

Panel Discussion 1: Perspectives on Decision-Making in the Early Stages of Instrument Development

*THIRD ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP*

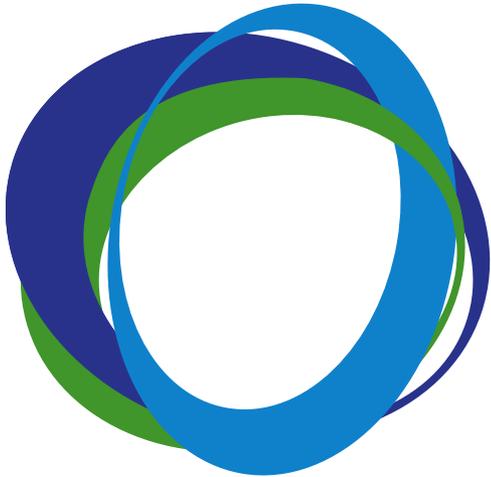
April 4, 2012 ■ Silver Spring, MD

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- Develop a strategy for critical decision-making during early stages of instrument development
- Appreciate the need to align drug development goals across disciplines within a company (clinical teams, health outcomes, labeling, marketing) and with others (FDA, academic consultants, etc.)
- Identify factors to consider when selecting a concept of measurement and a context of use
- Learn from recent examples of success

- Moderator
 - Laurie Burke, RPh, MPH
- Selection of concept of measurement
 - Vibeke Strand, MD, FACP FACR
- Selection of context of use
 - Debra Silberg, MD, PhD
- Instrument selection and development
 - Richard Levy, MD
- FDA response
 - Marc Walton, MD, PhD
- Industry response
 - Josephine Norquist, PhD
- Open floor discussion



OMERACT

Outcome Measures in Rheumatology

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Biopharmaceutical Consult

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OMERACT Structure

- Executive Committee:

Maarten Boers
Peter Brooks
Lee Simon
Vibeke Strand
Peter Tugwell



Clifton Bingham
Phil Conaghan
Maria Antonietta
D'Agostino
Laure Gossec
John Kirwan
Robert Landewe
Lyn March
Jas Singh
George Wells

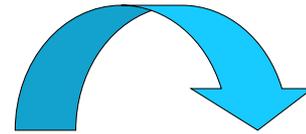
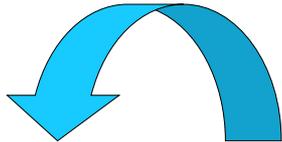
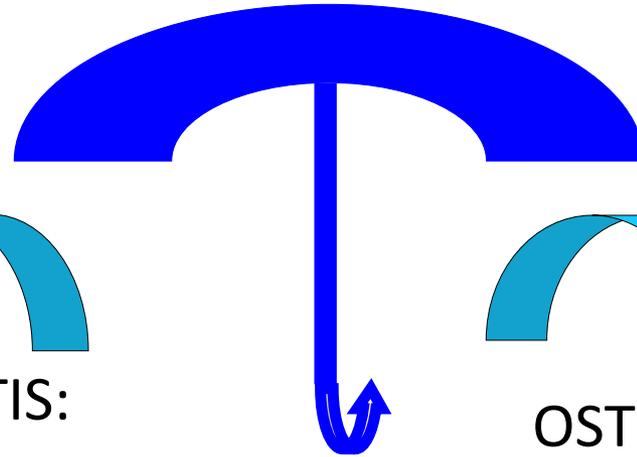
- Scientific Advisory Committee: Academic / Investigative Rheumatologists, including “Chairs” of working parties; Regulators
- Business Advisory Committee: Members of Pharma and Biotech Sponsors
- Attendees from North/Central/South America, Europe, Australasia, Africa

What is OMERACT?



- Presentation of evidence and development of consensus at each bi-yearly conference:
 - Literature reviews
 - Data mining from LOS and RCTs
- Goal: To Develop Recommendations for:
 - “Core Set” of minimum number of domains / outcome measures to be assessed in RCTs and LOS → Responder analyses
 - Working agenda identifying ‘need’ to focus future work
 - Advance methodology of selection, development and validation of measurement instruments
- Previous OMERACT Recommendations have been ratified by WHO/ ILAR in RA, OA, SLE, including HRQOL and Economic evaluations

The OMERACT 'Umbrella'



RHEUMATOID ARTHRITIS:

EULAR

ACR

JRA: PRCSG

SLE: SLICC / CLASI

EULAR

PsO/PsA: GRAPPA

OSTEOARTHRITIS: OARSI

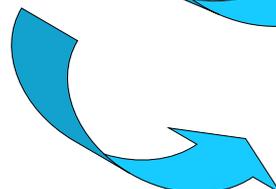
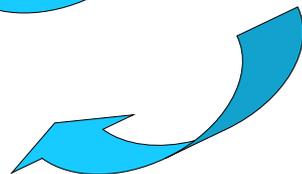
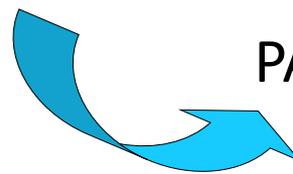
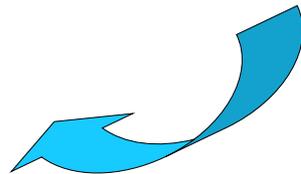
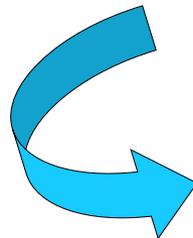
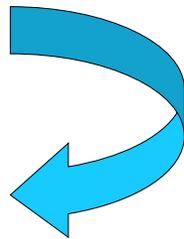
ANKYLOSING

SPONDYLITIS: ASAS

ASDAS

PAIN: IMMPACT

MYOSITIS: IMACS



- TRUTH:

- Face, content, construct and criterion validity

- Is the measure truthful, free from bias, relevant?

- Does it measure what is intended?

- Does it show convergence with appropriate variables and divergence between groups?

- Can it be compared with a gold standard measure?

- DISCRIMINATION:

- Reliability, reproducibility and sensitivity to change

- Is it internally consistent and stable?

- Does the measure discriminate between states of interest – at one timepoint, different timepoints?

- FEASIBILITY:

- Can the outcome easily be measured given constraints of time and costs?

- Is it easy to score and interpret?

Rheumatoid Arthritis: OMERACT I 1992



- Identified important 'domains' for assessment in RCTs
- Facilitated development of ACR Response Criteria:
Requires $\geq 20\%$ improvement in 5 of 7 measures:
 - Tender and Swollen Joint Count and 3 of the following 5:
 - » MD Global
 - » Physical function: HAQ
 - » Pain by VAS
 - » Patient Global
 - » ESR and/or CRP
- Facilitated broader acceptance of DAS28 and EULAR Response Criteria
- Facilitated Guidance Documents from EMEA and FDA which led to approval of 10 new DMARDs in RA from 1998 – 2010
- Emphasized importance of radiographic and HRQOL data when evaluating promising therapies

Strength of FDA Rheumatoid Arthritis Guidance Document



- Tricenter agreement; Proven track record → 10 approvals!
- Tiered Label Indications:
 - Improvement in Signs and Symptoms including 3 PROs
 - » By ACR Response Criteria
 - » At 6 or 12 months; now 3
 - Inhibition of Radiographic Progression
 - » Sharp Scores [erosions + JSN]
 - » At 12 months; now 6
 - Improvement in physical function and HRQOL using PROs:
 - » HAQ and SF-36
 - » Over 2-5 years
- May be achieved in a single protocol using prespecified outcome criteria and Hochberg analysis

- Demonstrated that ‘generic’ measures of HRQOL are sensitive to change in RA RCTs
- With patients, identified ‘MCID’ for HAQ and SF-36.....facilitating:
 - Comparisons across products, disease populations
 - Economic evaluations
- Helped to show impact of ‘Rheumatic Diseases’ to WHO
 - In the ‘Bone and Joint Decade’
 - Economic analyses have identified importance of Rheumatic Diseases relative to CV, DM, HTN, OP....
 - [Hopefully] → allocation of more resources to identify and treat Rheumatic Diseases.....
- ACR/EULAR Preliminary Definition of Remission of RA for RCTs

How did Patients become involved in OMERACT?

- In 2000, OMERACT 5 considered what might be a 'clinically important change' in response to treatment
- It occurred to participants in the final plenary session that it might be sensible to seek patients' opinions about this
- It was resolved to invite patients to participate in OMERACT 6

1992 Maastricht, Netherlands

1994 Ottawa, Canada

1996 Cairns, Australia

1998 Cancun Mexico

2000 Toulouse, France

2002 Brisbane, Australia

2004 Asilomar, US

2006 St. Julian's Bay, Malta

2008 Kananaskis, Canada

2010 Borneo, Malaysia

2012 Pinehurst, US

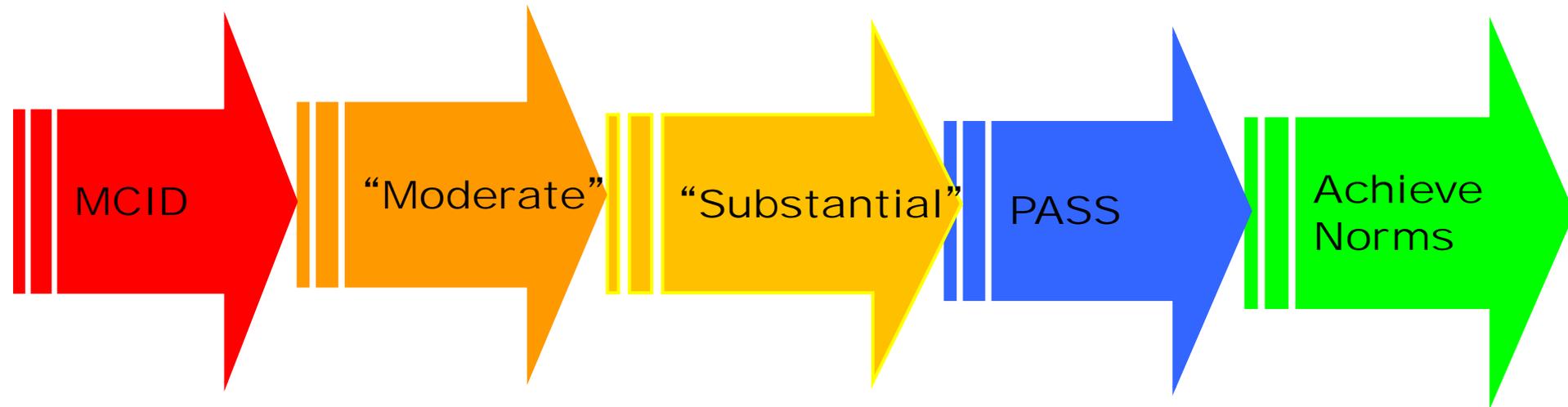
www.omeract.org

Minimum Clinically Important Differences



- MCID = Degree of improvement
 - **Perceptible to patients** = clinically important/ meaningful
 - Defined by patient query, delphi technique
 - OMERACT: 33-36% improvement; 18% > placebo
 - Confirmed by statistical correlations with patient global assessments in RCTs
 - **MCID values are consistent across agents and patient populations;**
 - **Improvements in disease specific measures highly correlated with generic measures, eg HAQ and SF-36**
- MID = improvement ≥ 0.5 SD of baseline value
- **Determination of proportion of patients with clinically important improvement provides a more interpretable result with direct clinical implications**

Spectrum of Improvements



The Impact of Patient Involvement



1. Enriched the OMERACT research agenda in RA
 - Assessment of fatigue in RA
 - Importance of assessment of HRQOL and “participation”:
 - Productivity within and outside the home
 - Presenteeism as well as Absenteeism
 - WPS-RA and WIS
 - Definition and assessment of “flare”
 - Working party of 50% patients and 50% HCPs
2. Insights into patient participation in research
 - Lessons we have learned
3. Standard for and stimulation of patient involvement
 - Should other organizations follow suit?

47 patients from 12 countries have attended OMERACT

- Patient participants identified fatigue as a specific problem in rheumatoid arthritis ^{1,2}
- Early descriptions at OMERACT 6 and 7 led to substantial qualitative research establishing importance of fatigue in RA^{3,4,5,6,7,8}
 - Focus groups in UK, Sweden and Ireland
- Subsequent qualitative work showed that measuring fatigue added new information to existing core set for RA ^{9,10,11,12}

1 Kirwan J et al. J Rheum 2003; 30:868-72.

2 Carr A et al. J Rheum 2003; 30:880-3.

3 Minnock P, Bresnihan B. A+ R 2004;50 :S471.

4 Hewlett S et al. Musculoskel Care 2005; 3: 131–142.

5 Kirwan JR et al. J Rheum 2005; 32: 2246-9.

6 Kirwan JR et al. J Rheum 2005;32:2250-6.

7 Hewlett S et al. AC&R 2005;53:697-702.

8 Ahlmen M et al. Rheumatology 2005;44:105-10.

9 Kirwan J et al. J Rheumatol 2009;36:2071–6

10 Kirwan J et al. J Rheumatol 2009;36:2067–70

11 Minnock P et al. Rheumatol 2009; 48:1533-1536.

12 Kirwan J, Hewlett S. J Rheum 2007; 34: 1171-3

Assessment of Fatigue in RA

- OMERACT 8 voted a measure of fatigue to be used alongside core set of outcome measures for RA, based on the following: ¹³
 - 23 instruments to measure fatigue evaluated¹⁴
 - Sufficient validation: FACIT; MAF; POMS; VAS¹⁵But cognition, coping, emotion, energy, frequency, impact, planning, quality of life, relationships, severity, sleep, and social life not / inadequately covered
- Development of Bristol RA Fatigue Multidimensional Questionnaire
 - Studies 1, 2, 3: explored patient perspective; drafted fatigue items in collaboration with patients; tested items for comprehension¹⁵
 - BRAF-MDQ (20 items) and short NRS and VAS scales for: severity of fatigue, effect and ability to cope¹⁶

<http://www3.interscience.wiley.com/journal/77005015/home>
- Tested in 229 RA patients with fatigue VAS scores ≥ 5 of 10

¹³ Kirwan J et al. J Rheum 2007; 34:1174-7.

¹⁴ Hewlett S et al. AC&R 2007; 57: 429-39.

¹⁵ Nicklin J et al. AC&R 2010; 62: 1552–8.

¹⁶ Nicklin J et al. AC&R 2010; 62: 1559–68.

Validation of BRAF-MDQ



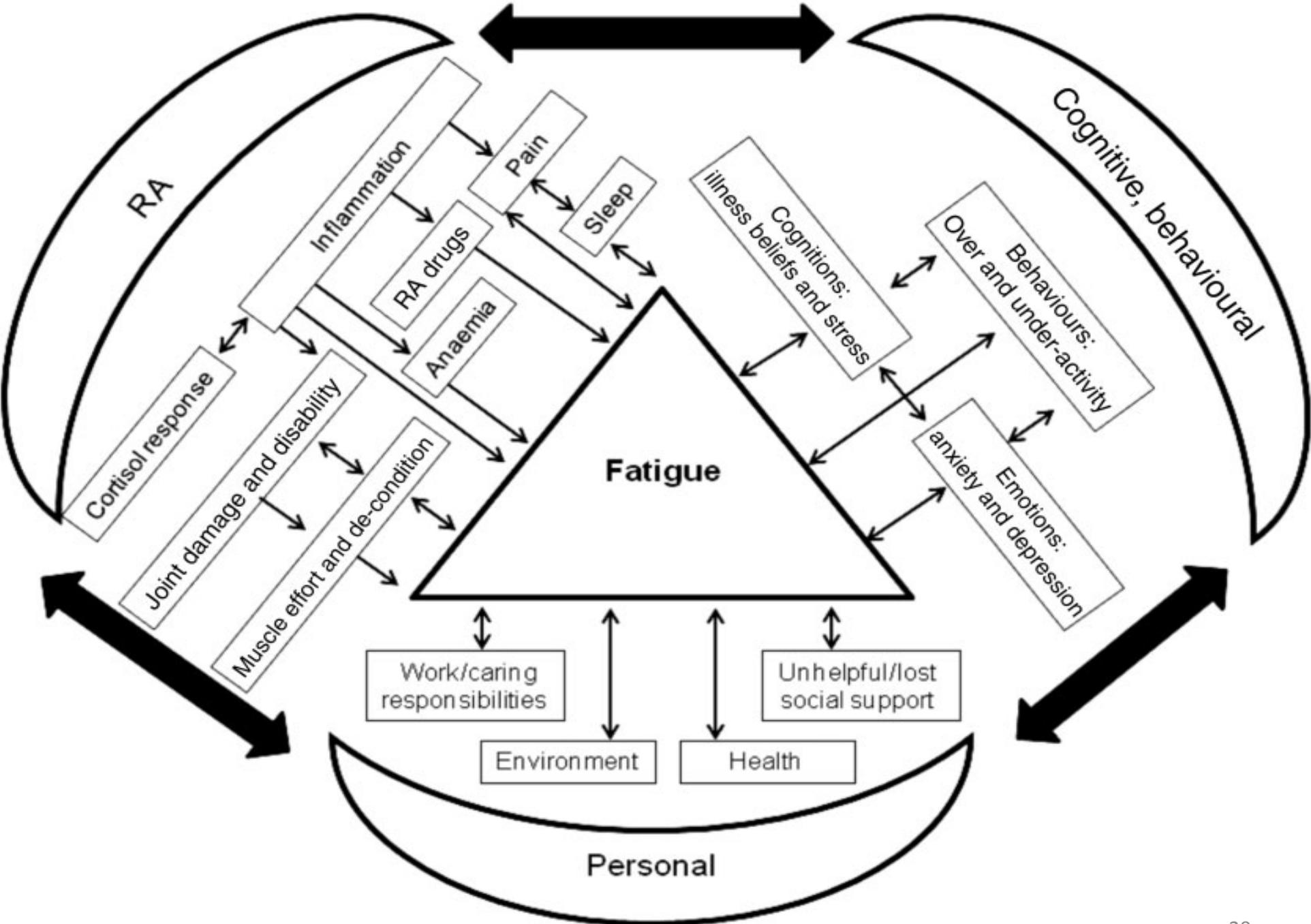
- 4 distinct dimensions (physical fatigue, living with fatigue, cognition fatigue, and emotional fatigue), which correlated well with MAF
- Internal consistency (Cronbach's $\alpha = 0.932$), criterion validity (correlation with other fatigue scales: $r = 0.643-0.813$), and construct validity (correlations with disability, mood, helplessness, and pain: $r = 0.340-0.627$)
- Global score correlated:
 - strongly with MAF, POMS and FACIT but not SF-36 vitality domain,
 - moderately with depression, anxiety, helplessness, and disability,
 - weakly with pain;
 - more strongly with emotions vs other instruments

Assessment of Fatigue in RA



“People with rheumatoid arthritis (RA) consider fatigue to be an important physical and cognitive symptom that is overwhelming, uncontrollable, unpredictable, unearned, and affects every aspect of life, and is experienced by up to 98% of patients (and 40% daily).”

“RA fatigue is complex and multicausal with components, such as pain, stress, depression, inflammation, and disability, that are likely to contribute in varying degrees at different times.”



Achieving consensus over measures involves:

- Content
 - Education in methodology
 - Agreement re:
 - » Purpose
 - » Domain(s)
 - » Applicability of specific measures
 - Iteration
- Process
 - Data-driven
 - Iterative, stepwise
 - Inclusivity
 - » Important role for dissenters
 - » Harsh data softened by political considerations

FDA Response

Marc Walton, MD, PhD

Associate Director for Translational Medicine

Office of Translational Sciences, CDER, FDA

PRO Instrument Development: Context of Use Example from GI

Debra Silberg, MD, PhD

Senior Director, Clinical Medicine Shire

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- Context of use
 - The environment in which the PRO data will be
 - Collected
 - Analyzed
 - Used
 - Impact of these on the PRO development

- Gastroenterology (luminal) diseases
 - Treatment driven by symptomatic endpoints
 - Overlapping symptoms in different diseases
 - Unclear correlation between physiological endpoints and symptoms
 - Multiple outcome tools, few developed post FDA guidance
 - Mix of signs and symptoms; patient reported and physician reported endpoints, daily and weekly recalls, QOL
 - Some examples of questionnaires used in GI
 - GERD: RDQ, ReQUEST, QOLRAD
 - Gastroparesis: GCSI
 - Crohn’s Disease: CDAI
 - Functional Dyspepsia: LDQ, NDI

- No physiological marker for disease
- Defined in terms of symptoms
- Large overlap in symptoms with GERD, gastroparesis and elements of irritable bowel syndrome
 - Some consider functional dyspepsia a continuum of IBS with upper GI symptoms
- Definition has been based on the Rome III criteria, which is from an international group of physicians that define the functional GI diseases

FUNCTIONAL DYSPEPSIA

Diagnostic criteria Must include:*

1. *One or more* of the following:
 - a. Bothersome postprandial fullness
 - b. Early satiation
 - c. Epigastric pain
 - d. Epigastric burning

AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

B1a. Postprandial Distress Syndrome

Diagnostic criteria Must include **one or both** of the following:*

1. Bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week
2. Early satiation that prevents finishing a regular meal, at least several times per week

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Supportive criteria

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present
2. Epigastric pain syndrome may coexist

B1b. Epigastric Pain Syndrome

*Diagnostic criteria** Must include **all** of the following:

1. Pain or burning localized to the epigastrium of at least moderate severity, at least once per week
2. The pain is intermittent
3. Not generalized or localized to other abdominal or chest regions
4. Not relieved by defecation or passage of flatus
5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders

* Criteria fulfilled for the 3 months with symptom onset at least 6 months prior to diagnosis

Supportive criteria

1. The pain may be of a burning quality, but without a retrosternal component
2. The pain is commonly induced or relieved by ingestion of a meal, but may occur while fasting
3. Postprandial distress syndrome may coexist

- Scoping document was based on the Rome III criteria and submitted for review to the FDA
- FDA response
 - Premature to proceed with instrument development in the absence of an **acceptable disease definition**
 - Team asked to construct eligibility criteria for drug development program
 - Rome III considered inadequate alone, specific inclusion and exclusion criteria needed to define target population
 - Confirmed that functional dyspepsia is a unique condition
 - Need to define a population without concomitant functional or structural GI disorders
 - Exclusions needed for gastroparesis, chronic constipation, IBS and GERD
- FDA needed to make certain we had the “disease defining concepts” prior to developing the endpoints

- Reaction to the letter
 - Unclear how to address the issues
 - Did we really need to define the disease? How could we do this, as experts have been working on this for years?
- Importance of meeting with the FDA (DGIEP and SEALD)
 - Not as much of a hurdle as we thought
 - Rational discussion on what next steps would be
 - Revise exclusion criteria
 - Take out sub-classifications
 - Enhance alarm symptom
- Clear path forward

Addressing FDA's concerns

- Utilizing the Rome III criteria, but dropped the distinction between the two subcategories
 - Will test whether there are subcategories during the concept elicitation stage
- More specific exclusion criteria to exclude other diseases with similar symptoms
 - Active symptoms of an excluded disease or past disease if chronic (e.g. heartburn while on a PPI)
 - Predominant signs and symptoms of an excluded disease (e.g. vomiting is more consistent with gastroparesis than functional dyspepsia)
 - Clearer exclusions for “alarm” symptoms

- Utilize existing information to start PRO development
 - Disease guidelines
 - Previous PROs or other instruments (may be able to adapt an existing instrument)
- Follow the FDA guidance
- Partner with the FDA
 - Important to have SEALD and specific division review the scoping document prior to starting development work
 - If possible, best to have discussion with the Agency, sometimes what seems insurmountable is not
 - Revise scoping document and have Agency review
 - Keep the Agency engaged throughout the process

- Does drug development stop while PROs are being developed?
 - What are acceptable endpoints?
 - Functional dyspepsia, IBS, Crohn’s disease
- With all of the exclusions, are there patients with “pure functional dyspepsia” since other diseases are common and co-exist
 - GERD and functional dyspepsia
- Endoscopy not practical in the PRO development phase, but would it be expected in a clinical trial for efficacy?
- Is there an opportunity to discuss these and other concerns with the Agency?
 - Often difficult to get the right people together and one consistent voice

FDA Response

Marc Walton, MD, PhD

Associate Director for Translational Medicine

Office of Translational Sciences, CDER, FDA

Jakafi™ (ruxolitinib) Approval for Myelofibrosis

Rapid and Successful Use of a Patient Reported Outcome Endpoint to Support Product Labeling

Richard Levy, M.D.
Executive Vice President
Chief Drug Development and Medical Officer
Incyte Corp.



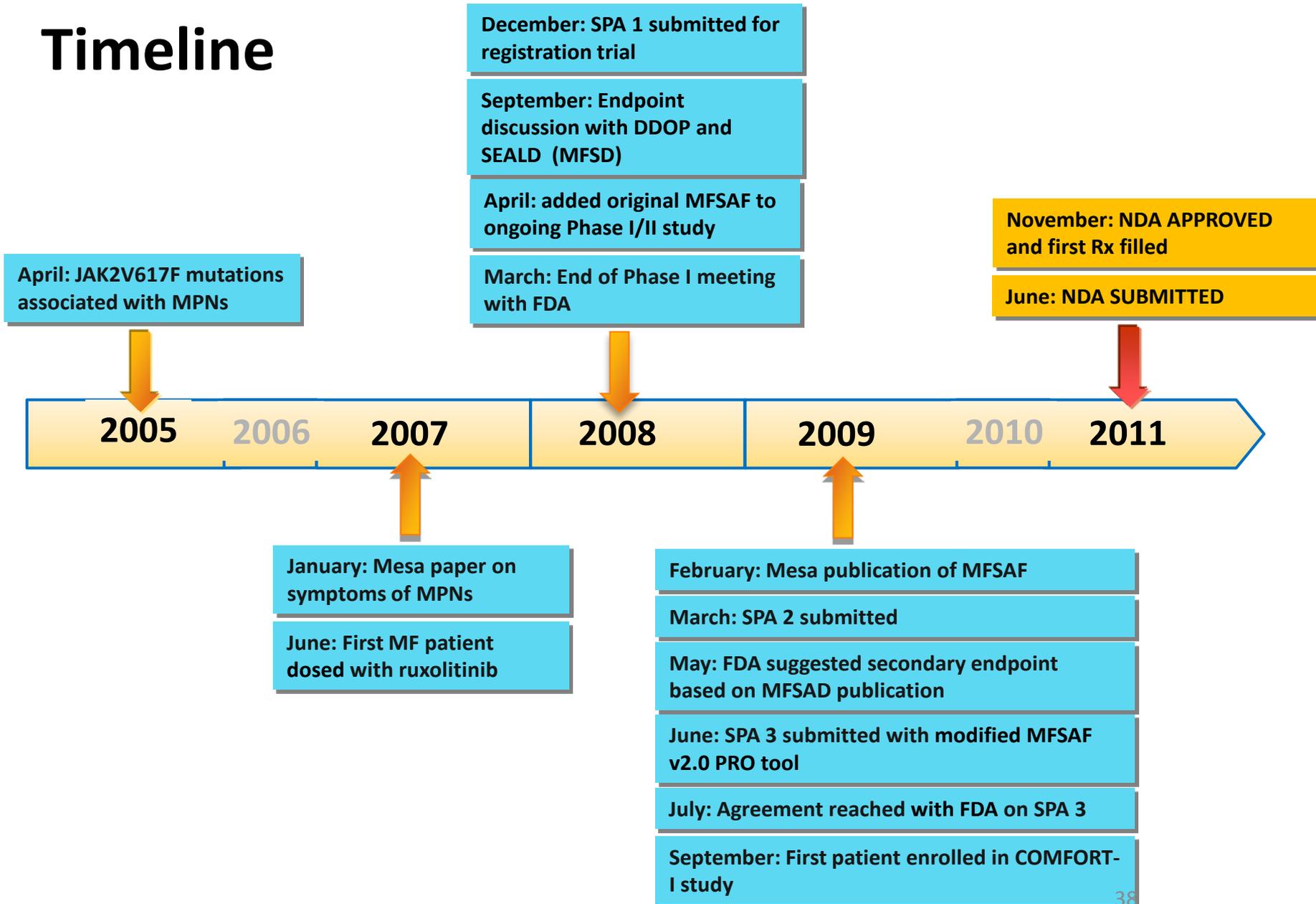
Jakafi™ (ruxolitinib)

Approval for Myelofibrosis



- Received FDA approval as a ‘first in class’ and ‘first in indication’ drug in less than 4.5 years and included patient reported outcome (PRO) information in the product label
- How did Incyte, a company of less than 200 people at the start of development:
 - Become the first company to obtain approval and labeling for an oncology indication using the FDA PRO Guidance?
 - Develop and demonstrate a PRO tool was “fit for purpose” and obtain approval in less than 4.5 years?
- Was this approach risky or worthwhile?

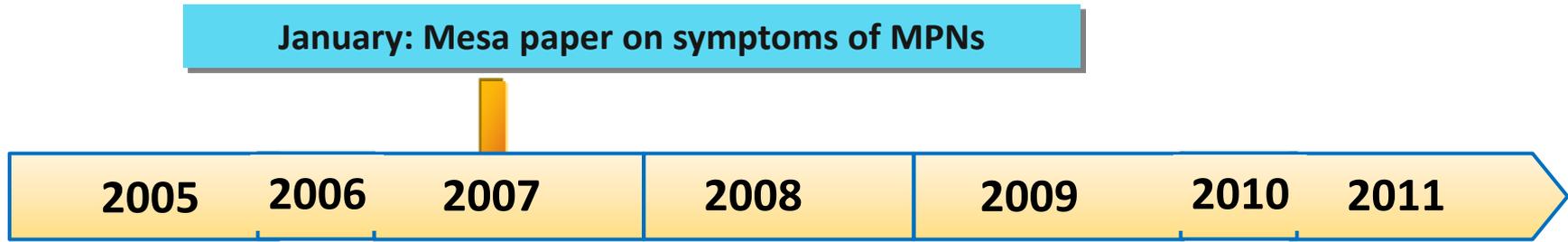
Timeline



April: JAK2V617F mutations associated with MPNs



- Several groups identified the association of the JAK2V617F mutation with myeloproliferative neoplasms (MPNs), including myelofibrosis in 2005
- At the time Incyte was already working to synthesize potent and selective JAK 1 and 2 inhibitors for development in inflammatory disorders and tumors driven by IL-6

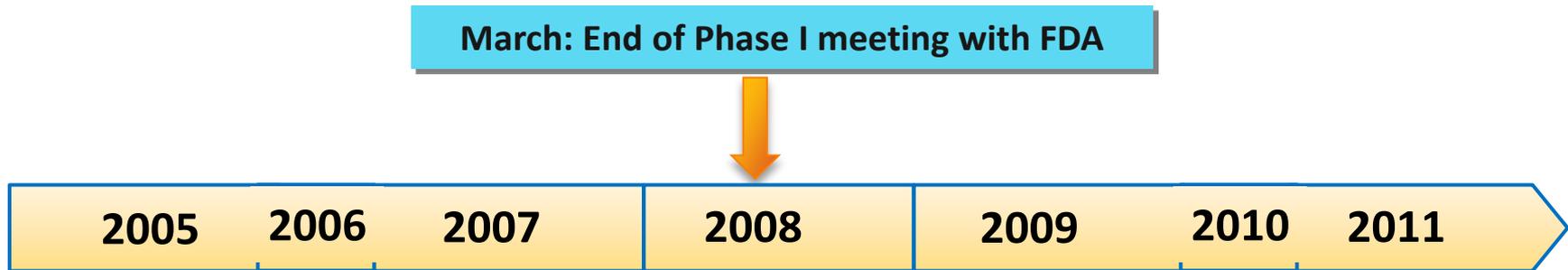


- Dr. Ruben Mesa published a paper demonstrating the symptomatic burden of patients with MF and other MPNs including polycythemia vera and essential thrombocythemia approximately five months prior to the first MF patient being dosed with ruxolitinib in a Phase I/II study
- Nevertheless, Incyte did not add symptom assessments to the Phase I study

June: First MF patient dosed with ruxolitinib



- The first patient was dosed on June 22, 2007
- The patient was sedentary and had a spleen palpable more than 30 cm below the costal margin
- At the one week follow-up visit the spleen was reduced to < 10 cm and the patient reported feeling like a new person
- During continued treatment with ruxolitinib, the patient's spleen became not palpable and he started playing golf, eventually walking 18 holes



- A meeting was held with DDOP to review efficacy and safety data and to discuss possible registration endpoints for a first ever indication of myelofibrosis
- FDA indicated that an objectively measured spleen size reduction as well as one other clinically relevant benefit might support registration
- Use of symptomatic improvement based on the FDA's PRO guidance was mentioned as a possible but difficult and risky approach

April: Original MFSAF added to ongoing Phase I/II study



- In April 2008 the ongoing Phase I/II protocol was amended to formally collect information on the severity of symptoms of MF
- The original MFSAF (for Myelofibrosis Symptom Assessment Form) tool (19 questions) was developed by co-investigator Dr. Mesa and his colleagues at Mayo Clinic and assessed many of the symptoms identified by Mesa in his 2005 paper
 - Filled out by the investigator at each visit based on answers given by the patient



- In the spring and summer of 2008
 - An additional amendment was put in place in the Phase I/II study to assess the spleen volume by MRI/CT as well as a number of other potential measures of clinically relevant improvement, including but not limited to, a 6-minute walk test
- Separately the most important and relevant symptoms of MF were identified from non-structured patients interviews
 - A 46-item PRO was developed based on a range of symptoms and signs
 - Evaluated these signs/symptoms based on severity, frequency, duration, and degree of bother.
 - This tool was called the MFSD for ‘Myelofibrosis Symptom Diary’
 - Cognitive testing with MF patients was successfully performed
- A meeting was requested with DDOP and SEALD to further consider endpoints for a registration study and review the MFSD

September: Endpoint discussion with DDOP and SEALD including MFSD

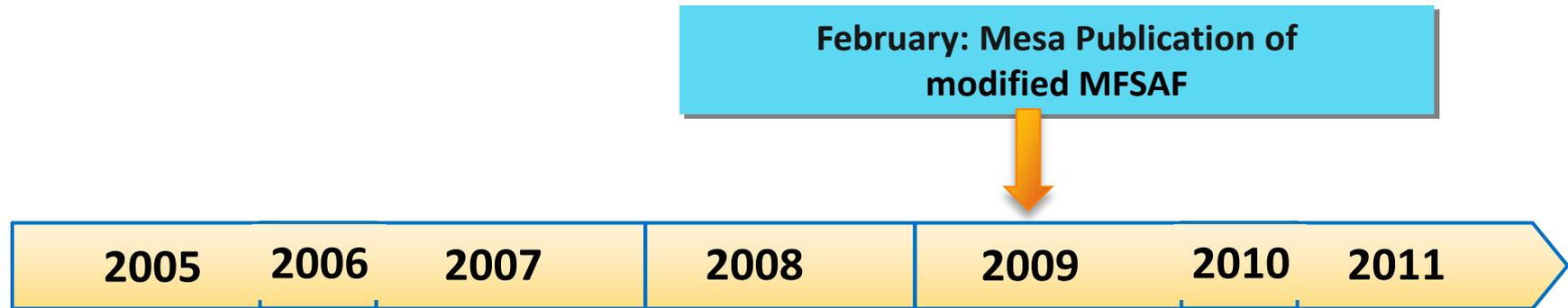


- Several potential co-primary or secondary endpoints were discussed
- The 6 minute walk test was recommended as the most viable of the co-primary endpoints
- The DDOP continued to take the position that an endpoint based on symptoms was risky
 - Also indicated that the concept of fatigue could not be adequately understood
- The SEALD team gave advice on the MFSD including: (1) focus on symptoms at their worst severity; (2) use 24-hour recall period and (3) 0-10 numeric rating scale
 - Also recommended additional patient interviews to establish content validity (which we subsequently conducted)

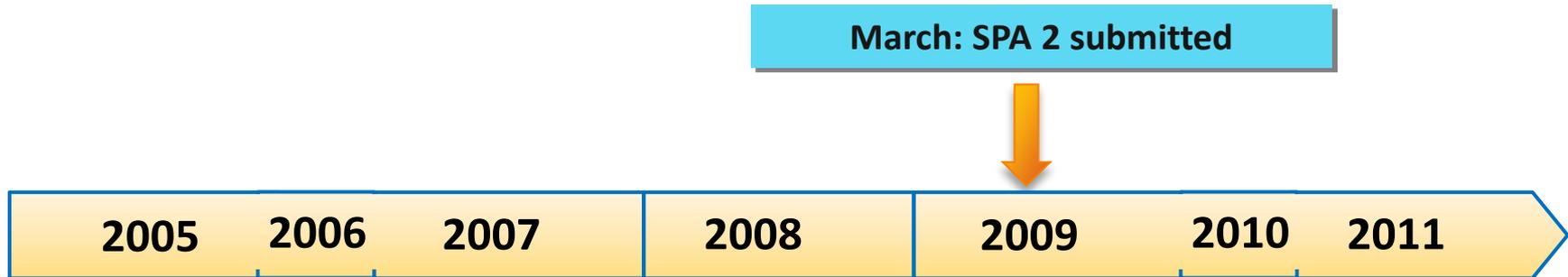
December: SPA 1 submitted for registration trial



- Based on excellent results with the 6-minute walk test, Incyte proposed co-primary endpoints based on reduction in spleen volume and improvement in 6-minute walk distance
- Symptoms of MF were proposed as a secondary endpoint without control of alpha spend and there was no expectation that results could be including in labeling
- No agreement was reached on the SPA because the only demonstration of impaired walk distance in MF was our own data
- FDA instead proposed that we submit a new SPA based on a novel definition of disease progression



- In Feb 2009 a paper by Mesa described an updated version of the original MFSAF we had been using in our ongoing Phase I /II trial
- Referred to this version as the modified MFSAF

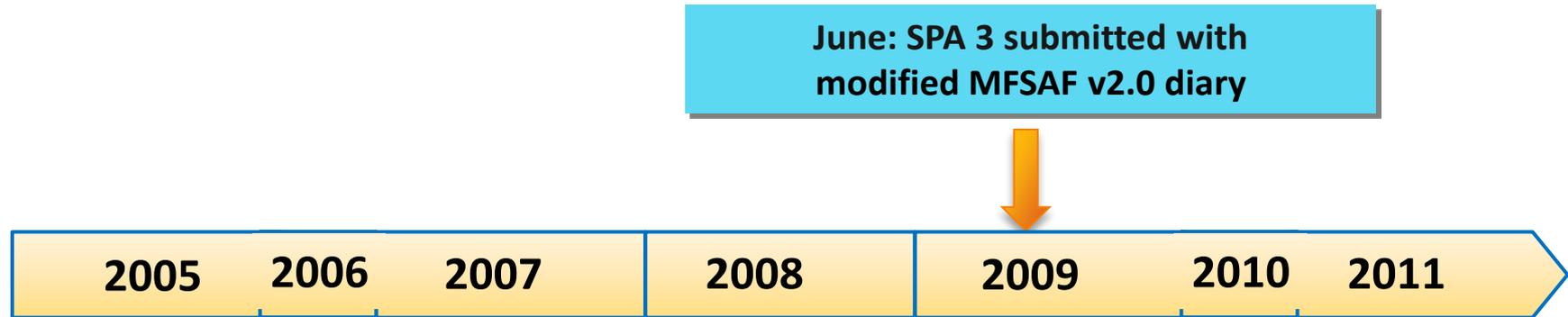


- In March of 2009 Incyte submitted a second SPA based on the FDA's proposed definition of disease progression
- Symptomatic improvement remained a secondary, non-alpha controlled endpoint
- FDA rejected the second SPA because it was expected that differences between the treatment arms would reach statistical significance well in advance of the median time to progression
- However, FDA offered another option which was immediately appealing to Incyte

May: FDA Suggested secondary endpoint based on MFSAF publication



- DDOP, in conjunction with SEALD, now recommended a secondary endpoint of using a daily diary which was a modified version of the MFSAF published by Mesa earlier that year
- We were advised to remove fatigue from the tool and to focus only on symptoms and not outcomes
- Prior to submitting a new SPA the qualitative patient interviews and cognitive testing were reevaluated and shown to support the new version of the MFSAF which we now call the modified MFSAF version 2.0 diary



- In the SPA it was proposed that the tool would be demonstrated to be “fit for purpose” by analyzing blinded data at 1 month of the 6 month randomized, placebo controlled trial and with the unblinded data obtained at the end of the study

Modified MFSAF v2.0 Diary

1. During the past 24 hours, how severe were your worst **night sweats** (or feeling hot or flushed) due to MF?

2. During the past 24 hours, how severe was your worst **itchiness** due to MF?

3. During the past 24 hours, how severe was your worst **abdominal discomfort** (feel uncomfortable, pressure or bloating) due to MF?

4. During the past 24 hours, how severe was your worst **pain under the ribs** on the left side due to MF?

5. During the past 24 hours, what was the worst feeling of fullness (**early satiety**) you had after beginning to eat due to MF?

6. During the past 24 hours, how severe was your worst **bone or muscle pain** due to MF (diffuse not joint or arthritis pain)?

7. During the past 24 hours, what was the worst degree of inactivity (including work and social activities) you had due to MF?

Each question answered with 0-10 point scale:

0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

July: Agreement reached on SPA 3

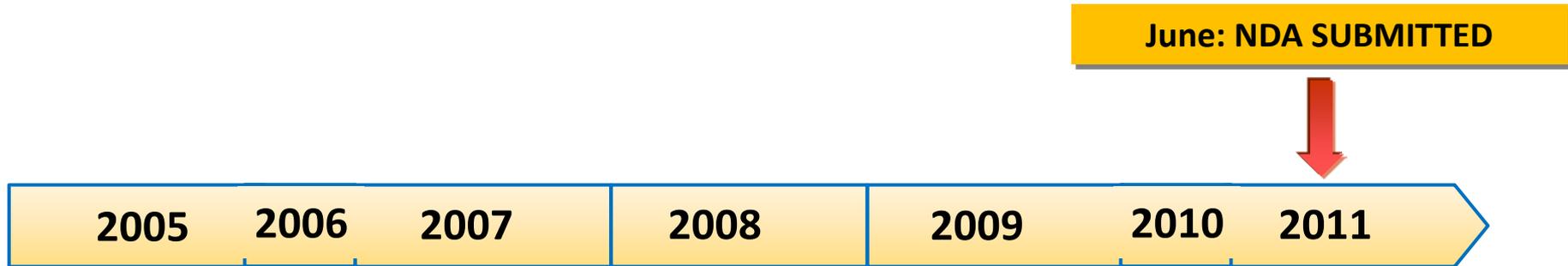


- The newly formed Division of Hematology Drug Products agreed to the SPA
- No comment was given on the acceptability of demonstrating “fit for purpose” within the registration study

Timeline

**September: First patient enrolled in
COMFORT-I study**





- The modified MFSAF v2.0 diary was demonstrated as “fit for purpose” by performing the required activities and analyses as outlined in the FDA PRO guidance
 - An Evidence Dossier was submitted with the NDA

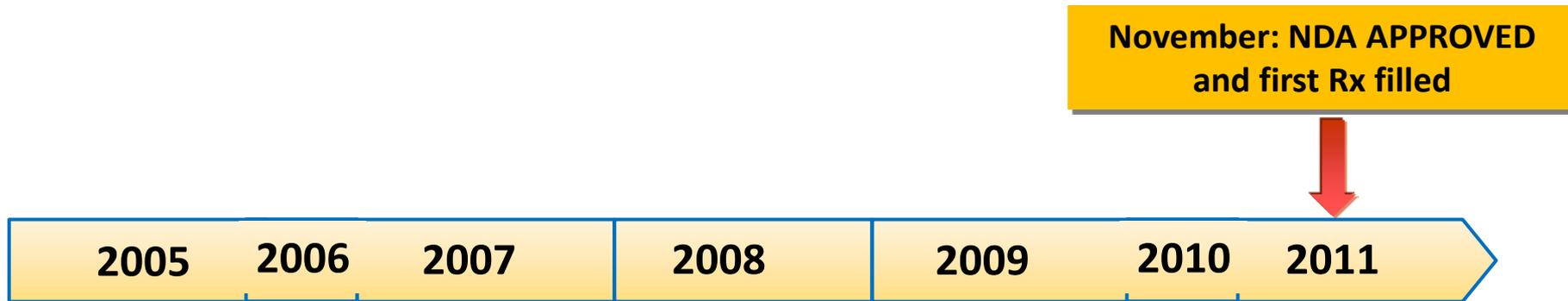
Modified MFSAF v2.0

Data Collection Metrics



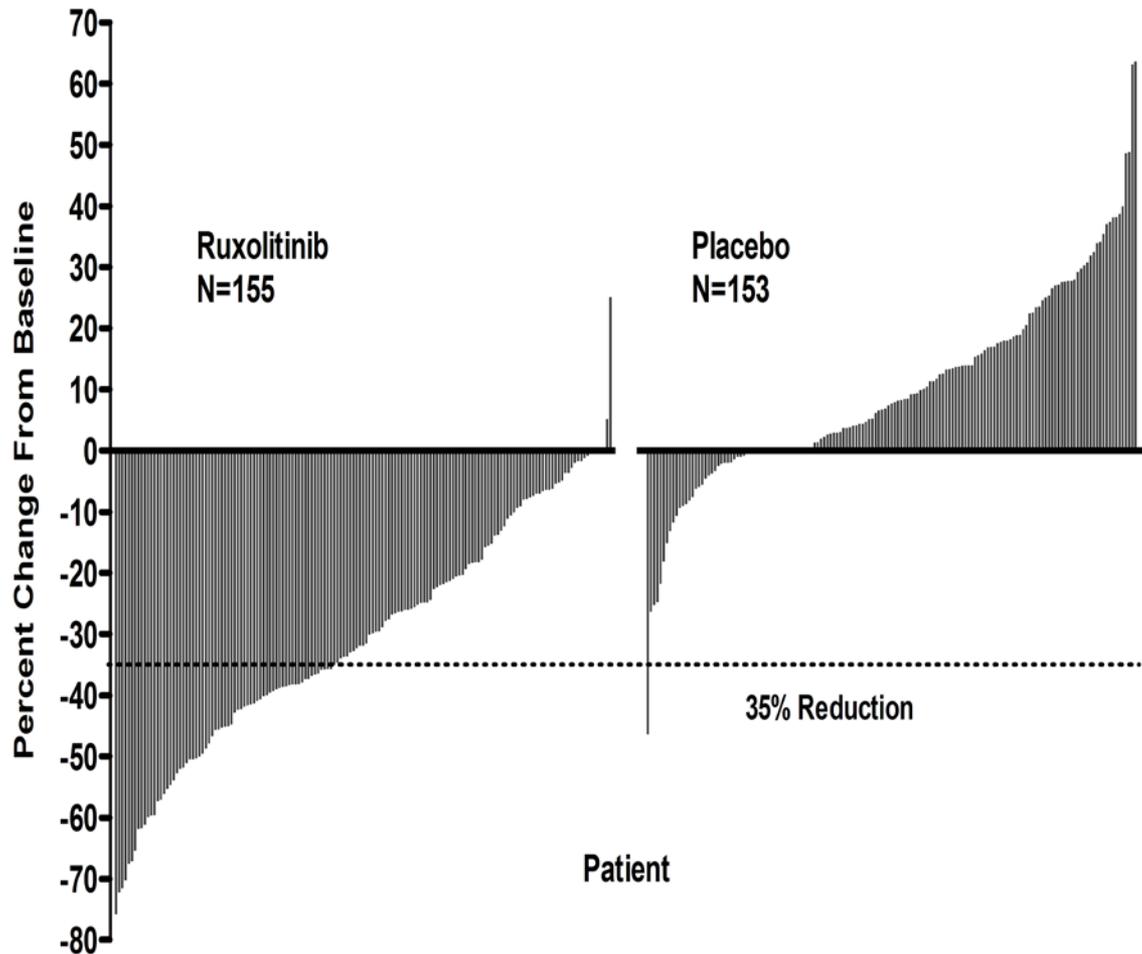
- Electronic handheld diaries provided by invivodata inc. were used to collect the patient reported symptom data
- Compliance with data entry
 - 96% of all expected data entered
 - 98% completed minimum requirement of 4 out of 7 baseline days
 - 95% completed minimum requirement of 20 out of 28 days during Month 6 of the trial
 - 94% completed the daily assessment in 1 minute or less
- Test- retest reliability correlation coefficient from Week 7 to Week 8 of 0.97 with placebo and 0.98 with ruxolitinib
- Correlation with pain items in MFSAF with pain scores in EORTC QLQ C30 and Brief Pain Inventory (BPI) of approximately 0.6

Timeline



- Full approval was obtained with FDA indicating that without the demonstration of clinical benefit using the data produced by the modified MFSAF v2.0 diary, it would have been hard to justify anything but accelerated approval
- The time to approval was shorter than if the registration had to be based on time to progression
- Labeling claims allow us to promote one of the most important benefits of the drug for patients with often debilitating symptoms

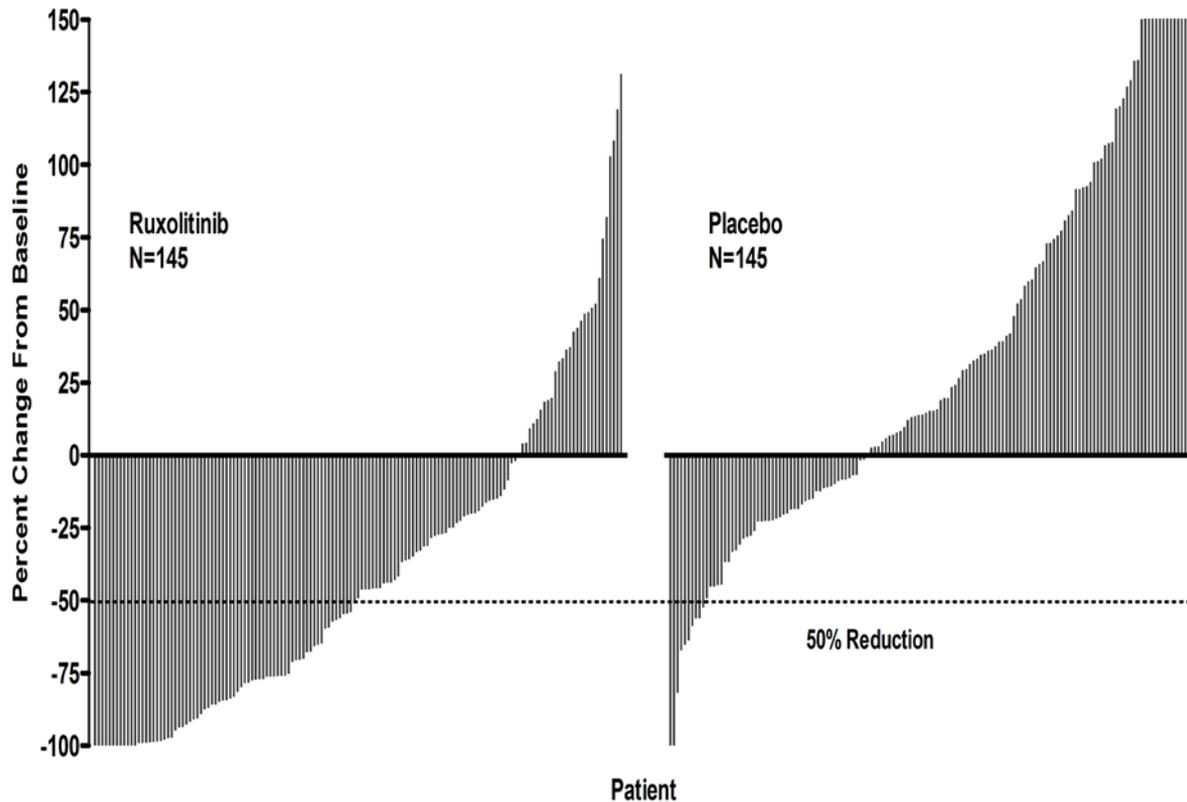
COMFORT I: Primary Endpoint Analysis: Change in Spleen Volume



Responder Analysis

Proportion with $\geq 35\%$ Reduction	
Ruxolitinib 41.9%	PBO 0.7%
P<0.0001	

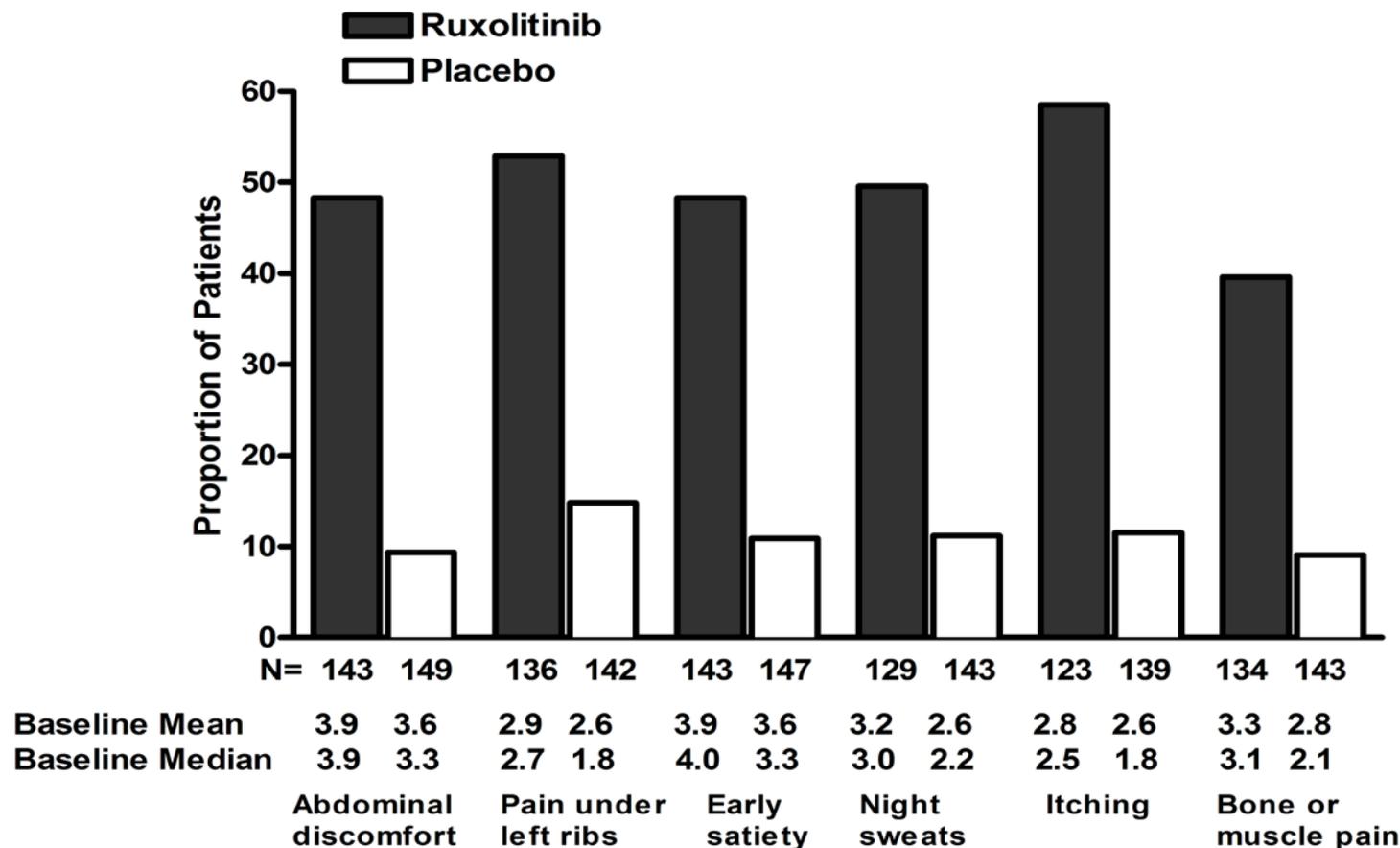
Secondary Endpoint: Total Symptom Score (TSS) Response



Responder Analysis

Proportion with $\geq 50\%$ Reduction	
Ruxolitinib 45.9%	PBO 5.3%
P<0.0001	

Individual Symptom Scores: Proportion of Patients with 50% or Greater Improvement



Individual score range = 0 to 10

- Treatment with Jakafi can cause hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia, which are each dose-related effects, with the most frequent being thrombocytopenia and anemia.
- Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections
- Active serious infections should have resolved before starting Jakafi.
- The three most frequent non-hematologic adverse reactions are bruising, dizziness and headache

How did Incyte do it so fast?



- Symptoms identified as a particularly prominent aspect of the disease before we started
- Focus on symptoms because of the remarkable improvement seen in the first patients treated
- Ability to use an existing PRO tool (e.g. Mesa MFSAF), modify it and then demonstrate it as a ‘fit for purpose’ instrument consistent with the FDA PRO guidance saved time
- Demonstration of “fit for purpose” within the registration study instead of in advance of the registration study

Was this approach risky?

- Incyte did not think so, because:
 - An SPA was in place for approval based on spleen size reduction as the only primary endpoint
 - It was clear from Phase 2 data that there was a very high likelihood that the secondary endpoint based on symptoms would be met
 - The risk was that the PRO tool would not be demonstrated as ‘fit for purpose’
 - We saw this primarily as a risk of not being able to include the symptom data in the package insert
 - We did not see this as a risk to approval because even if symptom data were not included in labeling, the clear symptomatic benefit would indicate a positive benefit risk profile with an achieved primary endpoint

Was this approach worthwhile?



- Absolutely!
 - Approval at least one year earlier than based on survival or progression free survival
 - Higher likelihood of success
 - Ability to directly promote the unprecedented symptomatic benefit in a disease characterized by often debilitating symptoms
 - Reputation of Incyte Corporation enhanced with FDA and across the industry

FDA Response

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Associate Director for Translational Medicine

Office of Translational Sciences, CDER, FDA

Industry Response

Josephine Norquist, MS
Merck Sharp & Dohme, Corp

BREAK