Second Annual Patient-Reported Outcome (PRO) Consortium Workshop

March 15, 2011 ■ Silver Spring, MD

Co-sponsored by

PRO Consortium
Working Group Updates

SECOND ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

March 15, 2011 ■ Silver Spring, MD

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FDA

Active Working Groups

PRO CONSORTIUM
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Irritable Bowel Syndrome

- Co-chairs: Mollie Baird and Charlie Baum

Cognition

- Co-chairs: Christopher Leibman and Usha Mallya

Asthma

- Co-chairs: Linda Nelsen and Sulabha Ramachandran

Depression

- Co-chair: Nicholas Greco

Non-Small Cell Lung Cancer

- Co-chairs: Ben Gutierrez and Peter Trask

Functional Dyspepsia

- Co-chairs: Mollie Baird and Robyn Carson

Rheumatoid Arthritis

- Co-chairs: Enkeleida Nikai and April Naegeli

Irritable Bowel Syndrome (IBS) Working Group

Mollie Baird, MPH
Associate Director, Clinical Operations
Ironwood Pharmaceuticals

IBS WG Participants

NAME	COMPANY
Co-Chairs	
Mollie Baird	Ironwood Pharmaceuticals
Charles Baum	Takeda Pharmaceuticals
Participants	
Robyn Carson, Steven Shiff	Forest Research Institute
Jeff Johnston	Ironwood Pharmaceuticals
Alex Kudrin	Takeda Pharmaceuticals
Non-Member Participants	
Nancy Norton	IFFGD
Lin Chang, Brennan Spiegel	UCLA
Jeff Lackner	University at Buffalo
Vendor	
Sheri Fehnel, Claire Ervin, Allen Mangel, Diana Goss	RTI Health Solutions

Introduction/Background

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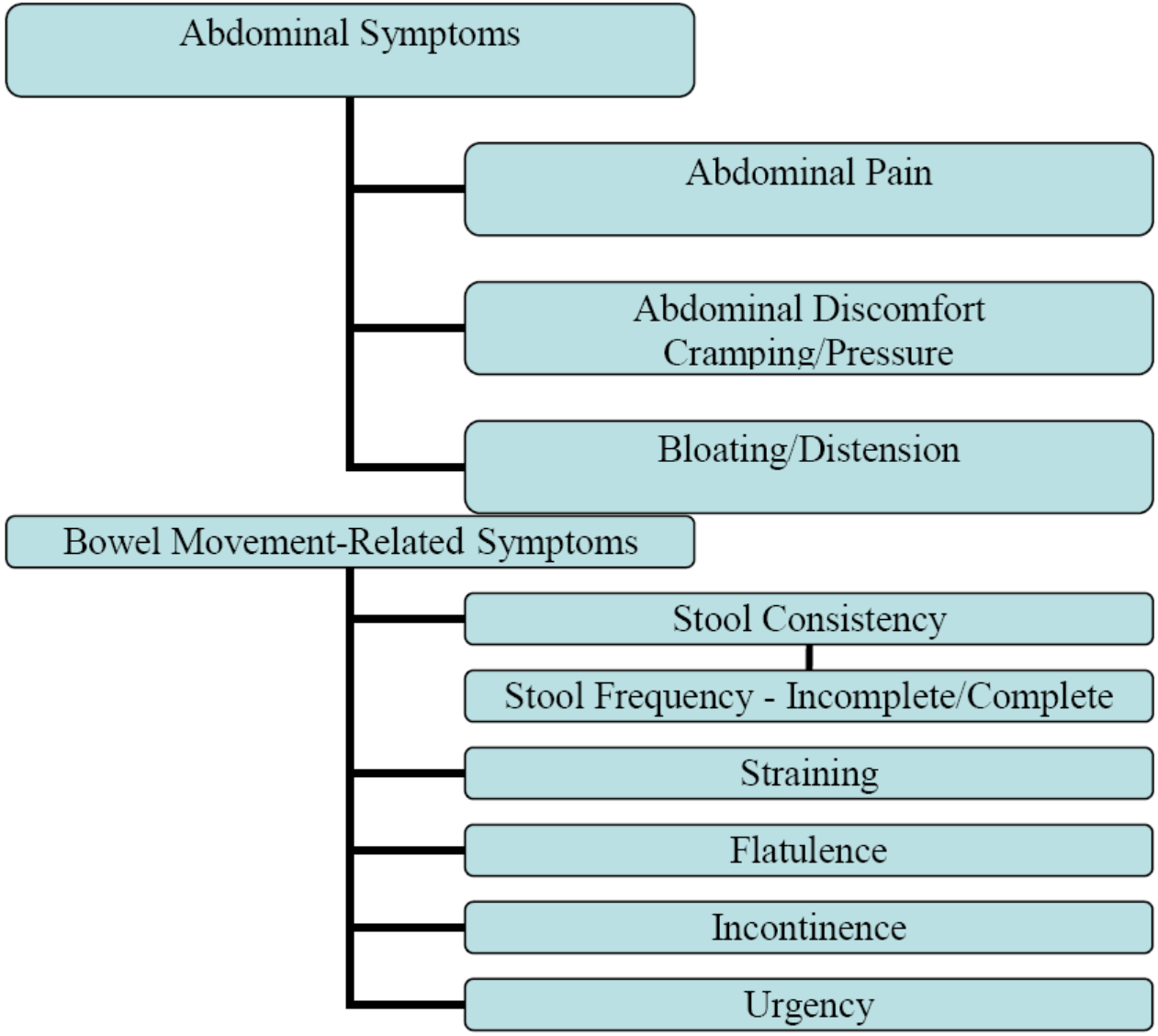
Objective: Develop a PRO instrument that can be qualified by the FDA for use as a primary endpoint in clinical trials

Disease: IBS-subtype (constipation-predominant, mixed or alternating pattern, and diarrhea-predominant)

Target population: Adult males/females meeting Rome III criteria for IBS-subtype

Targeted labeling language: The IBS PRO instrument would provide an indication of improvement in symptom severity. The claim would be treatment of IBS-subtype supported by an improvement in both abdominal symptoms and bowel movement-related symptoms

Proposed Initial Conceptual Framework



Status

News of interest since last report

- Qualitative research (concept elicitation) interviews are underway with RTI-HS
  - Round 1: Raleigh - Feb 28 – March 2
  - Round 2: San Antonio - March 7-9
  - Round 3: San Diego - March 16-18

Recent accomplishments

- Finalized IBS Concept Elicitation Protocol, Patient Interview Guide, and Targeted Review of the Literature

Next Steps

- Complete qualitative research
- Generate/revise item pool and draft instruments
- IBS WG Expert Panel meeting: June 10 in Raleigh, NC

Cognition Working Group

Christopher Leibman
Sr. Director, Health Economics/Market Access
Janssen Alzheimer Immunotherapy R&D, LLC

WG Participants

NAME	COMPANY
Co-Chairs	
Chris Leibman	Janssen AI (a Johnson & Johnson Company)
Usha Mallya	Novartis Pharmaceuticals
Participants	
Steven Hass, Nicholas Greco, Amy Duhig	Abbott Laboratories
Anna-Karin Berger, Daniel Eek, Lori Frank	AstraZeneca
Juergen Reess, Mark Gordon	Boehringer Ingelheim
David Budd, Lucinda Orsini	Bristol-Myers Squibb
Mallik Angalakuditi	Eisai
Loretto Lacey, Gary Romano	Janssen AI (a Johnson & Johnson Company)
Julie Chandler, Yi Mo	Merck Sharp & Dohme Corp
Ari Gnanasakthy, Simu Thomas	Novartis Pharmaceuticals

WG Participants cont.

NAME	COMPANY
Zoe S. Kopp, Joel Bobula	Pfizer, Inc.
Nina Hill, Judith Dunn, Todd Paporello, Glenn Morrison	Roche Laboratories
Vendor	
Kellee Howard, Leah Kleinman, William Lenderking, David Miller	United Biosource Corporation (UBC)

Introduction

Objective

- To develop a reliable, valid and FDA-qualified PRO to capture the patient's perspective on outcomes which would contribute to detection of disease, description of disease progression, and the measurement of treatment effect

Target Population (and stage)

- Patients diagnosed with MCI due to AD age 45 years and older.

Role of PRO measure in endpoint hierarchy

- Co-Primary

Targeted Labeling Language

- Focus on claims related to Interpersonal Functioning (IF) and Complex Activities of Daily Living (complex ADLs)

Background

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Submission feedback April, 2010:

- Concern about ability of patients (and caregivers) to report reliably even at early stages of AD
- Interpersonal functioning and complex ADLs are good targets for measurement
- Labeling will not be duplicative and will avoid implication of disease-modifying effects

Resubmission focus:

- Literature review on preservation of insight in MCI
- Revised endpoint model
- Conceptual Framework focusing on Interpersonal functioning and complex ADLs

Conceptual Framework - Core Concepts

Interpersonal functioning

- Interpersonal functioning is expressed as the ability to interact effectively and appropriately with other people across a wide range of relationships (e.g., as parent, spouse, employee).

Complex activities of daily living (ADL) task performance

- Everyday functioning is expressed by the ability to complete Complex Activities of Daily Living which are activities requiring cognitive skills beyond those required for Instrumental Activities of Daily Living.

Conceptual Framework - Interpersonal Functioning

Conversational Skill *"…ask you a question and you go 'duh,' …can't think how to answer" [pt]*

Dysnomia *"I don't remember names" [pt]*

Executive Functioning to Maintain Social Relationships *"We used to pick up our grandchildren a lot…I would say, 'Go write it down' because he wouldn't want to miss it." [cg]*

Maintaining Social Roles *"I'm not as interested in seeing people." [pt]*

Social Use of Language *"I purposely don't …try to tell them something that's important to me because I'm not going to get the words right." [pt]*

Working Memory *"Sometimes you don't know what you've already said." [pt]*

Conceptual Framework - Complex ADLs (CADLs)

Household Management *"…now I …lock the burners so he can't turn them on." [cg]*

Managing Finances *"One day I started comparing the checkbook with the bills, and was I in for a shocker." [cg]*

Navigating *"He wants to go a different direction than before, even some older places." [cg]*

Need for support *"He just doesn't remember. So I am forced into the whole mother thing again." [cg]*

Conceptual Framework - Complex ADLs (CADLs)

Organizing Information and Materials for Task Completion *"That's what he really gets a lot frustrated with is trying to find the pots and pans that he wants and everything in the cupboards and-so." [cg]*

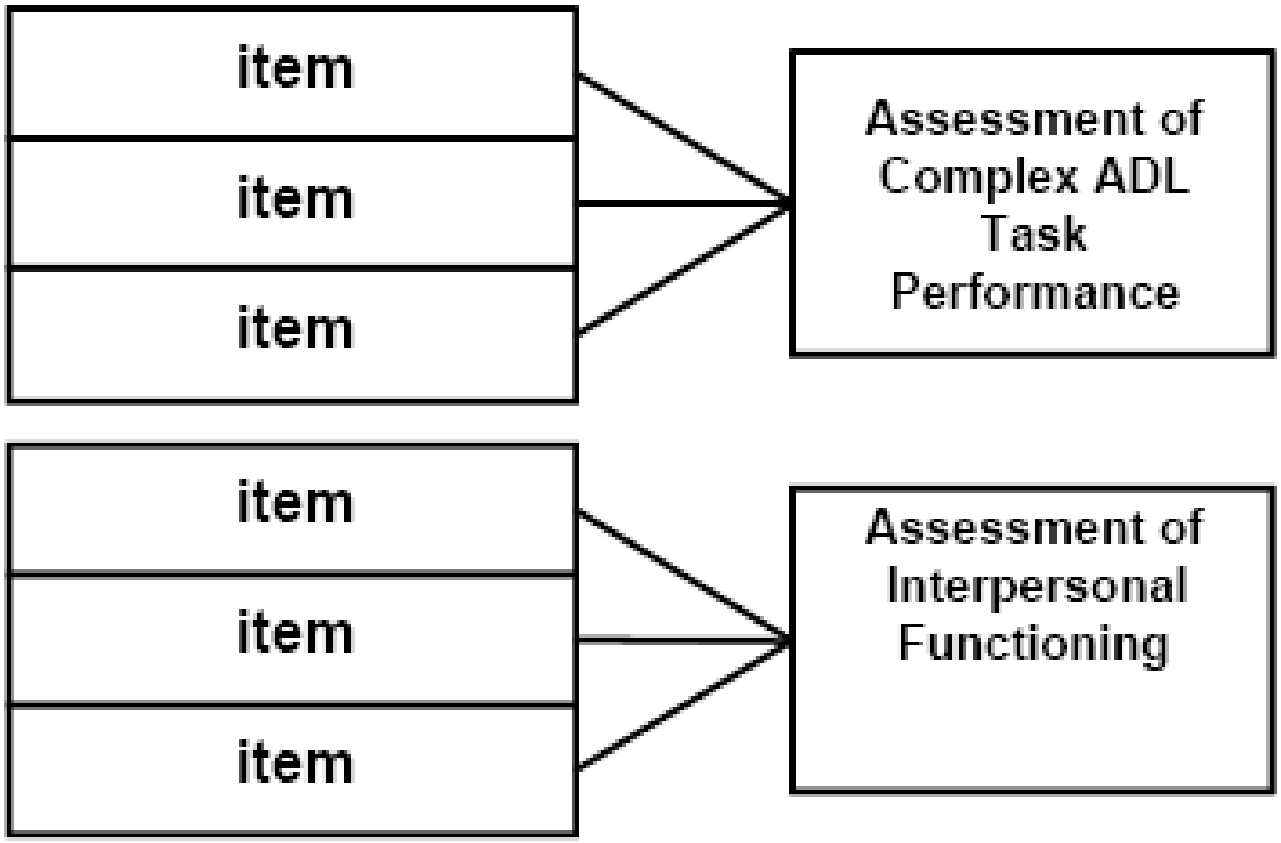
Planning Skills Required for Hobby and Task Completion *"Instructions are like the last thing he wants to deal with." [cg]*

Praxis *"I can answer it, and I can make calls…That's about all I can do." [pt]*

Using Memory in the Process of Task Completion *"…he'll even call me from the grocery store at times you know…" [cg]*

Conceptual Framework

Figure 1. Conceptual Framework



Status

News of interest since last report

- FDA Review of 'revised' SSSD – Response Received!
- ICAD 2011 Submission: Focused Research Symposium on "Measuring the Earliest Symptoms of Mild Cognitive Impairment"

Recent accomplishments

- Validity and Reliability of Patient Self Report in Early AD – 'Insight'
- Revised conceptual framework – focus on patient-report and core symptoms of IF and CADLs
- Completed individual interviews focusing on patient insight and concept elicitation
- Solicited Core Expert Feedback on Item Pool

Challenges

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Field is evolving quickly

- This group is developing information at the same time the field is struggling with lexicon and population characterization, i.e., diagnostic criteria and terminology are changing

Sustained advocacy for current effort

- We are one of many prodromal AD workstreams in the competition of ideas

Measurement target is complex

Next Steps

- Analyze latest wave of qualitative data
- Summarize expert opinion on the item pool and conceptual framework
- Evaluate FDA feedback and prepare response
- Plan 3rd Expert Panel to Review
- Draft Instrument
- Cognitive Debriefing of Draft Instrument
- Dissemination efforts

Asthma Working Group

Linda Nelsen, MHS
Associate Director, Epidemiology
Merck, Sharp & Dohme Corp

WG Participants

NAME	COMPANY
Co-Chairs	
Linda Nelsen	Merck Sharp & Dohme Corp
Sulabha Ramachandran	AstraZeneca
Participants	
Darren Talbot, Elke Hunsche	Actelion Pharmaceuticals
Brian Ortmeier, Gary Globe	Amgen
Kim Gilchrist	AstraZeneca
Michael Engel, Rozsa Schlenker-Herceg	Boehringer Ingelheim
Michelle Mocarski, Paul Rowe	Forest Research Institute
Margaret Tabberer, Priti Jhingran, Richard Stanford	GlaxoSmithKline
Jeff Johnston, Mollie Baird	Ironwood Pharmaceuticals
Linda Deal	Johnson & Johnson
Jie Zhang, Karoly Kulich	Novartis Pharmaceuticals

Introduction/Background

Objective

- To develop a daily diary of asthma symptoms

Target population

- Adolescents and adults aged 12 and older with a clinical diagnosis of mild to persistent asthma with:
  - Lung function impairment but without fixed airway obstruction
  - Requirement for asthma controller therapy based on current asthma management guidelines

Endpoint Hierarchy: Role of PROs

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Co-primary or key secondary endpoints

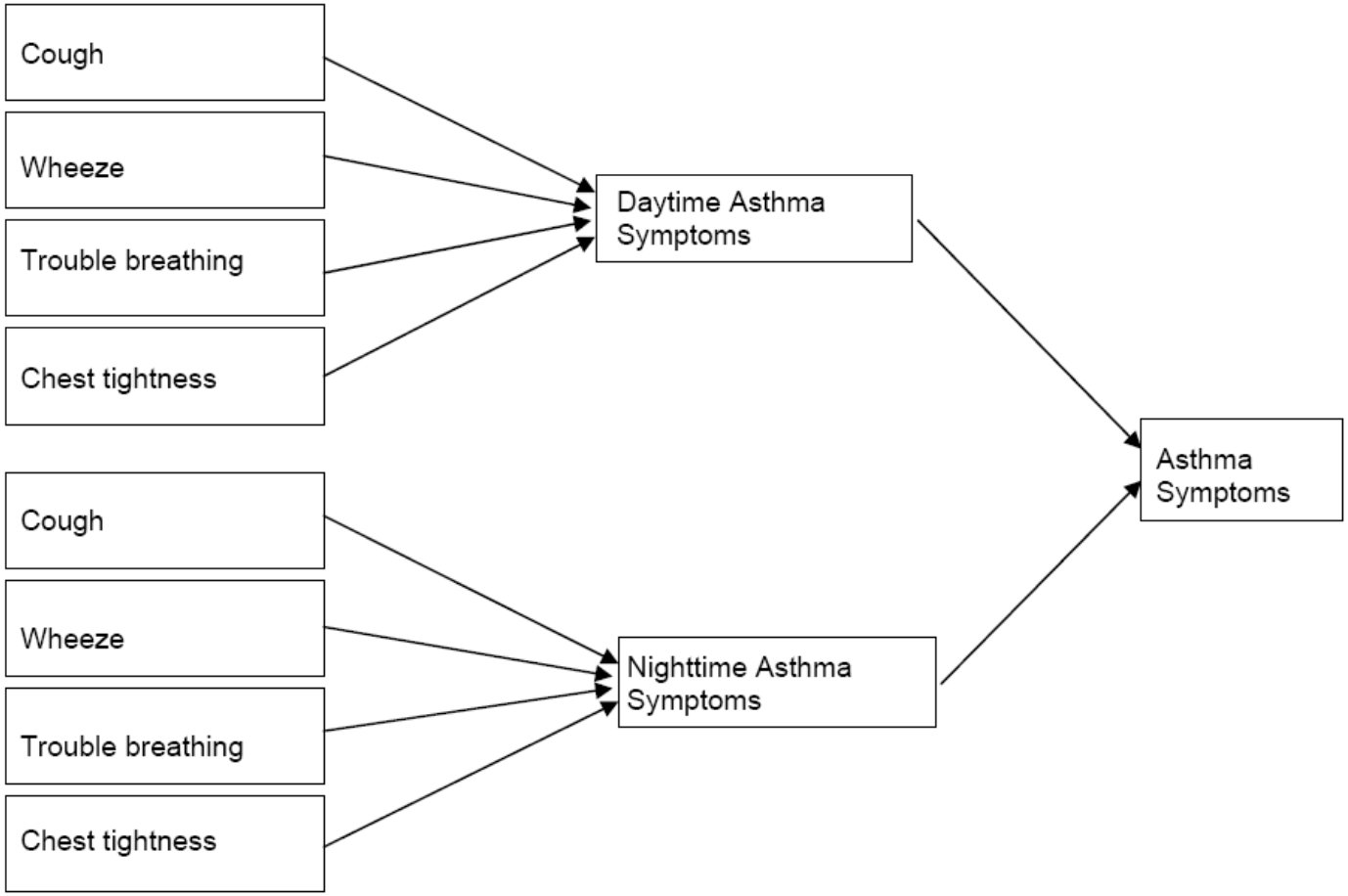
Efficacy Endpoint	**Measure**
Co-Primary Endpoints	
Improvement in airflow obstruction	Trough FEV1
Reduction in asthma symptoms	Asthma symptom score from Asthma Symptom Diary
Secondary Endpoints	
Symptom Free Days	Proportion of days without symptoms based on Asthma Symptom Diary
Nighttime symptoms	Reduction in nights with asthma symptoms based on Asthma Symptom Diary

Targeted Labeling Language

- Examples of summary statements to describe effect of treatment on symptom severity (e.g., frequency, intensity, and/or duration) include:

Overall	Patients treated with X reported significant reduction in asthma symptom *severity*
Daytime Symptoms	Significantly more patients treated with X reported improvements in daytime asthma symptom *severity*
Nighttime Symptoms	Patients treated with X reported significantly fewer nights with asthma symptoms
Individual Symptoms	Product X reduces the *severity* of wheeze

Conceptual Framework



RFP Responses indicated that while the conceptual framework is a good working model, it will be important to clarify the scope of the measure and confirm the proposed conceptual framework

News of Interest Since Last Report

- Scoping document led to discussion of need for an Asthma Symptom PRO **:**

  "*asthma…* *a priority area as it lacks a standard PRO instrument that is fit for the purpose of measuring important patient-experienced aspects of asthma…mission of the Asthma WG is to address this unmet need in close collaboration with regulatory agencies by evaluating and developing PRO instruments for use in clinical trials in accordance with the FDA PRO Guidance"*

- Led to a productive discussion with FDA regarding need for asthma symptom diary as key first step in development of appropriate PRO instruments for use in asthma clinical trials
- Areas for future focus include pediatric asthma symptoms, exacerbations & control

Status: Recent accomplishments

- Qualitative Research RFP
  - Released January 25, 2011
  - Seven proposals were received by the deadline, February 16, 2011

- Asthma WG has reviewed the proposals and is in the process of finalizing the selection of a vendor for the qualitative research

- Ten member firms have confirmed support for the qualitative research

Next Steps

- Finalize vendor selection
- Execute an agreement with selected vendor for the proposed scope of work
- Schedule the Project Kick-off meeting
  - Anticipated April 2011
- Conduct qualitative research

Depression Working Group

Nicholas Greco IV, M.S., BCETS, CATSM
Clinical Research Manager - Psychometrics and Assessment, Global Pharmaceutical Research & Development
Abbott Laboratories

Working Group Participants

NAME	COMPANY
Co-Chair	
Nicholas Greco	Abbott Laboratories
Participants	
Steven Hass, Amy Duhig	Abbott Laboratories
Peter Classi	Eli Lilly & Company
Abhilasha Ramasamy, Steven Blum	Forest Research Institute
Lucy Abraham, Zoe Kopp, Philip Ninan	Pfizer, Inc.
Omar Olhaye, Glenn Phillips	Sunovian Pharmaceuticals

Introduction/Background

Numerous patient-reported depression symptom inventories exist

- However, no existing instrument has been used consistently in clinical development programs
- A well-developed, patient-reported depression symptom inventory provides a basis for potential future development of other patient-reported aspects of depression and treatment

Existing inventories vary on

- Response options
- Anchoring, scoring algorithms
- Recall period

Introduction/Background

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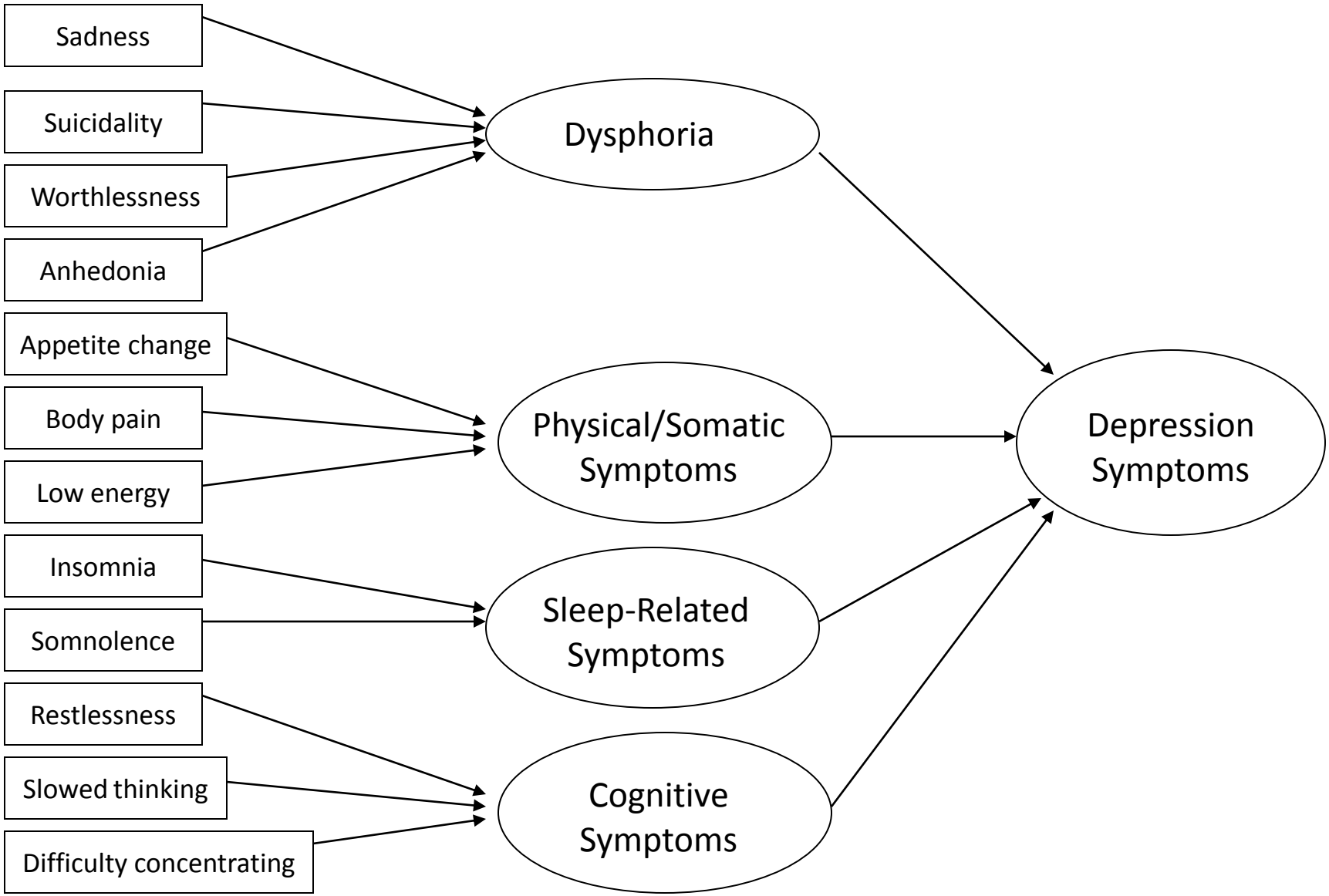
Objectives

- Assess adequacy of PRO instruments currently used in depression studies regarding the capture of important symptom information from the patient's self-report
- If the above assessment reveals there is an unmet need, either modify an existing instrument or develop a new depression symptom inventory

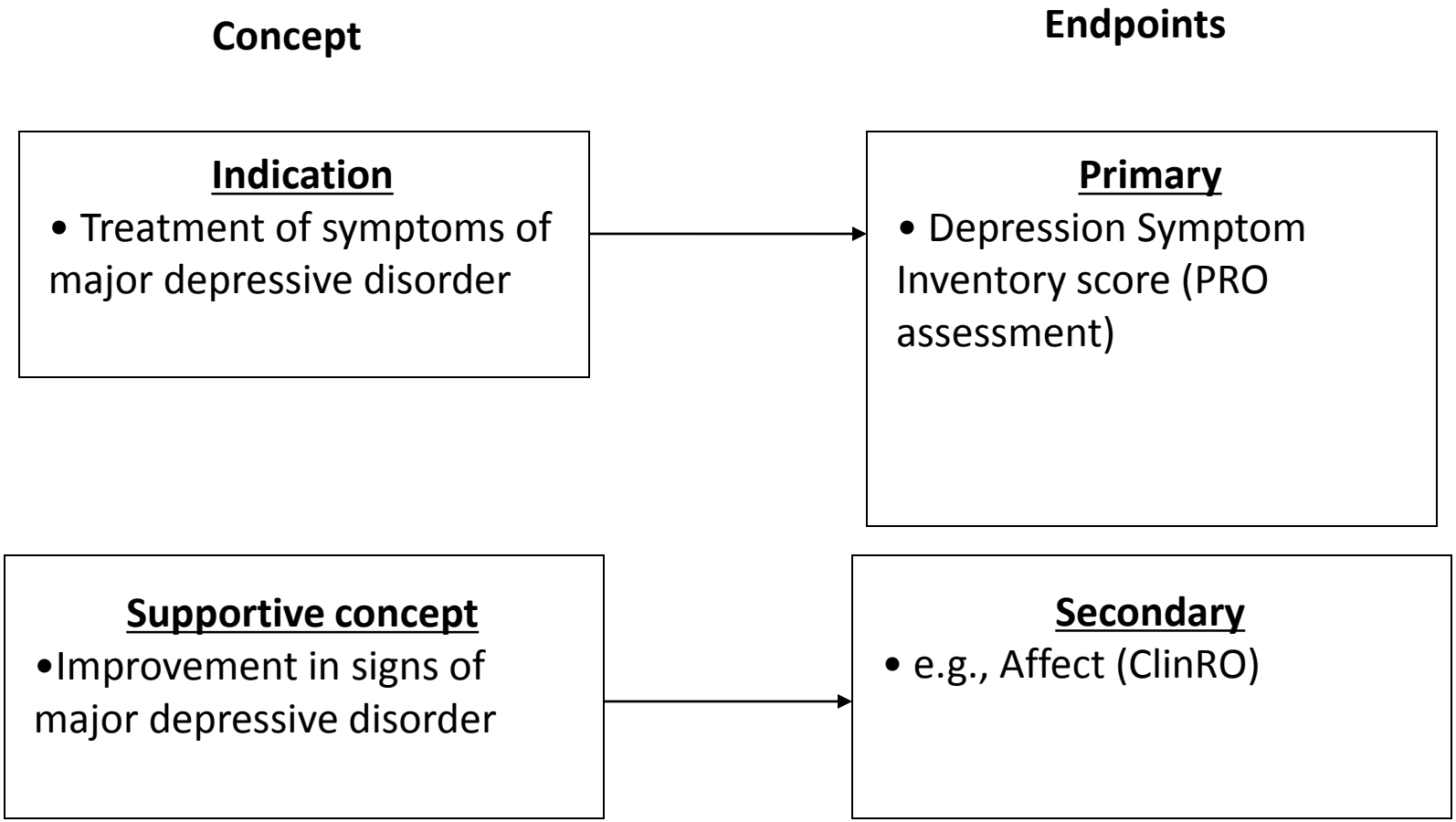
Target Population

- Male & female subjects aged 18-65 who have experienced a Major Depressive Episode within the last 6 months
- Ham-D-17 score $\geq$18
- Sponsors may target segments of the depression population based on proposed labeling claim and mechanism of action (e.g., "severe" or "treatment-resistant" depression)

Proposed Conceptual Framework



Proposed Endpoint Model



Targeted Labeling Language

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Based on group comparison using mean values:

- Patients treated with XX reported clinically meaningful reductions in depression symptom [frequency; severity] compared with treatment YY, as assessed by the ZZ symptom inventory

Based on group comparison using responder analysis:

- Compared with YY, significantly more patients treated with XX reported meaningful reductions in depression symptoms as assessed by the ZZ symptom inventory

Based on group comparison of number of days with symptoms:

- Compared with YY, patients treated with XX reported significantly fewer days with depression symptoms as assessed by the ZZ symptom inventory.

Based on group comparison of number of days to meaningful clinical response:

- Compared with YY, patients treated with XX reported significantly faster resolution of depression symptoms as assessed by the ZZ symptom inventory

Depression WG - Status

Feedback from the FDA

- The FDA cautioned on the use of redundant measures of the same concepts
- Symptoms related to cognition in depression have not been well-defined and may present a measurement challenge
- Empiric evidence is needed to define terms such as symptom onset and symptom resolution
- A specific methodology may be needed for selecting and modifying an existing depression PRO instrument

Recent accomplishments

- Depression WG's RFP was released on Friday, February 18, 2011
- Proposals were to be submitted by Friday, March 11, 2011

Next Steps

- Select vendor for the qualitative research
- Conduct qualitative research
- Prepare & submit *Qualitative Research Summary Document*, including draft instrument

Non-Small Cell Lung Cancer (NSCLC) Working Group

Ben Gutierrez, PhD
Director, Global HEOR
Bristol-Myers Squibb

Participants

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NAME	COMPANY
Co-Chairs	
Ben Gutierrez	Bristol-Myers Squibb
Peter Trask	Pfizer, Inc.
Participants	
Arijit Ganguli, Saurabh Ray	Abbott Laboratories
Kim Gilchrist, Durgesh Bhandary, Bhash Parasuraman	AstraZeneca
Andrine Swensen, Rajiv Mallick	Daiichi Sankyo, Inc.
Astra Liepa	Eli Lilly & Company
Maureen Neary	GlaxoSmithKline
Jay Pearson, Jean Marie Arduino	Merck Sharp & Dohme Corp
Jie Zhang	Novartis Pharmaceuticals
Connie Chen	Pfizer, Inc.
Yasuhiro Torigoe	Roche Laboratories

Introduction/Background

Objective

- To develop a patient reported symptom inventory for NSCLC for use in as a secondary endpoint in clinical trials

Disease

- Advanced Stage (Stage III/IV) NSCLC

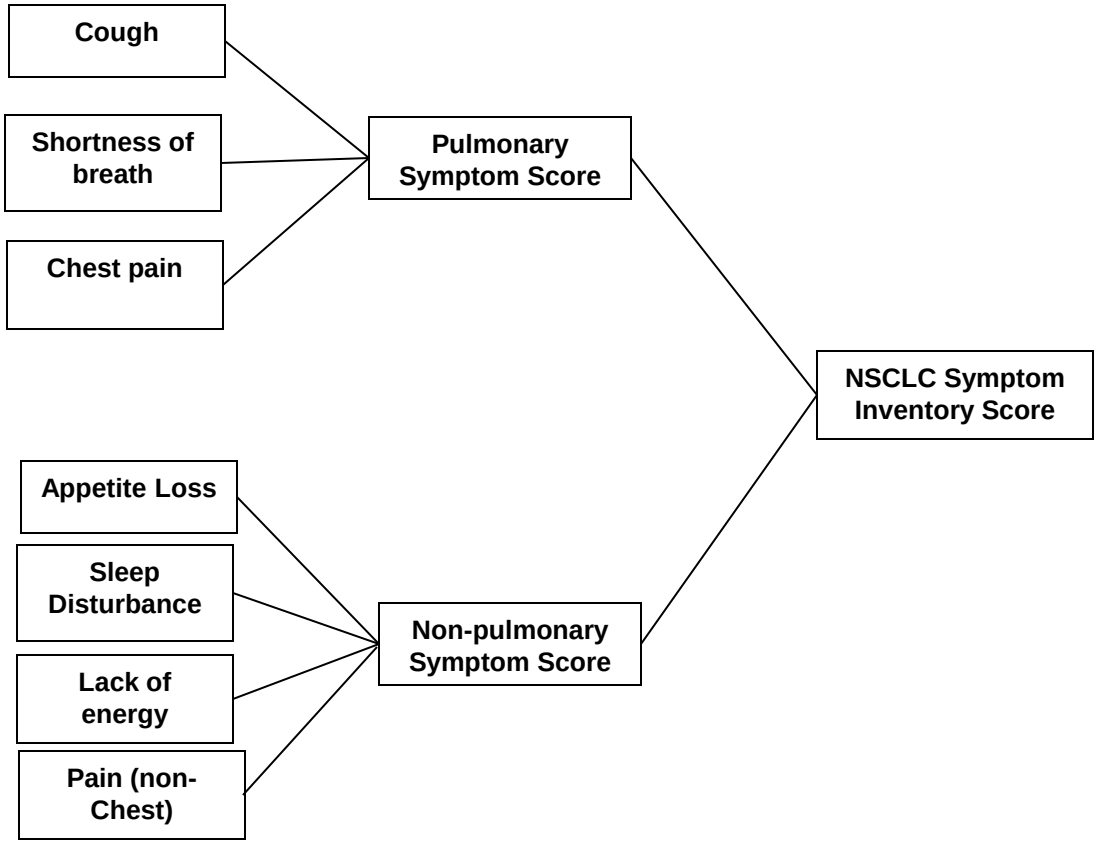
Target population

- Patients aged 18 and older with advanced stage NSCLC and ECOG status 0-2, regardless of line of therapy

Targeted Labeling Language

- Patients treated with Product X reported an improvement in the symptoms of NSCLC or delay in the time to deterioration of the symptoms if NSCLC

Conceptual Framework



Endpoint Model

Efficacy Endpoint	Measure
Primary Endpoints (Non-PRO)	
Delay in disease progression	Progression-free survival as determined by RECIST*
Longer life	Overall survival
Secondary Endpoints (PRO-based)	
Improvement in the symptoms of NSCLC OR a delay in the time to deterioration of the symptoms of NSCLC	NSCLC Symptom Inventory Score

*Response Evaluation Criteria in Solid Tumors

Status

- Received preliminary comments from FDA on the first draft of the NSCLC WG SSSD on September 1, 2010.
  - NSCLC WG reviewed the comments and drafted additional queries and replies.

- Changes in the revised SSSD
  - Addition of non-pulmonary symptoms to conceptual framework
  - Retained focus on advanced disease with ECOG 0-2
  - Requests clarification of initial responses regarding individual versus summary scoring

- Revised Scoping Stage Summary Document submitted to FDA Dec 13, 2010

Next Steps

- Awaiting feedback from FDA on revised SSSD
- Upon feedback, will review, with anticipated action being to submit RFP to vendors to begin the process of creating new NSCLC symptom measure.

Functional Dyspepsia Working Group

Robyn T. Carson, MPH
Assistant Director, HEOR
Forest Research Institute

Participants

NAME	COMPANY
Co-Chairs	
Mollie Baird	Ironwood Pharmaceuticals
Robyn Carson	Forest Research Institute
Participants	
Steven Shiff	Forest Research Institute
Jeff Johnston	Ironwood Pharmaceuticals
Ann Meulemans, Juliana Setyawan, Michael Keith	Shire Corp.
Betsy Pilmer, Charles Baum	Takeda Pharmaceuticals

Introduction/Background

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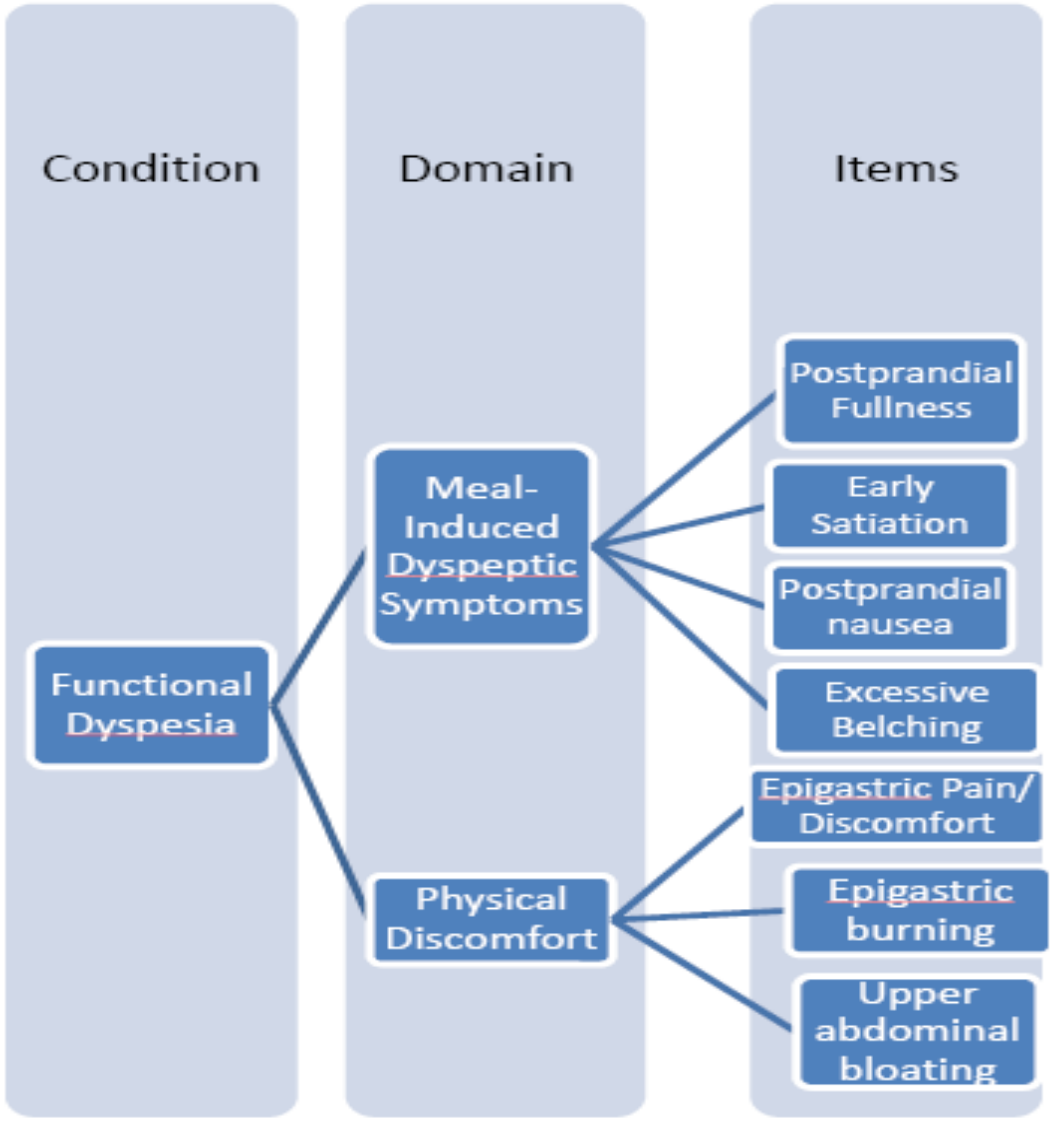
Objective: To develop a PRO instrument that is intended as a primary endpoint in support of the proposed indication of treatment of functional dyspepsia

- **Disease:** Functional dyspepsia (subtypes - epigastric pain syndrome and postprandial distress syndrome)

- **Target population:** Adult males/females that meet Rome III criteria for functional dyspepsia

- **Targeted labeling language:** Treatment of FD subtype (epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS))

Conceptual Framework



Status

News of interest since last report

- Draft 1 of scoping stage summary document under review by WG members
- Discussing WG member comments 3/21

Recent accomplishments

- Established WG with 4 member companies
- First draft of scoping document under review

Next steps

- Finalize scoping stage summary document and circulate for coordinating committee approval
- Develop scientific data disclosure plan
- Develop timeline

Rheumatoid Arthritis Working Group

Enkeleida Nikai, MSc Psych, M.B.
Senior Health Outcomes Manager,
Global Market Access
UCB Pharma S.A.

Working Group Members

Name	COMPANY
Co-Chairs	
April Naegeli	Eli Lilly & Co.
Enkeleida Nikai	UCB Pharma
Participants	
Smita Kothari	Astellas Pharma
Kimberly Sterling	Eli Lilly & Co.
Claude Schmidt, Priti Jhingran	GlaxoSmithKline
Linda Deal	Johnson & Johnson
Dena Ramey, Douglas Watson	Merck Sharp & Dohme Corp
Lewis Pollack, Lois Kotkoskie	Novo Nordisk
Alison Greene, Sarah Trease	Roche Pharmaceuticals
Paulo Carita	sanofi-aventis
Charles Baum, Ulrich Thienel	Takeda Pharmaceuticals
Christine De la Loge	UCB Pharma

Introduction/Background

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Objective

- Develop a new PRO instrument for assessing rheumatoid arthritis (RA)

Target population

- Adult patients with RA of all severities (i.e., mild to severe) and duration (i.e., early to late)
- The clinical trial population will include patients 18 years and older, males and females, with a diagnosis of adult-onset RA.

FDA feedback to the RA WG

- Development of an **adequate measure of symptoms and physical function could be useful** in the support of efficacy claims.

- **Assessment of stiffness should not be limited to "morning stiffness**”

- The Agency will **not participate in development of a "productivity" measure**.

- RA-related fatigue is important to RA patients, and thus, the **Agency would consider a "fatigue" claim in the clinical studies section of labeling**, provided that "fatigue" is clearly defined and well-measured.

Status (February-mid March 2011)

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- Sharing of previous work undertaken by member firms in RA (Eli Lilly, UCB)
- Discussions on the scope of the RA WG measurement concept(s)
- Development of a draft disease model
- Consultations with external experts

Next Steps

- Finalize the RA disease model
- Explore potential collaboration with external groups working in RA
- Define the hypothesized measurement concept(s)
- Clarify the role of the PRO instrument in the endpoint hierarchy
- Develop the *Scoping Stage Summary Document* for submission to the FDA