CoLab Network

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Drugs Health Technologies Health Systems

Protocol

Calcitonin Gene-Related Peptide Inhibitors for Migraine Prophylaxis

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This observational study is being conducted by the Alberta Drug and Technology Evaluation Consortium (ADTEC) and the CAnadian Network for Advanced Interdisciplinary Methods for comparative effectiveness research (CAN-AIM) through the Post-Market Drug Evaluation CoLab Network.

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Abbreviations

CGRP	calcitonin gene-related peptide
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CA	International Classification of Diseases, 10th Revision, Canadian Enhancement
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification

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Amendments and Updates

The following amendments were made during the implementation of the analyses.

Table 1: Protocol Version Tracking

Version	Version date	Section (heading/page)	Amendment description and rationale
1.2	April 25, 2024	Study variables, p. 10	Treatment resumption group dropped and now included in switcher groups
1.3	May 8, 2024	Study Team	Daniel Dutton and Devin Manning added as study members for Nova Scotia
1.3	May 8, 2024	Mock Tables	Updated tables to show CIMD measures of deprivation instead of Pampalon
1.4	September 2, 2024	Study Team	Sarah Trait added to study members
1.5	November 14, 2024	Data analysis/mock tables	IQR statistic replaced with Q1, Q3 statistics
1.5	November 14, 2024	Appendix	Updated treatment pattern figure to improve clarity and remove the treatment resumption references

Abstract

Background and Rationale

While calcitonin gene-related peptide (CGRP) inhibitors represent a recent advancement in targeted drugs for migraine prevention and have shown efficacy after the failure of conventional therapies, the impact of sequencing within this drug class on clinically important outcomes remains unclear. Sequential treatment with CGRP alternates will lead to resource use and exposure to patients. Public drug plan reimbursement criteria for CGRP inhibitors make no stipulation regarding prior use of drugs of the same class; sequencing may therefore be permissible. Evidence is needed to inform policies guiding the use of CGRP inhibitors for migraine prophylaxis for patients who were previously treated with a CGRP inhibitor.

Study Objectives

The main objective of this study is to describe trends, treatment patterns, and outcomes in the sequential utilization of CGRP inhibitors to prevent migraines. The specific objectives are as follows:

1. to identify trends in the utilization of CGRP inhibitors for migraine prophylaxis between the years 2018 and 2023
2. to describe treatment patterns of individuals using CGRP inhibitors for migraine prophylaxis between the years 2018 and 2023
3. to describe characteristics, including acute rescue medication use, of individuals using CGRP inhibitors who start, stop, or switch to a subsequent CGRP inhibitor.

Research Methods

Study Design

We will conduct a retrospective cohort study using administrative and billing health data.

Data Sources/Data Collection

Data sources that will be used include prescription drug dispensing/drug claims, health care coverage and insurance plans, sociodemographic information, inpatient and outpatient claims data from Canadian provinces between December 4, 2017, and March 31, 2023, and US MarketScan data from 2017 to 2022. In addition, publicly available data from Statistics Canada and US Census Bureau data will be obtained for annual population estimates by jurisdiction and demographic factors.

Study Population

Adults (aged ≥ 18 years) of both sexes, who received ≥ 1 CGRP inhibitor medication dispensation between the date of the earliest availability of CGRP inhibitors and the date of the most recent data availability, specifically between December 4, 2018, and March 31, 2023, in Canadian provinces, and between May 17, 2018, and December 31, 2022, in the US.

Data Analysis

Descriptive statistics will be used to investigate annual incidence and prevalence rates, treatment patterns, and characteristics, including acute rescue medication use of CGRP inhibitors by people who started, stopped, or switched to a subsequent CGRP inhibitor between 2018 and 2023. A Kaplan-Meier estimator will provide further insight into the longitudinal treatment patterns, considering different follow-up durations.

Background and Rationale

Migraine is a common neurologic disorder characterized by recurrent headaches of moderate-to-severe intensity, affecting more than 1 billion people globally,[1] with an estimated prevalence of 8.3% to 10.2% and a cumulative incidence of 12.4% among Canadians.[2,3] According to the 2019 Global Burden of Disease, migraine is the second most disabling disorder globally and highest ranked among all neurologic disorders.[4,5] The manifestations of migraine are diverse, including the 4 common phases of prodrome, aura (which may involve visual disturbances, sensory disturbances, and/or, less commonly, motor weakness), headache, and postdrome (marked by exhaustion or confusion). However, not all migraine sufferers experience each phase.[6,7] The 2 major types of migraine are migraine with aura and migraine without aura.[6, 7] Other types of migraine may include abdominal migraine, hemiplegic migraine, menstrual migraine, retinal migraine, or status migrainosus, which is a rare and severe type of migraine with disabling pain and nausea.[6, 7] If individuals experience fewer than 15 migraine attacks per month, it is classified as episodic migraine; chronic migraine is defined as experiencing 15 or more headache days per month for more than 3 months, of which 8 or more days have the features of migraine.[8]

The pathophysiology of migraine involves a complex interplay of neuronal and vascular factors, prominently involving the trigeminovascular system, with a genetic component also playing a role.[7] Research has identified CGRP as a key neuropeptide in migraine pain signalling.[9] CGRP-mediated neuronal sensitization, along with glutamate-based signalling, contributes to migraine pain.[10] While activation of certain serotonergic receptor subtypes inhibits CGRP release to provide migraine relief, blocking CGRP action has been central to the development of drugs aimed at aborting or preventing migraines.[9,11]

Migraine treatment is aimed at relieving symptoms and preventing future attacks.[6,7] Drug therapy for migraine is divided into acute rescue medications and prophylactic treatment.[6,7] Acute rescue medications are taken as soon as migraine symptoms occur to relieve pain and restore function, while prophylactic treatment involves medication taken regularly to reduce the frequency and severity of future attacks;[6,7] treatment can include migraine-specific and nonspecific pharmacotherapies. Acute rescue medications for migraine may include triptan drugs (targeting serotonin 5-HT1B/1D receptors); ergot derivative drugs (interacting with affinities for serotonin 5-HT, dopamine, and noradrenalin receptors); CGRP receptor antagonists such as ubrogepant (which is approved for oral use and initially entered the Canadian market on April 4, 2023, and the US market on December 23, 2019), zavegepant (which is not yet approved in Canada but was approved in the US on May 10, 2023, as a nasal spray), or rimegepant (which is not yet approved in Canada but was approved in the US in February 2020, for oral use); and ditans, a newer class of acute rescue medications specifically targeting the serotonin 5-HT1F receptor, available in the US since 2019 (lasmiditan) but not yet introduced to the Canadian market.[12-15] Nonspecific pharmacotherapies include nonprescription and prescription analgesics, combination analgesics, nonsteroidal anti-inflammatory drugs, nausea relief drugs, and prescribed narcotics.[16]

Prophylactic migraine pharmacotherapies primarily include off-label use of oral generic drugs such as anticonvulsants, beta-blockers, calcium channel blockers, and antidepressants.[17,18] OnabotulinumtoxinA (Botox) is an injectable pharmacotherapy (available since 2010 and administered by a trained health care provider) indicated for migraine prevention in patients with chronic migraine through multifaced mechanisms, primarily acting on cranial sensory neurons to inhibit nociception transmission by reducing the release of neurotransmitters like CGRP, substance P, and glutamate.[7,8,19] Recent advancements in targeted drugs for migraine prevention involve CGRP inhibitors, including the monoclonal antibody CGRP class — mAbs CGRP, including 3 mAb CGRP inhibitors for subcutaneous injection: erenumab (Aimovig) (December 4, 2018, and May 17, 2018 market dates in Canada and the US respectively), galcanezumab (Emgality) (October 2019 and September 2018 market dates in Canada and the US respectively), and fremanezumab (Ajovy) (August 2020 and September 2018 market dates in Canada and the US respectively), and eptinezumab for IV injection (Vyepti) (August 2022 and February 2020 market dates in Canada and the US respectively); and CGRP receptor antagonists for prophylaxis (gepants), including 2 agents for oral use: atogepant (Qulipta) (February 2023 and September 2021 market dates in Canada and the US respectively), and rimegepant (Nurtec) (May 2021 market date in the US).[13,15] These drugs have a fast onset of action, convenient dosing, and mild to moderate side effects.[18] CGRP inhibitors are typically considered after an individual has experienced inadequate response, intolerance, or contraindication to 2 or more conventional oral migraine prophylactic drugs.[18] Of note, atogepant (Qulipta) was not reimbursed in any Canadian

jurisdiction until early 2023. For all CGRP inhibitors, the drug coverage varies across commercial health plans in the US.

While CGRP inhibitors are effective after failure of conventional therapies, it is unclear how common sequencing occurs within this drug class, and if effectiveness in clinically important outcomes is observed with sequencing in patients experiencing intolerance or a suboptimal response to a CGRP inhibitor. It is unclear whether alternative CGRP inhibitors after initial CGRP treatment failure are effective. If the use of subsequent CGRP inhibitors is unlikely to provide clinical benefit, sequencing could lead to the wasteful use of resources and needless exposure for patients. Public drug plan reimbursement criteria for CGRP inhibitors make no stipulation regarding prior use of drugs of the same class; sequencing may, therefore, be permissible. Evidence is needed to inform policies guiding the use of CGRP inhibitors for migraine prophylaxis for patients who have been treated with a previous CGRP inhibitor.

Policy Question

Should CGRP inhibitors be reimbursed upon lack or loss of response to a previous CGRP inhibitor for migraine prophylaxis?

Policy Impact

The findings of this research study will be used to inform reimbursement criteria for the jurisdictional drug plans in Canada.

Research Questions

1. What are the treatment patterns of individuals using CGRP inhibitors for migraine prophylaxis between the years 2018 and 2023?
2. How frequently are acute rescue medications used among individuals treated with CGRP inhibitors for migraine?

Research Objectives

The main objective is to describe use, treatment patterns, and outcomes in the sequential use of CGRP inhibitors to prevent migraines. The specific objectives of the study are outlined in this section. It is important to note that due to variations in data availability across jurisdictions, the following specific objectives represent the most that can be achieved. Details on specific objective achievement per jurisdiction are presented in Table 4.

1. To describe the trends in the utilization of CGRP inhibitors for migraine prophylaxis between the years 2018 and 2023:
   - Estimate the annual incidence and prevalence of CGRP inhibitor usage between 2018 and 2023 (number and rate): overall, categorized by CGRP inhibitor product, and stratified by age and sex
2. To describe the treatment patterns of CGRP inhibitors for migraine prophylaxis between the years 2018 and 2023:
   a) Fixed follow-up durations: over 1, 2, 3, and 4 years after CGRP inhibitor initiation
      - Proportion of participants switching from an initial to a subsequent CGRP inhibitor
      - Proportion of participants switching from a CGRP inhibitor to another migraine prophylactic treatment
        - Nonspecific medications (not high-cost)
        - Migraine-specific medications (high-cost, such as botulinum toxin A)
      - Proportion of participants concurrently using CGRP inhibitor treatment and other migraine prophylactic treatments
        - Nonspecific medications (not high-cost)
        - Migraine-specific medications (high-cost, such as botulinum toxin A)
      - Proportion of participants taking a treatment break
      - Proportion of participants resuming migraine prophylactic treatment (CGRP inhibitor or other migraine prophylactic treatment)
      - Proportion of participants discontinuing CGRP inhibitor treatment
   b) Consider different follow-up durations if the sample sizes allow:
      - Time from CGRP inhibitor initiation to first treatment break, and probability of a treatment break at a particular interval (e.g., 1 year, 2 years)
      - Time from CGRP inhibitor initiation to first treatment resumption, and probability of a treatment resumption at a particular interval (e.g., 1 year, 2 years) Time from CGRP inhibitor initiation to discontinuation and probability of discontinuation at a particular interval
      - Time from CGRP inhibitor initiation to switching (to another CGRP inhibitor and to another prophylactic medication), and probability of switching at a particular interval
3. Describe people's characteristics, including acute rescue medication use of individuals using CGRP inhibitors:
   a) Migraine-related medication use
      - Migraine-related medication use during the 1-year preindex period (i.e., the year before the first-ever CGRP dispensation): overall, acute rescue medications, prophylactic medications

- Proportion of participants who used acute rescue medications while using CGRP inhibitors within the 6-month and 1-year follow-up durations
- Sociodemographic characteristics at the index year: Age, sex, location of residence, as well as socioeconomic status

b) Clinical characteristics

- Overall chronic health burden using Charlson Comorbidity Index during the 1-year preindex period
- Comorbid conditions during the 1-year preindex period
- Migraine-related health encounters during 1-year preindex and postindex periods

Research Methods

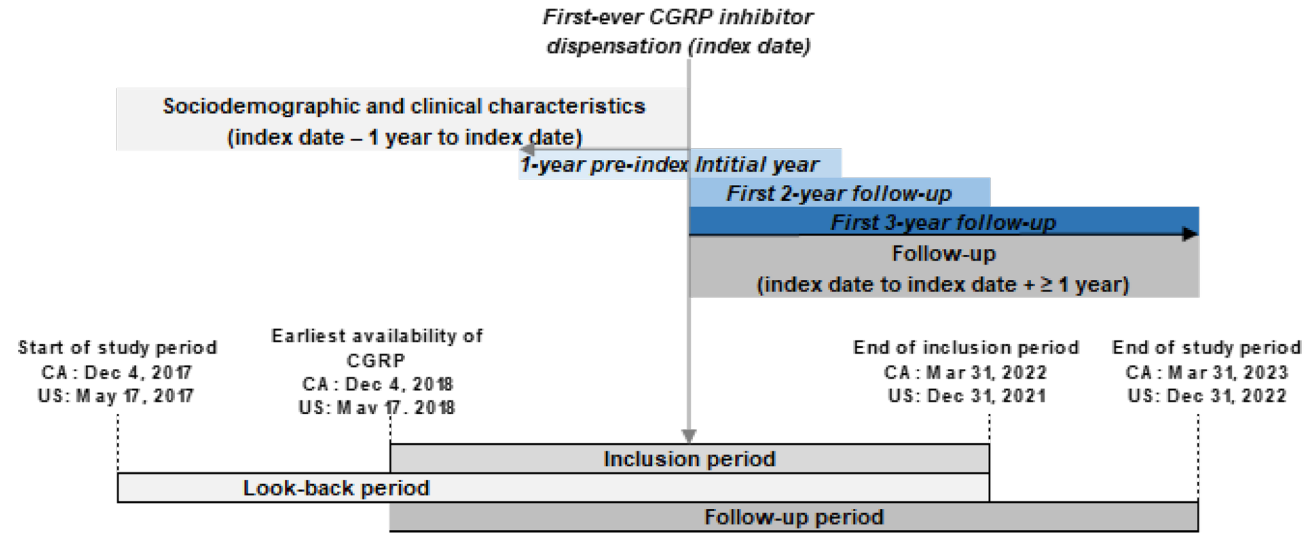
Study Design

This will be a retrospective cohort study, using administrative data without any intervention. No study participants will be placed at risk as a result of this study.

Study Population and Setting

The overall study period will be from 2017 to 2023, which comprises the inclusion period (December 4, 2018, or May 17, 2018 [the earliest availability of a CGRP inhibitor product in the Canadian and US markets, respectively], to March 31, 2022, or December 31, 2021 [for Canadian provinces and the US, respectively]); and a 1-year look-back period from as far back as December 4, 2017, or May 17, 2017 (for Canada and the US, respectively) for the assessment of characteristics, through a follow-up period to the end of data availability (March 31, 2023, or December 31, 2022, for Canada and the US, respectively). The index date is defined as the earliest dispensation date of a CGRP inhibitor medication (first-ever). The follow-up period is determined from the index date until the end of provincial health care coverage or US insurance plan (e.g., relocation out of province, no longer enrolled in an insurance plan, or death) or until the end of data availability (March 31, 2023, and December 31, 2022, for Canada and the US, respectively), whichever comes first. A schematic representation of the study is outlined in Figure 1.

Figure 1: Study Time Frame for the Cohort of CGRP Inhibitor Users Between 2018 and 2022 (Objective 2)



CA = Canada; CGRP = calcitonin gene-related peptide; Dec = December; Mar = March.

Eligibility Criteria

The cohort will include adult (aged ≥ 18 years) residents (who have provincial health care coverage or a health insurance plan) who received 1 or more CGRP inhibitor medication dispensations during the period between December 4, 2018, and March 31, 2023, for Canada, or between May 17, 2018, and December 31, 2022, for the US. Specifically, eligibility criteria are:

For Objective 1

- Received 1 or more outpatient pharmacy dispensations or infusion procedure records of CGRP inhibitor medication during the period between **December 4, 2018, and March 31, 2023, for Canada, or between May 17, 2018, and December 31, 2022, for the US**, and
- was aged 18 years or older at the index date.

For Objective 2

- Received 1 or more outpatient pharmacy dispensation or infusion procedure records of CGRP inhibitor medication during the period between **December 4, 2018, and March 31, 2022, for Canada, or between May 17, 2018, and December 31, 2021**, for the US, and
- was aged ≥ 18 years or older at the index date, and
- had provincial health care coverage or a health insurance plan for 1 year or more after the index date.

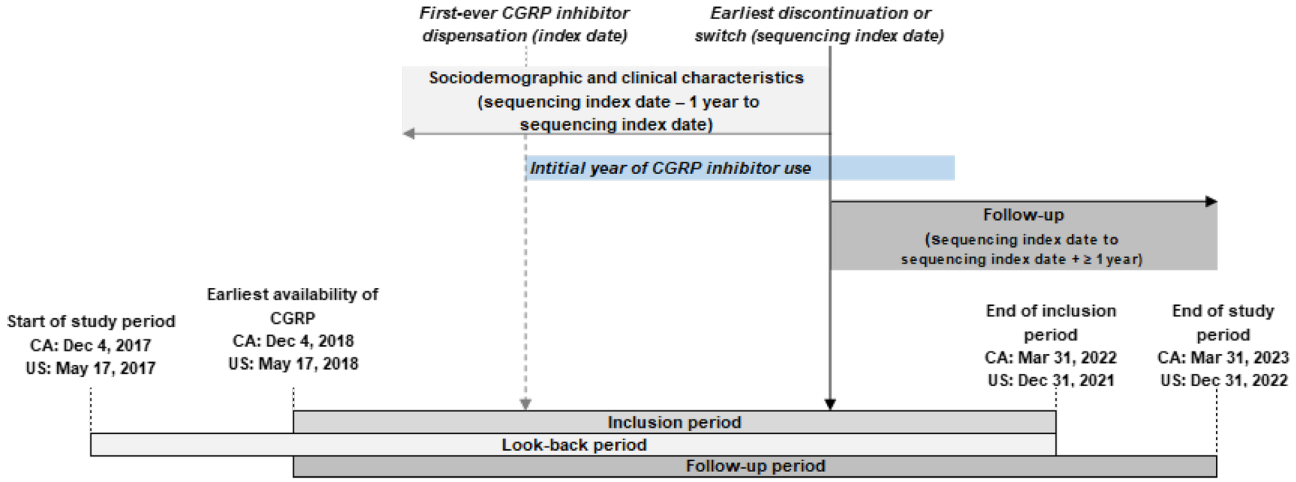
For Objective 3

- Received 1 or more outpatient pharmacy dispensations or infusion procedure records of CGRP inhibitor medication during the period between **December 4, 2018, and March 31, 2022, for Canada, or between May 17, 2018, and December 31, 2021, for the US**, and

- was aged 18 years or older at the index date, and
- had provincial health care coverage or a health insurance plan for 1 year or more before the index date and 1 year or more after the index date.

The subcohorts will include people who discontinued CGRP inhibitor treatment and those who switched to a different CGRP inhibitor. These individuals are defined as users of a CGRP inhibitor who received 1 or more CGRP inhibitor dispensations between December 4, 2018, and March 31, 2022, for the Canadian data, and between May 17, 2018, and December 31, 2021, for the US data, and subsequently discontinued or switched to another CGRP inhibitor within the first year of initiating CGRP inhibitor treatment without resuming the initial CGRP inhibitor within the first year of discontinuation or switch. The discontinuing/sequencing index date is determined as the earliest date of discontinuation or switch. The follow-up period for the subcohorts is determined from the discontinuing or sequencing index date until the end of provincial health care coverage or a health insurance plan (e.g., relocation out of province, no longer enrolled in an insurance plan, or death) or until the end of data availability (March 31, 2023, for Canada and December 31, 2022, for the US), whichever comes first. To ensure the subcohorts have 1 year or more of follow-up, individuals in the subcohorts are required to have provincial health care coverage or a health insurance plan for 1 year or more following the discontinuing or sequencing index date. The study time frame for the subcohorts is outlined in Figure 2.

Figure 2: Study Time Frame for the Subcohorts of CGRP Inhibitor Discontinuers and Switchers (Objective 3)



CA = Canada; CGRP = calcitonin gene-related peptide; Dec = December; Mar = March.

Study Variables

Identification of CGRP Inhibitor Users (Objective 1)

Incident (first-ever) and prevalent users of CGRP inhibitors will be identified from the outpatient community pharmacy dispensation or infusion record data from between December 4, 2018, and March 31, 2023, for Canada, or between May 17, 2018, and December 31, 2022, for the US. The list of CGRP inhibitors that

are available in the Canadian and US markets for migraine prophylaxis during this time frame is provided in Table 1.

Incident users are individuals who received their first-ever dispensation of a CGRP inhibitor. For each year from 2018 to 2023 (while the fiscal year will be used for Canada, the calendar year will be used for the US), incident users are defined as those who received their initial CGRP inhibitor dispensation within that year, with no prior CGRP inhibitors dispensations as far back December 4, 2018, or May 17, 2018 (the earliest availability of a CGRP inhibitor product in the Canadian or US markets, respectively).

Prevalent users are individuals who had at least 1 dispensation of CGRP inhibitors within the specific year of interest (regardless of the first CGRP ever used or subsequent therapies).

Table 2: Approved Indications for Available CGRP Inhibitors for Migraine Prophylaxis

Medication	Indication (approved)	Recommended dose	Earliest market date in Canada	Earliest market date in the US
Monoclonal antibody CGRP (mAb CGRP)				
erenumab (Aimovig)	Prevention of migraine in adults who have at least 4 migraine days per month	70 mg or 140 mg SC injection once monthly	December 4, 2018	May 22, 2018
galcanezumab (Emgality)	Prevention of migraine in adults who have at least 4 migraine days per month	Initial (loading) dose of 240 mg (administered as 2 consecutive SC injections of 120 mg), followed by once-monthly doses of 120 mg (1 injection)	October 2, 2019	September 27, 2018
fremanezumab (Ajovy)	Prevention of migraine in adults who have at least 4 migraine days per month	225 mg (1 injection) once monthly or 675 mg (3 separate SC injections of 225 mg one after another) every 3 months	August 4, 2020	September 15, 2018
eptinezumab (Vyepti)	Prevention of migraine in adults who have at least 4 migraine days per month	100 mg by IV infusion every 3 months	August 17, 2022	February 21, 2020
CGRP receptor antagonist (gepants)				
atogepant (Qulipta)	Prevention of episodic migraine (< 15 migraine days per month) in adults	10 mg, 30 mg, or 60 mg orally once daily	February 23, 2023	September 30, 2021
rimegepant (Nurtec ODT)	Prevention of episodic migraine in adults	75 mg orally once daily, up to 18 doses per month	March 25, 2024[a]	May 27, 2021

CGRP = calcitonin gene-related peptide; SC = subcutaneous.

[a]Rimegepant is only approved for acute migraine in Canada.

Source: Health Canada Drug Product Database and FDA drug approval document, updated to February 5, 2024.

Treatment Patterns

Fixed Follow-Up Durations (Objective 2a)

The following variables will be described for the initial year of CGRP inhibitor initiation (first-ever) as well as within the 2-year, 3-year, and 4-year durations after CGRP inhibitor initiation. Details regarding the treatment patterns definitions can be found in Appendix 2, Figure 4.

- **Switching from a CGRP inhibitor to another CGRP inhibitor** is defined as:
  - stopping the previously dispensed CGRP inhibitor for more than 120 consecutive days, and
  - starting a new CGRP inhibitor with or without any gap after the previously dispensed CGRP inhibitor treatment or while overlapping with the previously dispensed CGRP inhibitor treatment for fewer than 30 consecutive days.
  - The end date is determined as the last date of supply within a follow-up duration plus the duration of medication effect (e.g., 1 month for erenumab or 3 months for eptinezumab). The switching date is established as the dispensing date of the first dispensation of the switched CGRP inhibitor medication.
- **Switching from a CGRP inhibitor to another migraine prophylactic** treatment is defined as:
  - stopping the previously dispensed CGRP inhibitor for more than 120 consecutive days, and
  - starting at least 1 other migraine prophylactic medication dispensation (e.g., onabotulinumtoxinA injection)[20] after stopping the CGRP, or while overlapping with the previously dispensed CGRP inhibitor treatment for 30 or fewer consecutive days.
- **Concomitant CGRP inhibitor treatment with other migraine prophylactic** treatments (including other CGRP inhibitors) is defined as starting a new CGRP inhibitor or other migraine prophylactic treatment (e.g., onabotulinumtoxinA injection) while overlapping with the previously dispensed CGRP inhibitor treatment for more than 30 consecutive days.
- **Treatment break** is defined as more than 120 consecutive days without any CGRP inhibitor medications or other migraine prophylactic treatment, followed by the resumption of previously dispensed CGRP inhibitor medications.
- **Discontinuation** is defined as more than 120 consecutive days without any CGRP inhibitor or other migraine prophylactic treatment, and no switching, treatment break, or resumption of migraine prophylactic treatment. The end date of the last CGRP inhibitor dispensation is identified as the discontinuation date.

Considering Different Follow-Up Durations (Objective 2b)

- Time from CGRP inhibitors initiation to first treatment break, discontinuation, or first switching (in days or months)
- Probability of a treatment break, discontinuation, or first switching at a particular interval (e.g., 1 year, 2 years)

Characteristics of CGRP Inhibitor Users

Migraine-Related Medication Use (Objective 3a)

- Prior migraine-related medication use: Migraine-related medication dispensations from outpatient community pharmacies among CGRP inhibitor users during the 1-year preindex period will be reported overall, categorized by treatment type (acute rescue and prophylactic medications), and further subdivided by class. Detailed medication classifications are provided in Table 3. Further information regarding these medications can be found in Appendix 2, Table 14.
- Acute rescue medication use during CGRP inhibitors use for prophylaxis: CGRP inhibitor users who received acute rescue medications, defined as acute medications used to treat (not prevent) a migraine attack. This measurement will involve tracking any acute rescue medications dispensed from outpatient community pharmacies during the period of CGRP inhibitor use, spanning from the dispensing date to the end date. Follow-up durations to be considered include within 6 months and within 1 year.

Table 3: Migraine Prophylactic and Acute Rescue Medication Classification

Class	Migraine-specific	Approved use	Common agents	Earliest market date in Canada	Earliest market date in US
Acute rescue medications					
NSAIDs	No	Rescue	diclofenac ketorolac	N/A	N/A
Opioids	No	Rescue	oxycodone hydrochloride	N/A	N/A
Triptans	Yes	Rescue	sumatriptan zolmitriptan	N/A	N/A
Ergots	Yes	Rescue	dihydroergotamine	N/A	N/A
Gepants (CGRP receptor antagonist)	Yes	Rescue	ubrogepant (oral use) rimegepant (oral use) zavegepant (nasal spray)	April 4, 2023 March 25, 2024 Not yet available	December 23, 2019 March 5, 2020 June 1, 2023
Ditans	Yes	Rescue	lasmiditan (oral use)	Not yet available	October 11, 2019
Other prophylactic medications					
Antidepressants	No	Preventive	amitriptyline	N/A	N/A
Antiepileptics	No	Preventive	gabapentin	N/A	N/A
Antihypertensives	No	Preventive	propranolol	N/A	N/A
Calcium antagonist	No	Preventive	flunarizine	N/A	N/A
Serotonin and tryptamine antagonist	Yes	Preventive	pizotifen	1980	1980
Botulinum A toxin	Yes	Preventive	onabotulinumtoxinA	2012	2010

CGRP = calcitonin gene-related peptide; N/A = marketing date not relevant for this study; NSAIDs = nonsteroidal anti-inflammatory drugs.
Source: Health Canada Drug Product Database and FDA drug approval document, updated to February 5, 2024.

Sociodemographic Characteristics (Objective 3b)

Demographic factors will include age, sex, and region of residence (urban or rural), which will be identified on the index date. Whether the region of residence is urban or rural will be determined by the second postal code digit (0 for rural residence) in Alberta, the Statistical Area Classification (SAC) type from the Postal Code Conversion File Plus (PCCF+) Version 8A for other Canadian provinces (SAC types 1 to 3 as urban, and SAC types 4 to 8 as rural),[21] or as described by Creedon and colleagues for the US.[22] For the Canada analysis, socioeconomic status will be determined by either the Canadian Index of Multiple Deprivation (CIMD)[23] or the deprivation index developed by Pampalon and colleagues,[24] both derived from the 2021 Canadian Census of Population at the dissemination area level, which can be linked to postal codes and presented based on quintiles. The CIMD includes 4 dimensions of deprivation: residential instability, economic dependency, ethnocultural composition, and situational vulnerability, while the Pampalon et al. deprivation index includes a material deprivation index (based on education, employment status, and average income) and social deprivation index (based on living status, marital status, and number of parents in the household).

Clinical Characteristics (Objective 3c)

- Overall health burden will be assessed by a longitudinal Charlson Comorbidity Index score based on codes from the Canadian enhancement or clinical modification of the 10th revision of the International Classification of Diseases (ICD-10-CA or ICD-10-CM) and from the clinical modification of the ninth revision of the ICD (ICD-9-CM) of 17 different specific medical conditions weighted according to their potential for influencing mortality measured during the 1-year look-back period[25] (refer to Appendix 2, Table 15). Alternatively, a modified chronic disease score can be used.
- Comorbidities of interest include common health conditions associated with migraine (anxiety, asthma, cardiovascular disease, depression, epilepsy, hypertension, and obstructive sleep apnea), which will be measured during the 1-year look-back period. Each participant will be classified with respect to the presence or absence of these conditions (refer to Appendix 2, Table 16).
    - Migraine-related health care encounters will be measured during the 1-year postindex observation period and the 1-year preindex observation period and will include inpatient and outpatient encounters. For Canadian provinces, they are identified by an ICD-10-CA G43 code contained within the most responsible diagnosis field for inpatient hospitalizations and ambulatory care visits (i.e., nonemergent and emergency department visits) and an ICD-9-CM 346 code contained within any of the diagnostic fields for physician visits. For the US data, they are identified by an ICD-10-CM G43 code contained within the most responsible diagnosis field for inpatient and outpatient claims.

Data Analysis

Statistical Analysis Plan

Objective 1: Annual incidence and prevalence of the use of CGRP (mock results table can be found in Appendix 1, Table 5)

- Overall incidence and prevalence numbers and rates will be reported for each fiscal or calendar year from 2018 to 2023. For the Canada analysis, annual rates per 100,000 people will be calculated using each annual jurisdiction's population estimates from Statistics Canada. For the US analysis, annual rates per 100,000 insured individuals (enrollees) in a particular year will be used as the denominators.
- Incidence and prevalence numbers and rates will be stratified by age and sex. Annual age-specific and sex-specific rates per 100,000 people will be calculated using each jurisdiction's annual population estimates for age and sex strata (Canada analysis), or per 100,000 enrollees for age and sex strata (US analysis) as the denominators. Age- and sex-adjusted rates will also be calculated using the annual Canadian or US population by age and sex from Statistics Canada or the US Census Bureau respectively as the standard population structure (direct adjustment).
- Incidence and prevalence numbers will be categorized by **CGRP inhibitor product (erenumab, galcanezumab, fremanezumab, eptinezumab, atogepant, rimegepant)**. Proportions for each CGRP inhibitor product will be calculated among the total incident and prevalent CGRP users for each fiscal or calendar year from 2018 to 2022 (denominators).

Objective 2: Treatment pattern (mock result tables can be found in Appendix 1, Table 6, Table 7, and Table 8)

a. **Fixed follow-up durations**: The number and proportions of switching, concomitant use, treatment break (or CGRP inhibitor resumption), and discontinuation will be reported for the initial year of CGRP inhibitors initiation, and within the first 2, 3, and 4 years after CGRP inhibitors initiation. The denominator comprises the number of participants who initiated CGRP inhibitors and have the postindex follow-up time for at least 1, 2, 3, or 4 years. All participants have at least 1 year for follow-up or an observation period. For example, in Figure 1, the follow-up periods of participants who initiated CGRP inhibitors on April 1, 2020, will include the initial year (from April 1, 2020, to March 31, 2021), the 2-year period (from April 1, 2020, to March 31, 2022), and the 3-year period (from April 1, 2020, to March 31, 2023), provided if they continue to have health coverage or insurance plan coverage throughout these periods (i.e., no relocation out of province or death).

b. **Considering different follow-up durations if the sample sizes allow:** The Kaplan-Meier estimator will be used to account for different follow-up durations. Follow-up will start from the initiation of CGRP inhibitor treatment until the occurrence of the first event (first treatment break, discontinuation, or first switch), loss to follow-up (i.e., relocation out of the province or death), or the end of the study period, whichever occurs first. Mean (standard error) and median time from CGRP inhibitors initiation and probability at a particular interval (95% confidence interval) will be reported for the first treatment break, discontinuation, and first switch.

In addition, the treatment pattern pathways will be depicted in a tree diagram (Appendix 1, Figure 3).

Objective 3: Descriptive of other treatments (prior and rescue), sociodemographic characteristics, and clinical characteristics (mock result tables can be found in Appendix 1, Table 9, Table 10, Table 11, Table 12, and Table 13).

Characteristics, including rescue medication use, will be reported among users of CGRP inhibitors between December 4, 2018, and March 31, 2022, for Canada, and between May 17, 2018, and December 31, 2021, for the US with the (first-ever) index date; and among subcohorts (switchers or discontinuers) with the sequencing or discontinuing index date, if the sample sizes allow.

a. **Migraine-related medication use:** Descriptive statistics for migraine-related medication dispensations will be used to report overall migraine-related medication use, and by stratifications as follows:
    - Previous migraine-related medications (during the 1-year preindex period):
        - Frequency and proportion of users of CGRP inhibitors who have 1 or more dispensations of any migraine-related medication during the 1-year preindex period
        - Frequency and proportion of users of CGRP inhibitors who have 1 or more dispensations of acute rescue medication during the 1-year preindex period
            - Overall: the average number of days of supply and the number of classes dispensed
            - By class: nonsteroidal anti-inflammatory drugs, opioids, triptans, ergots, and ditans
        - Frequency and proportion of CGRP inhibitor users who have 1 or more dispensations of migraine-related prophylactic medication during the 1-year preindex period
            - Nonspecific medication: any medications, the average number of days of supply, and the number of classes dispensed, and by class
            - Botulinum toxin: any injections and the average number of injections
    - The number and proportion of participants who used rescue medications during the period of CGRP inhibitor use will be reported for 6-month and 1-year follow-up durations.
b. **Sociodemographic characteristics:** Counts and percentages will be reported for each category as follows:
    - Age: 18 to 44 years, 45 to 64 years; 65 years and older
    - Sex: Female and male
    - Location of residence: rural and urban
    - CIMD or Pampalon deprivation index: 1 (most well off) to 5 (most deprived) (for Canada only)
c. **Clinical characteristics:**
    - Overall chronic health burden: the Charlson Comorbidity Index score will be reported in means and standard deviations, and medians and minimum and maximum values. The score will also be

categorized as no comorbid condition (0), mild comorbidity (1 to 2), moderate comorbidity (3 to 4), and severe comorbidity (≥ 5).

- Comorbidities: Counts and percentages of participants with each comorbid condition will be calculated.
- Means and standard deviations and/or medians and interquartile ranges for the number of migraine-related health care encounters, as well as counts and percentages for participants with 1 or more migraine-related health care encounters, will be reported for the 1-year preindex and 1-year postindex periods. Repeated-measure analysis for the number of migraine-related health care encounters will be considered for before and after comparisons.

Data Sources

Health administrative and billing databases from Canadian provinces and the US (MarketScan data) will be used to address the study questions. Summaries of the data sources by objective are provided in Table 4.

Canada

Prescription drug dispensing data from Canadian provinces (potentially including Alberta, British Columbia, Manitoba, Newfoundland and Labrador, Nova Scotia, Quebec, and Saskatchewan) where full coverage of community pharmacy–dispensed prescription drug data are available, will be used. These databases contain all prescription medication dispensations from outpatient community pharmacies, regardless of payer. Data includes drug identification number (DIN), unique patient identifiers, age and sex on dispensing date, dispensing date, dose dispensed, and days' supply.

Canada provincial registry data containing demographic information and health plan coverage will be used to identify whether individuals have provincial health coverage during their follow-up period as well as determine their resident/vital status and dates of migration in and out of the province or death. Data may vary across provinces.

Prescription drug dispensing data from Canadian provinces will be linked with inpatient hospital discharge, ambulatory care reporting, and physician claims data. This linkage, using unique patient identifiers will enable the determination of overall health burden, comorbidities, and migraine-related health care encounters. While inpatient hospital discharge data are consistently available across provinces, ambulatory care data exhibit variability from one province to another.

Additionally, Statistics Canada (publicly available) will be used for population denominators overall by jurisdiction and by age and/or sex for incidence and prevalence calculation (Objective 1).

US

Prescription, in-hospital, and ambulatorial data in the US from MarketScan, Commercial Claims, and Medicare databases will be used.

The prescription database (Outpatient Pharmaceutical Claims, Table D) contains administrative claims for individuals covered by US commercial, Medicare Supplemental, and Medicaid insurance plans. Data

includes the National Drug Code and generic identifiers of the drug dispensed, encrypted unique patient identifiers, dispensing date, and quantity and days' supply.

The inpatient database (Inpatient Services, Table S; Inpatient Admissions, Table 1) and the outpatient database (Outpatient Services, Table O) contains medical claims for procedures and visits; diagnosis information can be obtained using ICD-10-CM, Procedural Terminology medical procedure codes (PTC), or the Healthcare Common Procedure Coding System (HCPCS).

Enrolment tables (A, T) will be used to define insured individuals (enrollees).

Data regarding resident and vital status are not available.

Additionally, US Census Bureau (publicly available) data will be used for population denominators overall by jurisdiction and by age and/or sex.

Limitations

The study is subject to a number of limitations that should be taken into consideration when interpreting results.

- The use of administrative data and algorithms as opposed to medical records may introduce misclassification of the study measures due to potential inaccuracies and incomplete reporting. To address this limitation, validated case-finding algorithms will be used when possible.
- The prescription drug dispensing database only provides information on prescription medication dispensations from community pharmacies and, therefore, may not represent actual medication uptake by individuals or in the fashion prescribed. Additionally, it is not known whether medications will be taken specifically for migraine or other conditions such as arthritis, depression, hypertension, or epilepsy. Use of over-the-counter medications and other nonpharmacotherapy, self-management techniques are not captured within provincial administrative data and are, therefore, not reported.
- Patients in the community may not receive an adequate trial of the medications or an appropriate dose. For instance, some patients may take up to 6 months to respond to treatment, but in a real-world setting, they may opt out of treatment before 6 months.
- The study's findings, based on administrative data, cannot definitively establish reasons for discontinuing or switching CGRP inhibitors. While comparing health care resource utilization before and after initiation may suggest the response to CGRP inhibitor treatment, direct conclusions regarding the lack or loss of response to a previous CGRP inhibitor for migraine prophylaxis cannot be drawn from the study results.

Table 4: Data Sources for Study Objectives

Objectives	Eligibility criteria	Data sources	Expected results	Data availability/attainment
Objective 1: Trends in the utilization of CGRP inhibitors for migraine prophylaxis between the years 2018 and 2023	1. Received ≥ 1 dispensation of CGRP inhibitor medication during the period from 2018 to 2023, and 2. was aged 18 years or older at the index date	• Prescription drug dispensing data for Canadian provinces • Prescription claims plus demographics data from US MarketScan databases • Population estimates from Statistics Canada and US Census Bureau data	Annual incidence and prevalence numbers and rates (denominator = provincial/US population): • Overall • Categorized by CGRP inhibitor product • Stratified by age and sex	All the following jurisdictions will be able to complete this objective: • CIHI + AB: BC, AB, SK, MB • HDRN Canada: BC, AB, SK, MB, NS, NL (other provinces report on publicly funded drugs) • QC: only people covered by the RAMQ drug insurance plan (approximately 45% of Quebec residents) will be included • US MarketScan
Objective 2a: Treatment patterns for fixed follow-up durations (within 1-year, 2-year, 3-year, 4-year durations)	1. Received ≥ 1 dispensations of CGRP inhibitor medication during the period from 2018 to 2022, and 2. was aged 18 years or older at the index date, and 3. had provincial health care coverage/health insurance plan ≥ 1 year after the index date	• Prescription drug dispensing data for Canadian provinces • Provincial registry data • Prescription claims plus eligibility data from US MarketScan databases	Numbers and proportions of individuals: • switching from an initial to a subsequent CGRP or switching from a CGRP inhibitor to another prophylactic treatment • concurrently using CGRP inhibitor treatment and other prophylactic treatments • on a treatment break or resuming treatment with a CGRP inhibitor • discontinuing CGRP inhibitor treatment	All jurisdictions should be able to achieve objective 2a, assuming resident status/access to health care coverage/health insurance plans. It is anticipated that this limitation is minor given the low rate of relocation or mortality. • CIHI: No data available regarding coverage • AB: Coverage information is accessible • QC to be done by INESSS • US MarketScan: Insurance plan types are available. Follow-up can be conducted for at least a 1-year duration
Objective 2b: Treatment patterns considering different follow-up time			Time from CGRP inhibitor initiation to and 1-year or 2-year probability of: • First treatment break	

Objectives	Eligibility criteria	Data sources	Expected results	Data availability/attainment
			• First switch • Discontinuation	
Objective 3a: Migraine-related medication use	1. Received ≥ 1 dispensation of CGRP inhibitor medication during the period from 2018 to 2022, and 2. was aged 18 years or older at the index date, and 3. had provincial health care coverage/health insurance plan for ≥ 1 years before and ≥ 1 years after the index date	• Prescription drug dispensing data for Canadian provinces • Provincial registry data • Prescription claims plus eligibility data from US MarketScan databases	• Migraine-related medications during the 1 year preindex and postindex for all users of CGRP inhibitors and for subgroups (those who discontinue and those who switch treatment, defined within 1 year of follow-up): overall, by treatment type, and by class • The number and proportion of all users of CGRP inhibitors and subgroups (those who discontinue and those who switch, defined within 1 year of follow-up) during the period of CGRP inhibitor use	All jurisdictions should be able to achieve Objective 3a, assuming resident status/access to health care coverage/health insurance plans.
Objective 3b: Sociodemographic characteristics		• Prescription drug dispensing for Canada provinces • Provincial registry data • Prescription claims plus demographics data from US MarketScan databases	Sociodemographic characteristics (at the index) of all users of CGRP inhibitors and of subgroups (those who discontinue and those who switch, defined within 1 year of follow-up) • Age • Sex • Location of residence • CIMD or Pampalon social/ material deprivation index	Objective 3b can be attained with AB data and CIHI data (if assuming resident status).

Objectives	Eligibility criteria	Data sources	Expected results	Data availability/attainment
Objective 3c: Clinical characteristics		• Inpatient hospitalization discharge and ambulatory care visit (ED and non-ED) data; physician claims data for Canadian provinces • Provincial registry data • Inpatient and outpatient claims plus eligibility data from US MarketScan databases	Clinical characteristics of all users of CGRP inhibitors and of subgroups (those who discontinue and those who switch, defined within 1 year of follow-up) • Charlson Comorbidity Index score Comorbidities • Premigraine- and postmigraine-related health encounters (6 months/1 year)	• Objective 3c can be attained fully with AB data. • ED and ambulatory care are very inconsistent from province to province. • QC to be done by INESSS. • CIHI: No claims data. • Service codes vary between provinces. • ICD-10-CM and Procedural Terminology medical procedure codes are used for US MarketScan. • Modified chronic disease score can be an alternative to identify overall health burden.

AB = Alberta; BC = British Columbia; CGRP = calcitonin gene-related peptide; CIHI = Canadian Institute for Health Information; CIMD = Canadian Index of Multiple Deprivation; ED = emergency department; HDRN = Health Data Research Network; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; INESSS = Institut national d'excellence en santé et services sociaux; MB = Manitoba; NL = Newfoundland and Labrador; NS = Nova Scotia; QC = Quebec; RAMQ = Régie de l'assurance maladie du Québec; SK = Saskatchewan.

References

1. Safiri, S., Pourfathi, H., Eagan, A., et al., Global, regional, and national burden of migraine in 204 countries and territories, 1990 to 2019. *Pain*, 2022. 163(2): p. e293-e309. PubMed
2. Ramage-Morin, P.L. and H. Gilmour, *Prevalence of migraine in the Canadian household population.* 2014. Ottawa, ON: Statistics Canada.
3. Graves, E.B., Gerber, B., Berrigan, P.S., et al., Epidemiology and treatment utilization for Canadian patients with migraine: a literature review. *J Int Med Res*, 2022. 50(9): p. 1-22. PubMed
4. Steiner, T.J., Stovner, L. J., Jensen, R., Uluduz, D., and Z. Katsarava, Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain*, 2020. 21(137): p. 1-4. PubMed
5. Steiner, T.J., Stovner, L. J., Vos, T., Jensen, R., and Z. Katsarava, Migraine is first cause of disability in under 50s: will health politicians now take notice? *J Headache Pain*, 2018. 19(1):17 p. 1-4. PubMed
6. National Institute of Neurological Disorders and Stroke. *Migraine*. [cited 2024 February 12]; Available from: https://www.ninds.nih.gov/health-information/disorders/migraine#toc-what-is-migraine.
7. Puledda, F., Messina, R., and P. J. Goadsby, Migraine: from pathophysiology to treatment. *Journal of Neurology*, 2023. 270(7): p. 3654-3666. PubMed
8. Headache Classification Committee of the International Headache Society (IHS), *The International Classification of Headache Disorders, 3rd edition.* Cephalalgia, 2018. **38**(1): p. 1-211.
9. Wattiez, A.S., L.P. Sowers, and A.F. Russo, Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. *Expert Opin Ther Targets*, 2020. 24(2): p. 91-100. PubMed
10. Russo, A.F., CGRP-based migraine therapeutics: how might they work, why so safe, and what next? *ACS pharmacology & translational science*, 2019. 2(1): p. 2-8. PubMed
11. Aggarwal, M., V. Puri, and S. Puri, Serotonin and CGRP in migraine. *Ann Neurosci*, 2012. 19(2): p. 88-94. PubMed
12. Peters, G.L., Migraine overview and summary of current and emerging treatment options. *Am J Manag Care*, 2019. 25(2 Suppl): p. S23-S34. PubMed
13. Health Canada, *Drug Product Database*. 2024: https://health-products.canada.ca/dpd-bdpp/search.
14. Ceriani, C.E.J., D.A. Wilhour, and S.D. Silberstein, Novel Medications for the Treatment of Migraine. *Headache*, 2019. 59(9): p. 1597-1608. PubMed
15. Chaudhari, K. and B.A. Syed, The pipeline and market for migraine drugs. *Nat Rev Drug Discov*, 2024. 23(4): p. 246-247. PubMed
16. Tzankova, V., W.J. Becker, and T.L.H. Chan, Diagnosis and acute management of migraine. *CMAJ*, 2023. 195(4): p. E153-E158. PubMed
17. Tzankova, V., W.J. Becker, and T.L.H. Chan, Pharmacologic prevention of migraine. *CMAJ*, 2023. 195(5): p. E187-E192. PubMed
18. Pleș, H., Florian I.A., Timis T.L., et al., Migraine: Advances in the pathogenesis and treatment. *Neurology International*, 2023. 15(3): p. 1052-1105. PubMed
19. Matak, I., Bölcskei K., Bach-Rojecky L., and Z. Helyes, Mechanisms of Botulinum Toxin Type A Action on Pain. *Toxins (Basel)*, 2019. 11(8):459 p. 1-24. PubMed
20. Gaul, C., Seidel K, Heuck A, et al., Real-world treatment patterns and healthcare resource utilization among migraine patients: a German claims database analysis. *J Med Econ*, 2023. 26(1): p. 667-678. PubMed
21. Statistics Canada, *Postal CodeOM Conversion File Plus (PCCF+) Version 7E, Reference Guide*. 2021: https://library.carleton.ca/sites/default/files/2022-06/PCCF%2BUserguide-2021.pdf.

22. Creedon, T.B., Schrader K.E., O'Brien P.L., et al., Rural-nonrural differences in telemedicine use for mental and substance use disorders among Medicaid beneficiaries. *Psychiatric services*, 2020. 71(8): p. 756-764. PubMed

23. Statistics Canada, *The Canadian Index of Multiple Deprivation: User Guide, 2021*. 2021: https://www150.statcan.gc.ca/n1/pub/45-20-0001/452000012023002-eng.htm.

24. Pampalon, R., Hamel D., Gamache P., et al., A deprivation index for health planning in Canada. *Chronic Dis Can*, 2009. 29(4): p. 178-91. PubMed

25. Charlson, M.E., Pompei P, Ales KL, et al., A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases*, 1987. 40(5): p. 373-383. PubMed

26. Marrie, R.A., Fisk J.D., Yu B.N., et al., Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. *BMC Neurology*, 2013. 13:16 p. 1-8. PubMed

27. Tonelli, M., Wiebe N., Fortin M., et al., Methods for identifying 30 chronic conditions: application to administrative data. *BMC Medical Informatics and Decision Making*, 2015. 15:31 p. 1-11. PubMed

28. Quan, H., Sundararajan V., Halfon P., et al., Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care*, 2005. 43(11): p. 1130-9. PubMed

29. Quan, H., Li B., Saunders L.D., et al., Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Services Research*, 2008. 43(4): p. 1424-41. PubMed

30. Tu, K., Mitiku T., Lee D.S., et al., Validation of physician billing and hospitalization data to identify patients with ischemic heart disease using data from the Electronic Medical Record Administrative data Linked Database (EMRALD). *Canadian Journal of Cardiology*, 2010. 26(7): p. e225-8. PubMed

31. Canadian Stroke Best Practices Stroke Quality Advisory Committee, *Quality of stroke care in Canada: Stroke key quality indicators and stroke case definitions*, Toronto, ON: Heart and Stroke Foundation. 2016.

32. Doktorchik, C., Patten S., Eastwood C., et al., Validation of a case definition for depression in administrative data against primary chart data as a reference standard. *BMC Psychiatry*, 2019. 19(1):9 p. 2-8. PubMed

33. Alaghehbandan, R., Macdonald D, Barrett B, et al., Using administrative databases in the surveillance of depressive disorders--case definitions. *Population Health Management*, 2012. 15(6): p. 372-80. PubMed

34. Reid, A.Y., St Germaine-Smith C., Liu M., et al., Development and validation of a case definition for epilepsy for use with administrative health data. *Epilepsy Res*, 2012. 102(3): p. 173-9. PubMed

35. Laratta, C.R., Tsai W.H., Wick J., et al., Validity of administrative data for identification of obstructive sleep apnea. *Journal of Sleep Research*, 2017. 26(2): p. 132-138. PubMed

36. Boklage, S.H., Malangone-Monaco E, Lopez-Gonzalez L, et al., Statin utilization patterns and outcomes for patients with acute coronary syndrome during and following inpatient admissions. *Cardiovascular Drugs and Therapy*, 2018. 32: p. 273-280. PubMed

37. Kumar, A., Lutsey P.L., St Peter W.L., et al., Prescription patterns of P2Y12 inhibitors following revascularization in the United States: 2013–2018. *Clinical and translational science*, 2023. 16(10): p. 1886-1897. PubMed

38. Hwang, Y.J., Chang HY, Metkus T, et al., Risk of Major Bleeding Associated with Concomitant Direct-Acting Oral Anticoagulant and Clopidogrel Use: A Retrospective Cohort Study. *Drug Safety*, 2024. 47(3): p. 251-260. PubMed

Appendix 1: Results Summary Templates

List of Mock Result Tables and Figures

Table 5: Annual Incidence and Prevalence of CGRP Inhibitor Use in Province/US, 2018 to 2022[a]

User category	2018	2019	2020	2021	2022
Incidence					
Overall, n (rate per 100,000 inhabitants/ enrollees)	To be completed	To be completed	To be completed	To be completed	To be completed
By product, n (% of CGRP new users)					
erenumab	To be completed	To be completed	To be completed	To be completed	To be completed
galcanezumab	To be completed	To be completed	To be completed	To be completed	To be completed
fremanezumab	To be completed	To be completed	To be completed	To be completed	To be completed
eptinezumab	To be completed	To be completed	To be completed	To be completed	To be completed
atopegant	To be completed	To be completed	To be completed	To be completed	To be completed
rimegepant	To be completed	To be completed	To be completed	US only	US only

User category	2018	2019	2020	2021	2022
By age, n (rate per 100,000 inhabitants/ enrollees)					
18 to 44	To be completed	To be completed	To be completed	To be completed	To be completed
45 to 64	To be completed	To be completed	To be completed	To be completed	To be completed
65+	To be completed	To be completed	To be completed	To be completed	To be completed
By sex, n (rate per 100,000 inhabitants/ enrollees)					
Female	To be completed	To be completed	To be completed	To be completed	To be completed
Male	To be completed	To be completed	To be completed	To be completed	To be completed
Age- and sex-adjusted rate per 100,000 inhabitants	To be completed	To be completed	To be completed	To be completed	To be completed
Prevalence					
Overall, n (rate per 100,000 inhabitants/ enrollees)	To be completed	To be completed	To be completed	To be completed	To be completed
By product, n (% of CGRP users)					
erenumab	To be completed	To be completed	To be completed	To be completed	To be completed
galcanezumab	To be completed	To be completed	To be completed	To be completed	To be completed
fremanezumab	To be completed	To be completed	To be completed	To be completed	To be completed
eptinezumab	To be completed	To be completed	To be completed	To be completed	To be completed
atopegant	To be completed	To be completed	To be completed	To be completed	To be completed
rimegepant	To be completed	To be completed	To be completed	US only	US only
By age, n (rate per 100,000 inhabitants/ enrollees)					
18 to 44	To be completed	To be completed	To be completed	To be completed	To be completed
45 to 64	To be completed	To be completed	To be completed	To be completed	To be completed
65+	To be completed	To be completed	To be completed	To be completed	To be completed

User category	2018	2019	2020	2021	2022
By sex, n (rate per 100,000 inhabitants/ enrollees)					
Female	To be completed	To be completed	To be completed	To be completed	To be completed
Male	To be completed	To be completed	To be completed	To be completed	To be completed
Age- and sex-adjusted rate per 100,000 inhabitants	To be completed	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide.

[a]Calendar year is used for US and fiscal year is used for Canada.

Table 6: Treatment Patterns of CGRP Inhibitors, 2018 to 2023

Treatment event	Initial year	Over 2-year follow-up	Over 3-year follow-up	Over 4-year follow-up
N =	To be completed	To be completed	To be completed	To be completed
Switching from a CGRP inhibitor to another CGRP inhibitor, n (%)				
Overall	To be completed	To be completed	To be completed	To be completed
By initial CGRP inhibitor product type	To be completed	To be completed	To be completed	To be completed
Switching from a CGRP inhibitor to Botulinum toxin injection, n (%)	To be completed	To be completed	To be completed	To be completed
Switching from a CGRP inhibitor to nonspecific prophylactic treatment, n (%)	To be completed	To be completed	To be completed	To be completed
Concomitant CGRP inhibitor treatment and Botulinum toxin injection, n (%)	To be completed	To be completed	To be completed	To be completed
Concomitant CGRP inhibitor treatment and nonspecific prophylactic treatment, n (%)	To be completed	To be completed	To be completed	To be completed
Treatment break, n (%)	To be completed	To be completed	To be completed	To be completed
Discontinuation, n (%)	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide.

Note: Treatment pattern (1-year follow-up) according to initial CGRP inhibitor (US only).

Table 7: Longitudinal Treatment Patterns of CGRP Inhibitors, 2018 to 2023

Initial year	Initial CGRP				
	Eremumab	Galcanezumab	Fremanezumab	Eptinezumab	Atopegant
N =	To be completed	To be completed	To be completed	To be completed	To be completed
Switching to a subsequent CGRP inhibitor, n (%)					
Overall	To be completed	To be completed	To be completed	To be completed	To be completed
By product type					

Initial year	Initial CGRP				
	Eremumab	Galcanezumab	Fremanezumab	Eptinezumab	Atopegant
Erenumab	—	To be completed	To be completed	To be completed	To be completed
Galcanezumab	To be completed	—	To be completed	To be completed	To be completed
Fremanezumab	To be completed	To be completed	—	To be completed	To be completed
Eptinezumab	To be completed	To be completed	To be completed	—	To be completed
Atogepant	To be completed	To be completed	To be completed	To be completed	—
Rimegepant	To be completed	To be completed	To be completed	To be completed	To be completed
Switching to Botulinum toxin injection, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed
Switching to nonspecific prophylactic treatment, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed
Concomitant treatment with Botulinum toxin injection, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed
Concomitant treatment with nonspecific prophylactic treatment, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed
Treatment break, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed
Discontinuation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed

— = empty cell.

Note: For Canadian data, we may not populate this table due to uncertain sample sizes and unnecessary complexity.

Table 8: Longitudinal Treatment Patterns of CGRP Inhibitors, 2018 to 2023

Treatment event	Time from CGRP inhibitor initiation (in days)		Probability of event	
	Mean (SE)	*Median*	At 1 year (95% CI)	At 2-year (95% CI)
First switch from an initial to a subsequent CGRP inhibitor	To be completed	To be completed	To be completed	To be completed
First switch from a CGRP inhibitor to Botulinum toxin injection	To be completed	To be completed	To be completed	To be completed
First treatment break	To be completed	To be completed	To be completed	To be completed
Discontinuation	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide; CI = confidence interval; SE = standard error.

Table 9: Migraine-Related Medication Use

Medication event/use	CGRP inhibitor users		CGRP inhibitor switchers		CGRP inhibitor discontinuers	
	1-year preindex	1-year postindex	1-year preindex	1-year postindex	1-year preindex	1-year postindex
Any migraine-related medication						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Acute rescue medications	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Overall						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of days supplied	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of classes dispensed, n (%)						
1	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
≥ 3	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Nonspecific						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
By class, n (%)						
NSAIDs	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Opioids	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-specific						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
By class, n (%)						
Triptans	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

Medication event/use	CGRP inhibitor users		CGRP inhibitor switchers		CGRP inhibitor discontinuers	
	1-year preindex	1-year postindex	1-year preindex	1-year postindex	1-year preindex	1-year postindex
Ergots	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Ditans	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Rescue medications dispensed during CGRP inhibitor use, n (%)						
Had ≥ 1 dispensation	NA	To be completed	To be completed	To be completed	To be completed	To be completed
By class						
Had ≥ 1 dispensation of nonspecific rescue medications	NA	To be completed	To be completed	To be completed	To be completed	To be completed
Had ≥ 1 dispensation of migraine-specific medications						
Triptans	NA	To be completed	To be completed	To be completed	To be completed	To be completed
Ergots	NA	To be completed	To be completed	To be completed	To be completed	To be completed
Ditans	NA	To be completed	To be completed	To be completed	To be completed	To be completed
Prophylactic medications						
Overall						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Nonspecific						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of days supplied	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of classes dispensed, n (%)						
1	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

Medication event/use	CGRP inhibitor users		CGRP inhibitor switchers		CGRP inhibitor discontinuers	
	1-year preindex	1-year postindex	1-year preindex	1-year postindex	1-year preindex	1-year postindex
≥ 3	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
By class						
Antidepressants	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Antiepileptics	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Antihistamines	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Antihypertensives	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Calcium antagonist	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Botulinum toxin						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of injections	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide; Q1,Q3 = quarter 1 and quarter 3 values; NA = not applicable; SD = standard deviation.

Table 10: Migraine-Related Medication Use by CGRP Inhibitor Type During Initial Year

Medication event/use	Initial CGRP[a]					
	Eremumab	Galcanezumab	Fremanezumab	Eptinezumab	Atopegant	Rime
Rescue medications dispensed during CGRP inhibitor use, n (%)						
Had ≥ 1 dispensation	NA	To be completed	To be completed	To be completed	To be completed	To be completed
By class						
Had ≥ 1 dispensation of nonspecific rescue medications	NA	To be completed	To be completed	To be completed	To be completed	To be completed

Medication event/ use	Initial CGRP[a]					
	Eremumab	Galcanezumab	Fremanezumab	Eptinezumab	Atopegant	Rime
Had ≥ 1 dispensation of migraine-specific medications	NA	To be completed	To be completed	To be completed	To be completed	To be completed
Triptans	NA	To be completed	To be completed	To be completed	To be completed	To be completed
Ergots	NA	To be completed	To be completed	To be completed	To be completed	To be completed
Ditans	NA	To be completed	To be completed	To be completed	To be completed	To be completed
Prophylactic medications						
Overall						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Nonspecific						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of days supplied	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of classes dispensed, n (%)						
1	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
≥ 3	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
By class						
Antidepressants	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Antiepileptics	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Antihistamines	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

Medication event/ use	Initial CGRP[a]					
	Eremumab	Galcanezumab	Fremanezumab	Eptinezumab	Atopegant	Rime
Antihypertensives	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Calcium antagonist	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Botulinum toxin						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of injections						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide; NA = not applicable; Q1,Q3 = quarter 1 and quarter 3 values; SD = standard deviation.

[a]US only. For Canadian data, we may not populate this table due to uncertain sample sizes and unnecessary complexity.

Table 11: Sociodemographic and Clinical Characteristics

Characteristics	CGRP inhibitor users	CGRP inhibitor switchers	CGRP discontinuers
Demographic			
Age (years)			
Mean (SD)	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed
Age (years): n (%)			
18 to 44	To be completed	To be completed	To be completed
45 to 64	To be completed	To be completed	To be completed
65+	To be completed	To be completed	To be completed
Sex: n (%)			
Female	To be completed	To be completed	To be completed
Male	To be completed	To be completed	To be completed
Residence location: n (%)			
Urban	To be completed	To be completed	To be completed
Rural	To be completed	To be completed	To be completed
Socioeconomic, n (%)			
Residential instability			
1 (most well off)	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed

Characteristics	CGRP inhibitor users	CGRP inhibitor switchers	CGRP discontinuers
3	To be completed	To be completed	To be completed
4	To be completed	To be completed	To be completed
5 (most deprived)	To be completed	To be completed	To be completed
Unknown	To be completed	To be completed	To be completed
Economic dependency			
1 (most well off)	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed
3	To be completed	To be completed	To be completed
4	To be completed	To be completed	To be completed
5 (most deprived)	To be completed	To be completed	To be completed
Unknown	To be completed	To be completed	To be completed
Situational vulnerability			
1 (most well off)	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed
3	To be completed	To be completed	To be completed
4	To be completed	To be completed	To be completed
5 (most deprived)	To be completed	To be completed	To be completed
Unknown	To be completed	To be completed	To be completed
Ethnocultural composition			
1 (most well off)	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed
3	To be completed	To be completed	To be completed
4	To be completed	To be completed	To be completed
5 (most deprived)	To be completed	To be completed	To be completed
Unknown	To be completed	To be completed	To be completed
Comorbidities			
Charlson Comorbidity Index			
Mean (SD)	To be completed	To be completed	To be completed
Median; min, max	To be completed	To be completed	To be completed
Category, n (%)			
0: no comorbid condition	To be completed	To be completed	To be completed
1 to 2: mild comorbidity	To be completed	To be completed	To be completed
3 to 4: moderate comorbidity	To be completed	To be completed	To be completed
≥ 5: severe comorbidity	To be completed	To be completed	To be completed

Characteristics	CGRP inhibitor users	CGRP inhibitor switchers	CGRP discontinuers
Comorbid condition, n (%)			
Cardiovascular disease	To be completed	To be completed	To be completed
Depression	To be completed	To be completed	To be completed
Anxiety	To be completed	To be completed	To be completed
Asthma	To be completed	To be completed	To be completed
Epilepsy	To be completed	To be completed	To be completed
Hypertension	To be completed	To be completed	To be completed
Obstructive sleep apnea	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide; Q1,Q3 = quarter 1 and quarter 3 values; SD = standard deviation.

Table 12: Premigraine- and Postmigraine-Related Health Care Encounters

Health care encounter	CGRP inhibitor users		CGRP inhibitor switchers		CGRP inhibitor discontinuers	
	One-year preindex	One-year postindex	One-year preindex	One-year postindex	One-year preindex	One-year postindex
Any migraine-related health care encounter						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of visits						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-related hospitalizations						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Length of hospital stay (day)						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-related ED visits						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of visits						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

Health care encounter	CGRP inhibitor users		CGRP inhibitor switchers		CGRP inhibitor discontinuers	
	One-year preindex	One-year postindex	One-year preindex	One-year postindex	One-year preindex	One-year postindex
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-related ambulatory care visits						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of visits						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-related physician visits						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of visits						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide; Q1,Q3 = quarter 1 and quarter 3 values; SD = standard deviation.

Table 13: Postmigraine-Related Health Care Encounters (US only[a])

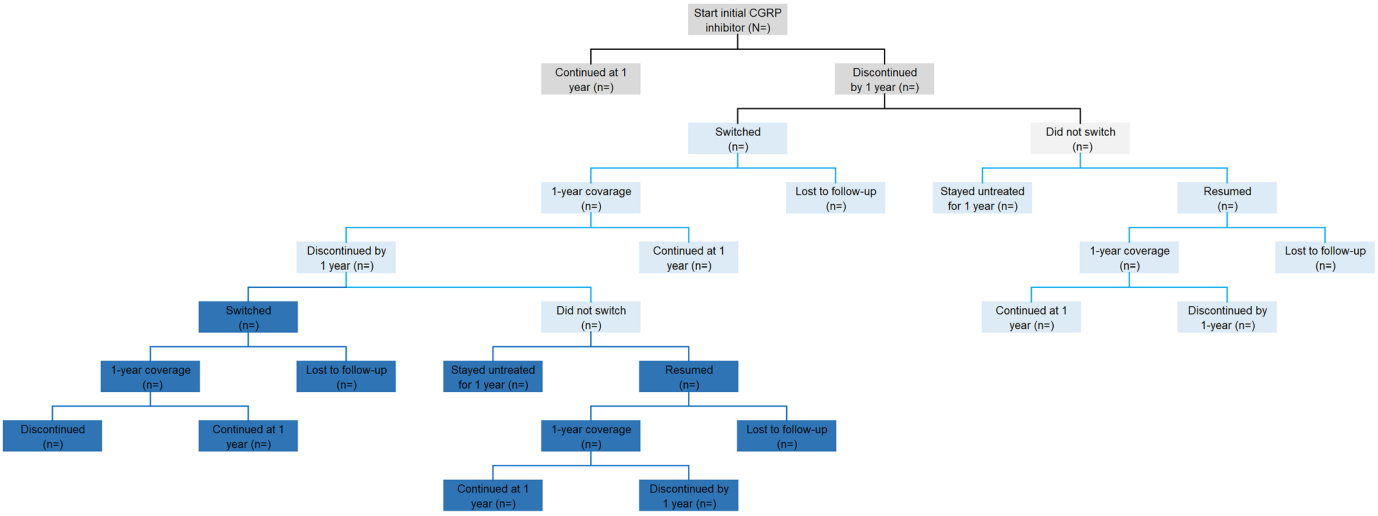
Health care encounter	Initial CGRP inhibitor					
	Eremumab	Galcanezumab	Fremanezumab	Eptinezumab	Atopegant	Rimegepant
Any migraine-related health care encounter						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of visits						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-related hospitalizations						

Health care encounter	Initial CGRP inhibitor					
	Eremumab	Galcanezumab	Fremanezumab	Eptinezumab	Atopegant	Rimegepant
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Length of hospital stay (day)						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-related ED visits						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of visits						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-related ambulatory care visits						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of visits						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-related physician visits						
Had ≥ 1 visit, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of visits						
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide; Q1,Q3 = quarter 1 and quarter 3 values; SD = standard deviation.

[a]For Canadian data, we may not populate this table due to uncertain sample sizes and unnecessary complexity.

Figure 3: Diagram for Treatment Pattern Pathways



Appendix 2: Additional/Supporting Information

Table 14: Migraine-Related Medications

Drug class	Therapy	ATC code	DIN code (Canada)	NDC (unless otherwise specified; e.g., HCPCS) (US)[a]
CGRP preventive				
Monoclonal antibody CGRP (mAb CGRP)	erenumab	N02CD01	02479613, 02487306	55513084001, 55513084100, 55513084101, 55513084301, 55513084201, 55513084300, 55513084002, 55513084102
	galcanezumab	N02CD02	02491060, 02491087, 02505134	00002237727, 00002143601, 00002143627, 00002237711, 00002143611, 00002311501, 00002143661, 00002237701, 00002311509
	fremanezumab	N02CD03	02497859, 02509474	51759020411, 51759020222, 51759020410, 51759020211, 51759020210
	eptinezumab	N02CD05	02510839	67386013051, 67386013091 HCPCS: C9063, J3032
Gepants (CGRP antagonist)	atogepant	N02CD07	02533979, 02533987, 02533995	00074709530, 00074709430, 00074709604, 00074709404, 00074709630
	rimegepant	NA	NA	72618300002, 72618300101, 72618300102
Acute rescue medications				
Nonspecific				
NSAIDs	diclofenac	M01AB05	excluding rectal route of administration: 02231506, 02231508, 02261928, 02261936, 00632732, 00632724	Generic name (oral, EV, IM, if applicable)
	ibuprofen	M01AE01	NA	Generic name (oral, EV, IM, if applicable)
	naproxen	M01AE02	excluding rectal route of administration: 02017237	Generic name (oral, EV, IM, if applicable)
	ketorolac	M01AB15	NA	Generic name (oral, EV, IM, if applicable)
Opioids	Any (including codeine, hydromorphone, morphine, oxycodone,	N02A	NA	Generic name (oral, EV, IM, if applicable)

Drug class	Therapy	ATC code	DIN code (Canada)	NDC (unless otherwise specified; e.g., HCPCS) (US)[a]
	tramadol, burprenorphine)			
Migraine-specific				
Triptans	almotriptan	N02CC05	NA	Generic name (oral, EV, IM, if applicable)
	eletriptan	N02CC06	NA	Generic name (oral, EV, IM, if applicable)
	frovatriptan	N02CC07	NA	Generic name (oral, EV, IM, if applicable)
	naratriptan	N02CC02	NA	Generic name (oral, EV, IM, if applicable)
	rizatriptan	N02CC04	NA	Generic name (oral, EV, IM, if applicable)
	sumatriptan (nasal spray, oral, subcutaneous)	N02CC01	NA	Generic name (oral, EV, IM, nasal, if applicable)
	zolmitriptan (oral, nasal spray)	N02CC03	NA	Generic name (oral, EV, IM, nasal, if applicable)
Ergots	dihydroergotamine (DHE) (nasal spray) / DHE mesylate (IV, intramuscular, subcutaneous)	N02CA01	NA	Generic name (oral, EV, IM, nasal, if applicable)
Gepants (CGRP antagonist)	ubrogepant (oral)	N02CD04	02532530, 02532581	00023649802, 00023650101, 00023650130, 00023649830, 00023650102, 00023649804, 00023649801, 00023650110, 00023649810, 00023649816, 00023650116
	zavegepant (nasal spray)	NA	NA	00069350001, 00069350002
	rimegepant	NA	NA	72618300002, 72618300101, 72618300102
Ditans	lasmitidan (oral use)	NA	NA	00002431208, 00002431261, 00002431262, 00002449108, 00002449161, 00002449162
Other preventive				
Nonspecific				
Antidepressants	amitriptyline (tricyclic)	N06AA09	NA	Generic name (oral, EV, IM, if applicable)
	nortriptyline (tricyclic)	N06AA10	NA	Generic name (oral, EV, IM, if applicable)

Drug class	Therapy	ATC code	DIN code (Canada)	NDC (unless otherwise specified; e.g., HCPCS) (US)[a]
	desvenlafaxine (SNRI)	N06AX23	NA	Generic name (oral, EV, IM, if applicable)
	venlafaxine (SNRI)	N06AX16	NA	Generic name (oral, EV, IM, if applicable)
Antiepileptics	gabapentin	N03AX12	NA	Generic name (oral, EV, IM, if applicable)
	topiramate	N03AX11	NA	Generic name (oral, EV, IM, if applicable)
	lamotrigine	N03AX09	NA	Generic name (oral, EV, IM, if applicable)
	divalproex sodium / sodium valproate	N03AG01	NA	Generic name (oral, EV, IM, if applicable)
Antihypertensives	atenolol (beta-blocker)	C07AB03	NA	Generic name (oral, EV, IM, if applicable)
	metoprolol tartrate (beta-blocker)	C07AB02	NA	Generic name (oral, EV, IM, if applicable)
	nadolol (beta-blocker)	C07AA12	NA	Generic name (oral, EV, IM, if applicable)
	propranolol (beta-blocker)	C07AA05	NA	Generic name (oral, EV, IM, if applicable)
	timolol (beta-blocker)	C07AA06	NA	Generic name (oral, EV, IM, if applicable)
	candesartan (angiotensin II antagonist)	C09CA06	NA	Generic name (oral, EV, IM, if applicable)
	verapamil	C08DA01	NA	Generic name (oral, EV, IM, if applicable)
Calcium antagonist	flunarizine	N07CA03	NA	Generic name (oral, EV, IM, if applicable)
Migraine-specific				
Botulinum A toxin	botulinum A toxin	—	01981501, 02456117, 02460203, 02324032, 02371081 CLM procedure code 13.59O	54868412300; 00023114501; 00023114502; 00023392102; 00023392103; 00023391950; 00023923201 HCPCS: J0585
Serotonin and tryptamine antagonist	pizotifen	N02CX01	NA	NA

— = empty cell, ATC = anatomical therapeutic chemical; DIN = drug identification number; HCPCS = Healthcare Common Procedure Coding System; NA = not applicable; NDC = National Drug Code; NSAIDs = nonsteroidal anti-inflammatory drugs; SNRI = serotonin–norepinephrine reuptake inhibitor.

[a]Source: https://nctr-crs.fda.gov/fdalabel/ui/search

Table 15: Diseases, and Their Associated Codes and Weights Included in the Charlson Comorbidity Index

Disease	ICD-9-CM codes	ICD-10-CA codes	ICD-10-CM codes	Weight
Myocardial infarction	410, 412	I21, I22, I25.2	I21, I22, I25.2	1
Congestive heart failure	398, 402, 425, 428	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0	I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0	1
Peripheral vascular disease	440, 441, 443, 447, 557	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.1, I79.8, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	430, 431, 432, 433, 434, 435, 436, 437, 438	G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H34.0	G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, H34.0-H34.2	1
Dementia	290, 294, 331	F00, F01, F02, F03, G30, F05.1, G31.1	F01, F02, F03, F04, F05, G30, F06.1, F06.8, G13.2, G13.8, G30, G31.0-G31.2, G91.4, R41.81, R54	1
Chronic pulmonary disease	416, 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, I27.8, I27.9, J68.4, J70.1, J70.3	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68.4, J70.1, J70.3	1
Connective tissue disease	446, 710, 714, 725	M05, M32, M33, M34, M06, M31.5, M35.1, M35.3, M36.0	M05, M06, M31.5, M32, M33, M34, M35.1, M35.3, M36.0	1
Peptic ulcer disease	531, 532, 533, 534	K25, K26, K27, K28	K25, K26, K27, K28	1
Mild liver disease	070, 570, 571, 573	B18, K73, K74, K70.0, K70.1, K70.2, K70.3, K70.9, K71.7, K71.3, K71.4, K71.5, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4	B18, K73, K74, K70.0, K70.1, K70.2, K70.3, K70.9, K71.7, K71.3, K71.4, K71.5, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4	1
Moderate/severe liver disease	456, 572	K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7, I85.0, I85.9, I86.4, I98.2	K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7, I85.0, I86.4	3
Diabetes (without complication)	250	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	E08-E11, E13 with E**.0x, E**.1x, E**.6x, E**.8x, E**.9x	1
Diabetes (with complication)	250	E10.2, E10.3, E10.4, E10.5, E10.7, E11.2, E11.3, E11.4, E11.5, E11.7, E12.2, E12.3, E12.4, E12.5, E12.7, E13.2, E13.3, E13.4, E13.5, E13.7,	E08-E11, E13 with E**.2, E**.3, E**.4, E**.5	2

Disease	ICD-9-CM codes	ICD-10-CA codes	ICD-10-CM codes	Weight
		E14.2, E14.3, E14.4, E14.5, E14.7		
Hemiplegia and paraplegia	334, 342, 343, 344	G81, G82, G04.1, G11.4, G80.1, G80.2, G83.0, G83.1, G83.2, G83.3, G83.4, G83.9	G81, G82, G04.1, G11.4, G80.0-G80.2, G83	2
Moderate or severe renal disease	403, 582, 583, 585, 586, 588, V56	N18, N19, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N25.0, I12.0, I13.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2	N18.1-N18.6, N18.9, N19, N03, N05, I12.0, I12.9, I13.0, I13.2, I13.10, I13.11, N25, Z49, Z94.0, Z99.2	2
Cancer	140 to 165, 170 to 172, 174 to 176, 179 to 195, 200 to 208, 238	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90- C97	C00-C29, C30-C34, C37-C41, C43, C45-C58, C60-C63, C76, C80.1, C81-C85, C88, C90-C99	2
Metastatic Carcinoma	196, 197, 198, 199	C77, C78, C79, C80	C77-C79, C80.0, C80.2	6
HIV/AIDS	042, 043, 044	B20, B21, B22, B24	B20	6

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CA = International Classification of Diseases, 10th Revision, Canadian Enhancement; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification.

Note: To be considered as having 1 of the listed diseases, an individual must have ≥ 1 hospitalization (associated ICD-10-CA code listed in any diagnostic field) or ≥ 2 physician claims (associated ICD-9-CM codes listed in any diagnostic field) of the corresponding ICD within ≤ 1-years. For US, ICD-10-CM is used for inpatient and outpatient claims.

Table 16: Case Definitions Using Administrative Data to Identify Comorbid Conditions, Canada

Comorbidity	Algorithm	ICD-9-CM codes	ICD-10-CA codes	Other codes	Source
Anxiety	1 hospitalization or 2 claims OR 1 claim and 2 prescription dispensations in ≤ 2 years	300.0, 300.2	F40, F41	*ATC codes:* N05AB06, N05AB12	26
Asthma	1 hospitalization or 3 ambulatory care visits in ≤ 2 years	NA	J45	NA	27
Cardiovascular disease (any of the following)					
Atrial fibrillation	1 hospitalization or 2 claims in ≤ 2 years	427.3	I48.0	NA	27-31
Chronic heart failure	1 hospitalization or 2 claims in ≤ 2 years	398.9, 402, 404, 425.4 to 425.9, 428	I09.9, I25.5, I42.0, I42.5–I42.9, I43, I50	NA	—
Coronary artery disease	1 hospitalization or 1 ambulatory care visit or 1 procedure or 2 claims in ≤ 2 years	410 to 413	I20–I25	*Procedure codes:* 1.IJ.57.GQ, 1.IJ.50, 1.IL.35, 1.IJ.76	—

Comorbidity	Algorithm	ICD-9-CM codes	ICD-10-CA codes	Other codes	Source
Peripheral artery disease	1 hospitalization or 1 ambulatory care visit or 1 claim in any years	440.2	I70.2	NA	—
Stroke	1 most responsible stroke hospitalization or emergency department OR 1 other diagnosis stroke and 1 most responsible z-code hospitalization or ambulatory care* in any years	NA	G45 (excluding subcode G45.4), H34.0, H34.1, I60, I61, I62.9, I63, I64, I67.6; Z50 (excluding subcodes Z50.2, Z50.3, Z50.4), Z54.8, Z54.9, *only Z51.5 applies to ambulatory care	NA	—
Depression	1 hospitalization or 2 claims in ≤ 2 years	300.4, 311	F32-F33, F34.1	NA	32, 33
Epilepsy	1 hospitalization or 2 claims in ≤ 2 years	345	G40, G41	NA	34
Hypertension	1 hospitalization or 2 claims in ≤ 2 years	401 to 405	I10–I13, I15	NA	27
Obstructive sleep apnea	1 hospitalization or 2 claims in ≤ 2 years	780.5	G47.3	NA	35

— = empty cell, ATC = Atomical Therapeutic Chemical; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CA = International Classification of Diseases, 10th Revision, Canadian Enhancement; NA = not applicable.

Table 17: Case Definitions Using Administrative Data to Identify Comorbid Conditions, US

Comorbidity	Algorithm	ICD-10-CM codes	Other codes	Source
Anxiety	1 hospitalization or 2 claims OR 1 claim and 2 prescription dispensations in ≤ 2 years	F40, F41	Generic name: Lorazepam, alprazolam (oral, EV, IM, if applicable)	—
Asthma	1 hospitalization or 3 ambulatory care visits in ≤ 2 years	J45	NA	—
Cardiovascular disease (any of the following)		—	ICD-9-PCS: 0066, 3601, 3602, 3603, 3605, 3606, 3607, 3609, 361, 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617, 3619, 362, 0210 ICD-10-PCS: 0270346, 027034Z, 0270356, 027035Z, 0270366, 027036Z, 0270376, 027037Z, 02703D6, 02703DZ, 02703ZZ, 0270046, 0271346, 027134Z, 0271356, 027135Z, 0271366, 027136Z, 0271376, 027137Z, 02713D6, 02713DZ, 02714E6, 02713EZ, 02714EZ, 02723FZ, 02733GZ, 02713E6, 02723F6, 02733G6, 0272366, 0273376,	—

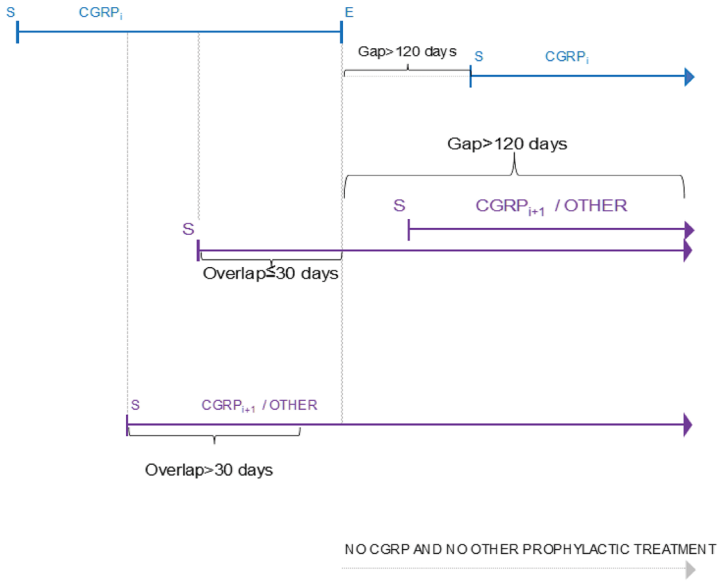
Comorbidity	Algorithm	ICD-10-CM codes	Other codes	Source
			027236Z, 027337Z, 02C03ZZ, 02C13ZZ, 02C23ZZ, 02C33ZZ, 02C03Z6, 02C13Z6, 02C23Z6, 02C33Z6, 021009W, 02100A3, 02100A8, 02100A9, 02100AC, 02100AF, 02100AW CPT: 33510 to 33514, 33516 to 33519, 33520 to 33523, 33530, 33533 to 33536, 33572, 33545, 37184, 37185, 37186, 37187, 37188, 92920 to 92921, 92924 to 92925, 92928 to 92929, 92933 to 92934, 92937 to 92938, 92941, 92943 to 92944, 92973, 92980 to 92982, 92984, 92995 to 92996 HCPCS: C9600 - C9606, G0290 - G0291	
Atrial fibrillation	1 hospitalization or 2 claims in ≤ 2 years	I48.0		36-38
Chronic heart failure	1 hospitalization or 2 claims in ≤ 2 years	I09.9, I25.5, I42.0, I42.5–I42.9, I43, I50		—
Coronary artery disease	1 hospitalization or 1 ambulatory care visit or 1 procedure or 2 claims in ≤ 2 years	I20–I25		—
Peripheral artery disease	1 hospitalization or 1 ambulatory care visit or 1 claim in any years	I70.2		—
Stroke	1 most responsible stroke hospitalization or emergency department OR 1 other diagnosis stroke and 1 most responsible z-code hospitalization or ambulatory care* in any years	G45 (excluding subcode G45.4), H34.0, H34.1, I60, I61, I62.9, I63, I64, I67.6; Z50 (excluding subcodes Z50.2, Z50.3, Z50.4), Z54.8, Z54.9, *only Z51.5 applies to ambulatory care		—
Depression	1 hospitalization or 2 claims in ≤ 2 years	F32-F33, F34.1	NA	32, 33
Epilepsy	1 hospitalization or 2 claims in ≤ 2 years	G40, G41	NA	34
Hypertension	1 hospitalization or 2 claims in ≤ 2 years	I10–I13, I15	NA	27
Obstructive sleep apnea	1 hospitalization or 2 claims in ≤ 2 years	G47.3	NA	35

— = empty cell, ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; NA = not applicable.

Figure 4: Treatment Patterns Definitions Using Prescription Drug Dispensing/Claim Data

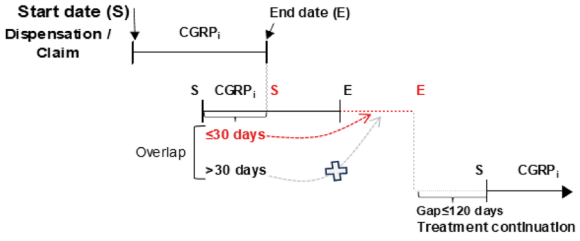
TREATMENT PATTERNS

Treatment break	Dispensation / Claim [from Start date (S) to End date(E)] >120 consecutive days without any CGRP inhibitor or other migraine prophylactic treatment, and followed by the resumption of previously dispensed CGRP inhibitor.
Switching to another CGRP inhibitor / other migraine prophylactic treatment	Starting another CGRP inhibitor / other migraine prophylactic treatment either after stopping (for >120 days) the previously dispensed CGRP inhibitor or within 30 consecutive days before the stopping date (i.e., considered an early switch before exhausting the supply of the previously dispensed treatment).
Concurrent use with another CGRP inhibitor / other prophylactic treatment	Starting a new CGRP inhibitor / other migraine prophylactic treatment while overlapping with the previously dispensed CGRP inhibitor treatment for >30 consecutive days (i.e., to rule out early refill or early switching)
Treatment discontinuation	>120 consecutive days without any CGRP inhibitor or other migraine prophylactic treatment, and does not qualify for switching / treatment break



Other definitions and notes

"For each CGRP inhibitor dispensation or claim:
Start date = Dispensation date
End date = Dispensation date + number of days supplied / typical treatment effect duration for the supply
For injection products, the number of days supplied is recorded as the typical treatment effect duration for the supply (e.g., the typical treatment effect duration for each dose multiplied by the number of doses supplied), or as the quantity of doses (sometimes). For example, the number of days supplied can be recorded as either 28/30 or 1 if 1 dose of erenumab is supplied; or recorded as either 90 or 3 if 3 doses of erenumab are supplied. Details regarding the typical treatment effect duration for each dose are as follows: erenumab with 70 or 140 mg/dose for 30 days; galcanezumab with loading dose of 240 mg or monthly dose of 120 mg for 30 days; fremanezumab with 225 mg/dose for 30 days; fremanezumab with 675 mg/dose for 90 days; eptinezumab with 100 mg/dose for 90 days; atogepant with 10, 30, or 60 mg/dose for 1 day; and preventive rimegepant with 75 mg/dose for 2 days and/or the number of doses per month ≤18 [US only, as of May 27, 2021 - differentiated from rescue rimegepant (the average daily dose =75mg and/or the number of doses per month ≤9)].
On average, a 3-month supply is typical, but this can vary depending on the doctor and frequency of follow-up visits. We assume that the maximum supply prescribed for CGRP inhibitors for migraine prophylactic treatment is 6 months. Therefore:
If the number of days supplied ≤7, then End date = (Dispensation date + the number of days supplied*typical treatment effect duration for each day supplied); for the first dispensation of galcanezumab only: if 2≤ number of days supplied ≤7, then End date = [Dispensation date + 30 + (the number of days supplied - 2)*30], if number of days supplied =1, then End date = [Dispensation date + 30]. If the number of days



Appendix 3: Canadian Institute for Health Information Data Analysis

The Canadian Institute for Health Information will conduct analyses for British Columbia, Manitoba, and Saskatchewan data used to generate the following tables for all recipients of CGRPs regardless of payment source and age.

Table 18: Annual Incidence and Prevalence of CGRP Inhibitor Use in Province, 2018 to 2022[a]

User category	2018	2019	2020	2021	2022
Incidence					
Overall, n (rate per 100,000 inhabitants)	To be completed	To be completed	To be completed	To be completed	To be completed
By product, n (% of CGRP new users)					
erenumab	To be completed	To be completed	To be completed	To be completed	To be completed
galcanezumab	To be completed	To be completed	To be completed	To be completed	To be completed
fremanezumab	To be completed	To be completed	To be completed	To be completed	To be completed
eptinezumab	To be completed	To be completed	To be completed	To be completed	To be completed
atopegant	To be completed	To be completed	To be completed	To be completed	To be completed
By age, n (rate per 100,000 inhabitants)					
18 to 44	To be completed	To be completed	To be completed	To be completed	To be completed
45 to 64	To be completed	To be completed	To be completed	To be completed	To be completed
65+	To be completed	To be completed	To be completed	To be completed	To be completed
By sex, n (rate per 100,000 inhabitants)					
Female	To be completed	To be completed	To be completed	To be completed	To be completed
Male	To be completed	To be completed	To be completed	To be completed	To be completed
Age- and sex-adjusted rate per 100,000 inhabitants	To be completed	To be completed	To be completed	To be completed	To be completed
Prevalence					
Overall, n (rate per 100,000 inhabitants)	To be completed	To be completed	To be completed	To be completed	To be completed
By product, n (% of CGRP users)					

User category	2018	2019	2020	2021	2022
erenumab	To be completed	To be completed	To be completed	To be completed	To be completed
galcanezumab	To be completed	To be completed	To be completed	To be completed	To be completed
fremanezumab	To be completed	To be completed	To be completed	To be completed	To be completed
eptinezumab	To be completed	To be completed	To be completed	To be completed	To be completed
atopegant	To be completed	To be completed	To be completed	To be completed	To be completed
By age, n (rate per 100,000 inhabitants)					
18 to 44	To be completed	To be completed	To be completed	To be completed	To be completed
45 to 64	To be completed	To be completed	To be completed	To be completed	To be completed
65+	To be completed	To be completed	To be completed	To be completed	To be completed
By sex, n (rate per 100,000 inhabitants)					
Female	To be completed	To be completed	To be completed	To be completed	To be completed
Male	To be completed	To be completed	To be completed	To be completed	To be completed
Age- and sex-adjusted rate per 100,000 inhabitants	To be completed	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide.

[a]Fiscal year is used.

Table 19: Treatment Patterns of CGRP Inhibitors, 2018 to 2023

Treatment event	Initial year	Over 2-year follow-up	Over 3-year follow-up	Over 4-year follow-up
N =	To be completed	To be completed	To be completed	To be completed
Switching from a CGRP inhibitor to another CGRP inhibitor, n (%)				
Overall	To be completed	To be completed	To be completed	To be completed
By initial CGRP inhibitor product type	To be completed	To be completed	To be completed	To be completed
Switching from a CGRP inhibitor to Botulinum toxin injection, n (%)	To be completed	To be completed	To be completed	To be completed
Switching from a CGRP inhibitor to nonspecific prophylactic treatment, n (%)	To be completed	To be completed	To be completed	To be completed

Treatment event	Initial year	Over 2-year follow-up	Over 3-year follow-up	Over 4-year follow-up
Concomitant CGRP inhibitor treatment and Botulinum toxin injection, n (%)	To be completed	To be completed	To be completed	To be completed
Concomitant CGRP inhibitor treatment and nonspecific prophylactic treatment, n (%)	To be completed	To be completed	To be completed	To be completed
Treatment break, n (%)	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide.

Note: Reporting of longer follow-up times may be limited by lack of registration data.

Table 20: Migraine-Related Medication Use

Medication event/use	CGRP inhibitor users		CGRP inhibitor switchers		CGRP inhibitor discontinuers	
	One-year preindex	One-year postindex	One-year preindex	One-year postindex	One-year preindex	One-year postindex
Any migraine-related medication						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Acute rescue medications						
Overall						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of days supplied	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of classes dispensed, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
1	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
≥ 3	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Nonspecific						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

Medication event/use	CGRP inhibitor users		CGRP inhibitor switchers		CGRP inhibitor discontinuers	
	One-year preindex	One-year postindex	One-year preindex	One-year postindex	One-year preindex	One-year postindex
By class, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
NSAIDs	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Opioids	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Migraine-specific						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
By class, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Triptans	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Ergots	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Rescue medications dispensed during CGRP inhibitor use, n (%)						
Had ≥ 1 dispensation	NA	To be completed	To be completed	To be completed	To be completed	NA
By class						
Had ≥ 1 dispensation of nonspecific rescue medications	NA	To be completed	To be completed	To be completed	To be completed	NA
Had ≥ 1 dispensation of migraine-specific medications	NA	To be completed	To be completed	To be completed	To be completed	NA
Triptans	NA	To be completed	To be completed	To be completed	To be completed	NA
Ergots	NA	To be completed	To be completed	To be completed	To be completed	NA
Prophylactic medications						
Overall						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Nonspecific						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of days supplied	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

Medication event/use	CGRP inhibitor users		CGRP inhibitor switchers		CGRP inhibitor discontinuers	
	One-year preindex	One-year postindex	One-year preindex	One-year postindex	One-year preindex	One-year postindex
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1, Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of classes dispensed, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
1	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
2	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
≥ 3	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
By class						
Antidepressants	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Antiepileptics	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Antihypertensives	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Calcium antagonist	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Pizotifen	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Botulinum toxin						
Had ≥ 1 dispensation, n (%)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Number of injections	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Mean (SD)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed
Median (Q1,Q3)	To be completed	To be completed	To be completed	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide; Q1, Q3 = quarter 1 and quarter 3 values; NA = not applicable; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation.

Table 21: Sociodemographic Characteristics

Characteristics	CGRP inhibitor users	CGRP inhibitor switchers	CGRP discontinuers
Demographic			
Age (years)			
Mean (SD)	To be completed	To be completed	To be completed
Median (Q1, Q3)	To be completed	To be completed	To be completed
Age (years): n (%)			
18 to 44	To be completed	To be completed	To be completed
45 to 64	To be completed	To be completed	To be completed
65+	To be completed	To be completed	To be completed
Sex: n (%)			
Female	To be completed	To be completed	To be completed
Male	To be completed	To be completed	To be completed
Socioeconomic, n (%)			
Canadian Index of Multiple Deprivation	To be completed	To be completed	To be completed
Residence location: n (%)			
Urban	To be completed	To be completed	To be completed
Rural	To be completed	To be completed	To be completed

CGRP = calcitonin gene-related peptide; Q1, Q3 = quarter 1 and quarter 3 values; SD = standard deviation.

For more information on CoLab and its work, visit colab.cda-amc.ca.

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CDA-AMC is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with the Post-Market Drug Evaluation Program to produce credible and timely evidence on postmarket drug safety and effectiveness.