# Migraine:
## Understanding the Enigma of a Prevalent Neurological Disorder

INGENŪ CRO

# Introduction

**Migraine is not merely a headache; it is a sophisticated neurological condition that impacts millions worldwide, representing a significant challenge in both diagnosis and treatment.**

Today, the neurovascular model is at the forefront of migraine research. This model suggests that migraine is a result of complex interactions between neural and vascular components. The release of inflammatory substances around nerves and blood vessels in the brain is a critical factor. This understanding has paved the way for targeted treatments that have revolutionized patient care, offering new hope and improved outcomes.

The impact of migraine extends beyond the individual sufferer. It is a public health concern, affecting productivity and quality of life, and imposes a significant economic burden. In the United States alone, migraines account for billions of dollars in direct medical costs and lost productivity. This makes the condition not only a medical challenge but also a societal issue, demanding attention, and resources.

iNGENŪ CRO

# Book a Discovery Call to learn how iNGENū can deliver high-quality, cost-efficient, FDA-compliant research for your next clinical trial

## Why Choose iNGENū CRO?

iNGENū is the FDA-centric Australian CRO championing disruptive, innovative biotech firms. We are physician-led, providing access to the full spectrum of clinical and non-clinical research services.

**Local Trials, Global Approvals**

Australian expertise combined with direct FDA submission capabilities, offering a streamlined path for global approval.

**Disciplined, Cost-Efficient Execution**

Every dollar is strategically allocated, eliminating unnecessary costs while maintaining the highest quality.

**Australian Headquartered, Asia-Pacific Reach**

Access high-quality trials in the Asia-Pacific region, enhancing speed and scalability.

**Expertise From the Start**

Engage directly with our team of highly qualified doctors and PhD scientists from the outset.

**Ready to discuss your Clinical Trial?**
For further information on how iNGENū can assist you to conduct your clinical trial, book a Discovery Call with one of our Advisors.

# The Global and Diverse Epidemiology of Migraine

**The incidence of migraine highlights notable variations across age groups, racial and ethnic backgrounds, geographic locations, and genetic predispositions. These variations offer a unique opportunity for US based biotechs and researchers to explore tailored treatment strategies and personalized medicine approaches.**

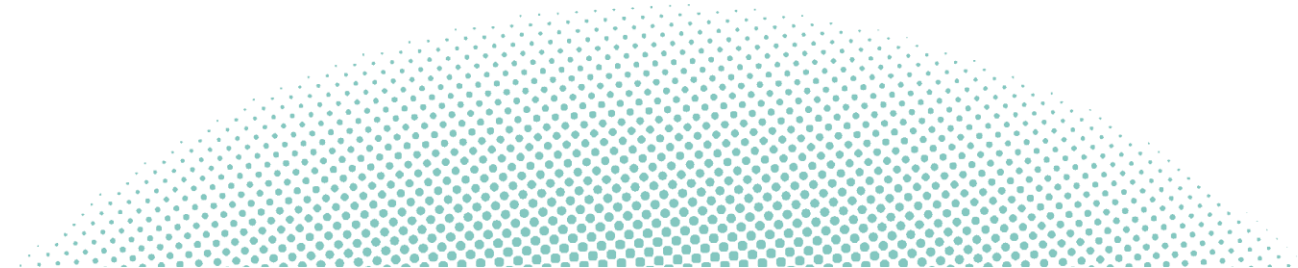
### Age:
Migraine most commonly affects individuals between the ages of 25 and 55, impacting their most productive years. This age-related prevalence underscores the need for early intervention and sustained management strategies.

### Gender:
Women are disproportionately affected, with hormonal factors playing a significant role. Understanding these gender-specific aspects is crucial for developing targeted therapies.

### Racial and Ethnic Disparities:
Prevalence and severity of migraine vary across racial and ethnic groups, indicating potential genetic and environmental influences. This diversity necessitates a more inclusive approach in clinical trials and research.

### Geographical Variations:
The prevalence of migraine also shows geographical variations, influenced by factors such as climate, lifestyle, and access to healthcare. These factors are vital in understanding the global burden of migraine and in designing international clinical studies.

### Genetic Predisposition:
Genetics play a significant role in migraine susceptibility, with family history being a strong risk factor. Research into genetic markers and their interaction with environmental factors can pave the way for groundbreaking treatments.



# Migraine Diagnosis – A Comparative Analysis

## ICD 11 vs. DSM 5: A Detailed Comparison

### Frequency and Duration:

ICD-11 requires a minimum of five attacks for diagnosis, with each lasting between 4-72 hours (about 3 days) if untreated.

DSM-5 criteria are similar but place greater emphasis on the patient's personal and occupational distress.

### Symptomatology:

Both ICD-11 and DSM-5 highlight symptoms like unilateral location, pulsating quality, moderate-to-severe pain intensity, aggravation by routine physical activity, nausea, and sensitivity to light and sound.

However, DSM-5 delves deeper into the psychological aspects, emphasizing the impact on the patient's daily functioning.

### Aura and Complications:

ICD-11 provides a more nuanced classification of migraine with aura and recognizes complications like status migrainosus.

DSM-5 is less detailed in this regard.

## The Evolution of Diagnostic Criteria

The diagnosis of migraine has undergone a significant transformation, marking the progress from a subjective understanding to a more evidence-based approach. The International Classification of Diseases, 11th Revision (ICD-11), and the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), are pivotal in this evolution.

The transition from ICD-10 to ICD-11 and DSM-IV to DSM-5 represents a shift towards a more patient-centric approach, recognizing the multifaceted nature of migraine. These changes reflect a growing understanding that migraine is not just a physical ailment but an interplay of neurological, psychological, and environmental factors.

NGENŪ CRO

# FDA-Approved Drugs for Migraine

| Drug Name | Year of Approval | Sponsor | Mechanism of Action | Therapeutic Effects |
|---|---|---|---|---|
| Sumatriptan (Imitrex) | 1991 | GlaxoSmithKline | Serotonin (5-HT1) receptor agonist, vasoconstrictor | Reduces acute migraine symptoms |
| Zolmitriptan (Zomig) | 1998 | AstraZeneca | Serotonin (5-HT1) receptor agonist | Treats acute migraine with or without aura |
| Topiramate (Topamax) | 2004 | Johnson & Johnson | Anticonvulsant, blocks sodium channels, increases GABA activity | Prevents migraine headaches |
| Botox (OnabotulinumtoxinA) | 2010 | Allergan | Neurotoxin, inhibits release of pain neurotransmitters | Prevents chronic migraines |
| Erenumab (Aimovig) | 2018 | Amgen | CGRP receptor antagonist | Preventive treatment for migraine |
| Fremanezumab (Ajovy) | 2018 | Teva Pharmaceutical | CGRP monoclonal antibody | Preventive treatment for chronic and episodic migraine |
| Galcanezumab (Emgality) | 2018 | Eli Lilly | CGRP monoclonal antibody | Preventive treatment for migraine |
| Ubrogepant (Ubrelvy) | 2020 | Allergan | CGRP receptor antagonist | Acute treatment of migraine with or without aura |
| Rimegepant (Nurtec ODT) | 2020 | Biohaven Pharmaceuticals | CGRP receptor antagonist | Acute treatment of migraine and preventive treatment |

# Pivotal Endpoints

## The Essence of Pivotal Endpoints in Migraine Research

Pivotal endpoints in clinical trials are critical in determining the efficacy and safety of new migraine treatments. As an Australian CRO with a global perspective, we understand the importance of these endpoints, especially for US-based biotechs and scientists.

## Correlation to Patient Outcomes

The goal of these trials is to improve patient outcomes. This requires a focus not just on the physiological aspects of migraine relief but also on the overall quality of life improvements. Endpoints must therefore be relevant to daily living and long-term health.

## Common Pivotal Endpoints in Migraine Trials

**Reduction in Monthly Migraine Days:**

A primary measure of efficacy, assessing the decrease in the frequency of migraine attacks.

**Pain Relief at 2 Hours:**

Used in trials for acute treatments, this endpoint measures the effectiveness of a drug in providing pain relief within a specific period.

**Responder Rate:**

A percentage of patients who achieve a predefined level of symptom reduction, such as a 50% decrease in monthly migraine days.

**Patient-Reported Outcome Measures:**

Including tools like the Migraine Disability Assessment Score (MIDAS) or the Headache Impact Test (HIT-6), which assess the impact of migraines on daily life.

# General Overview of Some Notable Failed Drug Candidates

| Drug Candidate | Company | Targeted Mechanism/Class | Phase of Trial Failure | Primary Reason for Failure |
|---|---|---|---|---|
| Telcagepant | Merck | CGRP Receptor Antagonist | Phase III | Liver toxicity concerns |
| MK-3207 | Merck | CGRP Receptor Antagonist | Phase II | Liver toxicity concerns |
| BI 44370 TA | Boehringer Ingelheim | CGRP Receptor Antagonist | Phase II | Lack of efficacy |
| Semorinemab (RG6100) | Genentech | Anti-Tauprotein Antibody | Phase II | Lack of efficacy |
| LY2951742 | Eli Lilly | CGRP Monoclonal Antibody | Phase II | Discontinued for strategic reasons |
| Atogepant | Allergan | CGRP Receptor Antagonist | Phase II | Strategic reprioritization |
| Lasmiditan | CoLucid Pharmaceuticals | 5-HT1F Receptor Agonist | Phase III | Efficacy concerns in broader patient groups |
| Alder-403 | Alder Biopharmaceuticals | CGRP Monoclonal Antibody | Phase II | Discontinued after acquisition |

# Analyzing the Patterns of Failed Drug Candidates

## Common Patterns and Reasons for Failure

### Inadequate Efficacy:

Some compounds failed to demonstrate a significant improvement over existing treatments or placebo in reducing migraine frequency or severity.

### Safety Concerns:

Adverse effects, some severe, led to the discontinuation of certain drug candidates, emphasizing the need for a balanced approach between efficacy and safety.

### Poor Pharmacokinetics:

Issues like low bioavailability or rapid clearance affected the effectiveness of some drugs.

### High Placebo Responses:

Several trials faced challenges with unexpectedly high placebo effects, complicating the assessment of the drug's true efficacy.

### Target Selection:

Misjudgment in targeting specific pathways or mechanisms in pathophysiology sometimes led to ineffective treatments.

## Analysis and Trends

### Shift in Treatment Targets:

Initially, many drug candidates focused on vasoconstriction mechanisms. Recent trends show a shift towards targeting neuropeptides and inflammatory pathways.

### Increased Focus on Safety:

Recent failures have led to a heightened focus on safety profiles, particularly concerning long-term effects and comorbidities.

### Precision Medicine Approach:

Recognizing the heterogeneity in migraine presentations, there is a growing trend towards personalized medicine in migraine treatment.

INGENŪ CRO

# Enhancing Protocol Design – Strategies for FDA Approval

The development of clinical trial protocols that meet FDA approval standards is crucial for the success of new migraine treatments. As an Australian CRO with considerable experience in guiding US-based biotechs through the regulatory landscape, we offer key strategies to enhance protocol design and increase the likelihood of FDA approval.

## Key Strategies for Protocol Improvement

- Patient Selection & Stratification
- Endpoint Selection
- Innovative Trial Design
- Objective & Subjective Outcome Measures
- Regulatory Insight & Compliance
- Patient-Centric Approach

## Conclusion: A Collaborative Path to Successful Migraine Treatments

We invite US-based biotech firms, doctors, and scientists to collaborate with us in enhancing the design of migraine clinical trials. Our joint efforts will contribute to advancing migraine care, offering new hope to millions affected by this debilitating condition. Let us work together to set new standards in migraine research and treatment development.

# iNGENū CRO

**The Australian CRO championing innovative biotech firms for global success.**
Delivering high-quality, FDA-compliant clinical research.

If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:


**Dr Sud Agarwal**
**Chief Executive Officer**
*BSc (Hons), MB ChB FANZCA DDU*
dr.sudhanshu@ingenucro.com



**Adam Moodie**
**Director, Scientific Engagement**
*BSc*
adam.moodie@ingenucro.com



Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com