Migraine: A Tale of Two Paths to PRO-Based Product Labeling

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Session Objectives

- Discuss the critical role of patients in the evaluation of the clinical benefit of treatments for migraine, which is a common, disabling neurological disease

- Through presentation of high-level timelines and interactions with FDA, describe and discuss two very different approaches that sponsors took in seeking similar novel PRO-based label claims within a new class of migraine drugs.

- Describe and discuss FDA's perspective and thinking regarding de novo measure development vs. use/modification of an existing measure for the assessment of efficacy endpoints within clinical trials

Session Participants

Moderator

- *Stephen Joel Coons, PhD* – Executive Director, PRO Consortium and Senior Vice President, Clinical Outcome Assessment Program, C-Path

Opening Remarks

- *Billy Dunn, MD* – Director, Office of Neuroscience, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Presenters

- *Pooja Desai, PhD* – Director, US Health Economics, Therapeutic Area Lead-Inflammation, Nephrology and Bone, Amgen
- *Elizabeth (Nicki) Bush, MHS* – Senior Advisor and Head, Patient-Focused Outcomes Center of Expertise, Eli Lilly and Company

Additional Panelists

- *Eric Bastings, MD* – Acting Director, Division of Neurology I, Deputy Director, Office of Neuroscience, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *Nick Kozauer, MD* – Director, Division of Neurology II, Office of Neuroscience, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- *Elektra Papadopoulos, MD, MPH* – Acting Deputy Director, Division of Clinical Outcome Assessment, Office of Drug Evaluation Sciences, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Introduction (1)

- In this era of patient-focused drug development, there is an increasing emphasis on incorporating more patient-reported information in medical product labels.
- Although the PRO Consortium was not involved in the case studies presented in this session, we want to highlight and discuss two different PRO assessment strategies or paths taken (almost concurrently) by Amgen and Lilly for products in a new class of migraine drugs for very similar concepts of interest.
- The two paths taken during drug development were…
  - Amgen created a new PRO measure—the *Migraine Physical Function Impact Diary* (*MPFID*).
  - Lilly selected and supported the use of an existing PRO measure—the *Migraine-Specific Quality of Life Questionnaire* version 2.1 (*MSQ v2.1*).
- **The bottom line is that both paths led to novel PRO-based label claims**

Introduction (2)

- Migraine is a common, disabling primary headache disorder that affects roughly 12% of the US population. It is considered the third most prevalent illness and the sixth most disabling illness globally (Migraine Research Foundation).

- There are several different types of migraine, but a major distinction is between episodic and chronic, simplistically described as follows:
  - Episodic migraine (EM): headaches on fewer than 15 days per month
  - Chronic migraine (CM): headaches on 15 or more days per month

- **It should be noted that in treatment trials for migraine (acute and preventive therapies), patients have routinely been the source of clinical benefit data. The symptoms and sensations associated with migraine can only be reported by people experiencing them.**

Introduction (3)

For migraine preventive therapies, the primary efficacy endpoints are customarily based on patient-reported headache (or migraine headache) frequency data.

However, the patient-reported consequences or proximal impacts of migraine on daily activities had not been routinely addressed in migraine product labeling claims.

The two PRO measurement strategies we are discussing in this session successfully addressed that void.

Opening Remarks

Billy Dunn, MD
Director, Office of Neuroscience
Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Assessment of Impact of Migraine on Everyday Activities and Physical Impairment

Pooja Desai, PhD
Director, US Health Economics, Therapeutic Area Lead-Inflammation, Nephrology and Bone
Amgen

Background for the Development of a *de novo* Tool to Articulate an Individual's Physical Functioning

- The Aimovig® (erenumab-aooe) clinical development program consisted of two episodic migraine (EM) trials and 1 chronic migraine (CM) trial[1,2,3]
- The primary endpoint in the pivotal trials was reduction from baseline in mean monthly migraine days[1,2]
- The Migraine Physical Function Impact Diary (MPFID) was a de novo tool developed in accordance with the FDA PRO Guidance; patient input was key
  - Qualitative phase consisted of concept elicitation and cognitive interviews[4,5]
  - Usability testing for the electronic version of the MPFID[6]
  - This was followed by a quantitative phase to establish reliability and validity[7]
- MPFID assesses physical functioning in patients and has 13 items across 2 domains (both included in the label)[7]
  - Impact on everyday activities
  - Physical Impairment
  - One global item on the overall impact on everyday activities (not included as a pre-specified secondary endpoint or on the label)
- MPFID has a 24-hour recall period[4,5,7]
- The two domains of the MPFID were pre-specified secondary endpoints in the pivotal trials[1,2]
- The MPFID is available for licensing to external users

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Amgen Consulted and Worked with the FDA Continuously Throughout the Development and Implementation of Aimovig® PRO Strategy

March 2013	• Type C meeting (live): Amgen reviewed **PRO strategy** with the FDA and gained alignment on the need to develop a **de novo physical functioning** PRO tool
June 2014	• Type C meeting (live): Amgen and FDA engaged and aligned on the need for **1 instrument across EM and CM**
March 2015	• End of Phase 2 meeting
Aug 2015	• Type C meeting (live): FDA agreed with **two domains** for MPFID and **cross-sectional psychometric properties**
April 2016	• Type C meeting (written responses): Amgen engaged in discussions with the FDA around how to define **clinical meaningfulness of response** on the MPFID
Jan 2017	• **Pre BLA meeting (live) + PRO dossier and draft Aimovig label with MPFID data** submitted to FDA
May 2018	• During label negotiations, the **FDA agreed to add MPFID specific data to the label**

MPFID: Migraine Physical Function Impact Diary

The Final Version of the Migraine Physical Function Impact Diary (MPFID) Used in Phase 3 Studies has 13 Items Across 2 Domains

Concepts/Items – 24-hour recall

1. Difficulty doing household chores
2. Difficulty doing activities outside the home
3. Difficulty keeping to daily routine or schedule
4. Difficulty doing activities requiring concentration
5. Difficulty getting ready for the day
6. Duration of time avoiding interactions with people
7. Duration of time needing to rest or lie down

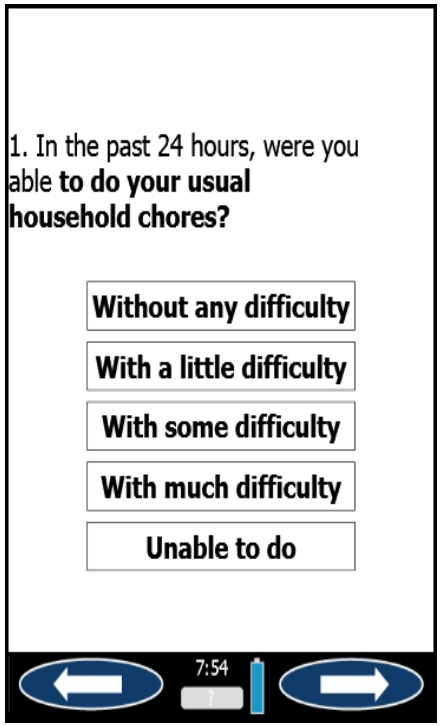
→ Impact on Everyday Activities

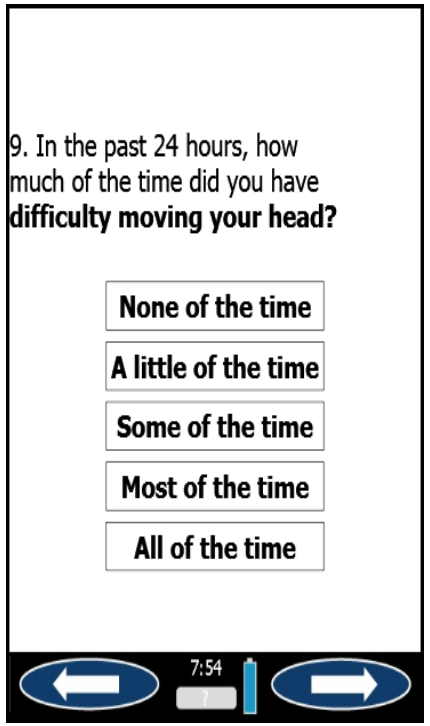
8. Overall difficulty doing usual activities

→ Global Item: Overall Impact on Everyday Activities

9. Duration of time with difficulty moving head
10. Duration of time with difficulty moving body
11. Difficulty getting out of bed
12. Difficulty bending over
13. Difficulty doing activities requiring physical effort

→ Physical Impairment





Link to Aimovig® USPI

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761077s000lbl.pdf

Assessment of Impact of Migraine on Daily Activities

Elizabeth (Nicki) Bush, MHS
Senior Advisor and Head, Patient-Focused Outcomes Center of Expertise
Eli Lilly and Company

Background

- Emgality® (galcanezumab-gnlm) is indicated for the preventive treatment of migraines in adults[1,2,3,4]
- Efficacy was evaluated in three pivotal, multi-center, randomized, double-blind, placebo-controlled studies -- 2 evaluating prevention of episodic migraine (EM); 1 evaluating prevention of chronic migraine (CM)[2,3,4]
- *Impact of migraine on daily activities* was assessed using the Migraine-Specific Quality of Life Questionnaire v2.1 (MSQ v2.1) Role Function-Restrictive (RFR) domain score[2,3,4]
- Mean change from baseline in the average MSQ v2.1 RFR domain score was included as a key secondary endpoint in the three pivotal studies; mean change from baseline of monthly migraine headache days (MHDs) was the primary endpoint in each study.[2,3,4]

MSQv2.1 ePRO

The Migraine-Specific Quality of Life Questionnaire v2.1 (MSQv2.1 ePRO)

- Migraine-specific patient-reported outcome instrument assessing "quality of life and functioning" in past four weeks and consists of three domains:
  - Role Function-Restrictive (RFR) – 7 items*
  - Role Function-Preventive (RFP) – 4 items
  - Emotional Function (EF) – 3 items
- Original version developed 1992; modified to v2.1 in 1998; migrated to ePRO for current program[5,6,7]
- Development and refinement included patient and clinician interviews (concept elicitation and cognitive interviewing) as well as assessment of other measurement properties[5,6,7]
- Lilly-sponsored activities: concept elicitation, cognitive interviewing, ePRO device usability, assessment of other measurement properties[8,9]

*Each item has 6 response options ranging from "None of the time" to "All of the time"

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Timeline – Select US regulatory interactions[10]

- March 2011 – IND submitted
- December 2013 – Change in sponsorship (back to Lilly)
- April 2014 – Type C interaction
- September 2015 – End of Phase 2 (Type B) meeting
- February 2017 – Type C interaction
- April 2017 – Written communication
- July 2017 - Pre-BLA (Type B) meeting
- September 2017 – Submission
- September 2018 – Approval

Current Initiative: MiCOAS

The goal of the Migraine Clinical Outcome Assessment System (MiCOAS) grant is to recommend/develop a standardized set of core outcomes and associated measures for use in acute and preventive migraine clinical trials.

- Phase 1: Qualitative work conducted during the first phase of the grant provided substantial evidence of widespread personal, physical, and social burden associated with migraine. In particular, patients detailed a broad array of factors associated with migraine-related functional impact and disability.
- Phase 2: Evaluate existing PROMs related to migraine functional impact or disability and if needed, develop new PROM(s) for use in clinical trials.
    - The MiCOAS team is currently preparing for a second round of qualitative work focused on instrument identification/development/refinement. Data will then be collected for rigorous psychometric evaluation of the instrument(s).

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Panel Discussion

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Resources

Migraine Physical Function Impact Diary (*MPFID*)

- Licensing Information:
  - Evidera (https://www.evidera.com/what-we-do/patient-centered-research/coa-instrument-management-services/)
  - Contact: Adam Bailey, adam.bailey@evidera.com

Migraine-Specific Quality-of-Life Questionnaire (*MSQ Version 2*.1)

- Licensing Information:
  - Mapi Research Trust (https://eprovide.mapi-trust.org/instruments/migraine-specific-quality-of-life-questionnaire)