From Clinical Outcome Assessment to Clinical Trial Endpoint to Medical Product Labeling

Eighth Annual Patient-Reported Outcome Consortium Workshop

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Session Participants

Moderator
- Michelle Campbell, PhD – Reviewer and Scientific Coordinator, COA Qualification Program, COA Staff, OND, CDER, FDA

Presenters
- Ashley F. Slagle, MS, PhD – Principal, Regulatory and Scientific Consulting, Aspen Consulting, LLC
- David S. Reasner, PhD – Vice President, Data Science and Head, Study Endpoints, Ironwood Pharmaceuticals
- Emily Edson Heredia, MPH – Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company
- Ari Gnanasakthy, MSc, MBA – Principal Scientist, Patient-Centered Outcomes Assessments, RTI Health Solutions

Panelists
- Wen-Hung Chen, PhD – Reviewer COA Staff, OND, CDER, FDA
- Ann Marie Trentacosti, MD – Medical Lead, Labeling Development Team, CDER, FDA
From Concepts to Claims – and everything in between

Ashley F. Slagle, M.S., PhD, Aspen Consulting, LLC
Beginning with the End in Mind – From Concepts to Claims

- Each of these components are linked to each other, with the ultimate link being between the concept and the labeling claim (or other value message)
- When links are maintained, thoughtfully considered, and discussed with stakeholders, the resulting claims are more interpretable and impactful
- Critical to begin with an understanding of what messages are important to key stakeholders
Beginning with the End in Mind – From Concepts to Claims

- **Concepts** – select and prioritize
  - Generally based on literature review, clinician, and patient interviews
  - For US labeling, more proximal concepts prioritized (e.g., symptoms, immediate impacts)

- **Items** – selected or developed to assess prioritized concepts
  - Develop de novo items
  - Map concepts onto existing instrument
  - Combination – select existing instrument and develop new items to fill gaps in content
Scores – combine items into score(s) and test

- Total scores, domain scores, item scores developed, as needed, based on conceptual considerations and quantitative methods
- New scores can be created for de novo instruments OR by rescoring existing instruments into new domains
- Consider: raw sum, averaged, weighted...
  - Recommend keeping as simple as possible
  - Provide rationale for scoring algorithm
- Consider: single daily (or weekly) score, average of daily (or weekly) scores over 1 week (or month)
- Evaluate psychometric properties
• Meaningful change – determine what is a meaningful amount of change on newly created scores
  • Use anchor based methods
    • Distribution methods as supportive
  • Possibility of incorporating qualitative findings into evaluation of meaningful change
Beginning with the End in Mind – From Concepts to Claims

- **Endpoint Specification** – determine how to use scores and meaningful change guidelines to create endpoint(s)
  - Consider symptom improvement vs symptom deterioration
  - Group level change vs patient level change (e.g., responder analysis)
    - Group level saves statistical power, but is more difficult to interpret in terms of meaningful benefit
    - Patient level is more intuitively meaningful, but often at a loss of statistical power
Beginning with the End in Mind – From Concepts to Claims

- Endpoint hierarchy – where does the endpoint(s) fit into the hierarchy
  - For US labeling, endpoint should be a prespecified primary, co-primary, or secondary endpoint and included in the multiplicity plan
  - When group level change is specified as secondary endpoint, consider patient level change exploratory endpoint for further supportive evidence of meaningful benefit
Beginning with the End in Mind – From Concepts to Claims

- All of the preceding steps link together and are critical to supporting the intended claims or value messages
Concepts to claims – hypothetical example of “bad links”

**Gastroparesis Symptoms**

**Two Items**: Nausea and Vomiting (0-10 NRS)

**Average score, range 0-10**

Meaningful change threshold established using anchor based (PGIS and PGIC) methods

Responder analysis: proportion of patients who achieve meaningful threshold of improvement

**Primary Endpoint**

Improvement in the “symptoms of gastroparesis”
Concepts to claims – hypothetical example of “bad links”

**Concepts**
- Items
- Scores
- Meaningful Change
- Endpoint Specification
- Endpoint Hierarchy
- Labeling and Value Messages

**Ovarian Cancer Symptoms**
- Instrument includes 30 items related to: condition related sx, treatment related sx, PF impacts, other impacts
- Average score of all 30 items
- Meaningful change threshold established using anchor based (PGIS and PGIC) methods
- Change in symptoms score - baseline to week N for tx vs comparator
- Exploratory Endpoint
- Labeling claim for: improvement in the “symptoms of ovarian cancer”
From COA to Clinical Endpoint to Medical Product Labeling

David S. Reasner, PhD
Ironwood Pharmaceuticals
• Guidance for Industry: IBS - Clinical Evaluation of Drugs for Treatment
• PRO Guidance Redux
• Clinical Endpoints
• Irritable Bowel Syndrome – Medical Product Labeling
• Irritable Bowel Syndrome – DTC Communication
• The goal for efficacy endpoints in IBS clinical trials is to assess the treatment effect on the core disease-defining signs and symptoms of IBS in a well-defined and reliable way.

• The PRO measure(s) should capture all of the clinically important signs and symptoms of the IBS target population (e.g., IBS-C or IBS-D).
• **Provisional Endpoints** for, as an example, IBS-C Clinical Trials:
  • Weekly Stool Frequency, as measured by the number of complete spontaneous bowel movements (CSBM) per week
  • Weekly Percent Change from Baseline in Abdominal Pain intensity, as measured by a numeric rating scale (i.e., 0 to 10) that asks patients to rate their worst abdominal pain
  • Overall Responder: A responder in greater than 50% of the treatment period weeks where response is both a decrease in abdominal pain intensity of at least 30% and an increase of at least 1 CSBM per week, both relative to baseline
Irritable Bowel Syndrome - Clinical Evaluation of Drugs for Treatment

Stool Frequency (Six different questions – C|S)

• For IBS-C, the defecation component of the proposed primary endpoint can be evaluated by assessing stool frequency.
Abdominal Pain

- If a drug is developed specifically to improve only one of the major signs or symptoms of IBS (e.g., abdominal pain), based on the drug’s mechanism of action, it is still important to assess the other important signs and symptoms to document that the drug has not negatively affected those components.
i. Hypothesize Conceptual Framework
   - Outline hypothesized concepts & potential claims
   - Determine intended population
   - Determine intended application characteristics (type of scores, mode & frequency of administration)
   - Perform literature/expert review
   - Develop hypothesized conceptual framework
   - Place PROs within preliminary endpoint model
   - Document preliminary instrument development

ii. Adjust Conceptual Framework & Draft Instrument
   - Obtain patient input
   - Generate new items
   - Select recall period, response options & format
   - Select mode/method of administration/data collection
   - Conduct patient cognitive interviewing
   - Pilot test draft instrument
   - Document content validity

iii. Confirm Conceptual Framework & Assess Other Measurement Properties
   - Confirm conceptual framework with scoring rule
   - Assess score reliability, construct validity, & ability to detect change
   - Finalize instrument content, formats, scoring, procedures & training materials
   - Document measurement development

iv. Collect, Analyze, & Interpret Data
   - Prepare protocol & statistical analysis plan (final endpoint model and responder definition)
   - Collect & analyze data
   - Evaluate treatment response using cumulative distribution & responder definition
   - Document interpretation of treatment benefit in relation to claim

v. Modify Instrument
   - Change wording of items, populations, response options, recall period, or mode/method of administration/data collection
   - Translate & culturally adapt to other languages
   - Evaluate modifications as appropriate
   - Document all changes

Outline hypothesized concepts & potential claims
Labeling Goals
Guidance Appendix – The “Dossier” [eCTD 5.3.5.3]

Sections
I. Instrument
II. Targeted Claims or TPP [Target Product Profile]
III. Endpoint Model
IV. The PRO Instrument’s Conceptual Framework
V. Content Validity Documentation
VI. Assessment of Other Measurement Properties
VII. Interpretation of Scores
VIII. Language Translation and Cultural Adaptation
IX. Data Collection Method
X. Modifications
XI. PRO-Specific Plans Related to Clinical Trial Design and Data Analysis
XII. Key References

Appendix A – User Manual
Appendix B – Item Tracking Matrix
Appendix C - Transcripts
Key Section List

1. Indications and Usage
2. Dosage and Administration
3. Dosage Forms and Strengths
4. Contraindications
5. Warnings and Precautions
6. Adverse Reactions
7. Drug Interactions
8. Use in Specific Populations
9. Drug Abuse and Dependence
10. Overdosage
11. Description
12. Clinical Pharmacology
13. Nonclinical Toxicology
14. Clinical Studies
15. References
16. How Supplied/Storage and Handling
17. Patient Counseling Information
PRO Instrument Development and Modification: Endpoint Model

i. Hypothesize Conceptual Framework
   - Outline hypothesized concepts & potential claims
   - Determine intended population
   - Determine intended application/characteristics (type of scores, mode & frequency of administration)
   - Perform literature/expert review
   - Develop hypothesized conceptual framework
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Modified Wheel & Spokes

Place PROs within preliminary endpoint model

(final endpoint model and responder definition)
## Endpoint Model: Treatment of Disease X

<table>
<thead>
<tr>
<th>Concept</th>
<th>Link</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication:</strong></td>
<td></td>
<td><strong>Primary:</strong></td>
</tr>
<tr>
<td>Treatment of Disease X</td>
<td></td>
<td>Physiological Effect</td>
</tr>
<tr>
<td><strong>Supportive Concepts:</strong></td>
<td></td>
<td><strong>Secondary:</strong></td>
</tr>
<tr>
<td>Improvement in Symptoms/Signs of Disease X</td>
<td></td>
<td>Symptoms Diary [PRO]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signs Diary [PRO]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical Exam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical Performance [possibly PRO]</td>
</tr>
</tbody>
</table>
Sponsors should define the role a PRO endpoint is intended to play in the clinical trial (i.e., a primary, key secondary, or exploratory endpoint) so that the instrument development and performance can be reviewed in the context of the intended role, and appropriate statistical methods can be planned and applied. It is critical to plan these approaches in what can be called an endpoint model.

“PRO instrument adequacy depends on its role as depicted in the endpoint model. The endpoint model explains the exact demands placed on the PRO instrument to attain the evidence to meet the clinical trial objectives and support the targeted claims corresponding to the concepts measured.”
Irritable Bowel Syndrome – Example

- Linzess® approval 30-Aug-2012
- FDA issues final IBS Guidance May-2012
- FDA issues draft IBS Guidance Mar-2010
- End of Phase 2 Meeting 07-Aug-2008
  - The FDA recommended developing an instrument based on patient input. The instrument should be shown to represent “a complete, meaningful, appropriate, and interpretable instrument of the major manifestations of IBS-C” for use as the primary endpoint. In the meeting, the sponsor said that they would submit a new study design and information to support a co-primary endpoint of abdominal pain and constipation. In addition, the sponsor said it would “submit information from their qualitative studies to support the use of their proposed PRO instruments.” [from NDA #202-811 Summary Review]
Table 3: Efficacy Responder Rates in the Two Placebo-controlled IBS-C Trials: at Least 6 Out of 12 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined Responder</strong></td>
<td><strong>LINZESS 290 mcg (N=405)</strong></td>
<td><strong>LINZESS 290 mcg (N=401)</strong></td>
</tr>
<tr>
<td>(Abdominal Pain and</td>
<td>Placebo (N=395)</td>
<td>Placebo (N=403)</td>
</tr>
<tr>
<td>CSBM Responder)</td>
<td>Treatment Difference [95% CI]</td>
<td>Treatment Difference [95% CI]</td>
</tr>
<tr>
<td><strong>33.6%</strong></td>
<td><strong>21.0%</strong></td>
<td><strong>33.7%</strong></td>
</tr>
<tr>
<td><strong>12.6% [6.5%, 18.7%]</strong></td>
<td><strong>19.8% [14.0%, 25.5%]</strong></td>
<td></td>
</tr>
<tr>
<td>**Abdominal Pain</td>
<td><strong>50.1%</strong></td>
<td><strong>48.9%</strong></td>
</tr>
<tr>
<td>Responder**</td>
<td><strong>Placebo (N=395)</strong></td>
<td><strong>Placebo (N=403)</strong></td>
</tr>
<tr>
<td>(≥ 30% Abdominal</td>
<td><strong>37.5%</strong></td>
<td><strong>34.5%</strong></td>
</tr>
<tr>
<td>Pain Reduction)</td>
<td>Treatment Difference [95% CI]</td>
<td>Treatment Difference [95% CI]</td>
</tr>
<tr>
<td><strong>12.7% [5.8%, 19.5%]</strong></td>
<td><strong>14.4% [7.6%, 21.1%]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CSBM Responder</strong></td>
<td><strong>48.6%</strong></td>
<td><strong>47.6%</strong></td>
</tr>
<tr>
<td>(Increase ≥ 1 CSBM from</td>
<td><strong>29.6%</strong></td>
<td><strong>22.6%</strong></td>
</tr>
<tr>
<td>Baseline)</td>
<td>Treatment Difference [95% CI]</td>
<td>Treatment Difference [95% CI]</td>
</tr>
<tr>
<td><strong>19.0% [12.4%, 25.7%]</strong></td>
<td><strong>25.1% [18.7%, 31.4%]</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Primary Endpoint, ** Secondary Endpoints
Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2
CI = Confidence Interval
Irritable Bowel Syndrome – DTC Communication

• If you suffer from IBS-C, LINZESS may help you
  • Feel less belly (abdomen) pain
  • Have more frequent and complete bowel movements

• If you suffer from CIC, LINZESS may help you
  • Have more frequent and complete bowel movements
  • Experience softer stools
Irritable Bowel Syndrome with Constipation (IBS-C)

- I’ve tried juggling water, laxatives, and exercise for my belly pain and constipation, and it still comes right back.
• For full prescribing information, important risk information, and patient medication guide see...

• https://www.linzess.com
Itch from concept to label: the Taltz™ (ixekizumab) experience

Emily E. Heredia, MPH, Research Scientist, Eli Lilly and Company
• Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A.

• It is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

For full prescribing information please see
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125521s000lbl.pdf
Accessed 15 February 2017
Psoriasis: a complex disease model

Rewind to 2010

• Ixekizumab phase 2 study underway
• Four major psoriasis biologics in US market
• **None** had any PRO-based claims in US label despite numerous PRO concepts studied in their phase 3 registration trials:
  • Health-related quality of life
  • Work productivity
  • Symptom severity
  • Health status
Itch severity concept rose to top

- Lilly health outcomes initiated literature review which suggested itch is a highly prevalent\(^1\)-\(^2\) and bothersome\(^3\) symptom of psoriasis
  - Lilly health outcomes online patient survey bore this out
  - Lilly market research supportive

\(^3\)Globe D, Bayliss MS, Harrison DJ. The impact of itch symptoms in psoriasis: results from physician interviews and patient focus groups. Health Qual Life Outcomes 2009; 7: 62.
Itch severity concept, cont.

- Itch is a “proximal” impact concept
- Itch severity can be evaluated in simple, single item tool similar to pain severity which appeared in other products’ FDA labels
The Plan

• In phase 2 study
  • Concept: itch severity
  • Endpoint: change from baseline
  • Instrument: Itch Visual Analog Scale 0-100 single item

• Repeat above for phase 3 study

• Conduct concept elicitation and cognitive debriefing in parallel

• Assess psychometric properties using phase 2 data
First FDA Feedback

• Recommended changes to the instrument:
  • Numeric Rating Scale format instead of VAS
  • Recall period from “at the present time” to “past 24 hours”
  • Include wording that refers to “worst” level of itching
The New Plan

• Updated itch instrument format and recall period
• Could not use ixekizumab phase 2 data for psychometrics!
  → leveraged another psoriasis program in phase 2 development (baricitinib)
Qualitative Work

- Concept elicitation
- Cognitive debriefing

Clinical trial

The Worst Itch Numeric Rating Scale for patients with moderate to severe plaque psoriasis or psoriatic arthritis

April N. Naegeli¹, DrPH, MPH, Emuella Flood², BA, Jennifer Tucker², PhD, Jennifer Devlen², PhD, and Emily Edson-Heredia³, MPH

Please rate the itching severity due to your psoriasis by circling the number that best describes your worst level of itching in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

0 = No itching 10 = Worst itch imaginable

Table 2. Characterizations of itching in patients with psoriatic disease

<table>
<thead>
<tr>
<th>Psoriasis group (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency and duration</td>
</tr>
<tr>
<td>9 of 12 patients reported itching on a regular or frequent basis</td>
</tr>
<tr>
<td>Severity</td>
</tr>
<tr>
<td>• A burning sensation might accompany the itching and may be felt underneath the skin</td>
</tr>
<tr>
<td>• Dry, tight skin may result in itching, burning pain that may crack and bleed</td>
</tr>
<tr>
<td>Spontaneous mention of the terms “itch” and “scratch”</td>
</tr>
<tr>
<td>Descriptions</td>
</tr>
<tr>
<td>• Mosquito bites</td>
</tr>
<tr>
<td>• Intense</td>
</tr>
<tr>
<td>• Uge to scratch</td>
</tr>
<tr>
<td>• Stinging sensation</td>
</tr>
<tr>
<td>• Uncomfortable/irritation</td>
</tr>
<tr>
<td>• As if one has dried out skin</td>
</tr>
<tr>
<td>• Uge to level a scale or remove scales</td>
</tr>
<tr>
<td>• Horrible/absolutely awful/drive you crazy</td>
</tr>
<tr>
<td>• Needle points</td>
</tr>
<tr>
<td>• Painful itch</td>
</tr>
<tr>
<td>• Subconscious need to scratch</td>
</tr>
</tbody>
</table>

More FDA Feedback

• FDA agreed qualitative work and psychometric work to date demonstrated validity of Itch NRS

• However FDA expressed concerns over proposed responder definition (% change from baseline) which was anchored to patient global assessment score

• Wanted to see
  • Baseline Itch NRS score taken into account
  • Itch NRS score tied to clinically meaningful change
Responder Definition

Method

• Used ClinRO measure from RCT co-primary endpoint as anchor variable (static Physician Global Assessment = sPGA)
• ROC analysis with Itch NRS as predictor variable of sPGA = 0,1
• Youden Index summary measure identified optimal Itch NRS change threshold predictive of sPGA = 0,1

Result

• Itch NRS score change from baseline ≥4 identified as responder definition*

Psychometric properties of the Itch Numeric Rating Scale in patients with moderate-to-severe plaque psoriasis*

A.B. Kimball,1 A.N. Naegeli,2 E. Edson-Heredia,3 C.-Y. Lin,2 C. Galch,2 E. Nikaï,2 K. Wyrewich3 and G. Yosipovitch4

Table 3: Known-groups validity of the Itch Numeric Rating Scale (Itch NRS) using static Physician’s Global Assessment (sPGA) groups at week 12 for studies JADP, RHAZ, RHBC and RHBA

<table>
<thead>
<tr>
<th>Study</th>
<th>sPGA category at week 12</th>
<th>sPGA 0–1</th>
<th>sPGA ≥ 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>JADP, n per group</td>
<td></td>
<td>67</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD change</td>
<td>−5.4 ± 2.92</td>
<td>−2.9 ± 3.10</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>in Itch NRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHAZ, n per group</td>
<td></td>
<td>698</td>
<td>592</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD change</td>
<td>−6.0 ± 2.69</td>
<td>−1.4 ± 3.18</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>in Itch NRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHBC, n per group</td>
<td></td>
<td>773</td>
<td>563</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD change</td>
<td>−5.1 ± 2.70</td>
<td>−2.5 ± 3.31</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>in Itch NRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHBA, n per group</td>
<td></td>
<td>675</td>
<td>538</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD change</td>
<td>−5.4 ± 2.72</td>
<td>−2.2 ± 3.15</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>in Itch NRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Mean change in Itch Numeric Rating Scale (Itch NRS) scores from baseline at week 12 among Psoriasis Area and Severity Index (PASI) improvement groups at week 12 for studies JADP, RHAZ, RHBC and RHBA.
Impact of ixekizumab on psoriasis itch severity and other psoriasis symptoms: Results from 3 phase III psoriasis clinical trials

Among patients with a baseline itch NRS score of ≥4, improvements of ≥4 points were achieved by 76.8% to 85.9% of patients who received ixekizumab at week 12 (P<.001 vs placebo or etanercept).

“Subjects treated with TALTZ 80 mg Q2W experienced improvement in itch severity when compared to placebo at Week 12.”

http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125521s000lbl.pdf
Accessed 19 January 2017
DOES YOUR PSORIASIS EVER GET IN THE WAY OF A TOUCHING MOMENT?
You can embrace the chance of completely clear skin with Taltz.

The facts are clear

**SIGNIFICANT IMPROVEMENT**
With Taltz, up to 90% of people saw a significant improvement of their psoriasis plaques

**COMpletely CLEAR SKIN**
4 out of 10 achieved completely clear skin

Additionally, in clinical trials Taltz was shown to achieve clear skin even in people who have used other biologic treatments in the past and was shown to significantly reduce the severity of itch at 3 months.

Accessed 19 January 2017
Desirable Value Messages based on Patient-Reported Outcome Data

Ari Gnanasakthy
RTI-Health Solutions
27 April 2017
Overall goal – Impactful value messages

- Value messages often evolve over time during product development
- Product labels constitute only a small proportion of value messages
Value messages can be based on . . .

- Efficacy
- Safety
- Treatment satisfaction
- Work productivity
- Compliance
- HRQL
- . . .
Value messages drive endpoints

- Endpoints may be based on
  - Group means
  - Number of events / event rates
  - Percent change / absolute change
  - Time to outcome (positive / negative)
  - Event free time
  - Percent of responders (at a given time)
Desired value messages must be based on...

- Understanding of the disease
- Understanding of the treatment benefit to patients
- Internal evaluation
  - Study design
  - Assessment of competitor landscape
  - Assessment of:
    - commercial value of the value messages
    - resource and time constraints
    - ‘go with the herd’ or ‘go it alone’
- Value messages must be impactful
  - Simple and easily understood
You may have a chance to live longer . . .
Examples of some recent PRO related value messages
(from patient package insert)

- “...effective in treating the symptoms of OAB”
- “...demonstrated statistically significant improvement in CF symptoms (such as cough, sputum production and difficulty breathing)...”
- “Significantly reduced the number and severity of moderate to severe hot flushes...”
- “...improvement of itch severity...”
- “The overall patient-reported satisfaction and self-perceived visual attributes showed greater improvement...”
“...effective in treating the symptoms of OAB”
Improvement in symptoms

ORENCIA is an RA treatment that works differently. It’s a prescription medication used to treat adults with moderate to severe RA who have not been helped enough by other medications for RA. It's been shown to:
- Relieve the pain, swelling, and fatigue of RA
- Control the advance of joint damage
- Help improve physical and emotional health-related quality of life

Relieves the pain, swelling, and fatigue
Improvement in symptoms and function

Lyrica can help reduce the unique pain and improve function
Improvement in feelings

Felt the urge to light up a cigarette leaving me. It was amazing.
Overall patient-reported satisfaction

“The overall patient-reported satisfaction and self-perceived visual attributes showed greater improvement...”
“Health-related quality of life was measured using the St. George’s Respiratory Questionnaire (SGRQ) in all six confirmatory COPD clinical trials. SGRQ is a disease-specific patient reported instrument which measures symptoms, activities, and its impact on daily life. At week 12, pooled data from these trials demonstrated an improvement over placebo in SGRQ total score of -3.8 with a 95% CI of (-5.3, -2.3) for the ARCAPTA NEOHALER 75 mcg dose, -4.6 with a 95% CI of (-5.5, -3.6) for 150 mcg, and -3.8 with a 95% CI of (-4.9, -2.8) for 300 mcg. The confidence intervals for this change are widely overlapping with no dose ordering. Results from individual studies were variable, but are generally consistent with the pooled data results.”
PRO-based labeling not always utilized in product promotion

• Zytiga (abiraterone acetate) - Indicated for treatment of Metastatic Castration-Resistant Prostate Cancer
  • Labeling granted for ‘delay in pain progression’
  • No mention of this in the product website

PRO-based labeling not always utilized in product promotion

Unfavorable or inconsistent findings may be problematic

“communication should accurately characterize and contextualize the relevant information about the product, including by disclosing unfavorable or inconsistent findings”.

Guidance to Industry (January 2017) Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers.
Unfavorable or inconsistent findings may be problematic

- Treatment for Primary Immunodeficiency
- Assessment of patient experience was an objective -
- Study included 74 patients (23 patients < 16 years old)
- PROMs: LQI, TSQM-9, SF-36, and PedsQL

<table>
<thead>
<tr>
<th>Scale</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 Physical Component Score</td>
<td>0.89</td>
<td>0.067</td>
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<tr>
<td>SF-36 Mental Component Score</td>
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<td>0.976</td>
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<tr>
<td>Total Score (PedsQL)</td>
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<tr>
<td>Treatment Interference (LQI)</td>
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<tr>
<td>Convenience (TSQM-9)</td>
<td>11.11</td>
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Inconsistent findings may be problematic

To treat hyperuricemia associated with gout when used in combination with a xanthine oxidase inhibitor (XOI)

Primary endpoint - Reduction in serum uric acid

Secondary endpoints – PRO-based
  • SF-36, HAQ-DI, TSQM, SDS and Patient global assessment

Contradiction between evidence of treatment benefit based on primary and secondary endpoints led to regulatory challenges

Approved to maintain “consistency with previous approvals in this space”*

Inconsistent findings may be problematic

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  - SF-36, HAQ-DI, TSQM, SDS and Patient global assessment

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- Approved to maintain “consistency with previous approvals in this space”*

Inconsistent findings may be problematic

• “convincing statistical evidence that lesinurad lowers serum uric acid levels in patients with gout when used in combination with a xanthine oxidase inhibitor”.

• “. . . it is notable that there was no evidence of benefit, nor any consistent trends toward benefit . . . there were slight but relatively consistent trends toward worse outcomes on lesinurad 200 mg than placebo for patient-reported outcomes such as HAQ-DI, patient pain score, SF-36 physical component summary (PCS), and patient global assessment of disease activity score”
Most common mistakes

- Strategy based on PRO measures
- PROs - an afterthought (late start)
  - Phase 2 may be too late
- Copy what another company has done
  - Often a symptom of starting late
- Unrealistic expectation of resources (time, money, and personnel)
  - New PRO measures, translations, data collection, licenses, etc. can be resource intensive
- Poor implementation
  - Impacts data quality
  - Sign of lack of commitment
- Inappropriate assessment schedule
  - Especially disease with outbreaks / flares / episodes / remission
- Lack of expertise
  - To monitor regulatory environment, define best practice/process, advice senior managers, challenge internal teams, etc.
Conclusion

• Impactful value messages drive endpoints; endpoints drive measurement strategy
  • Strategies based on hope often lead to unintended consequences

• Impactful value messages are results of well thought-out and well implemented strategies
  • Early commercial input is key for creating value messages
  • Simple value messages enable efficient communication

• Being prepared is half the victory
  • Start planning early with the right pool of talent
Panel Discussion and Q & A

Moderator
- Michelle Campbell, PhD – Reviewer and Scientific Coordinator, COA Qualification Program, COA Staff, OND, CDER, FDA

Presenters
- Ashley F. Slagle, MS, PhD – Principal, Regulatory and Scientific Consulting, Aspen Consulting, LLC
- David S. Reasner, PhD – Vice President, Data Science and Head, Study Endpoints, Ironwood Pharmaceuticals
- Emily Edson Heredia, MPH – Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company
- Ari Gnanasakthy, MSc, MBA – Principal Scientist, Patient-Centered Outcomes Assessments, RTI Health Solutions

Panelists
- Wen-Hung Chen, PhD – Reviewer COA Staff, OND, CDER, FDA
- Ann Marie Trentacosti, MD – Medical Lead, Labeling Development Team, CDER, FDA
The End