【エムガルティ皮下注 120mg オートインジェクター、皮下注 120mg シリンジ】に関する費用対効果評価 [第 1.0 版]

【提出者名】日本イーライリリー株式会社

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Abbreviation	Full description
AAN	American Academy of Neurology
ACE	Angiotensin-converting enzyme
ADA	Anti-drug antibodies
AE	Adverse event
AHS	American Headache Society
ARB	Angiotensin II receptor blocker
BSC	Best supportive care
C2H	Core2 Health
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost effectiveness acceptability threshold
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
DSA	Deterministic sensitivity analysis
EANC	European Academy of Neurology Congress
EHF	European Headache Foundation
EM	Episodic Migraine
EUCTR	EU Clinical trials register
GMB	Galcanezumab
HD	Headache days
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICHD	International Classification of Headache Disorders
ICER	Incremental cost effectiveness threshold
ICTRP	International Clinical Trials Registry Platform
IHS	International Headache Society
ITC	Indirect Treatment Comparison
ITT	Intention to treat

JHS	Japanese Headache Society
JMACCT	Japanese Medical Association Center for Clinical Trials
MFDS	Ministry of Food and Drug Safety
Mg	Milligram
MHD	Migraine headache days
MHLW	Ministry of Health, Labor and Welfare
MIBS	Migraine Interictal Burden Scale
MIDAS	Migraine Disability Assessment Scale
MSQ	Migraine-Specific Quality of Life
NDB	National Database of Health Insurance Claims and Specific Health Checkups of Japan
NMA	Network meta-analysis
OnaA	OnabotulinumtoxinA
OUGL	Optimised used guidelines
PBAC	Pharmaceutical Benefits Advisory Committee
PHQ	Patient Depression Questionnaire
PICOS	Population, Intervention(s), Comparator(s), Outcome(s) and Study design
PMDA	Pharmaceutical and Medical Device Agency
PRISMA	Preferred Reporting Items in Systematic Review and Meta-Analysis
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomized controlled trial
SAE	Serious adverse event(s)
SD	Standard deviation
SE	Standard error
SFHD	Symptom-free headache days
SLR	Systematic literature review
SoC	Standard of Care
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
YLD	Years lost to disability

0. 要旨

分析対象技術名 [1.1 節]	エムガルティ皮下注 120mg オートインジェクター、皮下注 120mg シリンジ（ガルカネズマブ）
他国の医療技術評価機関における評価結果 [1.8 節]	イギリス NICE: Recommended with conditions SMC: Recommended with conditions フランス HAS: SMR – important, ASMR – V ドイツ IQWiG: Hint of a considerable additional and No additional benefit カナダ Recommended with conditions オーストラリア Recommended with conditions
対象とする疾患･集団 [2.1 節]	対象疾患：片頭痛 以下の片頭痛患者をそれぞれ分析対象集団とする （a）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者 （b）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者 （c）片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者 （d）片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者
比較対照技術名 [2.2 節]	（a）（b）:プロプラノロール （c）（d）: Best Supportive Care
分析の立場と費用の範囲 [2.3 節]	分析の立場は公的医療の立場、費用の範囲は公的医療費を用いる
使用する効果指標 [2.4 節]	質調整生存年(Quality-adjusted life year: QALY)を用いる
設定した分析期間 [2.5 節]	25 年
割引率 [2.6 節]	費用･効果ともに年率 2%を用いる

<table>
<tr><td>システマティックレビューのクリニカルクエスチョン [3.1/3.3 節]</td><td>
<table>
<tr><th>項目</th><th>内容</th></tr>
<tr><td>対象集団</td><td>Adult (18+) patients (males and females) suffering from migraine</td></tr>
<tr><td>介入</td><td>All preventive pharmacological interventions for the treatment of migraine relevant to Japan</td></tr>
<tr><td>比較対照</td><td>All preventive pharmacological interventions for the treatment of migraine relevant to Japan, compared to each other or to placebo</td></tr>
<tr><td>アウトカム</td><td>Efficacy outcomes:
• Monthly Migraine Headache Days
• Monthly Headache Days
• Monthly Migraine Headache Attacks
• Monthly Headache Attacks
• Monthly use of acute migraine treatment
• 50% Reduction in Monthly Migraine Headache days
• 75% Reduction in Monthly Migraine Headache days
• 100% Reduction in Monthly Migraine Headache days
HRQoL outcomes:
• PGI-S score
• MIDAS Total Score, Absenteeism Score, Presenteeism Score, Days of lost productivity Score
• MSQoL Questionnaire (Total score, role function-preventive, role function-restrictive, emotional function domains)
• EQ-5D Score

Safety and discontinuation outcomes:
• AEs due to any cause
• SAEs due to any cause
• Discontinuation due to any cause
• Discontinuation due to AEs
• Discontinuation due to lack of efficacy</td></tr>
<tr><td>研究デザイン</td><td>Phase II, III, IV randomised controlled trials (Crossover up to time of crossover)
Conference abstracts from 2017-current
Language English and Japanese (other languages will be excluded)</td></tr>
<tr><td>文献検索期間</td><td>1946 年から 2021 年 10 月 29 日まで
(Conference abstracts:2017-2021)</td></tr>
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</td></tr>
<tr><td>システマティックレビュー結果の概要 [3.2/3.4 節]</td><td>同定された 195 件の結果より、ガルカネズマブのデータは7試験であった。このうち、日本人を対象とした試験と海外の第 3 相試験（CGAG/CGAH/CGAI）のデータを含めてメタアナリシス及び間接比較に使用した。比較対照技術についてのデータはシステマティックレビューから同定されず、別途定義された基準で採択し使用した。</td></tr>
<tr><td>間接比較の結果 [3.7 節]</td><td>（a）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者
ガルカネズマブ 120mg はプロプラノロールに比較して統計的に有意な差を示した。(mean difference: [redacted] ([redacted]) P=[redacted])
（b）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者
ガルカネズマブ 120mg はプロプラノロールに比較して統計的に</td></tr>
</table>

	有意な差を示した。(mean difference: [redacted] ([redacted]) P=[redacted]) (c)片頭痛予防薬の3剤目の治療を中止した反復性片頭痛患者 ガルカネズマブ 120mg は BSC に比較して統計的に有意な差を示した。(mean difference: [redacted] ([redacted]) P[redacted]) (d)片頭痛予防薬の3剤目の治療を中止した慢性片頭痛患者 ガルカネズマブ 120mg は BSC に比較して統計的に有意な差を示した。(mean difference: [redacted] ([redacted]) P[redacted])
追加的有用性の有無 [3.8節]	(a)片頭痛予防薬の2剤目の治療又は3剤目の治療を行う反復性片頭痛患者 ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」 (b)片頭痛予防薬の2剤目の治療又は3剤目の治療を行う慢性片頭痛患者 ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」 (c)片頭痛予防薬の3剤目の治療を中止した反復性片頭痛患者 ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」 (d)片頭痛予防薬の3剤目の治療を中止した慢性片頭痛患者 ■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」
費用対効果の分析方法の概要 [4.1.1項、4.2節等]	本分析はガルカネズマブとプロプラノロールまたは Best supportive care の治療の費用対効果を評価するためセミマルコフモデルにより費用対効果分析を実施した。マルコフモデルの健康状態は、①3ヵ月目の反応評価前の治療中、②反応評価後の治療中(4ヵ月目以降)、③治療中止、④死亡の4つからなり、それぞれの健康状態は、月あたりの片頭痛日数と関連して設定されている。それぞれガルカネズマブ、プロプラノロール、best supportive care の治療開始時に「①3ヵ月目の反応評価前の治療中」となり、その3か月間後に、治療への反応性をもとに responder または non-responder に分類し(response

	assessment)、responder はその後それぞれの治療を継続するが(「②反応評価後の治療中(4 ヵ月目以降)」への移行)、non-responder は「③治療中止」に移行する(図 4-1 参照)。その後は 1 ヵ月サイクルで健康状態が移行する。Response assessment 前後いずれにおいても、有害事象等を想定した所定の割合に応じ「③治療中止」に移行する。いずれの状態からも、国民の標準死亡率に従い死亡する。また、Distribution approach を用い、費用と QALY それぞれが持つ非線形な関係性をモデル化した。
結果の概要 [5.1 節]	(a) 片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者 ベースケースにおける ICER が¥6,077,875 であり、500 万円以上 750 万円以下の区間にあると判断された。 (b) 片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者 ベースケースにおける ICER が¥2,691,706 であり、500 万円/QALY 以下の区間にあると判断された。 (c) 片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者 ベースケースにおける ICER が¥2,850,240 であり、500 万円/QALY 以下の区間にあると判断された。 (d) 片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者 ベースケースにおける ICER が¥1,441,739 であり、500 万円/QALY 以下の区間にあると判断された。
ICER の所属する確率が最も高いと考える区間	(a) 片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者 □　費用削減あるいはドミナント □　500 万円以下 (750 万円以下) ■　500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □　750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □　1000 万円超 (1500 万円超) □　効果が同等(あるいは劣り)、かつ費用が高い (b) 片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性

	片頭痛患者 □　費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □　500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □　750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □　1000 万円超 (1500 万円超) □　効果が同等（あるいは劣り）、かつ費用が高い （c）片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者 □　費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □　500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □　750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □　1000 万円超 (1500 万円超) □　効果が同等（あるいは劣り）、かつ費用が高い （d）片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者 □　費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □　500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □　750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □　1000 万円超 (1500 万円超) □　効果が同等（あるいは劣り）、かつ費用が高い

1．対象となる医薬品･医療機器の性質

1.1 名称

・ 販売名：エムガルティ皮下注 120mg オートインジェクター、皮下注 120mg シリンジ
・ 一般名：ガルカネズマブ（遺伝子組換え）

1.2 保険償還価格

本剤は 2021 年 4 月 21 日に薬価収載された。詳細は以下のとおりである。

表 1-1 薬価の算定方式

	算定方式		原価計算方式	
	原価計算		オートインジェクター（120mg1mL1 キット）	シリンジ（120mg1mL1 筒）
		製品総原価	31,530 円	32,197 円
		営業利益	5,477 円	5,593 円
		流通経費	3,001 円	3,064 円
		消費税	4,001 円	4,085 円
	補正加算		なし	
	外国平均価格調整		（調整前）44,008 円 → （調整後）45,165 円	なし
	算定薬価		エムガルティ皮下注 120mg オートインジェクター （120mg1mL1 キット） 45,165 円	エムガルティ皮下注 120mg シリンジ （120mg1mL1 筒） 44,940 円

1.3 治療効果のメカニズム

本薬は、カルシトニン遺伝子関連ペプチド（Calcitonin-gene related peptide：CGRP）に結合する遺伝子組換えヒト化 IgG4 モノクローナル抗体である。本薬は CGRP に高い親和性（KD=31pM）と選択性を有し、CGRP 受容体や CGRP 関連ペプチド（アドレノメデュリン、アミリン、カルシトニン及びインテルメジン）には明らかな結合性を示さない（CGRP に対する親和性はこれらペプチドに対する親和性の 10000 倍より大きい）。CGRP は主に三叉神経節で発現する神経ペプチドで、血管拡張、炎症促進、侵害受容における役割がある。片頭痛患者では血中 CGRP 濃度が上昇しており、片頭痛患者に CGRP を投与すると片頭痛発作が誘導される。したがって、本品の CGRP 活性の阻害作用により、片頭痛発作の発症を抑制することが期待される。

1.4 対象疾患

本品の効能または効果は、以下のとおりである（添付文書より抜粋 [1]）
片頭痛発作の発症抑制、ただし、以下の場合に限る。

(a) 前兆のある又は前兆のない片頭痛の発作が月に複数回以上発現している、又は慢性片頭痛である
(b) 非薬物療法、片頭痛発作の急性期治療等を適切に行っても日常生活に支障をきたしている患者

・ 分析対象とする疾患の疫学的性質(有病率、新規発症者数、好発年齢等)

1 国際頭痛分類 (ICHD) を用いた日本での疫学研究では、日本人の片頭痛有病率は 8.4%で、男女比（女/男）が約 3.6 と推定され [2]、 30 歳代及び 40 歳代の女性における片頭痛の有病率は男性の有病率に比べて高いことが知られている [3]。また、反復性片頭痛と慢性片頭痛は発作の頻度で区別されるが、片頭痛としての病態に差異はないと考えられ、

実際、疫学調査の結果では 1 年あたり 2.5%の反復性片頭痛患者が慢性片頭痛に移行したという報告 [4]がある一方で、2 年間の観察で慢性片頭痛患者の 26%が反復性片頭痛等へ寛解したという報告 [5]もある。これらの報告は反復性片頭痛と慢性片頭痛が互いに行き来する 2 つの状態であることを示している。

2 片頭痛は男女とも 20～50 歳代の勤労世代に多く見られる疾患であること [2] から生産性の低下による経済的損失による医療経済への影響が無視できない。その中でも、片頭痛は 30 歳代から 40 歳代の女性を中心とする若年者に有病率が高く、これらの年齢層においてとくに日常生活及び社会生活に支障をきたす疾患である。頭痛による生産性の低下により、毎年 2880 億円の経済的損失が日本経済にもたらされていると推定されている [6]。

・ 分析対象とする疾患における当該医薬品･医療機器の使用(見込)者数

保険償還時の使用見込み数は、ピーク時市場規模予測で 4.8 万人である。

・ 当該医薬品･医療機器を使用する患者の主な年齢(層)や性別等

株式会社 MDV の医療機関ベースのレセプトデータから、上市以降、本剤が使用された患者数を年齢・性別に分けて下記に示す（表 1-2）。40 歳代の女性に最も多く使用されているが、片頭痛の有病率と同じく 30-50 歳代の女性に広く使用されている。

表 1-2 2021 年 4 月から 2021 年 9 月までに本剤が使用された患者数

年齢	男性	女性	総計	年齢割合
18-29 歳	22	69	91	11%
30-39 歳	31	131	162	19%
40-49 歳	51	218	269	32%
50-59 歳	29	162	191	23%
60-69 歳	14	77	91	11%
70-79 歳	2	30	32	4%
80-89 歳	3	2	5	1%
90 歳以上	0	0	0	0%
総計	152	689	841	100%
男女割合	18%	82%	100%	NA

出典：MDV Analyzer

1.5 使用方法等

【医薬品】

本品の用法及び用量は、通常、成人にはガルカネズマブ（遺伝子組換え）として初回に 240mg を皮下投与し、以降は1ヵ月間隔で 120mg を皮下投与する。本品使用時の概要は下記のとおりである。

表 1-3 使用方法

投与経路	皮下投与
投与方法	単独で使用する
投与量	初回 240mg、以降 120mg
投与頻度	1 か月間隔

1.6 対象疾患の治療における当該医薬品･医療機器の位置づけ

1.6.1 片頭痛の分類

片頭痛は一次性頭痛のなかで最も臨床的に重要な疾患である。典型的には、片側性で拍動性の中等度から重度の頭痛発作が繰り返し生じ、発作は4～72時間持続する。頭痛に加えて、悪心、嘔吐、光過敏、音過敏などを伴うことも多く、日常動作で頭痛が増悪するため生活に大きな支障をきたす。国際頭痛分類ではこれらの臨床的特徴をもって片頭痛の診断基準としている。片頭痛患者では片頭痛発作に先立って前兆と呼ばれる特徴的な症状が自覚されることがあり、片頭痛は前兆の種類や有無によって更に分類される。また、片頭痛はその頭痛発作の頻度によっても分類され、3 ヵ月にわたり月に 4 日から 14 日以内の頻度で片頭痛がみられた場合には反復性片頭痛と分類される。また、片頭痛のうち、3 ヵ月にわたり月に 15 日以上の頻度で頭痛がみられ、少なくとも月に 8 日の頭痛が片頭痛の特徴を持つ場合には慢性片頭痛と分類され、反復性片頭痛と区別される。

国際頭痛分類（ICHD 第 3 版）は、日本頭痛学会により日本語訳がなされ臨床現場に広く使用されている[7]。

1.6.2 片頭痛治療における本剤の位置づけ

片頭痛治療には、頭痛発作の痛みを軽減するための急性期治療と頭痛発作の回数自体を軽減する予防療法の2つに大別される。2021 年 10 月に刊行された頭痛の診療ガイドライン　2021[8]において予防療法は片頭痛発作が月に2回以上、あるいは生活に支障をきたす頭痛が月に3日以上ある患者、および急性期治療のみでは片頭痛発作による日常生活の支障がある患者では予防療法の実施の検討が推奨されている。また，急性期治療のみでは片頭痛発作による日常生活の支障がある場合、急性期治療薬が使用できない場合、永続的な神経障害をきたすおそれのある特殊な片頭痛に対しても予防療法が推奨されている。

本剤は大規模臨床試験でプラセボに対して有意な片頭痛予防効果が示されていることから、既に上述の診療ガイドラインにおいて片頭痛の新規予防療法として推奨の強さは強い/弱いの 2 段階で「強い」、エビデンスの確実性は A-C の 3 段階で「A」、薬効の group は 1（有効）から 5（無効）の 5 段階で「1（有効）」に位置づけられている。

1.6.3 最適使用推進ガイドラインにおける本剤の使用基準

＜施設について＞

本品が適応となる患者の選択及び投与継続の判断は、適切に行われることが求められ、本剤の投与に際しては適切な片頭痛とそれ以外の頭痛疾患を鑑別することが必要である。　また、本剤の投与により重篤な副作用が発現した際にも適切な対応をすることが必要なため、①～③の全てを満たすことが最適使用推進ガイドラインにおいて記載されている。以下に一部抜粋して示す。

- 片頭痛の病態、経過と予後、診断、治療（参考：慢性頭痛の診療ガイドライン　2013[9]）を熟知し、本剤についての十分な知識を有している医師（医師要件あり※）が本剤に関する治療責任者として配置されていること、また、二次性頭痛との鑑別のために MRI 等による検査が必要と判断した場合、専門医との連携体制が整っている施設であること。
- 院内の医薬品情報管理体制が整っている。
- 当該施設又は近隣医療機関の専門性を有する医師と連携し、副作用の診断や対応に関して指導及び支援を受け、副作用の診断対応に関して直ちに適切な処置ができる等の体制が整っている。

※＜医師要件＞ 以下の基準を満たすこと。

1. 医師免許取得後 2 年の初期研修を修了した後に、頭痛を呈する疾患の診療に 5 年以上の臨床経験を有していること。
2. 本剤の効果判定を定期的に行った上で、投与継続の是非についての判断を適切に行うことができること。

3. 頭痛を呈する疾患の診療に関連する以下の学会の専門医の認定を有していること。
・日本神経学会 ・日本頭痛学会 ・日本内科学会（総合内科専門医） ・日本脳神経外科学会

＜投与対象となる患者＞
最適使用推進ガイドライン[10]では、投与対象となる患者を以下のように記載している。

【患者選択について】
投与の要否の判断にあたっては、以下の 1.～4.のすべてを満たす患者としている。
- 国際頭痛分類（ICHD 第３版）を参考に十分な診療を実施し、前兆のある又は前兆のない片頭痛の発作が月に複数回以上発現している、又は慢性片頭痛であることが確認されている。
- 本剤の投与開始前 3 カ月以上において、1 カ月あたりの Migraine headache days (MHD)が平均４日以上である。
- 睡眠、食生活の指導、適正体重の維持、ストレスマネジメント等の非薬物療法及び片頭痛発作の急性期治療等を既に実施している患者であり、それらの治療を適切に行っても日常生活に支障をきたしている。
- 本邦で既承認の片頭痛発作の発症抑制薬（プロプラノロール塩酸塩、バルプロ酸ナトリウム、ロメリジン塩酸塩等）のいずれかが、下記①～③のうちの 1 つ以上の理由によって使用又は継続できない。
  ①効果が十分に得られない
  ②忍容性が低い
  ③禁忌、又は副作用等の観点から安全性への強い懸念がある

【投与の継続・中止について】
本剤投与中は症状の経過を十分に観察し、本剤投与開始後 3 カ月（3 回投与後）を目安に治療上の有益性を評価して症状の改善が認められない場合には、本剤の投与中止を考慮すること。
またその後も定期的に投与継続の要否について検討し、頭痛発作発現の消失・軽減等により日常生活に支障をきたさなくなった場合には、本剤の投与中止を考慮すること。
なお、日本人を対象とした臨床試験において、本剤の 18 カ月を超える使用経験はない。

1.7 主な有害事象
本剤の主な有害事象として、リスク管理計画書に示された重篤な有害事象（重要な特定されたリスク）は重篤な過敏症である。
モノクローナル抗体の投与は過敏症反応を引き起こす可能性があり、実臨床下において、アナフィラキシー反応を含む重篤な過敏症は、迅速かつ適切な処置を施さないと生命に危険が及ぶ可能性があることから、本品のベネフィット・リスクプロファイルに重大な影響を及ぼし得ると考えられる。これまでに実施した本剤の国内臨床試験で認められた主な過敏症は、蕁麻疹、発疹、そう痒症であり、重症度はその多くが軽度から中等度で、アナフィラキシー反応を含む重篤な過敏症は認められなかった。一方、海外の製造販売後の自発報告においては本薬との因果関係が否定できない過敏症として、アナフィラキシー、血管性浮腫、発疹等の発現が報告されているが、重篤な過敏症の発現割合は低く、死亡例は報告されていない。

1.8 他国の医療技術評価機関における評価結果

表 1-4 主要国における評価の一覧表

国名	機関名	評価結果（記載例）	リスト価格（現地通貨建）

イギリス	NICE	·Recommended with conditions (specifically: Galcanezumab is recommended as an option for preventing migraine in adults, only if: 1. they have 4 or more migraine days a month 2. at least 3 preventive drug treatments have failed and 3. the company provides it according to the commercial arrangement · Evaluation status: final guidance (18 November 2020)	£450.00 (without VAT)
	SMC	· Recommended with conditions (specifically: for the treatment of patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments. This advice applies only in the context of an approved NHS Scotland Patient Access Scheme · Evaluation status: final guidance (12 April 2021)	
フランス	HAS	· SMR: important · ASMR: **V** · efficiency evaluation: not performed	Not available
ドイツ	IQWiG	· Hint of a considerable additional and No additional benefit • Subpopulation A: For naive patients and patients that have failed/not tolerated at least 1 prophylactic treatment → No added benefit • Subpopulation B: Patients that have failed the following substance classes: Metoprolol/propranolol, topiramate, amitriptylin, flunarizine → No added benefit • Subpopulation C: Patients that failed all other treatments (substance classes) → Hint of a considerable additional benefit	€ 490.21
カナダ	CADTH	· Recommended with conditions	Not available yet
オーストラリア	PBAC	· Recommended with conditions	$AUD 559.02

【各国における費用対効果評価の詳細】

1. 評価の有無の一覧

表 1-5 評価の有無の一覧

国名	機関名	評価結果の有無
イギリス	NICE	あり
	SMC	あり
フランス	HAS	あり
ドイツ	IQWiG	あり
カナダ	CADTH	あり
オーストラリア	PBAC	あり

2. 評価結果の詳細

表 1-6 評価結果の詳細

国名	イギリス（イングランド/ウェールズ）
機関名	NICE
評価結果の URL など	https://www.nice.org.uk/guidance/ta659/chapter/1-Recommendations
評価対象技術	ガルカネズマブ
評価結果	Recommended with conditions
条件付き推奨の場合は、その条件の詳細	Galcanezumab is recommended as an option for preventing migraine in adults, only if: 1. they have 4 or more migraine days a month 2. at least 3 preventive drug treatments have failed and 3. the company provides it according to the commercial arrangement. • Stop galcanezumab after 12 weeks of treatment if: • in episodic migraine (less than 15 headache days a month) the frequency does not reduce by at least 50% in chronic migraine (15 headache days a month or more with at least 8 of those having features of migraine) the frequency does not reduce by at least 30%.
評価対象疾患	Episodic and chronic migraine in patients who have a history of at least 3 prior preventive treatment failures
使用方法（※）	The recommended dose is 120 mg galcanezumab injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.
比較対照	Best supportive care for episodic migraine, and botulinum toxin type A and best supportive care for chronic migraine
主要な増分費用効果比の値	Episodic migraine compared to BSC: £22,633 Chronic migraine compared to BSC: £8,796 Chronic migraine compared to Botox: £15,636

国名	イギリス（スコットランド）
機関名	SMC
評価結果の URL など	https://www.scottishmedicines.org.uk/medicines-advice/galcanezumab-emgality-full-smc2313/
評価対象技術	ガルカネズマブ
評価結果	Recommended with conditions
条件付き推奨の場合は、その条件の詳細	For the treatment of patients with chronic and episodic migraine who have had prior failure on three or more migraine preventive treatments. The treatment benefit should be assessed within 3 months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter. Treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine.
評価対象疾患	Episodic and chronic migraine in patients who have a history of at least 3 prior preventive treatment failures
使用方法（※）	The recommended dose is 120 mg galcanezumab injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.
比較対照	Erenumab, fremanezumab
主要な増分費用効果比の値	N/A (費用効果分析は行われなかった)

国名	フランス
機関名	HAS
評価結果の URL など	Haute Autorité de Santé - EMGALITY (has-sante.fr)
評価対象技術	ガルカネズマブ
評価結果	Recommended with conditions
条件付き推奨の場合は、その条件の詳細	Favourable opinion for reimbursement in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients having had a myocardial infarction, unstable angina, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), stroke, deep-vein thrombosis (DVT) or other serious cardiovascular risk).
評価対象疾患	High-Frequency Episodic and chronic migraine patients with a treatment history of at least 2 prior failures
使用方法（※）	The recommended dose is 120 mg galcanezumab injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.
比較対照	Best supportive care (trial) in the clinical

	assessment
主要な増分費用効果比の値	N/A

国名	ドイツ
機関名	IQWiG
評価結果のURLなど	https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/450/#english
評価対象技術	ガルカネズマブ
評価結果	Population A: Additional benefit not proven. Population B: Additional benefit not proven. Population C: Hint for a considerable additional benefit
条件付き推奨の場合は、その条件の詳細	Generally, the entire label population is reimbursed in Germany, ie. EM and CM patients with 4+ MHDs. However, we didn't show an additional benefit in the naïve patients or those who failed only 1 or 2 treatments, hence the German authorities provided a guidance (treatment advice) highlighting that Galca has only shown a benefit in the more severe patient population as highlighted by Julie below. Physicians can prescribe outside of this treatment advice but may be penalised if they are audited, especially if they cannot provide/ a rationale on why they prescribed outside of the treatment advice. However, this budget audit is done on a subnational level and more a control mechanism for budget purposes. Since the audit can lead to financial payback requirements of the physician to the statutory health insurance and it is very administrative heavy, you will find that a lot of the physician follow the treatment advice to avoid a potential audit. However, despite this advice the entire label is reimbursed.
評価対象疾患	• Subpopulation A: Naive patients and patients that have failed/not tolerated at least 1 prophylactic treatment • Subpopulation B: Patients that have failed the following substance classes: Metoprolol/propranolol, topiramate, amitriptylin, flunarizine Subpopulation C: Patients that failed all other treatments (substance classes)
使用方法（※）	The recommended dose is 120 mg galcanezumab injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.
比較対照	● Subpopulation A: Metoprolol or propranolol or flunarizine or topiramate or amitriptyline, taking into account marketing authorization and the previous therapy ● Subpopulation B: Valproic acid[1] or Clostridium botulinum toxin type A[2] ● Subpopulation C: Best supportive care [1]. According to Annex VI to Section K of the Pharmaceuticals Directive: if treatment with any other authorised medicinal

	product has not been successful or is contraindicated. [2]. According to the marketing authorisation for chronic migraines.
主要な増分費用効果比の値	N/A(費用効果分析は行われていない)

国名	カナダ
機関名	CADTH
評価結果のURLなど	https://www.cadth.ca/sites/default/files/DRR/2021/SR0693%20Emgality%20-%20CADTH%20Final%20Rec.pdf
評価対象技術	ガルカネズマブ
評価結果	Recommended with conditions
条件付き推奨の場合は、その条件の詳細	1. The patient has a confirmed diagnosis of episodic or chronic migraine according to the International Headache Society criteria, defined as either of the following: 1.1. Episodic migraine: migraine headaches on at least 4 days per month and less than 15 headache days per month for more than 3 months. 1.2. Chronic migraine: headaches for at least 15 days per month for more than 3 months of which at least eight days per month are with migraine 2. The patient has experienced an inadequate response, intolerance, or contraindication to at least two oral prophylactic migraine medications of different drug classes. 3. The physician must provide the number of headache and migraine days per month at the time of initial request for reimbursement. 4. The maximum duration of initial authorization is six months. 5. The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a reduction of at least 50% in the average number of migraine days per month at the time of first renewal compared with baseline. At subsequent renewals the physician must provide proof that the initial 50% reduction in the average number of migraine days per month has been maintained. 6. The maximum duration of subsequent authorizations following the initial authorization is six months 7. The patient should be under the care of a physician who has appropriate experience in the management of patients with migraine headaches. 8. Galcanezumab should not exceed the drug program cost of treatment with the least expensive CGRP inhibitor for the treatment of migraine.
評価対象疾患	Episodic and chronic migraine at least 2 prior preventive treatment.
使用方法（※）	Approved dose is a loading dose of 240 mg (administered as 2 consecutive injections) followed by once monthly doses of 120 mg (1 injection).

比較対照	Best supportive care
主要な増分費用効果比の値	CADTH re-analysis: Episodic migraine, ≥2 prior preventative therapies: ICER = $273,560 per QALY Chronic migraine, ≥ 2 prior preventative therapies: ICER = $109,325 per QALY

国名	オーストラリア
機関名	PBAC
評価結果のURLなど	Pharmaceutical Benefits Scheme (PBS) | Galcanezumab (chronic migraine): Injection 120 mg in 1 mL pre-filled pen; Emgality®
評価対象技術	ガルカネズマブ
評価結果	Recommended with conditions
条件付き推奨の場合は、その条件の詳細	Treatment criteria: Must be treated by a neurologist Clinical criteria: Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with this drug for this condition AND Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with this drug for this condition AND The treatment must not be in combination with botulinum toxin AND Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with this drug
評価対象疾患	Chronic migraine in patients who have a treatment history of at least 3 prior preventive treatments
使用方法（※）	The recommended dose is 120 mg galcanezumab injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.
比較対照	Chronic migraine: Botulinum toxin type A and best supportive care
主要な増分費用効果比の値	N/A

2. 費用効果分析における分析条件の設定

2021 年 8 月 27 日に実施された費用対効果評価専門組織において決定された分析枠組みについて以下に示す。

2.1 分析対象とする集団

2021 年 8 月 27 日に実施された費用対効果評価専門組織において決定された分析対象とする集団について以下に示す。

以下の片頭痛患者をそれぞれ分析対象集団とする。
（a）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者
（b）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者
（c）片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者
（d）片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者

2.2 比較対照

2021 年 8 月 27 日に実施された費用対効果評価専門組織において決定された比較対照技術と選定理由（追加提供のナショナルデータベース （NDB）の共同解析の結果を含む）について以下に示す。

<table>
<tr><th>分析対象とする集団</th><th>比較対照技術名</th><th>比較対照技術を選定
した理由</th></tr>
<tr><td>（a）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者</td><td rowspan="2">主に 2 剤目・3 剤目に用いられる既存の片頭痛予防薬（プロプラノロール、バルプロ酸）のうち、最も安価なもの</td><td rowspan="2">「慢性頭痛の診療ガイドライン 2013[9]」によると、片頭痛予防薬で十分な効果が得られなかった場合、有効性の観点から他の予防薬に切り替えて治療を行うことが推奨される一方で、予防薬の有効性の優劣や使用順序は明確に示されていない。このことは臨床専門家への聴取結果によっても支持された。1 剤目にロメリジンが多く使用されていること等を踏まえ、当該分析対象集団の比較対照技術は既存の片頭痛予防薬（プロプラノロール、バルプロ酸）のうち最も安価なものとすることが適当であると考えられる。</td></tr>
<tr><td>（b）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者</td></tr>
<tr><td>（c）片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者</td><td rowspan="2">Best Supportive Care</td><td rowspan="2">当該患者集団では保険適用のある片頭痛予防薬の選択肢が限られるため、Best Supportive Care を比較対照技術とすることが適当であると考えられる。</td></tr>
<tr><td>（d）片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者</td></tr>
</table>

また、本剤の費用対効果評価にかかる分析枠組みの中で、感度分析として以下のシナリオ分析を行うことが指示された。
1. 片頭痛予防薬の2剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない反復性片頭痛患者
2. 片頭痛予防薬の2剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない慢性片頭痛患者
3. 片頭痛予防薬の3剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用

できない反復性片頭痛患者
4. 片頭痛予防薬の3剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない慢性片頭痛患者
それぞれの分析対象集団に対して、以下の比較対照技術とする。
・分析対象集団1および2:既存の片頭痛予防薬（プロプラノロール、バルプロ酸）のうち、当該集団に対して禁忌ではないもの
・分析対象集団 3 および 4: Best Supportive Care

従って、比較対照技術を選定する目的で、片頭痛予防薬の 1 人 1 日あたりの使用量に関する NDB の共同解析を実施した。NDB の 2021 年 3 月の 1 か月分のレセプトデータを使用し、他の疾患の傷病名がないが片頭痛の傷病名（ICD10: G43）のある症例を対象とし、片頭痛に適用のある予防薬それぞれの 1 人 1 日あたりの使用量を集計した。その際、添付文書上の最大使用量の 2 倍を超えている症例を解析対象から除外した。その結果、1 日あたりの薬価の平均値はそれぞれ、バルプロ酸が 36.3 円、プロプラノロールが 29.5 円、中央値はバルプロ酸が 36.4 円、プロプラノロールが 23.2 円となったため、上記表の「最も安価なもの」はプロプラノロールであると科学院と合意した。比較対照技術（プロプラノロール）の使用方法は下記の通りである。

比較対照技術（プロプラノロール）の使用方法

項目	内容
投与経路	経口
投与方法	1 日 20～30mg より投与をはじめ、効果が不十分な場合は 60mg まで漸増し、1 日 2 回あるいは 3 回に分割経口投与する （成人）
投与頻度	毎日
平均処方量	*25.4 mg/日

*NDB のレセプトデータによる平均処方量

従って、対象集団（a）（b）の比較対照技術はプロプラノロール、感度分析 1 および 2 の比較対照技術はバルプロ酸で合意した。

2.3 分析の立場と費用の範囲
HTA ガイドラインに基づき、分析の立場は公的医療の立場、費用の範囲は公的医療費とした。

2.4 効果指標
HTA ガイドラインに基づき、効果指標は QALY とした。

2.5 分析期間
HTA ガイドラインに基づき、分析期間は 25 年に設定した。

2.6 割引率
HTA ガイドラインに基づき、割引率は費用･効果ともに年率 2%とした。

2.7 分析条件の設定の要約
・ 下表にしたがい、分析を実施する集団ごとに 2.1 節から 2.6 節までの内容をまとめる。

分析対象とする集団	（a）片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者

	(b)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者 (c)片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者 (d)片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者
比較対照	(a)(b):プロプラノロール (c)(d): Best Supportive Care
比較対照を選定した理由	(a)(b):「慢性頭痛の診療ガイドライン　2013」によると、片頭痛予防薬で十分な効果が得られなかった場合、有効性の観点から他の予防薬に切り替えて治療を行うことが推奨される一方で、予防薬の有効性の優劣や使用順序は明確に示されていない。このことは臨床専門家への聴取結果によっても支持された。1 剤目にロメリジンが多く使用されていること等を踏まえ、当該分析対象集団の比較対照技術は既存の片頭痛予防薬(プロプラノロール、バルプロ酸)のうち最も安価なものとすることが適当であると考えられる。従って、片頭痛予防薬の使用量に関する NDB 共同解析を行い、プロプラノロールが比較対象技術として選定された。 (c)(d): 当該患者集団では保険適用のある片頭痛予防薬の選択肢が限られるため、Best Supportive Care を比較対照技術とすることが適当であると考えられる。
分析の立場と費用の範囲	分析の立場は公的医療の立場、費用の範囲は公的医療費
効果指標	質調整生存年(Quality-adjusted life year: QALY)
分析期間	25 年
割引率	費用･効果ともに年率 2%

3. 追加的有用性

片頭痛に対して診療ガイドラインで推奨されている薬剤に対して広く国内外のエビデンスを網羅するべく、英語及び日本語によるシスマティックレビューを実施した。分析ガイドラインには、文献検索終了時点について「分析枠組みが決定された後から製造販売業者による分析提出までの一時点に決める」と規定されているが、分析提出までの期間が非常に限られていることから、2020 年 2 月 21 日に 3.2.2 に記載の海外の文献データベース（MEDLINE, EMBASE など）で、2020 年 3 月 12 日に 3.2.2 に記載の国内の文献データベース（医中誌など）においてシステマティックレビューを実施し、分析枠組みの合意後の 2021 年 10 月 29 日に前回実施以降に更新された国内と海外の文献に基づきシステマティックレビューを実施、更新した。なお、2020 年に実施したシステマティックレビューでは該当する対象集団を含む臨床試験の数が限定的であったため、クリニカルクエスチョンの「研究デザイン」を観察研究としたシステマティックレビューも別途 2020 年 5 月 7 日に実施し、分析枠組みの決定後の 2021 年 10 月 29 日にシステマティックレビューを実施、更新した。ガルカネズマブに関しては、システマティックレビューの結果から同定された試験のうち、対象集団が含まれている試験および日本人を対象とした試験の社内データを追加的有用性の評価に用いた。プロプラノロールに関しては、システマティックレビューで同定された試験にガルカネズマブとの直接比較がなかったことと有効性のアウトカムが異なっていたため、PICOS（ (PICOS):Population, Intervention(s), Comparator(s), Outcome(s) and Study design）の対象集団の条件を変更して abstract screening から再度実施した。なお、観察研究についてはシステマティックレビューの結果、今回の対象となる試験が同定されなかったため組み込まれていない（同定された 1 文献は Botulinum toxin を対象としていた）。

以下に詳細を述べる。

3.1 クリニカルクエスチョン

RCT を対象としたシステマティックレビューのクリニカルクエスチョンは表 3-1 の通り設定した。

表 3-1 クリニカルクエスション

項目	内容
対象集団	Adult (18+) patients (males and females) suffering from migraine
介入	All preventive pharmacological interventions for the treatment of migraine relevant to Japan
比較対照	All preventive pharmacological interventions for the treatment of migraine relevant to Japan, compared to each other or to placebo
アウトカム	Efficacy outcomes: • Monthly Migraine Headache Days • Monthly Headache Days • Monthly Migraine Headache Attacks • Monthly Headache Attacks • Monthly use of acute migraine treatment • 50% Reduction in Monthly Migraine Headache days • 75% Reduction in Monthly Migraine Headache days • 100% Reduction in Monthly Migraine Headache days HRQoL outcomes: • PGI-S score

	• MIDAS Total Score, Absenteeism Score, Presenteeism Score, Days of lost productivity Score • MSQoL Questionnaire (Total score, role function-preventive, role function-restrictive, emotional function domains) • EQ-5D Score Safety and discontinuation outcomes: • AEs due to any cause • SAEs due to any cause • Discontinuation due to any cause • Discontinuation due to AEs • Discontinuation due to lack of efficacy
研究デザイン	Phase II, III, IV randomised controlled trials (Crossover up to time of crossover) Conference abstracts from 2017-current Language English and Japanese (other languages will be excluded)
文献検索期間	1946 年から 2021 年 10 月 29 日まで (Conference abstracts: 2017-2021)

3.2 システマティックレビュー

3.2.1 臨床研究の組み入れ基準や除外基準

システマティックレビューの主な組み入れ基準と除外基準を以下に示す。なお、今回は臨床試験を対象とした 2020 年 2 月 21 日の海外文献データベース、2020 年 3 月 12 日の国内文献データベース、2021 年 10 月 29 日に実施した双方のアップデートおよび観察研究を対象とした 2020 年 5 月 7 日、2021 年 10 月 29 日に実施したアップデートでの検索に対して、同じ基準を用いた。

表 3-2 Study selection criteria for randomised controlled trials

Criteria		Inclusion	Exclusion
POPULATION	Abstract selection	• Adult (18+) patients (males and females) suffering from migraine. • Patients may suffer from either episodic or chronic forms of migraine with or without other additional headache conditions, such as cluster headache	• Pediatric populations will be excluded
	Full-text selection	• Adult (18+) patients (males and females) suffering from migraine. • Patients may suffer from either episodic or chronic forms of migraine; or from other additional headache conditions, such as cluster headache.	
TREATMENT/ INTERVENTION	Abstract & full-text selection	• All preventive pharmacological interventions for the treatment of migraine relevant to Japan, including: • Antiepileptic drugs (Valproic acid, topiramate, gabapentin, levetiracetam) • Beta-blockers (Atenolol, metoprolol, nadolol, propranolol) • Antidepressants (Amitriptyline) • Calcium channel blockers (Verapamil, lomerizine) • ARB/ACE inhibitors (Lisinopril, candesartan) • CGRP receptor antagonists (Erenumab, galcanezumab, fremanezumab) • Others (Botulinum toxin type A, magnesium preparation, tizanidine)	• Acute therapies not concomitant to any preventive therapies • Non-invasive therapies (e.g. physical therapy) • Alternative therapies (e.g. Chinese herbs) • Devices

Criteria		Inclusion	Exclusion
COMPARATOR	Abstract & full-text selection	• Interventions above compared to each other, or to placebo	• If multiple arms in RCT, at least two arms need to be of interest (for example, a 3-arm RCT comparing acute vs. preventive vs. placebo will be included whilst only data from the preventive and placebo arm are of interest.)
OUTCOMES	Abstract selection	• No selection on outcomes	• No selection on outcomes

Criteria	Inclusion	Exclusion
Full-text selection	• Efficacy outcomes: • Monthly Migraine Headache Days* • Monthly Headache Days* • Monthly Migraine Headache Attacks* • Monthly Headache Attacks* • Monthly use of acute migraine treatment* • 50% Reduction in Monthly Migraine Headache days • 75% Reduction in Monthly Migraine Headache days • 100% Reduction in Monthly Migraine Headache days • HRQoL outcomes*: • PGI-S score • MIDAS Total Score, Absenteeism Score, Presenteeism Score, Days of lost productivity Score • MSQoL Questionnaire (Total score, role function-preventive, role function-restrictive, emotional function domains) • EQ-5D Score • Safety and discontinuation outcomes: • AEs due to any cause • SAEs due to any cause • Discontinuation due to any cause • Discontinuation due to AEs • Discontinuation due to lack of efficacy	

Criteria		Inclusion	Exclusion
STUDY DESIGN	Abstract & full-text selection	• Phase II, III, IV randomised controlled trials • (Crossover up to time of crossover) • Conference abstracts from 2017-current • Language English and Japanese (other languages will be excluded)	• Phase I clinical trials • Case-control studies, case reports and database analyses • Methodology studies or protocols • Pharmaco-economic studies • Pharmacokinetics, Pharmacodynamics • Reviews, letter, report, expert opinion • Genetics studies • Biomarkers studies • Observational studies • Guidelines • SLR, meta-analyses and NMA[†]

ACE – Angiotensin-converting enzyme; AEs – Adverse events; ARB – Angiotensin II receptor blocker; CGRP – Calcitonin gene-related peptide; MIDAS – Migraine Disability Assessment Test; MSQoL – Migraine-Specific Quality of Life; NMA – Network meta-analysis; PGI-S – Patient Global Impression of Severity; RCT – Randomised Controlled Trial; SAEs – Serious adverse events; SLR – Systematic literature review

*All time-points were of interest in the SLR, however, if outcome data was reported more frequently than monthly, data was extracted on a monthly basis into the data extraction form. For instance, if a study reported outcome data at 4, 12 and 18 weeks, all data was extracted. However, if a study reported outcome data at 4, 6, 8, 10 and 12 weeks, only the data at 4, 8 and 12 weeks was extracted.

[†]Reviews and meta-analyses are excluded from data extraction since aggregated results cannot be used in our analysis. However, good quality meta-analysis and systematic reviews will be used for crosschecking of references.

表 3-3 Study selection criteria for observational studies

Criteria		Inclusion	Exclusion
POPULATION	Abstract selection	• Adult (18+) patients (males and females) suffering from migraine. • Patients may suffer from either episodic or chronic forms of migraine with or without other additional headache conditions, such as cluster headache	• Pediatric populations will be excluded
	Full-text selection	• Adult (18+) patients (males and females) suffering from migraine. • Patients may suffer from either episodic or chronic forms of migraine; or from other additional headache conditions, such as cluster headache.	
TREATMENT/ INTERVENTION	Abstract & full-text selection	• All preventive pharmacological interventions for the treatment of migraine relevant to Japan, including: • Antiepileptic drugs (Valproic acid, topiramate, gabapentin, levetiracetam) • Beta-blockers (Atenolol, metoprolol, nadolol, propranolol) • Antidepressants (Amitriptyline) • Calcium channel blockers (Verapamil, lomerizine) • ARB/ACE inhibitors (Lisinopril, candesartan) • CGRP receptor antagonists (Erenumab, galcanezumab, fremanezumab) • Others (Botulinum toxin type A, magnesium preparation, tizanidine)	• Acute therapies not concomitant to any preventive therapies • Non-invasive therapies (e.g. physical therapy) • Alternative therapies (e.g. Chinese herbs) • Devices

Criteria		Inclusion	Exclusion
COMPARATOR	Abstract & full-text selection	• Interventions above compared to each other, or to placebo	• If multiple arms in RCT, at least two arms need to be of interest (for example, a 3-arm RCT comparing acute vs. preventive vs. placebo will be included whilst only data from the preventive and placebo arm are of interest.)
OUTCOMES	Abstract selection	• No selection on outcomes	• No selection on outcomes

Criteria	Inclusion	Exclusion
Full-text selection	• Efficacy outcomes: • Monthly Migraine Headache Days* • Monthly Headache Days* • Monthly Migraine Headache Attacks* • Monthly Headache Attacks* • Monthly use of acute migraine treatment* • 50% Reduction in Monthly Migraine Headache days • 75% Reduction in Monthly Migraine Headache days • 100% Reduction in Monthly Migraine Headache days • HRQoL outcomes*: • PGI-S score • MIDAS Total Score, Absenteeism Score, Presenteeism Score, Days of lost productivity Score • MSQoL Questionnaire (Total score, role function-preventive, role function-restrictive, emotional function domains) • EQ-5D Score • Safety and discontinuation outcomes • AEs due to any cause • SAEs due to any cause • Discontinuation due to any cause • Discontinuation due to AEs • Discontinuation due to lack of efficacy	• Any outcomes not listed under inclusion

Criteria		Inclusion	Exclusion
STUDY DESIGN	Abstract & full-text selection	• Observational studies • Conference abstracts from 2017-current • Language English and Japanese (other languages will be excluded)	• Phase I-III clinical trials • Case-control studies and case reports • Methodology studies or protocols • Pharmaco-economic studies • Pharmacokinetics, Pharmacodynamics • Reviews, letter, report, expert opinion • Genetics studies • Biomarkers studies • Guidelines • SLR, meta-analyses and NMA†
GEOGRAPHIC LOCATION	Abstract & full-text selection	• Japan	• Any country not listed under inclusion

ACE – Angiotensin-converting enzyme; AEs – Adverse events; ARB – Angiotensin II receptor blocker; CGRP – Calcitonin gene-related peptide; MIDAS – Migraine Disability Assessment Test; MSQoL – Migraine-Specific Quality of Life; NMA – Network meta-analysis; PGI-S – Patient Global Impression of Severity; RCT – Randomised Controlled Trial; SAEs – Serious adverse events; SLR – Systematic literature review

*All time-points were of interest in the SLR, however, if outcome data was reported more frequently than monthly, data was extracted on a monthly basis into the data extraction form. For instance, if a study reported outcome data at 4, 12 and 18 weeks, all data was extracted. However, if a study reported outcome data at 4, 6, 8, 10 and 12 weeks, only the data at 4, 8 and 12 weeks was extracted.

†Reviews and meta-analyses are excluded from data extraction since aggregated results cannot be used in our analysis. However, good quality meta-analysis and systematic reviews will be used for crosschecking of references.

3.2.2 使用したデータベース

使用したデータベースを以下に示す。

海外の文献データベース:

- MEDLINE
- MEDLINE In-Process & Other Non-Indexed Citations
- EMBASE
- CENTRAL (note: search performed for RCTs only, CENTRAL was not in scope for Observational studies)
- CDSR

日本の文献データベース:

- 医中誌

海外の文献データベースの MEDLINE, EMBASE, CENTRAL, CDSR については Ovid を使用し、検索は 2020 年の 2 月 21 日に実施された。国内のデータベースである医中誌については、2020 年 3 月 12 日に検索を実施した。その後、分析枠組み決定後の 2021 年 10 月 29 日に双方をアップデートした。

下記の 2017 年以降の学会発表についても、Ovid に掲載されているものは前述の検索に含まれていると想定し、Ovid に含まれていないものを追加的に検索した。検索は以下の関連サイトにアクセスして実施した。

- International Headache Society (IHS): 2017-current (2017-2018: search in Ovid; 2019: hand search)
- American Headache Society (AHS): 2017-current (search in Ovid)
- European Academy of Neurology Congress (EANC): 2017-current (search in Ovid)
- American Academy of Neurology (AAN): 2017-current (search in Ovid)
- The European Headache Federation (EHF): 2017-current (search in Ovid)
- Japanese Headache Society (JHS; abstracts in Japanese): 2017-current (hand search)

また、下記の臨床試験データベースに対しても検索の対象とした。検索は以下の関連サイトにアクセスして実施した。

- ✓ Clinicaltrials.gov – US National institute of Health
- ✓ International Clinical Trials Registry Platform (ICTRP) – World Health Organization
- ✓ EU Clinical trials register (EUCTR)
- ✓ Japanese Medical Association Center for Clinical Trials (JMACCT) Clinical Trial Registry

3.2.3 使用した検索式

検索式は、臨床試験(RCT)と観察研究のそれぞれに設定し、疾患(MeSH and text)、研究デザインおよび介入に対する用語を組み合わせた。MEDLINE および EMBASE での臨床試験の検索には、Cochrane で検証された手法を用いた。HTA ガイドラインに従って、検索はデータベースごとに実施した。検索式は Appendix 3-1a および 3-1b にそれぞれ記載した。

3.2.4 システマティックレビューの実施

2020 年から 2021 年にかけて実施した海外と国内の文献に対するシステマティックレビューの概要を下記に記載する。

The methods used for the SLR are in line with the Cochrane collaboration[11] and PRISMA (Preferred Reporting Items in Systematic Review and Meta-Analysis[12]).

The process for study selection was performed in two stages. The first stage involved the review of the records title and abstract by two researchers against the pre-determined eligibility criteria for PICOS. If exclusion of a record based on its title/abstract was not possible, the full-text publication was retrieved and evaluated against the eligibility criteria in the second stage of screening. All screening decisions were documented in Excel screening files. This second stage was also performed by two researchers. When consensus was not achieved, an independent quality controller was involved. The inclusion and exclusion process was documented including reviewers' initials, the reason for exclusion (if applicable), and additional comments on the decision.

Results:
In total, the literature search identified 4,420 records from bibliographic databases (3,703), trial registries (717), study tables from Eli Lilly trials (5), and key publications that were retrieved through reference mining. In total, 195 publications relating to 100 individual trials were included for data extraction. A flow diagram of the numbers of studies included and excluded at each stage of the selection process is provided in 図 3-1.

図 3-1 PRISMA flow chart of RCT studies

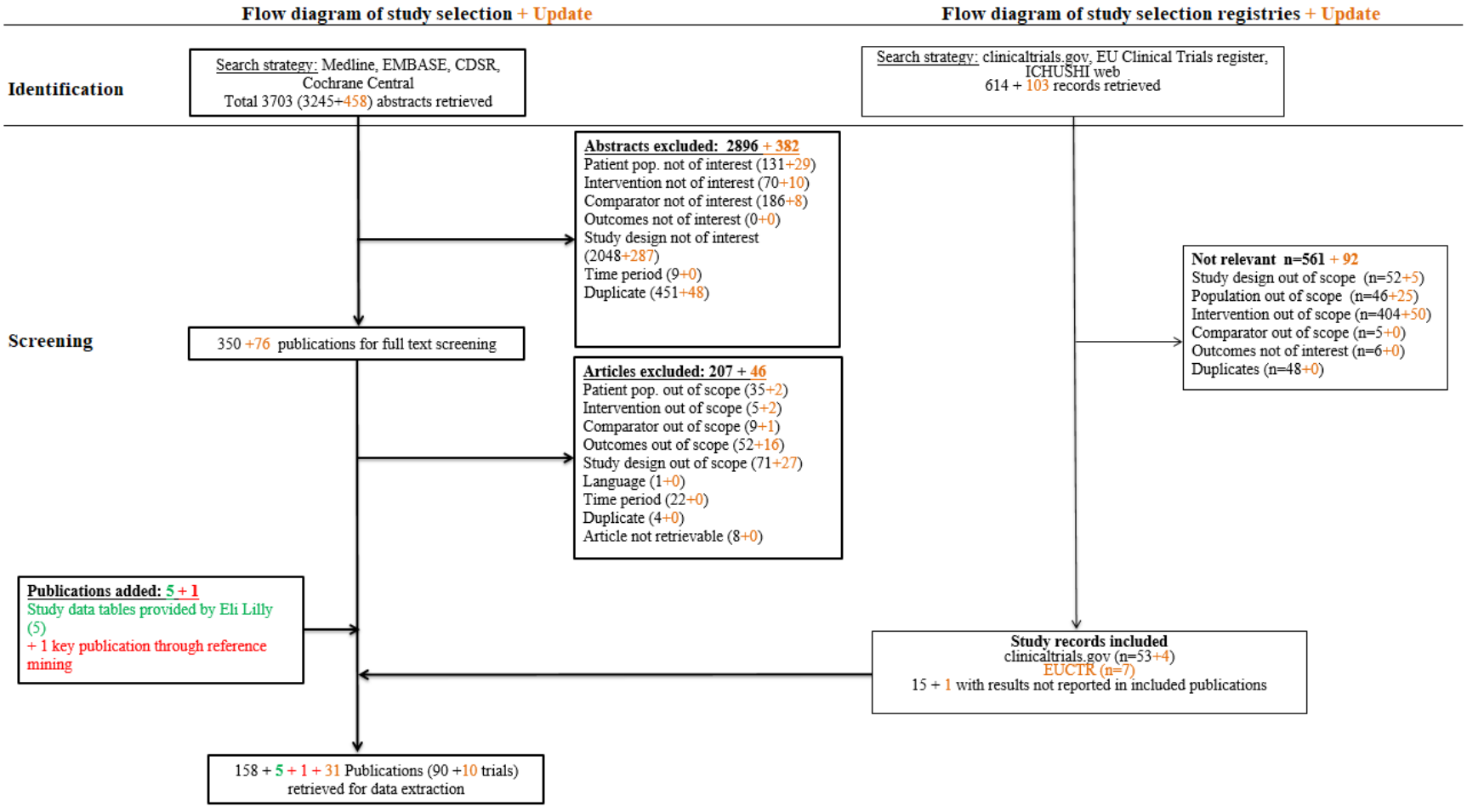


図 3-2 PRISMA flow chart of observational studies

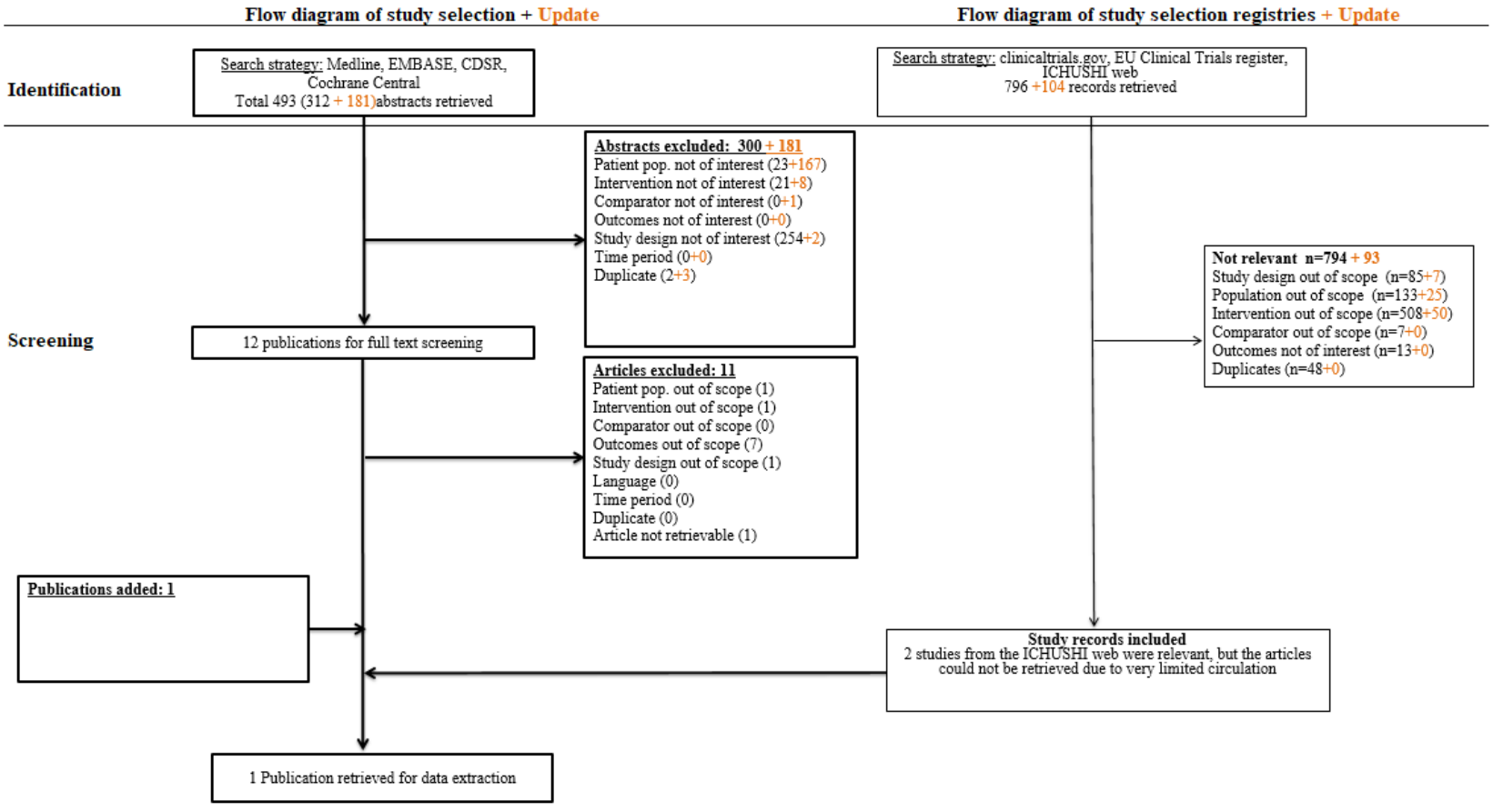


図 3-1 においては、オレンジで 2021 年のアップデートの検索時における追加文献数を示している。緑で示した 5 つの研究は、システマティックレビューで同定された自社試験のうち論文に含まれていないデータを追加したものである。赤で示した 1 つの研究はプロトコルに規定のプロセスにより抽出したものである。

表 3-4 Number of Identified publications

# of hits	Original search	Update Search	Total
Galcanezumab	27	10	37
Valproic acid	7	1	8
Propranolol	12	1	13
Lomerizine	0	0	0
Other	128	19	147
Total	164	31	195

195 件の結果より、ガルカネズマブの7試験が同定された。このうち、CGAN（第Ⅱ相）、CGAW（第Ⅲ相）は日本人を対象としているが、定義された対象集団のデータが限定されているため、海外の第 3 相試験（CGAG/CGAH/CGAI）のデータを含めてメタアナリシス及び間接比較に使用した。除外された 2 試験は、それぞれ反復性頭痛と慢性頭痛が分かれていない、用法用量が異なっていたという理由で除外された。

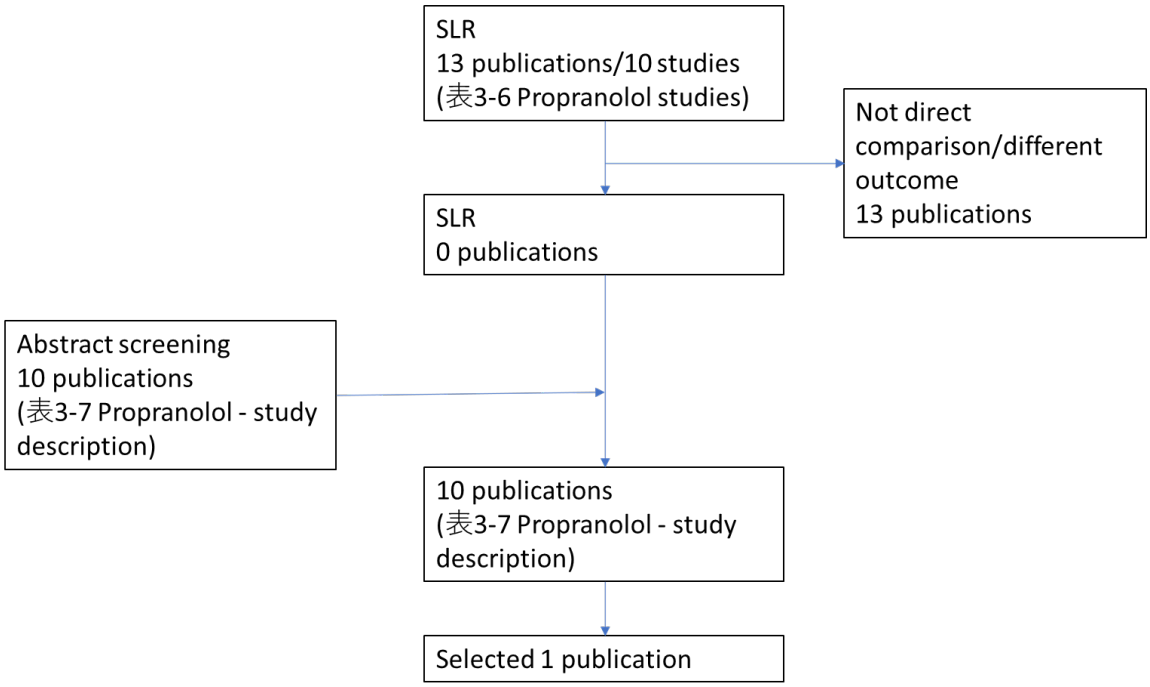
各試験の詳細なデータについては、3.5　章および　4　章に記載した。

表 3-5　同定した弊社主導の本剤の臨床研究(論文)の一覧

臨床試験名	介入	比較対照	サンプルサイズ	対象患者	Reference
ART-01 NCT01625988	Galcanezumab	Placebo	217	Unspecified	Goadsby 2019[13] Dodick 2014[14]
CGAB NCT02163993	Galcanezumab	Placebo	410	EM/0-2 SOC failure	Ayer 2018[15] Skljarevski 2018[16] Oakes 2018 [17]
CGAG (EVOLVE-1) NCT02614183	Galcanezumab	Placebo	858	EM/0-2 SOC failure	Detke 2020[18] Stauffer 2018[19] Ford 2019[20]
CGAH (EVOLVE-2) NCT02614196	Galcanezumab	Placebo	915	EM/0-2 SOC failure	Skljarevski 2018[21] Ford 2019[20]
CGAI (REGAIN) NCT02614261	Galcanezumab	Placebo	1113	CM/0-2 SOC failure	Detke 2018[22]
CGAW (CONQUER) NCT03559257	Galcanezumab	Placebo	462 (incl. Japanese patients n=42)	EM+CM/ 2-4 SOC failure	Mulleners WM 2020[23] Reuter 2021[24]
CGAN NCT02959177	Galcanezumab	Placebo	459 (Japanese patients)	EM/0-2 SOC failure	Sakai 2020[25] Shibata 2020[26] Tatsuoka 2021[27]

プロプラノロールの RCT は 13 件報告されている。しかし、システマティックレビューで同定された試験にガルカネズマブとの直接比較がなかったことと有効性のアウトカムが異なっていたため、PICOS の対象集団の条件を変更して abstract screening から再度実施した。図 3-3 のプロセスに従い、間接比較に最も適した研究を選択した。以下に詳細を記載する。

図 3-3 Selection process on propranolol studies



The majority of propranolol studies were performed in populations with unspecified migraine (8), one trial included patients with chronic migraine, and one included patients with episodic migraine. The relatively high proportion of patient populations with unspecified migraine may, in part, be explained by the study years. Six of the propranolol studies were conducted prior to the year 2000, while the definition of chronic migraine was included only in the 2nd edition of the International Classification of Headache Disorders (ICDH-II), published in 2004. Four studies compared propranolol with placebo; two, with topiramate; two, with nadolol; one, with amitriptyline; and one, with valproate. Selected studies for propranolol are shown in 表 3-6.

表 3-6 Propranolol studies

Author	Title	Reference
Pradalier et al 1989	Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study.	Cephalalgia (1989) 9(4): 247-53.[28]
Mathew et al 1981	Prophylaxis of Migraine and Mixed Headache. A Randomized Controlled Study	Headache (1981) 21(3): 105-9.[29]
Ryan et al 1984	Comparative study of nadolol and propranolol in prophylactic	American Heart Journal (1984) 108:1156.[30]

	treatment of migraine	
Sargent et al 1985	A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache	Headache (1985) 25(6): 320-324.[31]
Sudilovsky et al 1987	Comparative efficacy of nadolol and propranolol in the management of migraine.	Headache (1987) 27(8): 421-426.[32]
Diener et al 1996	Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol.	Cephalalgia (1996) 16(6): 441-7.[33]
Diener et al 2004*	Topiramate in migraine prophylaxis Results from a placebo-controlled trial with propranolol as an active control	J Neurol (2004) 251: 943–950.[34]
Ashtari et al 2008	A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis	Acta Neurol Scand (2008) 118: 301–305.[35]
Jafarpour et al 2016	Effect of a traditional syrup from Citrus medica L. fruit juice on migraine headache: A randomized double blind placebo controlled clinical trial	Journal of Ethnopharmacology (2016) 179: 170–176[36]
Dakhale et al 2019	Low-dose sodium valproate versus low-dose propranolol in prophylaxis of common migraine headache: A randomized, prospective, parallel, open-label study	Indian J. Pharmacol. (2019) 51(4): 255-262[37]

*This paper was excluded from the main body NMA and SLR update due to the fact it enrolled adolescent patients (SLR focused on adult patients with migraine defined as those aged ≥18 years), but due to the limited evidence base available for propranolol, to support the identification of the best evidence base to conduct an ITC, Lilly re-introduced the paper as a possible option for evidence selection to drive ITC versus propranolol.

In order to decide which propranolol data could be used to form the foundation for the indirect treatment comparison analysis, Lilly identified most suitable evidence as below. This evidence, as a pre-requisite needed to report the effectiveness of propranolol in prophylactic migraine based on input measures that drive the cost effectiveness model, namely the change from baseline in migraine headache days and response rate.

As such, one of the minimum requirements for the evidence base for propranolol are:

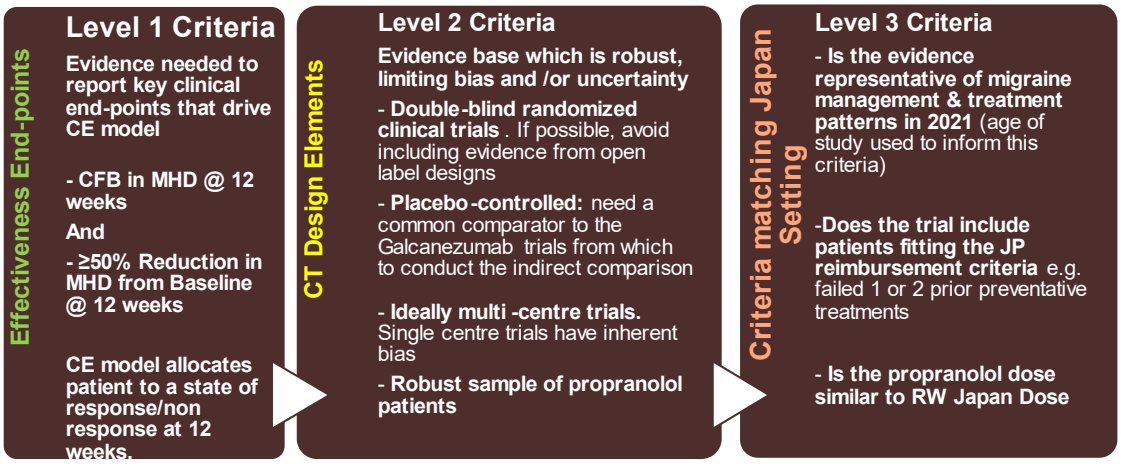
- Report Mean Change from Baseline (CFB) in Migraine Headache Days. If Migraine Headache Days was not available, consideration was given to consider evidence reporting the mean CFB in Headache days (ie non-specific for migraine) AND

- Report Response Criteria. The CE model allocates the patient to a state of response or non-response at 12 weeks. The clinically meaningful response in episodic migraine is regarded as ≥50% reduction in monthly migraine headache days and for chronic migraine the clinical meaningful response is set at ≥30% reduction in monthly migraine headache days. Given these criteria, as a minimum, in order to allocate patients by response state: responder or non-responder, the evidence for propranolol needed to report at least the 50% reduction in Migraine Headache days (or as a fall back the less specific 50% reduction in Headache days).

Key Criteria Used to Inform Selection of Propranolol Evidence to Drive Indirect Treatment Comparison (ITC):
In addition to the criteria on key effectiveness measures, Lilly identified other key criteria in determining the best evidence for selection to inform the ITC (see 図 3-4).

1. Lilly strove to select a trial where the evidence was unbiased. The goal was to select evidence based on double blind randomized controlled trials, ideally multi-centre trials. Single centre trials can include a level of bias.
2. The evidence needed to be placebo controlled. We wanted to select evidence that includes a common comparator as was included in the Galcanezumab pivotal trials so an indirect comparison can be drawn based on placebo adjustment.
3. In addition, ideally but not as a pre-requisite, we were looking to select a study reflecting a robust sample of propranolol patients.
4. Then there were secondary criteria (i.e. Level 3 criteria), which were influencing evidence selection including trying to identify evidence which is representative of current migraine management in Japan. Lilly determined age of study to represent a proxy of the likelihood the study was representative of current prophylactic migraine management. Ideally, we would want to select a study which evaluated propranolol at a dose as close to as possible as the real world (RW) dose of propranolol used in Japan. In the event, there was no study that reflected a dose close to RW propranolol dose in Japan, the goal was to select a study with a dose higher than is used in Japan, so that the evidence would result in propranolol effectiveness higher than what would be expected in Japan. It was important not to bias the results against propranolol, favouring to select evidence based on higher RW use which would expect to deliver the same or better efficacy than the dose used in Japan in the Real World setting.
5. Finally, an ideal situation would be to select a study enrolling patients who had failed 1 or more prior preventative treatments to more closely represent patient archetype who are eligible for galcanezumab in the Japan Real World setting according to the guidance of optimal use guideline in Japan. If a study focused purely on patients with 1 or 2 prior preventative treatments was not available, the next best option was to include evidence based on a mixed cohort including naïve and possibly patients with 1 or more prior preventative failures. The least desired evidence was to include a trial focused on migraine prophylaxis naïve patients as these patients are likely to perform better on propranolol than those who would be treated under the Japan reimbursement criteria, with a risk of over inflating the propranolol effect size.

図 3-4 Decision criteria for selecting propranolol evidence to inform the indirect treatment comparison versus galcanezumab



Based on the criteria above, 9 of the 10 published manuscripts including propranolol evidence were rejected, leaving one manuscript selected as the foundational evidence to drive the indirect treatment comparisons versus propranolol. The selected manuscript still had limitations and was unable to satisfy all criteria (discussed below), however it was able to satisfy the key criteria.

Rationale for the rejection of 9 of 10 available papers focused on evaluating propranolol evidence in prophylactic management of migraine.

The only published evidence which assessed mean change in Migraine Headache Days was Diener et al 2004[34]. Sargent et al 1985[31] did record mean change in headache days which could have been used as a surrogate, however Sargent et al 1985[31] did not record the proportion of patients who achieved a clinically meaningful response defined as ≥50% reduction in headache days at week 12. This meant Lilly still could not leverage Sargent et al 1985 because there was no ability to inform the % of patients meeting response/non-response at week 12 which is foundational to the architecture of the CE model (see 表 3-7).
The majority of other papers focused their effectiveness measure on reduction in number of headache attacks or migraine headache attacks [29, 30, 32, 35, 36, 37].
Despite the possibility to consider evaluation of a different effectiveness measure, other limitations in the papers recording change in frequency of migraine headache attacks or headache attacks rendered their evidence not suitable.
表 3-7 records the reasons why a specific trial was rejected.

表 3-7 Propranolol – Reason to exclude

	Age of study	Design	Multi-centre	Placebo-controlled	Cross-over	Entry Criteria (focused on # MHD/attacks to enroll in the study)	Enrolled Population
Diener, 2004[34] (Episodic Migraine) - selected study -	2004: Old but possibly reflects current day practice	Randomized Double-Blind	Yes	Yes	No	Subjects with 3 to 12 migraine headaches (periods) and no more than 15 headache days Propranolol arm: Mean 6.1 migraine headache days per month	Mixed Population: Migraine naïve and indication that some patients had prior treatment as their preventative medication was noted as being withdrawn during the wash out period
Pradalier, 1998[28] (Episodic Migraine)	Old study, patients not likely to reflect existing treatment patterns and patient management today	Randomized Double-Blind	Yes	Yes	No	8 Attacks/Month	Unclear if patients had received prior preventative treatment
Mathew, 1981[29]	Study evaluated patients between 1976-1980: Due to time study will not be reflective of existing treatment patterns and patient management today	Randomized Double-Blind	No	No	No	Nonspecific and does not indicate the # MHDs to qualify to be enrolled: Patients with migraine and patients with mixed migraine and muscle contraction headache were randomly allocated.	Not recorded if patients had received prior preventative therapy
Ryan, 1984[30]	Very old and not reflective of existing treatment patterns	Randomized Double-Blind	Yes	No	No	minimum of 3 migraine attacks/month	Probably a mixed population as the wash-out phase allowed for the wash-out of previous medication
Sargent, 1985[31]	Very old and not reflective of existing treatment patterns	Randomized, parallel, double-Blind	Yes	Yes	No	an average of 12 migraine headache days over at least six migraine attacks in the 3 months prior to entry into the study	Unclear
Sudilovsky 1987[32]	Very old and not reflective of existing treatment patterns	Randomized Double-Blind	Yes	No	No	At least 3 Migraine attacks per month	Unclear: patients were deemed to require preventative medication, but no mention patients had received prior preventative

							medication
Ashtari 2008[35]	Patients were enrolled in 2003-2004 and results published in 2008. This study is old but more likely to be reflective of todays current treatment pattern and management	Randomized Double-Blind	No	No (Topiramate not considered in Japan)	No	Frequency of three or more migraine headache attacks per month during a 3-month period before entry	Mixed Population: inclusion criteria indicate: concomitant migraine prophylactics were withdrawn 1 month prior to entry into this trial.
Jafarpour 2016[36]	Recent study more reflective of current treatment patterns and patient management	Randomized, parallel, double-Blind	No	Yes	Yes	Clinical diagnosis of migraine headache without aura were selected according to (ICHD-2) Inclusion criteria: male or female aged >18 years, presence of ≥4 migraine attacks/month in the absence of medication overuse and not due to any other disease, pain refractory to preventive medications, no current prophylactic treatment for migraine, no clinical conditions that precluded the use of any of the drugs of the study.	Unclear but probably a mixed population: patients had to have migraine prophylactics withdrawn 1 month prior to entry into this trial.

Dakhale 2019[37]	Very recent study conducted between 2016-2017 where the treatment pattern and patient management would be consistent with current practice	A randomized, prospective, parallel, open-label study Risk of bias due to open-label design	No	No (Comparison to sodium valproate)	No	Patients with a history of migraine without aura for at least 6 months before evaluation (as per ICHD definition [2.1.1]) Patients experiencing 2–6 migraine attacks/month, but not ≥15 attacks/month	Migraine prophylactic therapy-naive patients who satisfied the selection criteria. The population in this study are not consistent with the criteria of the population likely to be eligible for reimbursement for Galcanezumab. The results of propranolol in this study are likely to be overestimated given the population are naive to prior preventative therapies.
Diener 1996[33]	Very old study: Patients were enrolled in the study in Sept 1991-April 1994 and thus the treatment pattern then is not reflective of todays treatment pattern	Controlled, Double blind	Yes	Yes	No	Patients with a migraine with and/or without aura according to the IHS criteria; migraine history of at least 12 months duration; a mean number of 2-10 migraine attacks per month within the last 3 months prior to the study	Unclear patients on prior preventive medication were withdrawn within the 4-week run-in period

	Age of participants	% Female	N of propranolol	Propranolol dose	Titration	Country participation
Diener, 2004 (Episodic Migraine) - selected study -[34]	14 - 66 years Median 41 years	76-83%	143	160mg once daily: *Mean dose higher than RW Japanese propranolol dose. Results inflated in favour of propranolol due to higher propranolol dose used*	Yes: 8 weeks so patient assessment was based on optimized dose	Multi-country(n=13): Germany, Sweden, Spain, Italy, Taiwan, South Africa, Korea, UK, Australia, Denmark, Finland, France and Netherlands
Pradalier, 1998 (Episodic Migraine)[28]	18-65 years	Propranolol: 77.5%	31	160mg Long Acting once daily *Mean dose higher than RW Japanese propranolol dose. Results inflated in favour of propranolol due to higher propranolol dose used*	No	France
Mathew, 1981[29]	19-57 years	92.7% *This cohort is nearly all female and not representative of a Japan demographic where male suffers are more frequent than <10%*	44	20mg thrice daily: *Mean dose higher than RW Japanese propranolol dose. Results inflated in favour of propranolol due to higher propranolol dose used*	No	Probably USA
Ryan, 1984[30]	21 - 60 Years	73%	16	160mg Once daily: *Mean dose higher than RW Japanese propranolol dose. Results inflated in favour of propranolol due to higher propranolol dose used*	No	USA
Sargent, 1985[31]	18-65 years	79%	44	40mg thrice daily: 120mg in total. *Dose lower than other studies but remains higher than RW Japanese propranolol dose. Results in favour of propranolol due to higher propranolol dose used*	Patients were titratrated up from propranolol 40mg/2 daily in the 2 week prior to randomization to 40mg/ 3 times daily	USA
Sudilovsky 1987[32]	18-60 years	Propranolol arm: 77%	44	80mg twice daily: *Mean dose higher than RW Japanese propranolol dose. Results inflated in favour of propranolol due to higher propranolol dose used*	No	USA
Ashtari 2008[35]	18-65 years	Propranolol: 76.7%	30	80mg daily: *Mean dose higher than RW Japanese propranolol dose. Results inflated in favour of propranolol due to higher propranolol dose used*	No	Iran: *Not likely to be representative of a Japan demographic*
Jafarpour 2016[36]	>18 years	83%-88% female	26	20mg thrice daily: *Trial reflected a lower propranolol total daily dose. The dose in this study is still higher than mean propranolol dose used in RW in Japanese patients*	Unclear	India: *Not likely to be representative of a Japan demographic/Japan migraine management*

Dakhale 2019[37]	18-60 years	Propranolol arm: 63% female (19/30)	30	Low dose 40mg SR once daily This study evaluated the lowest propranolol dose of 40mg once daily, which is more consistent with the RW mean dose prescribed for propranolol in Japanese patients. Patients could increase the dose to 40mg SR twice daily if there was little to no response	Yes: dose up titration to 40mg SR twice daily was allowed based on response	India: *Not likely to be representative of a Japan demographic/Japan migraine management*
Diener 1996[33]	18-60 Years (mean age 39 across all treatment arms (+/-12 years))	78% across all treatment arms are female	78 randomised, evaluable patients on propranolol in ITT 68	Propranolol 40mg three times daily (120mg total daily dose): *Mean dose higher than RW Japanese propranolol dose. Results inflated in favour of propranolol due to higher propranolol dose used*	No	Germany

	Timepoint (primary endpoint)	# of patients in Propranolol Arm completing the study/evaluable @ time of primary end-point	Mean change in mean MHD (availability)	Mean Change in HD	30% response rate in MHD	50% response rate in MHD	Monthly rescue data recorded
Diener, 2004 (Episodic Migraine) - selected study -[34]	26 weeks (includes 8 week titration): 18 weeks of double blind treatment. As assessment >12 weeks optimized propranolol efficacy	102	Yes	Not needed as CFB in MHD available	No	Yes: 50% reduction in mean migraine frequency	Yes: change in utilization of rescue medication captured
Pradalier, 1998[28] (Episodic Migraine)	12 weeks	22 Completed: 31 patients were randomized to propranolol 160mg after the run period and 9 discontinued and thus were not evaluable	No	No	No	No	Yes
Mathew, 1998[29]	12 weeks	38 completed the trial can could be assessed for effectiveness evaluations	No	No: Only have improvement in average weekly index	No	Average % improvement but not the % who achieved a 50% improvement	Rescue was allowed but not recorded
Ryan, 1984[30]	12 weeks	12: very very small cohort with evaluable results. Risk results not representative of a general cohort treated with propranolol	No	No	No	No	Rescue was allowed but not recorded
Sargent, 1985[31]	12 weeks	<44 patients: Authors indicated that 20 patients discountinued before 12 week assessment and thus were not evaluable but did not indicate which treatment arm the patients were discontinued	No	Yes	No	No	Rescue was allowed but not recorded
Sudilovsky 1987[32]	12 weeks	30	No	No	No	Yes but only for 50% reduction in headache intensity	Rescue was allowed but not recorded
Ashtari 2008[35]	8 weeks: *Assessment at 8 weeks likely to suboptimize propranolol efficacy biasing the results in favour of Galcanezumab. This was a key factor in determining whether to select this study to run indirect treatment comparisons*	29	No	No	No	No	Unclear

	Timepoint (primary endpoint)	# of patients in Propranolol Arm completing the study/evaluable @ time of primary end-point	Mean change in mean MHD (availability)	Mean Change in HD	30% response rate in MHD	50% response rate in MHD	Monthly rescue data recorded
Jafarpour 2016[36]	4 weeks: *Assessment at 4 weeks likely to suboptimize propranolol efficacy biasing the results in favour of Galcanezumab. This was a key factor in determining whether to select this study to run indirect treatment comparisons*	21: 5 patients were recorded as having discontinued on propranolol leaving 21/26 with evaluable results	No	No	No	No	Allowed to use rescue medication which may bias the results
Dakhale 2019[37]	12 weeks	28: 2 patients discontinued in the propranolol arm	No	No	No	No: trial evaluated a 50% reduction in migraine attacks but did not report 50% reduction in migraine headache days	Yes was recorded but not recorded in the results
Diener 1996[33]	12 weeks	68	No	No	N0	No: trial evaluated a 50% reduction in migraine attacks but did not report 50% reduction in migraine headache days	Acute medication was allowed for migraine attacks up to 12 days/ month. Post hoc analysis which demonstrated propranolol was not superior to placebo when rescue medication was accounted for

Green boxes indicate that the trial fulfils the criteria, amber indicates that the criteria is fulfilled but with some limitations and red indicates that the criteria is not fulfilled (see 図 3-4 Decision criteria for selecting propranolol evidence to inform the indirect treatment comparison versus galcanezumab).

表 3-8 同定したプロプラノロールの臨床研究（論文）の一覧表

臨床試験名	介入	比較対照	サンプルサイズ	Reference
NCT00236561	Propranolol	Placebo	143	Diener (2004)[34]

以下に Diener et al.のみがプロプラノロールの臨床研究として同定された根拠を述べる。

1: Change in monthly migraine headache days

- With the exception of Diener 2004[34], none of the other publications included mean change from baseline in Migraine Headache Days.
- Sargent et al 1985 did evaluate reduction in headache days but unfortunately did not report the proportion of patients who met the clinically meaningful response criteria.

2: Response Criteria: Clinically Meaningful Response (≥30% reduction for episodic migraine and ≥50% reduction for chronic migraine) at Week 12

- Pradalier et al 1989[28], Mathew et al 1981[29], Ryan et al 1984[30] , Sargant et al 1985[31], Diener et al 1996[33], Jafarpour et al 2016[36] did NOT record any data to indicate the % of patients who met a clinically meaningful response which meant all these papers needed to be rejected as the CE model is driven by allocation of patients by responder/non responder status at week 12.
- Ashtari et al 2008[35] and Jafarpour et al 2016[36] assessed effectiveness at week 8 and week 4 respectively. It is likely that the peak effectiveness of propranolol is NOT reached at week 4 or 8 and thus both these trials would underestimate the effect size for propranolol, biasing the ITC in favour of galcanezumab. On this basis, both these trials were disregarded on the basis of the timing of the effectiveness, plus other reasons below.

3: Robustness of Evidence: Double-blind, Randomized Placebo-controlled Trial; Multi-centre

- Dakhale et al 2019[37] did not meet the criteria for robustness of evidence. Dakhale et al 2019[37] is an open label single centre study which is subject to significant bias.
- Mathew et al 1981[29], Ashtari 2008[35], Jafarpour et al 2016[36] were all single-centre studies where there is a risk of bias.
- Mathew et al 1981[29], Ryan 1984 et al[30], Sudilovsky et al 1987[32], Ashtari 2008 et al[35] and Dakhale et al 2019[37] are NOT placebo controlled. There is no common comparator with the galcanezumab trials making it impossible to perform an indirect treatment comparison with propranolol.

4: Robustness of Evidence: Evaluable Propranolol Patient Cohort

- Many of the studies had very small evaluable propranolol cohorts. Smaller cohorts are subject to the impact of heterogeneity factors based on enrolled population. The goal was to select evidence with larger propranolol cohorts.
- Diener et al 2004[34] enrolled 143 patients, and had 102 evaluable propranolol patients at 12 weeks. So across all studies this was the largest of all evaluable propranolol groups.
- Lilly believes there is significant limitation in the <u>following studies</u> as a result of very small number of evaluable propranolol patients.
  - Ryan et al 1984[30]: 12 evaluable propranolol patients
  - Sudilovsky et al 1987[32]: 30 evaluable propranolol patients
  - Ashtari et al 2008[35]: 29 evaluable propranolol patients
  - Jafarpour et al 2016[36]: 21 evaluable propranolol patients

- Dakhale et al 2019[37]: 28 evaluable propranolol patients

5: Enrolled population

None of the published propranolol evidence focused enrolment on a population who had 1 or 2 prior preventative failure medication.

The description of the population studied was not well recorded in the majority of trials.

- In Diener et al 2004[34] we know that the population was a mix of naïve and patients who had received prior preventative treatment as the study indicated that current preventative medication was tapered during the washout period.
- Dakhale et al 201937 specifically included migraine naive patients and is not representative of the patient population eligible for galcanezumab in Japan. The results of this study would likely over estimate the effect of propranolol in a population who have 1 or 2 prior preventative treatments. This is another reason to reject Dakhale et al 201937 as viable evidence.

6: Age of Study

- A possible limitation of the evidence is the age of the study. The older the study, the less likely the study results would reflect prophylactic migraine management currently.
- For this reason Lilly felt studies that pre-dated 2000 may not reflect current migraine practice[28,29, 30, 32, 33].

Rationale for Selection of Diener et al 2004[34]

- It was the only study that captured the mean change in Migraine Headache Days.
- It included a response criteria assessment at week 12: defined as at least a 50 % reduction in average monthly migraine frequency.
- Study was robust: Double blind, randomized, multi-centre. It appears to be the only multi-country study and included enrolment of Asian patients from Taiwan and S Korea where the management of migraine is likely to be representative of that in Japan.
- The study had the largest number of propranolol evaluable patients: 102. All other studies were much smaller.
- 8 week titration phase of propranolol dose ensured the effectiveness assessment of propranolol was optimized.
- The study population was a mix of naïve and those who had been pre-treated with prior preventative therapies. This was the only study where we can be certain that some of the patients randomized to propranolol had received prior preventative therapy and thus were somewhat reflective of the population likely to be eligible for galcanezumab, ie failed 1 or 2 prior preventative treatments.

Limitations of Diener et al 2004[34]

- Age of enrollees included adolescents. Cohort age range was 14-66 years with a median age of 46 years. Given the median age is 41 years, the number of adolescents enrolled is likely to be low. It is possible that adolescents are more likely to be migraine treatment naïve (not confirmed by paper) and possibly may perform better on propranolol. The limitation of this study including treatment naive adolescent's is only likely to result in an effectiveness bias in the ITC in favour of propranolol.

- Enrolled Population: Subjects with 3 to 12 migraine headaches (periods) and no more than 15 headache days. The mean monthly migraine headaches at baseline in the propranolol group is 6.1 (SD 2.7). The eligibility for reimbursement of galcanezumab is at least 4 migraine headache days per month. Given the mean monthly migraine headache days was 6.1, a minority number of enrollees may have lower number headache days than 4 which would be considered not eligible for galcanezumab. It is likely that patients with less severe disease are more likely to achieve a 50% response rate as the required CFB in reduction in headache days is lower and thus again favouring the effectiveness of propranolol biasing any ITC results in favour of propranolol.
- The study duration was 26 weeks, while for galcanezumab outcomes considered in the evidence synthesis were reported at month 3 disadvantaging galcanezumab.
- The maintenance dose of propranolol reported in Diener et al (2004)34 was 160mg/day with a median average daily dose for the core double-blind phase (titration and maintenance) of 129.6mg/day. The dosing of propranolol in Diener et al (2004)34 is substantially higher than the Japanese mean average dose of 21.56mg/day (JMDC 2021 (Appendix 4-1)). Thus, the effectiveness of propranolol applied in the model represents the upper end of the effectiveness that would be expected in the Japanese real-life setting.

3.3 クリニカルクエスチョン(異なる比較対照あるいは単群試験) [該当する場合のみ]
該当なし

3.4 システマティックレビュー (異なる比較対照あるいは単群試験) [該当する場合のみ]
該当なし

3.5 既存データの再解析
3.2 で同定された以下の 5 つのガルカネズマブの試験（CGAG, CGAH, CGAW, CGAI, CGAN）の有効性の結果を、片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う部分集団、及び 3 剤目の治療を中止した部分集団に対して、反復性頭痛（CGAG, CGAH, CGAW and CGAN）と慢性頭痛（CGAI and CGAW）の結果を分けて、12 週における平均片頭痛日数のベースラインからの変化量について再解析した。

表 3-9 Episodic studies and source documents considered

Study name and acronym	Study acronym/ identifier	Source document
CGAG: Evaluation of Galcanezumab in the Prevention of Episodic Migraine- the EVOLVE-1 Study (Evolve-1)	I5Q-MC-CGAG NCT02614183	Eili Lilly and Company. Production report[38]
CGAH: Evaluation of Galcanezumab in the Prevention of Episodic Migraine- the EVOLVE-2 Study (Evolve-2)	I5Q-MC-CGAH NCT02614196	Eili Lilly and Company. Production report[38]
CGAW: A Study of Galcanezumab (LY2951742) in Adults With Treatment-Resistant Migraine (CONQUER)	I5Q-MC-CGAW NCT03559257	Eili Lilly and Company. Production report[38]

CGAN: A Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 (Galcanezumab) in Japanese Patients with Episodic Migraine	I5Q-JE-CGAN NCT02959177	Eili Lilly and Company. Production report[38]

表 3-10 Chronic studies and source documents considered

Study name and acronym	**Study acronym/ identifier**	**Source document**
CGAI: Evaluation of Galcanezumab in the Prevention of Chronic Migraine (Regain)	I5Q-MC-CGAI NCT02614261	Eili Lilly and Company. Production report[38]
CGAW: A Study of Galcanezumab (LY2951742) in Adults With Treatment-Resistant Migraine (CONQUER)	I5Q-MC-CGAW NCT03559257	Eili Lilly and Company. Production report[38]

3.6 メタアナリシスの詳細 [該当する場合のみ]

以下のガルカネズマブの 5 試験を対象として、Best Supportive Care を比較対象技術とした反復性片頭痛と慢性片頭痛における((c)片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者および(d)片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者の対象集団)12 週後の片頭痛日数の変化を有効性のアウトカムとしたメタアナリシスについて以下に記載する。

表 3-11 メタアナリシスに用いた試験

試験名	含まれる患者集団	介入:ガルカネズマブ	プラセボ
CGAN	反復性片頭痛	○	○
CGAW	反復性片頭痛・慢性片頭痛	○	○
CGAG	反復性片頭痛	○	○
CGAH	反復性片頭痛	○	○
CGAI	慢性片頭痛	○	○

以下に分析の詳細を記載する。

3.6.1 Meta-analyses methods

For a continuous outcome, meta-analyses were conducted for the mean difference using the inverse variance method for pooling and the DerSimonian-Laird method for tau which is used for the random effect.

The heterogeneity between the studies on each direct treatment comparison was assessed through the inconsistency parameter (I^2) statistic and the p-value of the Q-statistic. The I^2 can be interpreted as the proportion of total variability attributed to heterogeneity rather than chance. The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (for example, p-value from the chi-squared test, or a confidence interval for I2). As a guide, the parameter can be interpreted as follows (from the Cochrane handbook, section 9.5.2 (Higgins and Green, 2011[39])) is as follows:

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

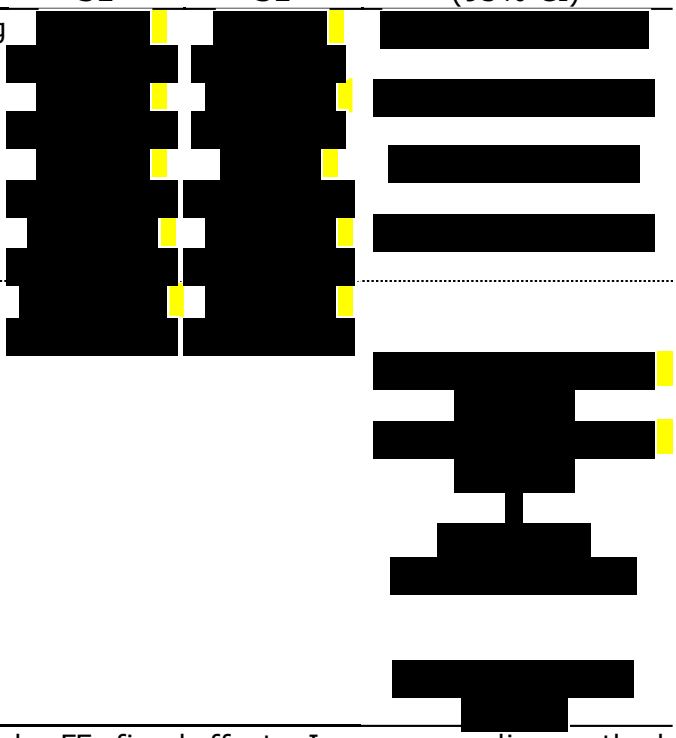
The heterogeneity statistic Q, which follows a central chi-squared distribution with degrees of freedom of the number of studies minus 1, was used. The test depends on the number of studies and has a low power when few studies and a high power when many studies. Therefore, this p-value was interpreted with caution and in light of the number of studies included in the meta-analysis. In the absence of heterogeneity, the results of fixed effects (FE) and random effects (RE) models are expected to be identical. Between studies variance τ^2, with 95% CI and p-value were reported.

3.6.2 Meta-analyses results

メタアナリシスの結果を以下に述べる。対象集団(c)片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者および(d)片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者の結果は、それぞれ表 3-12 および表 3-13 の通りである。専門組織に指定された感度分析のデータは、Appendix 3-2 に示す。

表3-12 12 週における平均片頭痛日数のベースラインからの変化量:片頭痛予防薬の3剤目の治療を中止した反復性片頭痛患者- Galcanezumab 120mg vs BSC (Placebo)

Trial	Comparison	Test N, Mean(SD), SE	Control N, Mean(SD), SE	Mean Difference (95% CI)
CGAG	galca 120mg vs. placebo			
CGAH				
CGAN				
CGAW				
Pooled data				
FE Meta-analysis /Inverse/				
RE Meta-analysis /Inverse/ tau2 /DL/ I2 [%]				
Test of heterogeneity: Q (df)				
Test of funnel plot asymmetry: t (df)				



DL - tau estimator: DerSimonian-Laird; FE: fixed effects; Inverse - pooling method: Inverse variance weighting; linreg - weighted linear regression of the treatment effect on its standard error; RE: random effects.

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表 3-13 12 週における平均片頭痛日数のベースラインからの変化量：片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者- Galcanezumab 120mg vs BSC (Placebo)

Trial	Comparison	Test N, Mean(SD), SE	Control N, Mean(SD), SE	Mean Difference (95% CI)
CGAI	galca 120mg vs. placebo			
CGAW				
Pooled data				
FE Meta-analysis /Inverse/				
RE Meta-analysis /Inverse/ tau2 /DL/ I2 [%]				
Test of heterogeneity: Q (df)				

DL - tau estimator: DerSimonian-Laird; FE: fixed effects; Inverse - pooling method:

Inverse variance weighting; RE: random effects.
Source:
¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_Icpropanolol_validated_v4.xlsb.xlsx___Base.case.cm___tfls.rtf Table B.2.d

3.7 間接比較やネットワークメタアナリシスの結果 [該当する場合のみ]

システマティックレビューでガルカネズマブとプロプラノロールを直接比較する試験は同定されなかったため、以下のガルカネズマブの 5 試験およびプロプラノロールの 1 試験を対象として、プロプラノロールを比較対象技術とした反復性片頭痛と慢性片頭痛における（(a)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者および(b)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者）12 週後の片頭痛日数の変化を有効性のアウトカムとした間接比較を実施した。以下に詳細を記載する。感度分析に用いたバルプロ酸のデータは Appendix 3-2 に示す。

表 3-14 間接比較に含まれる試験

試験名	含まれる患者集団	介入	比較対照技術
CGAN	反復性片頭痛	ガルカネズマブ	プラセボ
CGAW	反復性片頭痛・慢性片頭痛	ガルカネズマブ	プラセボ
CGAG	反復性片頭痛	ガルカネズマブ	プラセボ
CGAH	反復性片頭痛	ガルカネズマブ	プラセボ
CGAI	慢性片頭痛	ガルカネズマブ	プラセボ
Diener et al.[34]	反復性片頭痛・慢性片頭痛	プロプラノロール	プラセボ

以下に詳細を述べる。

3.7.1 Indirect comparison methods

The ITC is a statistical method used to pool results across a number of trials with comparable patient populations linked by common comparators. The technique is based on the assumption that, on a suitable scale, one can add and subtract the within-study estimates of relative treatment effects. For example, direct data comparing treatment A with C and B with C can be used to indirectly compare A and B. This is under the assumption that the following relationship between the estimated treatment effects holds: (A–B) = (A–C)–(B–C).

Frequentist adjusted indirect comparisons were conducted for each 2 by 2 comparisons, as described by Bucher et al 1997[40], using both fixed and random effects. The fixed effect estimates were computed with the inverse variance approach for a continuous outcome and the Mantel-Haenszel approach for a binary endpoint while the random effects were calculated with the DerSimonian-Laird method. The base case was the random effect model, given heterogeneity observed given limited sample size of some studies due to post-hoc subgroup analyses, and differences in study design/populations from comparator studies.

3.7.2 Software

The ITC analyses were performed using the Cheetah-tool (Indirect Comparison on results from 2 Meta-Analyses version 1.1), a Lilly developed program based on Qualified R version 3.4.4 package Meta. Treatment effects are estimated, following the approach proposed by Bucher et al 1997[40].

3.7.3 Indirect comparison results

表 3-15 12 週における平均片頭痛日数のベースラインからの変化量：片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者 - Galcanezumab 120mg vs Propranolol via Placebo

Trial	Comparison	Test N, Mean(SD), SE	Control N, Mean(SD), SE	Mean Difference (95% CI)
CGAG	galca 120mg vs. placebo			
CGAH				
CGAN				
CGAW				
Pooled data				
FE Meta-analysis /Inverse/				
RE Meta-analysis /Inverse/ tau2 /DL/ I2 [%]				
Test of heterogeneity: Q (df)				
Test of funnel plot asymmetry: t (df)				
Diener et al.*	Propranolol vs. placebo			
Pooled data				
FE Meta-analysis /Inverse/				
RE Meta-analysis /Inverse/ tau2 /DL/ I2 [%]				
Test of heterogeneity: Q (df)				
FE Indirect Comparison	galca 120mg vs. Propranolol			
RE Indirect Comparison	galca 120mg vs. Propranolol			

DL - tau estimator: DerSimonian-Laird; FE: fixed effects; Inverse - pooling method: Inverse variance weighting; linreg - weighted linear regression of the treatment effect on its standard error; RE: random effects.

* As Diener et al. reports only change in monthly (28-day) migraine frequency averaged over the entire core double-blind phase (26 weeks) vs the frequency at baseline, the outcome measure was used as the proxy of MHD change at week 12.

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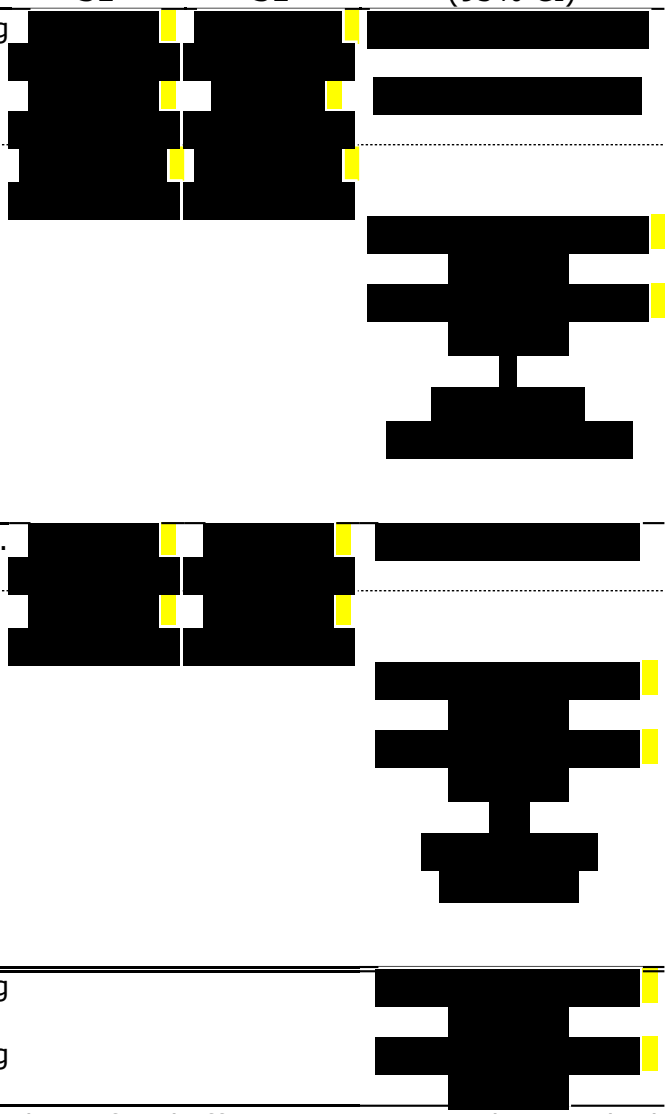
表3-16 12 週における平均片頭痛日数のベースラインからの変化量：片頭痛予防薬の2剤目の治療又は3剤目の治療を行う慢性片頭痛患者- Galcanezumab 120mg vs Propranolol via Placebo

Trial	Comparison	Test N, Mean(SD), SE	Control N, Mean(SD), SE	Mean Difference (95% CI)
CGAI	galca 120mg vs. placebo			
CGAW				
Pooled data				
FE Meta-analysis /Inverse/				
RE Meta-analysis /Inverse/				
tau2 /DL/				
I2 [%]				
Test of heterogeneity: Q (df)				
Diener et al.*	Propranolol vs. placebo			
Pooled data				
FE Meta-analysis /Inverse/				
RE Meta-analysis /Inverse/				
tau2 /DL/				
I2 [%]				
Test of heterogeneity: Q (df)				
FE Indirect Comparison	galca 120mg vs. Propranolol			
RE Indirect Comparison	galca 120mg vs. Propranolol			



DL - tau estimator: DerSimonian-Laird; FE: fixed effects; Inverse - pooling method: Inverse variance weighting; RE: random effects.
* As Diener et al. reports only change in monthly (28-day) migraine frequency averaged over the entire core double-blind phase (26 weeks) vs the frequency at baseline, the outcome measure was used as the proxy of MHD change at week 12.
Source: ¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_Icpropanolol_validated_v4.xlsb.xlsx___Base.case.cm___tfls.rtf Table B.2.c

3.8 追加的有用性の有無に関する評価

対象集団ごとに追加的有用性の有無に関する評価を下記に記載した。

表 3-17 追加的有用性の有無に関する評価のまとめ

対象集団	(a)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者
介入	ガルカネズマブ
比較対照	プロプラノロール
アウトカム	12 週における平均片頭痛日数のベースラインからの変化量
追加的有用性の有無	■ 追加的有用性あり □「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	■ RCT のメタアナリシス □ 単一の RCT □ 前向きの比較観察研究 ■ RCT の間接比較 □ 単群試験の比較 □ 臨床データなし
追加的有用性の有無を判断した理由	ガルカネズマブ 120mg はプロプラノロールに比較して統計的に有意な差を示した。(mean difference: [redacted] ([redacted], [redacted]) P=[redacted])

対象集団	(b)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者
介入	ガルカネズマブ
比較対照	プロプラノロール
アウトカム	12 週における平均片頭痛日数のベースラインからの変化量
追加的有用性の有無	■ 追加的有用性あり □「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	■ RCT のメタアナリシス □ 単一の RCT □ 前向きの比較観察研究 ■ RCT の間接比較 □ 単群試験の比較 □ 臨床データなし
追加的有用性の有無を判断した理由	ガルカネズマブ 120mg はプロプラノロールに比較して統計的に有意な差を示した。(mean difference: [redacted] ([redacted], [redacted]) P=[redacted])

対象集団	(c)片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者
介入	ガルカネズマブ
比較対照	Best Supportive Care (BSC)
アウトカム	12 週における平均片頭痛日数のベースラインからの変化量
追加的有用性の有無	■ 追加的有用性あり □「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	■ RCT のメタアナリシス □ 単一の RCT □ 前向きの比較観察研究 □ RCT の間接比較 □ 単群試験の比較 □ 臨床データなし
追加的有用性の有無を判断した理由	ガルカネズマブ 120mg は BSC に比較して統計的に有意な差を示した。(mean difference: [redacted] ([redacted], [redacted]) P[redacted])

対象集団	(d)片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者

介入	ガルカネズマブ
比較対照	Best Supportive Care (BSC)
アウトカム	12 週における平均片頭痛日数のベースラインからの変化量
追加的有用性の有無	■ 追加的有用性あり □「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	■ RCT のメタアナリシス □ 単一の RCT □ 前向きの比較観察研究 □ RCT の間接比較 □ 単群試験の比較 □ 臨床データなし
追加的有用性の有無を判断した理由	ガルカネズマブ 120mg は BSC に比較して統計的に有意な差を示した。 (mean difference: [redacted] ([redacted], [redacted]) P[redacted])

4. 分析方法の詳細

4.1 分析方法

本分析はガルカネズマブとプロプラノロールまたは Best supportive care の治療の費用対効果を評価するためセミマルコフモデルにより費用対効果分析を実施した。マルコフモデルの健康状態は、①3ヵ月目の反応評価前の治療中、②反応評価後の治療中（4ヵ月目以降）、③治療中止、④死亡の 4 つからなり、それぞれの健康状態は、月あたりの片頭痛日数と関連して設定されている。それぞれガルカネズマブ、プロプラノロール、best supportive care の治療開始時に「①3ヵ月目の反応評価前の治療中」となり、その 3 か月間後に、治療への反応性をもとに responder または non-responder に分類し（response assessment）、responder はその後それぞれの治療を継続するが（「②反応評価後の治療中（4ヵ月目以降）」への移行）、non-responder は「③治療中止」に移行する（図 4-1 参照）。その後は 1ヵ月サイクルで健康状態が移行する。Response assessment 前後いずれにおいても、有害事象等を想定した所定の割合に応じ「③治療中止」に移行する。いずれの状態からも、国民の標準死亡率に従い死亡する。また、Distribution approach[41]を用い、費用と QALY それぞれが持つ非線形な関係性をモデル化した。以下に詳細を述べる。本章ではバルプロ酸に関する感度分析に用いたパラメータも併せて記載する。

4.1.1 費用対効果の算出方法

The economic model has a semi-Markov model structure comprised of four health states; on-treatment prior to response assessment at month 3, on-treatment after response assessment (4-month onwards), off-treatment and death (図 4-1). The model has an assessment period (month 1 to 3) and post-assessment period (after month 3). Each of the health states is associated with a mean monthly migraine headache day frequency, and the response assessment period allows for differentiation between responders and non-responders.

Clinical parameters were derived from the subgroup of episodic or chronic migraine patients that had a history of 1 or 2 prior preventive treatment failures (ie. 2nd or 3rd line preventive treatment), exactly 1 preventive treatment failures (ie. 2nd line preventive treatment), exactly 2 prior preventive treatment failures (ie. 3rd line preventive treatment) or at least 3 prior preventive treatment failures (ie. at least 4th line of preventive treatment) from the galcanezumab clinical trial program.

- Responder and non-responder mean change from baseline in the monthly number of migraine headache days at month 3 ('responder criterion', BSC comparison only) – pooled galcanezumab clinical trial data
- Mean change from baseline in the monthly number of migraine headache days ('combined criterion', propranolol or valproic acid)
  - Galcanezumab and propranolol - Indirect treatment comparison separately for episodic and chronic migraine
  - Galcanezumab and valproic acid - Indirect treatment comparison separately for episodic and chronic migraine
- Proportion of patients responding to galcanezumab, BSC, propranolol or valproic acid at month 3 (response rate)
  - Galcanezumab and BSC, EM – ≥ 50% response rate - pooled galcanezumab clinical trial data (episodic migraine only)
  - Galcanezumab and BSC, CM – ≥ 30% response rate - pooled galcanezumab clinical trial data (chronic migraine only)
  - Propranolol - Indirect treatment comparison separately for episodic and chronic migraine
  - Valproic acid – real world database analysis on patients remaining on treatment at month 3 (JMDC 2021 (Appendix 4-1))

At the start of the model patients initiate treatment and after 3 months are assessed for response in line with the galcanezumab Package Insert[1] and Optimal Use Guideline[10].-

①Assessment period (month 1 to 3)
Pooled galcanezumab clinical trial data were used to inform the proportion of episodic and chronic migraine patients who met a 50% or greater reduction from baseline in monthly migraine headache days (episodic migraine only) or a 30% or greater reduction from baseline in monthly migraine headache days (chronic migraine only). The assessment response rate chosen to apply to the separate populations are clinically meaningful endpoints for the prevention of migraine[42,43]. As such, these are applied as appropriate treatment continuation rules in the model.

- Patients who do not achieve a response at 3 months: will transition to the off-treatment health state where they have the mean change in monthly migraine headache days of a non-responder and return to baseline monthly migraine headache days over time. Those patients will only incur costs of BSC and baseline utility associated with the respective migraine headache day value for the remainder of the time horizon.
- For patients in the BSC arm who respond to treatment, they are assumed to remain on-treatment and maintain their responder mean migraine headache day change and return to baseline monthly migraine headache days over 12 months. This assumption is aligned with the NICE committee's preferred assumptions from the NICE technology appraisal for fremanezumab[44] and galcanezumab[45].
- For galcanezumab patients who respond to treatment: assumed to remain on-treatment and maintain their responder mean migraine headache day change and only return to baseline monthly migraine headache days over time if they discontinue treatment for any reason.
- For propranolol or valproic acid patients who respond to treatment: assumed to remain on-treatment and maintain their responder mean migraine headache day change and only return to baseline monthly migraine headache days over 24 months based on a persistency analysis conducted in JMDC database (JMDC 2021 (Appendix 4-1)).

The 3-month assessment period is informed directly from the double-blind treatment period of the galcanezumab clinical trial program.
Episodic and chronic migraine patients treated with galcanezumab can discontinue for any reason during the assessment period. The discontinuation rate due to all-cause prior to assessment of response (first 3 months of model) is aligned with the double-blind treatment period of the galcanezumab clinical trial program. The discontinuation rate is applied as a one-off discontinuation probability at the end of the assessment period. The galcanezumab patients who discontinue go to the off-treatment health state and are assumed to rebound to the baseline monthly migraine headache days over a waning period attributed to galcanezumab. For galcanezumab, this was based on the observed migraine headache days during the washout period of the pivotal clinical trials (CGAH for episodic migraine; CGAI for chronic migraine; see Section 4.2.1). The discontinuation rate for patients on BSC is assumed to be zero. No additional discontinuation rate is assumed for propranolol or valproic acid to avoid double counting, in particular in the post-assessment period.

②Post-assessment period (after month 3)

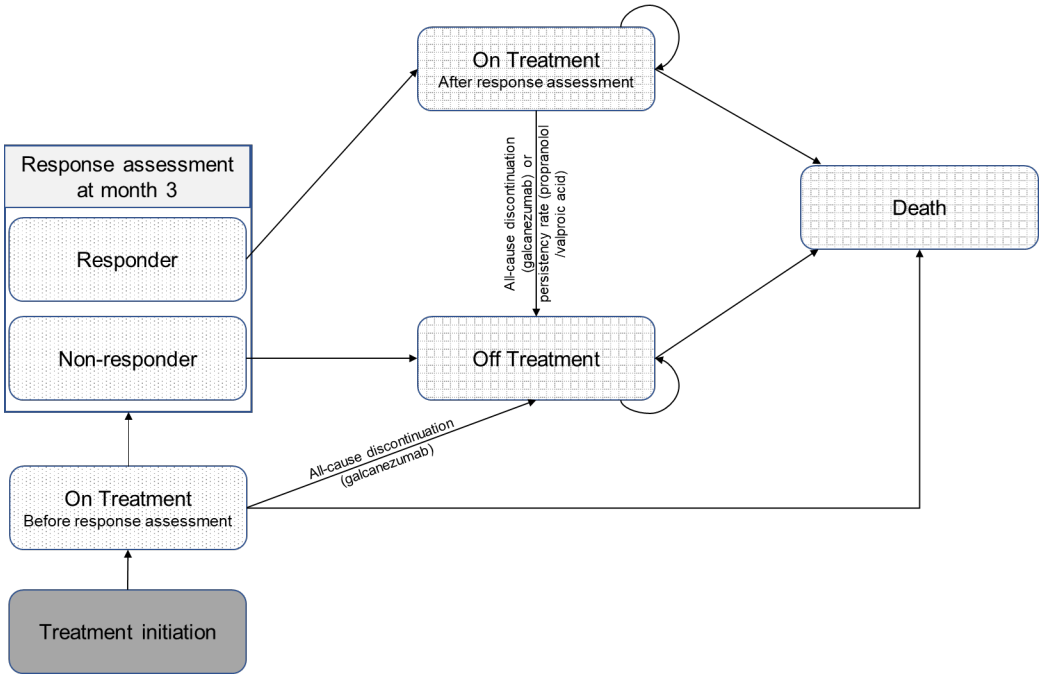
- BSC comparison - For the BSC comparison, change from baseline in monthly migraine headache days was analysed by responder status using pooled galcanezumab clinical trial data, which allowed to model the mean reduction in monthly migraine headache days for responders and non-responders separately ('responder criterion').

- Propranolol or valproic acid comparison - The reduction in monthly migraine headache days stratified by responder and non-responder status was not available for propranolol or valproic acid; therefore, the combined (responder and non-responder) mean change in monthly migraine headache days was applied for the comparison to propranolol or valproic acid in patients with episodic or chronic migraine ("combined criteria").

The change from baseline was applied to the baseline population specific to monthly migraine headache days. The monthly migraine headache days is limited in the model between the bounds of 0 and 30, based on the number of days in a treatment cycle from the galcanezumab trials. The mean change from baseline in monthly migraine headache days was applied to each health state in the model and used in the distribution to calculate the number of patients experiencing each frequency of migraine headache days. The responder criteria were defined as the mean change in monthly migraine headache days for responders and non-responders separately, defined either by a 30% (CM) or 50% (EM) mean reduction in monthly migraine headache days from baseline; the combined criteria were defined as responder and non-responder mean change in monthly migraine headache days combined.
Beyond the trial data, the mean change in monthly migraine headache days for responders who remain on treatment after the response assessment at month 3 was assumed to remain constant until the end of the modelled time horizon for galcanezumab. Patients who discontinued galcanezumab treatment, returned back to baseline over 13 cycles. The stable effect on reduction in migraine headache days over time was supported by long-term follow-up data from CGAI (CM), CGAJ, and the recently published 5-year open-label results of erenumab (EM)[46]. In addition, this assumption was aligned with other economic models in the preventive treatment of migraine[44,47].

③Discontinuation due to any reason is a key transition point in the post assessment period, thus a second discontinuation due to any reason was included for those patients who respond to treatment at month 3. For galcanezumab, these values have been taken from the pooled open-label studies CGAP and CGAJ to reflect the long-term discontinuation in the model and are applied at a per cycle (i.e. 'month') probability for the duration of the post assessment period in the model. When patients discontinue treatment, they are also assumed to rebound to the baseline monthly migraine headache days in the base case and the same waning assumptions apply as for those patients who discontinued during the assessment period. Patients will incur costs of BSC and baseline utility associated with the corresponding migraine headache day value at baseline. The discontinuation rate for patients on BSC is assumed to be zero in the post assessment period. No separate discontinuation rate is captured for propranolol and valproic acid in the post-assessment period to avoid double counting. Patients on valproic acid and propranolol stop treatment in line with the performed persistency analysis on those treatments in the JMDC database.
④Patients could die from any health state and had an equal risk of death in all health states based on life tables of the Japanese general population (i.e. no excess mortality was assumed).

図 4-1 Model structure



Distribution approach

The model includes a second structure, whereby the mean change in monthly migraine headache days in each health state are used to estimate the number of patients experiencing each frequency of monthly migraine headache days. This is achieved by employing a statistical distribution (see Section 4.2.1) to estimate the full range of monthly migraine headache days from the mean monthly migraine headache days. Based on the assessment of appropriate distributions, the model includes two different distributions, the beta binomial and the negative binomial, and different distributions are applied to the model populations in the base case:

- Episodic migraine: Negative binomial distribution (base case), beta-binomial distribution (scenario analysis)
- Chronic migraine: Beta binomial distribution (base case), negative binomial distribution (scenario analysis)

The choice of distribution was based on goodness-of-fit analyses.

Since the mean change in monthly migraine headache days does not capture the full range and distribution around the mean of individual monthly migraine headache day frequencies, this second aspect captures the non-linear impact on costs and QALYs due to the fluctuating nature of disease (month-to-month variation of migraine headache days experienced by patients). The number of patients experiencing each frequency of monthly migraine headache days is used to calculate the costs and QALYs. While migraine severity is an important patient outcome and has an impact on patient's HRQoL, adding migraine severity as an additional clinical outcome to migraine headache day frequency would considerably increase the model complexity and there is a lack of data to inform the granularity that would be required to incorporate severity within the current health states of the model, particularly to combine with the current individual migraine headache days distribution structure. Severity is also difficult to capture accurately as it is a subjective measure and differs from person to person. Furthermore, it was not deemed feasible to synthesis such clinical inputs indirectly for active comparators (i.e. propranolol or valproic acid) given the lack of evidence identified in the SLR.

Each of the health states is associated with a mean change in monthly migraine headache days based on the change from baseline in monthly migraine headache days from the galcanezumab clinical trial program (see Section 4.2.1).

表 4-1 provides a summary overview of the key model characteristics.

表 4-1 Model characteristics

Component	Description	Justification
Modelling approach	Semi-Markov model	Based on a review of literature and early scientific advice relating to a Markov model grouping categories of migraine headache days as employed in the Botulinum toxin A model[48] being too complicated
Perspective	Japanese public healthcare payer	C2H 2019[49]
Cycle length	Monthly (30 days)	Cycle length is chosen to match the monthly duration in the Phase 3 trials as well as the Phase 2 Japanese clinical trial of galcanezumab
Time horizon	25 years (lifetime)	C2H, 2019[49]
Outcome measures	QALYs (base case)	C2H, 2019[49]
Discount rate (costs)	2.0% per annum	C2H, 2019[49]
Discount rate (benefits)	2.0% per annum	C2H, 2019[49]
Sources of utility	Patient-level MSQ v.2.1 data from CGAN, CGAG, CGAH, CGAI and CGAW (for patients with history of 1 or 2 prior treatments or at least 3 prior preventive treatments) mapped onto EQ-5D-3l utility scores using an existing mapping function	While EQ-5D is generally the preferred measure by HTA jurisdictions, only CGAW collected EQ-5D data. The EQ-5D was administered at baseline and once again at 3 months at the end of the double-blind study period of CGAW. The recall period of "today" is particularly insufficient in migraine as the EQ-5D was administered during the study visit and patients experiencing a migraine would have been unlikely to attend a study visit in person. Thus, the full impact of migraine on HRQoL may not have been captured when using the EQ-5D. In comparison, the MSQ questionnaire, which was collected in all Phase 3 trials as well as the Japanese clinical trial, was administered monthly throughout the randomised and open-label phases of the trials and has a 4-week recall period. Therefore, the MSQ instrument was able to better

		capture more granular changes in health-related quality of life compared to EQ-5D-5L.
Sources of drug costs	NHI drug list	C2H, 2019[49]
Sources of other costs	Instruction on medical care fee points (April 2021)	C2H, 2019[49]
Resource use, acute medication use	Trial-specific data for acute medication use	Provided the granularity of use as it applied to each Migraine Headache Days for which costs could be applied to
Resource use, direct health care	Published Japanese data by Kikui et al. [50]	Provided Japanese local health care resource use associated with migraine based on the Japanese National Health and Wellness Survey
Mortality	Normal population-level mortality[51]	A literature review was conducted to assess whether migraine is associated with an increased risk of death. However, no clear evidence was identified to support an excess mortality beyond the normal population-level mortality due to migraine.
Half-cycle correction applied	No	The cycle length (one month) is considered to be sufficiently short so that half-cycle corrections do not need to be applied. Furthermore, it has been argued that half-cycle corrections do not affect estimated incremental costs and benefits and may therefore not be needed in economic evaluations[52]

4.1.2 モデルで使用した仮定

モデルおよび費用対効果算出のための分析における仮定には、2つの key assumptions が存在し、それに基づき、シナリオ分析を実施した。使用した仮定を以下に述べる。

- The first key assumption is the use of a negative binomial or beta-binomial distribution and validity of the regression model used to estimate the dispersion parameter, respectively intra-correlation coefficient. This approach assumes that the entire treatment effect is captured through migraine headache days. This is a required assumption to accurately model the effect of comparator treatments and is tested by testing an alternative distribution.
- Another key assumption of the model pertains to the extrapolation of the migraine headache days after the trial data, the base case assumes that it is sustained from the point of assessment of response until the end of the time horizon.

The model made several other assumptions, which are outlined in 表 4-2.

表 4-2 Summary of assumptions applied in the economic model

Assumptions	Justification
Cycle length	The model utilised monthly cycles (30 days) over which transitions are modelled and costs and outcomes accrued. This is both convenient for modelling the treatment regimens and appropriate given the treatment cycle of galcanezumab and the trial definition of migraine headache days per month applied in the Phase 2 and Phase 3 RCT programme of galcanezumab.
Responder, non-responder migraine headache days derived separately based on galcanezumab trials and applied to the galcanezumab and BSC arms of the model.	The galcanezumab Package Insert and the Optimised used guidelines (OUGL) state that doctors should review treatment after 3 months and continue if patients benefit from it. To reflect these criteria in the model, change from baseline in monthly migraine headache days was analysed by responder status applying the clinical meaningful response criteria of 30% or 50% or greater reduction in migraine headache days for CM, respectively EM patients. This allows to model the mean reduction in monthly migraine headache days for responders and non-responders separately. This analysis is only considered for the comparison to BSC, for which individual patient level data are available from the galcanezumab clinical trial program.
A combined criterion was applied to non-responder and responder mean change migraine headache days to galcanezumab when compared to propranolol or valproic acid	Since no publicly available information by responder/non-responder status could be identified in the SLR, the mean difference derived from the ITC is applied for the mean change from baseline in monthly migraine headache days for propranolol and valproic acid.

Treatment responders on galcanezumab remain on treatment and are assumed to maintain response, or combined mean change migraine headache days, until the end of the time horizon and only stop treatment for all-cause discontinuation	Efficacy data for galcanezumab are available for up to one year. Results from CGAP and CGAJ, the 12-month open-label safety studies in patients with episodic or chronic migraine support galcanezumab' durability of effect for up to a year[53, 54]. A decrease in the number of monthly migraine headache days was observed at month 1 (decreases of 4.5 days for the 120 mg dose, with an initial 240mg dose for the first month), with plateauing of effect several months later and maintenance of effect throughout 12 months (with decreases of 6.4 days at Month 12[53]). Data from the 9-month, open-label extension phase of CGAI in patients with chronic migraine indicated that reductions in migraine headache days during the 3 –month double blind period were sustained during the OLE phase, and the percentages of patients with clinically meaningful reductions in migraine headache days increased from the rates observed in the double-blind period[55,56]. The findings from galcanezumab open-label extensions is further supported by the 5 year open label extension data of erenumab in episodic migraine, which showed a continuous effect of erenumab at year 5[46]. Galcanezumab or CGRP concentrations were similar when compared across various ADA titre categories suggesting that ADA has no appreciable effect on the PK of galcanezumab nor does it interfere with the binding of the CGRP ligand to the galcanezumab antibody[55]. Consequently, no treatment waning is expected while on treatment.
Patients who discontinue active treatment due to non-response or lack of persistency (valproic acid or propranolol) or all-cause discontinuation (galcanezumab) switch to BSC treatment only and revert to baseline monthly migraine headache days for the remainder of the time horizon	This assumption is consistent with the NICE committee's conclusions for the appraisals of erenumab[47], fremanezumab[44] and galcanezumab[45].
Patients who discontinue active treatment are assumed to wane back to baseline monthly migraine headache days at different rates based on available data for the respective modelled treatments	The waning period attributed to each modelled active treatment is informed by the observed migraine headache days during the washout period of the pivotal clinical trials (CGAH for EM and CM; CGAI for scenario analysis). No such washout data was available for propranolol or valproic acid. Given the lack of washout period data and that propranolol and valproic acid are daily orals it is assumed that the half-life cycle of the treatment is very short. Therefore, similar to BSC, patients on valproic acid and propranolol return to baseline migraine headache days immediately after they

	discontinued treatment.
There is no placebo response modelled. BSC responder, non-responders discontinue treatment after the assessment period at different rates back the baseline monthly migraine headache days. Non-responders, immediately in the next cycle. Responders, wane back over 12 months	Aligned with the NICE committee's preferred assumptions from the NICE technology appraisal for fremanezumab and galcanezumab, responders in the BSC arm in the model return back to baseline migraine headache days at 12 months[44],[45].
No excess mortality in the model	Given conflicting evidence in the literature regarding migraine-specific mortality, no excess mortality was considered in the model (Gudmundsson et al, 2010[57]; Asberg et al, 2016[58]). Therefore, patients from the on-treatment and off-treatment health state had an equal probability of transitioning to the health state 'death'. The background mortality risk does not differ by treatment. This is also consistent with past NICE technology appraisals in migraine[44,45,47,48].
Discontinuation is captured through the assessment of response and due to all-cause (galcanezumab) and persistency for propranolol and valproic acid.	The proportion of patients being persistent to propranolol or valproic acid treatment in Japan was based on a local Japanese claims analysis. (JMDC 2021 (Appendix 4-1)). For galcanezumab, no longterm data from routine clinical-practice are available. Hence an all-cause discontinuation rate was considered to align with the persistency analysis for propranolol and valproic acid since reasons for non-persistence is not known. No additional discontinuation rate was considered for propranolol or valproic acid.
Placebo arms from the trial assumed as a proxy for BSC in the model	It is assumed appropriate that the placebo arm in the randomised controlled trials of galcanezumab is representative of best supportive care in patients who experienced either 1 or 2 or at least 3 prior preventive treatment failures. Patients in the placebo group of the clinical trials were allowed acute medication to manage their symptoms.

25-year lifetime horizon	Given that migraine is a chronic disease, it is important to capture all relevant costs and outcomes associated with the intervention. In addition, migraine affects predominately women and the natural course of disease suggests that prevalence of migraine reduces significantly after menopause[59]. Therefore, the time horizon of the model is set to 25 years in the base case. 25-years was deemed appropriate to capture all material effects on benefits and costs while considering the natural course of the disease. Any longer time horizons would result to propagate the uncertainty of short-term clinical trial data though the model and inherently make any longer-term estimates unreliable.
Treatment – specific utility values	This approach considers that utility values differ between BSC and galcanezumab treatment arms. This is based on an observed statistically significant treatment effect between galcanezumab and BSC in the galcanezumab clinical trial program. In addition, migraine headache days alone is poorly correlated with other specific measures of health status used to capture the impact of migraine on HRQoL, thus implying important aspects of HRQoL are not captured in the economic analysis, which may underestimate galcanezumab's cost effectiveness compared to BSC. This assumption was endorsed by NICE in the galcanezumab assessment[45]. For the comparison to active treatments, the same utility values as for galcanezumab are applied.

4.2 分析で使用したパラメータ

ベースケース分析、シナリオ分析および感度分析の概要を(マルコフモデルにおける推移確率等を含む)を以下に述べる。

表 4-3 分析で使用したパラメータ

Parameter	**Episodic**	**Chronic**
Perspective	Payer perspective	Payer perspective
Discount rate, costs and benefits	2.0% and 2.0%	2.0% and 2.0%
Responder rate	50%	30%
Negative discontinuation rule at 3 months (responder assessment)	Yes	Yes
Statistical distribution	Negative Binomial	Beta Binomial
Mean change from baseline in MHD (BSC comparison)	Responder criterion	Responder criterion
Mean change from baseline in MHD (active comparison)	Combined efficacy	Combined efficacy
Placebo effect of BSC responders modelled beyond month 12 Placebo effect of BSC-responders modelled up to 12 months	No Yes	No. Yes
Mean change Migraine Headache Days applied to discontinuers and non-responders (BSC comparison)	Switch to non-responder mean change migraine headache days and return to baseline migraine headache days	Switch to non-responder mean change migraine headache days and return to baseline migraine headache days
Wane rate after discontinuation	Galcanezumab – 13 cycles BSC – immediately after the next cycle	Galcanezumab – 13 cycles BSC – immediately after the next cycle

	Propranolol – immediately after the next cycle Valproic acid – immediately after the next cycle	Propranolol – immediately after the next cycle Valproic acid – immediately after the next cycle
Discontinuation rate during the assessment period	Galcanezumab -all-cause BSC – none Propranolol – none Valproic acid – none	Galcanezumab -all-cause BSC – none Propranolol – none Valproic acid – none
Discontinuation rate in the post-assessment period (after month 3)	Galcanezumab - all-cause BSC – none Propranolol – persistency rate Valproic acid – persistency rate	Galcanezumab - all-cause BSC – none Propranolol – persistency rate Valproic acid – persistency rate
Utility values	Treatment-specific utility values (BSC comparison) Galcanezumab utility values (active comparison)	Treatment-specific utility values (BSC comparison) Galcanezumab utility values (active comparison)
Acute medication use	Number of migraine headache days with acute medication use by categories estimated from the galcanezumab trial program	Number of migraine headache days with acute medication use by categories estimated from the galcanezumab trial program

A summary of the base case settings for the model and scenario analyses conducted (as described below) is provided in 表 4-4. Extensive deterministic sensitivity analyses were conducted to evaluate the robustness of the CE estimates considering the standard error for the clinical efficacy parameters to assess the statistical uncertainty.
The scenario analyses involved replacing a parameter (or group of parameters) with another plausible value(s) in order to examine the impact of a new "scenario". This provided a single ICER estimate (for each comparator) associated with the new scenario. This type of analysis can be used to assess both parameter and structural uncertainty.

表 4-4 Model setting

Parameter	Base case	Scenario
General settings		
Discount rates (costs, benefits)	Costs: 2.0% and Benefits: 2.0% /year	0.0% and 4.0%/year
Outcomes	Cost per QALY	Cost per QALY
Time horizon	25 years	5, 10 and 45 years
Clinical outcomes		
Response rate, CM	30%	50%
Response rate, EM	50%	50%
Mean Migraine Headache Days improvement for comparison in BSC	Efficacy specific to responders and non-responders	Efficacy specific to responders and non-responders
Mean Migraine Headache Days improvement for comparison to propranolol/valproic acid	Combined efficacy (pooled responder and non-responder)	Combined efficacy (pooled responder and non-responder)
Time of treatment waning after discontinuation, Galcanezumab, EM	Based on washout data from CGAH, 13 months (cycles) until baseline migraine headache days	Assuming 5 cycles until baseline migraine headache days Assuming 13 cycles for responder and 1 for non-responders
Time of treatment waning after discontinuation, Galcanezumab, chronic	Based on washout data from CGAH, 13 months (cycles) until baseline migraine headache days	The post treatment per data from the CGAI trial was used. The analysis focused on the galcanezumab 120mg dose. Based on the observed data at 12 months and the change to Month 16 an overall change on MHD of 0.9 was converted to a per month change of 0.23.
BSC waning effect	BSC loses effect after 12 months of treatment after assessment period	BSC loses effect after 12 months of treatment after assessment period
Propranolol and valproic acid waning effect	% of patients on propranolol and valproic acid is informed by an analysis conducted in local Japanese claims database (JMDC 2021 (Appendix 4-1))	% of patients on propranolol and valproic acid is informed by an analysis conducted in local Japanese claims database (JMDC 2021 (Appendix 4-1))
Distribution around Migraine Headache Days, EM	Negative Binomial	Beta-binomial
Distribution around Migraine Headache Days, chronic	Beta-Binomial	Negative binomial

Utilities		
MSQ mapped to the EQ-5D using CGAG, CGAH, CGAI, CGAN and CGAW for patients with 1 or 2 prior preventive treatments or 3 or more prior preventive treatments, BSC	Treatment-specific utility values	Treatment-specific utility values
MSQ mapped to the EQ-5D using CGAG, CGAH, CGAI, CGAN and CGAW for patients with 1 or 2 prior preventive treatments or 3 or more prior preventive treatments, active treatment	Galcanezumab utility value	Galcanezumab utility value
Resource use	Kikui et al 2021[50]	Kikui et al 2021[50]
Discontinuation rate, galcanezumab	Due to all-cause	Due to adverse events (BSC only)
Perspective	Payer	Payer

4.2.1 有効性･安全性等のパラメータの詳細

臨床パラメータは、ガルカネズマブの臨床試験において、過去に 1 剤または 2 剤の予防治療を中止（すなわち、2 剤目または 3 剤目の予防治療）、1 剤の予防治療を中止（すなわち、2 剤目の予防治療）、2 剤の予防治療を中止（すなわち、3 剤目の予防治療）、または少なくとも 3 剤の予防治療の中止（すなわち、少なくとも 4 剤目の予防治療）の治療歴を持つ、反復性または慢性の片頭痛患者のサブグループから得た。以下に詳細を述べる。

The baseline patient characteristics used in the model are specific to the population of interest and are shown in 表 4-5. No differences in population characteristics are assumed between interventions. The age and gender parameters are used to calculate the background mortality (see Section 4.2.1). The mean baseline migraine headache days, shown below, is required to model the change from baseline in migraine headache days over the time horizon of the model. See also section 4.2.1 for further description.

表 4-5 Baseline patient characteristics

Migraine population	**N**	**Age (years) Mean (SD)**	**Gender (% Female)**	**Mean MHD (SD)**
Episodic patients who fail 1 treatment	[redacted]	[redacted]	[redacted]	[redacted]
Episodic patients who fail 2 treatments	[redacted]	[redacted]	[redacted]	[redacted]
Episodic patients who fail 1 or 2 treatments	[redacted]	[redacted]	[redacted]	[redacted]
Episodic patients who fail >=3 treatments	[redacted]	[redacted]	[redacted]	[redacted]
Chronic patients who fail 1 treatment	[redacted]	[redacted]	[redacted]	[redacted]
Chronic patients who fail 2 treatments	[redacted]	[redacted]	[redacted]	[redacted]
Chronic patients who fail 1 or 2 treatments	[redacted]	[redacted]	[redacted]	[redacted]
Chronic patients who fail >=3 treatments	[redacted]	[redacted]	[redacted]	[redacted]

MHD – Migraine Headache Day
Source: /prd/ly2951742/hta_submission/output/shared/hta_japan/pooled_baseline_estimates.xlsx

Post-hoc analyses were conducted on the clinical trial program of galcanezumab for the subgroup of episodic or chronic migraine patients with a

- history of 1 or 2 preventive treatment failures (ie. 2nd or 3rd line preventive treatment)
- history of exactly 1 preventive treatment failure (ie. 2nd line preventive treatment)
- history of exactly 2 preventive treatment failures (ie. 3rd line preventive treatment)
- history of at least 3 prior preventive treatment failures (ie. ≥4th line preventive treatment)

If more than one study of galcanezumab provided information for the same outcome and population of interest, the corresponding treatment effect and variance considered in the equations of the Bucher method is a pooled estimator obtained through meta-analysis using for binary outcomes the Mantel-Haenszel method. Pooling of continuous outcomes is conducted by assigning inverse variance weights to the individual studies. The inverse variance refers to the relative effect of each individual study which is considered in the pooling. The long-term open-label studies CGAJ and CGAP (patients with episodic and chronic migraine) informed the post-assessment discontinuation rates.

The following data sources informed the baseline parameters as well as the efficacy and safety parameters, where feasible:

表 4-6 Data sources of each parameters

Parameter	**Episodic Migraine**	**Chronic Migraine**	**Section**
Baseline characteristics	CGAG, CGAH, CGAN, CGAW	CGAI, CGAW	4.2.1
Statistical distribution to model Migraine Headache Days	Based on data from CGAG, CGAH and checked against CGAJ, CGAN and CGAW	Based on data from CGAI and checked against CGAJ and CGAW	4.2.1
Change from baseline in Migraine Headache Days			
Galcanezumab	CGAG, CGAH, CGAN, CGAW	CGAI, CGAW	4.2.1
Propranolol	ITC	ITC^	
Valproic Acid	ITC	ITC^	
BSC	CGAG, CGAH, CGAN, CGAW	CGAI, CGAW	
Response rate			
Galcanezumab and BSC	CGAG, CGAH, CGAN, CGAW	CGAI, CGAW	4.2.1
Propranolol	ITC	ITC^*	4.2.1
Valproic Acid	JMDC 2021 (Appendix 4-1)	JMDC 2021 (Appendix 4-1)	4.2.1
Discontinuation rate			
Galcanezumab (assessment period)	CGAG, CGAH, CGAN, CGAW	CGAI, CGAW	4.2.1
Galcanezumab (post-assessment period)	CGAJ and CGAP	CGAJ and CGAP	4.2.1
Treatment waning			4.2.1
Galcanezumab	CGAH	CGAI	
Utilities	CGAG, CGAH, CGAN, CGAI, CGAW	CGAG, CGAH, CGAN, CGAI, CGAW	4.2.3
Persistency analysis			
Propranolol and Valproic Acid	JMDC 2021 (Appendix 4-1)	JMDC 2021 (Appendix 4-1)	
Number of Migraine Headache Days with acute medication class use	CGAG, CGAH, CGAN, CGAI, CGAW	CGAG, CGAH, CGAN, CGAI, CGAW	4.2.1

^the indirect treatment comparison is based on data identified for the episodic migraine patient population. In the SLR, no data was identified for chronic migraine.
*no information was identified for 30% or greater reduction in migraine headache days.

4.2.1.1 Distribution parameters

To approximate the distribution of monthly migraine headache days around the mean monthly migraine headache day in the post assessment period (second part of the model), distributions of monthly migraine headache days in patients with migraine were estimated based on the observed mean migraine headache days using a parametric approach as described in Tanna and colleagues (2019)[60], such that a monthly migraine headache days distribution can be estimated when no individual patient-level data is available. The patient level data from four phase III randomized, placebo-controlled clinical trials and one phase III, long-term, open-label safety study were used to estimate the distribution of monthly migraine headache days in episodic and chronic migraine patients separately. The clinical development program included one phase II study in Japanese outpatients with episodic migraine (CGAN), two phase III studies in patients with episodic migraine (CGAG and CGAH) [61,62]; one study in patients with chronic migraine (CGAI) [63]; and an open-label safety study (CGAJ) that evaluated patients with episodic or chronic migraine for up to 1 year[64]. CGAW was a 3-month double-blind, placebo-controlled study specifically conducted in patients with episodic or chronic migraine with previous failure of 2 to 4 migraine preventive medication categories[65].

- CGAI was used to estimate the distribution of monthly migraine headache days in chronic migraine patients.
- CGAG and CGAH were pooled and used to estimate the distribution in the episodic migraine patient population.
- CGAJ and CGAW were used to check the estimations performed with CGAI, CGAG and CGAH.
- CGAN was used to check the estimations performed with CGAG and CGAH in the Japanese population.

The following steps were conducted on the patient-level data from double-blind and follow-up periods of

- the CGAI studies at every month from Month 1 to Month 12 in chronic migraine patients, and independently,
- the pooled CGAG and CGAH studies at every month from Month 1 to Month 10 in episodic migraine patients.

1. At every month and for each treatment group, the observed migraine headache days were plotted as bar charts with the fitted Poisson, negative binomial, binomial, beta-binomial distribution and zero-inflated negative distributions. Each fitted distribution was compared with the raw data using visual inspection of the plots and the residual plot of observed versus simulated observations to assess overfitting. Goodness of fit of the distributions was assessed based on the root mean square error (RMSE). A smaller RMSE indicates a better fit.
2. The estimation of a parametric approach to estimate the distributions of patients with migraine headache days based only on the mean migraine headache days was done with
    - Negative binomial distribution that depends on the sample mean and a dispersion parameter (bound between 0 and infinity), and
    - Beta-binomial distribution that depend on the sample mean with an intra-class correlation parameter (bound between 0 and 1)
3. For each of the fitted (negative binomial and beta-binomial) distributions from Step 1, ordinary least square regression models were run to predict the second (dispersion or intra-class correlation) parameter as a function of the mean number of migraine headache days using a series of transformations.

4. The best fitting model was selected based on visual inspection, Akaike's information criterion (AIC) and parsimony at the different time points. Differences between the estimated and the fitted negative binomial distribution as well as residuals at each month for each study treatment were also visually assessed.
5. The equations developed in Step 2 were assessed using independent datasets - patients with episodic migraine from a safety study of galcanezumab (CGAJ), the phase 2 study CGAN in Japanese outpatients suffering from episodic migraine, and the CGAW study conducted in patients with previous failure to 2 to 4 migraine preventive medication categories.
6. The equations were also tested using the following subpopulations of CGAG and CGAH, CGAI, CGAN and CGAW

- Patients with at least 8 migraine headache days at baseline from CGAG and CGAH,
- Patients who failed at least 2 preventive treatments from CGAG and CGAH[66] and CGAI[67],
- Patients with at least 8 migraine headache days and who failed at least 2 preventive treatments from CGAG and CGAH
- Subpopulation of CGAW with patients who failed at least 3 migraine preventive medication categories
- Subpopulation of CGAN with patients who failed 1 or 2 migraine prevention treatments.

The negative binomial and beta binomial were chosen based on goodness of fit statistics and applied to the episodic and chronic populations, respectively. The distributions were fitted to the whole naïve and treatment experienced trial population migraine headache days from CGAG, CGAH and CGAI, and checked against the naïve and treatment-resistant populations from CGAI, CGAN and CGAW. 表 4-7 presents the results from the regression analysis, associated with the negative binomial and beta-binomial distributions, to estimate the dispersion parameter around the mean migraine headache days.

表 4-7 Distribution parameters

Chronic migraine	Episodic migraine
Negative binomial distribution – dispersion parameter	
$4.7967 - 1.0206*mean + 0.0664*mean^2$	$5.3837 - 2.0538*mean + 0.2526*mean^2$
Beta-binomial distribution – intra-class correlation parameter	
Maximum of $(0.4776 - 0.0158*mean)$ and 0.01	Maximum of $(-0.0489+0.0741*mean-0.0076*mean^2)$ and 0.01

図 4-2 displays the observed, estimated and fitted distributions, applying the equations described in 表 4-3 using the intention to treat Japanese migraine population (CGAN). Based on visual assessment, the fitted and estimated beta-binomial and negative binomial distributions are similar, therefore the estimated negative binomial distribution is adequate to estimate the observed distribution of the monthly migraine headache days. The same applies to the beta-binomial distribution.
Residuals of the estimated and fitted distributions were also plotted in 図 4-3 with the aim to

visually assess them. Each graph displays the difference between the observed proportion of patients and the estimated (or fitted) proportion of patients for a given number of migraine headache days ranging from 0 to 30 days.
Residuals between observed and estimated distributions for all are nearly within the 8% margin. This indicates that the negative binomial and beta-binomial distributions are a good fit of the CGAN study data. Residuals from the fitted and estimated distributions are very similar, indicating that the estimated distributions using the observed mean migraine headache days are very similar to the fitted distributions.

図 4-2 Observed, fitted, and estimated parametric migraine headache days distributions at months 1, 2, and 3 - CGAN Episodic - All comers population - patients on Placebo and Galcanezumab

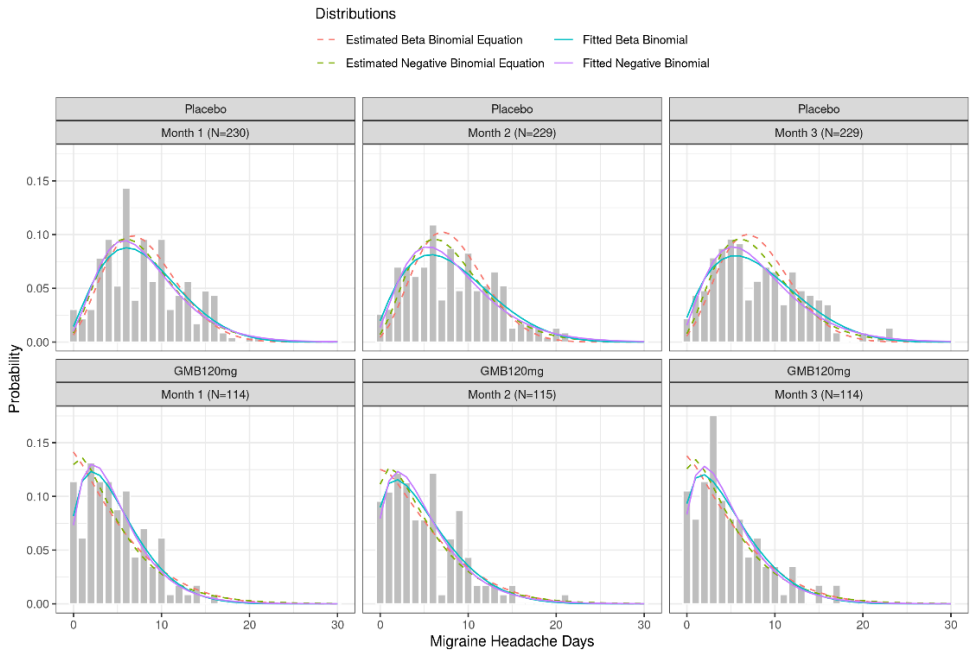
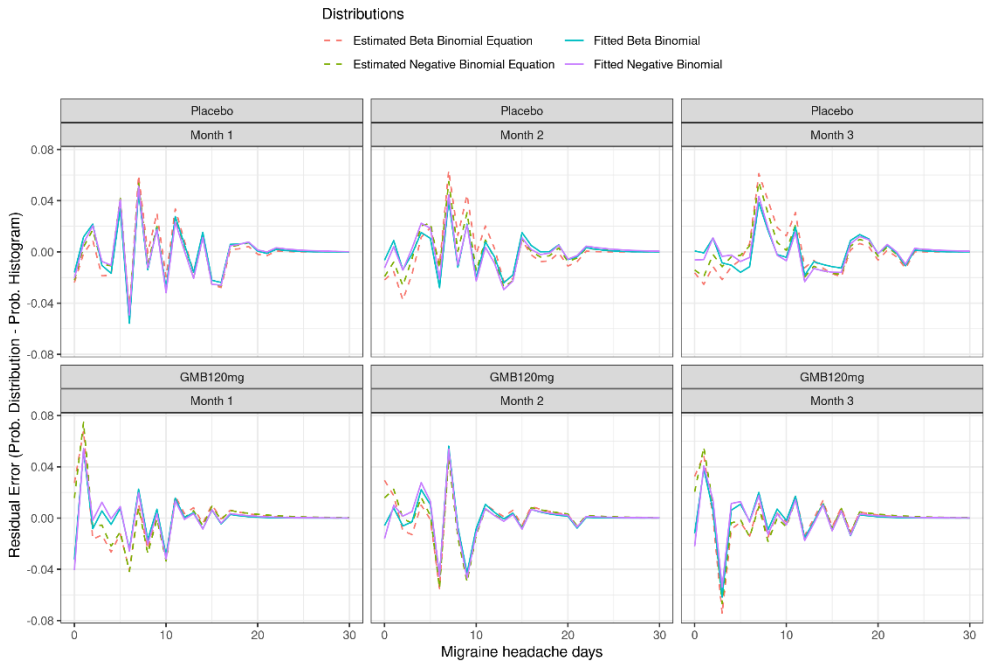


図 4-3 Residual errors of migraine headache days for estimated and fitted negative binomial and beta-binomial at months 1, 2, and 3 - CGAN Episodic - All comers population - patient on Galcanezumab



4.2.1.2 Mean change from baseline in monthly migraine headache days

The change from baseline in migraine headache days is dependent upon population and assessed over the first 3 months after treatment initiation. The change from baseline is applied to the population specific baseline migraine headache days (see 表 4-1). The number of migraine headache days is limited in the model between the bounds of 0 and 30, based on the number of days in a treatment cycle from the galcanezumab trials. The mean change from baseline in migraine headache days is applied to each health state in the model and used in the distribution to calculate the number of patients experiencing each frequency of migraine headache days. When comparing to propranolol or valproic acid, outcomes could only be estimated from the ITC for mean change from baseline in monthly migraine headache days which is not split by responder and non-responders but since the model stratifies the population by responders and non-responders at the point of response assessment, the mean change of migraine headache days considers both responders and non-responders in the analysis (‘combined criterion) when comparing galcanezumab to propranolol and valproic acid. Taking this conservative approach may underestimate the cost effectiveness of galcanezumab compared to propranolol or valproic acid.

Response based mean change from baseline in monthly migraine headache days (‘responder criterion’)

For the analysis compared to BSC that considers direct head-to-head data from the galcanezumab clinical trial program, the mean change from baseline in monthly migraine headache days is linked to the response criteria (50% or greater response for episodic migraine or 30% or greater reduction for chronic migraine). Individual patient level data for each trial were analysed and results for each trial subsequently pooled. The results for the mean change from baseline in monthly migraine headache days stratified by responder and non-responder are shown in 表 4-8. The change from baseline in monthly migraine headache days at month 3 has been analysed for patients who either met or didn’t meet the response definition at month 3. The results of this analysis show that responders have typically a comparable mean change from baseline in monthly migraine headache days when stratified by response status,

regardless of galcanezumab or BSC treatment. It is important to note that the proportion of patients achieving this change from baseline in monthly migraine headache days is greater in patients receiving galcanezumab compared to BSC in the galcanezumab clinical trial program. This suggests that the difference in treatment is mainly driven by differences in response rates.

表 4-8 Change from baseline in Migraine Headache Days for responders and non-responders at month 3 – BSC comparison only ('responder criterion')

Population and intervention	Responders		Non-responders		Source
	N	Mean CFB in MHD (SE)	N	Mean CFB in MHD (SE)	
30% response rate – Chronic Migraine					
Patients who have experienced 1 or 2 prior medication failures (ie. 2nd or 3rd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.2.c.3 [2] and Table B.2.c.4 [2]
BSC	[redacted]		[redacted]		
Patients who have experienced ≥3 prior medication failures					
Galcanezumab	[redacted]		[redacted]		Table B.2.d.3 [2] and Table B.2.d.4 [2]
BSC	[redacted]		[redacted]		
Patients who have experienced 1 prior medication failure (ie. 2nd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.2.a.3 [2] and Table B.2.a.4 [2]
BSC	[redacted]		[redacted]		
Patients who have experienced 2 prior medication failures (ie. 3rd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.2.b.3 [2] and Table B.2.b.4 [2]
BSC	[redacted]		[redacted]		
50% response rate – Episodic Migraine					
Patients who have experienced 1 or 2 prior medication failures (ie. 2nd or 3rd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.1.c.1 [1] and Table B.1.c.2 [1]
BSC	[redacted]		[redacted]		
Patients who have experienced ≥3 prior medication failures (ie. ≥4th line preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.1.d.1 [1] and Table B.1.d.2 [1]
BSC	[redacted]		[redacted]		
Patients who have experienced 1 prior medication failure (ie. 2nd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.1.a.1 [1] and Table B.1.a.2 [1]
BSC	[redacted]		[redacted]		
Patients who have experienced 2 prior medication failures (ie. 3rd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.1.b.1 [1] and Table B.1.b.2 [1]
BSC	[redacted]		[redacted]		
50% response rate – Chronic migraine					
Patients who have experienced 1 or 2 prior medication failures (ie. 2nd or 3rd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.2.c.1 [2] and Table B.2.c.2

BSC	[redacted]		[redacted]		[2]
Patients who have experienced ≥3 prior medication failures (ie. ≥4th line preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.2.d.1 [2] and Table B.2.d.2 [2]
BSC	[redacted]		[redacted]		
Patients who have experienced 1 prior medication failure (ie. 2nd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.2.a.1 [2] and Table B.2.a.2 [2]
BSC	[redacted]		[redacted]		
Patients who have experienced 2 prior medication failures (ie. 3rd line of preventive treatment)					
Galcanezumab	[redacted]		[redacted]		Table B.2.b.1 [2] and Table B.2.b.2 [2]
BSC	[redacted]		[redacted]		

BSC – Best Supportive Care, CFB – Change from Baseline, MHD – Migraine Headache Days
Source:
[1]¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_Icpropanolol_validated_v4.xlsb.xlsx___Base.case.em___tfls.rtf and
[2]¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_Icpropanolol_validated_v4.xlsb.xlsx___Base.case.cm___tfls.rtf

Combined mean change from baseline in monthly migraine headache days ('combined criterion')

The mean change from baseline in monthly migraine headache day was populated from the ITC compared to propranolol or valproic acid. The ITC estimated the change from baseline directly for galcanezumab compared to propranolol or valproic acid. Since the model splits the population by responders and non-responders at the point of assessment of response (month 3), the mean change is thus applied to both groups when looking at a combined population of responders and non-responders for the comparison to propranolol or valproic acid. The response assessment still takes place to account for the negative discontinuation rule, defined by either 50% (EM) or 30% (CM) or greater reduction in monthly migraine headache days at 3 months. It is important to highlight that the ITC to propranolol was based on change from baseline in migraine headache days (combined criterion) at month 3 as well as response rate at month 3 taken directly from the galcanezumab clinical trial program, and one randomized, 26-week core double-blind period, multicentre trial enrolling episodic migraine patients in 13 countries. The study reporting data on propranolol included an 8 weeks of dose up-titration followed by 18 weeks of stable propranolol dose [34]. The outcomes for propranolol were reported for the entire 26-week core double-blind treatment period, which is longer than the timepoint at which galcanezumab data were assessed (ie. 3 months to align with the cost-effectiveness analysis). In addition, the effectiveness of propranolol reported in Diener et al 2004[34] was based on a propranolol dose of 160mg once daily. The median average daily dose for the core double-blind phase (titration and maintenance) was 129.6mg/day. This median dose is approximately 6 times higher than the mean dose of propranolol (21.59mg/day) reported in the JMDC analysis conducted in local Japanese data (JMDC 2021 (Appendix 4-1)). Similar to propranolol, the average dose reported in the clinical trials for valproic acid is higher than what is observed in Japanese routine clinical practice. The average dose of valproic acid reported in the studies considered for the ITC ranged from 871mg/day to 1087mg/day, which is up to 3 times higher than the Japanese mean average dose of valproic acid of 334.76mg/day (JMDC 2021 (Appendix 4-1)). Thus the effectiveness of propranolol and valproic acid applied in the model represents the upper end of the effectiveness that would be expected in the Japanese real-life setting.

表 4-9 shows the mean change from baseline in monthly migraine headache days for the different populations considered in the model.

表 4-9 Change from baseline in Migraine Headache Days for total population at month 3 ('Combined criterion')

	N	CFB in MHD (SE)	Source
Episodic migraine			
Patients who have experienced 1 or 2 prior medication failures			
Galcanezumab	[redacted]	[redacted]	Table B.1.c [1]
BSC	[redacted]	[redacted]	
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: mean difference of [redacted]* (random effects model), Table B.1.c [1]
Valproic Acid	[redacted]	[redacted]	Indirect comparison of galcanezumab versus valproic acid: mean difference of [redacted] (random effects model), Table SA2.1.c [1]
Patients who have experienced 1 prior medication failure			
Galcanezumab	[redacted]	[redacted]	Table B.1.a [1]
BSC	[redacted]	[redacted]	
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: mean difference of [redacted]* (random effects model), Table B.1.a [1]
Valproic Acid	[redacted]	[redacted]	Indirect comparison of galcanezumab versus valproic acid: mean difference of [redacted] (random effects model), Table SA2.1.a [1]
Patients who have experienced 2 prior medication failures			
Galcanezumab	[redacted]	[redacted]	Table B.1.b [1]
BSC	[redacted]	[redacted]	
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: mean difference of [redacted] (random effects model), Table B.1.b [1]
Valproic Acid	[redacted]	[redacted]	Indirect comparison of galcanezumab versus valproic acid: mean difference of [redacted] (random effects model), Table SA2.1.b [1]
Chronic migraine			
Patients who have experienced 1 or 2 prior medication failures			
Galcanezumab	[redacted]	[redacted]	Table B.2.c [2]
BSC	[redacted]	[redacted]	
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: mean difference of [redacted]* (random effects model), Table B.2.c [2]
Valproic Acid	[redacted]	[redacted]	Indirect comparison of galcanezumab versus valproic acid: mean difference of [redacted] (random effects model), Table SA2.1.f [2]
Patients who have experienced 1 prior medication failure			
Galcanezumab	[redacted]	[redacted]	Table B.2.a [2]
BSC	[redacted]	[redacted]	
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: mean difference of [redacted] (random effects model), Table B.2.a [2]

Valproic Acid	[redacted]	[redacted]	Indirect comparison of galcanezumab versus valproic acid: mean difference of [redacted] (random effects model), Table SA2.1.d [2]
Patients who have experienced 2 prior medication failures			
Galcanezumab	[redacted]	[redacted]	Table B.2.b [2]
BSC	[redacted]	[redacted]	
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: mean difference of [redacted]* (random effects model), Table B.2.b [2]
Valproic Acid	[redacted]	[redacted]	Indirect comparison of galcanezumab versus valproic acid: mean difference of [redacted] (random effects model), Table SA2.1.e [2]

*p<0.05. BSC – Best Supportive Care, CFB – Change from Baseline, MHD – Migraine Headache Days.
Source:
[1]¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_ICpropanolol_validated_v4.xlsb.xlsx___Base.case.em___tfls.rtf and
[2]¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_ICpropanolol_validated_v4.xlsb.xlsx___Base.case.cm___tfls.rtf

4.2.1.3 Response rates

Assessment of response has been included in the model in line with clinical guidelines, specifically the optimal use guideline[10] and the galcanezumab package insert[1]. Response to treatment is assessed at month 3. To identify the proportion of patients continuing treatment beyond month 3, the base case assumes a response rate as a reduction in monthly migraine headache days of 50% or greater from baseline for patients with EM and 30% or greater for chronic migraine patients. This response criterion is considered clinical meaningful in its respective patient population[42,43].

The proportion of patients with a history of 1 or 2 prior preventive treatment failures, exactly 1 failure, exactly 2 failures or at least 3 prior preventive treatment failures experiencing a 30% or 50% or greater reduction in migraine headache day response rate was informed by CGAG, CGAH, CGAN and CGAW for episodic migraine and CGAI and CGAW for chronic migraine. 表 4-10 shows the proportion of patients with a 50% or greater reduction in monthly migraine headache days and 表 4-11 the results for 30% or greater reduction in monthly migraine headache days. Patients classified as non-responders are transitioned to the off-treatment health state where the migraine headache days returns to the baseline level.

Patients in the BSC arm who respond to treatment were assumed to remain on-treatment and maintain their responder mean migraine headache days change and placebo effect dissipates after 12 cycles resulting in monthly migraine headache days returning back to baseline level. Responders who do not discontinue for any reason in the galcanezumab arm are assumed to maintain their mean change monthly migraine headache days until the end of the modelled time horizon. Patients who discontinue galcanezumab treatment for any reason wane back to baseline migraine headache days over 13 cycles. Patients on propranolol or valproic acid who respond to treatment will discontinue treatment over a total 24 months based on Japanese real-world evidence (JMDC 2021 (Appendix 4-1)).

表 4-10 Probability of achieving a 50% or greater reduction in migraine headache days at month 3

	n/N	Response rate	Source
Episodic migraine			

Patients who have experienced 1 or 2 prior medication failures (ie. 2nd or 3rd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.1.c [1]
BSC			
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.1.c [1]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)
Patients who have experienced at least 3 prior medication failures i(e. ie. ≥4th line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.1.d [1]
BSC			
Patients who have experienced 1 prior medication failure (ie. 2nd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.1.a [1]
BSC			
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.1.a [1]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)
Patients who have experienced 2 prior medication failures (ie. 3rd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.1.b [1]
BSC			
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.1.b [1]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)
Chronic migraine			
Patients who have experienced 1 or 2 prior medication failures (ie. 2nd or 3rd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.2.c [2]
BSC			
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.2.c [2]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)
Patients who have experienced at least 3 prior medication failures (ie. ≥4th line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.2.d [2]
BSC			
Patients who have experienced 1 prior medication failure (ie. 2nd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.2.a [2]
BSC			
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.2.a [2]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)
Patients who have experienced 2 prior medication failures (ie. 3rd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.2.b [2]
BSC			
Propranolol	[redacted]	[redacted]	Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.2.b [2]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)

BSC – Best Supportive Care, N/A – not applicable
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[1]¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_Icpropanolol_validated_v4.xlsb.xlsx___Base.case.em___t

fls.rtf and
[2]¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_Icpropanolol_validated_V4.xlsb.xlsx___Base.case.cm___t
fls.rtf

表 4-11 Probability of achieving a 30% or greater reduction in migraine headache days at month 3

	n/N	Response rate	Source
Chronic migraine			
Patients who have experienced 1 or 2 prior medication failures (ie. 2nd or 3rd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.2.c.1 [2]
BSC			
Propranolol	[redacted]	[redacted]	Assumption same relative risk assumed as for 50% RR given lack of data, Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.2.c [2]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)
Patients who have experienced at least 3 prior medication failures (ie. ≥4th line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.2.d.1 [2]
BSC			
Patients who have experienced 1 prior medication failure (ie. 2nd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.2.a.1 [2]
BSC			
Propranolol	[redacted]	[redacted]	Assumption same relative risk assumed as for 50% RR given lack of data, Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.2.a [2]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)
Patients who have experienced 2 prior medication failures (ie. 3rd line preventive treatment)			
Galcanezumab	[redacted]	[redacted]	Table A.2.b.1 [2]
BSC			
Propranolol	[redacted]	[redacted]	Assumption same relative risk assumed as for 50% RR given lack of data, Indirect comparison of galcanezumab versus propranolol: relative risk: [redacted] (random effects model), Table A.2.b [2]
Valproic Acid	[redacted]	[redacted]	JMDC 2021 (Appendix 4-1)

BSC – Best Supportive Care, N/A – not applicable
Source:
[1]¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_Icpropanolol_validated_v4.xlsb.xlsx___Base.case.em___t
fls.rtf and
[2]¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_Icpropanolol_validated_v4.xlsb.xlsx___Base.case.cm___tf
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4.2.1.4 Persistency to oral preventive migraine treatment

Low adherence and persistence with current migraine preventive medications

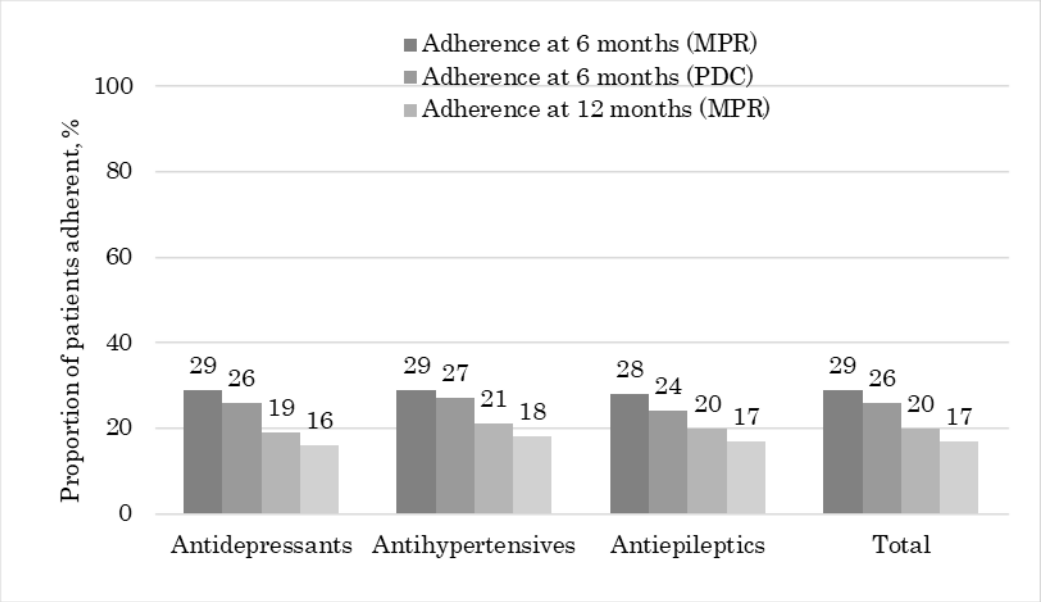
The success of migraine prophylaxis is crucially dependent on patient adherence to treatment[68]. In a systematic review of 33 relevant studies (observational, n=14; RCT, n=19), it was reported that adherence and persistence to propranolol exhibited a downward trend overtime, with rates of adherence and persistence below acceptable thresholds (≤80%) within 6 months of initiating therapy[68].

Adherence to antiepileptics, antidepressants, and β-blockers for migraine prophylaxis was reported in 4634 patients identified from a large US health insurance claims database[69]. Poor rates of adherence (with nonadherence indicated by a medication possession ratio [MPR] of <0.80) were observed regardless of drug type, with mean MPR values of 0.48, 0.51, and 0.51

for antidepressants, antiepileptics, and β-blockers, respectively, at 6 months[69]. Rates of nonadherence at 6 months for each drug class were 73.4%, 70.2%, and 67.6%, respectively. Given guideline recommendations that preventive medications should be used for 2–3 months to ascertain effectiveness it is concerning that relatively few patients may remain adherent over this timescale[69].

Two studies using a large US healthcare claims database have specifically evaluated adherence and persistence to preventive medications in patients with CM[70,71]. In the first study, adherence to commonly prescribed oral treatments for migraine prophylaxis (antidepressants, antihypertensives, and antiepileptics) was calculated using both the MPR and proportion of days covered (PDC; the formulas for which are described in 図 4-4) in 8,688 patients. When MPR ≥80% was used to classify rates, only 29% and 20% of patients were adherent at the end of 6 and 12 months of therapy, respectively (図 4-3). Using PDC ≥80% as the threshold, even fewer patients were adherent at 6 or 12 months of follow-up (図 4-4).

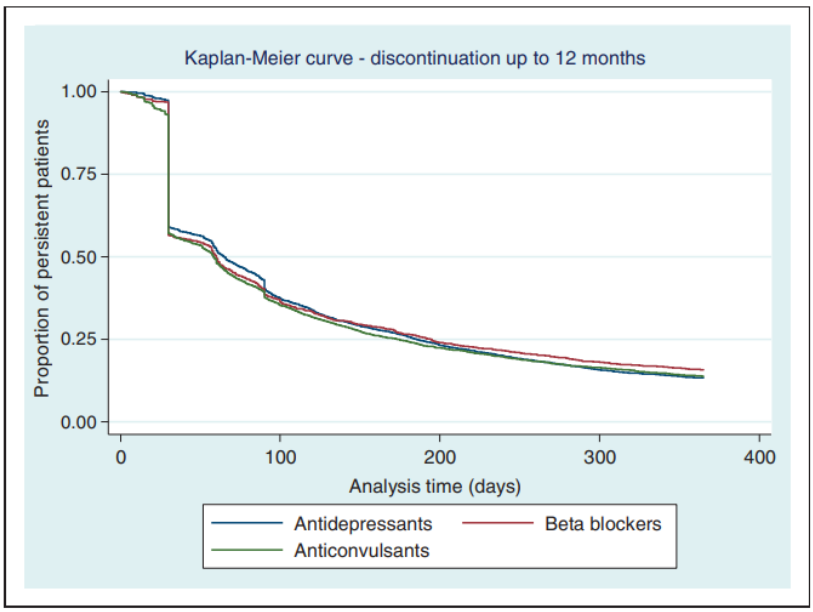
図 4-4 Rate of adherence to oral migraine preventive medications in patients with CM[70]



MPR is calculated as the total number of days' supply divided by the total number of days in the follow-up period.
PDC is calculated as the total number of days the drug is available divided by the total number of days in the follow-up period.
CM, chronic migraine; MPR, medication possession ratio; PDC, proportion of days covered.

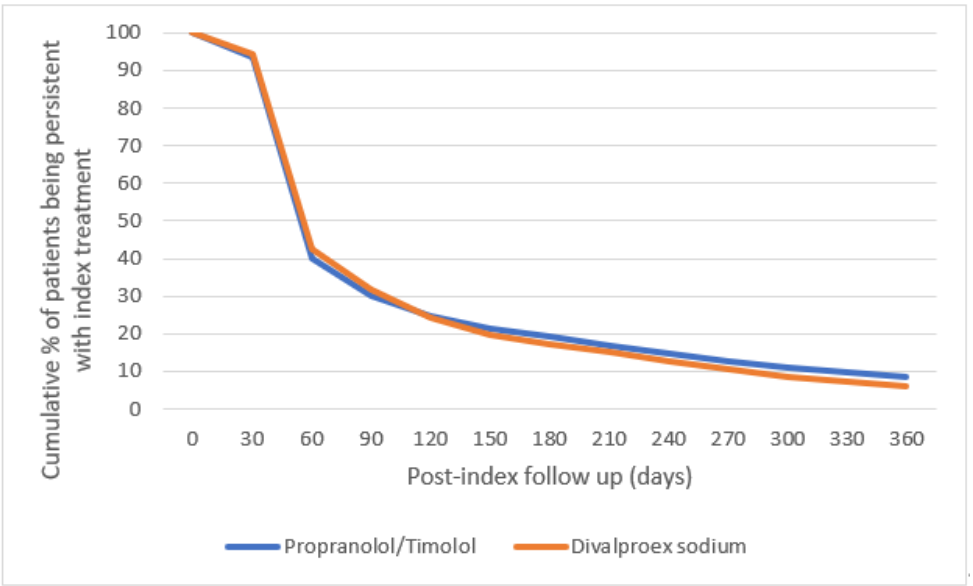
In the second study, persistence, defined as the length of time a patient remains on a drug after initial prescription with migraine preventive agents, was evaluated in 8707 patients with CM[71]. Persistence rates to the initial medication were low at both 6-month and 12-month follow-up (25% and 14%, respectively)[71]. Furthermore, the data indicated that switching is common, and persistence decreases even further as a patient cycles through multiple preventive agents. The average time to discontinuation was 2–3 months. This corresponds with guideline recommendations for an adequate preventive drug trial; however, Kaplan–Meier curves demonstrated a sharp drop-off in persistence at 30 days, with over half of patients discontinuing by ~60 days (図 4-5). Similar trends regarding time to discontinuation were observed with the second and third preventive drug.

図 4-5 Time to discontinuation up to 12 months' follow-up from the initial prophylactic, stratified by class of oral migraine preventive medication[71]



An additional US study assessed the persistency of migraine patients with propranolol/timolol (N=2718) or divalproex sodium (N=1644) using the Health Core Integrated Research Database. Similar to the previous studies persistency was low with more than half of the patients not continuing their treatment beyond 60 days post-index and less than 10% of patients were still on treatment 306 days post-index (図 4-6[72]).

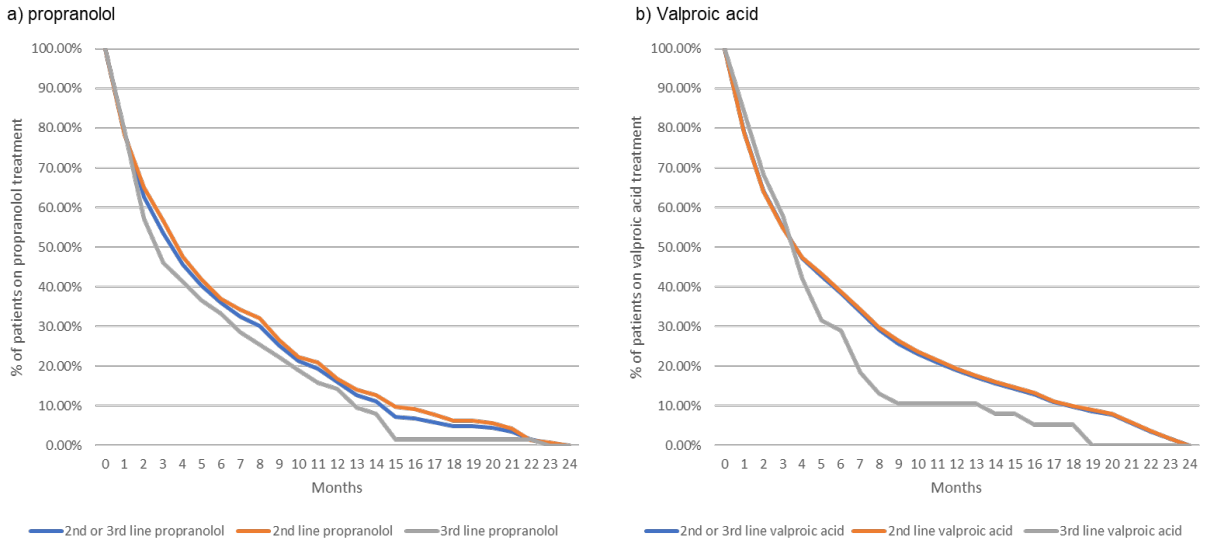
図 4-6 Persistency with propranolol/timolol or divalproex sodium in patients with migraine[72]



4.2.1.4 Persistency on Propranolol and Valproic Acid (JMDC 2021 (Appendix 4-1))

Given the lack of published Japanese data on persistency rates for propranolol and valproic acid, an analysis of the JMDC dataset was performed to analyse the proportion of Japanese patients on propranolol and valproic acid treatment across 24-months. To meet this objective, adult patients enrolled in the JMDC dataset with a diagnosis for migraine (G43) and a prescription for both preventive and acute treatment for migraine with an index date between July 2013 – December 2018 were analysed. Over a 24 months follow-up period, patients were assessed on whether they continued valproic acid or propranolol by line of treatment. Discontinuation was defined as ending treatment with the preventive portion of the index migraine treatment regimen without evidence of another refill for the same medication within 60 days of exhausting the drug supply for the prior prescription. The grace period of 60 days was adapted to 35 days in case the medication is categorized 'as needed' or the prescriptions days are unknown. Patients who refilled the medication of interest after 61 days are considered as discontinuers. This also applies to patients who switch back to their initial preventive medication. The results of this analysis are displayed in 図 4-7.

図 4-7 Persistency rate with propranolol or valproic acid treatment in Japanese routine clinical practice (JMDC 2021 (Appendix 4-1))



The result of the JMDC analysis shows a comparable trend to the non-Japan specific studies discussed in the previous section with a sharp drop off by month 3 and a low number of patients remaining on treatment at 6 months, respectively at 12 months irrespective of line of treatment. All patients discontinued treatment at 24 months. In contrast to the analysis conducted by Hepp and colleagues 2017[71] or Yaldo and colleagues 2008[72], a greater proportion of patients were still on treatment at month 3 and 6.

The pattern displayed in 図 4-7 is modelled in the cost-effectiveness analysis by considering that patients stop treatment at month 6, month 9 and month 12. This is a conservative assumption as this would imply that all patients still on treatment at month 12 remain on treatment and accrue the benefits of the associated reduction in migraine headache days and related HrQoL gain up to month 24 despite the fact that patients drop out every month (see 図 4-7). No additional discontinuation due to adverse event or for other reasons is considered in the model beyond the proportion of patients being persistent at month 6, month 9 or month 12 to avoid double-counting (see 表 4-12).

表 4-12 Proportion of patients persistent with propranolol or valproic acid at month 6, 9 and 12 (JMDC 2021 (Appendix 4-1))

	Fail 1 or 2 treatments (ie. 2nd or 3rd line)	Fail 1 treatment (ie. 2nd line)	Fail 2 treatments (ie. 3rd line)
Persistency rate on propranolol treatment			
6 months	35.92%	37.06%	33.33%
9 months	25.24%	26.57%	22.22%
12 months	16.02%	16.78%	14.29%
Persistency rate on valproic acid			
6 months	38.25%	38.67%	28.95%
9 months	25.65%	26.33%	10.53%
12 months	18.96%	19.34%	10.53%

*since the JMDC analysis was done for the overall migraine population not by subtype, the same values are applied for episodic and chronic migraine patients

4.2.1.5 Discontinuation

As displayed in 図 4-1, patients can discontinue from treatment in the following ways:

1. Discontinuation due to lack of response (50% or greater response rate for EM and 30% or greater response rate for CM patients) at the end of the assessment period (month 3) – See description below: "Discontinuation due to lack of response (50% or greater response rate for EM and 30% or greater response rate for CM patients) at the end of the assessment period"
2. Discontinuation due to all-cause during the first 3 months – See description below "Discontinuation due to any reason during the assessment period"
3. Long-term discontinuation due to all-cause in the post assessment period (month 4 onwards) – See description below "Long-term discontinuation due to any reason (after month 3)
4. Discontinuation due to lack of persistency in the post assessment period (month 4 onwards) – See description below "Long-term discontinuation due to any reason (after month 3)

表 4-13 中止理由の詳細

	中止理由の詳細		
中止理由	Galcanezumab	Propranolol (Valproic acid)	BSC
1.有効性の判定	投与開始後 3 か月時点にて有効性を判定し、以下の基準を満たさない場合は中止 EM: MHD のベースラインからの 50%減少 CM: MHD のベースラインからの 30%減少		
2.投与開始後 3 か月時点での All cause discontinuation	投与開始後 3 か月時点にて、表 4-14 に示す割合で中止する。	本理由での中止は適用しない	本理由での中止は適用しない
3.投与開始後 4 か月以降の All cause discontinuation	投与開始後 4 か月以降に、表 4-15 に示す月率にて中止する。	本理由での中止は適用しない	本理由での中止は適用しない
4.JMDC の Persistency に基	本理由での中止は適用しない	投与開始後 6、9、12 か月時点にて、表 4-12 に示す割合で中止する。	本理由での中止は適用しない

づ く Discontinuation			

Discontinuation due to lack of response (50% or greater response rate for EM and 30% or greater response rate for CM patients) at the end of the assessment period

All patients considered to be non-responders at month 3 transition to an off-treatment health state where they receive BSC, ie. acute medication. The proportion of patients who discontinue due to lack of efficacy (defined as not meeting the response threshold of 50% for episodic migraine or 30% for chronic migraine at month 3) is informed directly from the clinical trial program for galcanezumab and BSC. Data from the indirect treatment comparison for propranolol informed the proportion of patients who are responders to propranolol at 3 months. Due to lack of available data for valproic acid, an indirect treatment comparison could not be performed, hence data from the Japan routine clinical practice (JMDC 2021 (Appendix 4-1)) were used as a proxy instead (see 表 4-10).

Discontinuation due to any reason during the assessment period

Patients on galcanezumab could discontinue due to all-cause at the end of the assessment period. The values used in the model are based on the ITT population of CGAG, CGAH, CGAI, CGAN and CGAW independently for episodic and chronic migraine. Discontinuation rates for CGAG, CGAH and CGAN were adjusted to 3-month rates assuming events leading to discontinuation are equally distributed across the 6-months double-blind treatment period. After discontinuing galcanezumab treatment, patients go back to baseline monthly migraine headache days over time, which was informed by the washout period data from galcanezumab trials. 表 4-14 summarises the discontinuation rate for the assessment period. Discontinuation due to adverse events is explored in a scenario analysis. No discontinuation rate due to all-cause is assumed for BSC, which is a conservative assumption since patients discontinued the placebo-arm in the clinical trials of galcanezumab. No discontinuation rates are considered for propranolol and valproic acid since discontinuation is captured by the persistency analysis of the JMDC dataset.

表 4-14 Probability of discontinuation due to all cause discontinuation or adverse events at the end of the assessment period

	Probability of discontinuation	Source
All-cause discontinuation		
Episodic migraine – patients, for whom prior preventive treatments failed		
Galcanezumab	[redacted]	Table S.1.a, CGAN, CGAG and CGAH adjusted for 3 months assuming linear distribution of discontinuation [3]
Chronic migraine - patients, for whom prior preventive treatments failed		
Galcanezumab	[redacted]	Table S.2.a[3]
Discontinuation due to AE		
Episodic migraine – patients, for whom prior preventive treatments failed		
Galcanezumab	[redacted]	Table S.1.b, CGAN, CGAG and CGAH adjusted for 3 months assuming linear distribution of discontinuation, CGAW had zero events and is manually added in the calculation [3]
Chronic migraine - patients, for whom prior preventive treatments failed		
Galcanezumab	[redacted]	Table S.2.b [3]

Source:

[3]Y:¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_ICpropanolol_validated_v2.xlsb.xlsx___Base.case.safety___tfls.rtf

Long-term discontinuation due to any reason (after month 3)

After the initial 3 months of treatment, patients who did respond to treatment could further discontinue galcanezumab due to all-cause (e.g. loss of efficacy, patients decision, adverse events). Data from both CGAP and CGAJ, two phase III, multicentre, randomised, open-label studies assessing the long-term (12-month) safety and tolerability of galcanezumab in patients with episodic migraine or chronic migraine were pooled to inform the discontinuation rate for galcanezumab[53,54]. 表 4-15 summarises the discontinuation rate after the assessment period (month 3). Based on the data from the studies, galcanezumab was well-tolerated and has quite low discontinuation rate due to AE after month 3. Considering the safety profile and the maintenance of the efficacy of galcanezumab, it was reasonable to anticipate low discontinuation rate after the assessment period if the patient was evaluated as a responder at the time of month 3. Discontinuation due to adverse events is explored in a scenario analysis. No discontinuation rate is assumed for BSC up to 12 months after which the placebo effect dissipates. To avoid double counting, no additional discontinuation rate beyond the proportion of patients being persistent at month 6, 9 and 12 is considered for propranolol or valproic acid during the post-assessment period. All patients on valproic acid and propranolol discontinue treatment by 24 months in line with the JMDC analysis (Appendix 4-1).

表 4-15 Rate of discontinuation beyond assessment period (after months 3)

	Probability of discontinuation	Source
All-cause discontinuation		
Galcanezumab	[redacted]	Table S.1.c, adjusted for monthly cycle rate, same rate is applied for episodic and chronic migraine [3]
Discontinuation due to AE		
Galcanezumab	[redacted]	Table S.1.d, adjusted for monthly cycle rate, same rate is applied for episodic and chronic migraine [3]

Source:
[3]Y:¥prd¥ly2951742¥hta_submission¥output¥shared¥hta_japan¥masterfile_meta_ICpropanolol_validated_v2.xlsb.xlsx___Base.case.safety___tfls.rtf

Mean change of migraine headache days after discontinuation (BSC, propranolol or valproic acid)

For patients on BSC, propranolol or valproic acid who discontinue for non-response, the mean change monthly migraine headache days return to the baseline value based on patients losing their effect immediately in the next month.

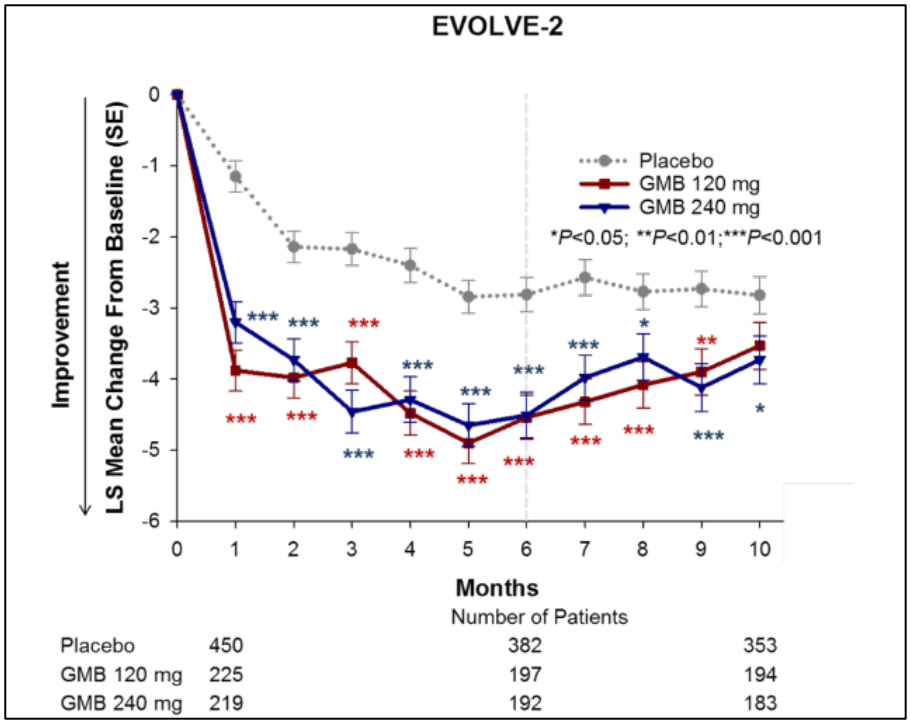
For patients on BSC who respond at the point of assessment at month 3, it is assumed that these patients return to baseline monthly migraine headache days after a total of 12 cycles, ie. the placebo effect dissipates. A return to baseline monthly migraine headache days for both BSC responders and non-responders means that the placebo effects encountered in the trial are negligible in the model. This assumption is based on the NICE committee's preferred assumptions from NICE technology appraisal of fremanezumab[44] where it states that the placebo response observed during the clinical trial would not be seen in clinical practice. This assumption was also accepted by NICE in their guidance of galcanezumab[45]. The base case assumptions for the BSC arm is applied to both the episodic and chronic migraine analyses.

For patients on propranolol or valproic acid who respond at the point of assessment at month 3, it is assumed that these patients return to baseline monthly migraine headache days after 24 months in line with the persistency analysis conducted in the JMDC database, which shows that patients stop being on their 2nd or 3rd line treatment by month 24 (see 図 4-7). No additional discontinuation rate was considered for propranolol or valproic acid to avoid double counting.
Given the lack of washout period data and that propranolol and valproic acid are daily orals it is assumed that the half-life cycle of the treatment is very short. Therefore, similar to BSC, patients on valproic acid and propranolol return to baseline migraine headache days immediately after they discontinued treatment.

Mean change of migraine headache days after discontinuation (galcanezumab arm)

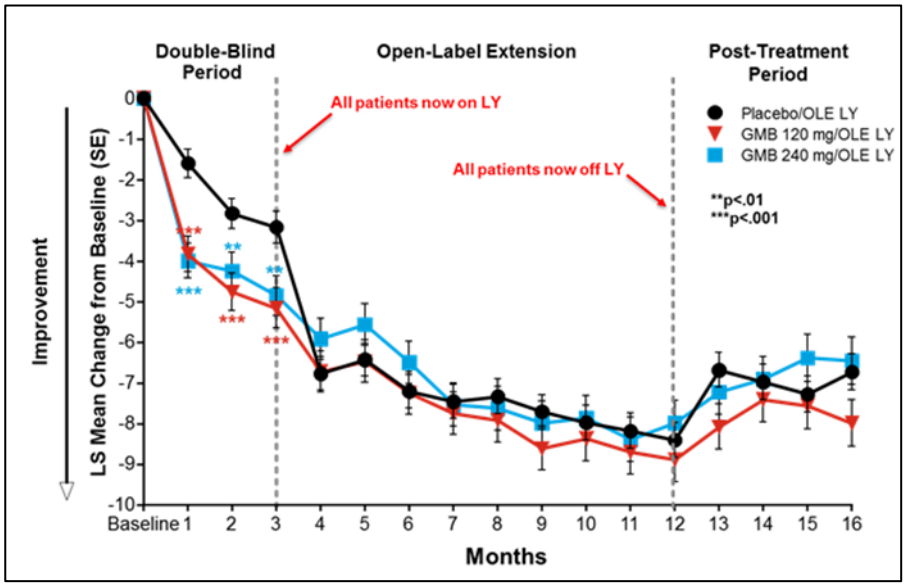
Patients who discontinue galcanezumab, due to either non-response or all-cause reasons, transition to the off-treatment health state, in which they wane back to baseline monthly migraine headache days, are assumed to receive BSC only. These patients are assigned the non-responder mean change monthly migraine headache days and return to baseline monthly migraine headache days values over time. The wane back to baseline monthly migraine headache days occurs at different rates for patients with episodic and chronic migraine. In the base case, EM patients who discontinue treatment return to baseline over 13 cycles based on the last observation of the double-blind treatment period (month 6) and the monthly migraine headache day reductions observed in the washout period from CGAH (ie. month 7-month 10). A simple quadratic function was fitted to the last five observations (month 6-10) (shown in 図 4-8) to predict the time required when migraine headache days return to baseline, which resulted in the following function: $y=$ [redacted] x^2+ [redacted] $x-$ [redacted] ($R^2=0.9926$).

図 4-8 Washout data –CGAH[73]



For the patients with chronic migraine, the same treatment waning is assumed as for episodic migraine, ie. 13 cycles.
A scenario analysis is being conducted, which is informed by the open-label extension of the CGAI trial (shown in 図 4-9). During the OLE period all patients received galcanezumab from month 3 to month 12 and in contrast to EM, data on discontinued patients cannot be compared between galcanezumab treatment and placebo. Due to this, the rate of mean change in monthly migraine headache day decline has been calculated from the wash out period from month 12 to 16. A rate of decline of 0.225 per cycle was applied to the chronic population based on this data. The calculated rate of change is used for all chronic populations in a scenario analysis, however due to differences in treatment efficacy and baseline values for migraine headache days, the time it takes for the return to baseline is different for each population.

図 4-9 Washout data – CGAI



To note, the estimated rate of treatment waning after discontinuation for the galcanezumab arms is based on the total population enrolled in the pivotal trials.

Summary mean change
A summary of the mean change and the data sources over time has been provided in 表 4-16.

表 4-16 Summary of mean change in monthly Migraine Headache Days

Model treatment arm	**Discontinuation due to all-cause – assessment period**	**Responders**	**Non-responders**	**Discontinuation due to all-cause – post assessment**
Galcanezumab	· One-off rate of [redacted]% (EM) or [redacted]% (CM) applied once at time of response assessment (month 3) · Discontinue active treatment and switch to BSC · Switch to non-responder Migraine Headache Days and wane back to baseline Migraine Headache Days over time (over 13 cycles for EM and CM) · Baseline Migraine Headache Days maintained until end of time horizon	· Continue with active treatment · Maintain responder Migraine Headache Days until end of time horizon (comparison to BSC) · Maintain combined (responder and non-responder) Migraine Headache Days until end of time horizon (comparison to propranolol or valproic acid)	· Active treatment until month 3 then switch to BSC · Non-responder stratified mean change Migraine Headache Days from baseline applied from month 3 and effect wanes back to baseline Migraine Headache Days over time (over 13 cycles) · Baseline Migraine Headache Days maintained until end of time horizon	· Per cycle discontinuation rate of [redacted]% applied until end of time horizon · Switch to non-responder stratified mean change Migraine Headache Days from baseline applied from month 3 and effect wanes back to baseline Migraine Headache Days over time (over 13 cycles) · Baseline Migraine Headache Days maintained until end of time horizon
Best Supportive Care (BSC)	· 0% discontinue due to all-cause within trial period.	· BSC until day 90 response assessment · BSC responder mean change Migraine Headache Days waned back to baseline Migraine Headache Days over 12 cycles · Baseline Migraine Headache Days maintained until end of time horizon	· BSC treatment until months 3 · Mean change from baseline until month 3 Migraine Headache Days then switch to baseline Migraine Headache Days in the next cycle	· 0% discontinue due to all-cause per cycle · No patients remain on BSC mean change Migraine Headache Days in the post assessment period beyond 12 months

Propranolol/valproic acid	· No discontinuation assumed in the first 3 months	· Continue with active treatment · Persistency analysis informs proportion of patients who discontinue treatment at month 6, month 9 and month 12 · Patients persisting to treatment maintain combined population (responder and non-responder) MHDs until end of 24 months of treatment · Baseline Migraine Headache Days maintained until end of time horizon	· Active treatment until day 90 then switch to BSC · Switch to combined population (responder and non-responder) Migraine Headache Days and wane back to baseline mean change Migraine Headache Days in the next cycle. · Baseline Migraine Headache Days maintained until end of time horizon	· Patients are stopping treatment in line with the persistency analysis conducted in JMDC at month 6, month 9 and month 12 · Switch to combined population (responder and non-responder) Migraine Headache Days and wane back to baseline mean change Migraine Headache Days in the next cycle. · Baseline Migraine Headache Days maintained until end of time horizon

4.2.1.6 Adverse events

Adverse events have not been explicitly modelled due to the small number of patients experiencing serious adverse events, their transient nature, the limited impact these would have on resource use and subsequently on the overall results, and to avoid double counting since discontinuation due to all-cause has been included in the model.
The impact of the adverse events on the utility values from the trial is still included in the model by modelling discontinuation due to all-cause, therefore explicitly capturing the impact of adverse events on health-related quality of life would lead to double counting.

4.2.1.7 Mortality

In the cost-effectiveness analysis, only all-cause mortality, based on the national Japanese life tables[51], is considered. Applying the population specific characteristics (see 表 4-3) to the life tables, allows the calculation of a monthly (cycle) mortality rate. Given conflicting evidence shown in the literature regarding migraine-specific mortality, no additional mortality rate was considered in the model[74,75].

4.2.2 QOL 値の詳細

Quality of life in migraine

Migraine is a complex neurological condition and its impact on patient's HRQoL is multifaceted. Health-state utility values (HSUVs) were estimated using the migraine-specific quality of life questionnaire (MSQ) collected within the trials, with estimates predicted on data for reductions in migraine headache days. The interplay between the complex nature of the 'ictal' burden (that is, the experience of the migraine attack itself) and 'interictal burden (that is, the experience in between migraine attacks) on HRQoL is unlikely captured through reduction in migraine headache days alone. Thereby underestimating the impact preventative treatments such as galcanezumab have on HRQoL and also its cost effectiveness particularly compared to best supportive care treatments. Hence, the application of a treatment effect to HSUVs may capture the additional HRQoL benefit of preventative treatment such as reductions in the intensity/severity of pain associated with migraine attacks, disability caused by migraine attacks and the interictal burden between attacks.
Several studies have been performed to qualitatively and quantitatively capture the complex nature of symptoms that impact patient's HRQoL.

General impact of migraine

Migraine causes negative effects on various areas of patients' lives. A cross-sectional study in adults with episodic migraine (EM) or chronic migraine (CM) in Germany, Italy, and the USA who completed an online survey reported important limitations resulting from migraine in private, professional, and social aspects of life, mainly the disruption of daily routines, significant strain in personal relationships, difficulty caring for children, and missed days of work, deadline, or social events[76]. In addition, anxiety and frustration were frequently cited as the emotional consequences of migraine in private/social life and professional life.
A number of studies have also highlighted the substantial impact of migraine on patients' physical health. Patients have remarked on the intensity of pain and the discomfort caused by light and noise during attacks, and how this has made sleep difficult, and had various other effects, including bodily pain, tiredness, sweating, and loss of memory[77]. Poor sleep quality, in particular, has been shown to be associated with poor health, significant functional and cognitive impairment, and psychiatric comorbidity[78].

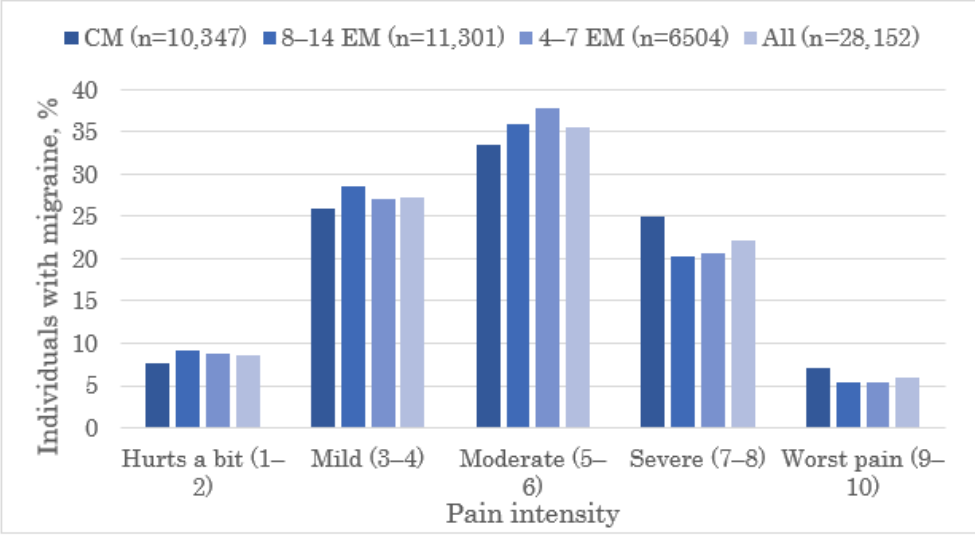
The different psychosocial difficulties related to migraine were investigated in a systematic review of 51 papers reporting clinical trials and observational studies [79]. A total of 34 psychosocial difficulties were identified. The most frequently studied were related to eight areas: emotional problems, decreased vitality and fatigue, pain, difficulties at work, decreased physical health, decreased mental health, poor social functioning, and increased global disability. The review found that there were two major determinants of improvements in psychosocial difficulties: (1) decreased frequency of headaches; and (2) migraine treatments. Symptomatic medications in the included studies were triptans, which showed evidence for improving emotional problems and work efficiency. However, the most important determinants of improvements in psychosocial difficulties were preventatives medications, which showed evidence for improving emotional problems, work efficiency, global disability, physical health, and mental health [79].

In regard to the economic relationship, research has reported predictive factors for higher total costs among patients treated for migraine, which included lower health index utility score per the SF-6D (Short Form 6 Dimension) and lower physical functioning per the PCS (physical composite summary) of the SF-12 (Short-Form Health Survey) [80]. Notably, comorbidities were not statistically significant predictors of being in the highest cost category. Measures associated with the frequency of migraine, including preventive eligibility per current or past use of migraine preventives and preventive eligibility per acute medication overuse, were also significant predictors in the model. This research further demonstrated the importance of variables that capture the ictal and interictal disease burden when evaluating economic outcomes.

Pain

Patients report that pain is the most intense and disabling symptom during a migraine attack. In a US cross-sectional, real-world analysis, pulsating/throbbing pain and unilateral pain were the most bothersome symptoms associated with migraine (i.e. impacted lifestyle or work), being reported as such in >50% of patients, both EM and CM[81]. This was despite patients taking acute and/or preventatives treatment. Pain was also the most commonly self-reported symptom of migraine in 91.7% of users in an analysis of data from the Migraine Buddy© smartphone application [82]. Overall, 63.6% of all migraine records from the application (n=28,152 attacks recorded in 3900 individuals) reported a pain intensity of ≥5 (on a scale of 1–10, where 10 = worst pain), which corresponded to an inability of individuals to perform some of even any activities[82]. Pain intensity was similar regardless of migraine frequency (see 図 4-10).

図 4-10 Pain intensity reported in migraine records captured by the Migraine Buddy© smartphone application across 17 European countries[82]



CM, chronic migraine; EM, episodic migraine

Other migraine symptoms

In addition to pain, several other symptoms that are characteristic of migraine attacks have been described by patients. The importance of non-pain symptoms has been highlighted by regulatory agencies. Both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) emphasize the value of measuring symptoms from the patient perspective and recommend the assessment of migraine-associated symptoms (N/V, photophobia, phonophobia) when evaluating migraine treatment efficacy [83].

In the Swedish population-based survey of 423 patients with self-considered migraine (45% diagnosed by a physician), symptoms of migraine attacks included photo-/phonophobia (96% of patients), throbbing/aggravation (87%), prodrome (81%), nausea and vomiting (N/V; 79%), unilateral pain (77%), and aura (44%) (Linde and Dahlof et al, 2004[84]). Aura was more frequently reported by patients with a physician's diagnosis of migraine versus those with self-considered migraine (61% vs 29%). The most troublesome symptoms during migraine attacks were photophobia (in 6% of patients), phonophobia (3%), and nausea (5%). As described above, 86% of patients described pain as the most troubling symptom.

Migraine symptoms related to mood and cognition were commonly reported in an analysis of data captured by the Migraine Buddy© smartphone application across 17 European countries (n=28,152 attacks in 3900 self-diagnosed individuals). Symptoms that included nausea, anxiety, confusion, blurred vision, moodiness, or giddiness were reported in 87.3% of individuals. Symptoms related to environment such as tinnitus, and sensitivity to light, noise, or smell were reported in 85.5% of individuals[82]. A relatively high rate of anxiety and/or depression during a migraine attack (as a symptom or trigger) was also reported in 44.8% of individuals with CM, 40.9% with EM and 8–14 migraine days/month, and 34.7% with EM and 4–7 migraine days/month[82].

Health-related quality of life between migraine attacks

Migraine not only adversely affects patient's HRQoL during an attack, but also has an impact between attacks[85]. Interictal burden has been defined as 'any loss of health or well-being

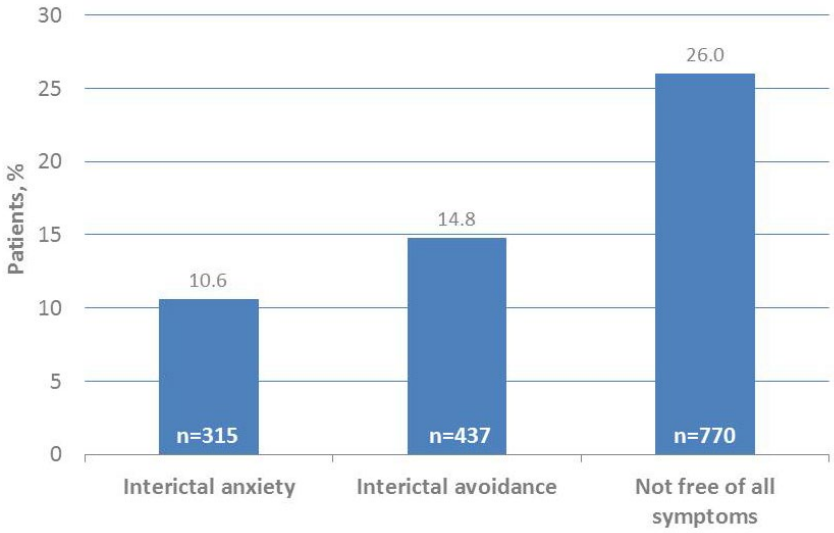
attributable to a headache disorder reportedly experienced while 'headache-free'[86]. There are numerous reasons why patients with migraine continue to experience the negative impact of their disease between attacks; for example, in those experiencing frequent attacks, excessive worry, and fear about when the next attack will strike may occur[86]. Avoidance behaviours might also occur, with patients trying to limit triggers through lifestyle compromises that may ultimately diminish pleasure in life. The importance of interictal burden lies in the fact that this period is typically present for more days in the month than the ictal period, especially in those with EM[86].

The extent of interictal burden in 6455 patients with headache (2959 of which had migraine, 45.8%) was determined in a European cross-sectional survey using modified cluster sampling from the adult population (18–65 years of age) in nine countries (the EuroLight Project) [86,87] . EuroLight involved the administration of a questionnaire that included questions with 'yes/no' answers regarding elements of headache burden likely to be experienced interictally, as follows:

- Q1. Were you anxious or worried about your next headache episode?
- Q2. Was there anything you could not do or did not do because you wanted to avoid getting a headache?
- Q3. Did you feel completely free from all headache symptoms?

>70% of patients with migraine gave an 'adverse response' to one of the three questions (i.e. yes to Q1 and Q2, and 'no' to Q3), indicating the considerable degree of interictal burden experienced[87]. 図 4-11 presents in detail the results to response of each question.

図 4-11 Participants with migraine in the EuroLight Project reporting interictal burden[86]



Lilly has conducted an analysis to determine if treatment with galcanezumab can reduce interictal burden, i.e. migraine-related impairment between attacks. A correlation analysis was subsequently conducted on patient-reported outcomes (PROs) collected in the CGAW study (表 4-17) to assess whether the interictal burden was adequately captured in other measures included in the study [88].

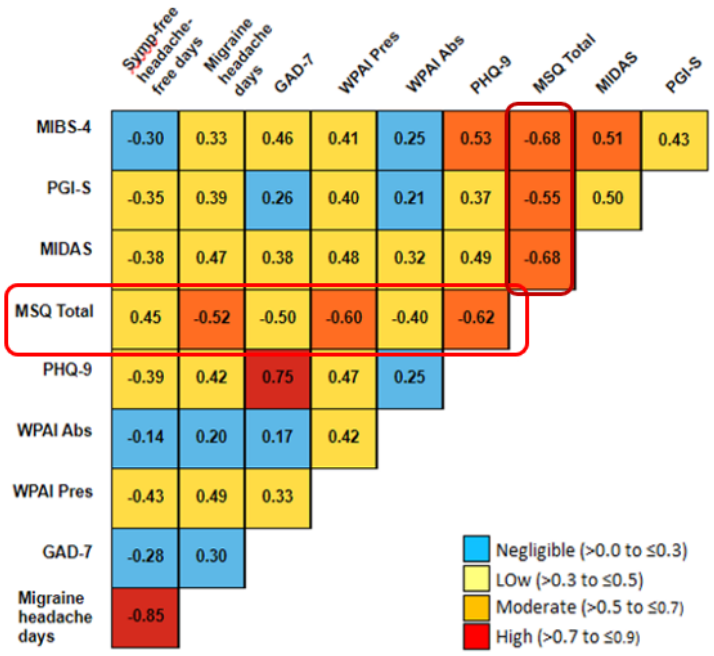
表 4-17 Outcomes included in the correlation analysis

Patient-Reported Outcomes		Outcome Measurement
MIBS-4	Migraine Interictal Burden Scale	Disruptions to life on days without

		headache
MIDAS	Migraine Disability Assessment	Disability due to migraine headache
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire	Functioning in various aspects of life
PGI-S	Patient Global Impression of Severity	Severity of overall migraine illness
GAD-7	Generalized Anxiety Disorder	Anxiety symptoms
PHQ-9	Patient Health Questionnaire	Depression symptoms
WPAI	Work Productivity and Activity Impairment	Impact of migraine on ability to do work and regular activities
Additional Outcomes		Outcome Measurement
Monthly migraine headache days		Days per month with migraine headache
Symptom-free headache-free days		Days per month with no headache or other migraine symptoms

Patients treated with galcanezumab experienced statistically significant greater reductions in interictal burden (LS mean change, -1.8 point reduction on the MIBS-4 scale) compared to placebo (LS mean change, -0.8 point reduction on the MIBS-4 scale). The Spearman's Rank Correlation Coefficients (Rho) were determined for MSQ Total correlation to other PRO outcome measures. The correlation analysis of the MSQ-total and monthly migraine headache days was moderate (-0.52 at month 3), indicating that 'ictal' measures, such as migraine headache days, do not fully capture the HRQoL in migraine. MSQ-Total was most strongly correlated with PHQ-9, MIBS, MIDAS and PHQ-9 (図 4-12). This result is not surprising since the MSQ was designed to measure both ictal and interictal burden of migraine (recall period of 4 weeks)[88].
The review of HRQoL data above presents a qualitative and quantitative review of the 'ictal' and interictal burden of migraine that impacts patient's HRQoL. Not all can be attributed to a change in monthly frequencies of MHDs. HRQoL, measured with the MSQ, is unlikely to be explained through a change MHD frequency alone. Contributing factors are also symptoms associated with the intensity and severity of pain of a migraine headache day, disability caused by migraine headache days, as well as the ictal an interictal burden (see 図 4-12). However, these could be explained by the administration of preventative medication which has been shown as one of the most important determinants of improvements in psychosocial difficulties, which evidence showed improved emotional problems, work efficiency, global disability, physical health, and mental health [89].

図 4-12 Heat maps show correlations between outcomes examined at Months 3, CGAW ITT



Migraine-Specific Quality of Life Questionnaire version 2.1

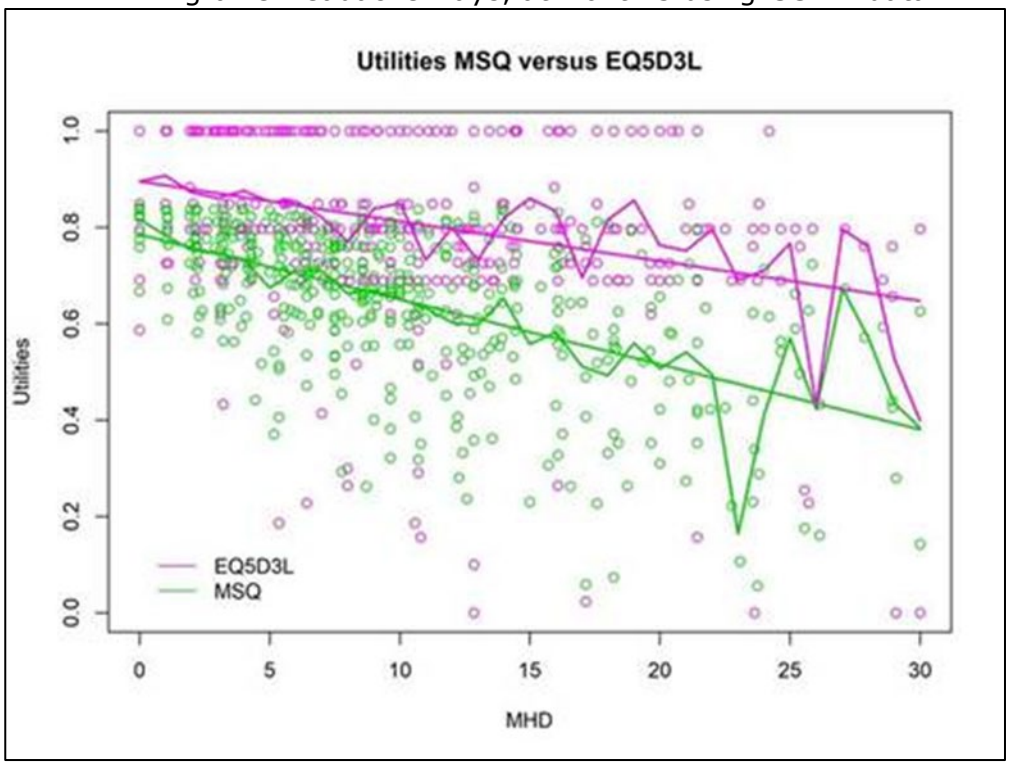
CGAG, CGAH, CGAI, CGAN and CGAW studies all collected the migraine-specific quality of life questionnaire (MSQ v2.1), which is a disease specific quality of life instrument. The Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) is a self-administered health status instrument that was developed to address the physical and emotional impact on functioning that is of specific concern to individuals suffering from migraine headaches. The instrument consists of 14 items that address 3 domains: (1) Role Function-Restrictive; (2) Role Function-Preventive; and (3) Emotional Function [90]. The restrictive domain specifically measures disability as related to the impact on performance of normal activities, with the preventive domain addressing complete functional impairment and the emotional domain assessing the feelings related to disabling monthly migraine headache days. Responses are given using a 6-point Likert-type scale, ranging from "none of the time" to "all of the time." Raw scores for each domain are computed as a sum of item responses, with the collective sum providing a total raw score that is then converted to a 0 to 100 scale, with higher scores indicating a better health status, and a positive change in scores reflecting functional improvement[91,92]. The instrument was designed with a 4-week recall period and is considered reliable, valid, and sensitive to change in functional impairment due to migraine[90,93].

The EQ-5D-5L quality-of-life instrument was administered in the CGAW study only, which excluded patients with one prior preventive treatment failure. Despite this limiting factor, the trial results from CGAW for MSQ v2.1 and EQ-5D-5L (mapped to the EQ-5D-3L) were compared to assess which instrument produced reliable results for the economic analysis. Past NICE appraisals for onabotulinumtoxinA, erenumab, and fremanezumab (NICE, 2012; 2019a and b) for preventing migraine have preferred the MSQ over the EQ-5D, stating that the EQ-5D may not be sensitive and does not capture all the important symptoms of disease that impact patient's quality-of-life. A reason for this may be the insufficient recall period of "today" for the EQ-5D in migraine and the frequency of administration in clinical trials.

The EQ-5D-5L instrument collects HRQoL information at a single point in time, as it asks patients to complete the questionnaire based on how they feel "today". In addition, the

instrument was administered at baseline and once again at study visit at 3 months at the end of the double-blind period of CGAW. Patients who experienced a migraine were unlikely to attend a study visit on that specific day. Given the recall period being today, it is therefore more likely to capture utility results similar to that of the population norm (see 図 4-13). This may explain the differing results observed between the two instruments, since patients were asked to complete the questionnaire when they may not have been experiencing a migraine attack.
In contrast, the MSQ was administered monthly throughout the randomized phases of CGAG, CGAH, CGAI, CGAN and CGAW. The MSQ has a 4-week recall period; therefore, it may have the ability to capture interictal burden, or impairment between attacks[94], as well as capturing more granular changes in HRQoL due to attacks in the preceding 4-weeks, which the EQ-5D is not able to do given the short "one point in time" recall period.
A visual assessment of the individual patient utility values, the observed mean, and the estimated mean utility values as a function of Migraine Headache Days from CGAW are shown in 図 4-13. This shows that there is minimal change in utility when measured using the EQ-5D compared to the MSQ with increasing monthly migraine headache days.

図 4-13 Utilities derived from the MSQ and from the EQ-5D-3L estimates, for each number of Migraine Headache Days, at Month 3 using CGAW data



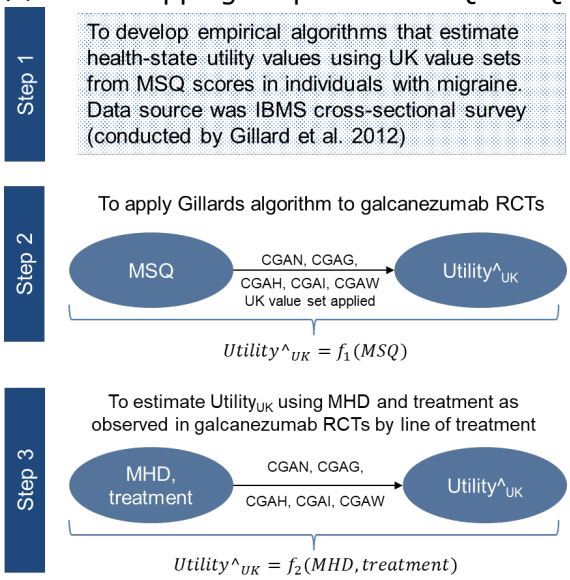
Utilities derived from the Migraine Specific Quality of Life instrument
A literature review was conducted during the model development; however the search yielded no results related to utility data while on galcanezumab treatment. As such, MSQ utility data, collected in the galcanezumab clinical trial program, were mapped to the EQ-5D-3L to estimate the quality of life of patients for the populations indicated in the analytical framework provided by C2H, for the purpose of the Japanese economic model. Using trial-specific information

allows to more accurately depict the impact of small changes in migraine headache days on HRQoL and to capture the treatment specific effect of galcanezumab over placebo ('BSC') on HRQoL.

前述の通り片頭痛の発作が QOL 値に与える影響を EQ-5D により正しく評価することはできない。このため企業は、以下のようなプロセスにより MHD を UK のタリフをもとにした EQ-5D-3L のスコアに換算する回帰式を作成し、使用した。
1. 片頭痛の疾患特異的尺度である MSQ を EQ-5D-3L にマッピングし、換算するアルゴリズムを提供する (Gillard et al. 2012[95])を用い、CGAN、CGAH、CGAG、CGAI、CGAW 試験により評価された MSQ から EQ-5D-3L(UK タリフ)による QOL 値を求めた。
2. CGAN、CGAH、CGAG、CGAI、CGAW 試験において評価された MHD を用い、単回帰分析により、MHD から 1. で求めた QOL 値を推定する回帰式を作成した。
上記のプロセスは、Gillard et al.にて提供されたアルゴリズムを使用しているが、これは UK のタリフをもとにしている。日本のタリフを用いた同様の研究はないため、日本のタリフを用いた同様の回帰式を作成することはできない。
実現可能性の制約からやむを得ず UK のタリフを用いる必要があったが、この方法により片頭痛の疾患特異的尺度を用いた評価により MHD を QOL 値に換算することができるというメリットがあり、このメリットはタリフの差異によるデメリットを上回ると考えられた。
上記方法の詳細について以下に説明する。

Following a technical document from the NICE Decision Support Unit, which states that mapping can be used to predict EQ-5D data [96], utilities were derived using a previously independently derived and published mapping algorithm by Gillard and colleagues 2012[95]. The mapping function was derived based on data from the International Burden of Migraine Study (IBMS). The IBMS study is a global, cross-sectional web-based survey, which enrolled patients from Australia, Canada, France, Germany, Italy, Spain, United Kingdom, Taiwan, Brazil and US and was conducted from February to April 2009. Patients were at least 18 years of age who experienced headaches over the last 3 months and met the ICHD-II criteria. The total sample consisted of ~10,000 patients. The survey collected information using the MSQ v2.1 questionnaire as well as the EQ-5D-3l. Based on this dataset, Gillard and colleagues (2012)[95] estimated a function, which allows to map the results of the Migraine-Specific Quality-of-Life Questionnaire (MSQ) domain scores collected at each month for episodic and chronic migraine patients to the EQ-5D-3l using the UK country-specific utility tariffs. Ordinary least squared regression models were constructed to estimate EQ-5D questionnaire utility values from MSQ v2.1 domain scores. The UK valuation set for raw EQ-5D questionnaire scores were used as the dependent variable, while the disease specific scores of the MSQ (RP, RR, EF) were considered as independent variables resulting in the following model:
EQ-5D questionnaire = $\alpha + \beta_1$ MSQ-RP + β_2 MSQ-RR + β_3 MSQ-EF + error.
Gillard and colleagues 2012[95] also derived an alternative regression model considering type of migraine with additional covariates, which was stated to be the preferred model. However, some of the covariates were not clearly defined. For example, they considered "headache medication" as a covariate without specifying what specifically counted as headache medication. Therefore, it was decided to use the model without covariates as highlighted in 図 4-14.
No other published mapping function allowing for the inclusion of alternative country-specific utility sets were identified in the literature. The following steps were undertaken to derive the utilities for the Japanese cost-effectiveness model.

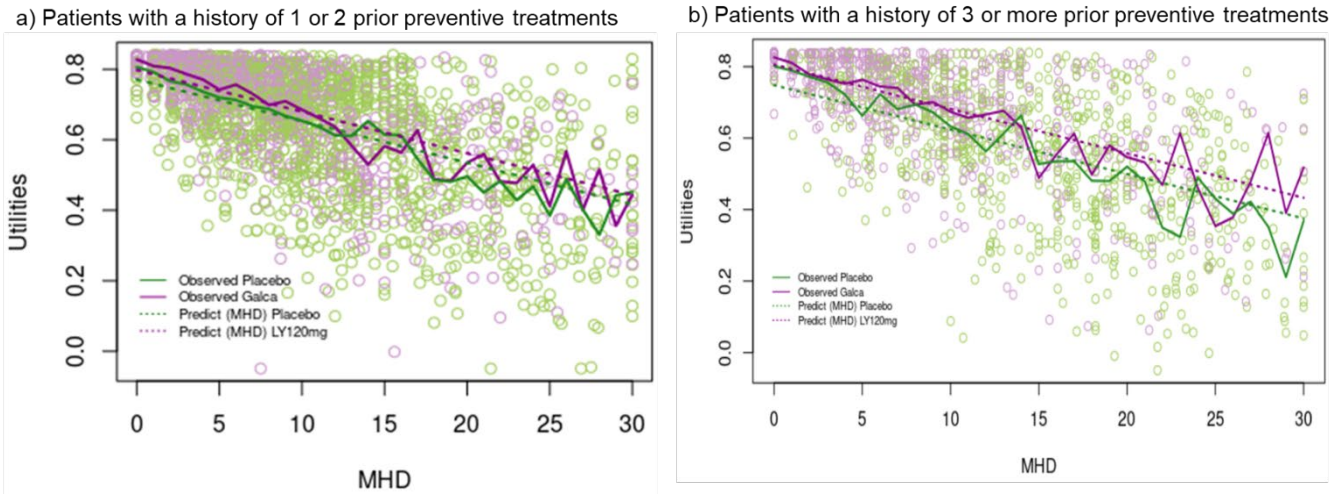
図 4-14 Mapping steps from MSQ to EQ-5D-3l



f1 refers to the Model 1 ($Utility\hat{}_{UK} = a + \beta_1$ MSQ-RP+ β_2 MSQ-RR+ β_3 MSQ-EF + error)
Utility^UK is the health index score with the EQ-5D UK value sets applied

Utility values were estimated for each migraine headache day frequency ranging from 0 to 30 to match the patient population with 1 or 2 prior preventive treatment failures and for those who have more than 3 prior preventive treatment failures for baseline, representing the health state 'off treatment' and month 1-3, representing the health state 'on-treatment' using the mapping function developed by Gillard et al 2012[95]. The utility models specified by Gillard et al 2012[95] were used to further investigate whether the treatment effect variable should be included into the regression.
A linear model was used to estimate the utilities associated with the monthly migraine headache days at baseline using the observations for the subpopulations of interest in CGAG, CGAH, CGAI, CGAN and CGAW. Independently, migraine headache days as observed in month 1 to 3 were modeled using a mixed model for repeated measures with migraine headache days and study treatment as covariates and an unstructured variance covariance matrix. This model allowed to account for the full extent of the longitudinal data structure as highlighted in Griffiths 2017[97]. The observations and predictions for the patient population with a history of 1 or 2 prior preventive treatments or those with at least 3 prior preventive treatments is presented in 図 4-15.

図 4-15 Mixed model for repeated measures to predict utilities considering observations at month 1, 2 and 3



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Considering the statistically significant covariate 'study treatment', differential utilities values for the analysis of galcanezumab compared to best supportive care (BSC) were applied, taking account of the observed treatment effect in the clinical trials. Doing so, can account for additional aspects of migraine which may impact HRQoL not captured solely through the change in the frequency of migraine headache days (see also section 3.2, 表 4-18). The treatment effect is statistically significant across both patient populations of interest using CGAG, CGAH, CGAI, CGAN and CGAW. For the comparison to propranolol and valproic acid, the utility values associated with galcanezumab for the health state 'on-treatment' are applied for both galcanezumab and either propranolol or valproic acid depending on the comparison.

表 4-18 Regression parameters of the mixed model considering month 1 to 3 using trial data from CGAG, CGAH, CGAI, CGAN and CGAW

	Failed 1 or 2 preventatives	**Failed 1 or 2 preventatives Pr(>|t|)**	**Failed ≥3 prior preventatives**	**Failed ≥3 prior preventatives Pr(>|t|)**
(Intercept)	0.76960	<0.0001	0.74830	<0.0001
MHD	-0.01182	<0.0001	-0.01242	<0.0001
Treatment	0.02687	<0.01	0.05771	<0.001
Observations	2408		1436	
AIC	-4143.2		-2305.6	
BIC	-4114.2		-2279.3	

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Differences in HRQoL are therefore captured in the cost-effectiveness model through differences in the frequency in migraine headache days and the treatment applied to the model and subsequently whether patients are in the 'on-treatment' or 'off-treatment' health state. The 'on'-and 'off-treatment' utilities were selected for use in the economic model using migraine headache days and treatment effect as the only covariates in the model (see 表 4-

19).

表 4-19 Alternative utility values used for the comparison to BSC, propranolol or valproic acid with base case settings

Health-State	Base case	Galcanezumab	Comparator
First-cycle	Initiate treatment	Off-treatment	Off-treatment
Responder	vs BSC	Galcanezumab	BSC
	vs propranolol/valproic acid	Galcanezumab	Galcanezumab
Discontinuation due to non-response (3-month assessment)	Patients return to baseline migraine headache days	Off-treatment	Off-treatment
Discontinuation due to All-cause (long-term, per-cycle)	Patients return to baseline migraine headache days	Off-treatment	Off-treatment

表 4-20 presents the number of observations from CGAG, CGAH, CGAI, CGAN and CGAW and the predicted utility values as a function of number of migraine headache days and treatment covariate for the population with a history of 1 or 2 prior preventive treatment(s) and separately for those patients with a history of at least 3 prior preventive treatments. No utilities were predicted for the subpopulation of patients who only use a 2nd line preventive treatment or only use a 3rd line preventive treatment due to the limited number of observations, which will impact the precision of estimates. Hence, for those two subpopulations, the same utilities are applied as for the patients with a treatment history of 1 or 2 prior preventive treatments.

表 4-20 Trial utilities for subgroup of patients failed 1 or 2 preventive treatments or at least 3 preventive treatments - EQ-5D-3L values (mapped from MSQ)

No. of MHD	Population with a history of 1 or 2 prior preventive treatments						Population with a history of at least 3 prior preventive treatments					
	Baseline		Galcanezumab		BSC		Baseline		Galcanezumab		BSC	
	N	Utility value	N	Utility value	N	Utility value	N	Utility value	N	Utility value	N	Utility value
0	NA	0.7874	58	0.7965	26	0.7696	NA	0.7681	41	0.8060	4	0.7483
1	NA	0.7700	49	0.7847	37	0.7578	NA	0.7514	28	0.7936	7	0.7359
2	NA	0.7526	51	0.7728	63	0.7460	NA	0.7347	35	0.7812	13	0.7235
3	NA	0.7351	79	0.7610	65	0.7341	NA	0.7180	37	0.7688	21	0.7110
4	31	0.7177	71	0.7492	91	0.7223	9	0.7014	43	0.7563	30	0.6986
5	37	0.7003	63	0.7374	76	0.7105	13	0.6847	39	0.7439	23	0.6862
6	39	0.6829	60	0.7256	90	0.6987	13	0.6680	48	0.7315	33	0.6738
7	58	0.6655	25	0.7137	67	0.6869	13	0.6513	25	0.7191	25	0.6614
8	57	0.6480	67	0.7019	86	0.6750	32	0.6346	41	0.7067	33	0.6489
9	63	0.6306	53	0.6901	105	0.6632	29	0.6179	38	0.6942	39	0.6365
10	56	0.6132	45	0.6783	110	0.6514	39	0.6012	37	0.6818	50	0.6241
11	67	0.5958	34	0.6665	68	0.6396	33	0.5845	29	0.6694	47	0.6117
12	48	0.5784	34	0.6546	79	0.6278	29	0.5679	19	0.6570	39	0.5993
13	42	0.5609	27	0.6428	89	0.6159	22	0.5512	26	0.6446	35	0.5868
14	53	0.5435	28	0.6310	54	0.6041	36	0.5345	21	0.6321	33	0.5744
15	25	0.5261	17	0.6192	42	0.5923	31	0.5178	6	0.6197	23	0.5620
16	24	0.5087	20	0.6074	59	0.5805	16	0.5011	17	0.6073	34	0.5496
17	27	0.4912	11	0.5955	38	0.5687	11	0.4844	15	0.5949	37	0.5372
18	29	0.4738	15	0.5837	37	0.5568	24	0.4677	6	0.5825	46	0.5247
19	26	0.4564	10	0.5719	33	0.5450	19	0.4510	12	0.5700	34	0.5123
20	28	0.4390	12	0.5601	17	0.5332	23	0.4343	13	0.5576	28	0.4999
21	19	0.4216	14	0.5483	23	0.5214	18	0.4177	15	0.5452	24	0.4875
22	20	0.4041	12	0.5364	26	0.5096	16	0.4010	7	0.5328	24	0.4751
23	17	0.3867	5	0.5246	18	0.4977	11	0.3843	5	0.5204	14	0.4626
24	17	0.3693	6	0.5128	22	0.4859	15	0.3676	9	0.5079	23	0.4502
25	14	0.3519	9	0.5010	13	0.4741	10	0.3509	4	0.4955	30	0.4378
26	14	0.3345	5	0.4892	21	0.4623	7	0.3342	4	0.4831	11	0.4254

27	13	0.3170	3	0.4773	13	0.4505	12	0.3175	6	0.4707	13	0.4130
28	10	0.2996	3	0.4655	14	0.4386	9	0.3008	3	0.4583	9	0.4005
29	7	0.2822	4	0.4537	8	0.4268	4	0.2841	3	0.4458	6	0.3881
30	NA	0.2648	7	0.4419	21	0.4150	NA	0.2675	4	0.4334	12	0.3757

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4.2.3 費用のパラメータの詳細

4.2.3.1 Cost and resource use

The cost effectiveness model considers the resource use and cost of emergency room department (outpatient visits), hospitalisations (DPC service), physician visits, administration costs and acute medications. Costs and resource use relating to each component are described in subsequent sections.

4.2.3.2 Drug acquisition costs

Drug acquisition costs were calculated by combining the cost per unit and the required number of units per cycle. The drug costs per pack, dosing and frequency of dose administration is shown in 表 4-21. Drug costs were sourced from the NHI price list[98]. If available branded drug prices were used. Allowing a unit per cycle costing gives detailed reflections of the annual costs associated with each treatment. The most relevant comparators are propranolol, valproic acid (sensitivity analysis only) and BSC for episodic and chronic migraine patients. BSC comprises of self-administration of acute medications and resource use associated with the specific mean change migraine headache days. BSC was not associated with additional costs as both galcanezumab and active comparators are assumed to be given with the same acute medication received in BSC. The daily dose for propranolol and valproic acid was informed by the analysis of the local claims database (JMDC 2021 (Appendix 4-1)).

表 4-21 Drug costs, dosing and frequency of dose administration

	Galcanezumab 120mg	**Propranolol**	**Valproic Acid**
mg/unit	120	10	100
Unit cost	¥45,165[a]	¥11.60[a]	¥10.10[a]
Loading dose	240mg for first injection[b]	N/A	N/A
Dose (mg)	120mg[b]	21.59mg[c]	334.76mg[c]
Administration/cycle	1	30	30
Frequency (day)	30	30	30
Dose/cycle	120mg	647.70mg	10042.80mg
Source	[a]NHI price list (2021)[98] [b]PMDA, 2021[1]	[a]NHI price list (2021)[98], [c] JMDC 2021 (Appendix 4-1)	[a]NHI price list (2021)[98], [c] JMDC 2021 (Appendix 4-1)

The model allows for a loading dose and different dosing cycles based on the product characteristics for the respective treatment. For the loading dose of galcanezumab, this is applied in the first cycle of treatment and is applied in addition to the maintenance dose.

4.2.3.3 Resource use and unit costs

Healthcare professional use

The model considers resource use, like healthcare professional use by each migraine headache day, which was informed from an analysis conducted by Kikui et al 2020 [50] using data from the Japanese National Health and Wellness Survey (NHWS) collected in 2017. The study enrolled a sample of the general Japanese population, which was divided into a migraine cohort defined by the ICHD-3 criteria with at least 4 migraine headache days (N=378) and a matched non-migraine control cohort (N=1,512).

The study reported 6-month average medical resource use for the number of physician visits (migraine cohort: 7.23; non-migraine cohort: 3.96), emergency room visits (migraine cohort: 0.03; non-migraine cohort: 0.01) and hospitalisations (migraine cohort: 0.80; non-migraine cohort: 0.49). Considering that not all medical resource use in the migraine cohort may be attributable to migraine, it was assumed that the surplus of the difference between the migraine and matched non-migraine cohort is an appropriate proxy for the medical resource use associated with migraine. This results in 3.27 physician visits/6 months, 0.31 hospitalisation/6 months and 0.02 emergency room visits/6 months. The migraine patients had on average 46 migraine episodes over a 6-month period resulting in 7.67 mean monthly migraine headache days assuming that an episode equals a day. Medical resource use per migraine headache day was estimated by dividing the 6-month average use by the mean number of migraine headache days reported over a 6-month period by patients. The unit costs for each resource category (emergency department visits, hospitalizations, and physician visits and pharmacy dispensing fee) are calculated using Instruction on medical care fee points (April 2021). 表 4-22 shows the costs used per resource and the associated use per migraine headache day.

表 4-22 Resource use and costs

	Emergency room use (outpatient)	Hospitalisation^ (DPC service)	Physician visit*
Cost	¥34,165	¥170,817	¥3,130
Average use per migraine day	0.00043	0.00674	0.07109

^assuming 4 days in hospital, *Physician visit (including tests etc is considered as an emergency situation but not using emergency room)

Using published medical resource use by Kikui et al 2020[50] had some limitations: (i) it was not specific to the target population who had a history of either 1 or 2 prior preventive treatments or ≥3 prior preventative treatments or by subtype of migraine, (ii) it is based on survey information not medical records and self-reported migraine. However, the strengths of the approach taken by Kikui et al 2020 [50] is that it does allow to estimate the rate of medical resource use associated with each migraine headache day due to the inclusion of the migraine and matched non-migraine cohort. Being able to calculate the resource use by number of migraine headache days is aligned with the underlying model structure. Moreover, the evidence for healthcare professional resource use was based on local Japanese data from the general population increasing the transposability of the results.

In addition to the healthcare professional resource use depending by migraine headache day frequency (表 4-21), an additional physician consultation and prescription fee is assumed for the administration of galcanezumab every month at a cost of ¥3,330/visit and for propranolol and valproic acid every other month at a cost of ¥3,990/visit.

Acute medication use per migraine headache day frequency

The economic analysis also captures acute medication use per migraine headache day

frequency by applying a binomial distribution to predict the frequency of acute medication use with triptans, acetaminophen (paracetamol and containing products) and NSAIDs, with each migraine headache day frequency. The number of monthly migraine headache days with use of triptans or NSAIDs/aspirin or acetaminophen/paracetamol were collected daily via an eDiary in CGAG, CGAH, CGAI, CGAN and CGAW. For this analysis all observations at month 3 were considered for the subgroups of patients with a

I. history of 1 or 2 preventive treatment failures (ie. 2nd or 3rd line preventive treatment)
II. history of at least 3 prior preventive treatment failures (ie. ≥4th line preventive treatment)

No separate analysis was performed for those patients who have a history of 1 failure (ie. 2nd line) or 2 failures (ie. 3rd line) due to lower number of observations given the smaller sample and subsequently the greater uncertainty around the predictions. The results for population (I) were therefore also applied for those patients who have a history of 1 failure (ie. 2nd line) or 2 failures (ie. 3rd line). Although several distributions were tested to predict the acute medication use by frequency of migraine headache days, only the binomial distribution predicted no use of acute medication when patients experienced no migraine headache days. Given the definition of this variable and clinical plausibility, this distribution was chosen.

The weighted cost per day was based on the mean average daily dose informed by the JMDC analysis (Appendix 4-2), the pack size, local uptake and branded drug cost, if available, in line with the Japanese HTA guideline[49]. This results in daily costs for triptans of ¥933.13, for acetaminophen/paracetamol of ¥23.04 and for NSAID/Aspirin of ¥23.38.

A summary of frequencies of resource use by category, excluding administration cost, and the resultant total management costs by monthly migraine headache day frequency is provided in 表 4-23. The same number of healthcare professional visits was assumed for patients irrespective of line of treatment, while acute medication use was estimated for the patients with a history of 1 or 2 prior preventive treatments or at least 3 prior preventive treatments resulting in slightly different total management costs across the range of possible number of migraine headache day frequency, irrespective of treatment, as seen in 表 4-23.

表 4-23 Summary of medical resource use frequency and total cost by monthly migraine headache days

No. of MHD	Physician visits	Hospitalisation (DPC service)	AE visit (outpatient)	Failed 1 or 2 prior treatments				Failed at least 3 prior treatments			
				Paracetamol use	NSAID Use	Triptan use	Total costs	Paracetamol use	NSAID Use	Triptan use	Total costs
0	0.0000	0.0000	0.0000	0.00	0.00	0.00	¥0	0.00	0.00	0.00	¥0
1	0.0711	0.0517	0.0033	0.18	0.46	0.56	¥9,733	0.07	0.33	0.58	¥9,747
2	0.1422	0.1033	0.0067	0.36	0.91	1.11	¥19,456	0.15	0.68	1.16	¥19,495
3	0.2133	0.1550	0.0100	0.54	1.35	1.65	¥29,168	0.23	1.03	1.74	¥29,243
4	0.2843	0.2067	0.0133	0.72	1.79	2.18	¥38,871	0.31	1.39	2.31	¥38,981
5	0.3554	0.2583	0.0167	0.90	2.21	2.70	¥48,564	0.41	1.76	2.88	¥48,720
6	0.4265	0.3100	0.0200	1.08	2.63	3.21	¥58,246	0.51	2.13	3.45	¥58,459
7	0.4976	0.3617	0.0233	1.27	3.04	3.72	¥67,928	0.61	2.52	4.01	¥68,189
8	0.5687	0.4133	0.0267	1.45	3.45	4.21	¥77,591	0.72	2.91	4.56	¥77,909
9	0.6398	0.4650	0.0300	1.64	3.84	4.70	¥87,253	0.84	3.31	5.12	¥87,639
10	0.7109	0.5167	0.0333	1.82	4.23	5.17	¥96,895	0.97	3.72	5.67	¥97,360
11	0.7820	0.5683	0.0367	2.01	4.61	5.64	¥106,537	1.10	4.14	6.21	¥107,071
12	0.8530	0.6200	0.0400	2.20	4.98	6.09	¥116,158	1.24	4.57	6.75	¥116,782
13	0.9241	0.6717	0.0433	2.39	5.35	6.54	¥125,780	1.39	5.01	7.29	¥126,494
14	0.9952	0.7233	0.0467	2.58	5.70	6.98	¥135,392	1.55	5.46	7.82	¥136,197
15	1.0663	0.7750	0.0500	2.77	6.06	7.41	¥144,994	1.72	5.91	8.35	¥145,899
16	1.1374	0.8267	0.0533	2.96	6.40	7.83	¥154,585	1.90	6.38	8.88	¥155,603
17	1.2085	0.8783	0.0567	3.15	6.73	8.24	¥164,166	2.08	6.85	9.40	¥165,296
18	1.2796	0.9300	0.0600	3.35	7.06	8.64	¥173,738	2.28	7.33	9.92	¥174,991
19	1.3507	0.9817	0.0633	3.54	7.38	9.04	¥183,309	2.49	7.83	10.43	¥184,675
20	1.4217	1.0333	0.0667	3.74	7.69	9.42	¥192,860	2.70	8.33	10.94	¥194,360
21	1.4928	1.0850	0.0700	3.93	8.00	9.79	¥202,401	2.93	8.84	11.45	¥204,046
22	1.5639	1.1367	0.0733	4.13	8.30	10.16	¥211,942	3.17	9.36	11.95	¥213,722
23	1.6350	1.1883	0.0767	4.33	8.59	10.51	¥221,463	3.43	9.89	12.45	¥223,399
24	1.7061	1.2400	0.0800	4.52	8.88	10.86	¥230,984	3.69	10.42	12.94	¥233,066
25	1.7772	1.2917	0.0833	4.72	9.15	11.20	¥240,494	3.97	10.97	13.43	¥242,734
26	1.8483	1.3433	0.0867	4.92	9.42	11.53	¥249,995	4.26	11.53	13.92	¥252,402
27	1.9193	1.3950	0.0900	5.13	9.69	11.85	¥259,486	4.57	12.10	14.40	¥262,061
28	1.9904	1.4467	0.0933	5.33	9.94	12.16	¥268,966	4.89	12.67	14.87	¥271,711
29	2.0615	1.4983	0.0967	5.53	10.19	12.46	¥278,436	5.22	13.26	15.35	¥281,371
30	2.1326	1.5500	0.1000	5.74	10.44	12.76	¥287,907	5.57	13.85	15.82	¥291,021

5. 分析結果

5.1 基本分析(費用対効果評価専門組織で決定された分析枠組みによる分析)の結果

費用対効果評価専門組織で決定された分析枠組みに基づき、4 つの対象集団に対して下記の通り分析を実施した。

(a)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者

■ 費用効果分析(増分費用効果比を算出する)
□ 費用最小化分析(効果は同等として費用を比較する)

(b)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者

■ 費用効果分析(増分費用効果比を算出する)
□ 費用最小化分析(効果は同等として費用を比較する)

(c)片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者

■ 費用効果分析(増分費用効果比を算出する)
□ 費用最小化分析(効果は同等として費用を比較する)

(d)片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者

■ 費用効果分析(増分費用効果比を算出する)
□ 費用最小化分析(効果は同等として費用を比較する)

5.1.1 基本分析の増分費用、増分効果、増分費用効果比

分析対象集団ごとの分析の結果および費用の内訳は下記の通りである。

(a)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者

・分析結果の要約

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER(円 /QALY)
評価対象技術 Galcanezumab 120mg	12.570	0.230	¥5,500,826	¥1,396,932	¥6,077,875
比較対照技術 Propranolol	12.340	/	¥4,103,894	/	/

・費用の内訳の詳細

費用	評価対象技術: Galcanezumab 120mg	比較対照技術: Propranolol
予防治療薬剤費	¥1,522,571	¥6,387
外来診察費用	¥105,599	¥16,958
救急・入院費用	¥2,813,546	¥2,965,757
急性期治療薬剤費	¥1,059,111	¥1,114,791

(b)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者

・分析結果の要約

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER(円 /QALY)

評価対象技術 Galcanezumab 120mg	9.398	0.509	¥9,879,533	¥1,371,145	¥2,691,706
比較対照技術 Propranolol	8.889	/	¥8,508,388	/	/

・ 費用の内訳の詳細

費用	評価対象技術: Galcanezumab 120mg	比較対照技術: Propranolol
予防治療薬剤費	¥1,701,604	¥6,553
外来診察費用	¥118,799	¥17,401
救急・入院費用	¥6,047,006	¥6,372,062
急性期治療薬剤費	¥2,012,124	¥2,112,371

(c) 片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者

・ 分析結果の要約

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER(円/QALY)
評価対象技術 Galcanezumab 120mg	12.158	0.381	¥5,539,801	¥1,087,066	¥2,850,240
比較対照技術 BSC	11.777	/	¥4,452,735	/	/

・ 費用の内訳の詳細

費用	評価対象技術: Galcanezumab 120mg	比較対照技術: BSC
予防治療薬剤費	¥1,376,635	¥0
外来診察費用	¥94,839	¥0
救急・入院費用	¥2,882,664	¥3,155,769
急性期治療薬剤費	¥1,185,662	¥1,296,966

(d) 片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者

・ 分析結果の要約

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER(円/QALY)
評価対象技術 Galcanezumab 120mg	9.439	0.735	¥9,853,551	¥1,059,682	¥1,441,739
比較対照技術 BSC	8.704	/	¥8,793,870	/	/

・ 費用の内訳の詳細

費用	評価対象技術: Galcanezumab 120mg	比較対照技術: BSC
予防治療薬剤費	¥1,699,115	¥0
外来診察費用	¥118,615	¥0
救急・入院費用	¥5,758,503	¥6,304,054

急性期治療薬剤費	¥2,277,318	¥2,489,815

5.1.2 感度分析

5.1.2.1 専門組織の指示に基づく感度分析

本剤の費用対効果評価にかかる分析枠組みの中で指示された感度分析としてのシナリオ分析を行った。それぞれの対象集団と比較対照技術は以下の通りである。

1. 片頭痛予防薬の2剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない反復性片頭痛患者
2. 片頭痛予防薬の2剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない慢性片頭痛患者
3. 片頭痛予防薬の3剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない反復性片頭痛患者
4. 片頭痛予防薬の3剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない慢性片頭痛患者

・分析対象集団1および2:既存の片頭痛予防薬（プロプラノロール、バルプロ酸）のうち、当該集団に対して禁忌ではないもの＝基本分析をプロプラノロールで実施したので、バルプロ酸を選択
・分析対象集団３および４: Best Supportive Care

結果を以下に示す。

1　片頭痛予防薬の2剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない反復性片頭痛患者

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER(円 /QALY)
Galcanezumab 120mg	12.564	0.242	¥5,572,347	¥1,422,129	¥5,882,887
Valproic Acid	12.323	/	¥4,150,219	/	/

2　片頭痛予防薬の2剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない慢性片頭痛患者

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER(円 /QALY)
Galcanezumab 120mg	9.395	0.572	¥10,047,701	¥1,465,894	¥2,562,916
Valproic Acid	8.823	/	¥8,581,806	/	/

3　片頭痛予防薬の3剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない反復性片頭痛患者

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER(円 /QALY)
Galcanezumab 120mg	12.674	0.324	¥5,218,126	¥1,216,247	¥3,751,390
BSC	12.349	/	¥4,001,879	/	/

4　片頭痛予防薬の3剤目の治療において既存の片頭痛予防薬が禁忌又は副作用のため使用できない慢性片頭痛患者

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER(円 /QALY)
Galcanezumab 120mg	9.524	0.604	¥9,490,615	¥1,086,106	¥1,798,947
BSC	8.920	/	¥8,404,509	/	/

本剤の費用対効果分析において、片頭痛予防薬の 2 剤目の治療の対照薬としてプロプラノロールについて記述したが、プロプラノロールの添付文書上の禁忌疾患として以下の疾患が該当する。

- 気管支喘息，気管支痙攣のおそれのある患者，糖尿病性ケトアシドーシス，代謝性アシドーシスのある患者，高度又は症状を呈する徐脈，房室ブロック(II，III 度)，洞房ブロック，洞不全症候群のある患者、心原性ショックの患者，肺高血圧による右心不全のある患者，うっ血性心不全のある患者，低血圧症の患者，長期間絶食状態の患者，重度の末梢循環障害のある患者，未治療の褐色細胞腫の患者，リザトリプタン安息香酸塩を投与中の患者

発生頻度を勘案した上で、気管支喘息，低血圧症，および徐脈について片頭痛患者における併存疾患として罹患している割合を株式会社 JMDC の健保ベースのレセプトデータより 2005 年から 2021 年の期間で検討した。その結果を以下の表に示す。

	ICD10 コード		禁忌疾患該当患者数	片頭痛患者（n=35,116）における割合
	片頭痛	禁忌疾患		
気管支喘息	G43	J45	2,670	7.6%
低血圧症	G43	I95	561	1.6%
徐脈	G43	R001	30	0.08%
			総計	9.3%

出典：JDM-PV

片頭痛予防薬の 2 剤目の治療において、プロプラノロールの禁忌疾患のためにバルプロ酸を使用する患者は 9.3%である。

5.1.2.2 Deterministic sensitivity analyses (DSA)

基本分析に対する感度分析の結果を述べる。

- **Episodic Migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (Propranolol comparison)**

The result of the deterministic sensitivity analysis (DSA) in the episodic migraine patient population with a history of 1 or 2 prior preventive treatments (ie. 2nd or 3rd line preventive treatment) comparing galcanezumab to propranolol is presented in 図 5-1 and 表 5-1. The most impactful parameters are the utility treatment effect observed in the clinical trial program of galcanezumab, followed by the mean change from baseline in monthly migraine headache days for galcanezumab and discount rates for QALYs. All upper and lower bound ICERs remain below the ¥7,500,000 willingness to pay threshold. 表 5-1 provides a comprehensive overview of the results of various variables tested in the DSA in the episodic migraine patient population with a history of 1 or 2 prior preventive treatments comparing galcanezumab to propranolol.

図 5-1 DSA in the episodic migraine patient population with a history of 1 or 2 prior preventive treatments (propranolol comparison)

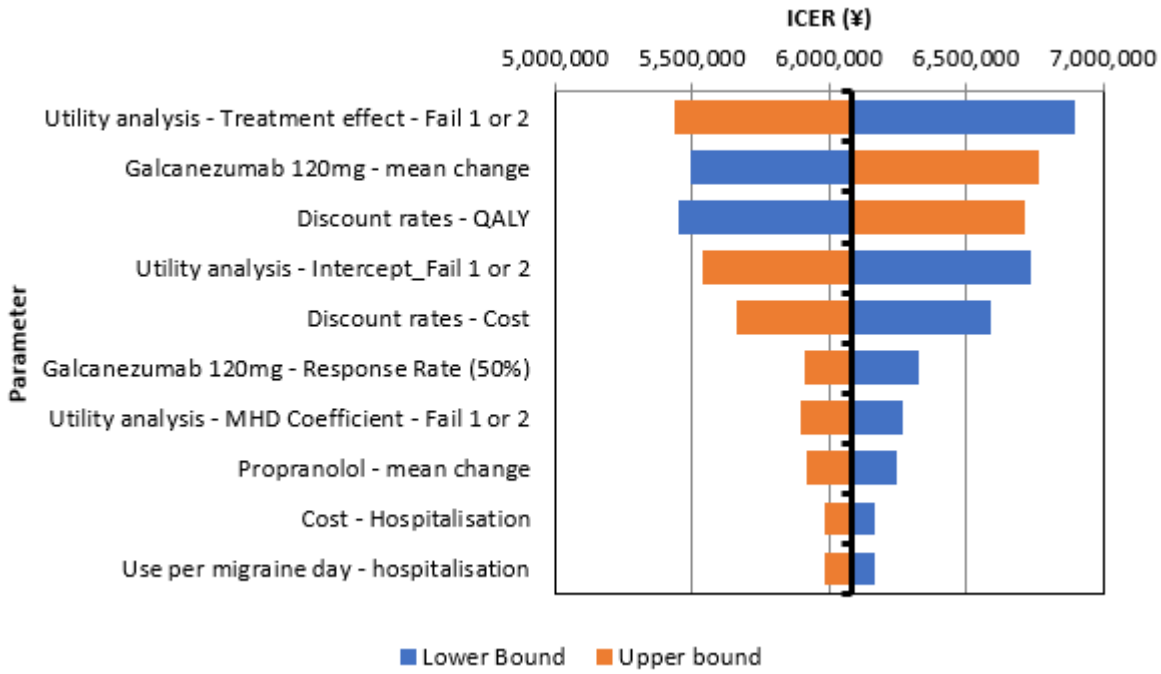


表 5-1 Detailed results of the DSA for the episodic migraine patient population with a history of 1 or 2 prior preventive treatments (Propranolol comparison)

Parameter	Range	Galcanezumab		Propranolol		Incremental		ICER	Δ ICER in %
		Cost	QALY	Cost	QALY	Cost	QALY		
Base case		**¥5,500,826**	**12.5698**	**¥4,103,894**	**12.3400**	**¥1,396,932**	**0.2298**	**¥6,077,875**	
Discount rate - QALY	LB (0.00%)	¥5,500,826	15.6860	¥4,103,894	15.4295	¥1,396,932	0.2565	¥5,446,813	-10.38%
	UB (4.00%)	¥5,500,826	10.3157	¥4,103,894	10.1075	¥1,396,932	0.2081	¥6,712,299	10.44%
Discount rate - Cost	LB (0.00%)	¥6,651,384	12.5698	¥5,136,269	12.3400	¥1,515,115	0.2298	¥6,592,073	8.46%
	UB (4.00%)	¥4,658,322	12.5698	¥3,357,967	12.3400	¥1,300,355	0.2298	¥5,657,680	-6.91%
Baseline - Age	LB (42.55)	¥5,507,190	12.5873	¥4,109,698	12.3573	¥1,397,492	0.2300	¥6,076,977	-0.01%
	UB (44.11)	¥5,494,025	12.5511	¥4,097,705	12.3214	¥1,396,320	0.2297	¥6,078,846	0.02%
Baseline - Gender	LB (85.45%)	¥5,498,529	12.5634	¥4,101,770	12.3336	¥1,396,759	0.2298	¥6,078,150	0.00%
	UB (90.50)	¥5,502,953	12.5757	¥4,105,861	12.3458	¥1,397,092	0.2299	¥6,077,621	0.00%
Baseline - MHD	LB (8.84)	¥5,408,162	12.6372	¥4,011,437	12.4096	¥1,396,725	0.2276	¥6,135,705	0.95%
	UB (9.26)	¥5,593,398	12.5024	¥4,196,233	12.2703	¥1,397,165	0.2320	¥6,021,333	-0.93%
GMB response rate (50%)	LB (39.25%)	¥5,281,318	12.5260	¥4,103,894	12.3400	¥1,177,424	0.1861	¥6,327,598	4.11%
	UB (56.89%)	¥5,721,630	12.6138	¥4,103,894	12.3400	¥1,617,737	0.2739	¥5,907,179	-2.81%
Propranolol response rate (50%)	LB (48.87%)	¥5,500,826	12.5698	¥4,104,170	12.3379	¥1,396,656	0.2319	¥6,023,080	-0.90%
	UB (69.41%)	¥5,500,826	12.5698	¥4,103,627	12.3419	¥1,397,199	0.2279	¥6,131,768	0.89%
GMB - mean MHD change	LB (-4.07)	¥5,467,479	12.5881	¥4,103,894	12.3400	¥1,363,586	0.2481	¥5,495,217	-9.59%
	UB (-3.05)	¥5,534,241	12.5515	¥4,103,894	12.3400	¥1,430,347	0.2115	¥6,762,258	11.26%
Propranolol - mean MHD change	LB (-3.29)	¥5,500,826	12.5698	¥4,094,840	12.3446	¥1,405,986	0.2252	¥6,242,283	2.71%
	UB (-1.57)	¥5,500,826	12.5698	¥4,112,904	12.3354	¥1,387,922	0.2344	¥5,920,211	-2.59%
Propranolol costs	LB (¥10)	¥5,500,826	12.5698	¥4,102,843	12.3400	¥1,397,983	0.2298	¥6,082,446	0.08%
	UB (¥14)	¥5,500,826	12.5698	¥4,104,944	12.3400	¥1,395,882	0.2298	¥6,073,304	-0.08%
Costs for physician visits	LB (¥2,634)	¥5,429,317	12.5698	¥4,028,516	12.3400	¥1,400,801	0.2298	¥6,094,707	0.28%
	UB (¥3,662)	¥5,577,458	12.5698	¥4,184,672	12.3400	¥1,392,786	0.2298	¥6,059,837	-0.30%
Cost for hospitalisation	LB (¥143,724)	¥5,130,860	12.5698	¥3,713,913	12.3400	¥1,416,947	0.2298	¥6,164,958	1.43%
	UB (¥199,851)	¥5,897,299	12.5698	¥4,521,816	12.3400	¥1,375,483	0.2298	¥5,984,553	-1.54%
Cost for A&E visit	LB (¥28,746)	¥5,496,052	12.5698	¥4,098,861	12.3400	¥1,397,190	0.2298	¥6,078,999	0.02%
	UB (¥39,972)	¥5,505,942	12.5698	¥4,109,286	12.3400	¥1,396,655	0.2298	¥6,076,671	-0.02%
Use per migraine day - physician visits	LB (0.060)	¥5,429,317	12.5698	¥4,028,516	12.3400	¥1,400,801	0.2298	¥6,094,707	0.28%
	UB (0.083)	¥5,577,458	12.5698	¥4,184,672	12.3400	¥1,392,786	0.2298	¥6,059,837	-0.30%
Use per migraine	LB (0.006)	¥5,130,860	12.5698	¥3,713,913	12.3400	¥1,416,947	0.2298	¥6,164,958	1.43%

day - hospitalisation	UB (0.008)	¥5,897,299	12.5698	¥4,521,816	12.3400	¥1,375,483	0.2298	¥5,984,553	-1.54%
Use per migraine day - A&E visit	LB (0.000)	¥5,496,052	12.5698	¥4,098,861	12.3400	¥1,397,190	0.2298	¥6,078,999	0.02%
	UB (0.001)	¥5,505,942	12.5698	¥4,109,286	12.3400	¥1,396,655	0.2298	¥6,076,671	-0.02%
Cost of Triptans	LB (¥830)	¥5,331,286	12.5698	¥3,925,443	12.3400	¥1,405,843	0.2298	¥6,116,645	0.64%
	UB (¥1,156)	¥5,670,365	12.5698	¥4,282,344	12.3400	¥1,388,021	0.2298	¥6,039,106	-0.64%
Cost of paracetamol containing products	LB (¥19)	¥5,499,421	12.5698	¥4,102,413	12.3400	¥1,397,009	0.2298	¥6,078,208	0.01%
	UB (¥27)	¥5,502,230	12.5698	¥4,105,374	12.3400	¥1,396,856	0.2298	¥6,077,542	-0.01%
Cost of NSAID/Aspirin	LB (¥20)	¥5,497,561	12.5698	¥4,100,458	12.3400	¥1,397,104	0.2298	¥6,078,621	0.01%
	UB (¥27)	¥5,504,090	12.5698	¥4,107,329	12.3400	¥1,396,761	0.2298	¥6,077,129	-0.01%
Galcanezumab discontinuation	LB (4.18%)	¥5,517,638	12.5734	¥4,103,894	12.3400	¥1,413,744	0.2335	¥6,055,069	-0.38%
	UB (7.02%)	¥5,482,202	12.5658	¥4,103,894	12.3400	¥1,378,308	0.2258	¥6,103,994	0.43%
Utility analysis - MHD Coefficient - Fail 1 or 2	LB (-0.0125)	¥5,500,826	12.5595	¥4,103,894	12.3368	¥1,396,932	0.2227	¥6,271,377	3.18%
	UB (-0.0111)	¥5,500,826	12.5801	¥4,103,894	12.3431	¥1,396,932	0.2369	¥5,895,956	-2.99%
Utility analysis - Intercept Fail 1 or 2	LB (0.7578)	¥5,500,826	12.5401	¥4,103,894	12.3327	¥1,396,932	0.2074	¥6,734,257	10.80%
	UB (0.7814)	¥5,500,826	12.5994	¥4,103,894	12.3472	¥1,396,932	0.2522	¥5,538,083	-8.88%
Utility analysis - Treatment effect - Fail 1 or 2	LB (0.0125)	¥5,500,826	12.5336	¥4,103,894	12.3311	¥1,396,932	0.2025	¥6,898,932	13.51%
	UB (0.0412)	¥5,500,826	12.6060	¥4,103,894	12.3488	¥1,396,932	0.2572	¥5,431,464	-10.64%

- **Chronic Migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (Propranolol comparison)**

The result of the DSA in the chronic migraine patient population with a history of 1 or 2 prior preventive treatments (ie. 2nd or 3rd line preventive treatment) comparing galcanezumab to propranolol is presented in 図 5-2 and 表 5-2. The most impactful parameters are the mean change from baseline in monthly migraine headache days for galcanezumab and discount rates for QALYs and costs. All upper and lower bound ICERs remain well below the ¥5,000,000 willingness to pay threshold. 表 5-2 provides a comprehensive overview of the results of various variables tested in the deterministic sensitivity analysis in the chronic migraine patient population with a history of 1 or 2 prior preventive treatments comparing galcanezumab to propranolol.

図 5-2 DSA in the chronic migraine patient population with a history of 1 or 2 prior preventive treatments (Propranolol comparison)

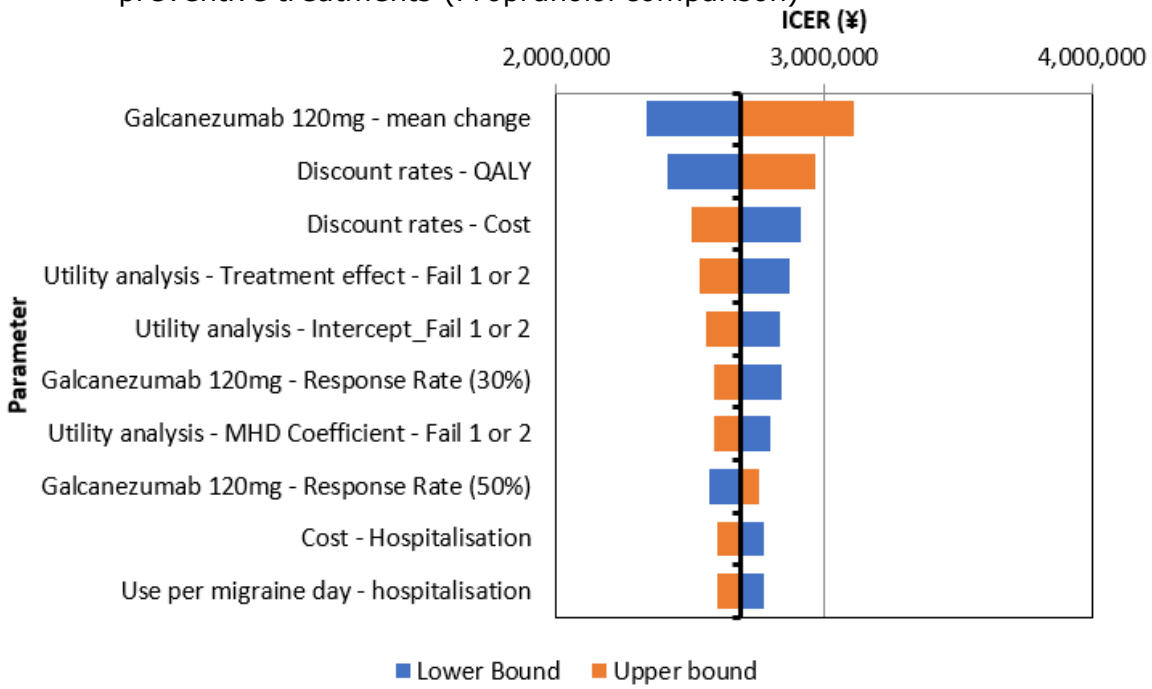


表 5-2 Detailed results of the DSA for the chronic migraine patient population with a history of 1 or 2 prior preventive treatments (Propranolol comparison)

Parameter	Range	Galcanezumab		Propranolol		Incremental		ICER	Δ ICER in %
		Cost	QALY	Cost	QALY	Cost	QALY		
Base case		**¥9,879,533**	**9.3985**	**¥8,508,388**	**8.8891**	**¥1,371,145**	**0.5094**	**¥2,691,706**	
Discount rate - QALY	LB (0.00%)	¥9,879,533	11.6685	¥8,508,388	11.1007	¥1,371,145	0.5678	¥2,415,000	-10.28%
	UB (4.00%)	¥9,879,533	7.7530	¥8,508,388	7.2912	¥1,371,145	0.4618	¥2,969,262	10.31%
Discount rate - Cost	LB (0.00%)	¥12,141,675	9.3985	¥10,656,304	8.8891	¥1,485,371	0.5094	¥2,915,943	8.33%
	UB (4.00%)	¥8,234,535	9.3985	¥6,956,740	8.8891	¥1,277,795	0.5094	¥2,508,449	-6.81%
Baseline - Age	LB (41.25)	¥9,895,123	9.4142	¥8,523,306	8.9044	¥1,371,817	0.5097	¥2,691,220	-0.02%
	UB (43.37)	¥9,862,446	9.3813	¥8,492,049	8.8722	¥1,370,397	0.5090	¥2,692,247	0.02%
Baseline - Gender	LB (84.74%)	¥9,874,559	9.3934	¥8,503,595	8.8841	¥1,370,964	0.5093	¥2,691,837	0.00%
	UB (90.84%)	¥9,884,072	9.4031	¥8,512,761	8.8936	¥1,371,311	0.5095	¥2,691,586	0.00%
Baseline - MHD	LB (19.01)	¥9,710,586	9.5258	¥8,339,877	9.0213	¥1,370,710	0.5045	¥2,716,793	0.93%
	UB (19.79)	¥10,048,305	9.2711	¥8,676,724	8.7568	¥1,371,582	0.5143	¥2,667,093	-0.91%
GMB response rate (30%)	LB (44.45%)	¥9,662,508	9.2948	¥8,508,388	8.8891	¥1,154,121	0.4058	¥2,844,301	5.67%
	UB (64.78%)	¥10,092,992	9.5004	¥8,508,388	8.8891	¥1,584,604	0.6113	¥2,592,085	-3.70%
Propranolol response rate (30%)	LB (56.55%)	¥9,879,533	9.3985	¥8,509,427	8.8853	¥1,370,106	0.5132	¥2,669,936	-0.81%
	UB (76.24%)	¥9,879,533	9.3985	¥8,507,412	8.8926	¥1,372,121	0.5059	¥2,712,423	0.77%
GMB - mean MHD change	LB (-7.56)	¥9,803,495	9.4428	¥8,508,388	8.8891	¥1,295,107	0.5537	¥2,338,857	-13.11%
	UB (-5.56)	¥9,955,401	9.3541	¥8,508,388	8.8891	¥1,447,013	0.4651	¥3,111,469	15.59%
Propranolol - mean MHD change	LB (-6.10)	¥9,879,533	9.3985	¥8,493,942	8.8967	¥1,385,591	0.5017	¥2,761,644	2.60%
	UB (-3.34)	¥9,879,533	9.3985	¥8,522,782	8.8814	¥1,356,751	0.5171	¥2,623,941	-2.52%
Propranolol costs	LB (¥10)	¥9,879,533	9.3985	¥8,507,310	8.8891	¥1,372,223	0.5094	¥2,693,822	0.08%
	UB (¥14)	¥9,879,533	9.3985	¥8,509,466	8.8891	¥1,370,068	0.5094	¥2,689,589	-0.08%
Costs for physician visits	LB (¥2,634)	¥9,725,842	9.3985	¥8,346,435	8.8891	¥1,379,407	0.5094	¥2,707,924	0.60%
	UB (¥3,662)	¥10,044,235	9.3985	¥8,681,944	8.8891	¥1,362,292	0.5094	¥2,674,325	-0.65%
Cost for hospitalisation	LB (¥143,724)	¥9,084,385	9.3985	¥7,670,497	8.8891	¥1,413,889	0.5094	¥2,775,615	3.12%
	UB (¥199,851)	¥10,731,653	9.3985	¥9,406,313	8.8891	¥1,325,340	0.5094	¥2,601,784	-3.34%
Cost for A&E visit	LB (¥28,746)	¥9,869,273	9.3985	¥8,497,576	8.8891	¥1,371,697	0.5094	¥2,692,788	0.04%
	UB (¥39,972)	¥9,890,529	9.3985	¥8,519,974	8.8891	¥1,370,554	0.5094	¥2,690,545	-0.04%
Use per migraine day - physician visits	LB (0.060)	¥9,725,842	9.3985	¥8,346,435	8.8891	¥1,379,407	0.5094	¥2,707,924	0.60%
	UB (0.083)	¥10,044,235	9.3985	¥8,681,944	8.8891	¥1,362,292	0.5094	¥2,674,325	-0.65%
Use per migraine	LB (0.006)	¥9,084,385	9.3985	¥7,670,497	8.8891	¥1,413,889	0.5094	¥2,775,615	3.12%

day - hospitalisation	UB (0.008)	¥10,731,653	9.3985	¥9,406,313	8.8891	¥1,325,340	0.5094	¥2,601,784	-3.34%
Use per migraine day - A&E visit	LB (0.000)	¥9,869,273	9.3985	¥8,497,576	8.8891	¥1,371,697	0.5094	¥2,692,788	0.04%
	UB (0.001)	¥9,890,529	9.3985	¥8,519,974	8.8891	¥1,370,554	0.5094	¥2,690,545	-0.04%
Cost of Triptans	LB (¥830)	¥9,557,873	9.3985	¥8,170,717	8.8891	¥1,387,156	0.5094	¥2,723,136	1.17%
	UB (¥1,156)	¥10,201,193	9.3985	¥8,846,058	8.8891	¥1,355,135	0.5094	¥2,660,275	-1.17%
Cost of paracetamol containing products	LB (¥19)	¥9,876,419	9.3985	¥8,505,104	8.8891	¥1,371,316	0.5094	¥2,692,040	0.01%
	UB (¥27)	¥9,882,647	9.3985	¥8,511,672	8.8891	¥1,370,975	0.5094	¥2,691,371	-0.01%
Cost of NSAID/Aspirin	LB (¥20)	¥9,873,342	9.3985	¥8,501,888	8.8891	¥1,371,454	0.5094	¥2,692,311	0.02%
	UB (¥27)	¥9,885,724	9.3985	¥8,514,887	8.8891	¥1,370,837	0.5094	¥2,691,100	-0.02%
Galcanezumab discontinuation	LB (3.81%)	¥9,901,819	9.4091	¥8,508,388	8.8891	¥1,393,431	0.5200	¥2,679,460	-0.45%
	UB (7.72%)	¥9,853,929	9.3862	¥8,508,388	8.8891	¥1,345,542	0.4972	¥2,706,418	0.55%
Utility analysis - MHD Coefficient – Fail 1 or 2	LB (-0.0125)	¥9,879,533	9.3716	¥8,508,388	8.8819	¥1,371,145	0.4897	¥2,799,714	4.01%
	UB (-0.0111)	¥9,879,533	9.4253	¥8,508,388	8.8963	¥1,371,145	0.5290	¥2,591,721	-3.71%
Utility analysis - Intercept – Fail 1 or 2	LB (0.7578)	¥9,879,533	9.3650	¥8,508,388	8.8816	¥1,371,145	0.4834	¥2,836,563	5.38%
	UB (0.7814)	¥9,879,533	9.4319	¥8,508,388	8.8965	¥1,371,145	0.5354	¥2,560,924	-4.86%
Utility analysis - Treatment effect – Fail 1 or 2	LB (0.0125)	¥9,879,533	9.3576	¥8,508,388	8.8800	¥1,371,145	0.4776	¥2,870,710	6.65%
	UB (0.0412)	¥9,879,533	9.4393	¥8,508,388	8.8982	¥1,371,145	0.5412	¥2,533,715	-5.87%

- **Episodic Migraine population with a history of treatment failure to at least 3 prior preventive migraine treatments (BSC comparison)**

The result of the DSA in the episodic migraine patient population with a history of 3 or more prior preventive treatments (ie. at least 4th line preventive treatment) comparing galcanezumab to BSC is presented in 図 5-3 and 表 5-3. The most impactful parameters are the utility treatment effect and utility intercept estimated based on the clinical trial program of galcanezumab for the patient population who had a treatment history of 3 or more prior preventive treatments followed by the mean change from baseline in monthly migraine headache days for galcanezumab patients who achieved at least a 50% response rate. All upper and lower bound ICERs remain well below the ¥5,000,000 willingness to pay threshold. 表 5-3 provides a comprehensive overview of the results of various variables tested in the deterministic sensitivity analysis in the episodic migraine patient population with a history of 3 or more prior preventive treatments comparing galcanezumab to BSC.

図 5-3 DSA in the episodic migraine patient population with a history of 3 or more prior preventive treatments (BSC comparison)

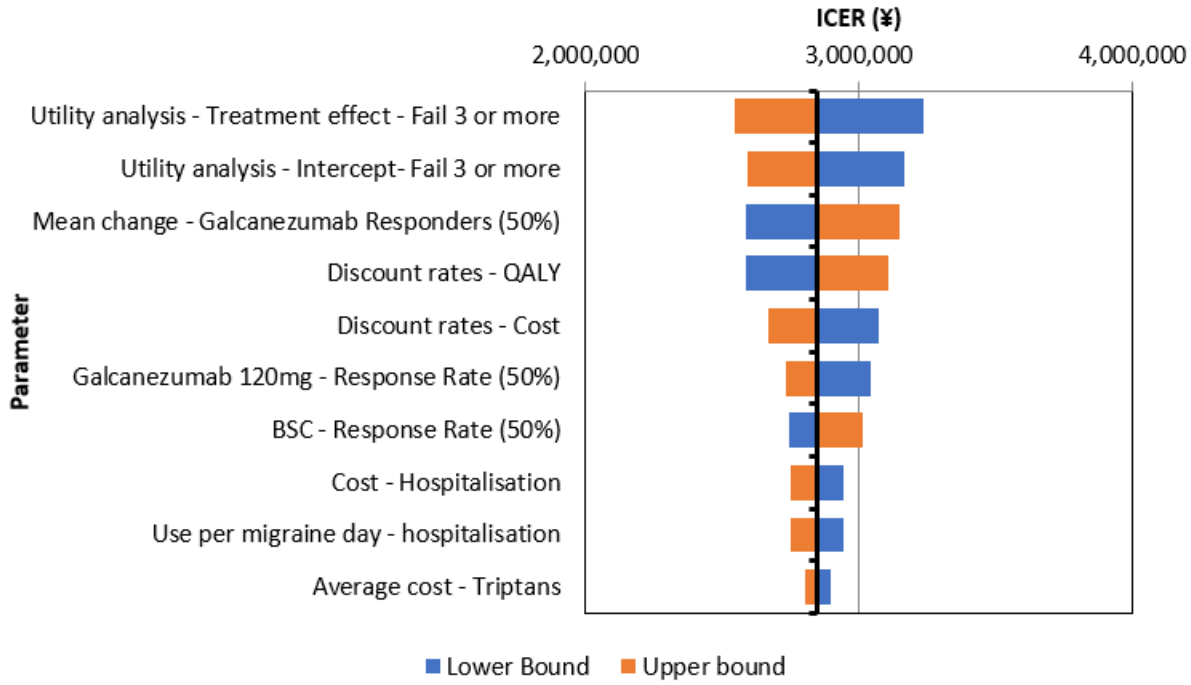


表 5-3 Detailed results of the DSA for the episodic migraine patient population with a history of 3 or more prior preventive treatments (BSC comparison)

Parameter	Range	Galcanezumab		BSC		Incremental		ICER	Δ ICR in %
		Cost	QALY	Cost	QALY	Cost	QALY		
Base case		**¥5,539,801**	**12.1581**	**¥4,452,735**	**11.7767**	**¥1,087,066**	**0.3814**	**¥2,850,240**	
Discount rate - QALY	LB (0.00%)	¥5,539,801	15.1408	¥4,452,735	14.7210	¥1,087,066	0.4198	¥2,589,673	-9.14%
	UB (4.00%)	¥5,539,801	9.9978	¥4,452,735	9.6478	¥1,087,066	0.3500	¥3,105,702	8.96%
Discount rate - Cost	LB (0.00%)	¥6,743,737	12.1581	¥5,571,914	11.7767	¥1,171,824	0.3814	¥3,072,472	7.80%
	UB (4.00%)	¥4,661,289	12.1581	¥3,643,512	11.7767	¥1,017,777	0.3814	¥2,668,569	-6.37%
Baseline - Age	LB (45.09)	¥5,552,711	12.1904	¥4,464,858	11.8086	¥1,087,853	0.3817	¥2,849,672	-0.02%
	UB (47.43)	¥5,525,718	12.1229	¥4,439,496	11.7419	¥1,086,223	0.3810	¥2,850,848	0.02%
Baseline - Gender	LB (82.01%)	¥5,534,431	12.1446	¥4,447,641	11.7633	¥1,086,789	0.3813	¥2,850,440	0.01%
	UB (90.00%)	¥5,544,653	12.1703	¥4,457,338	11.7888	¥1,087,315	0.3815	¥2,850,059	-0.01%
Baseline - MHD	LB (9.37)	¥5,402,710	12.2517	¥4,315,802	11.8728	¥1,086,907	0.3789	¥2,868,780	0.65%
	UB (9.97)	¥5,676,784	12.0646	¥4,589,574	11.6806	¥1,087,211	0.3839	¥2,831,910	-0.64%
GMB response rate (50%)	LB (31.50%)	¥5,316,325	12.0603	¥4,452,735	11.7767	¥863,590	0.2836	¥3,045,334	6.84%
	UB (54.31%)	¥5,769,916	12.2588	¥4,452,735	11.7767	¥1,317,180	0.4821	¥2,732,078	-4.15%
BSC response rate (50%)	LB (3.60%)	¥5,539,801	12.1581	¥4,467,258	11.7673	¥1,072,543	0.3908	¥2,744,521	-3.71%
	UB (31.36%)	¥5,539,801	12.1581	¥4,431,760	11.7903	¥1,108,041	0.3678	¥3,012,471	5.69%
GMB responders - mean MHD change	LB (-7.98)	¥5,497,480	12.1807	¥4,452,735	11.7767	¥1,044,745	0.4040	¥2,585,922	-9.27%
	UB (-6.44)	¥5,581,965	12.1355	¥4,452,735	11.7767	¥1,129,230	0.3588	¥3,147,414	10.43%
GMB non-responders - mean MHD change	LB (-1.90)	¥5,534,185	12.1621	¥4,452,735	11.7767	¥1,081,450	0.3853	¥2,806,484	-1.54%
	UB (-0.52)	¥5,545,409	12.1542	¥4,452,735	11.7767	¥1,092,674	0.3774	¥2,894,890	1.57%
BSC responders - mean MHD change	LB (-8.51)	¥5,539,801	12.1581	¥4,449,296	11.7785	¥1,090,505	0.3796	¥2,872,685	0.79%
	UB (-5.91)	¥5,539,801	12.1581	¥4,456,151	11.7749	¥1,083,650	0.3832	¥2,828,076	-0.78%
BSC non-responders - mean MHD change	LB (-0.02)	¥5,539,801	12.1581	¥4,451,756	11.7774	¥1,088,045	0.3807	¥2,857,978	0.27%
	UB (1.16)	¥5,539,801	12.1581	¥4,453,713	11.7760	¥1,086,088	0.3821	¥2,842,534	-0.27%
Costs for physician visits	LB (¥2,634)	¥5,466,535	12.1581	¥4,372,528	11.7767	¥1,094,007	0.3814	¥2,868,440	0.64%
	UB (¥3,662)	¥5,618,316	12.1581	¥4,538,689	11.7767	¥1,079,627	0.3814	¥2,830,736	-0.68%
Cost for hospitalisation	LB (¥143,724)	¥5,160,746	12.1581	¥4,037,769	11.7767	¥1,122,977	0.3814	¥2,944,399	3.30%
	UB (¥199,851)	¥5,946,014	12.1581	¥4,897,434	11.7767	¥1,048,581	0.3814	¥2,749,334	-3.54%
Cost for A&E visit	LB (¥28,746)	¥5,534,910	12.1581	¥4,447,381	11.7767	¥1,087,529	0.3814	¥2,851,455	0.04%
	UB (¥39,972)	¥5,545,042	12.1581	¥4,458,474	11.7767	¥1,086,569	0.3814	¥2,848,938	-0.05%
Use per migraine	LB (0.060)	¥5,466,535	12.1581	¥4,372,528	11.7767	¥1,094,007	0.3814	¥2,868,440	0.64%

day - physician visits	UB (0.083)	¥5,618,316	12.1581	¥4,538,689	11.7767	¥1,079,627	0.3814	¥2,830,736	-0.68%
Use per migraine day - hospitalisation	LB (0.006)	¥5,160,746	12.1581	¥4,037,769	11.7767	¥1,122,977	0.3814	¥2,944,399	3.30%
	UB (0.008)	¥5,946,014	12.1581	¥4,897,434	11.7767	¥1,048,581	0.3814	¥2,749,334	-3.54%
Use per migraine day - A&E visit	LB (0.000)	¥5,534,910	12.1581	¥4,447,381	11.7767	¥1,087,529	0.3814	¥2,851,455	0.04%
	UB (0.001)	¥5,545,042	12.1581	¥4,458,474	11.7767	¥1,086,569	0.3814	¥2,848,938	-0.05%
Average cost of Triptans	LB (¥830)	¥5,348,610	12.1581	¥4,243,618	11.7767	¥1,104,992	0.3814	¥2,897,244	1.65%
	UB (¥1,156)	¥5,730,991	12.1581	¥4,661,853	11.7767	¥1,069,139	0.3814	¥2,803,236	-1.65%
Average cost of paracetamol containing products	LB (¥19)	¥5,538,992	12.1581	¥4,451,842	11.7767	¥1,087,150	0.3814	¥2,850,461	0.01%
	UB (¥27)	¥5,540,610	12.1581	¥4,453,629	11.7767	¥1,086,981	0.3814	¥2,850,019	-0.01%
Average cost of NSAID/Aspirin	LB (¥20)	¥5,536,777	12.1581	¥4,449,414	11.7767	¥1,087,362	0.3814	¥2,851,018	0.03%
	UB (¥27)	¥5,542,825	12.1581	¥4,456,056	11.7767	¥1,086,769	0.3814	¥2,849,462	-0.03%
Galcanezumab discontinuation	LB (4.18%)	¥5,551,924	12.1634	¥4,452,735	11.7767	¥1,099,189	0.3867	¥2,842,470	-0.27%
	UB (7.02%)	¥5,526,371	12.1522	¥4,452,735	11.7767	¥1,073,636	0.3755	¥2,859,102	0.31%
Utility analysis - MHD Coefficient – Fail 3 or more	LB (-0.0134)	¥5,539,801	12.1515	¥4,452,735	11.7749	¥1,087,066	0.3766	¥2,886,526	1.27%
	UB (-0.0114)	¥5,539,801	12.1647	¥4,452,735	11.7785	¥1,087,066	0.3862	¥2,814,855	-1.24%
Utility analysis - Intercept – Fail 3 or more	LB (0.7292)	¥5,539,801	12.1150	¥4,452,735	11.7715	¥1,087,066	0.3435	¥3,164,331	11.02%
	UB (0.7674)	¥5,539,801	12.2012	¥4,452,735	11.7820	¥1,087,066	0.4193	¥2,592,872	-9.03%
Utility analysis - Treatment effect – Fail 3 or more	LB (0.0376)	¥5,539,801	12.1126	¥4,452,735	11.7767	¥1,087,066	0.3359	¥3,236,131	13.54%
	UB (0.0779)	¥5,539,801	12.2036	¥4,452,735	11.7767	¥1,087,066	0.4269	¥2,546,575	-10.65%

- **Chronic Migraine population with a history of treatment failure to at least 3 prior preventive migraine treatments (BSC comparison)**

The result of the DSA in the chronic migraine patient population with a history of 3 or more prior preventive treatments (ie. at least 4th line preventive treatment) comparing galcanezumab to BSC is presented in 図 5-4 and 表 5-4. The most impactful parameters are the mean change from baseline in monthly migraine headache days in patients treated with galcanezumab who achieved a 30% response rate, followed by discount rate for QALYs and the utility treatment effect of galcanezumab over BSC. All upper and lower bound ICERs remain well below the ¥5,000,000 willingness to pay threshold. 表 5-4 provides a comprehensive overview of the results of various variables tested in the deterministic sensitivity analysis in the hronic migraine patient population with a history of 3 or more prior preventive treatments comparing galcanezumab to BSC.

図 5-4 DSA results for the chronic migraine patient population with a history of 3 or more prior preventive treatments (BSC comparison)

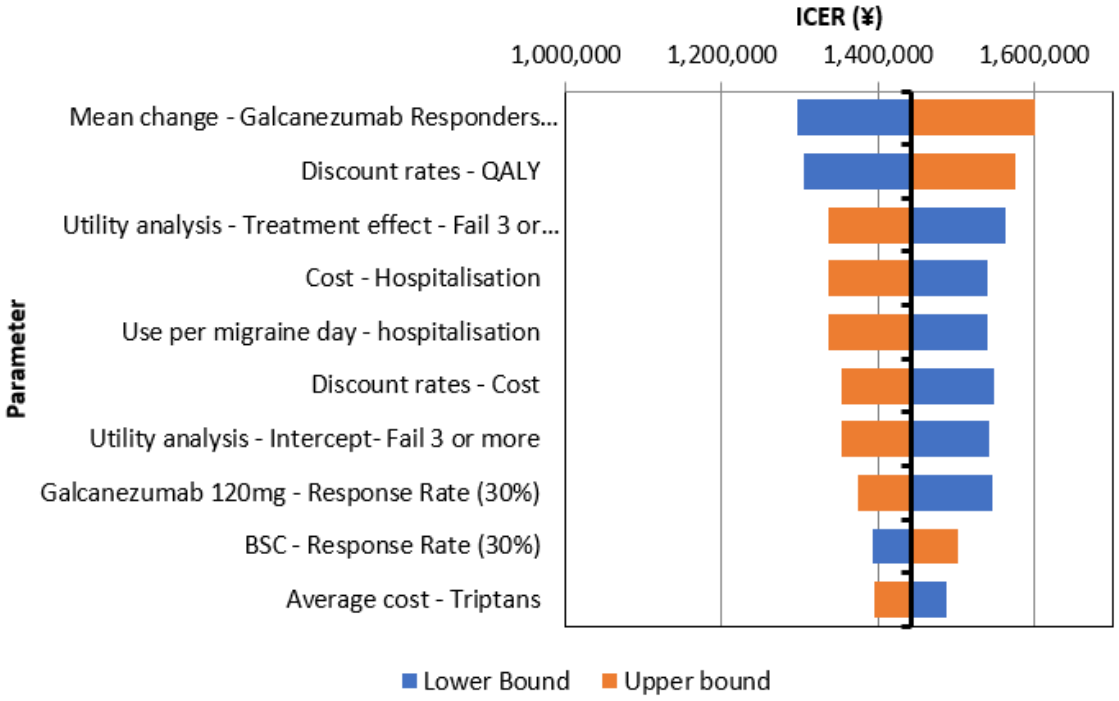


表 5-4 Detailed results of the DSA for the chronic migraine patient population with a history of 3 or more prior preventive treatments (BSC comparison)

Parameter	Range	Galcanezumab		BSC		Incremental		ICER	Δ ICER in %
		Cost	QALY	Cost	QALY	Cost	QALY		
Base case		**¥9,853,551**	**9.4390**	**¥8,793,870**	**8.7040**	**¥1,059,682**	**0.7350**	**¥1,441,739**	
Discount rate - QALY	LB (0.00%)	¥9,853,551	11.6873	¥8,793,870	10.8756	¥1,059,682	0.8117	¥1,305,479	-9.45%
	UB (4.00%)	¥9,853,551	7.8063	¥8,793,870	7.1340	¥1,059,682	0.6723	¥1,576,214	9.33%
Discount rate - Cost	LB (0.00%)	¥12,144,665	9.4390	¥11,005,834	8.7040	¥1,138,830	0.7350	¥1,549,423	7.47%
	UB (4.00%)	¥8,189,754	9.4390	¥7,194,770	8.7040	¥994,984	0.7350	¥1,353,714	-6.11%
Baseline - Age	LB (44.31)	¥9,877,182	9.4622	¥8,816,789	8.7265	¥1,060,393	0.7357	¥1,441,382	-0.02%
	UB (46.67)	¥9,827,887	9.4138	¥8,768,963	8.6795	¥1,058,923	0.7343	¥1,442,120	0.03%
Baseline - Gender	LB (81.46%)	¥9,844,517	9.4301	¥8,785,061	8.6953	¥1,059,455	0.7348	¥1,441,854	0.01%
	UB (89.09%)	¥9,861,803	9.4471	¥8,801,915	8.7119	¥1,059,889	0.7352	¥1,441,634	-0.01%
Baseline - MHD	LB (18.80)	¥9,636,568	9.5878	¥8,577,220	8.8579	¥1,059,349	0.7299	¥1,451,419	0.67%
	UB (19.76)	¥10,070,437	9.2901	¥9,010,422	8.5500	¥1,060,016	0.7401	¥1,432,194	-0.66%
GMB response rate (30%)	LB (43.37%)	¥9,689,114	9.2829	¥8,793,870	8.7040	¥895,244	0.5789	¥1,546,385	7.26%
	UB (65.89%)	¥10,014,961	9.5922	¥8,793,870	8.7040	¥1,221,091	0.8882	¥1,374,787	-4.64%
BSC response rate (30%)	LB (11.31%)	¥9,853,551	9.4390	¥8,810,593	8.6903	¥1,042,958	0.7486	¥1,393,146	-3.37%
	UB (33.77%)	¥9,853,551	9.4390	¥8,774,114	8.7201	¥1,079,437	0.7189	¥1,501,514	4.15%
GMB responders - mean MHD change	LB (-12.40)	¥9,790,969	9.4729	¥8,793,870	8.7040	¥997,100	0.7689	¥1,296,810	-10.05%
	UB (-10.59)	¥9,916,086	9.4051	¥8,793,870	8.7040	¥1,122,217	0.7011	¥1,600,609	11.02%
GMB non-responders - mean MHD change	LB (-1.12)	¥9,847,042	9.4436	¥8,793,870	8.7040	¥1,053,172	0.7396	¥1,423,884	-1.24%
	UB (0.88)	¥9,860,057	9.4343	¥8,793,870	8.7040	¥1,066,187	0.7304	¥1,459,815	1.25%
BSC responders - mean MHD change	LB (-10.31)	¥9,853,551	9.4390	¥8,789,969	8.7060	¥1,063,583	0.7329	¥1,451,102	0.65%
	UB (-8.23)	¥9,853,551	9.4390	¥8,797,767	8.7019	¥1,055,785	0.7371	¥1,432,433	-0.65%
BSC non-responders - mean MHD change	LB (0.33)	¥9,853,551	9.4390	¥8,793,053	8.7046	¥1,060,498	0.7344	¥1,443,995	0.16%
	UB (1.41)	¥9,853,551	9.4390	¥8,794,685	8.7034	¥1,058,866	0.7356	¥1,439,487	-0.16%
Costs for physician visits	LB (¥2,634)	¥9,707,193	9.4390	¥8,633,646	8.7040	¥1,073,548	0.7350	¥1,460,604	1.31%
	UB (¥3,662)	¥10,010,396	9.4390	¥8,965,573	8.7040	¥1,044,823	0.7350	¥1,421,522	-1.40%
Cost for hospitalisation	LB (¥143,724)	¥9,096,340	9.4390	¥7,964,921	8.7040	¥1,131,419	0.7350	¥1,539,340	6.77%
	UB (¥199,851)	¥10,665,016	9.4390	¥9,682,211	8.7040	¥982,805	0.7350	¥1,337,145	-7.25%
Cost for A&E visit	LB (¥28,746)	¥9,843,780	9.4390	¥8,783,173	8.7040	¥1,060,607	0.7350	¥1,442,998	0.09%
	UB (¥39,972)	¥9,864,022	9.4390	¥8,805,333	8.7040	¥1,058,690	0.7350	¥1,440,389	-0.09%
Use per migraine	LB (0.060)	¥9,707,193	9.4390	¥8,633,646	8.7040	¥1,073,548	0.7350	¥1,460,604	1.31%

day - physician visits	UB (0.083)	¥10,010,396	9.4390	¥8,965,573	8.7040	¥1,044,823	0.7350	¥1,421,522	-1.40%
Use per migraine day - hospitalisation	LB (0.006)	¥9,096,340	9.4390	¥7,964,921	8.7040	¥1,131,419	0.7350	¥1,539,340	6.77%
	UB (0.008)	¥10,665,016	9.4390	¥9,682,211	8.7040	¥982,805	0.7350	¥1,337,145	-7.25%
Use per migraine day - A&E visit	LB (0.000)	¥9,843,780	9.4390	¥8,783,173	8.7040	¥1,060,607	0.7350	¥1,442,998	0.09%
	UB (0.001)	¥9,864,022	9.4390	¥8,805,333	8.7040	¥1,058,690	0.7350	¥1,440,389	-0.09%
Average cost of Triptans	LB (¥830)	¥9,488,370	9.4390	¥8,394,690	8.7040	¥1,093,680	0.7350	¥1,487,995	3.21%
	UB (¥1,156)	¥10,218,732	9.4390	¥9,193,049	8.7040	¥1,025,684	0.7350	¥1,395,483	-3.21%
Average cost of paracetamol containing products	LB (¥19)	¥9,851,083	9.4390	¥8,791,136	8.7040	¥1,059,947	0.7350	¥1,442,100	0.03%
	UB (¥27)	¥9,856,020	9.4390	¥8,796,603	8.7040	¥1,059,416	0.7350	¥1,441,378	-0.03%
Average cost of NSAID/Aspirin	LB (¥20)	¥9,846,615	9.4390	¥8,786,244	8.7040	¥1,060,371	0.7350	¥1,442,677	0.07%
	UB (¥27)	¥9,860,487	9.4390	¥8,801,495	8.7040	¥1,058,992	0.7350	¥1,440,801	-0.07%
Galcanezumab discontinuation	LB (3.81%)	¥9,868,794	9.4534	¥8,793,870	8.7040	¥1,074,924	0.7495	¥1,434,240	-0.52%
	UB (7.72%)	¥9,836,040	9.4224	¥8,793,870	8.7040	¥1,042,171	0.7184	¥1,450,726	0.62%
Utility analysis - MHD Coefficient - Fail 3 or more	LB (-0.0134)	¥9,853,551	9.4153	¥8,793,870	8.6993	¥1,059,682	0.7161	¥1,479,892	2.65%
	UB (-0.0114)	¥9,853,551	9.4626	¥8,793,870	8.7087	¥1,059,682	0.7540	¥1,405,504	-2.51%
Utility analysis – Intercept - Fail 3 or more	LB (0.7292)	¥9,853,551	9.3847	¥8,793,870	8.6978	¥1,059,682	0.6869	¥1,542,736	7.01%
	UB (0.7674)	¥9,853,551	9.4933	¥8,793,870	8.7102	¥1,059,682	0.7831	¥1,353,153	-6.14%
Utility analysis - Treatment effect - Fail 3 or more	LB (0.0376)	¥9,853,551	9.3817	¥8,793,870	8.7040	¥1,059,682	0.6777	¥1,563,629	8.45%
	UB (0.0779)	¥9,853,551	9.4963	¥8,793,870	8.7040	¥1,059,682	0.7923	¥1,337,478	-7.23%

5.1.2.3 Probabilistic sensitivity analyses

基本分析に関する確率的感度分析の概要と結果を以下に述べる。

A probabilistic sensitivity analysis (PSA) was conducted by assigning distributions to all input parameters and randomly sampling from these distributions over 1,000 Monte Carlo simulations to calculate the uncertainty in costs and outcomes. A summary of the distributions chosen for the probabilistic parameters in the model is provided in 表 5-5.

表 5-5 Model parameter summary

Parameter	Distribution	Justification	Description
Age	Normal distribution	Based on the information available from the trial data	Section 4.2.1
Gender	Beta distribution	Based on natural limit between 0 and 100%.	Section 4.2.1
Baseline Migraine Headache Days	Normal distribution	Based on the information available from the trial data	Section 4.2.1
Distribution parameters	Variance covariance matrix	Used to account for uncertainty in regression parameters	Section 4.2.1
Mean change in Migraine Headache Days	Normal distribution	Aligned with galcanezumab trial program	Section 4.2.1
Response rate	Beta distribution	Based on natural limit between 0 and 100%.	Section 4.2.1
Drug costs	Normal distribution	Assumption of uncertainty around the mean	Section 4.2.3
Resource costs	Gamma distribution	Based on an anticipated skewed distribution	Section 4.2.3
Resource use	Gamma distribution	Based on the information available from the trial data	Section 4.2.3
Discontinuation	Beta distribution	Based on natural limit between 0 and 100%.	Section 4.2.1
Utility values	Normal distribution	Variance taken from trial analysis	Section 4.2.2

- **Episodic Migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (Propranolol comparison)**

表 5-6, 図 5-5 and 図 5-6 show the findings from the PSA for the episodic migraine patient population with a history of 1 or 2 prior preventive treatments (ie. 2nd or 3rd line preventive treatments) comparing to propranolol. The mean ICER derived from the PSA run with 1,000 iterations (表 5-6) is marginally lower

compared to the deterministic base case analysis (¥5,839,366 compared to ¥6,077,875).

表 5-6 Probabilistic results for the episodic migraine patient population failed 1 or 2 prior preventive migraine treatments (Propranolol comparison)

Treatment	QALY	Δ QALY	Cost (yen)	Δ Cost (yen)	ICER (yen/QALY)
Galcanezumab 120mg	15.687	0.258	¥6,641,876	¥1,506,531	¥5,839,366
Propranolol	15.429	/	¥5,135,345	/	/

図 5-5 shows the cost-effectives plane from the PSA, and therefore the level of uncertainty surrounding model parameters. The findings for the episodic migraine patient population with a history of 1 or 2 prior preventive treatments (ie. 2nd or 3rd line preventive treatments) comparing to propranolol show that all iterations fall within the north-east quadrant for the cost-effectives plane. This finding suggests that galcanezumab will result in both incremental costs and QALY gains compared to propranolol. The three lines of treatment reflect the willingness to pay thresholds of ¥5,000,000 (grey line), ¥7,500,000 (blue line) and ¥10,000,000 (red line) and the blue dots reflect each individual draw. The red dot represents the average ICER across the 1,000 iterations. All iterations are below the WTP threshold of ¥7,500,000 (blue line).

図 5-5 Scatterplot for the episodic migraine patient population failed 1 or 2 prior preventive migraine treatments (Propranolol comparison)

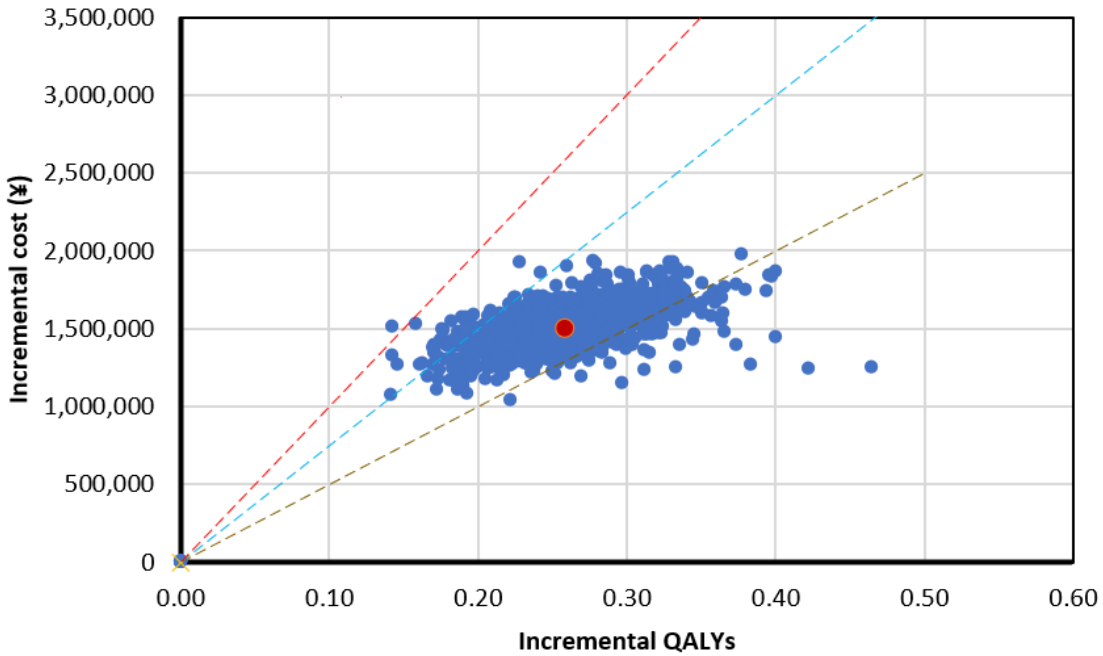
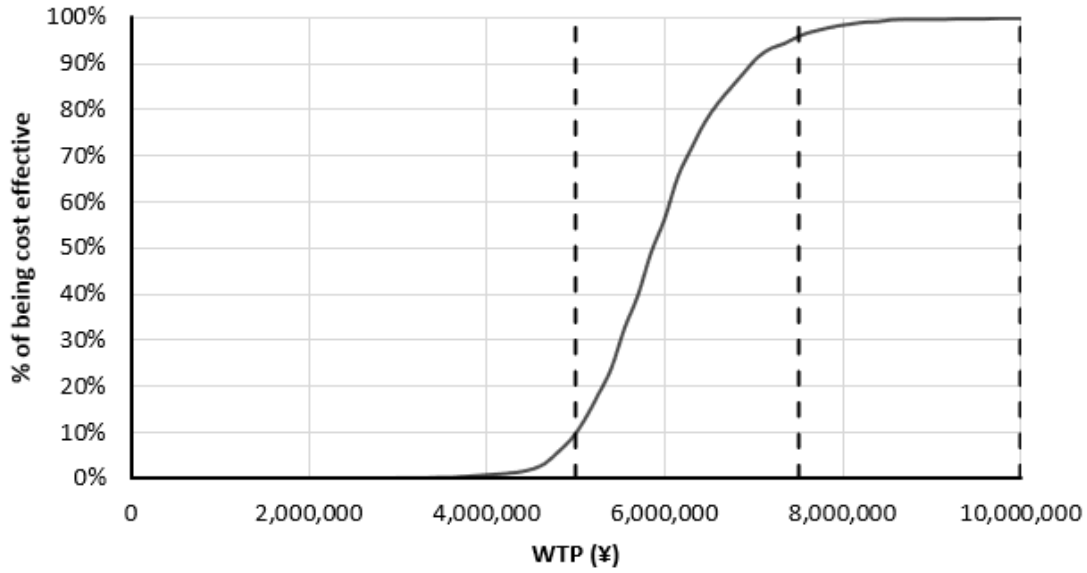


図 5-6 shows the probability of galcanezumab being cost-effectiveness at various WTP thresholds. In general, when the willingness to pay (WTP) threshold increases, so does the probability of cost-effectiveness for galcanezumab. The dotted lines represent the willingness to pay thresholds of ¥5,000,000;

¥7,500,000 and ¥10,000,000. Galcanezumab has a probability of being cost-effective compared to propranolol in the episodic migraine patient population with a history of 1 or 2 prior migraine treatments of 9.5% at a WTP threshold of ¥5,000,000; 96.0% at ¥7,500,000 and 99.9% at ¥10,000,000.

図 5-6 Cost effectiveness acceptability curve (CEAC) for the episodic migraine patient population failed 1 or 2 prior preventive migraine treatments (Propranolol comparison)



- **Chronic Migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (Propranolol comparison)**

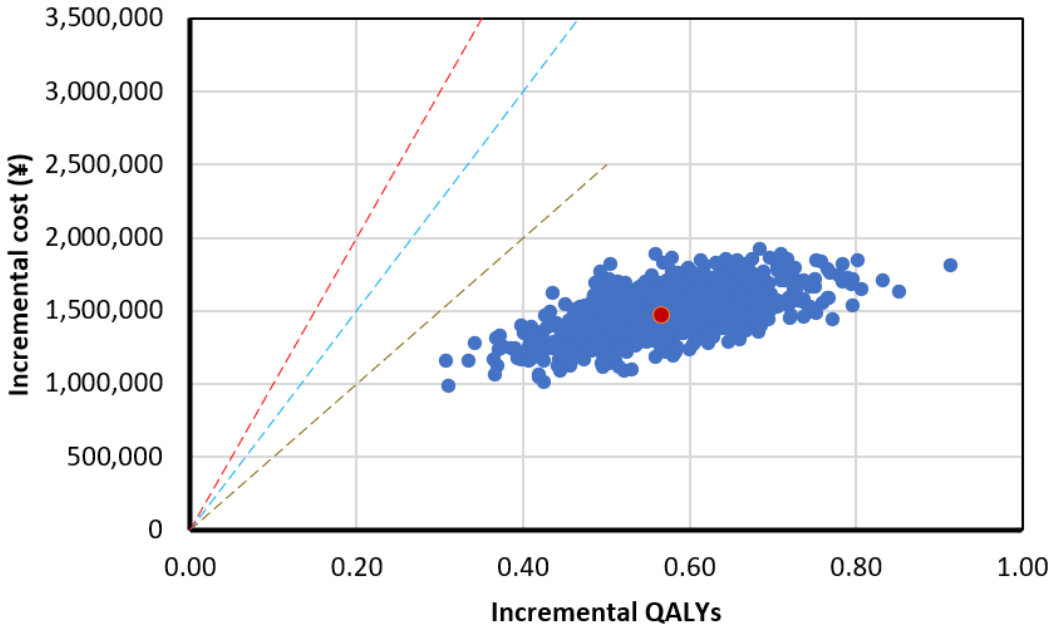
表 5-7, 図 5-7 and 図 5-8 show the findings from the PSA for the chronic migraine patient population with a history of 1 or 2 prior preventive treatments (ie. 2nd or 3rd line preventive treatments) comparing to propranolol. The mean ICER derived from the PSA run with 1,000 iterations (表 5-7) is comparable to the deterministic base case analysis (¥2,601,300 compared to ¥2,691,706).

表 5-7 Probabilistic results for the chronic migraine patient population failed 1 or 2 prior preventive migraine treatments (Propranolol comparison)

Treatment	QALY	Δ QALY	Cost (yen)	Δ Cost (yen)	ICER (yen/QALY)
Galcanezumab 120mg	11.665	0.566	¥12,167,640	¥1,472,982	¥2,601,300
Propranolol	11.099	/	¥10,694,658	/	/

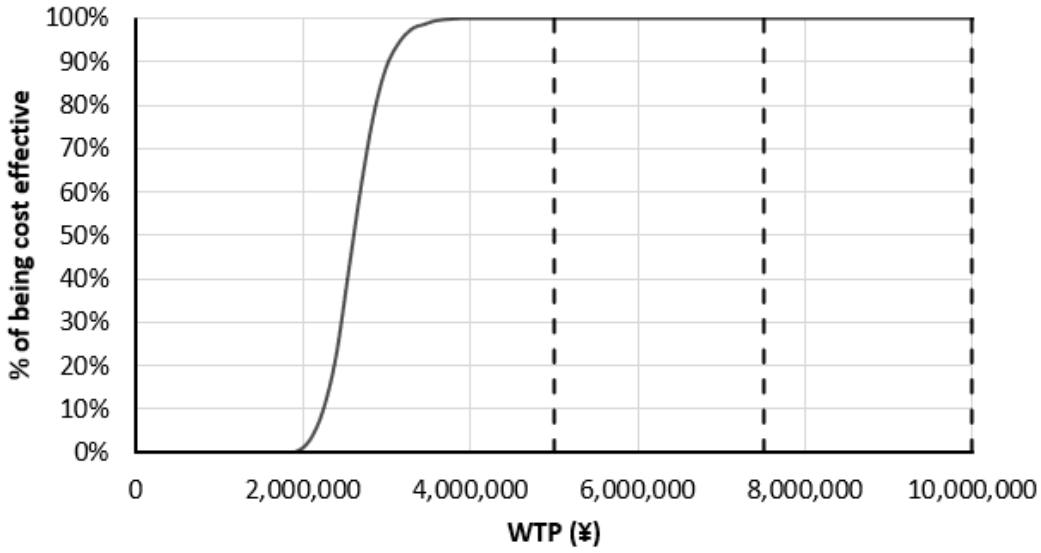
The findings of the cost-effectiveness plane for the episodic migraine patient population with a history of 1 or 2 prior preventive treatments (ie. 2nd or 3rd line preventive treatments) comparing to propranolol show that all iterations fall within the north-east quadrant. This suggests that galcanezumab will result in both incremental costs and QALY gains compared to propranolol (図 5-7). All 1,000 iterations are below the ¥5,000,000 WTP threshold.

図 5-7 PSA scatterplot for the chronic migraine patient population failed 1 or 2 prior preventive migraine treatments (Propranolol comparison)



Galcanezumab has a 100% probability of being cost-effective compared to propranolol in the chronic migraine patient population with a history of 1 prior migraine treatment at all three WTP thresholds (図 5-8).

図 5-8 CEAC for the chronic migraine patient population failed 1 or 2 prior preventive migraine treatments (Propranolol comparison)



- **Episodic Migraine population with a history of treatment failure to at least 3 prior preventive migraine treatments (BSC comparison)**

表 5-8, 図 5-9 and 図 5-10 show the findings from the PSA for the episodic migraine population with a history of 3 or more prior preventive treatments (ie.

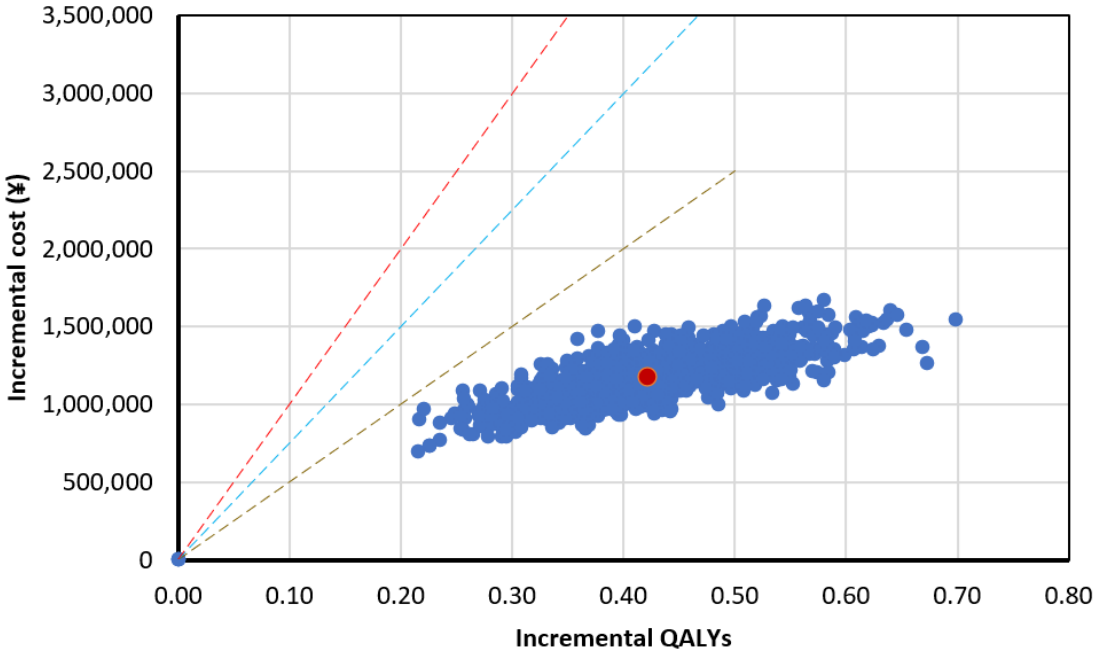
at least 4th line preventive migraine treatment) comparing to BSC. The mean ICER derived from the PSA run with 1,000 iterations (表 5-8) is marginally lower compared to the deterministic base case analysis (¥2,786,587 compared to ¥2,850,240).

表 5-8 Probabilistic results for the episodic migraine patient population failed 3 or more prior preventive migraine treatments (BSC comparison)

Treatment	QALY	Δ QALY	Cost (yen)	Δ Cost (yen)	ICER (yen/QALY)
Galcanezumab 120mg	15.142	0.422	¥6,735,933	¥1,175,460	¥2,786,587
BSC	14.720	/	¥5,560,473	/	/

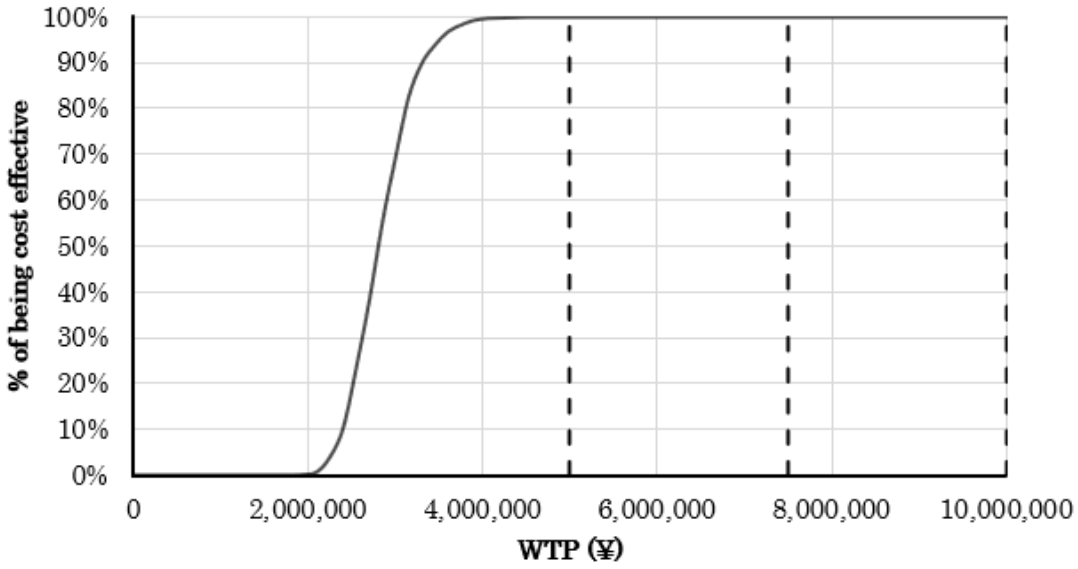
The findings from the PSA scatterplot for the episodic migraine patient population with a history of 3 or more prior preventive treatments (ie. at least 4th line preventive treatment) comparing to BSC show that all iterations fall within the north-east quadrant for the cost-effectives plane. This suggests that galcanezumab will result in both incremental costs and QALY gains compared to BSC (図 5-9).

図 5-9 PSA scatterplot for the episodic migraine patient population failed 3 or more prior preventive migraine treatments (BSC comparison)



Galcanezumab has a 100.0% probability of being cost-effective compared to BSC in the episodic migraine patient population with a history of 3 or more prior migraine treatments at all WTP thresholds (図 5-10).

図 5-10 CEAC for the episodic migraine patient population failed 3 or more prior preventive migraine treatments (BSC comparison)



- **Chronic Migraine population with a history of treatment failure to at least 3 prior preventive migraine treatments (BSC comparison)**

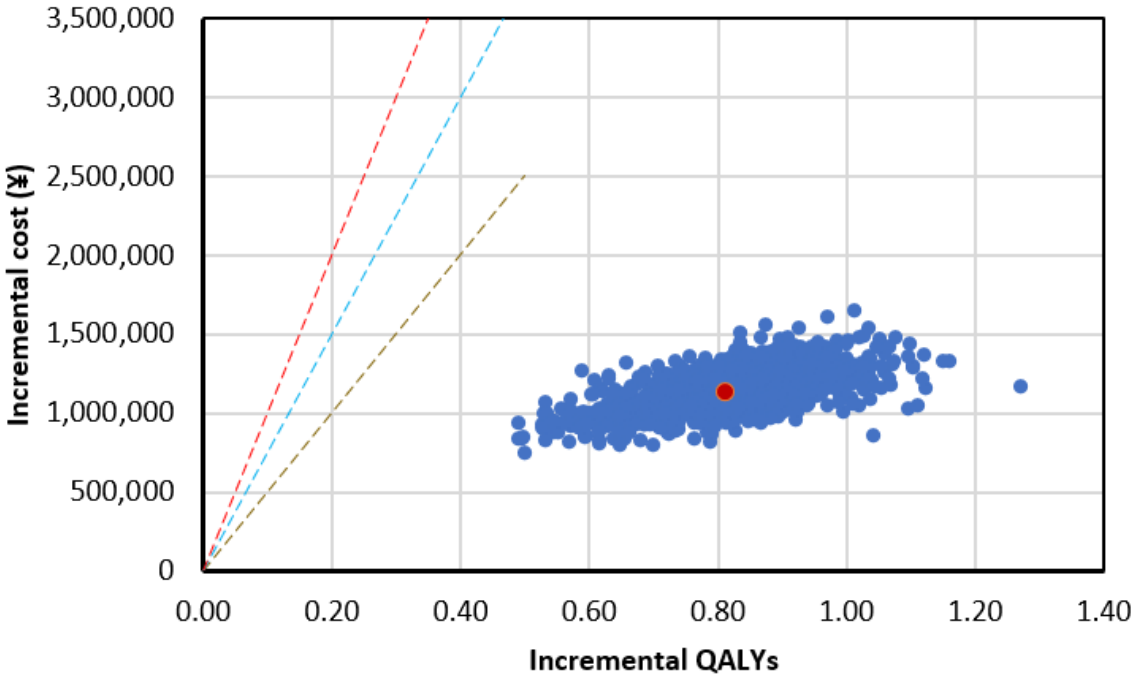
表 5-9, 図 5-11 and 図 5-12 show the findings from the PSA for the chronic migraine population with a history of 3 or more prior preventive treatments (ie. at least 4th line preventive migraine treatment) comparing to BSC. The mean ICER derived from the PSA run with 1,000 iterations (表 5-9) is comparable to the deterministic base case analysis (¥1,400,388 compared to ¥1,441,739).

表 5-9 Probabilistic results for the chronic migraine patient population failed 3 or more prior preventive migraine treatments (BSC comparison)

Treatment	QALY	Δ QALY	Cost (yen)	Δ Cost (yen)	ICER (yen/QALY)
Galcanezumab 120mg	11.689	0.811	¥12,118,743	¥1,136,299	¥1,400,388
BSC	10.878	/	¥10,982,443	/	/

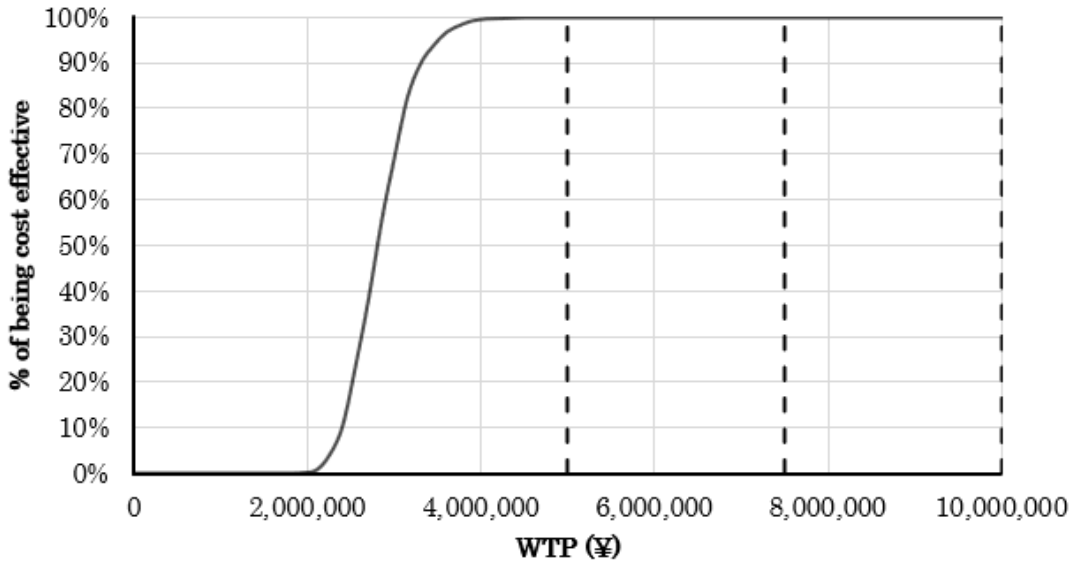
The findings from the PSA scatterplot for the chronic migraine patient population with a history of 3 or more prior preventive treatments (ie. line preventive treatment) comparing to BSC show that all iterations fall within the north-east quadrant for the cost-effectives plane. This suggests that galcanezumab will result in both incremental costs and QALY gains compared to BSC (図 5-11).

図 5-11 PSA scatterplot for the chronic migraine patient population failed 3 or more prior preventive migraine treatment (BSC comparison)



Galcanezumab has a 100% probability of being cost-effective compared to BSC in the chronic migraine patient population with a history of 3 or more prior migraine treatments at all WTP thresholds (図 5-12).

図 5-12 CEAC for the chronic migraine patient population failed 3 or more prior preventive migraine treatment (BSC comparison)



5.1.2.4 Scenario analysis

1.Episodic Migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (Propranolol comparison)

表 5-10 shows the ICERs derived from the scenario analyses for the episodic migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (ie. 2nd or 3rd line preventive treatment) comparing galcanezumab to Propranolol. A shorter time horizon and assuming that patients on galcanezumab loose return to baseline already 5 months after stopping treatment appeared to have the most significant impact on the ICER. Apart from these analyses, all others were in the range of the base case or even below the base case results. All ICERs remained below the WTP threshold of ¥7,500,000.

表 5-10 Scenario analyses in the episodic migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (Propranolol comparison)

Scenario	Scenario Details	ICER	Δ (¥)
Base Case		**¥6,077,875**	
Discount rates (costs, benefits)	0%	¥5,907,622	-2.80%
	4%	¥6,248,243	2.80%
Time horizon	5 years	¥7,469,101	22.89 %
	10 Years	¥6,410,513	5.47%
	45 Years	¥6,063,498	-0.24%
Distribution around Migraine Headache Days, EM	Beta-Binomial	¥6,079,175	0.02%
Persistency rate	Upper level: 1.25	¥6,269,869	3.16%
	Lower level: 0.75	¥5,896,856	-2.98%
Treatment waning, galcanezumab	5 cycles for both responders and non-responders	¥6,679,060	9.89%
	13 cycles for responders and 1 cycle for non-responders	¥6,318,895	3.97%

2.Chronic Migraine population with a history of treatment failure to 1 or

2 prior preventive migraine treatments (Propranolol comparison)

表 5-11 shows the ICERs derived from the scenario analyses for the chronic migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (ie. 2nd or 3rd line preventive treatment) comparing galcanezumab to Propranolol. A shorter time horizon and considering a 50% or greater reduction in migraine headache days appeared to have the most significant negative impact on the ICER, while the treatment waning period informed by REGAIN had the most significant positive impact on the ICER in favour of galcanezumab. Apart from these analyses, all others were in the range of the base case or even below the base case results. All ICERs remained well below the WTP threshold of ¥5,000,000.

表 5-11 Scenario analyses in the chronic migraine population with a history of treatment failure to 1 or 2 prior preventive migraine treatments (Propranolol comparison)

Scenario	**Scenario Details**	**ICER**	**Δ (¥)**
Base Case		**¥2,691,706**	
Discount rates (costs, benefits)	0%	¥2,616,185	-2.81%
	4%	¥2,767,109	2.80%
Time horizon	5 years	¥3,301,206	22.64 %
	10 Years	¥2,838,702	5.46%
	45 Years	¥2,685,276	-0.24%
Distribution around Migraine Headache Days, EM	Negative-Binomial	¥2,773,867	3.05%
Response rate	50%	¥2,980,861	10.74 %
Persistency rate	Upper level: 1.25	¥2,774,555	3.08%
	Lower level: 0.75	¥2,613,060	-2.92%
Treatment waning, galcanezumab	Return to baseline using a rate of 0.23 MHD/cycle	¥1,694,657	-37.04 %

3.Episodic Migraine population with a history of treatment failure to 3 or more prior preventive migraine treatments (BSC comparison)

表 5-12 shows the ICERs derived from the scenario analyses for the episodic migraine population with a history of treatment failure to 3 or more prior preventive migraine treatments (ie. at least 4th line preventive treatment) comparing galcanezumab to BSC. A shorter time horizon and assuming that patients on galcanezumab loose return to baseline already 5 months after stopping treatment appeared to have the most significant impact on the ICER. Apart from these analyses, all others were in the range of the base case or even below the base case results. All ICERs remained below the WTP threshold of ¥5,000,000.

表 5-12 Scenario analyses in the episodic migraine population with a history of treatment failure to 3 or more prior preventive migraine treatments (BSC comparison)

Scenario	**Scenario Details**	**ICER**	**Δ (¥)**
Base Case		**¥2,850,240**	
Discount rates (costs, benefits)	0%	¥2,791,588	-2.06%
	4%	¥2,907,748	2.02%
Time horizon	5 years	¥3,259,714	14.37 %
	10 Years	¥2,956,101	3.71%
	45 Years	¥2,845,703	-0.16%
Distribution around Migraine Headache Days, EM	Beta-Binomial	¥2,848,415	-0.06%
Discontinuation, galcanezumab	Due to adverse events	¥2,683,789	-5.84%
Treatment waning, galcanezumab	5 cycles for both responders and non-responders	¥3,052,558	7.10%
	13 cycles for responders and 1 cycle for non-responders	¥2,917,590	2.36%

4.Chronic Migraine population with a history of treatment failure to 3 or more prior preventive migraine treatments (BSC comparison)

表 5-13 shows the ICERs derived from the scenario analyses for the chronic migraine population with a history of treatment failure to 3 or more prior preventive migraine treatments (ie. at least 4th line preventive treatment) comparing galcanezumab to BSC. A shorter time horizon appeared to have the most significant negative impact on the ICER, while the treatment waning period informed by REGAIN, the 50% or greater reduction in monthly migraine headache days and discontinuation due to adverse events had the most significant positive impact on the ICER in favour of galcanezumab. Apart from these analyses, all others were in the range of the base case results. All ICERs remained well below the WTP threshold of ¥5,000,000.

表 5-13 Scenario analyses in the chronic migraine population with a history of treatment failure to 3 or more prior preventive migraine treatments (BSC comparison)

Scenario	**Scenario Details**	**ICER**	**Δ (¥)**
Base Case		**¥1,441,739**	
Discount rates (costs, benefits)	0%	¥1,402,986	-2.69%
	4%	¥1,479,979	2.65%
Time horizon	5 years	¥1,720,253	19.32%
	10 Years	¥1,512,519	4.91%
	45 Years	¥1,438,696	-0.21%
Distribution around Migraine Headache Days, EM	Negative-Binomial	¥1,481,667	2.77%
Response rate	50%	¥1,225,422	-15.00%
Discontinuation, galcanezumab	Due to adverse events	¥1,340,426	-7.03%
Treatment waning, galcanezumab	Return to baseline using a rate of 0.23 MHD/cycle	¥1,023,067	-29.04%

5.1.3 分析の妥当性の検討

本分析結果は、分析フレームワークに従って分析したものであるが、プロプラノロールの長期有効性に関するエビデンスが限定的であるため、プロプラノロールの有効性とマルコフモデルの外部妥当性は十分に評価されていない。JMDC　のデータでは、治療期間は　24 ヶ月までであり、本分析は実臨床を適切に反映したものである。医療資源の使用頻度についても菊井らによる報告[50]を使用しているので、実臨床を反映していると考える。

5.1.4 分析結果の解釈

表 5-14 分析結果の解釈

対象集団	(a)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者
比較対照	プロプラノロール
ICER の基準値	■通常の品目 □ 配慮が必要な品目
ICER の所属する確率が最も高いと考える区間	□　費用削減あるいはドミナント □ 500 万円以下 (750 万円以下) ■　500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □　750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □　1000 万円超 (1500 万円超) □　効果が同等(あるいは劣り)、かつ費用が高い
そのように判断した理由	プロプラノロールと比較した場合の本対象集団の ICER は、ベースケースで 6,077,875 円であった。DSA によれば、検討されたすべてのシナリオで ICER は 500 万円から 750 万円の間である。また、PSA の CEAC によると、ICER が 500 万円未満になる確率は 9.5%、750 万円以上になる確率は 4.0%(100.0% - 96.0%＝4.0%) で、いずれも低いと想定される。したがって、このグループの ICER は「500 万円以上、750 万円以下」の確率が最も高いと推測される。

対象集団	(b)片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者
比較対照	プロプラノロール
ICER の基準値	■通常の品目 □ 配慮が必要な品目
ICER の所属する確率が最も高いと考える区間	□　費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □　500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □　750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □　1000 万円超 (1500 万円超) □　効果が同等(あるいは劣り)、かつ費用が高い
そのように判断した理由	プロプラノロールと比較した本対象集団の ICER は、ベースケースで 2,691,706 円であった。DSA によると、ICER が 500 万円を超えるシナリオはない。また、PSA の CEAC では、ICER が 500 万円以下となる確率は

	100%であることが示されている。したがって、このグループの ICER は「≦500 万円」である可能性が最も高いと推測される。

対象集団	(c) 片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者
比較対照	Best Supportive Care
ICER の基準値	■通常の品目 □ 配慮が必要な品目
ICER の所属する確率が最も高いと考える区間	□ 費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □ 500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □ 750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □ 1000 万円超 (1500 万円超) □ 効果が同等(あるいは劣り)、かつ費用が高い
そのように判断した理由	BSC と比較した場合の 本対象集団の ICER は、ベースケースで 2,850,240 円である。DSA によると、ICER が 500 万円を超えるシナリオはない。また、PSA の CEAC では、ICER が 500 万円以下となる確率は 100%であることが示されている。したがって、このグループの ICER は「≦500 万円」である可能性が最も高いと推測される。

対象集団	(d) 片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者
比較対照	Best Supportive Care
ICER の基準値	■通常の品目 □ 配慮が必要な品目
ICER の所属する確率が最も高いと考える区間	□ 費用削減あるいはドミナント ■ 500 万円以下 (750 万円以下) □ 500 万円超 (750 万円超)かつ 750 万円以下 (1125 万円以下) □ 750 万円超 (1125 万円超)かつ 1000 万円以下 (1500 万円以下) □ 1000 万円超 (1500 万円超) □ 効果が同等(あるいは劣り)、かつ費用が高い
そのように判断した理由	BSC と比較した場合の 本対象集団の ICER は、ベースケースで 1,441,739 円であった。DSA によると、ICER が 500 万円を超えるシナリオはない。また、PSA の CEAC では、ICER が 500 万円以下となる確率は 100%であることが示されている。したがって、このグループの ICER は「≦500 万円」である可能性が最も高いと推測される。

5.1.5 価格調整率の重み [該当する場合のみ]

価格調整率の重みについて以下に詳細を述べる。

5.1.5.1 片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う患者と片頭痛予防薬の 3 剤

目の治療を中止した患者の割合

分析対象とする集団は、片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う患者と片頭痛予防薬の 3 剤目の治療を中止した患者に大別される。費用対効果評価専門組織より、片頭痛予防薬の 1 剤目はロメリジンと指定されているので、ロメリジン中止後にバルプロ酸およびプロプラノロールを 2 剤目もしくは 3 剤目として使用して継続及び中止した患者の割合を C2H との NDB の共同解析より抽出した結果を以下の図 5-13 および表　5-11 に示す。

図 5-13　片頭痛予防治療薬のライン分析結果　(NDB 共同解析)

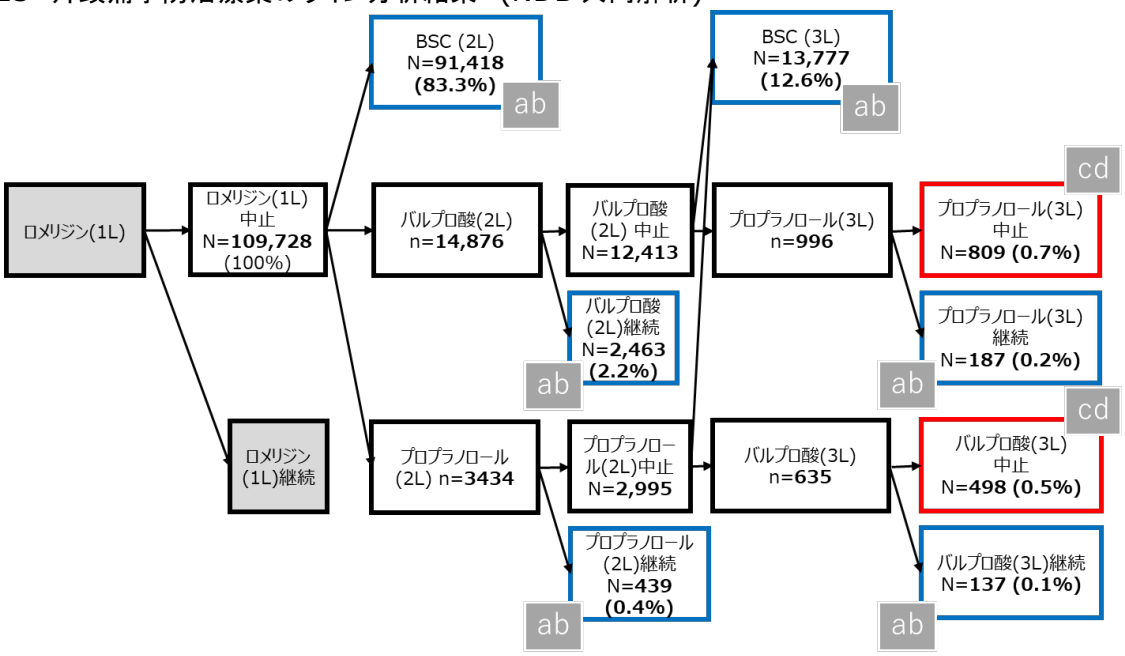


表 5-15　片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う患者と片頭痛予防薬の 3 剤目の治療を中止した患者の割合（NDB 共同解析）

集計項目	患者数	分析対象集団
ロメリジン（中止）	91,418	2 剤目の治療又は 3 剤目の治療を行う患者
ロメリジン（中止）→バルプロ酸（継続）	2,463	
ロメリジン（中止）→プロプラノロール（継続）	439	
ロメリジン（中止）→バルプロ酸（中止）	11,417	
ロメリジン（中止）→プロプラノロール（中止）	2,360	
ロメリジン（中止）→バルプロ酸（中止）→プロプラノロール（継続）	187	
ロメリジン（中止）→プロプラノロール（中止）→バルプロ酸（継続）	137	
ロメリジン（中止）→バルプロ酸（中止）→プロプラノロール（中止）	809	3 剤目の治療を中止した患者
ロメリジン（中止）→プロプラノロール（中止）→バルプロ酸（中止）	498	
総計	109,728	

1 剤目としてロメリジンを中止した総患者数 109,728 人に対して、2 剤目の治療又は 3 剤目の

治療を行う患者の割合はロメリジン中止後に実際は 2 剤目の治療を実施しなかった患者割合、および 2 剤目のバルプロ酸もしくはプロプラノロールの治療中止後に実際は 3 剤目の治療を実施しなかった患者割合も含めて 98.8%であった。実際に 3 剤目としてプロプラノロールもしくはバルプロ酸による治療を実施した上で中止した患者の割合は 1.2%であった。
なお、本分析における 2 剤目の治療はプロプラノロールとしているが、科学院との合意により 2 剤目にバルプロ酸を用いている患者も分析に含めた。

5.1.5.2 EM と CM の患者割合

本剤の処方対象患者が最適使用推進ガイドラインで限られていることから一般的な疫学データより患者割合を出すことは不適切と考えられる。また、ヘルスケアシステムの違いから既に上市している海外における本剤使用の実績から EM と CM の患者割合を日本で採用することもまた不適切と考えられた。よって、[redacted]
[redacted] EM は 52.7%、CM は 47.3%であった。

表 5-16　調査概要

調査方法	[redacted]
標本台帳	[redacted]
調査地域	[redacted]
対象者条件	[redacted]
抽出方法	[redacted]
サンプルサイズ	[redacted]
実施期間	[redacted]

表 5-17 [redacted] EM/CM 別人数と割合

[redacted]		EM, n (%)	CM, n (%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]

5.1.5.3 価格調整率の重み

5.1.5.1 および 2 より、対象集団別の価格調整率の重みは以下のとおりである。

対象集団		計算式	患者割合
a	片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う反復性片頭痛患者	98.8%x52.7%	52.1%
b	片頭痛予防薬の 2 剤目の治療又は 3 剤目の治療を行う慢性片頭痛患者	98.8%x47.3%	46.7%
c	片頭痛予防薬の 3 剤目の治療を中止した反復性片頭痛患者	1.2%x52.7%	0.6%
d	片頭痛予防薬の 3 剤目の治療を中止した慢性片頭痛患者	1.2%x47.3%	0.6%
		合計	100.0%

5.1.6 価格の引き上げ [該当する場合のみ]

該当なし

5.2 公的介護費用や生産性損失を含めた分析 [該当する場合のみ]

該当なし

5.3 その他の分析 [該当する場合のみ]

該当なし

6. 再分析用のデータ

使用したソフトウェア	バージョン	ファイル名	提出メディア
Microsoft Excel and Visual Basic for Applications	Microsoft® Excel® for Microsoft 365 MSO (Version 2109) VBA: 7.1.1113 VBA7.1	056160 Galcanezumab Migraine CEM Japan_FINAL_JP_10012022.xlsm	E メール

7. 実施体制

名前：[redacted]
所属：[redacted]
役割：エムガルティの費用対効果評価実施に対する医療経済学的見地からの助言
利益相反： Eli Lilly Japan から本役割を含むアドバイザリー業務に対する委嘱料を受領

名前：[redacted]
所属：[redacted]
役割：エムガルティの費用対効果評価実施に対する臨床的見地からの助言
利益相反： Eli Lilly Japan から本役割を含むアドバイザリー業務に対する委嘱料を受領

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