Patients EU 2020

'How Regulations are Incorporating the Patient Voice``

Experience in fibromyalgia clinical development

Nico Merante

London, 27 January 2020
Conflict of interest /background/discussion points

• I have no conflict of interest to declare.

• Currently am not employed as was recently made redundant by Sosei Heptares, Cambridge, UK;

• Full MD registration in Italy since Dec. 1988 and in the UK with the GMC since Sep. 1998; 12 years of working experience in the Italian NHS as emergency doctor;

• MD specialist of endocrinology and diabetes since Oct. 1993 (University and St. Chiara Hospital of Pisa/Italy);

• Formerly, Chief Medical Officer at Nave Ammiraglio Magnaghi in the Italian Navy (1990-1993);

• I have been working in the pharmaceutical industry since 1994 covering national/global clinical roles in ph. 1-4;

• Currently working in projects aiming to target multiple indications in migraine/pain, endocrine and metabolic conditions; my key interest is to design and to conduct clinical studies with patient-centric approach.

Discussion points include but are not limited to:

1) What’s the overview of the regulatory landscape regarding patient involvement?
2) How are evolving regulations making it easier for patient and caregiver voices to be heard?
3) How are changing regulations impacting industry expectations and ambitions?
4) How is industry currently guiding patients to navigate evolving regulatory environment?
5) Case study to be shared
Clinical Drug Development Requires Continuous Engagement with Patients

- Phase II trials
- Phase III trials
- Phase IIIb / IV trials

Approval → Reimbursement

Scientific Advice

NDA Review

RMP / REMS
Implementation

Pharmacovigilance / PSUR

HTA Evaluation

Periodic Reevaluation

Patient Advocacy Engagement

Disease Awareness Campaigns

Patient Education Programs

The biopharmaceutical industry has long operated on the belief that enrolling patients in clinical trials is easy enough, provided that the protocol is right and that the best investigator sites have been enlisted. The facts, however, suggest that although this might have been the case in simpler times, it is no longer so.

Consider that:

- 11% of selected sites never enrol a single patient;
- 48% of all sites underperform, meaning that they do not deliver the number of patients they expect;
- Sponsors’ original timelines for Phase II-IV studies usually end up doubling in order to meet the enrolment desired levels;
- Nearly 80% of clinical trials fail to meet their enrolment timelines;
- Although results vary widely by therapeutic area, on average, only half of all patients screened complete clinical trials.

Historical engagement of the FDA and EMA with Patients over the last 30 years

[Diagram showing the evolution of patient engagement at FDA]

- FDA Patient Network website launched
- Patient-Focused Drug Development initiative established under PDUFA
- MedWatch encourages voluntary reporting
- FDA Patient Engagement Advisory Committee (PEAC) established
- FDA Patient Representative Program expands, patients now serve as consultants to reviewers during review cycle
- HIV/AIDS group expands to include cancer and other special health issues
- First FDA Patient Representative sits on FDA Advisory Committee

[Graph showing the number of patients involved in scientific advice, protocol assistance, HTA]

- Key:
  - CMMI = Center for Devices and Radiological Health
  - FDAA = Food and Drug Administration Safety and Innovation Act
  - EMA = European Medicines Agency
  - CTTI = Chronic Traumatic Trauma Initiative
  - NORD = National Organization for Rare Disorders
  - PAS = Patient Affairs Staff
  - PDDO = Patient-Directed Data Organization

[Graph showing the percentage of patients involved in different roles]

- Endpoints: 19%
- Population: 10%
- Quality of Life: 12%
- Standard of care: 13%
- Comparator choice: 11%
- Study feasibility: 11%
- Other: 12%

[Links]
- PatientEngagementCollaborative@fda.hhs.gov
Clinical Development - **Patient-Relevant Endpoints**

**How To Understand In Depth The Patient Experience?**

- **Regulatory Endpoints**
- **Quality of Life Endpoints**
- **Clinically Relevant Measures for Distressing Symptoms or Side Effects**

Example:
Measuring antidepressant and anxiolytic efficacy and sleep quality as additional benefit to pain reduction.

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Fibromyalgia (FM) is a clinical condition characterized by chronic musculoskeletal and soft-tissue pain and tenderness and other symptoms associated with debilitating sleep problems, fatigue, depression, and anxiety.

Fibromyalgia is characterized by an amplified pain response.

- **Hyperalgesia**: (when a pinprick causes an intense stabbing sensation)
- **Allodynia**: (hugs that feel painful)

Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors

**Group 1 (n=50)**
- Low tenderness
- Moderate depression/anxiety
- Moderate catastrophizing
- Moderate control over pain

**Group 2 (n=31)**
- High tenderness
- High depression/anxiety
- High catastrophizing
- Low control over pain

**Group 3 (n=16)**
- High tenderness
- Low depression/anxiety
- Low catastrophizing
- High control over pain

Subgroups of fibromyalgia patients, based on a psychosocial domain (depression/anxiety), a cognitive domain (catastrophizing/control over pain), and a neurobiologic domain (tenderness).

Table 1: Count of Docket Comments that Describe Specific Fibromyalgia Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized*</td>
<td>160</td>
</tr>
<tr>
<td>Headaches</td>
<td>140</td>
</tr>
<tr>
<td>Burning/Stabbing</td>
<td>120</td>
</tr>
<tr>
<td>Muscle Stiffness</td>
<td>100</td>
</tr>
<tr>
<td>Muscle Spams</td>
<td>80</td>
</tr>
<tr>
<td>Skin/Nerve</td>
<td>60</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
</tr>
<tr>
<td>Sleep Issues</td>
<td>30</td>
</tr>
<tr>
<td>Cogitive</td>
<td>20</td>
</tr>
<tr>
<td>Depression/Anxiety</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8</td>
</tr>
<tr>
<td>Sensory Overload</td>
<td>6</td>
</tr>
<tr>
<td>Balance</td>
<td>4</td>
</tr>
<tr>
<td>Vision</td>
<td>2</td>
</tr>
<tr>
<td>Restless Leg Syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

Descriptions of Pain Manifestation, categorized in six unique ways.
Localized* - Includes joints & tender points

FDA received approximately 400 comment submissions to the public docket that supplemented the Patient-Focused Drug Development meeting on fibromyalgia. The majority of comments were submitted by patients, with a few comments from patient caregivers. FDA also received comments from three advocacy groups, National Fibromyalgia Partnership (NFP), National Fibromyalgia & Chronic Pain Association (NFMCPA) and PatientsLikeMe (PLM) Fibromyalgia Community. Each organization gathered perspectives of fibromyalgia patients and submitted the results to the public docket.
6.5. Fibromyalgia Syndrome

The Fibromyalgia Syndrome (FMS) may be categorized with the soft tissue pain syndromes of unknown aetiology. The predominant symptom is chronic widespread pain with tenderness and low pain tolerance. FMS patients typically exhibit a wide spectrum of symptoms such as chronic sleep disorders, fatigue, cognitive dysfunctions and mood disturbances. Associations with conditions such as irritable bowel syndrome or bladder pain syndrome are described. The pathophysiology of FMS is not well characterised. It may be largely a functional disorder in many patients but there is some evidence for alterations in pain and sensory processing in the CNS in FMS. The established diagnostic criteria for FMS (American College of Rheumatology Fibromyalgia Diagnostic Criteria (ACR FDC) including Widespread Pain Index (WPI) and Symptom Severity Scale (SSS)) do not emphasise pain intensity exclusively. Thus, a simple demonstration of an effect on pain scores is not considered sufficient to support a specific indication for the treatment of FMS. It would be expected that effects on other domains of FMS including functional improvement would be of clear clinical significance, and the applicability of the results to the broad population meeting the standard diagnostic criteria would need to be justified. Maintenance of efficacy with long term treatment would need to be demonstrated. Regional differences in medical and social culture largely preclude extrapolation of data from non-EU studies. FMS is not an appropriate pain model for a clinical data package to support a general pain indication.
Conclusions from most studies in fibromyalgia in Europe

- Small numbers of patients studied in Europe;
- Modest average effects on pain intensity - smaller than that observed in neuropathic studies;
- However in most studies these effects are not related to anxiety or mood and a subgroup of patients might be good responders to a new Investigational Product;
- Some effects on sleep and global impression of change;
- Inconsistent effects on other outcome measures;

- Perform studies with enrichment design;
- Assess sleep and PGIC (Patient Global Impression of Change: this as co-primary endpoint);
  Multidimension fibromyalgia questionnaire: FIQ
  (Fibromyalgia Impact Questionnaire: primary endpoint);
- Try to better define good responders (sleep, comorbidities, lack of prior therapeutic failures...).
FDA outlines plans for new guidance on developing pain drugs

30 August 2018 - The Food and Drug Administration intends to withdraw its existing analgesic guidance for developing new pain drugs and will issue a new guidance in 2019. The decision, said FDA Commissioner Scott Gottlieb, M.D., is in response to the shifting nature of the nation's opioid epidemic.

https://www.fda.gov/media/90052/download;

2. Specific/Narrow Pain Indications

a. Condition- or population-specific

For specific/narrow indications that are determined to be appropriate based on the safety and efficacy of the new drug product, such as the pain of osteoarthritis, chronic low back pain, or pain of fibromyalgia, two clinical trials in the specific condition typically will be adequate to support a finding of efficacy for that indication. Relatively narrow indications may be appropriate for drugs that have shown clinical efficacy in only limited therapeutic settings, or when substantial safety concerns result in an acceptable risk-benefit analysis only in limited, defined situations of use.

224-235 Chronic Pain. To obtain approval for the broad indication of the treatment of chronic pain, sponsors should meet the recommendations for general neuropathic pain (i.e., at least four trials per four conditions including one in central neuropathic pain) as outlined above. In addition, sponsors should conduct two successful trials in one non-neuropathic pain condition plus one successful trial in each of two additional non-neuropathic pain conditions (at least four trials per three non-neuropathic conditions). Non-neuropathic pain conditions that are suitable for this purpose include osteoarthritis, chronic low back pain, chronic visceral pain, cancer pain, and fibromyalgia. Thus for an overall indication of the treatment of chronic pain, sponsors should conduct at least eight trials in seven conditions. However, we encourage sponsors to study as many conditions as possible to more fully characterize the properties and potential populations likely to benefit from treatment.

269-281 Additional Claims

Additional claims of treatment benefit based on clinical domains relevant to analgesia may be appropriate for some clinical populations that are defined by those domains. Claims of treatment benefit should represent findings that are not directly a result of a change in pain, but if subjects sleep better merely because they have less pain, the improved sleep is not a direct positive effect of the drug. For example, fibromyalgia is a syndrome that includes pain as well as fatigue and trouble sleeping. A properly designed evaluation of sleep during a clinical trial in subjects with fibromyalgia may demonstrate positive effects for pain as well as sleep. In contrast, subjects treated with a sedating analgesic may sleep more, but this may not represent improved sleep, and these subjects may experience the sedating effects during the day as well. Replicated findings from adequately designed studies incorporating instruments demonstrating substantial, clinically meaningful improvement can support such claims.
As of today, there is still a gap to fill for a global regulatory guidance for the clinical development of new molecules aiming to treat fibromyalgia.
Double blind study design: ALDAY Fibromyalgia phase 3 program

Advocacy collaborations:

• The team (Sponsor/CRO) had reached out to the European Network of Fibromyalgia Associations (ENFA) via Fibromyalgia Association UK (FMA);

• The team worked directly with sites to establish additional advocacy groups to work with;

• Relationships being established in Germany, Spain, Norway, Netherlands and US.
Efficacy and safety of mirogabalin for the treatment of fibromyalgia: results from three 13-week randomized, double-blind, placebo- and active-controlled, parallel-group studies and a 52-week open-label extension study

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ABSTRACT

Objective: To investigate the efficacy and safety of mirogabalin, a preferentially selective α5β ligand, in patients with fibromyalgia (FM).

Methods: In three 13-week, multicenter, double-blind, phase 3 studies (studies A, B, and C), patients with FM (n = 1203, 1270, and 1301, respectively) were randomized (1:1:1) to placebo, pregabalin 150 mg twice daily, mirogabalin 15 mg once daily or mirogabalin 15 mg twice daily. The primary endpoint was the change in weekly average daily worst pain score (ADPS) at week 13. Key secondary endpoints included Patient Global Impression of Change and change in the Fibromyalgia Impact Questionnaire total score. Long-term safety of mirogabalin was assessed in a 52-week extension study.

Results: Neither mirogabalin dose demonstrated a significant ADPS reduction from baseline vs. placebo at week 13 in any of the three studies. Pregabalin significantly reduced ADPS from baseline vs. placebo in studies B and C (p < .0008 and .0001, respectively). The effect of mirogabalin compared with placebo on key secondary endpoints was variable across the studies. Mirogabalin was well tolerated at most patients in the phase 3 studies; no unexpected adverse events occurring during the 52-week extension study.

Conclusion: While both mirogabalin doses were well tolerated by most patients and showed potential for reducing pain associated with FM, the primary endpoint of significant pain reduction in patients on mirogabalin compared with placebo was not achieved in any of the three randomized controlled studies.

Clinical trial registration: NCT02146430; NCT02187159; NCT02187471; and NCT02234583 (extension study).
Always acknowledge patients contribution in a clinical study alongside any published data

**Acknowledgements**

The authors would like to acknowledge and thank all of the patients, investigators and study sites across the globe who participated in this large clinical program in fibromyalgia. Writing and editorial assistance was provided by Claire Daniele, PhD of AlphaBioCom LLC, King of Prussia, PA, and supported by Daiichi Sankyo Inc, Basking Ridge, NJ. Parts of this study were presented at 16th World Congress on Pain; 26–30 September 2016; Yokohama, Japan.
Close communication with patients is key for improving clinical research and lessons learned so far

1. Listening to, understanding patients advice and the relevance of their symptoms; speaking as much as possible the same language of patients;

2. Addressing those learning points into a clinical study design and study endpoints to hopefully obtain more insightful and clinically relevant data;

3. Building reputation and trust by working together with patients groups and patients associations;

4. Consolidating a collaborative platform with patients based on sustained/long-term and transparent relationship.

5. Working closely with patients groups, regulators, physicians to produce one global, harmonised disease/patient focused guideline for the clinical development of new medicines.

6. Following all necessary steps of clinical development from phase 1 to phase 3 and LCM; improving on patients characterisation.

7. Choosing appropriate size of studies, feasible study procedures & frequency of study visits.

D. Merante. ‘The migabalin ALDAY phase 3 program in pain associated with fibromyalgia: the lessons learned’. In press. CMRO, 2020
The journey continues…

Thank you for your attention!