10.3), p<0.001
				GAL 240 mg	184	32.1 (SE 1.32)	MD 7.4 (95% CI: 4.8-10.0), p<0.001
				Placebo	377	24.7 (SE 1.07)	NA
EVOLVE-2[91]	Low	4–6 months	MSQ RFR	GAL 120 mg	213	28.5 (SE 1.2), p<0.001	MD 8.80 (95% CI: 5.86, 11.74), p<0.00001
				GAL 240 mg	210	27 (SE 1.2), p<0.001	MD 7.30 (95% CI: 4.36, 10.24), p<0.00001
				Placebo	396	19.7 (SE 0.9)	NA
Sakai et al 2020a[93,96,97]	Low	6 months	MSQ RFR	GAL 120 mg	112	16.6 (NR)	NR
				GAL 240 mg	112	16.3 (NR)	NR
				Placebo	228	9.7 (NR)	NR
		4–6 months	MSQ RFR	GAL 120 mg	115	17.13 (SE 1.03), p<0.001	MD 7.01 (95% CI: 4.55, 9.47), p<0.00001
				GAL 240 mg	114	15.91 (SE 1.03), p<0.001	MD 5.79 (95% CI: 3.33, 8.25), p<0.00001
				Placebo	230	10.12 (SE 0.72)	NA
			MSQ RFP	GAL 120 mg	112	9.64 (NR)	NR

	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Mean chance in MSQ	Difference between interventions
				GAL 240 mg	112	8.35 (NR)	NR
				Placebo	228	4.8 (NR)	NR
			MSQ EF	GAL 120 mg	112	10.04 (NR)	NR
				GAL 240 mg	112	7.73 (NR)	NR
				Placebo	228	3.46 (NR)	NR
			MSQ total	GAL 120 mg	112	13.46 (NR)	NR
				GAL 240 mg	112	11.98 (NR)	NR
				Placebo	228	7.14 (NR)	NR
Skljarevski et al 2018[101]	Low	3 months	MSQ RFP	GAL 120 mg	60	19.8 (SE NR)	MD 6.3 (95% CI: 0.476,12.185), p=0.0342
				Placebo	127	13.4 (SE NR)	
			MSQ RFR	GAL 120 mg	60	31.9 (SE NR)	MD 9.6 (95% CI: 2.636, 16.518), p=0.0071
				Placebo	127	22.4 (SE NR)	
			MSQ EF	GAL 120 mg	60	26.6 (SE NR)	MD 9.7 (95% CI: 2.789, 16.674), p=0.0063
				Placebo	127	16.9 (SE NR)	
			MSQ total	GAL 120 mg	60	27.4 (SE NR)	MD 8.7 (95% CI: 2.450, 15.008), p=0.0067
				Placebo	127	18.6 (SE NR)	
PERSIST 2022[112]	Low	Months 1-3	MSQ RFR	GAL 120 mg	260	21.01 (SE 0.85)	MD 7.07 (95% CI: 5.20, 8.95), p<0.0001
				Placebo	258	13.94 (SE 0.88)	NA
			MSQ RFP	GAL 120 mg	260	18.79 (SE 0.87)	MD 6.03 (95% CI: 4.10, 7.95), p<0.0001
				Placebo	258	12.76 (SE 0.90)	NA
			MSQ EF	GAL 120 mg	260	17.88 (SE 0.98)	MD 4.16 (95% CI: 2.00, 6.32), p=0.0002
				Placebo	258	13.72 (SE 1.02)	NA
			MSQ total	GAL 120 mg	260	19.73 (SE 0.81)	MD 6.17 (95% CI: 4.39, 7.95), p<0.0001
				Placebo	258	13.56 (SE 0.84)	NA
Chronic migraine							
REGAIN[102]	Low	Month 3	MSQ RFR	GAL 120 mg	273	21.8 (SE 1.4)	MD 5.1 (95% CI: 2.1, 8.0), p<0.001
				GAL 240 mg	274	23.1 (SE 1.6)	MD 6.3 (95% CI: 3.0, 9.6), p<0.001
				Placebo	538	16.8 (SE 1.2)	NA
			MSQ RFP	GAL 120 mg	273	18.0 (SE 1.4)	MD 7.0 (95% CI: 4.2, 9.8),

	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Mean chance in MSQ	Difference between interventions
							p<0.001
				GAL 240 mg	274	16.1 (SE 1.4)	MD 5.1 (95% CI: 2.3, 7.9), p<0.001
				Placebo	538	11.0 (SE 1.2)	NA
			MSQ EF	GAL 120 mg	273	21.0 (SE 1.9)	MD 7.0 (95% CI: 3.2, 10.8), p<0.001
				GAL 240 mg	274	20.7 (SE 1.9)	MD 6.6 (95% CI: 2.8, 10.4), p<0.001
				Placebo	538	14.1 (SE 1.6)	NA
Chronic and episodic migraine							
CGAJ[105] [113]*	High	12 months	MSQ RFR	GAL 120 mg	130	31.6 (SE 1.2)	MD 1.9 (95% CI: -1.3, 5.0)
				GAL 240 mg	135	33.4 (SE 1.2)	
			MSQ RFP	GAL 120 mg	NR	NR	MD 1.3 (95% CI: -1.7, 4.2)
				GAL 240 mg	NR	NR	
			MSQ EF	GAL 120 mg	NR	NR	MD 3.1 (95% CI: -0.5, 6.6)
				GAL 240 mg	NR	NR	
		14 months**	MSQ RFR	GAL 120 mg	100	-7.1 (SE 1.8)	MD -2.4 (95% CI: -7.1, 2.3)
				GAL 240 mg	113	-9.5 (SE 1.7)	
			MSQ RFP	GAL 120 mg	100	-5.6 (SE 1.6)	MD -1.1 (95% CI: -5.4, 3.2)
				GAL 240 mg	113	-6.7 (SE 1.5)	
			MSQ EF	GAL 120 mg	100	-9.1 (SE 2.0)	MD 1.4 (95% CI: -3.9, 6.6)
				GAL 240 mg	113	-7.8 (SE 1.9)	
		16 months[13]	MSQ RFR	GAL 120 mg	99	-8.7 (SE 1.9)	MD -1.6 (95% CI: -6.5, 3.3)
				GAL 240 mg	115	-10.3 (SE 1.7)	
			MSQ RFP	GAL 120 mg	99	-6.6 (SE 1.7)	MD -1.6 (95% CI: -6.1, 2.9)
				GAL 240 mg	115	-8.2 (SE 1.6)	
			MSQ EF	GAL 120 mg	99	-8.4 (SE 2.2)	MD -1.5 (95% CI: -7.2, 4.2)
				GAL 240 mg	115	-9.9 (SE 2.0)	
Subgroups of patients with >2 prior treatment failures - episodic migraine							
CONQUER[106,107]	Low	3 months, patients with 2 prior Tx failures	MSQ RFR	GAL 120 mg	137	23.4 (SE 1.8)	MD 11.5 (95% CI: 7.1, 15.9), p<0.0001
				Placebo	132	11.9 (SE 1.8)	
	Low	3 months, patients with 3–4 prior Tx failures	MSQ RFR	GAL 120 mg	54	22.7 (SE 3.4)	MD 8.2 (SE 4.0), p=0.0426
				Placebo	43	14.5 (SE 3.6)	
			MSQ RFP	GAL 120 mg	54	19.2 (SE 3.0)	MD 8.3 (SE 3.6), p=0.0233
				Placebo	43	10.9 (SE 3.2)	
			MSQ EF	GAL 120 mg	54	24.2 (SE 4.0)	MD 9.5 (SE 4.7), p=0.0479
				Placebo	43	14.7 (SE 4.1)	
Subgroups of patients with >2 prior treatment failures - chronic migraine							
CONQUE	Low	3 months,	MSQ	GAL 120 mg	95	20.6 (SE 2.1)	MD 13.9 (95%

	ROB	Timepoint of assessment	Outcome	Intervention and dose	n	Mean chance in MSQ	Difference between interventions
R[106,107]		patients with 2 prior Tx failures	RFR	Placebo	98	6.7 (SE 2.0)	CI: 8.9, 18.9), p<0.0001
	Low	3 months, patients with 3–4 prior Tx failures	MSQ RFR	GAL 120 mg	40	25.2 (SE 3.6)	MD 20.5 (SE 4.2), p<0.0001
				Placebo	41	4.7 (SE 3.4)	
			MSQ RFP	GAL 120 mg	40	18.7 (SE 3.3)	MD 15.2 (SE 3.8), p=0.0001
				Placebo	41	3.5 (SE 3.1)	
			MSQ EF	GAL 120 mg	40	28.3 (SE 4.4)	MD 19.0 (SE 5.0), p=0.0003
				Placebo	41	9.2 (SE 4.0)	
REGAIN[103]	Low	3 months	MSQ RFR	GAL 120 mg	64	19.13 (SE 2.87)	MD 8.45 (SE 2.99), p<0.01
				GAL 240 mg	94	19.24 (SE 2.61)	MD 8.57 (SE 2.64), p<0.01
				Placebo	160	10.67 (SE 2.12)	NA

Abbreviations

CI = confidence interval, **EF** = Emotional Function, **GAL** = galcanezumab, **n** = number of patients, **MD** = mean difference, **MSQ** = Migraine-Specific Quality of Life questionnaire, **NA** = not applicable, **NR** = not reported, **RFR** = Role Function Restrictive, **RFP** = Role Function Preventative, **RoB** = risk of bias, **SE** = standard error, **Tx** = treatment.

Notes

Blue text indicates RACS calculated comparisons.

* In the CGAJ trial there were two treatment groups; GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% of patients had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% of patients had chronic migraine.

** In the CGAJ trial, 12-month data was used as the baseline for the outcomes measured at 14 and 16 months.

HIT-6

Table A49 HIT-6 in patients receiving erenumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
Episodic migraine						
ARISE[15]	Low	3 months	ERU 70 mg	282	-4.9 (SE 0.4)	MD -2.3 (95% CI: -3.3, -1.3), p<0.001
			Placebo	288	-2.6 (SE 0.4)	
EMPOwER[17]	High	1 month	ERU 70 mg	329	-5.33 (SE 0.39)	MD -1.90 (95% CI: -2.96, -0.85), p<0.001
			ERU 140 mg	219	-6.10 (SE 0.47)	MD -2.67 (95% CI: -3.85, -1.49), p<0.001
			Placebo	330	-3.43 (SE 0.39)	NA
		2 months	ERU 70 mg	329	-7.63 (SE 0.44)	MD -2.01 (95% CI: -3.20, -0.83), p<0.001
			ERU 140 mg	219	-8.11 (SE 0.53)	MD -2.49 (95% CI: -3.81, -1.17), p<0.001
			Placebo	330	-5.61 (SE 0.43)	NA
		3 months	ERU 70 mg	329	-8.39 (SE 0.45)	MD -1.77 (95% CI: -2.99, -0.56), p=0.004
			ERU 140 mg	219	-9.34 (SE 0.54)	MD -2.71 (95% CI: -4.07, -1.36), p<0.001
			Placebo	330	-6.62 (SE 0.44)	NA
LIBERTY[19]	Low	4 weeks	ERU 140 mg	119	-4.1 (SE NR)	MD -1.9 (95% CI: -3.1, -0.6), p=0.003
			Placebo	124	-2.2 (SE NR)	
		8 weeks	ERU 140 mg	119	-5.5 (SE NR)	MD -3.4 (95% CI: -4.8, -2.0), p<0.001
			Placebo	124	-2.1 (SE NR)	
		12 weeks	ERU 140 mg	119	-5.3 (SE NR)	MD -3.0 (95% CI: -4.5, -1.4), p<0.001
			Placebo	124	-2.4 (SE NR)	
Sakai et al 2019[23]	Low	4–6 months	ERU 70 mg	135	-4.3 (95% CI: -5.2, -3.4)	MD -2.1 (95% CI: -3.3, -0.9), p<0.001
			ERU 140 mg	136	-4.2 (95% CI: -5.1, -3.3)	MD -2.0 (95% CI: -3.2, -0.8), p=0.001
			Placebo	136	-2.2 (95% CI: -3.1, -1.3)	NA
STRIVE[28]	Low	4–6 months	ERU 70 mg	312	-6.7 (SE 0.3)	MD -2.1 (95% CI: -3.0, -1.1), p<0.001
			ERU 140 mg	318	-6.9 (SE 0.3)	MD -2.3 (95% CI: -3.2, -1.3), p<0.001
			Placebo	316	-4.6 (SE 0.4)	NA
Sun et al 2016[35]	Low	4 weeks	ERU 70 mg	104	NR	MD -1.2 (95% CI: -2.7, 0.4), p=0.13
			Placebo	151	NR	
		8 weeks	ERU 70 mg	104	NR	MD -2.1 (95% CI: -3.6, -0.6), p=0.007
			Placebo	151	NR	
		12 weeks	ERU 70 mg	104	NR	MD -1.0 (95% CI: -2.5, 0.6),

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
			Placebo	151	NR	p=0.22
Chronic migraine						
Tepper et al 2017[44]	Low	3 months	ERU 70 mg	188	-5.6 (95% CI: -6.5, -4.6)	MD -2.5 (95% CI: -3.7, -1.2), p<0.001
			ERU 140 mg	187	-5.6 (95% CI: -6.5, -4.6)	MD -2.5 (95% CI: -3.7, -1.2), p<0.001
			Placebo	281	-3.1 (95% CI: -3.9, -2.3)	NA
Episodic and chronic migraine						
HER-MES[49]*	Low	4–6 months	ERU 70 or 140 mg	379	-10.9 (SE 0.4)	MD -3.2 (95% CI: -4.3, -2.1), p<0.001
			Topiramate 25–100 mg	377	-7.7 (SE 0.4)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **HIT-6** = Headache Impact Test-6, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error.
Notes
* In HER-MES, the following number of patients were included: For Erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%) Chronic (≥15 MMDs) = 42 (10.8%).

Table A50 HIT-6 in patients receiving eptinezumab

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
Chronic migraine						
Dodick et al 2019[57]	Some concerns	3 months	EPT 300 mg	106	-10.0 (SD 8.4)	MD -4.20 (95% CI: -6.31, -2.09), p<0.0001
			EPT 100 mg	107	-6.9 (SD 7.4)	MD -1.10 (95% CI: -3.07, 0.87), p=0.27
			Placebo	110	-5.8 (SD 7.4)	NA
PROMISE-2[58]	Low	week 4	EPT 100 mg	356	-6.9 (NR)	MD -2.3 (95% CI: -3.4, -1.2), p=NR
			EPT 300 mg	350	-8.6 (NR)	MD -4.0 (95% CI: -5.1, -2.8), p=NR
			Placebo	366	-4.6 (NR)	NA
		week 12	EPT 100 mg	356	-6.2 (Range: -34, 10)	MD -1.7 (95% CI: -2.8, -0.7), p=0.001
			EPT 300 mg	350	-7.3 (Range: -40, 10)	MD -2.9 (95% CI: -3.9, -1.8), p<0.0001
			Placebo	366	-4.5 (Range: -32, 15)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
DELIVER 2022[110,111]	Low	Week 4	EPT 100 mg	277	-6.7 (SE 0.6)	MD -4.9 (95% CI: -6.0, -3.7), p<0.0001
			EPT 300 mg	283	-6.9 (SE 0.6)	MD -5.1 (95% CI: -6.2, -3.9), p<0.0001
			Placebo	288	-1.8 (SE 0.6)	NA

Trial name	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
		Week 12	EPT 100 mg	277	-6.9 (SE 0.6)	MD -3.8 (95% CI: -5.0, -2.5), p<0.0001
			EPT 300 mg	283	-8.5 (SE 0.6)	MD -5.4 (95% CI: -6.7, -4.2), p<0.0001
			Placebo	288	-3.1 (SE 0.6)	NA
		Week 24	EPT 100 mg	277	-8.9 (SE 0.6)	MD -5.0 (95% CI: -6.3, -3.7), p<0.0001
			EPT 300 mg	283	-9.9 (SE 0.6)	MD -6.0 (95% CI: -7.3, -4.7), p<0.0001
			Placebo	288	-3.9 (SE 0.6)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **HIT-6** = Headache Impact Test-6, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SD** = standard deviation.
Notes
Blue text indicates RACS calculated comparisons.

Table A51 HIT-6 in patients receiving fremanezumab

	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
Chronic migraine						
HALO CM[76]	Low	12 weeks	FRE 225 mg	375	-6.8 (SE 0.4)	MD -2.4 (95% CI: -3.55, -1.05), p=0.0003
			FRE 675 mg	375	-6.4 (SE 0.5)	MD -1.9 (95% CI: -3.29, -0.51), p=0.007
			Placebo	371	-4.5 (SE 0.5)	NA
Sakai et al 2021a[83]	Low	16 weeks	FRE 225 mg	182	-8.1 (SE 0.7)	MD -1.6 (95% CI: -2.94, -0.19), p=0.026
			FRE 675 mg	180	-8.0 (SE 0.7)	MD -1.5 (95% CI: -2.91, -0.15), p=0.030
			Placebo	179	-6.5 (SE 0.7)	NA
Episodic and chronic migraine						
FOCUS[85]	Low	4 months	FRE quarterly	276	-5.2 (SE 0.6)	MD -3.0 (95% CI: -4.1, -1.8), p<0.0001
			FRE monthly	283	-6.1 (SE 0.5)	MD -3.8 (95% CI: -5.0, -2.7), p<0.0001
			Placebo	278	-2.2 (SE 0.5)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
FOCUS[86]	Low	3 months 2 Tx failures	FRE quarterly	140	-5.3 (0.78)	MD -2.5 (95% CI: -4.21, -0.88), p=0.003
			FRE monthly	133	-6.4 (0.78)	MD -3.6 (95% CI: -5.32, -1.93), p<0.0001
			Placebo	141	-2.7 (0.77)	NA
		3 months 3 Tx failures	FRE quarterly	85	-5.4 (0.96)	MD -2.8 (95% CI: -4.95, -0.57), p=0.014
			FRE	98	-5.8 (0.94)	MD -3.2 (95% CI: -5.28, -

			monthly			1.11), p=0.003
			Placebo	82	-2.6 (0.90)	NA
		4 months 4 Tx failures	FRE quarterly	49	-5.0 (1.18)	MD -5.6 (95% CI: -8.16, -3.03), p<0.001
			FRE monthly	50	-6.2 (1.04)	MD -6.8 (95% CI: -9.25, -4.43), p<0.001
			Placebo	54	0.6 (1.19)	NA

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **HIT-6** = Headache Impact Test-6, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **ROB** = risk of bias, **SD** = standard deviation.

Notes

Blue text indicates RACS calculated comparisons.

Table A52 HIT-6 in patients receiving galcanezumab

	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in HIT-6	Difference between interventions
Episodic migraine						
Skljarevski et al 2018[101]	Low	3 months	GAL 120 mg	60	-10.2 (SE NR)	MD -2.5 (95% CI: -5.107, 0.144), p=0.0638
			Placebo	127	-7.7 (SE NR)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **HIT-6** = Headache Impact Test-6, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **ROB** = risk of bias, **SE** = standard error.

MIDAS

Table A53 MIDAS in patients receiving erenumab

Trial name	ROB	Timepoint of assessment	MIDAS type	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
Episodic migraine							
ARISE[15]	Low	3 months	mMIDAS	ERU 70 mg	282	-5.5 (SE 0.5)	MD -1.7 (95% CI: -3.1, -0.3), p=0.021
				Placebo	288	-3.8 (SE 0.5)	
EMPOwER[17]	High	1 month	mMIDAS	ERU 70 mg	329	-5.89 (SE 0.49)	-2.41 (95% CI: -3.75, -1.08), p=0.0005
				ERU 140 mg	219	-6.44 (SE 0.60)	-2.96 (95% CI: -4.46, -1.47), p=0.0001
				Placebo	330	-3.48 (SE 0.49)	NA
		2 months		ERU 70 mg	329	-7.51 (SE 0.48)	-2.48 (95% CI: -3.78, -1.18), p=0.0002
				ERU 140 mg	219	-7.83 (SE 0.58)	-2.80 (95% CI: -4.24, -1.35), p=0.0002
				Placebo	330	-5.04 (SE 0.47)	NA
		3 months		ERU 70 mg	329	-8.11 (SE 0.43)	-1.52 (95% CI: -2.69, -0.35), p=0.011
				ERU 140 mg	219	-8.99 (SE 0.52)	-2.40 (95% CI: -3.70, -1.10), p=0.0004
				Placebo	330	-6.59 (SE 0.43)	NA
STRIVE[28]	Low	4–6 months	mMIDAS	ERU 70 mg	312	-6.7 (SE 0.4)	-2.1 (95% CI: -3.3, -0.9), p<0.001
				ERU 140 mg	318	-7.5 (SE 0.4)	-2.8 (95% CI: -4.0, -1.7), p<0.001
				Placebo	316	'-4.6 (SE 0.4)	NA
Sun et al 2016[35]	Low	12 weeks	MIDAS	ERU 70 mg	93	NR	MD -5.3 (95% CI: -10.9, 0.3), p=0.064
				Placebo	134	NR	
Chronic migraine							
Tepper et al 2017[44]	Low	3 months	MIDAS	ERU 70 mg	188	-19.4 (95% CI: -25.2, -13.6)	MD -11.9 (95% CI: -19.3, -4.4), p=0.002
				ERU 140 mg	187	-19.8 (95% CI: -25.6, -14.0)	MD -12.2 (95% CI: -19.7, -4.8), p=0.001
				Placebo	281	-7.5 (95% CI: -12.4, -2.7)	NA
DRAGON 2022[109]	Some concerns	Week 12	mMIDAS	ERU 70 mg	263	-14.67 (SE 1.20)	MD -1.74 (95% CI: -5.06, 1.58), p=0.305
				Placebo	268	-12.93 (SE 1.19)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **mMIDAS** = modified Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS calculated comparisons.

MIDAS in patients receiving eptinezumab

No studies identified.

Table A54 MIDAS in patients receiving fremanezumab

	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
Episodic migraine						
Bigal et al 2015b[65]	Low	9–12 weeks	FRE 225 mg	NR	NR	MD -14.50 (95% CI: -26.79, -2.20), p=0.021
			FRE 675 mg	NR	NR	MD -15.20 (95% CI: -27.62, -2.78), p=0.017
			Placebo	NR	NR	NA
HALO EM[68]	High	12 weeks	FRE 225 mg	287	-24.6 (95% CI: -27.68, -21.45)	MD -7.0 (95% CI: -10.51, -3.53), p<0.001
			FRE 675 mg	288	-23.0 (95% CI: -26.10, -19.82)	MD -5.4 (95% CI: -8.90, -1.93), p=0.002
			Placebo	290	-17.5 (95% CI: -20.62, -14.47)	NA
Sakai et al 2021b[71]	Low	16 weeks	FRE 225 mg	118	-12.6 (SE 1.4)	MD -5.2 (95% CI: -8.14, -2.33), p<0.0001
			FRE 675 mg	113	-12.6 (SE 1.5)	MD -5.1 (95% CI: -8.09, -2.20), p<0.0001
			Placebo	112	-7.4 (SE 1.5)	NA
Episodic and chronic migraine						
FOCUS[85]	Low	4 months	FRE quarterly	276	-19.7 (SE 3.3)	MD -12.7 (95% CI: -19.5, -6.0), p=0.0002
			FRE monthly	283	-24.7 (SE 3.2)	MD -17.7 (95% CI: -24.5, -11.0), p<0.0001
			Placebo	278	-7.0 (SE 3.2)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
FOCUS[86]	Low	4 months 2 Tx failures	FRE quarterly	140	-14.7 (4.15)	MD -8.7 (95% CI: -17.47, 0.15), p=0.054
			FRE monthly	133	-21.5 (4.11)	MD -15.5 (95% CI: -24.47, -6.46), p<0.001
			Placebo	141	-6.1 (4.10)	NA
		4 months 3 Tx failures	FRE quarterly	85	-18.9 (5.69)	MD -9.8 (95% CI: -22.68, 3.08), p=0.14
			FRE monthly	98	-25.3 (5.56)	MD -16.2 (95% CI: -28.51, -3.90), p=0.010
			Placebo	82	-9.1 (5.34)	NA
		4 months 4 Tx failures	FRE quarterly	49	-25.0 (10.43)	MD -31.7 (95% CI: -54.07, -9.37), p=0.006
			FRE monthly	50	-23.2 (9.12)	MD -29.9 (95% CI: -51.12, -8.70), p=0.006
			Placebo	54	6.7 (10.59)	NA

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error, **Tx** = treatment.

Table A55 MIDAS in patients receiving galcanezumab

	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
Episodic migraine						
CONQUER[106]	Low	3 months	GAL 120 mg	137	-19.0 (SE 3.6)	MD -16.4 (95% CI: -24.9, -7.9), p=0.0002
			Placebo	132	-2.6 (SE 3.7)	
EVOLVE-1[89]	Low	6 months	GAL 120 mg	195	-21.16 (SE 1.65)	MD -6.29 (95% CI: -9.45, -3.13), p<0.001
			GAL 240 mg	189	-20.06 (SE 1.68)	MD -5.19 (95% CI: -8.39, -1.98), p=0.002
			Placebo	389	-14.87 (SE 1.37)	NA
EVOLVE-2[91]	Low	6 months	GAL 120 mg	231	-21.2 (SE 1.6)	MD -9.20 (95% CI: -13.24, -5.16), p<0.0001
			GAL 240 mg	223	-20.2 (SE 1.6)	MD -8.20 (95% CI: -12.24, -4.16), p<0.0001
			Placebo	461	-12 (SE 1.3)	NA
Sakai et al 2020a[93]	Low	6 months	GAL 120 mg	115	-7.06 (95% CI: -9.67, -4.44)	MD -4.90 (95% CI: -8.04, -1.76), p=0.002
			GAL 240 mg	114	-5.13 (95% CI: -7.69, -2.58)	MD -2.97 (95% CI: -6.07, 0.13), p=0.06
			Placebo	230	-2.16 (95% CI: -3.96, -0.36)	NR
PERSIST 2022[112]	Low	3 months	GAL 120 mg	260	-22.61 (SE 2.96)	MD -12.43 (95% CI: -18.81, -6.05), p=0.0001
			Placebo	258	-10.18 (SE 3.06)	NA
Chronic migraine						
CONQUER[106]	Low	3 months	GAL 120 mg	95	-20.3 (SE 6.4)	MD -18.6 (95% CI: -33.4, -3.8), p=0.0142
			Placebo	98	-1.7 (SE 6.2)	
REGAIN[102]	Low	3 months	GAL 120 mg	273	-20.3 (SE 4.1)	MD -8.7 (95% CI: -16.4, -1.1), p=0.025
			GAL 240 mg	274	-17.0 (SE 4.1)	MD -5.5 (95% CI: -13.1, 2.1), p= 0.157
			Placebo	538	-11.5 (SE 3.4)	NA
Episodic and chronic migraine						
CGAJ[105] [113]	High	12 months	GAL 120 mg	124	-33.6 (SE 2.1)	MD 0.9 (95% CI: -4.7, 6.5), p=0.76
			GAL 240 mg	130	-32.7 (SE 2.0)	
Subgroups of patients with >2 prior treatment failures - episodic migraine						

	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in MIDAS	Difference between interventions
CONQUER[107]	Low	3 months	GAL 120 mg	55	-18.2 (5.2)	MD 10.2 (95% CI: -12.32, -8.08), p<0.0001
			Placebo	43	-8.0 (5.4)	
Subgroups of patients with >2 prior treatment failures - chronic migraine						
CONQUER[107]	Low	3 months	GAL 120 mg	40	-31.0 (11.8)	MD -39.93 (95% CI: -44.74, -35.06), p<0.0001
			Placebo	42	8.9 (10.5)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **MD** = mean difference, **MIDAS** = Migraine Disability Assessment, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error.
Notes
Blue text indicates RACS calculated comparisons.

EQ-5D

Table A56 EQ-5D in patients receiving erenumab

Trial name	ROB	Timepoint of assessment	EQ-5D type	Intervention and dose	n	Mean change in EQ-5D	Difference between interventions
Episodic migraine							
EMPOwER [17]	High	1 month	EQ-5D-5L	ERU 70 mg	329	4.98 (SE 0.75)	MD 3.01 (95% CI: 0.97, 5.04), p=0.004
				ERU 140 mg	219	6.31 (SE 0.91)	MD 4.34 (95% CI: 2.06, 6.61), p<0.001
				Placebo	330	1.97 (SE 0.74)	NA
		2 months		ERU 70 mg	329	6.32 (SE 0.74)	MD 2.43 (95% CI: 0.43, 4.44), p=0.018
				ERU 140 mg	219	7.55 (SE 0.89)	MD 3.66 (95% CI: 1.43, 5.89), p=0.001
				Placebo	330	3.89 (SE 0.73)	NA
		3 months		ERU 70 mg	329	7.08 (SE 0.79)	MD 1.86 (95% CI: −0.28, 4.00), p=0.088
				ERU 140 mg	219	8.13 (SE 0.96)	MD 2.91 (95% CI: 0.52, 5.29), p=0.017
				Placebo	330	5.22 (SE 0.78)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **EQ-5D** = EuroQol 5-dimension questionnaire; **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **ROB** = risk of bias, **SE** = standard error.

Table A57 EQ-5D in patients receiving eptinezumab

Trial name	ROB	Timepoint of assessment	EQ-5D type	Intervention and dose	n	Mean change in EQ-5D	Difference between interventions
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine							
DELIVER 2022[111]	Low	Week 4	EQ-5D-5L	EPT 100 mg	281	1.5 (SE 1.4)	MD 4.7 (95% CI: 1.9, 7.6), p≤0.05
				EPT 300 mg	287	2.0 (SE 1.4)	MD 5.2 (95% CI: 2.4, 8.0), p≤0.05
				Placebo	288	-3.2 (SE 1.4)	NA
		Week 12		EPT 100 mg	281	2.0 (SE 1.4)	MD 5.1 (95% CI: 2.2, 8.1), p≤0.05
				EPT 300 mg	287	4.4 (SE 1.4)	MD 7.5 (95% CI: 4.5, 10.4), p<0.0001
				Placebo	288	-3.1 (SE 1.4)	NA
		Week 24		EPT 100 mg	281	2.0 (SE 1.4)	MD 4.7 (95% CI: 1.8, 7.7), p≤0.05
				EPT 300 mg	NR	5.2 (SE 1.4)	MD 8.0 (95% CI: 5.1, 10.8), p<0.0001
				Placebo	288	-2.8 (SE 1.4)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **EQ-5D** = EuroQol 5-dimension questionnaire; **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **ROB** = risk of bias, **SE** = standard error.

Table A58 EQ-5D in patients receiving fremanezumab

Trial name	ROB	Timepoint of assessment	EQ-5D type	Intervention and dose	n	Mean change in EQ-5D	Difference between interventions
Episodic and chronic migraine							
FOCUS [85]	Low	4 months	EQ-5D	FRE quarterly	276	4.7 (SE 1.4)	3.0 (95%CI: 0.1, 5.9), p=0.0426
				FRE monthly	283	7.2 (SE 1.4)	5.6 (95%CI: 2.7, 8.5), p=0.0002
				Placebo	278	1.6 (SE 1.4)	NA
Chronic migraine							
HALO CM[79]	Low	16 weeks	EQ-5D-5L	FRE 225 mg	375	4.8 (SE NR)	2.6 (SE 1.18), p=0.0291
				FRE 675 mg	375	4.6 (SE NR)	2.4 (SE 1.18), p=0.0402
				Placebo	371	2.2 (SE NR)	NA

Abbreviations
CI = confidence interval, **EQ-5D** = EuroQol 5-dimension questionnaire; **FRE** = fremanezumab; **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **ROB** = risk of bias, **SE** = standard error.

SF-36

Table A59 SF-36 in patients receiving erenumab

Trial name	ROB	Timepoint of assessment	SF-36 domain	Intervention and dose	n	Mean change in SF-36	Difference between interventions
Episodic and chronic migraine							
HER-MES[49]*	Low	4–6 months	Physical component	ERU 70 or 140 mg	378	5.5 (SE 0.4)	1.9 (95% CI: 1.0, 2.8), p<0.001
				Placebo	374	3.6 (SE 0.4)	NA
			Mental component	ERU 70 or 140 mg	378	1.0 (SE 0.5)	2.2 (95% CI: 1.0, 3.3), p<0.001
				Placebo	374	-1.2 (SE 0.5)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **ROB** = risk of bias, **SE** = standard error, **SF-36** = 36-Item Short Form Health Survey.
Notes
***** In HER-MES, the following number of patients were included: For Erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%) Chronic (≥15 MMDs) = 42 (10.8%).

Table A60 SF-36 in patients receiving eptinezumab

Trial name	ROB	Timepoint of assessment	SF-36 domain	Intervention and dose	n	Mean change in SF-36	Difference between interventions
Episodic and chronic migraine							
PROMISE-1[55 56]	High	6 months	Physical component	EPT 100 mg	221	2.7 (SD 6.84)	NR
				EPT 300 mg	222	3.2 (SD 6.02)	NR
				Placebo	222	1.3 (SD 6.42)	NA
			Mental component	EPT 100 mg	221	0.5 (SD 8.89)	NR
				EPT 300 mg	222	1.4 (SD 7.86)	NR
				Placebo	222	0.6 (SD 7.63)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **MD** = mean difference, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **ROB** = risk of bias, **SE** = standard error, **SF-36** = 36-Item Short Form Health Survey.

Migraine pain intensity

Table A61 Migraine/headache pain intensity in patients receiving erenumab

	ROB	Timepoint of assessment	Intervention and dose	n	Mean change in migraine pain intensity*	Difference between interventions
Episodic migraine						
Sun et al 2016[35]	Low	12 weeks	ERU 70 mg	101	-0.1 (SE 0.04)	0.1 (95% CI: -0.04, 0.2), p=0.2
			Placebo	153	-0.2 (SE 0.04)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **ROB** = risk of bias, **SE** = standard error.
Notes:
Severity scale of migraine pain: 1 = Mild, 2 = Moderate, 3 = Severe.

Migraine/headache pain intensity in patients receiving eptinezumab

No studies identified.

Migraine/headache pain intensity in patients receiving fremanezumab

No studies identified.

Migraine/headache pain intensity in patients receiving galcanezumab

No studies identified.

Adverse events

Table A62 Adverse events in patients receiving erenumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Episodic migraine						
ARISE[16]	Low	3 months	ERU 70 mg	283	136 (48.1)	OR 0.77 (95% CI: 0.55, 1.07), p=0.11
			Placebo	289	158 (54.7)	
EMPOWER[17]	High	6 months	ERU 70 mg	335	117 (34.9)	OR 0.93 (95% CI: 0.67, 1.27), p=0.63
			ERU 140 mg	224	77 (34.4)	OR 0.90 (95% CI: 0.63, 1.29), p=0.57
			Placebo	335	123 (36.7)	NA
LIBERTY[18]	Low	3 months	ERU 140 mg	119	65 (55)	OR 1.02 (95% CI: 0.62, 1.70), p=0.93
			Placebo	124	67 (54)	
Sakai et al 2019[23]	Low	6 months	ERU 70 mg	135	95 (70.4)	OR 1.14 (95% CI: 0.68, 1.90), p=0.63
			ERU 140 mg	137	95 (69.3)	OR 1.08 (95% CI: 0.65, 1.80), p=0.76
			Placebo	136	92 (67.6)	NA
STRIVE[26]	Low	4–6 months	ERU 70 mg	314	180 (57.3)	OR 0.79 (95% CI: 0.57, 1.08), p=0.14
			ERU 140 mg	319	177 (55.5)	OR 0.73 (95% CI: 0.53, 1.00), p=0.05
			Placebo	319	201 (63.0)	NA
Sun et al 2016[35]	Low	3 months	ERU 70 mg	106	57 (54)	OR 1.01 (95% CI: 0.61, 1.66), p=0.98
			Placebo	153	82 (54)	
Chronic migraine						
Tepper et al 2017[40]	Low	3 months	ERU 70 mg	190	83 (44)	OR 1.21 (95% CI: 0.83, 1.76), p=0.31
			ERU 140 mg	188	88 (47)	OR 1.38 (95% CI: 0.95, 2.00), p=0.09
			Placebo	282	110 (39)	NA
DRAGON 2022[109]	Some concerns	Week 12	ERU 70 mg	279	127 (45.5)	OR 0.92 (95% CI: 0.66, 1.29), p=0.64
			Placebo	278	132 (47.5)	NA
Subgroups of patients with >2 prior treatment failures - episodic migraine						
Tepper et al 2017[41]	Low	3 months	ERU 70 mg	92	39 (42.4)	OR 0.94 (95% CI: 0.55, 1.59), p=0.81
			ERU 140 mg	92	53 (57.6)	OR 1.73 (95% CI: 1.02, 2.94), p=0.04
			Placebo	141	62 (44.0)	NA
Subgroups of patients with >2 prior treatment failures - chronic migraine						
STRIVE[26]	Low	6 months	ERU 70 mg	49	33 (67.3)	OR 0.87 (95% CI: 0.38, 2.00),

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
						p=0.74
			ERU 140 mg	58	35 (60.3)	OR 0.64 (95% CI: 0.29, 1.41), p=0.27
			Placebo	54	38 (70.4)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Adverse events in patients receiving eptinezumab

There were no studies reporting AEs among patients receiving eptinezumab.

Table A63 Adverse events in patients receiving fremanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Episodic migraine						
HALO EM[68]	High	3 months	FRE 225 mg	290	192 (66.2)	OR 1.40 (95% CI: 1.0, 1.96), p=0.05
			FRE 675 mg	291	193 (66.3)	OR 1.41 (95% CI: 1.0, 1.97), p=0.05
			Placebo	293	171 (58.4)	NA
Chronic migraine						
HALO CM[76]	Low	3 months	FRE 225 mg	379	270 (71)	OR 1.39 (95% CI: 1.03, 1.89), p=0.03
			FRE 675 mg	376	265 (70)	OR 1.34 (95% CI: 0.99, 1.82), p=0.06
			Placebo	375	240 (64)	NA
Episodic and chronic migraine						
FOCUS[85*]	Low	3 months	FRE quarterly	276	151 (55)	OR 1.29 (95% CI: 0.92, 1.80), p=0.14
			FRE monthly	285	129 (45)	OR 0.88 (95% CI: 0.63, 1.23), p=0.46
			Placebo	277	134 (48)	NA
Subgroups of patients with >2 prior treatment failures - Episodic and chronic migraine						
FOCUS[86]	Low	3 months 2 Tx failures	FRE quarterly	140	67 (48)	OR 1.20 (95% CI: 0.75, 1.93), p=0.44
			FRE monthly	134	58 (43)	OR 1.0 (95% CI: 0.62, 1.61), p=1.0
			Placebo	141	61 (43)	NA

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
		3 months 3 Tx failures	FRE quarterly	85	51 (60)	OR 1.62 (95% CI: 0.87, 2.99), p=0.13
			FRE monthly	99	47 (47)	OR 0.97 (95% CI: 0.54, 1.75), p=0.93
			Placebo	81	39 (48)	NA
		3 months 4 Tx failures	FRE quarterly	49	31 (63)	OR 1.01 (95% CI: 0.45, 2.26), p=0.97
			FRE monthly	50	23 (46)	OR 0.50 (95% CI: 0.23, 1.10), p=0.08
			Placebo	54	34 (63)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias, **Tx** = treatment.
Notes
Blue text indicates RACS calculated comparisons.
* In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A64 Adverse events in patients receiving galcanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Episodic migraine						
Dodick et al 2014a[88]	Low	6 months	GAL 150 mg	107	77 (72)	OR 1.25 (95% CI: 0.70, 2.23), p=0.45
			Placebo	110	74 (67)	

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **OR** = odds ratio, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Treatment related adverse events

Table A65 Treatment related adverse events (TRAE) in patients receiving erenumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Episodic migraine						
EMPOwER[17]	High	6 months	ERU 70 mg	335	38 (11.3)	OR 1.21 (95% CI: 0.74. 1.99), p=0.45
			ERU 140 mg	224	24 (10.7)	OR 1.14 (95% CI: 0.65, 1.99), p=0.65
			Placebo	335	32 (9.6)	NA
Chronic migraine						
DRAGON 2022[109]	Some concerns	Week 12	ERU 70 mg	279	36 (12.9)	OR 0.96 (95% CI: 0.59, 1.58), p=0.88
			Placebo	278	37 (13.3)	NA
Episodic and chronic migraine						
HER-MES[49]*	Low	24 weeks	ERU 70 or 140 mg	388	215 (55.4)	OR 0.29 (95% CI: 0.21, 0.40), p<0.00001
			Topiramate 25–100 mg	388	315 (81.2)	

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = Odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.
* In HER-MES, the following number of patients were included: For erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%). Chronic (≥15 MMDs) = 42 (10.8%).

Table A66 Treatment related adverse events (TRAE) in patients receiving eptinezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
DELIVER 2022[110]	Low	Week 24	EPT 100 mg	299	127 (42)	OR 1.11 (95% CI: 0.8, 1.54), p=0.53
			EPT 300 mg	294	120 (41)	OR 1.04 (95% CI 0.75, 1.44), p=0.83
			Placebo	298	119 (40)	NA

Abbreviations
EPT = eptinezumab, **n** = number of patients, **OR** = Odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Table A67 Treatment related adverse events (TRAE) in patients receiving fremanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Episodic migraine						
Bigal et al 2015b[65]	Low	3 months	FRE 225 mg	96	26 (27)	OR 1.24 (95% CI: 0.65, 2.35), p=0.51
			FRE 675 mg	96	24 (25)	OR 1.11 (95% CI: 0.58, 2.13), p=0.75
			Placebo	104	24 (23)	NA
HALO EM[68]	High	3 months	FRE 225 mg	290	138 (47.6)	OR 1.53 (95% CI: 1.10, 2.13), p=0.01
			FRE 675 mg	291	137 (47.1)	OR 1.50 (95% CI: 1.08, 2.09), p=0.02
			Placebo	293	109 (37.2)	NA
Chronic migraine						
Bigal et al 2015a[73]	Low	3 months	FRE 675/225 mg*	88	25 (29)	OR 1.96 (95% CI: 0.95, 4.03), p=0.07
		3 months	Placebo	89	15 (17)	
Episodic and chronic migraine						
FOCUS[85]**	Low	3 months	FRE quarterly	276	57 (21)	OR 1.05 (95% CI: 0.69, 1.59), p=0.82
		3 months	FRE monthly	285	55 (19)	OR 0.97 (95% CI: 0.64, 1.46), p=0.87
		3 months	Placebo	277	55 (20)	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.
* In Bigal et al 2015a patients received 675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles.
** In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A68 Treatment related adverse events (TRAE) in patients receiving galcanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of adverse events	Difference between groups
Episodic migraine						
EVOLVE-1[89]	Low	6 months	GAL 120 mg	206	135 (65.5)	OR 1.25 (95% CI: 0.88, 1.76), p=0.21
			GAL 240 mg	220	149 (67.7)	OR 1.37 (95% CI: 0.98, 1.94), p=0.07
			Placebo	432	261 (60.4)	NA
PERSIST 2022[112]	Low	3 months	GAL 120 mg	261	130 (49.8)	OR 1.3 (95% CI: 0.92, 1.84), p=0.13
			Placebo	259	112 (43.2)	NA

Abbreviations
CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Serious adverse events

Table A69 Serious adverse events (SAE) in patients receiving erenumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Episodic migraine						
ARISE[15]	Low	3 months	ERU 70 mg	283	3 (1.1)	OR 0.61 (95% CI: 0.14, 2.57), p=0.50
			Placebo	289	5 (1.7)	
EMPOwER[17]	High	6 months	ERU 70 mg	335	3 (0.9)	OR 1.50 (95% CI: 0.25, 9.06), p=0.66
			ERU 140 mg	224	0 (0)	OR 0.30 (95% CI: 0.01, 6.22), p=0.43
			Placebo	335	2 (0.6)	NA
LIBERTY[18]	Low	3 months	ERU 140 mg	119	2 (2)	OR 2.10 (95% CI: 0.19, 23.50), p=0.55
			Placebo	124	1 (1)	
Sakai et al 2019[23]	Low	6 months	ERU 70 mg	135	1 (0.7)	OR 0.25 (95% CI: 0.03, 2.23), p=0.21
			ERU 140 mg	137	1 (0.7)	OR 0.24 (95% CI: 0.03, 2.20), p=0.21
			Placebo	136	4 (2.9)	NA
STRIVE[26]	Low	4–6 months	ERU 70 mg	314	8 (2.5)	OR 1.17 (95% CI: 0.42, 3.25), p=0.77
			ERU 140 mg	319	6 (1.9)	OR 0.85 (95% CI: 0.28, 2.57), p=0.78
			Placebo	319	7 (2.2)	NA
Sun et al 2016[35]	Low	3 months	ERU 70 mg	106	1 (1)	OR 4.36 (95% CI: 0.18, 108.18), p=0.37
			Placebo	153	0 (0)	
Chronic migraine						
Tepper et al 2017[40]	Low	3 months	ERU 70 mg	190	6 (3)	OR 1.28 (95% CI: 0.42, 3.87), p=0.66
			ERU 140 mg	188	2 (1)	OR 0.42 (95% CI: 0.09, 2.06), p=0.29
			Placebo	282	7 (2)	NA
DRAGON 2022[109]	Some concerns	Week 12	ERU 70 mg	279	7 (2.5)	OR 1.00 (95% CI: 0.34, 2.88), p=0.99
			Placebo	278	7 (2.5)	NA
Episodic and chronic migraine						
Takeshima et	Low	6 months	ERU 70 mg	130	2 (1.5)	OR 1.01 (95% CI: 0.14, 7.26),

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
al 2021[51]*			Placebo	131	2 (1.5)	p=0.99
HER-MES[50]**	Low	24 weeks	ERU 70 or 140 mg	388	10 (2.58)	OR 0.51 (95% CI: 0.24, 1.12), p=0.09
			Topiramate 25–100 mg	388	19 (4.90)	
Subgroups of patients with >2 prior treatment failures - episodic migraine						
Tepper et al 2017[41]	Low	3 months	ERU 70 mg	92	3 (3.3)	OR 1.15 (95% CI: 0.25, 5.28), p=0.85
			ERU 140 mg	92	1 (1.1)	OR 0.38 (95% CI: 0.04, 3.42), p=0.39
			Placebo	141	4 (2.8)	NA
Subgroups of patients with >2 prior treatment failures - chronic migraine						
STRIVE[30]	Low	6 months	ERU 70 mg	49	2 (4.1)	OR 5.74 (95% CI: 0.27, 122.50), p=0.26
			ERU 140 mg	58	3 (5.2)	OR 6.87 (95% CI: 0.35, 136.24), p=0.21
			Placebo	54	0 (0.0)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias, **SAEs** = serious adverse events.
Notes
Blue text indicates RACS calculated comparisons.
* Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine.
** In HER-MES, the following number of patients were included: For erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%). Chronic (≥15 MMDs) = 42 (10.8%).

Table A70 Serious adverse events (SAE) in patients receiving eptinezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Episodic migraine						
PROMISE-1[56]	High	56 weeks	EPT 100 mg	223	4 (1.79)	OR 0.66 (95% CI: 0.18, 2.36), p=0.52
			EPT 300 mg	224	3 (1.34)	OR 0.49 (95% CI: 0.12, 1.98), p=0.32
			Placebo	222	6 (2.7)	NA
Chronic migraine						
Dodick et al 2019[57]	Some concerns	3 months	EPT 300 mg	121	7 (5.8)	OR 7.37 (95% CI: 0.89, 60.83), p=0.06
			EPT 100 mg	122	4 (3.3)	OR 4.07 (95% CI: 0.45, 36.93), p=0.21
			Placebo	121	1 (0.8)	NA
PROMISE-2[64]	Low	1–32 weeks	EPT 100 mg	356	3 (0.84)	OR 1.03 (95% CI: 0.21, 5.13), p=0.97

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
			EPT 300 mg	350	4 (1.14)	OR 1.40 (95% CI: 0.31, 6.30), p=0.66
			Placebo	366	3 (0.82)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
DELIVER 2022[110]	Low	Week 24	EPT 100 mg	299	5 (2)	OR 1.25 (95% CI: 0.33, 4.7), p=0.74
			EPT 300 mg	294	7 (2)	OR 1.79 (95% CI: 0.52, 6.19), p=0.35
			Placebo	298	4 (1)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **NA** = not applicable, **OR** = odds ratio, **RoB** = risk of bias, **SAEs** = serious adverse events.
Notes
Blue text indicates RACS calculated comparisons.

Table A71 Serious adverse events (SAE) in patients receiving fremanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Episodic migraine						
Bigal et al 2015b[65]	Low	3 months	FRE 225 mg	96	2 (2)	OR 5.53 (95% CI: 0.26, 116.64), p=0.27
			FRE 675 mg	96	2 (2)	OR 5.53 (95% CI: 0.26, 116.64), p=0.27
			Placebo	104	0 (0)	NA
HALO EM[68]	High	3 months	FRE 225 mg	290	3 (1.0)	OR 0.43 (95% CI: 0.11, 1.67), p=0.22
			FRE 675 mg	291	3 (1.0)	OR 0.43 (95% CI: 0.11, 1.66), p=0.22
			Placebo	293	7 (2.4)	NA
Sakai et al 2021b[71]	Low	3 months	FRE 225 mg	121	0 (0)	Not estimable
			FRE 675 mg	118	0 (0)	Not estimable
			Placebo	117	0 (0)	NA
Chronic migraine						
Bigal et al 2015a[73]	Low	3 months	FRE 675/225 mg	88	1 (1)	OR 1.01 (95ICI: 0.06, 16.43), p=0.99
			Placebo	89	1 (1)	
HALO CM[76]	Low	3 months	FRE 225 mg	379	5 (1)	OR 0.82 (95% CI: 0.25, 2.72), p=0.75
			FRE 675 mg	376	3 (<1)	OR 0.49 (95% CI: 0.12, 1.99), p=0.32
			Placebo	375	6 (2)	NA
Sakai et al 2021a[83]	Low	3 months	FRE 225 mg	188	3 (1.6)	OR 3.08 (95% CI: 0.32, 29.89), p=0.33

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
			FRE 675 mg	190	1 (0.5)	OR 1.01 (95% CI: 0.06, 16.19), p=1.00
			Placebo	191	1 (0.5)	NA
Episodic and chronic migraine						
FOCUS[85]*	Low	3 months	FRE quarterly	276	2 (<1)	OR 0.50 (95% CI: 0.09, 2.74), p=0.42
			FRE monthly	285	4 (1)	OR 0.97 (95% CI: 0.24, 3.92), p=0.97
			Placebo	277	4 (1)	NA
Subgroups of patients with >2 prior treatment failures - Episodic and chronic migraine						
FOCUS[86]	Low	3 months 2 Tx failures	FRE quarterly	140	1 (<1)	OR 0.25 (95% CI: 0.03, 2.23), p=0.21
			FRE monthly	134	2 (1)	OR 0.52 (95% CI: 0.09, 2.88), p=0.45
			Placebo	141	4 (3)	NA
		3 months 3 Tx failures	FRE quarterly	85	0	Not estimable
			FRE monthly	99	2 (2)	OR 4.18 (95% CI: 0.20, 88.30), p=0.36
			Placebo	81	0	NA
		3 months 4 Tx failures	FRE quarterly	49	1 (2)	OR 3.37 (95% CI: 0.13, 84.70), p=0.46
			FRE monthly	50	0	Not estimable
			Placebo	54	0	NA

Abbreviations
CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias, **SAEs** = serious adverse events, **Tx** = treatment.
Notes
Blue text indicates RACS calculated comparisons.
* In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A72 Serious adverse events (SAE) in patients receiving galcanezumab

	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
Episodic migraine						
Dodick et al 2014a[88]	Low	6 months	GAL 150 mg	107	2 (1.9)	OR 0.50 (95% CI: 0.09, 2.82), p=0.44
			Placebo	110	4 (3.6)	
EVOLVE-1[89]	Low	6 months	GAL 120 mg	206	6 (2.9)	OR 2.56 (95% CI: 0.77, 8.49), p=0.12
			GAL 240 mg	220	0 (0)	OR 0.18 (95% CI: 0.01, 3.20), p=0.24

	ROB	Timepoint of assessment	Intervention and dose	n	Number (%) of SAEs	Difference between groups
			Placebo	432	5 (1.2)	NA
EVOLVE-2[91]	Low	6 months	GAL 120 mg	226	5 (2.2)	OR 2.06 (95% CI: 0.59, 7.20), p=0.26)
			GAL 240 mg	228	7 (3.1)	OR 2.89 (95% CI: 0.91, 9.20), p=0.07
			Placebo	461	5 (1.1)	NA
Sakai et al 2020a[93]	Low	6 months	GAL 120 mg	115	3 (2.6)	OR 14.34 (95% CI: 0.73, 280.05), p=0.08
			GAL 240 mg	114	1 (0.9)	OR 6.09 (95% CI: 0.25, 150.74), p=0.27
			Placebo	230	0 (0.0)	NA
Skljarevski et al 2018[98,100]	Low	1–12 weeks	GAL 120 mg	70	1 (1.43)	OR 5.94 (95% CI: 0.24, 147.6), p=0.28
			Placebo	137	0 (0)	
		12–24 weeks	GAL 120 mg	63	0 (0)	Not estimable
			Placebo	125	0 (0)	NA
PERSIST 2022[112]	Low	3 months	GAL 120 mg	261	2 (0.77)	OR 0.49 (95% CI: 0.09, 2.71), p=0.42
			Placebo	259	4 (1.54)	NA
Chronic migraine						
REGAIN[102]	Low	3 months	GAL 120 mg	273	1 (<1)	OR 0.51 (95% CI: 0.06, 4.58), p=0.55
			GAL 240 mg	282	5 (1.77)	OR 2.50 (95% CI: 0.67, 9.38), p=0.17
			Placebo	558	4 (<1)	NA
Episodic and chronic migraine						
CGAJ[105]*	High	12 months	GAL 120 mg	129	3 (2.3)	OR 0.46 (95% CI: 0.12, 1.80), p=0.26
			GAL 240 mg	141	7 (5.0)	
CONQUER[106] **	Low	3 months	GAL 120 mg	232	2 (1)	OR 0.99 (95% CI: 0.14, 7.10), p=0.99
			Placebo	230	2 (1)	

Abbreviations

CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias, **SAEs** = serious adverse events.

Notes

Blue text indicates RACS calculated comparisons.

* In the CGAJ trial there were two treatment groups; GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% of patients had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% of patients had chronic migraine.

** In the CONQUER trial there were two treatment groups, GAL 120 mg and Placebo. In the GAL 120 mg group 59% of patients had episodic migraine and 41% of patients had chronic migraine. In the placebo group, 58% of patients had episodic migraine and 43% of patients had chronic migraine.

Adverse events leading to discontinuation

Table A73 Adverse events leading to discontinuation, erenumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Numbers discontinued (%)	Difference between groups
Episodic migraine						
ARISE[15]	Low	3 months	ERU 70 mg	283	5 (1.8)	OR 5.18 (95% CI: 0.60, 44.62), p=0.13
			Placebo	289	1 (0.3)	
EMPOwER[17]	High	6 months	ERU 70 mg	335	0 (0)	OR 0.20 (95% CI: 0.01, 4.16), p=0.30
			ERU 140 mg	224	0 (0)	OR 0.30 (95% CI: 0.01, 6.22), p=0.43
			Placebo	335	2 (0.6)	NA
LIBERTY[18]	Low	3 months	ERU 140 mg	119	0	OR 0.34 (95% CI: 0.01, 68.54), p=0.52
			Placebo	124	1 (1)	
Sakai et al 2019[23]	Low	6 months	ERU 70 mg	135	2 (1.5)	OR 2.03 (95% CI: 0.18, 22.66), p=0.57
			ERU 140 mg	137	0 (0.0)	OR 0.33 (95% CI: 0.01, 8.13), p=0.50
			Placebo	136	1 (0.7)	NA
STRIVE[26]	Low	4–6 months	ERU 70 mg	314	7 (2.2)	OR 0.89 (95% CI: 0.32, 2.47), p=0.82
			ERU 140 mg	319	7 (2.2)	OR 0.87 (95% CI: 0.31, 2.43), p=0.79
			Placebo	319	8 (2.5)	NA
Sun et al 2016[35]	Low	3 months	ERU 70 mg	106	3 (3)	OR 2.20 (95% CI: 0.36, 13.39), p=0.39
			Placebo	153	2 (1)	
Chronic migraine						
Tepper et al 2017[40]	Low	3 months	ERU 70 mg	190	0 (0)	OR 0.29 (95% CI: 0.01, 6.17), p=0.43
			ERU 140 mg	188	2 (1)	OR 1.51 (95% CI: 0.21, 10.78), p=0.68
			Placebo	282	2 (<1)	NA
DRAGON 2022[109]	Some concerns	Week 12	ERU 70 mg	279	2 (0.7)	OR 1.00 (95% CI: 0.14, 7.12), p=0.99
			Placebo	278	2 (0.7)	NA

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Numbers discontinued (%)	Difference between groups
Episodic and chronic migraine						
HER-MES[49]*	Low	24 weeks	ERU 70 or 140 mg	388	41 (10.6)	OR 0.19 (95% CI: 0.13, 0.27) RR 0.27 (95% CI: 0.20, 0.37), p<0.001
			Topiramate 25–100 mg	388	151 (38.9)	
Takeshima et al 2021[51]**	Low	6 months	ERU 70 mg	130	0 (0)	Not estimable
			Placebo	131	0 (0)	
Subgroups of patients with >2 prior treatment failures - episodic migraine						
STRIVE[30]	Low	6 months	ERU 70 mg	49	1 (2.0)	OR 3.37 (95% CI: 0.13, 84.70), p=0.46
			ERU 140 mg	58	4 (6.9)	OR 9.00 (95% CI: 0.47, 171.23), p=0.14
			Placebo	54	0 (0)	NA
Subgroups of patients with >2 prior treatment failures - chronic migraine						
Tepper et al 2017[41]	Low	3 months	ERU 70 mg	92	0 (0.0)	OR 0.51 (95% CI: 0.02, 12.56), p=0.68
			ERU 140 mg	92	0 (0.0)	OR 0.51 (95% CI: 0.02, 12.56), p=0.68
			Placebo	141	1 (0.7)	NA

Abbreviations
CI = confidence interval, **ERU** = erenumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.
* In HER-MES, the following number of patients were included: For Erenumab, 4–7 MMDs = 94 (24.2%), Episodic = 248 (63.9%), Chronic = 43 (11.1%). For topiramate, 4–7 MMDs = 92 (23.7%). Episodic (8–14 MMDs) = 254 (65.5%). Chronic (≥15 MMDs) = 42 (10.8%).
** Takeshima et al 2021 did not report the number of patients who had chronic or episodic migraine.

Table A74 Adverse events leading to discontinuation, eptinezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
Episodic migraine						
PROMISE-1[54]	High	3 months	EPT 100 mg	223	6 (2.7)	OR 1.00 (95% CI: 0.32, 3.13), p=0.99
			EPT 300 mg	224	5 (2.2)	OR 0.82 (95% CI: 0.25, 2.73), p=0.75
			Placebo	222	6 (2.7)	NA
Chronic migraine						
PROMISE-2[58]	Low	1–12 weeks	EPT 100 mg	356	3 (<1)	OR 1.55 (95% CI: 0.26, 9.31), p=0.63

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
			EPT 300 mg	350	8 (2.3)	OR 4.26 (95% CI: 0.90, 20.19), p=0.07
			Placebo	366	2 (<1)	NA
Subgroups of patients with >2 prior treatment failures - episodic and chronic migraine						
DELIVER 2022[110]	Low	Week 24	EPT 100 mg	299	1 (<1)	OR 1.00 (95% CI: 0.06, 16.01), p=0.99
			EPT 300 mg	294	6 (2)	OR 6.19 (95% CI: 0.74, 51.71), p=0.09
			Placebo	298	1 (<1)	NA

Abbreviations
CI = confidence interval, **EPT** = eptinezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.
Notes
Blue text indicates RACS calculated comparisons.

Table A75 Adverse events leading to discontinuation, fremanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
Episodic migraine						
HALO EM[68]	High	12 weeks	FRE 225 mg	290	5 (1.7)	OR 0.40 (95% CI: 0.08, 2.08), p=0.28
			FRE 675 mg	291	5 (1.7)	OR 1.01 (95% CI: 0.29, 3.52), p=0.99
			Placebo	293	5 (1.7)	NA
Sakai et al 2021b[71]	Low	12 weeks	FRE 225 mg	121	1 (0.8)	OR 0.97 (95% CI: 0.06, 15.64), p=0.98
			FRE 675 mg	118	0 (0)	OR 0.33 (95% CI: 0.01, 8.13), p=0.50
			Placebo	117	1 (0.9)	NA
Chronic migraine						
Sakai et al 2021a[83]	Low	12 weeks	FRE 225 mg	188	0 (0)	OR 0.20 (95% CI: 0.01, 4.22), p=0.30
			FRE 675 mg	190	0 (0)	OR 0.20 (95% CI: 0.01, 4.17), p=0.30
			Placebo	191	2 (1.0)	NA
HALO CM[76]	Low	12 weeks	FRE 225 mg	379	7 (2)	OR 0.86 (95% CI: 0.31, 2.40), p=0.78
			FRE 675 mg	376	5 (1)	OR 0.62 (95% CI: 0.20, 1.91), p=0.40
			Placebo	375	8 (2)	NA
Episodic and chronic migraine						
FOCUS[85]*	Low	3 months	FRE quarterly	276	1 (<1)	OR 0.33 (95% CI: 0.03, 3.21), p=0.34
			FRE monthly	285	4 (1)	OR 1.30 (95% CI: 0.29, 5.86), p=0.73
			Placebo	277	3 (1)	NA
Subgroups of patients with >2 prior treatment failures - Episodic and chronic migraine						
FOCUS[86]	Low	3 months 2 Tx failures	FRE quarterly	140	1 (<1)	OR 0.33 (95% CI: 0.03, 3.22), p=0.34
			FRE monthly	134	1 (<1)	OR 0.35 (95% CI: 0.04, 3.37), p=0.36
			Placebo	141	3 (2)	NA
		3 months 3 Tx failures	FRE quarterly	85	0	Not estimable
			FRE monthly	99	3 (3)	Not estimable
			Placebo	81	0	NA
		3 months 4 Tx failures	FRE quarterly	49	0	Not estimable
			FRE monthly	50	0	Not estimable
			Placebo	54	0	NA

Abbreviations

CI = confidence interval, **FRE** = fremanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.

Notes

Blue text indicates RACS calculated comparisons.

* In the FOCUS trial, there were three treatment groups; FRE quarterly, monthly and placebo. In the FRE quarterly group, patients received 675 mg FRE and 107 (39%) had episodic migraine, while 169 (61%) had chronic migraine. In the FRE monthly group 110 (39%) patients had episodic migraine and received 225 mg FRE monthly while 173 (61%) of patients had chronic migraine and received 675 mg FRE as a loading dose then 225 mg monthly. In the placebo group, 112 (40%) of patients had episodic migraine while 167 (60%) had chronic migraine.

Table A76 Adverse events leading to discontinuation, galcanezumab

Study name	ROB	Timepoint of assessment	Intervention and dose	n	Number discontinued (%)	Difference between groups
Episodic migraine						
Dodick et al 2014a[88]	Low	6 months	GAL 150 mg	107	0 (0)	OR 0.34 (95% CI: 0.01, 8.43), p=0.51
			Placebo	110	1 (0.9)	
EVOLVE-1[89]	Low	6 months	GAL 120 mg	213	9 (4.2)	OR 1.87 (95% CI: 0.75, 4.66), p=0.18
			GAL 240 mg	212	7 (3.3)	OR 1.44 (95% CI: 0.54, 3.85), p=0.46
			Placebo	433	10 (2.3)	NA
EVOLVE-2[91]	Low	6 months	GAL 120 mg	226	5 (2.2)	OR 1.28 (95% CI: 0.41, 3.96), p=0.67
			GAL 240 mg	228	9 (4.0)	OR 2.33 (95% CI: 0.89, 6.11), p=0.09
			Placebo	461	8 (1.7)	NA
Sakai et al 2020a[93]	Low	6 months	GAL 120 mg	115	5 (4.4)	OR 22.95 (95% CI: 1.26, 418.66), p=0.03
			GAL 240 mg	114	2 (1.8)	OR 10.24 (95% CI: 0.49, 215.18), p=0.13
			Placebo	230	0 (0.0)	NA
Skljarevski et al 2018[100]	Low	1–12 weeks	GAL 120 mg	70	0 (0)	Not estimable
			Placebo	137	0 (0)	
		12–24 weeks	GAL 120 mg	63	0 (0)	Not estimable
			Placebo	125	0 (0)	
PERSIST 2022[112]	Low	3 months	GAL 120 mg	261	6 (2.3)	OR 6.07 (95% CI: 0.73, 50.78), p=0.09
			Placebo	259	1 (0.4)	NA
Episodic and chronic migraine						
CGAJ[105]*	High	12 months	GAL 120 mg	129	6 (4.7)	OR 0.89 (95% CI: 0.28, 2.62), p=0.79
			GAL 240 mg	130	7 (5.0)	
CONQUER[106]**	Low	3 months	GAL 120 mg	232	1 (<1)	OR 2.99 (95% CI: 0.12, 73.71), p=0.50
			Placebo	230	0	

Abbreviations

CI = confidence interval, **GAL** = galcanezumab, **n** = number of patients, **OR** = odds ratio, **NA** = not applicable, **RoB** = risk of bias.

Notes

Blue text indicates RACS calculated comparisons.

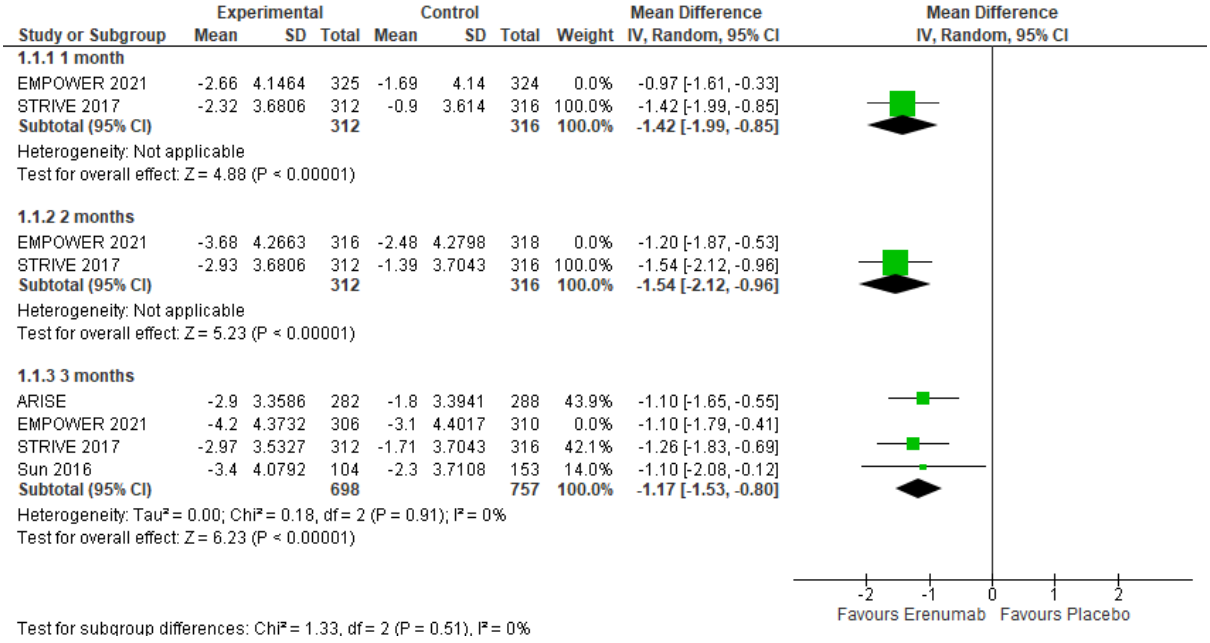
* In the CGAJ trial there were two treatment groups; GAL 120 mg and GAL 240 mg. In the GAL 120 mg group 80.7% of patients had episodic migraine and 19.3% of patients had chronic migraine. In the 240 mg group, 77.0% of patients had episodic migraine and 23.0% of patients had chronic migraine.

** In the CONQUER trial there were two treatment groups, GAL 120 mg and Placebo. In the GAL 120 mg group 59% of patients had episodic migraine and 41% of patients had chronic migraine. In the placebo group, 58% of patients had episodic migraine and 43% of patients had chronic migraine.

Appendix H: Sensitivity Analyses

Sensitivity analyses

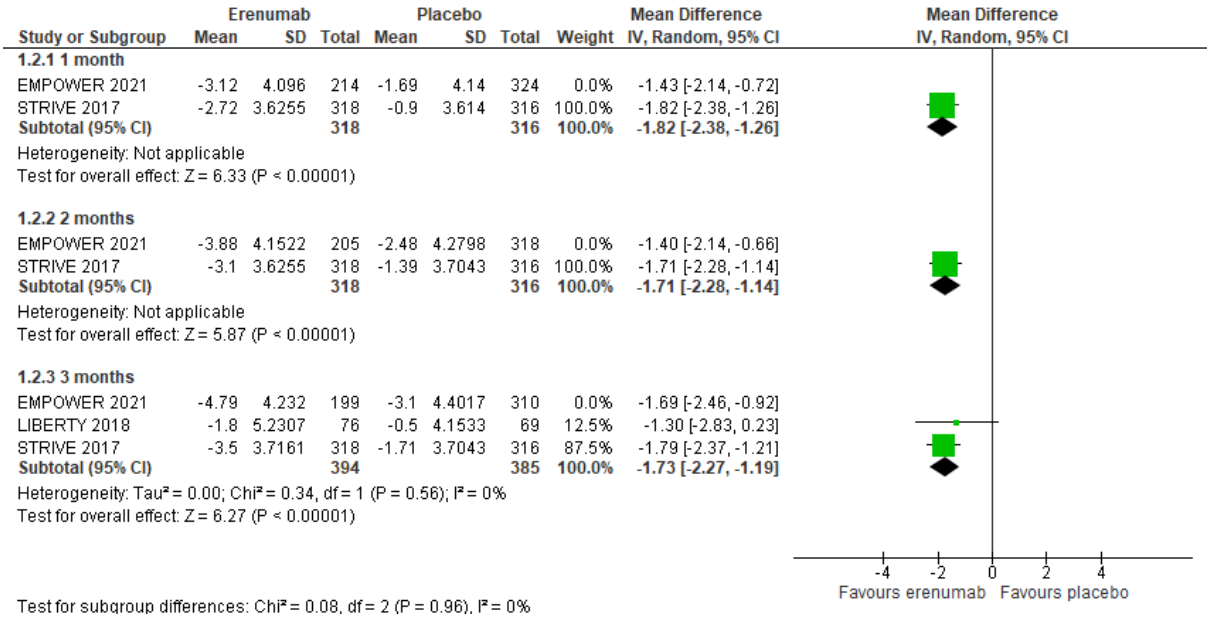
Figure A1 MMD, episodic migraine – Erenumab 70 mg



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

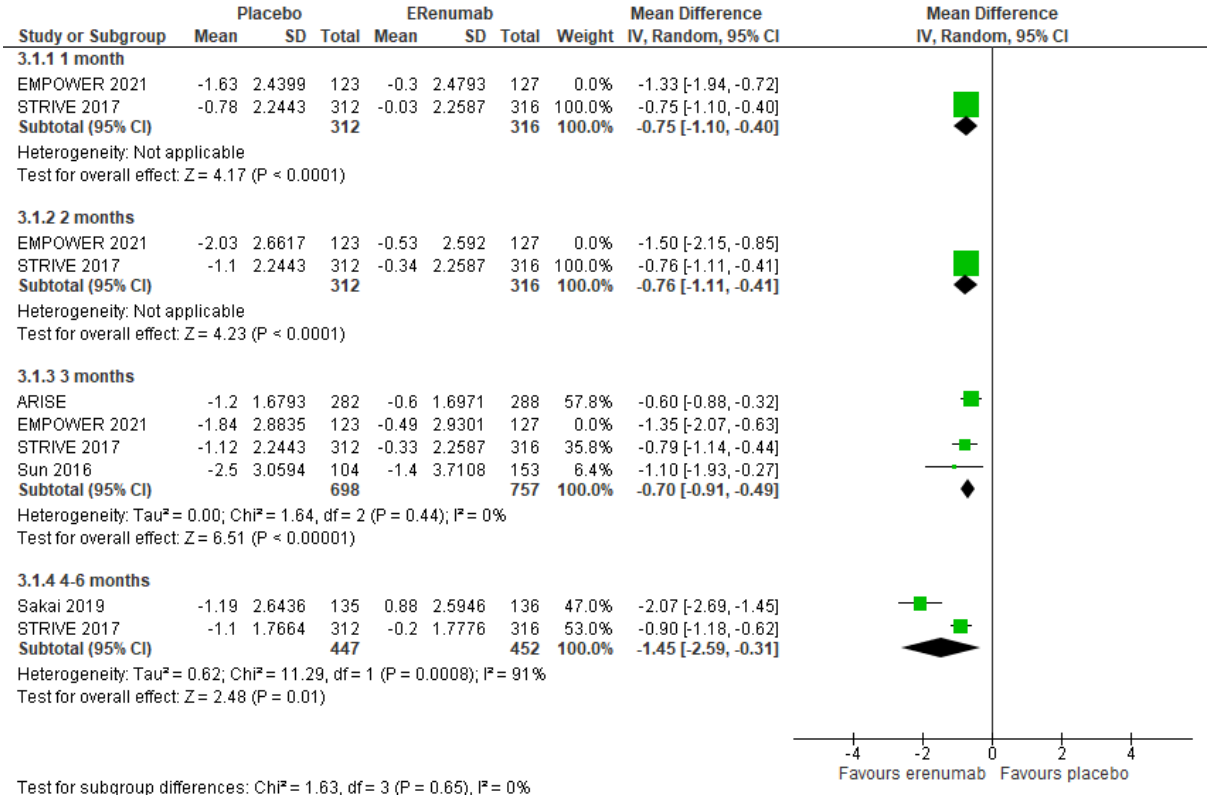
Figure A2 MMD, episodic migraine – Erenumab 140 mg



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

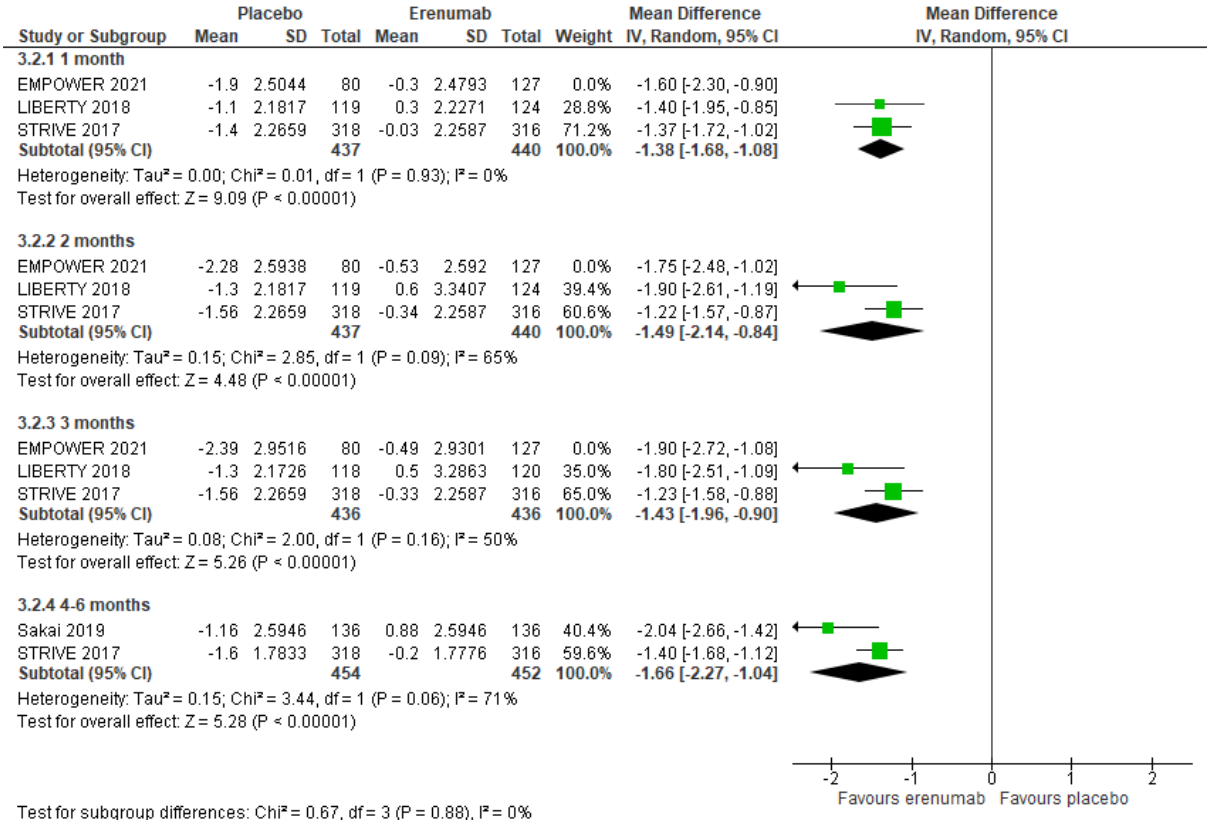
Figure A3 MHD with acute medication use, episodic migraine – Erenumab 70 mg



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

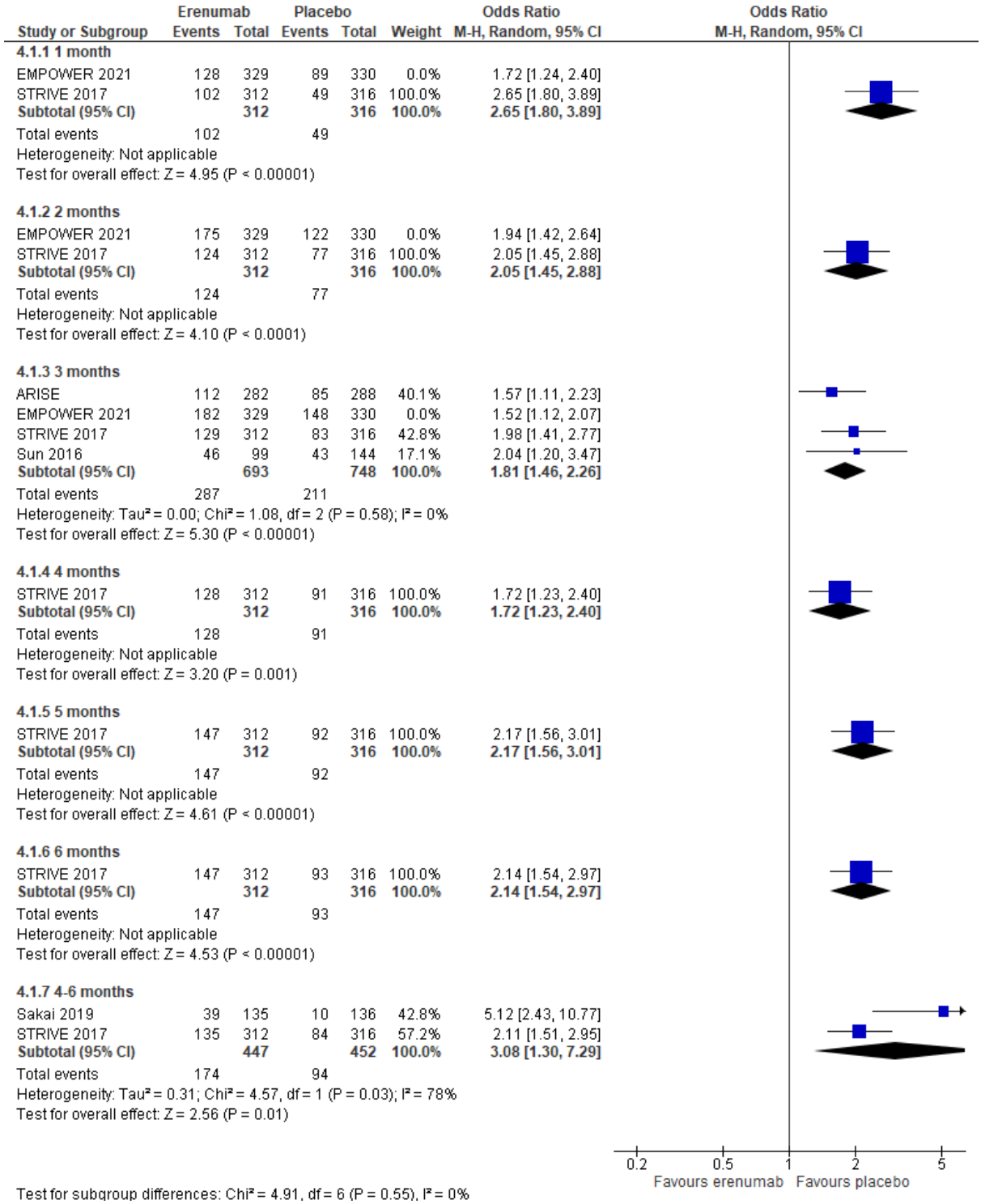
Figure A4 MHD with acute medication use, episodic migraine – Erenumab 140 mg



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

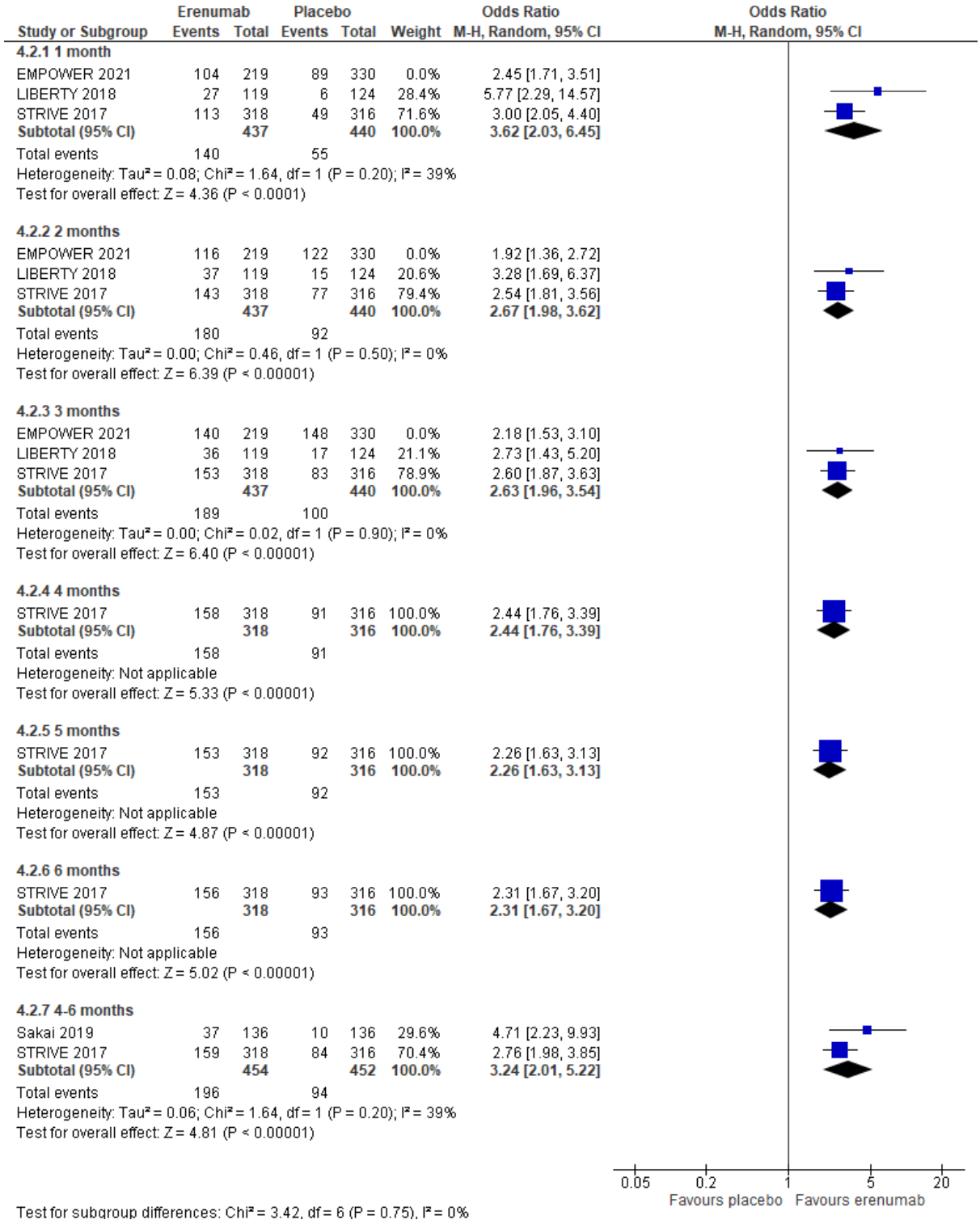
Figure A5 Response rate (>50%), episodic migraine – Erenumab 70 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

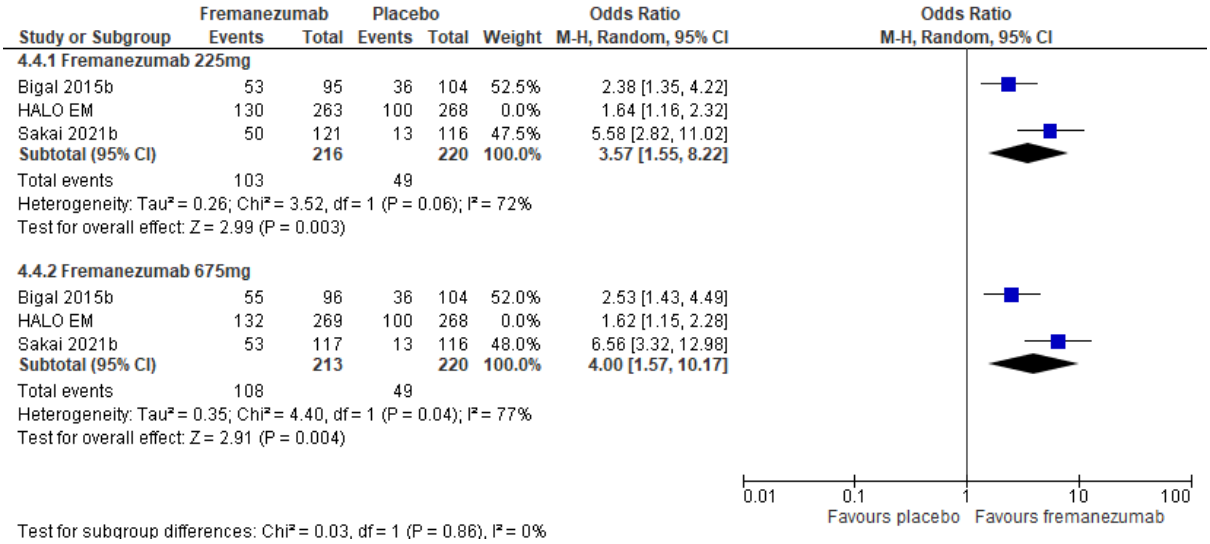
Figure A6 Response rate (>50%), episodic migraine – Erenumab 140 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

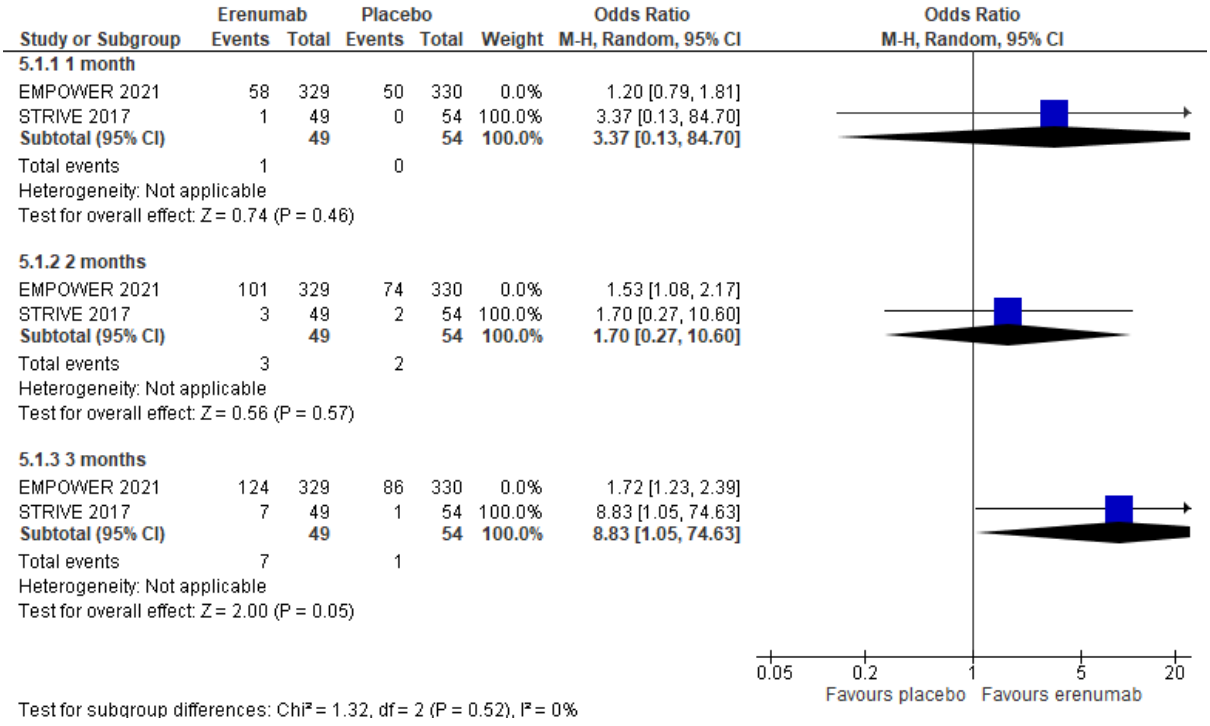
Figure A7 Response rate (>50%), episodic migraine – fremanezumab 225/675 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

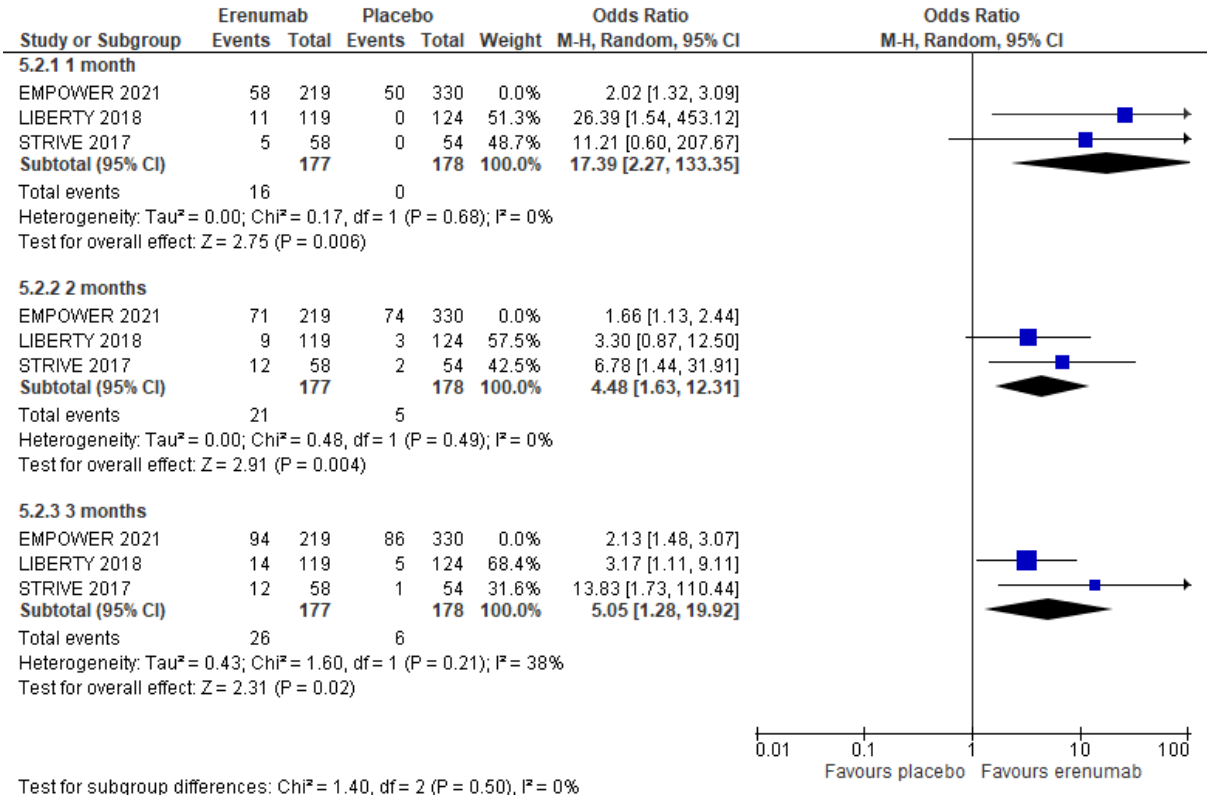
Figure A8 Response rate (>75%), episodic migraine - Erenumab 70 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

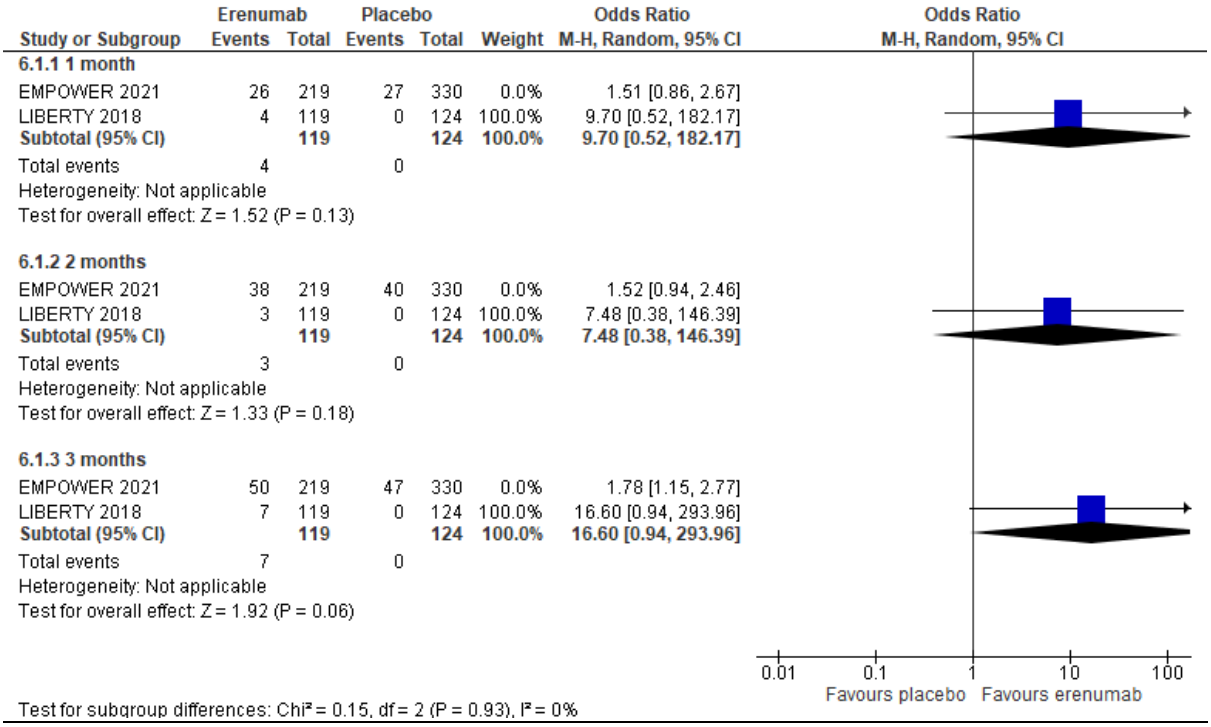
Figure A9 Response rate (>75%), episodic migraine – Erenumab 140 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

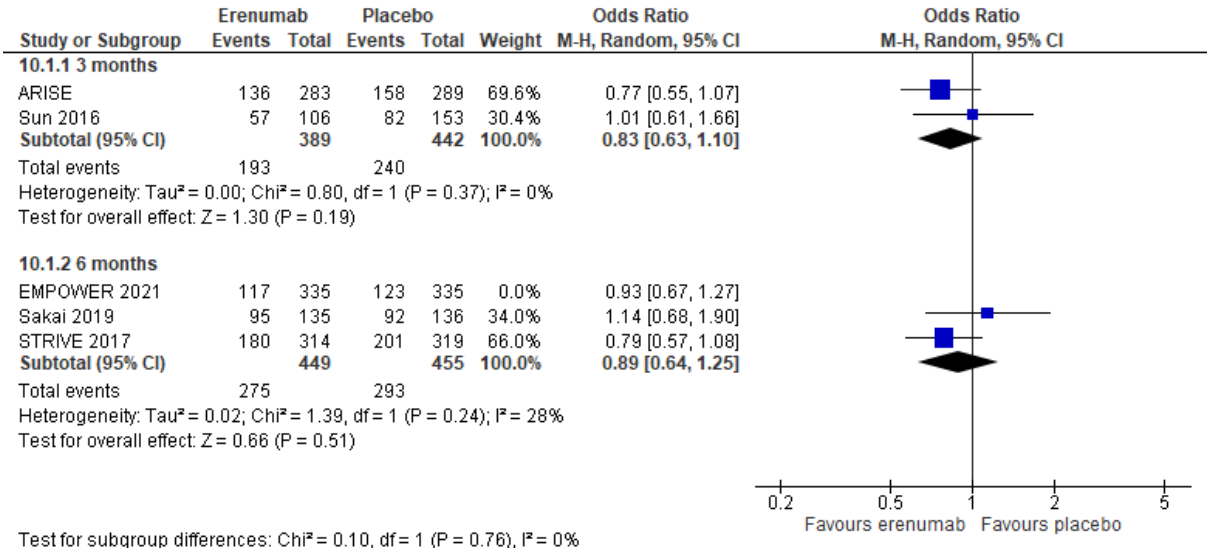
Figure A10 Response rate (100%), episodic migraine, erenumab 140 mg



Abbreviations

CI = confidence interval, **IV** = inverse variance, **SD** = standard deviation.

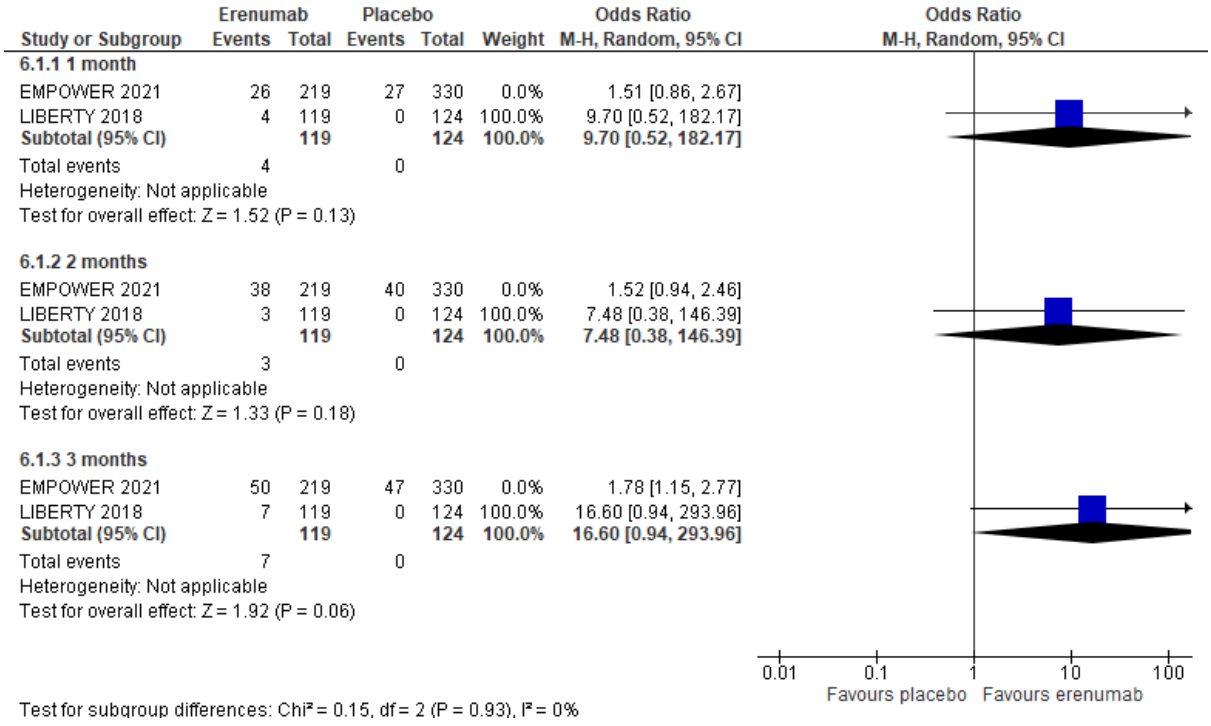
Figure A11 Adverse events, episodic migraine – Erenumab 70 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

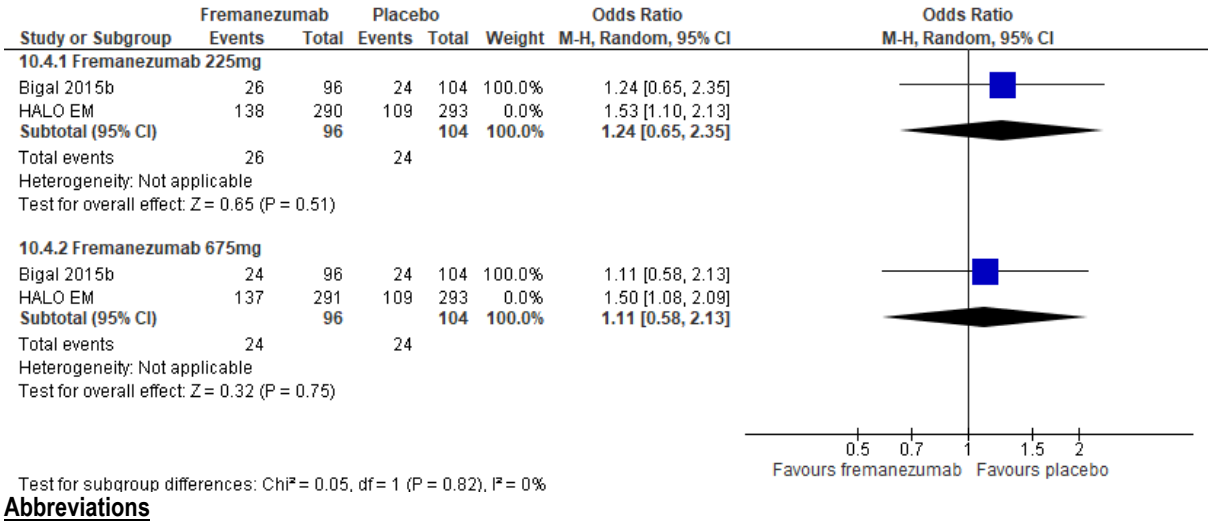
Figure A12 Adverse events, episodic migraine – Erenumab 140 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel

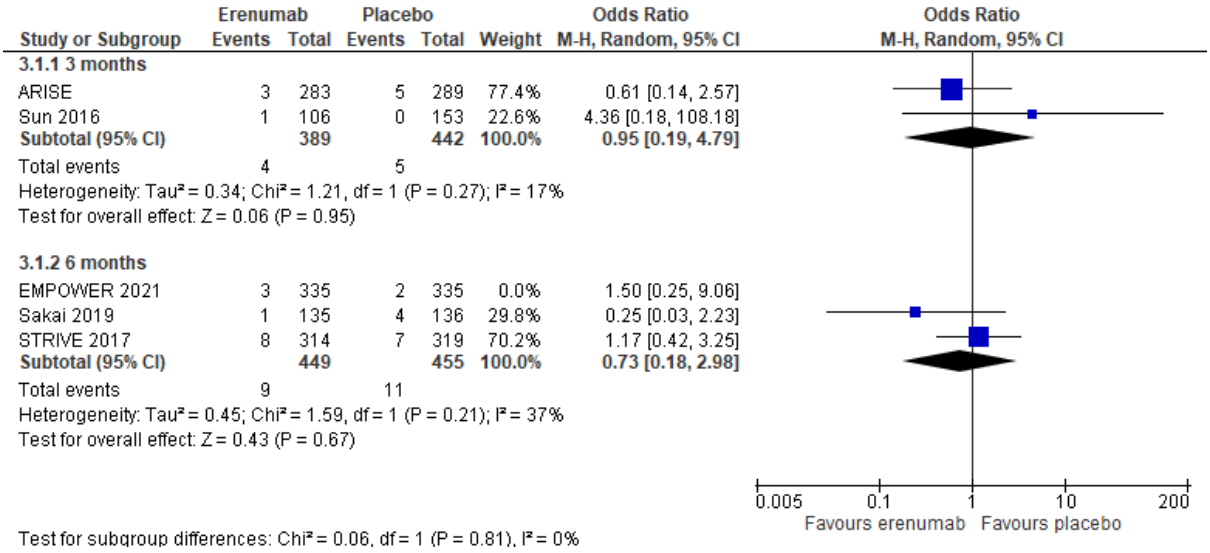
Figure A13 TRAEs, episodic migraine – Fremanezumab 225 mg and 675 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel

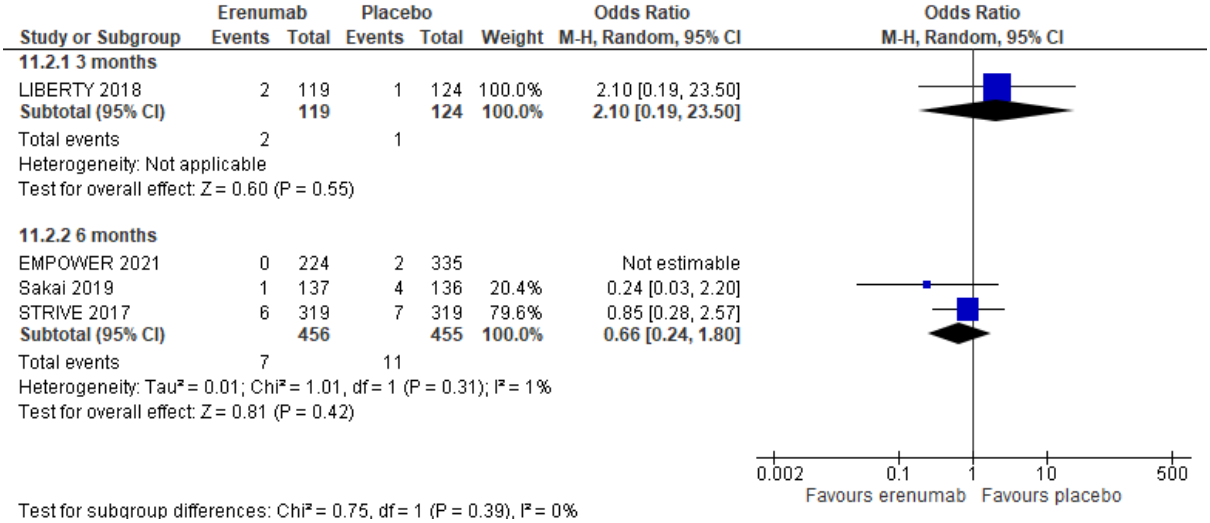
Figure A14 SAE, episodic migraine – Erenumab 70 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel

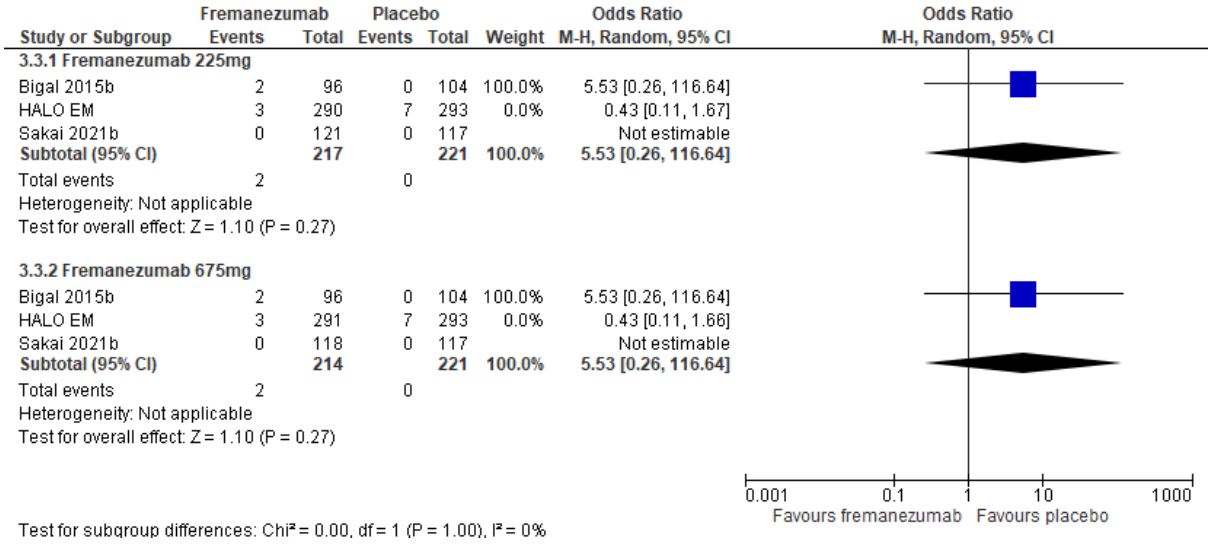
Figure A15 SAE, episodic migraine – Erenumab 140 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

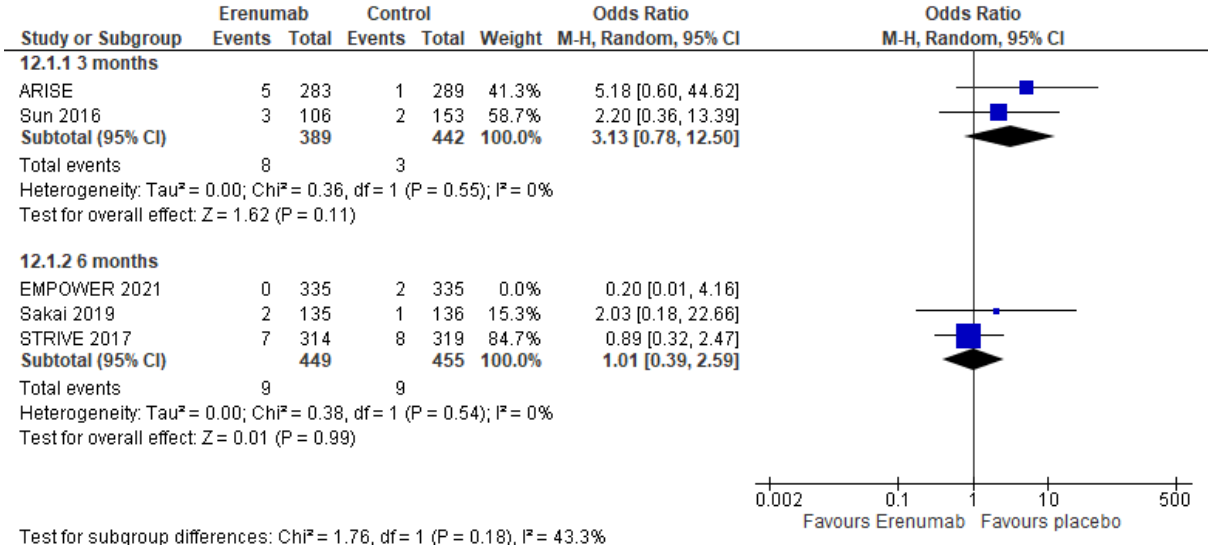
Figure A16 SAE, episodic migraine – Fremanezumab 225 mg and 675 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

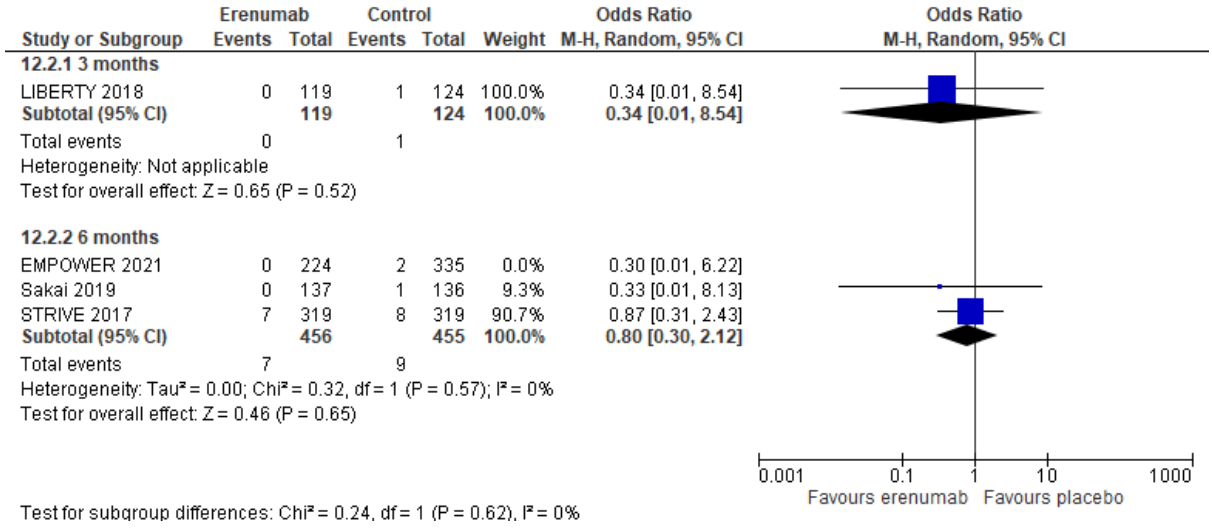
Figure A17 AEs leading to discontinuation, episodic migraine – Erenumab 70 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

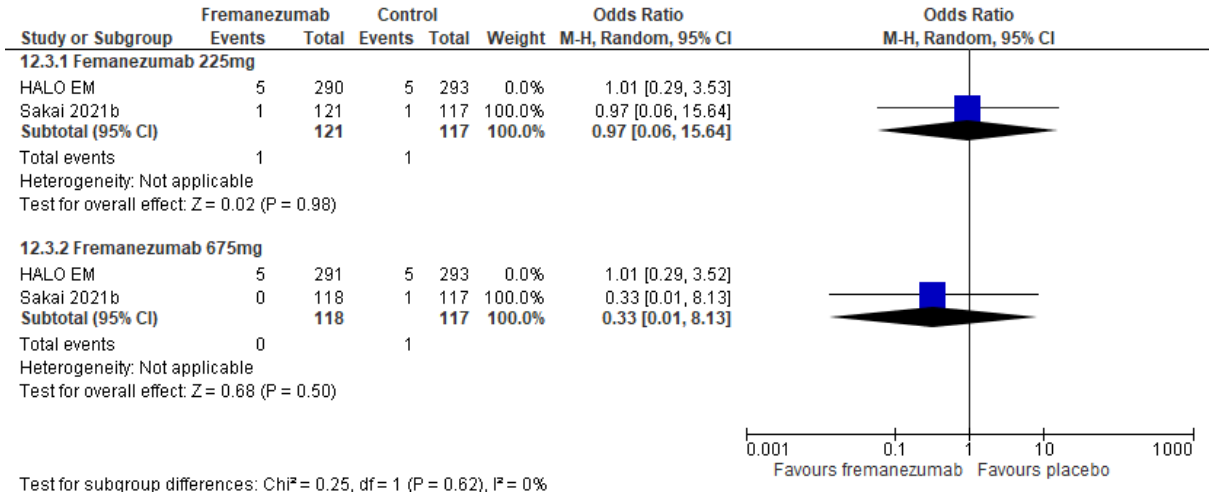
Figure A18 AEs leading to discontinuation, episodic migraine – Erenumab 140 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

Figure A19 AEs leading to discontinuation, episodic migraine – fremanezumab 225 mg and 675 mg



Abbreviations

CI = confidence interval, **M-H** = Mantel-Haenszel.

Appendix I: Economic evaluation study inclusion and exclusion overview

Table A77 Rationale for inclusion and exclusion

Study	Intervention	Comparator	Patient characteristics	Evaluation Outcome	Inclusion/Exclusion and Rationale
Included studies					
1. Mahon et al 2021[114]	-Erenumab	- standard of care	-At least 4 MMDs per month -Two or more previous preventive treatments failed	Cost per QALY gained	The cost-effectiveness study compared erenumab to BSC in the indicated population using costs per QALY gained as an outcome. It was included in our review.
2. Irimia et al 2021[115]	-Fremanezumab	-Erenumab -Galcanezumab -OnabotulinumtoxinA	-episodic migraine and/or CM -treatment duration of 12 weeks	Cost per patient	The costing study compared the cost of AEs for fremanezumab, with erenumab, galcanezumab, and onabotulinumtoxinA. It was included in our review.
3. Giannouchos et al 2019[116]	-Erenumab	-OnabotulinumtoxinA	Patients with CM	Cost per QALY gained	The cost-effectiveness study compared erenumab to onabotulinumtoxinA among chronic migraine patients using costs per QALY gained as an outcome. It was included in our review.
4. Porter et al 2019[117]	-Erenumab	-Placebo	-4–14 headache days, -≥ 15 days, of which ≥ 8 were migraine	Cost per migraine day	The costing study compared the cost of erenumab, with placebo. It was included in our review.
5. Sussman et al 2018[118]	-Erenumab	-OnabotulinumtoxinA -No preventive treatment	Adult, episodic and chronic migraine, failed preventive therapy	Cost per QALY gained	The cost-effectiveness study compared erenumab to onabotulinumtoxinA and no preventive treatment among episodic and chronic migraine patients using costs per QALY gained as an outcome. It was included in our review.
6. Lipton et al 2018[119]	-Erenumab	- standard of care -OnabotulinumtoxinA	episodic and chronic migraine, failed preventive therapy	Cost per QALY gained	The cost-effectiveness study compared erenumab to onabotulinumtoxinA and standard of care among episodic and chronic migraine patients using costs per QALY gained as an outcome. It was included in our review.

Study	Overview	Inclusion/Exclusion and Rationale
Excluded Studies		
7. Mahon et al 2020[120]	A systematic review was undertaken. 8 studies were included based on eligibility. They involved onabotulinumtoxinA and topiramate as interventions and are not included in our review (as below).	The study is presented in ***Table A78*** as background.

Study	Overview	Inclusion/Exclusion and Rationale
8. NICE 2012[121] and 9. Royle et al 2011[122]	Cost-utility analysis used a state-transition (Markov) model to estimate the cost-effectiveness of onabotulinumtoxinA vs placebo.	The studies involved a comparison of onabotulinumtoxinA vs placebo and was not included our review.
10. Batty et al 2013[123]	Cost-utility analysis used a state-transition (Markov) model to estimate the cost-effectiveness of onabotulinumtoxinA vs placebo.	The study involved a comparison of onabotulinumtoxinA vs placebo and was not included our review.
11. SMC 2017[124]	Cost-utility analysis used a state transition (Markov) model to estimate the cost-effectiveness of onabotulinumtoxinA injections given every 12 weeks vs standard of care.	The study involved a comparison of onabotulinumtoxinA vs standard of care and was not included our review.
12. SMC 2013 (cited in Mahon et al 2020)	Cost-utility analysis used a state transition (Markov) model to estimate the cost-effectiveness of onabotulinumtoxinA injections given every 12 weeks vs standard of care.	The study involved a comparison of onabotulinumtoxinA vs standard of care and was not included our review.
13. SMC 2017[125]	Cost-utility analysis used a state transition (Markov) model to estimate the cost-effectiveness of onabotulinumtoxinA injections given every 12 weeks vs standard of care.	The study involved a comparison of onabotulinumtoxinA vs standard of care and was not included our review.
14. SMC 2006 (cited in Mahon et al 2020) and 15. Brown et al 2006[126]	Cost-utility analysis used a decision-tree model to estimate the cost-effectiveness of topiramate vs no preventive treatment.	The studies involved a comparison of topiramate vs no treatment and was not included our review.
16. Ruggeri et al 2020[127]	A systematic review was undertaken. 11 studies were included based on eligibility. Three studies evaluated erenumab [Sussman,[118] Lipton,[119] Giannouchos[116]] and one study investigated GammaCore as a first-line treatment before administering erenumab [Mwambur[128]]. These studies are included in our review. The remaining six were excluded with five being detailed below. The review also included Batty et al 2013[123] which was excluded above.	The study is presented in ***Table A78*** as background.
17. Yu et al 2010[129]	Interventions included propranolol, timolol, divalproex sodium, amitriptyline, and topiramate.	The study did not include the relevant intervention and was excluded.
18. Hens et al 2014[130]	Early treatment with triptans economic study.	The study did not include the relevant intervention and was excluded.
19. Ruggeri 2014[131]	OnabotulinumtoxinA economic study.	The study did not include the relevant intervention and was excluded.
20. Hollier-Han et al 2020[132]	OnabotulinumtoxinA economic study.	The study did not include the relevant intervention and was excluded.
21. Shauly et al 2019[133]	Surgical decompression economic study.	The study did not include the relevant intervention and was excluded.
22. Amin et al 2021[134]	Cost and resource use study.	The study did not include the relevant intervention, however, provided helpful background about costs and resource use for migraine. It is presented in ***Table A78*** as other economic studies.
23. Badia et al 2012[135]	Cost and resource use study.	The study did not include the relevant intervention, however, provided helpful background about costs and resource use for migraine. It is presented in ***Table A78*** as other economic studies.
24. Chandler et al 2021[136]	Cost and resource use study.	The study did not include the relevant intervention,

Study	Overview	Inclusion/Exclusion and Rationale
		however, provided helpful background about costs and resource use for migraine. It is presented in ***Table A78*** as other economic studies.
25. Foster et al 2021[137]	Cost and resource use study.	The study did not include the relevant intervention, however, provided helpful background about costs and resource use for migraine. It is presented in ***Table A78*** as other economic studies.
26. McAllister et al 2021[138]	Cost and resource use study.	The study did not include the relevant intervention, however, provided helpful background about costs and resource use for migraine. It is presented in ***Table A78*** as other economic studies.
27. Pradalier et al 2004[139]	Cost and resource use study.	The study did not include the relevant intervention, however, provided helpful background about costs and resource use for migraine. It is presented in ***Table A78*** as other economic studies.
28. Di Tanna et al 2019[140]	Utility study.	The study did not include the relevant intervention, however, provided helpful background about utilities for migraine. It is presented in ***Table A78*** as other economic studies.
29. Matza et al 2019[141]	Utility study.	The study did not include the relevant intervention, however, provided helpful background about utilities for migraine. It is presented in ***Table A78*** as other economic studies.
30. Gerth et al 2001[142]	Burden of disease study.	The study did not include the relevant intervention, however, provided helpful background about migraine burden of disease. It is presented in ***Table A78*** as other economic studies.
31. Seddik et al 2021[143]	Burden of disease study.	The study did not include the relevant intervention, however, provided helpful background about migraine burden of disease. It is presented in ***Table A78*** as other economic studies.
32. Williams et al 2001[144]	Burden of disease study.	The study did not include the relevant intervention, however, provided helpful background about migraine burden of disease. It is presented in ***Table A78*** as other economic studies.
33. Akhtar et al 2019[145]	Review of clinical and economic evidence.	The study did not include the relevant intervention, however, provided helpful background about clinical and

Study	Overview	Inclusion/Exclusion and Rationale
		economic evidence. It is presented in ***Table A78*** as other economic studies.
HTA websites	HTA websites were searched, and results presented in ***Table A79***.	NICE and CADTH economic model reviews are presented in ***Table A80***. These HTA agency reviews were selected as they involved comprehensive review team assessments of Sponsor submitted economic models. Other HTA reviews were not as detailed.

Abbreviations:
AE = adverse event, **CADTH** = The Canadian Agency for Drugs and Technologies in Health, **HTA** = health technology assessment, **MMD** = monthly migraine days, **NICE** = National Institute for Clinical Excellence, **PSA** = probabilistic sensitivity analysis, **SMC** = Scottish Medicines Consortium, **QALY** = quality-adjusted life year.

Appendix J: Data extraction template for other relevant economic studies

Table A78 Data extraction template for other economic studies

Reviews

Study	Country	Study overview	Findings	Relevance for this study
Mahon et al 2020[120]	UK, Ireland	The authors undertook a systematic literature review of economic evaluations in migraine in the UK or Irish perspective. The review was conducted between July 2017 and September 2018. It covered pharmacological interventions for the treatment of chronic or episodic migraine, health state utility values for chronic or episodic migraine patients and cost and resource use data for chronic or episodic migraine patients. MEDLINE, MEDLINE Daily, MEDLINE In-Process, Epub Ahead of Print electronic databases and HTA agency websites were searched. The review was used to formulate their Mahon 2021[114] Markov model.	They identified 8 published economic evaluations and appraised their quality. They noted many studies were based on a similar core model and examined onabotulinumtoxinA vs placebo or standard of care in patients with chronic migraine. A state-transition (Markov) model was often employed and health states in the models varied from 6 health states based on headache days/month to 13 health states: 6 on-treatment, 6 off-treatment, and death (Batty[123]). EQ-5D utilities were typically mapped from MSQ and SF-36 data. Clinical trials were generally used for model parameters.	The authors developed a decision tree plus Markov structure for cost-effectiveness modelling of migraine therapies. Health state included patient distribution across MMD frequencies. The model had a response-based stopping rule, and benefits and costs were calculated using MMD frequency.
Ruggeri et al 2020[127]	Global	The authors reviewed economic evaluations involving prophylaxis and treatments for migraine published between 2009 and 2019. They searched PubMed, EMBASE and EconLit databases for trial-based non-experimental prospective studies or model-based economic evaluations.	A total of 227 articles were identified, and 11 studies were included based on eligibility. Three studies evaluated erenumab (Sussman,[118] Lipton,[119] Giannouchos[116]), and one study investigated GammaCore as a first-line treatment before administering erenumab (Mwamburi[128]).	The authors concluded that the review suggested that evidence on the economic value of acute or prophylactic migraine treatment was generalisable, but studies about prophylactic treatments were transferable.
Akhtar et al 2019[145]	Global	The authors reviewed the benefits and drawbacks of CGRP receptor blockers.	This was largely a review article of clinical evidence.	They noted double-blind placebo studies have demonstrated superior efficacy and minimal adverse effects and could be used in resource-limited countries. The high cost of these medications was suggested to be a major constraint in adoption in developing countries, despite the cost per QALY gained.

Costs and resource use

Study	Country	Study overview	Findings	Relevance for this study
Amin et al 2021[134]	USA	The study compared direct costs and HCRU for PMM-naïve patients and patients with up to 3 PMM category switches before initiating CGRP mAbs. The study was a retrospective analysis of the IBM MarketScan database, which included subjects who initiated injectable A CGRP mAbs between May 2018 and December 2019. They were assessed in 4 groups based on the number of prior non-CGRP PMM classes used during the 24-month pre-index period (e.g. 0,1,2,3). The comparison was made with and without propensity score matching.	A total of 23,288 patients were included with an average age of 45.4 (SD±12.0 years), 85.6% were females, and the mean Charlson Comorbidity Index was 0.69±1.2. The group with 3 prior non-CGRP PMM classes had the highest average annual unadjusted total healthcare costs per patient of (USD50,274±USD76,629); with the highest costs attributed to procedure/imaging-related expenses (USD20,105±USD36,401) and pharmacy (USD11,633±USD29,763). The group with no prior use had the lowest cost (USD25,288±USD41,427). Imaging and procedural, pharmacy and outpatient costs were major components of the total cost. Neurologists constituted approximately half total physician costs.	Results suggest total direct healthcare cost and HCRU increased significantly with increasing use of PMM classes; anti-epileptics were the most-often-used PMM class (48.9%), followed by beta blockers (32.5%), antidepressants (28.1%) and onabotulinumtoxinA (27.3%). In the clinical evidence base, the identification of the subgroups who have used non-CGRP PMM classes prior to treatment will be important as clinical response and costs are likely to be different for PMM-naïve patients.
Badia et al 2012[135]	Spain	The authors estimated national migraine costs in Spain using annual direct (pharmacy, primary care, specialist and emergency room visits) and indirect (missed workdays and reduced work performance) costs calculated using estimates of prevalence and 2001 Spanish unit costs. The study included a systematic review to attain prevalence estimates, unit costs from a Spanish healthcare costs database in 2001 values and IMS Health tracking information for medicines costs.	The national population with migraine was estimated to be 3.6 million with more than 92% being working age. Migraine was estimated to cost EUR1,076 million, with direct costs accounting for 32% of costs (EUR344 million), 39% for primary care, 29% for specialist visits, 21% for emergency treatment and 12% for drugs. Of the medicines costs, serotonin 5-HT1B/1D receptor agonists (triptans) accounted for 11% and ergots 1%. Pharmacy, primary, specialist and emergency care costs were specified at EUR23, EUR78, EUR57 and EUR41 per patient. The indirect cost was estimated at EUR732 million per year.	The model will need to include DRG, emergency and outpatient costs given the significance of primary, specialist and emergency care costs.
Chandler et al 2021[136]	USA	The authors undertook a retrospective review of US data using the IBM MarketScan Early View Databases until May 2019. They included adult patients newly treated with erenumab with a migraine claim in the year prior to first erenumab claim (index) and at least 1 year of continuous pre-index medical and pharmacy insurance coverage. This approach was used to assess pre- and post-erenumab migraine characteristics, comorbidities, healthcare resource utilisation and associated costs.	The study included 9,753 patients with an average age of 46 (SD 12) years; 85% of patients were female, and 64% had at least one claim for chronic migraine. Most (70%) erenumab patients had a starting dose of 70 mg; 77% of patients in the 6-month follow-up sample (n=4437) remained on their initial erenumab dose. Persistence at 6-month follow-up was 47.3% with a mean (95% CI) proportion of days covered of 0.68 (0.67, 0.68). The authors indicated that claims for non-migraine headaches and anxiety were reduced in the post-erenumab period, and there was a shift to decreased use of acute and preventive medications. Inpatient hospitalisation	This real-world evidence provides background data about dosing, persistence at 6-month and reductions in claims for comorbidities, and decreased use of acute and preventive migraine medications. Hospitalisation and outpatient office visits remained similar pre- and post-erenumab use.

Study	Country	Study overview	Findings	Relevance for this study
			and outpatient office visits changes were minimal.	
Foster et al 2021[137]	USA	The authors compared direct cost and HCRU among PMM-naïve patients and patients with up to 3 PMM categories before initiating CGRP mAbs between May 2018 and December. They were assessed in 4 groups based on the number of prior non-CGRP PMM classes (0,1,2,3). The comparison was made with and without propensity score matching.	A total of 23,288 patients were included with an average age of 45.4; 86% were female, and the mean Charlson Comorbidity Index was 0.69. Similar cost results were reported as per Amin et al 2021.[134]	Total direct healthcare cost and HCRU increased significantly with increasing use of PMM classes. Similar conclusions can be drawn as per Amin et al 2021.[134]
McAllister et al 2021[138]	USA	The authors examined HCRU and direct medical costs before and after fremanezumab treatment initiation using a retrospective, observational cohort study design. Data were sourced from September 2018 through June 2020 using the Midwest component of EMRClaims+®, an integrated health services database covering national commercial insurance claims, Medicare claims and regional electronic medical records. Patients included in the cohort analysis were age ≥18 years and were administered fremanezumab. Patient-reported headache frequency, migraine pain intensity, composite migraine symptoms and HCRU were assessed pre-index and ≥1 month after fremanezumab initiation.	A total of 172 patients were eligible and of those who self-reported (n=129), around 84% reported improvement in headache frequency or symptoms after fremanezumab treatment. Headache frequency decreased by 63%, which reflects headache frequency being 22.24 (9.29) days per month pre-index versus 8.24 (7.42) days per month post-index (P<0.0001). Average migraine pain intensity decreased by 18%, from 5.47 (3.19) pre-index versus 4.51 (3.34) post-index (P=0.014). Average emergency room (ER) visits per month decreased from 0.72 to 0.54 (P=0.003), and mean outpatient visits per month decreased from 1.04 to 0.81 (P<0.001). Mean hospitalisations per month decreased, but the results did not reach statistical significance (P=0.095). Hospitalisation and ER costs decreased, while outpatient costs increased, from pre-index to post-index; however, this was not statistically significant (P≥0.232).	The real-world evidence indicates significant reductions in headache frequency, migraine pain intensity and HCRU were observed after fremanezumab initiation in patients with migraine in the USA. This suggests clinical trial results are generalisable in practice.
Pradalier et al 2004[139]	France	The authors calculated national migraine costs in France from a general population sample of 10,585 individuals aged ≥15 years in 1999. The survey found 1,486 people experiencing headaches, who were interviewed about healthcare resource consumption in the previous 6 months. Unit costs were applied to use data for physician consultations, hospitalisation, medication use and diagnostic/laboratory tests and were evaluated from a healthcare system perspective.	A prevalence of migraine of 17% was found, and total annual direct healthcare costs were estimated to be EUR128 per individual with migraine in 1999, corresponding to EUR1,044 million when extrapolated to all individuals experiencing migraine and aged ≥15 years.	The authors concluded the direct healthcare costs of migraine have not increased significantly over the past decade, and small number of patients with more severe headaches accounted for most healthcare resources devoted to migraine. Prevalence estimates may be of value for budget impact scenarios.

Utilities

Study	Country	Study overview	Findings	Relevance for this study
Di Tanna et al 2019[140]	Global	The study mapped patient-reported outcomes from erenumab clinical studies (episodic migraine [NCT02456740 and NCT02483585] and chronic migraine [NCT02066415]) to the EQ-5D as a function of the MSQ and HIT-6™ using published algorithms.	A linear mixed-effects model with REML, a fractional response model with logit link, a fractional response model with probit link and a beta regression model were used to explain utility values as a function of MMDs. They had similar fit, and mapped utility values for patients treated with erenumab were generally greater than patients treated with placebo with similar MMDs. The beta regression model was the preferred option due to flexibility and previous use to model QALYs.	The study provides models for mapping patient utility values to MMDs. The beta regression model was preferred.
Matza et al 2019[141]	UK	The authors interviewed 400 UK participants (200 general population, 49% female, average age of 43.6 years; and 200 migraine patients, 74.5% female, average age of 45.8 years) using time trade-off interviews. They valued health state vignettes drafted based on literature, medication labels and clinician interviews. Eight health states that were randomly selected from a total of 15 were also included.	Average utilities of health states without aura were 0.79 with daily oral medication, 0.78 with one injection per month, and 0.72 with 31–39 injections once every 3 months. AEs associated with oral medications had the highest disutilities. They included −0.060 for fatigue and −0.098 for brain fog.	Utilities could be used in cost-utility models.

Other

Study	Country	Study overview	Findings	Relevance for this study
Gerth et al 2001[142]	Global	The authors estimated productivity losses. They used the MBQ which was self-administered by patients at a screening visit for 3 phase III clinical trials of rizatriptan. A total of 2670 persons (54.7% Europe, 16.5% Latin America, 23.1% North America, 5.5% other countries) completed the MBQ.	An average migraine attack frequency of 3.67 per month was reported, with 2.78 doctor visits, 0.53 emergency room visits and 0.06 hospitalisations related to migraine per year. Patients self-reported being only 46% effective while on the job with migraine symptoms.	The study provides average health service usage for this average migraine attack frequency.
Seddik et al 2021[143]	Germany	The authors simulated the incremental benefits of erenumab against the standard of care in Germany. The study included response rates, transition probabilities and discontinuation rates,	The study indicated erenumab could lead to a reduction of 166 million migraine days annually and reduce productivity losses in the range of 27 billion.	The DRGs used in Germany could be applicable to the Swiss context. The study does not report ICERs or cost per patient, so is not included in the main economic study

		and productivity estimates were derived from the erenumab clinical trial program. Five acute treatment combinations against migraine were included, selected in line with evidence-based recommendations. Costs per hospitalisation were derived from the DRG's online tool (B77Z) on reimbursement information. Transition probabilities derived from 4 clinical trials (NCT02456740, NCT02066415, NCT03096834 and NCT02483585).		data extraction.
Williams et al 2001[144]	UK	The authors developed a decision analytic model for stepped care or a stratified care regimen. A health service payer perspective was adopted, and the time horizon was 1 year. UK NHS costs were used.	Stratified care (which included zolmitriptan as the representative of high-end therapy) was estimated to be cost-effective.	Stratified care could be examined in scenario analysis.

Abbreviations

AE = adverse event, **CGRP** = calcitonin gene-related peptide, **DRG** = diagnosis-related group**, ER** = emergency room, **EQ-5D** = EuroQol-5D, **EUR** = euro, **HCRU** = healthcare resource utilisation, **HIT-6** = Headache Impact Test**, HTA** = health technology assessment, **ICERs** = incremental cost-effectiveness ratios, **mAbs** = monoclonal antibodies, **MBQ** = Migraine Background Questionnaire, **MMD** = monthly migraine days, **MSQ** = Migraine-Specific Quality of Life Questionnaire 2.1, **NHS** = National Health Service, **PMM** = preventive migraine medication, **QALY** = quality-adjusted life year, **QoL** = quality of life, **REML** = restricted maximum likelihood, **SD** = standard deviation, **SF-36** = 36-Item Short Form Health Survey, **UK** = United Kingdom, **USA** = United States of America, **USD** = United States dollar, **95% CI** = 95% confidence interval.

Appendix K: Economic evaluation search of HTA agency websites

Table A79 HTA agency relevant study search

Australia	HTA Websites	Search Terms: Erenumab or Fremanezumab or Galcanezumab or Eptinezumab
Adelaide Health Technology Assessment	https://www.adelaide.edu.au/ahta/pubs/	Nil
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips	Nil
Austria		
Austrian Institute for Health Technology Assessment	https://aihta.at/page/homepage/en	Nil
Gesundheit Österreich GmbH	http://www.goeg.at	Nil
Argentina		
Institute for Clinical Effectiveness and Health Policy	http://www.iecs.org.ar	Donato M, Augustovski F, Pichon-Riviere A, García Martí S, Alcaraz A, Bardach A, Ciapponi A. Erenumab en prevención de migraña. Documentos de Evaluación de Tecnologías Sanitarias, Informe de Respuesta Rápida Nº 721, Buenos Aires, Argentina. Junio 2019. ISSN 1668-2793. Disponible en www.iecs.org.ar.
Belgium		
Belgian Health Care Knowledge Centre	http://kce.fgov.be	Nil
Brazil		
National Committee for Technology Incorporation	http://conitec.gov.br/en/	Nil
Agência Nacional de Saúde Suplementar/ National Regulatory Agency for Private Health Insurance and Plans	https://www.gov.br/ans/pt-br	Consultas Públicas cp81 medicamentos RE_209_Erenumabe_Enxaqueca.pdf

Canada		
Institute of Health Economics	http://www.ihe.ca	Nil
Institut National d'Excellence en Santé et en Services	https://www.inesss.qc.ca/en/home.html	• https://www.inesss.qc.ca/thematiques/medicaments/medicaments-evaluation-aux-fins-dinscription/extrait-davis-au-ministre/ajovy-5368.html • https://www.inesss.qc.ca/en/themes/medicaments/drug-products-undergoing-evaluation-and-evaluated/extract-notice-to-the-minister/emgality-5901.html • https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Mars_2021/20210301_AvisMinistre.pdf • https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Mars_2021/20210301_AvisMinistre.pdf
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/	• https://www.cadth.ca/erenumab • https://www.cadth.ca/fremanezumab • https://www.cadth.ca/galcanezumab • https://www.cadth.ca/eptinezumab
Ontario Health	https://www.ontariohealth.ca/	Nil
Colombia		
Instituto de Evaluación Tecnológica en Salud	http://www.iets.org.co	Nil
Denmark		
Social & Health Services and Labour Market	http://www.defactum.net	Nil
Finland		
Finnish Coordinating Center for Health Technology Assessment	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx	Nil
France		
French National Authority for Health (Haute Autorité de Santé;)	http://www.has-sante.fr/	Nil

Assistance Publique – Hôpitaux de Paris	http://cedit.aphp.fr	Nil
Germany		
Institute for Quality and Efficiency in Health Care	http://www.iqwig.de	• https://www.iqwig.de/download/a18-71_erenumab_extract-of-dossier-assessment_v1-0.pdf • https://www.iqwig.de/download/a19-44_fremanezumab_nutzenbewertung-35a-sgb-v_v1-0.pdf • https://www.iqwig.de/download/a19-44_fremanezumab_extract-of-dossier-assessment_v1-0.pdf • https://www.iqwig.de/download/a19-28_galcanezumab_nutzenbewertung-35a-sgb-v_v1-0.pdf
Federal Joint Committee (Gemeinsamer Bundesausschuss)	https://www.g-ba.de/english/	• https://www.g-ba.de/beschluesse/5066/ • https://www.g-ba.de/beschluesse/4016/ • https://www.g-ba.de/beschluesse/3957/
Ireland		
Health Information and Quality Authority	http://www.hiqa.ie	Nil
Italy		
Agenzia Sanitaria e Sociale Regionale	http://www.inahta.org/members/assr/	Nil
HTA Unit in A. Gemelli Teaching Hospital	https://www.policlinicogemelli.it/	Nil
National Agency for Regional Health services	http://www.agenas.it	Nil
Kazakhstan		
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development	http://www.rcrz.kz	Nil
Korea		
National Evidence-based healthcare Collaborating Agency	www.neca.re.kr/eng	Nil

Malaysia		
Health Technology Assessment Section, Ministry of Health Malaysia	http://www.moh.gov.my	Nil
The Netherlands		
The Netherlands Organisation for Health Research and Development	http://www.zonmw.nl	Nil
Zorginstituut Nederland	https://www.zorginstituutnederland.nl/	Advise in Dutch
Norway		
The Norwegian Institute of Public Health	http://www.fhi.no/	Nil
Peru		
Institute of Health Technology Assessment and Research	http://www.essalud.gob.pe/ietsi/	Nil
Poland		
Agency for Health Technology Assessment and Tariff System	http://www.aotm.gov.pl	Nil
Republic of China, Taiwan		
Center for Drug Evaluation	http://www.cde.org.tw	Nil
Russian Federation		
Center for Healthcare Quality Assessment and Control	www.rosmedex.ru	Nil
Singapore		
Agency for Care Effectiveness	ace-hta.gov.sg	Nil
Spain		
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I / Health Technology Assessment Agency	http://publicaciones.isciii.es/	Nil

Agency for Health Quality and Assessment of Catalonia	http://aquas.gencat.cat	Nil
Andalusian HTA Agency	http://www.aetsa.org/	Nil
Basque Office for Health Technology Assessment	http://www.euskadi.eus/web01-a2ikeost/en/	Nil
Galician Agency for Health Technology Assessment	http://acis.sergas.es	Nil
Health Sciences Institute in Aragon	http://www.iacs.es/	Nil
Sweden		
Swedish Council on Technology Assessment in Health Care	http://www.sbu.se/en/	Nil
Switzerland		
Swiss Federal Office of Public Health	http://www.bag.admin.ch/hta	HTA-Protokoll, 29/7/2022
Tunisia		
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr	Nil
United Kingdom		
Healthcare Improvement Scotland	http://www.healthcareimprovementscotland.org	Nil
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/	Eptinezumab for preventing migraine [ID3803] https://www.nice.org.uk/guidance/indevelopment/gid-ta10677 Galcanezumab for preventing migraine [ID1372] https://www.nice.org.uk/guidance/ta659/evidence/committee-papers-pdf-8902011421 Fremanezumab for preventing migraine, Technology appraisal guidance [TA764] https://www.nice.org.uk/guidance/ta764/evidence/committee-papers-ta764-pdf-10952875693 Erenumab for preventing migraine, Technology appraisal guidance [TA682]

		https://www.nice.org.uk/guidance/ta682/evidence/appraisal-consultation-committee-papers-pdf-9021642589 https://www.nice.org.uk/guidance/ta682/evidence/final-appraisal-determination-2-committee-papers-pdf-9021642591 https://www.nice.org.uk/guidance/ta682/evidence/final-appraisal-determination-committee-papers-pdf-9021642590
Health Technology Wales	http://www.healthtechnology.wales	Nil
National Institute for Health Research	http://www.nets.nihr.ac.uk/programmes/hta	Nil
United States		
Agency for Healthcare Research and Quality	https://www.ahrq.gov/research/findings/index.html	Systematic Review on Acute Treatments for Episodic Migraine: Surveillance Report 1 and 2 https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/episodic-migraine-surveillance-report-1.pdf https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/episodic-migraine-surveillance-report-2.pdf
Uruguay		
Health Assessment Division, Ministry of Public Health	http://www.msp.gub.uy	Nil

Abbreviations:
CADTH = Canadian Agency for Drugs and Technologies in Health, **HTA** = health technology assessment, **NICE** = UK National Institute for Clinical Excellence.

Appendix L: Data extraction template for HTA agency economic studies

Table A80 Data extraction template for HTA agency economic studies

Reviews

Country; Agency	Medicine	Study Overview	Findings	Relevance for this study
Canadian Agency for Drugs and Technologies in Health (CADTH)	Erenumab.[146] The Sponsor sought a price of CAD532 per 70 mg or 140 mg autoinjector, with annual cost of CAD6,384 per patient.	The Sponsor submitted a model which included a base case intervention for adult patients who have at least 4 migraine days per month and reimbursement request analysis for adult patients who have at least 8 migraine days per month and who have previously failed at least 2 migraine preventive therapies. The comparator was best supportive care, which included treatment with acute medications and medical management involving GP and emergency department visits. Both populations were stratified for episodic migraine and chronic migraine sufferers, with episodic migraine being less than 15 monthly headache days, of which four to 15 are MMDs, and for chronic migraine sufferers, 15 or more monthly headache days, of which eight or more are MMDs. The base case analysis assumed 46% and 54% of patients suffered episodic and chronic migraine (derived from the CHORD study) and 68% and 32% had episodic and chronic migraine in the reimbursement request analysis. The model starting population was 82.8% female, and had a mean age of 42 years, which was derived from the STRIVE clinical trial. In addition to standard of care, erenumab 140 mg was compared with onabotulinumtoxinA in a scenario analysis for chronic migraine patients. Costs were calculated using the numbers of MMDs and analyses took the perspective of the Canadian publicly funded health care payer over 5-years. A discount rate of 1.5% per annum was included. A linear regression was used to estimate acute medications (triptans and analgesics) costs based on numbers of MMDs. No AE costs were estimated due to assumed similar safety on each arm of the model. Utility values were also a function of MMDs, derived from Migraine-Specific Quality of Life Questionnaire (MSQ) data collected from Tepper et al 2017 and STRIVE mapped to	The base-case analysis generated an ICUR of CAD89,773 for erenumab 70 mg verse standard of care and CAD84,204 for erenumab 140 mg. CADTH revised the base case, in the episodic migraine population, and 140 mg had an ICUR of CAD153,635, whereas 70 mg was extendedly dominated. A price reduction of 64% was required for 140 mg in the base analysis to attain a WTP threshold of CAD50,000 per QALY. CADTH indicated the Sponsors analysis had several limitations. These included, all relevant comparators were not covered, the model did not reflect the natural history of migraine (e.g., improvements or worsening in the natural course) and impact of migraine severity was not considered. Trial data was noted as being limited to 24 weeks for STRIVE; and 12 weeks for LIBERTY and Tepper et al 2017. These lengths of follow-up were highlighted as limiting confidence in longer-term projections.	The model analysis needs to consider the trial period (24 weeks for STRIVE; and 12 weeks for LIBERTY and Tepper et al 2017) and longer-term efficacy. ICURs will be presented for a trial (12 or 24 weeks), time horizon as part of sensitivity analyses. Efficacy should be based on the most up-to-date data, such as discontinuation rates from the open label extension Study 178. Scenarios will be included for differing natural histories. Care needs to be taken if trial data is pooled. CADTH noted trial populations were not homogenous and no adjustment was made to account for differences in

Country; Agency	Medicine	Study Overview	Findings	Relevance for this study
		EQ-5D. Like the published Mahon et al 2021[114] model, the Sponsor model included a decision tree for patient response to treatment during a 12-week assessment, then a Markov model to assess long-term treatment costs and benefits. Erenumab versus standard of care efficacy was derived from clinical trials for chronic migraine (Tepper et al 2017) and episodic migraine (STRIVE and LIBERTY) patients. Mortality was based on general population mortality which was similar for both arms of the model.		sample sizes or baseline characteristics.
	Fremanezumab.[147] The Sponsor submitted price was CAD585, or an annual cost of CAD7,020 per patient.	The Sponsor undertook a cost-utility analysis to assess fremanezumab for patients with episodic and chronic migraine patients stratified by the number of prior preventive migraine therapies. The base-case analyses compared fremanezumab with erenumab, galcanezumab, and standard of care. standard of care included acute migraine-specific and nonspecific treatments. OnabotulinumtoxinA was included as a comparator for chronic migraine patients and three oral preventive migraine therapies (amitriptyline, propranolol, topiramate) were considered as comparators in scenario analyses. Baseline MMDs for chronic migraine were 17.3 and 9.3 migraine days for EM. A baseline prevalence of 91% and 9% for episodic and chronic migraine was assumed using the CaMEO study in the USA. The model had a 10-year horizon and took the perspective of the public health care payer. A discount rate of 1.5% per year was used and the model cycle length was 28 days. A 3-state Markov model was developed which included preventive migraine treatments (On-Treatment, Off-Treatment) or death. Patients started in the On-Treatment state, and a proportion of patients discontinued each cycle. Patients in the Off-Treatment state received standard of care. The rate of discontinuation for fremanezumab and galcanezumab was assumed to be equal to that for erenumab. Apart from discontinuation, the key measure of efficacy was the reduction in the number of MMDs relative to standard of care. Utility values were derived from the Migraine-Specific Quality of Life (MSQ) questionnaire estimates from the FOCUS trial, mapped to the EuroQol 5-Dimensions (EQ-5D). Health care resource utilization was based on the number of MMDs.	The sponsor estimated ICUR for episodic migraine (2 prior preventive therapies) was CAD138,122 per QALY gained compared with standard of care, and chronic migraine (≥ 2 prior preventive therapies) CAD102,184 per QALY gained. Several limitations were identified by CADTH in the submission which included there was no head-to-head evidence comparing fremanezumab with other preventive migraine therapies. The sponsor used a network meta-analysis comparing fremanezumab, erenumab, galcanezumab, and onabotulinumtoxinA . Reductions in migraine severity and/or frequency were not considered, and patients who discontinue fremanezumab did not avail other preventive migraine treatments. Long term efficacy was not supported by evidence. The clinical effects of fremanezumab over a maximum follow-up of 12-week trials were sustained for 10 years. Health care resource use was based on utilization data from the USA and may not be applicable to migraine management in Canada.	The clinical effectiveness of fremanezumab relative to other currently reimbursed migraine preventive therapies is uncertain, due to a lack of direct comparative evidence. This issue may be evident in our economic modelling, dependant on the clinical evidence. The effects of treatment on migraine severity and adverse events related to treatment were not considered. They will be included in sensitivity analyses. As above, ICURS will be presented for a range of time horizons as part of sensitivity analyses (12-week trial, to lifetime).

Country; Agency	Medicine	Study Overview	Findings	Relevance for this study
	Galcanezumab.[148] The Sponsor sought CAD623 per 120 mg, or annual cost of CAD8,099 per patient in the first year, and CAD7,476 per patient thereafter.	The Sponsor submitted a reimbursement request for prevention of migraine in adults with at least 4 migraine days per month and who had failed at least 2 prophylactic migraine medications. The model compared prophylactic galcanezumab to standard of care among episodic and chronic migraine patients standard of care efficacy was based on the placebo group of the CONQUER trial and involved acute medication (triptans, nonsteroidal anti-inflammatory drugs, and acetaminophen or acetaminophen combinations, with some restrictions on opioids and barbiturates). The analyses used a 20-year time horizon and took a publicly funded health care payer perspective. A discount rate of 1.5% per year, and model cycle length of 30 days were employed. The Markov model had 4 health states (on treatment, off treatment due to nonresponse, off treatment due to AEs, and death). Patients started with medicines initiation and were assessed for response after 3 months. Responders were specified as having a 50% or greater reduction in MHDs from baseline for episodic migraine patients, or a 30% or greater reduction from baseline for chronic migraine patients. Death could occur in any health state, and data sourced from Canadian statistics was used for general population mortality rates. Utility values were also determined by MHDs and derived from MSQ estimates reported in the CONQUER trial. They were mapped to the EQ-5D. Utilities were also estimated by treatment group. Adverse events were not explicitly modelled. Resource use was also driven by MHDs per cycle.	Galcanezumab had an estimated ICUR of CAD39,010 per QALY gained among episodic migraine and 99.7% of iterations were cost-effective at a willingness-to-pay threshold of CAD50,000 per QALY. An ICUR of CAD16,594 per QALY gained was estimated for chronic migraine patients. CADTH noted the modelled population was only a subset of the indicated population in Canada. Other limitations included no head-to-head evidence being available that compared galcanezumab to active preventive therapies. Like other submissions, patients who discontinue galcanezumab or stop responding to standard of care were assumed to receive standard of care (acute migraine treatment) only, with no additional preventive therapy. These patients may receive another anti-CGRP, onabotulinumtoxinA, or oral treatment (e.g., propranolol, amitriptyline, or topiramate). Responders after 12 weeks of treatment were assumed to maintain their improved frequency of MHDs for the remainder of their time on treatment, up to the analysis time horizon. In contrast, standard of care patients who responded were assumed to sustain baseline for a year. The use of treatment-specific utilities was considered inappropriate as differences	No treatment effect will be included in health state utilities. Sensitivity analysis will be conducted around utility values and discussion of migraine severity will be included. The applicability of United States health utilisation data to the Swiss context will be discussed.

Country; Agency	Medicine	Study Overview	Findings	Relevance for this study
			in clinical effects and costs should be reflected in the model health states. Migraine severity was not captured in the model. Health care resource utilisation was taken from United States data in Lipton. This may not reflect Canadian migraine management.	
NICE	Erenumab.[149] Erenumab 70 mg or 140 mg administered every 4 weeks, subcutaneously.	The model submitted in the UK was similar to that assessed by CADTH. CADTH noted the structure included a decision tree for the 12-week assessment period (classifying patients as responders or non-responders), then Markov model with 12-week cycle lengths. Erenumab was compared to standard of care in EM, and onabotulinumtoxinA and standard of care in CM. Resource use was driven by MMDs and no AE costs were included. The treatment effect remained stable A while on treatment. Differences between the UK and Canadian models included the population which assumed adults with ≥ 3 prior failed treatments, and analyses were conducted for the whole migraine population, along with episodic and chronic migraine sub-populations. A time horizon of 10 years was used and 50:50 blended dose of erenumab 70 mg and erenumab 140 mg used for the intervention. Results of the ARISE trial, Tepper et al 2017, and STRIVE were used to map MSQ to EQ-5D using the Gillard algorithm. No AE disutility was applied. The NICE review recommended erenumab for preventing migraine in adults who experience 4 or more migraine days per month and at least 3 preventive drug treatments have failed.	The Sponsor base case for the whole population (episodic and chronic migraine) had an ICUR GBP22,309 per QALY gained verse standard of care. Some of the NICE review team noted limitations included that a sequential rather than pairwise analysis should be provided, episodic and chronic migraine should be considered separately to align with trials and ensure all with ≥ 4 MMDs were covered, two erenumab doses should be considered separately as no patient would be provided a blended dose. The 10-year time horizon was considered arbitrary, and not representative of a patient lifetime. Other concerns also raised by CADTH included that natural disease progression was not captured, and there was uncertain long-term efficacy.	Similar issues to that raised by CADTH for erenumab.
	Fremanezumab.[150]	The analysis of cost-effectiveness included episodic and chronic migraine analyses compared to standard of care. The model included a decision-tree (covering a 3-month assessment period), then Markov model. Transitions were determined by a statistical distribution, rather than use of probability matrices. The model had a cycle length of four weeks and a 10-year time horizon. A National Health Service and Personal Social Services perspective was taken and discounting at 3.5% per annum.	Several limitations were noted by the review group. They thought all patients would not self-administer and included a scenario analysis in which 10% of patients received nursing support. ICURs only reduced marginally. The review group highlighted the time	The review group applied a linear waning of effect over 5 years for positive stoppers, coupled with treatment re-initiation after a loss of half the effect. A waning effect scenario will be included

Country; Agency	Medicine	Study Overview	Findings	Relevance for this study
		The review team noted negative and positive discontinuation was included in the model, Negative discontinuing patients transitioned to standard of care monthly migraine day frequency, and alive positive discontinuers sustained prophylactic effect indefinitely. Response at initial assessment was derived from FOCUS trial data. The effectiveness of standard of care was based on the placebo control arm of the FOCUS trial. The review team indicated data from the disease-specific MSQ questionnaire were preferred by the Sponsor to EQ-5D data because it captured patient HRQoL over four weeks rather than just the day of clinic visit. A mapping technique was used to transform pooled episodic and chronic migraine scores to EQ-5D-3L scale utility values. NICE recommended fremanezumab for preventing migraine in adults who experience 4 or more migraine days per month and at least 3 preventative drug treatments have failed.	horizon of the base case analyses was ten years. The basis for this time frame was that >99% of patients were estimated to have discontinued treatment by this time given a positive stop rate of 20% annually. The review group concluded that "on balance a 10-year time horizon is reasonable given the competing requirements of capturing long-term treatment effect and avoiding increasing uncertainty as extrapolation lengthens." Long term treatment effect was not based on randomised controlled evidence. Observations from the 1 year HALO open label extension were used to support assumptions of an unchanging rate of prophylaxis discontinuation; and sustained full effect for patients on treatment as well as for positive discontinuers. In terms of utilities, it was noted that HRQoL data was collected from the full FOCUS trial population (of people who had used ≥2 prior prophylactic therapies, not the ≥3 prior model population. The review group indicated that the Sponsors preference for MSQ derived data over directly gathered EQ-5D data was reasonable given the limitation so of the EQ-5D design, requiring mapping to the EQ-5D scale. The review group indicated rates were based on a general migraine population,	in our model.

Country; Agency	Medicine	Study Overview	Findings	Relevance for this study
			with no specification of previous prophylactic history, therefore it is not known if rates are representative of the ≥3 prior prophylactic treatment population.	
	Galcanezumab.[151]	The Sponsor adopted the same modelling approach to that submitted for erenumab and fremanezumab. Analyses were conducted for episodic and chronic migraine patients, where the intervention was compared to standard of care, along with onabotulinumtoxinA for chronic migraine patients. The number of migraine headaches per 30-day model cycle drove utility (30 health states), along with costs weighted by proportions of patients in each state. The distribution of patients (MHD, 0 to 30 per month) was estimated by fitting a parametric distribution to trial data Goodness of fit analyses was used to derive the best model. A negative binomial distribution was used for episodic migraine patients using the EVOLVE-1 and EVOLVE-2 trials and beta binomial distribution for chronic migraine patients from the REGAIN trial.	The review team estimated and ICUR for galcanezumab was between GBP20k and GBP30k per QALY gained compared with standard of care in episodic migraine and GBP20k and GBP30k per QALY gained compared with onabotulinumtoxinA for CM. Several issues were identified by the review team. They included (p.425): a lifetime model time horizon (45 years) is preferred to 25 years, high frequency episodic migraine is not considered clinically distinct from episodic or chronic migraine, galcanezumab should be considered in treatment sequences before and after onabotulinumtoxinA, results from the indirect treatment comparison should be used for the different response rates between galcanezumab and onabotulinumtoxinA, it is appropriate to assume consistent discontinuation rates and waning periods for galcanezumab and onabotulinumtoxinA, alternative source should be used to generate HRQoL, and administration costs should be applied for 10% of people receiving galcanezumab. As in other reviews listed above, the review team were concerned about the effects of treatment at 90 days being extrapolated across the time horizon of the	The review team noted the model focused on migraine frequency rather than migraine severity and didn't consider natural history of migraine. Sensitivity analyses will be included around different utility values in our economic model to account for severity and response rates will be varied to include waning. A 25-year time horizon was thought by the Sponsor to be sufficient. They noted prevalence of migraine reduces significantly with age and particularly after the menopause. The review group considered 25-year time horizon reasonable for the modelled cohort of 46 years old. The review team also noted the committee preferences in the appraisal of erenumab and fremanezumab for a

Country; Agency	Medicine	Study Overview	Findings	Relevance for this study
			model. The Sponsor justified these estimates using long-term data from the REGAIN and CGAJ studies. The review group noted that these studies provide only limited follow up (maximum 1 year) and that neither were comparative. The review group indicated utility values were derived from the whole population in the CONQUER trial and not just those who had failed ≥ 3 previous treatments.	lifetime time horizon. A range of time horizons will be included in our model.

Abbreviations

AE = adverse events, **CADTH** = Canadian Agency for Drugs and Technologies in Health, **CM** = chronic migraine, **EM** = episodic migraine, **EQ-5D** = EuroQol-5D, **CAD** = Canadian dollar, **CGRP** = calcitonin gene-related peptide, **GBP** = British pound, **HRQoL** = EuroQol-5D health related quality of life, **ICUR** = incremental cost utility ratio, **MSQ** = Migraine-Specific Quality of Life Questionnaire, **MHDs** = monthly headache days, **MMDs** = monthly migraine days, **NICE** = UK, National Institute for Clinical Excellence, **QALY** = quality-adjusted life year, **UK** = United Kingdom, **USA** = United States of America, **WTP** = willingness to pay.

Appendix M: Ongoing clinical trials

Appendix N includes a table of ongoing clinical trials (i.e. recruiting, not yet recruiting, active not recruiting, enrolling by invitation) that meet the inclusion criteria for this assessment (***Table A81***). The aim of this table is to outline any upcoming evidence, to determine if new evidence that may affect the results of this assessment is likely to be published in the near future.

Table A81 Ongoing clinical trials fitting the inclusion criteria

Trial registry ID; Country	Indication; Sample size (n)	Intervention	Comparator	Primary outcomes	Recruitment status; Expected completion date
ClinicalTrials.gov					
NCT03867201 Multiple countries	Chronic migraine n = 577	Erenumab	Placebo	Change in MMDs	Active, not recruiting June 28, 2024
NCT03927144 Multiple countries	Episodic migraine n = 621	Erenumab	Oral prophylactic (type NR)	Proportion of subjects achieving at least 50% reduction from baseline in MMDs at month 12	Active, not recruiting October 7, 2022
NCT03963232 Multiple countries	Episodic migraine n = 486	Galcanezumab	Placebo	Mean change from baseline in number of monthly migraine headache days	Active, not recruiting February 28, 2022
NCT03971071 Multiple countries	Chronic migraine n = 687	Erenumab (70 mg) Erenumab (140 mg)	Placebo	Change from baseline in the number of MMDs	Recruiting June 29, 2023
NCT04041284 Multiple countries	Migraine (type NR) and major depressive disorder n = 340	Fremanezumab	Placebo	Mean change in MMDs	Recruiting July 23, 2022
NCT04084314 Germany	Episodic migraine n = 699	Erenumab (70 mg) Erenumab (140 mg)	NA	Long term safety (adverse events)	Active, not recruiting March 13, 2023
NCT04252742	Episodic migraine	Erenumab	Placebo	Change from baseline in moderate headache pain intensity	Recruiting

Trial registry ID; Country	Indication; Sample size (n)	Intervention	Comparator	Primary outcomes	Recruitment status; Expected completion date
Multiple countries	n = 576			measured on the NRS scale	July 21, 2024
NCT04361721 Italy	Chronic migraine n = 40	Erenumab	NA	Spinal sensitisation*	Recruiting June 30, 2021
NCT04418765 Multiple countries	Episodic or chronic migraine n = 892	Eptinezumab (100 mg) Eptinezumab (300 mg)	Placebo	Change from baseline in the number of MMDs	Active, not recruiting September 2, 2022
NCT04461795	Episodic or chronic migraine n = 40	Fremanezumab (225 mg)	NA	Change in MIBS-4	Recruiting March 9, 2022
NCT04465357 USA	Migraine (type NR) n = 54	Erenumab (140 mg/ml)	NA	Change in MFIQ	Recruiting December 31, 2021
NCT04603976 Denmark	Migraine (type NR) n = 1000	Erenumab (70 mg Erenumab (140 mg)	NA	Headache diary recording migraine-related data	Recruiting October 2022
NCT04628429 Austria	Episodic or chronic migraine n = 120	Erenumab Galcanezumab Fremanezumab	NA	Change from day 0 CAD at 5 months Change from days 1-31 CAD at 5 months†	Recruiting December 31, 2022
NCT04674020 Denmark	Migraine (type NR) n = 250	Erenumab	NA	Headache diary recording migraine related data	Recruiting July 2025
NCT04693533 USA	Episodic or chronic migraine n = 100	Fremanezumab	NA	Change in number of migraine days per month pre and post treatment Sleep quality pre and post treatment	Not yet recruiting December 2022
NCT04772742 Multiple countries	Migraine (type NR) n = 182	Eptinezumab (100 mg)	Placebo	Change from baseline in the number of MMDs	Active, not recruiting June 22, 2022
NCT04803513	Episodic or chronic migraine	Galcanezumab	NA	Change from baseline in the number of MMDs	Recruiting

Trial registry ID; Country	Indication; Sample size (n)	Intervention	Comparator	Primary outcomes	Recruitment status; Expected completion date
Italy	n = 300				August 31, 2022
NCT04825678 USA	Migraine (type NR) n = 322	Erenumab	NA	Change from baseline in the TSQM overall satisfaction scale score	Recruiting December 9, 2022
NCT04921384 Multiple countries	Chronic migraine n = 513	Eptinezumab (300 mg) Eptinezumab (100 mg)	Placebo	Change from baseline in the number of MMDs	Recruiting July 31, 2023
NCT05064371 Japan	Chronic migraine n = 100	Eptinezumab	NA	Number of participants with adverse events	Enrolling by invitation June 10, 2024
NCT05127486 USA	Episodic migraine n = 700	Galcanezumab	Placebo Rimegepant	Mean monthly percentage of participants with a 50% response rate defined as ≥50% reduction from baseline in monthly migraine headache days	Recruiting December 30, 2022
NCT05232942 Spain	Episodic or chronic migraine n = 200	Discontinuation of Galcanezumab, Fremanezumab or Eptinezumab	NA	The needed number of months elapsed until the patient has a number of headache days per month that equals the situation at the moment of the monoclonal antibody onset or the need of other prophylactic medication	Not yet recruiting August 15, 2024
EU Clinical Trials Register					
2019-004497-25 Multiple countries	Episodic or chronic migraine n = 840	Eptinezumab	Placebo	Change from baseline in the number of MMDs	Ongoing NR
2019-001989-15 Multiple countries	Migraine (type NR) n = 340	Fremanezumab	Placebo	Change from baseline in the number of MMDs	Ongoing NR

Trial registry ID; Country	Indication; Sample size (n)	Intervention	Comparator	Primary outcomes	Recruitment status; Expected completion date
2019-003646-33 Multiple countries	Episodic migraine n = 576	Erenumab	Placebo	Change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2 and 3	Ongoing NR
2018-001228-20 Multiple countries	Episodic migraine n = 600	Erenumab	Oral prophylactic (beta blockers, calcium antagonists, anticonvulsants, antidepressants)	Proportion of subjects who complete initially assigned treatment and achieve at least 50% reduction from baseline in monthly migraine days at month 12	Ongoing NR
2018-003342-16 Multiple countries	Chronic migraine n = 687	Erenumab	Placebo	Absence of MOH at month 6 as defined by mean monthly AHMD < 10 days over months 4, 5, and 6 (week 12 through 24) OR mean monthly headache days < 14 days over months 4, 5, and 6 (week 12 through 24)	Ongoing NR

Abbreviations

AHMD = acute headache medication days, **CAD** = Cardiovagal Autonomic Dysfunction, **ID** = identification, **MFIQ** = Migraine Functional Impact Questionnaire, **MIBS-4** = Migraine Interictal Burden Scale, **MMDs** = monthly migraine days, **MOH** = medication overuse headache, **n** = estimated/actual enrolment number, **NA** = not applicable, **NR** = not reported, **NRS** = Numerical Rating Scale, **TSQM** = Treatment Satisfaction Questionnaire for Medication, **USA** = United States of America.

Notes

*Secondary outcomes of relevance to this report include migraine disability index, headache impact (HIT-6), SF-36, and migraine-specific quality-of-life questionnaire (MSQ).

†Secondary outcomes of relevance to this report include The Headache Impact Questionnaire, the Migraine Disability Assessment Scale (MIDAS) and the Non-Headache Day Impact Questionnaire (Non-HIQ).

Appendix N: Clinical practice position statements and guidelines

Table A82 Summary of clinical guidelines and recommendations regarding CGRP antagonists for the prevention of migraine

Author, Country, Date	Recommendation (Strength of Recommendation)
Guidelines	
British Association for the Study of Headache[152], UK, 2019	*Preventative treatment initiation is recommended when:* - Patients have 4 or more migraine days per month, as this frequency is associated with significant disability - Due to lack of comparative studies, choice of preventative medicine depends primarily on side effect profile and coexisting comorbidities - Preventative medications should be titrated slowly to effective and maximum tolerable dosage and continued for 6–8 weeks to adequately measure effect - Gradual discontinuation of preventative medication should be considered after 6–12 months *Guidelines list the following CGRP antagonists for prevention of episodic and chronic migraine and their dosages, with maximum dose as per licensed indication:* - Erenumab 70–140 mg monthly - Fremanezumab 225 mg monthly, 675 mg threemonthly - Galcanezumab 120–240 mg monthly **(All recommendations are considered to have class A evidence[a] and have been recommended in two or more of the following guidelines: NICE, SIGN, AHS & EFNS)**
European Headache Federation, Europe, 2022 Sacco et al 2021[153]	- In individuals with episodic migraine, we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment **(moderate to high QoE – strong recommendation)[b]** - In individuals with chronic migraine, we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment **(moderate to high QoE – strong recommendation)[b]** - In individuals with episodic or chronic migraine we recommend erenumab over topiramate as preventive treatment **(low QoE – strong recommendation)[b]**
European Headache Federation, Europe, 2019	*Episodic migraine prevention:* Eptinezumab 1000 mg quarterly – suggested **(low QoE – weak recommendation)[b]** Erenumab 70 mg monthly – recommended **(high QoE – strong recommendation)[b]**

Sacco et al 2019[154]	Erenumab 140 mg monthly – recommended **(medium QoE – strong recommendation)[b]** Fremanezumab 225 mg monthly – recommended **(high QoE – strong recommendation)[b]** Fremanezumab 675 mg quarterly – recommended **(medium QoE – strong recommendation)[b]** Galcanezumab 240 mg loading dose + 120 mg monthly – recommended **(medium QoE – strong recommendation)[b]** Galcanezumab 240 mg monthly – recommended **(medium QoE – strong recommendation)[b]** *Chronic migraine prevention:* Erenumab 70 mg monthly – recommended **(medium QoE – strong recommendation)[b]** Erenumab 140 mg monthly – recommended **(medium QoE – strong recommendation)[b]** Fremanezumab 675 mg quarterly – recommended **(medium QoE – strong recommendation)[b]** Fremanezumab 675 mg loading dose + 225 mg monthly – recommended **(high QoE – strong recommendation)[b]** Galcanezumab 240 mg loading dose + 120 mg monthly – recommended **(medium QoE – strong recommendation)[b]** Galcanezumab 240 mg monthly – recommended **(medium QoE – strong recommendation)[b]**
French Headache Society, France, 2021 Ducros et al 2021[155]	Recommendations regarding CGRP antagonists: • Erenumab **(LoE for efficacy = high in episodic and chronic migraine, Strength of recommendation = strong[c] in episodic and chronic migraine)** • Eptinezumab **(LoE for efficacy = high in episodic and chronic migraine, Strength of recommendation = strong[c] in episodic and chronic migraine)** • Fremanezumab **(LoE for efficacy = high in episodic and chronic migraine, Strength of recommendation = strong[c] in episodic and chronic migraine)** • Galcanezumab **(LoE for efficacy = high in episodic and chronic migraine, Strength of recommendation = strong[c] in episodic and chronic migraine)**
	Recommendations regarding switching prophylaxis in episodic migraine: • After failure of at least two prophylactic treatments in patients with at least eight monthly migraine days, prescribe a CGRP antagonist selected among erenumab, fremanezumab and galcanezumab, based on the patient's preferences (**Strength of recommendation: strong[c]**)
	Recommendations regarding switching prophylaxis in chronic migraine: • After failure of at least two oral treatments including topiramate in chronic migraine, prescribe a treatment with onabotulinumtoxinA or a CGRP antagonist selected among erenumab, fremanezumab and galcanezumab, based on the patient's preferences (**Strength of recommendation: strong[c]**)
	Recommendations regarding prophylaxis of resistant or refractory migraine • After failure of CGRP antagonist in a patient with refractory episodic migraine, consider switching to another CGRP antagonist, with or without combination with an oral prophylactic medication (**Strength of recommendation: moderate[d]**) • After failure of a CGRP antagonist in a patient with chronic migraine, consider switching to another CGRP antagonist, or to treatment with onabotulinumtoxinA, both with or without combination with an oral treatment (**Strength of recommendation: moderate[d]**)
German Society for Neurology and German Migraine	- CGRP antagonists (eptinezumab, fremanezumab, galcanezumab and erenumab) are superior to placebo for preventative treatment of episodic AND chronic migraine

and Headache Society, Germany, 2019[156]	- Approval exists for the treatment of migraine with at least 4 migraine days/month. According to the decision of the Federal Joint Committee, a prescription for patients with *episodic migraine* is possible if at least 5 substances from the 4 available, approved medicinal pharmacological groups such as beta-blockers (metoprolol or propranolol), flunarizine, topiramate, valproic acid or amitriptyline were not effective, well tolerated or if there are contraindications to taking them. For *chronic migraine*, it is recommended patients have not responded to onabotulinumtoxinA - In the case of episodic and chronic migraine, therapeutic success is defined as a reduction in the average monthly headache days by 50% or more compared to prior treatment over a period of at least 3 months (diary documentation is recommended). OR significant improvement in validated, migraine-specific, patient-related outcome measures as follows: 30% reduction in MIDAS score when baseline score was > 20 or 5-point reduction in HIT-6 score - Therapy should initially last for 3 months. If there is no satisfactory therapy effect, the therapy is terminated. If the therapy is effective, a withdrawal attempt should be made after 6–9 months to check whether the therapy is still necessary - CGRP antagonists should not be used in pregnant women or during lactation. They should not be used in women who do not use contraception or do not use it adequately - As a precaution, CGRP antagonists should not be used in patients with coronary heart disease, ischemic stroke, subarachnoid haemorrhage, or peripheral arterial disease - Until further notice, CGRP antagonists should not be used in patients with inflammatory bowel disease, COPD, pulmonary hypertension, Raynaud's disease, wound healing disorders or transplant recipients. -There is no information for children and adolescents on the tolerability and safety of CGRP antagonists. **(Strength of recommendations: NR)**
Polish Headache Society, Poland, 2021 Stępień et al 2021[157]	*Indication for treatment with* CGRP antagonists *developed by the American Academy of Neurology:* 1. At least four days with migraine with or without aura per month. 2. Intolerance or inadequate response to at least a 6-week preventative treatment of at least two of the following: a. Topiramate, valproic acid b. Propranolol, metoprolol, timolol, atenolol, nadolol c. Amitriptyline, nortriptyline d. Venlafaxine, duloxetine e. Other Level A or B drugs 1. At least moderate disability resulting from pain measured with the MIDAS (> 11) and HIT-6 (> 50) *Dosage and route of administration:* <u>Erenumab</u> Indication: episodic and chronic migraine Dosage and route of administration: 140 mg or 70 mg per month subcutaneously once per month. <u>Eptinezumab</u> Indication: chronic migraine Dosage and route of administration: 300 mg or 100 mg per month intravenously once per month <u>Fremanezumab</u> Indication: episodic and chronic migraine

	Dosage and route of administration: 225 mg subcutaneously once per month or 675 mg once every three months subcutaneously Galcanezumab Indication: episodic or chronic migraine Dosage and route of administration: 120 mg or 240 mg per months subcutaneously once per month *Treatment efficacy and continuation of treatment:* Treatment efficacy should be assessed and the decision about the continuation of treatment made 3-6 months after the first administration of CGRP antagonists. Treatment is effective if at least one of the following is achieved: 1. A reduction in monthly headache days of 50% relative to the pre-treatment month (analysis based on the patient's diary is recommended but not required). 2. Functional improvement of the patient assessed as a MIDAS score of at least 5 points, with a baseline score ranging from 11 to 20. 3. A reduction in MIDAS score of 30% for patients achieving values close to 20 at baseline or a functional improvement assessed using other sources (e.g. MPFID, HIT-6, or improvement documented in the patient's diary. **(Strength of recommendations: NR)**
Portuguese Headache Society, Portugal, 2021 Parreira et al 2021[158]	Levels of evidence for CGRP antagonists for migraine prophylaxis: Erenumab, fremanezumab, galcanezumab and eptinezumab (**Level of evidence: A[e]**) **Episodic Migraines** *Recommendations for patient selection:* • These treatments are not first line, being indicated for the preventative treatment of episodic migraine in situations of failure (after administration at an adequate dose and time) or in the presence of adverse effects, intolerance or contraindication to other available oral preventives (**Grade of recommendation: I[f]**). • The SPC recommends that CGRP antagonists are used in the preventive therapy of patients with episodic migraine, with and without aura, who have more than 8 attacks per month or between 4–8 attacks per month if associated with disability (assessed by simples measures of impact), and have not had an adequate dose and time response (minimum 8 weeks and ideally 12 weeks) and/or have adverse effects, intolerance or contraindication to at least 4 previous oral preventive drugs (**Grade of recommendation: I[f]**). *Recommendations for maintenance and interruption:* • The SPC recommends that at the end of the third month of treatment, the response is evaluated. If the treatment is effective it should be maintained, if there is no response it should be stopped (**Grade of recommendation: I[f]**) • While there is no real-life evidence on the indicated duration of treatments, the SPC recommends discontinuing treatment after 6 to 12 months of sustained benefit (> 30% reduction in seizure frequency) or improvement in parameters considered relevant to the patient (**Grade of recommendation: NR**). **Chronic Migraines** Recommendation for patient selection: • SPC recommends that prescription be carried out by a tertiary centre by clinical experts following failure in adequate dose and time (or adverse effects, intolerance or contraindication) to at least 3 preventative drugs (preferably including topiramate and onabotulinumtoxinA). (**Grade of recommendation: NR**). Recommendations for maintenance and interruption:

	• It is recommended that patients comply with at least 3 monthly doses to make a decision as to whether or not they are responders (**Grade of recommendation: I[f])** • In cases of quarterly administration, it is recommended that the response be evaluated 3 months following the first injection. If there is no response, it is lawful to suspend the medication. If there is an answer, which the patient values, even if only subjective and partial, the situation should be reassessed after another 3 or 4 months (**Grade of recommendation: NR**). • SPC recommends interruption of treatment at the end of 6 to 12 months of sustained benefit (> 30% reduction in seizure frequency) or improvement in parameters considered relevant to the patient (**Grade of recommendation: NR**)
Swiss Headache Society[159], Switzerland, 2019	*When to initiate preventative treatment:* - More than 3 attacks per month (> 5 days) - Intense or long-lasting attacks - Prolonged or frequent aura - Contraindications to or poorly tolerated acute treatments - Presence or risk of headaches on drug abuse - Considerably reduced QoL - Patient choice *CGRP antagonist recommended dosage regime:* - Erenumab 70–140 mg - Fremanezumab 225–675 mg - Galcanezumab 120 mg Beneficial effect should be assessed after 8 weeks of treatment and if observed treatment should continue for 6–12 months. **(Strength of recommendations: NR)**
Doctorovich et al[160], Argentina, 2020	*General recommendations:* - In migraine patients without aura, preventative treatment is recommended in patients who have > 6 attacks per month during the last 3 months, regardless of the intensity of the attacks. - In migraine patients without aura, preventative treatment is recommended in patients who have > 3 attacks per month during the last 3 months, if the episodes cause moderate-severe disability. - In migraine patients with aura, preventative treatment is recommended in patients who experience on or more seizures per month during the last 3 months, regardless of the intensity of the episode. - Monotherapy is recommended to start migraine prevention, with increasing dose to evaluate treatment response. - Recommended preventative treatment failure definition: lack of efficacy if reduction in migraine episodes is < 50% with an adequate dose and a minimum treatment duration of 3 months OR due to adverse events requiring suspension (by the patient or professional) due to the occurrence of intolerable signs and symptoms coinciding with the start of treatment and that improve on discontinuation. - CGRP antagonists are not recommended in pregnant or lactating women.

	- Once prescribed, CGRP antagonists should be used for at least 3 months as indicated to assess treatment response. - Follow-up of patients using CGRP antagonists should equally evaluate effectiveness, safety and quality of life. - Follow-up must be carried out by a professional experienced in treating migraine. - This professional is also responsible for reporting adverse events thought to be associated with CGRP antagonist use or their lack of effectiveness, to the competent regulatory body. *Population: episodic migraine* - Use of CGRP antagonists shown to be effective and safe as preventative medication for frequent episodic migraine. - CGRP antagonists are indicated for all patients with frequent episodic migraine who have failed two or more previous treatments. - Use of CGRP antagonists can commence after (failed) preventative treatment has been discontinued. - CGRP antagonists should be stopped after 6–12 months of use in patients with controlled symptoms. *Population: chronic migraine* - Use of CGRP antagonists shown to be effective and safe as preventative medication for chronic migraine. - CGRP antagonists are indicated for all patients with chronic migraine who have failed two or more previous treatments. - Use of CGRP antagonists can commence after (failed) preventative treatment has been discontinued. - CGRP antagonists should be stopped after 6–12 months of use in patients with controlled symptoms. **(Strength of recommendations: NR)**
Mexican Association of Headaches and Migraine, Mexico, 2021 Velez-Jimenez et al 2021[161]	*Population: chronic migraine* Overall monoclonal antibodies directed to the CGRP receptor or ligand are safe as first-line or adjuvant treatments for chronic migraine, with minimal side effects and monthly or quarterly administration in adult patients **(strong recommendation[g] with a high QoE[h])** Specific recommendations are as follows: - Intravenous eptinezumab is recommended as first-line treatment for chronic migraine at a dosage of 300 mg quarterly for 9–12 months **(strong recommendation[g], high QoE[h])** - Subcutaneous galcanezumab is recommended as first line treatment for chronic migraine at a dosage of 240 mg (initial) and 120 mg (monthly) for an undefined time 9–12 months **(strong recommendation[g], high QoE[h])** - Subcutaneous erenumab is recommended as first-line treatment for chronic migraine at a dosage of 70 or 140 mg (monthly) for 9–12 months **(strong recommendation[g], high QoE[h])** - Subcutaneous fremanezumab is recommended as first-line or adjuvant treatment for chronic migraine at a dosage of 225 mg (monthly) or 675 mg (quarterly) for 9–12 months **(strong recommendation[g], high QoE[h])**
Position statements	

American Headache Society, USA, 2018[162]	*Use of* CGRP antagonists *approved when all the following are met:* - Prescribed by a licensed medical provider - Patient ≥ 18 years of age - Diagnosis of ICHD-3 migraine with or without aura (4–7 MHD) and at least moderate disability (MIDAS > 11, HIT-6 > 50) AND inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the following: 1. Topiramate 2. Divalproex sodium/valproate sodium 3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol 4. Tricyclic antidepressant: amitriptyline, nortriptyline 5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine 6. Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline - Diagnosis of ICHD-3 migraine with or without aura (8–14 MHD) and inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the above (1–6). - Diagnosis of ICHD-3 chronic migraine and inability to tolerate (due to side effects) or inadequate response to a 6-week trial of at least 2 of the above (1–6) OR inability to tolerate or inadequate response to a minimum of 2 quarterly injection (6 months) of onabotulinumtoxinA. **(Strength of recommendations: NR)** *Criteria for continuation of* CGRP antagonists *after initial use is approved if either of the following are met:* - Reduction in mean MHD of ≥ 50% relative to pre-treatment baseline - A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures: 1. MIDAS: reduction of ≥ 5 points when baseline score is 11–20 or reduction of ≥ 30% when baseline scores > 20 2. MPFID: reduction of ≥ 5 points 3. HIT-6: reduction of ≥ 5 points **(Strength of recommendations: NR)**
British Association for the Study of Headache[163], UK, 2021	- Erenumab and galcanezumab have been approved for both chronic (≥ 15 headache days per month, with at least 8 migraine days) and episodic (≥ 4 migraine days per month) migraine and fremanezumab has only been approved for chronic migraine. - All patients are required to have failed at least three previous preventive medications. - At three months, treatment can be continued if patients with episodic migraine have experienced a ≥ 50% reduction in migraine days, or those with chronic migraine have experienced a ≥ 30% reduction in migraine days. - Particular attention is recommended for patients with high frequency episodic migraine (> 8-10 migraine days per month) in whom treatment may prevent chronic migraine. - The choice of CGRP antagonist to start should be made by clinicians according to the NICE stipulations, local formulary guidelines, and clinical expertise.

	- CGRP antagonists should be prescribed by any doctor who is capable of diagnosing, managing, and following up patients with migraine (including, but not be limited to, neurologists in specialist headache clinics, general neurologists, and GPs with a special interest in headache). - All patients on CGRP antagonists must keep a headache diary (of any type capable of indicating monthly headache and migraine days). - Patients must have a mechanism to report any adverse effects relating to treatment, all three CGRP antagonists are yellow card medications. In particular, worsening or de novo hypertension in patients treated with erenumab. - Patients should remain under the care of the prescribing clinician until treatment is no longer required. Where possible, data should be collected for audit purposes, and for inclusion in a proposed national registry. - In patients that responded to CGRP antagonists at 3 months, an agreed length of further treatment should be instituted depending on the severity of their condition pre-treatment, but the need for ongoing treatment should be assessed on at least an annual basis. - There is emerging evidence that patients who do not respond to one CGRP antagonist may have a clinically meaningful response to another member of the class, and BASH recommend that clinicians consider trial of a second or subsequent CGRP antagonist if a patient does not respond to the first choice. **(Strength of recommendations: NR)**
Consensus statements	
American Headache Society, USA, 2021 Ailani et al 2021[164] Note: slight variation from 2018 position statement. Changes underlined.	*Use of* CGRP antagonists *approved when all the following are met:* - Prescribed by a licensed medical provider - Patient ≥ 18 years of age - Diagnosis of ICHD-3 migraine with or without aura (4–7 MHD) and at least moderate disability (MIDAS ≥ 11, HIT-6 > 50) AND inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least 2 of the following: 1. Topiramate 2. Divalproex sodium/valproate sodium 3. Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol 4. Tricyclic antidepressant: amitriptyline, nortriptyline 5. Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine 6. Other Level A or B treatments (established efficacy or probably effective) according to AAN scheme for classification of evidence - Diagnosis of ICHD-3 migraine with or without aura (8–14 MHD) and inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least 2 of the above (1-6). - Diagnosis of ICHD-3 chronic migraine and inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least 2 of the above (1-6) OR inability to tolerate or inadequate response to a minimum of 2 quarterly injection (6 months) of onabotulinumtoxinA. **(Strength of recommendations: NR)** *Criteria for continuation of* CGRP antagonists *after initial use is approved if either of the following are met:* - Reduction in mean MHD or headache days of at least moderate severity of ≥ 50% relative to pre-treatment baseline - A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:

	1. MIDAS: reduction of ≥ 5 points when baseline score is 11–20 or reduction of ≥ 30% when baseline scores > 20 2. MPFID: reduction of ≥ 5 points 3. HIT-6: reduction of ≥ 5 points **(Strength of recommendations: NR)**
Danish Headache Society, Denmark, 2021 Eigenbrodt et al 2021[165]	Diagnosis and management in 10 steps: CGRP antagonists (Erenumab, fremanezumab, galcanezumab and eptinezumab) are considered a third-line preventative medication for migraine (behind beta blockers (propranolol, metoprolol, atenolol, bisoprolol), topiramate, candesartan (first-line treatments) and flunarizine, amitriptyline, sodium valproatea (second-line treatments). Preventative medications are recommended for patients adversely affected by migraine on ≥ 2 days per month despite optimised acute therapy. Recommended dosages as follows: - Erenumab 70–140 mg subcutaneous every 4 weeks - Fremanezumab 225 mg subcutaneous every month or 675 mg subcutaneous every 3 months - Galcanezumab start dose 240 mg subcutaneous followed by 120 mg subcutaneous every month - Eptinezumab 100–300 mg intravenous every 3 months Contraindications include hypersensitivity, patients with a history of stroke, subarachnoid haemorrhage, coronary heart disease, inflammatory bowel disease, chronic obstructive pulmonary disease or impaired wound healing. **(Strength of recommendations: NR)**
Danish Headache Society, Denmark, 2021 Schytz et al 2021[166]	CGRP antagonists listed as one of several preventative treatments. Recommended doses as follows: - Erenumab 70–140 mg subcutaneous every 4 weeks - Fremanezumab 225 mg subcutaneous every month or 675 mg subcutaneous every 3 months - Galcanezumab start dose 240 mg subcutaneous followed by 120 mg subcutaneous every month - Eptinezumab 100–300 mg intravenous every 3 months In Denmark, erenumab and fremanezumab are currently recommended as possible preventive treatment for patients with chronic migraine who have experienced preventative treatment failure with at least one anti-hypertensive and one anti-epileptic. Medication overuse headache should be attempted to be treated before initiating CGRP antagonist treatment. In Denmark, the right to prescribe CGRP antagonists is limited to specialists in neurology who are employed in a hospital. CGRP antagonists are dispensed from hospital. **(Strength of recommendations: NR)**
Technology Appraisal Guidance	
National Institute for Clinical Excellence[167], UK, 2022[i]	Fremanezumab is recommended in adults, only if: - They have ≥ 4 migraine days per month - Failed ≥ 3 preventive drug treatments - The company provides it according to the commercial arrangement. Fremanezumab should be stopped after 12 weeks if:

	- Episodic (< 15 MHD) migraine frequency does not reduce by ≥ 50% or - Chronic (≥ 15 MHD with at least 8 having features of migraine) migraine frequency does not reduce by ≥ 30%. **(Strength of recommendations: NR)**
National Institute for Clinical Excellence[149], UK, 2021	Erenumab is recommended in adults, only if: - They have ≥ 4 migraine days per month - Failed ≥ 3 preventive drug treatments - A dose of 140 mg is used - The company provides it according to the commercial arrangement. Erenumab should be stopped after 12 weeks if: - Episodic (< 15 MHD) migraine frequency does not reduce by ≥ 50% or - Chronic (≥ 15 MHD with at least 8 having features of migraine) migraine frequency does not reduce by ≥ 30%. **(Strength of recommendations: NR)**
National Institute for Clinical Excellence[151], UK, 2020	Galcanezumab is recommended in adults, only if: - They have ≥ 4 migraine days per month - Failed ≥ 3 preventive drug treatments - The company provides it according to the commercial arrangement. Galcanezumab should be stopped after 12 weeks if: - Episodic (< 15 MHD) migraine frequency does not reduce by ≥ 50% or - Chronic (≥ 15 MHD with at least 8 having features of migraine) migraine frequency does not reduce by ≥ 30%. **(Strength of recommendations: NR)**

Abbreviations

AAN = American Academy of Neurology, **AHS** = American Headache Society, **BASH** = British Association for the Study of Headache, **CGRP** = calcitonin-gene-related peptide, **COPD** = chronic obstructive pulmonary disease, **EFNS** = European Federation of Neurological Societies, **GP** = general practitioner, **HIT-6** = 6 item Headache Impact Test, **ICHD** = International Classification of Headache Disorders, **LoE** = level of evidence, **MHD** = monthly headache days, **MIDAS** = Migraine Disability Assessment, **MPFID** = Migraine Physical Function Impact Diary, **NICE** = National Institute of Clinical Excellence, **NR** = not reported, **QoE** = quality of evidence, **QoL** = quality of life, **RCT** = randomised controlled trial, **SIGN** = Scottish Intercollegiate Guidelines Network, **SPC** = Portuguese Headache Society, **UK** = United Kingdom, **USA** = United States of America.

Notes

[a] Class A Evidence not defined.

[b] GRADE Approach used where quality of evidence was rated as high, medium, low or very low based on study design, study limitations, inconsistency, indirectness, imprecision, publication bias, effect size, dose response and confounding and strength (strong or weak) and direction (for or against) of recommendation were determined on basis of balance between desirable and undesirable effects, quality of evidence, values and preferences and costs.

[c] Strength of recommendation: strong = benefits clearly outweigh risks and burdens for most patients – can apply to most patients in most circumstances.

[d] Strength of recommendation: moderate = benefits clearly outweigh risks and burdens for most patients – can apply to most patients, but there is a chance the recommendation may change with more research.
[e] Level A = Information collected from several randomised clinical trials or meta-analyses
[f] Grade of recommendation: I = There is evidence and/or a general consensus that a certain procedure/treatment is beneficial, useful and effective.
[g] Strong recommendation (GRADE Approach) where benefits of action outweigh disadvantages, the recommendation is helpful (independent of the QoE supporting it).
[h] High QoE = at least two or more systematic reviews or controlled clinical trials.
[i] Guidance for eptinezumab was in development at the time of search (8/3/22).

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