# PRO Consortium Working Group Updates

Presented at:

***FIRST ANNUAL***
***PATIENT-REPORTED OUTCOMES (PRO) CONSORTIUM WORKSHOP***

**March 23, 2010 – Bethesda, MD**

# Current Working Groups

- IBS
  - Co-Chairs: Charles Baum and Barbara Lewis
- Cognition
  - Co-Chairs: Usha Mallya and Marc Cantillon
- Asthma
  - Co-Chairs: Linda Nelsen and Sulabha Ramachandran
- Depression
  - Chair: Ken LaPensee
- Non-Small Cell Lung Cancer
  - Chair: Bhash Parasuraman
- Advanced Breast Cancer
  - Chair: Bonnie Teschendorf

# Irritable Bowel Syndrome Working Group (WG)

Presenter: Charles Baum, MD, MS, FACG

Executive Medical Director, GI and

Internal Medicine, Global Medical Affairs

Takeda Pharmaceuticals

# IBS WG - Participants

| Company | Name |
|---|---|
| **CO-CHAIRS** | |
| Takeda | Charlie Baum |
| Ironwood | Barbara Lewis |
| **PARTICIPANTS** | |
| Takeda | Gale Kennedy |
| Forest | Robyn Carson |
| Ironwood | Jeff Johnston |
| **NONMEMBER PARTICIPANTS** | |
| UCLA/Rome Foundation | Lin Chang |
| SUNY Buffalo | Jeff Lackner |
| IFFGD | Nancy Norton |

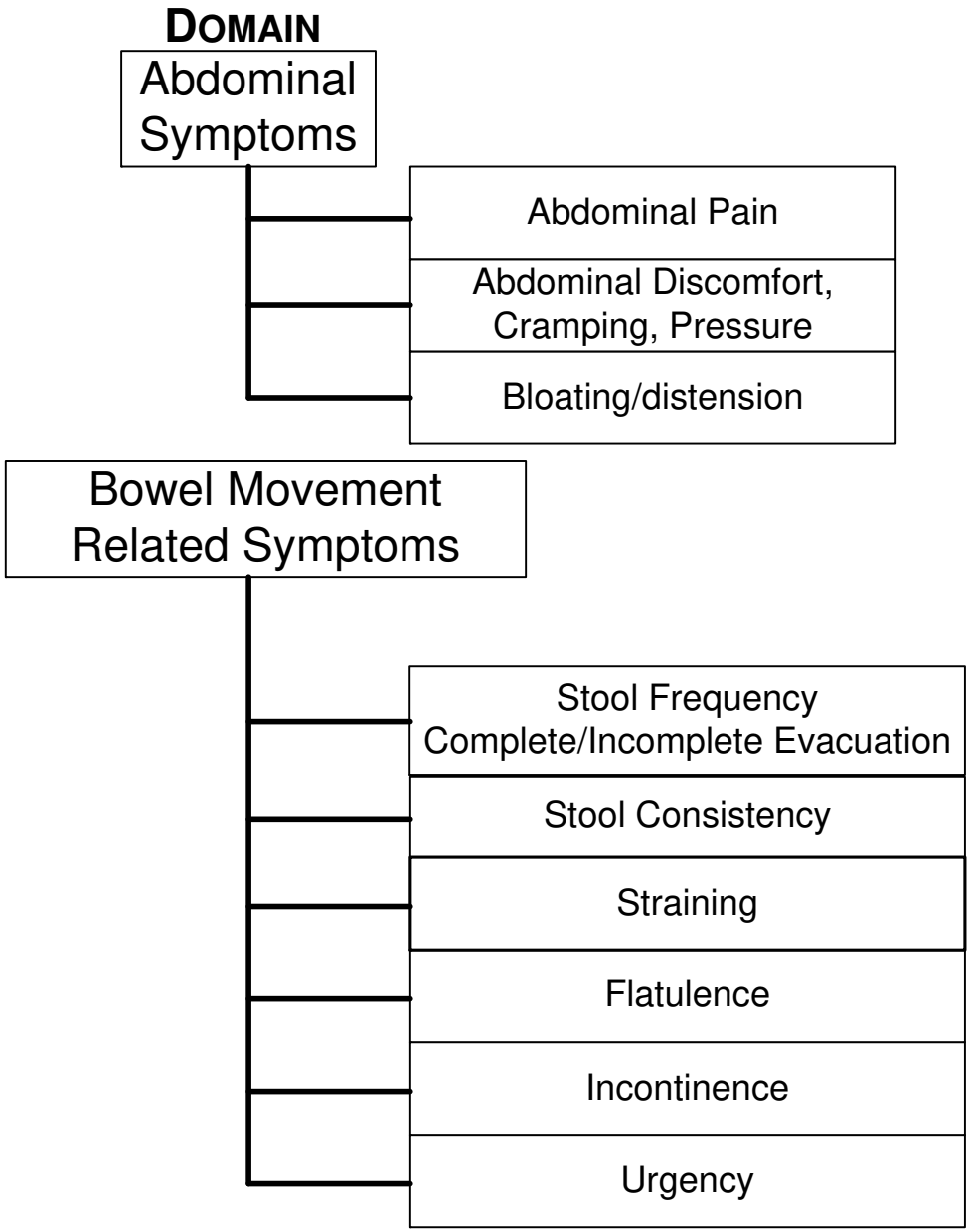
# IBS WG - Overview

- Objectives
  - To replace non-validated PRO measures
- Target Population
  - Adults aged 18+
  - IBS subtypes (constipation, diarrhea, and mixed) diagnosed by Rome III criteria

# IBS WG - FDA Feedback

- After discussion with the GI Review Division and SEALD team, there was agreement on changes to the scoping document and agreement from the FDA to participate in the qualification process of the IBS Composite Symptom Severity Index
- Clarification was provided on future use of PRO instrument in drug development:
  - It remains an empirical question whether the same or different instruments can be used for each IBS subtype.
  - If an alternative indication is sought and a subset of symptoms is considered as the primary endpoint, all of the other clinically important symptoms which comprise the IBS Composite Symptom Severity Index would still need to be measured.

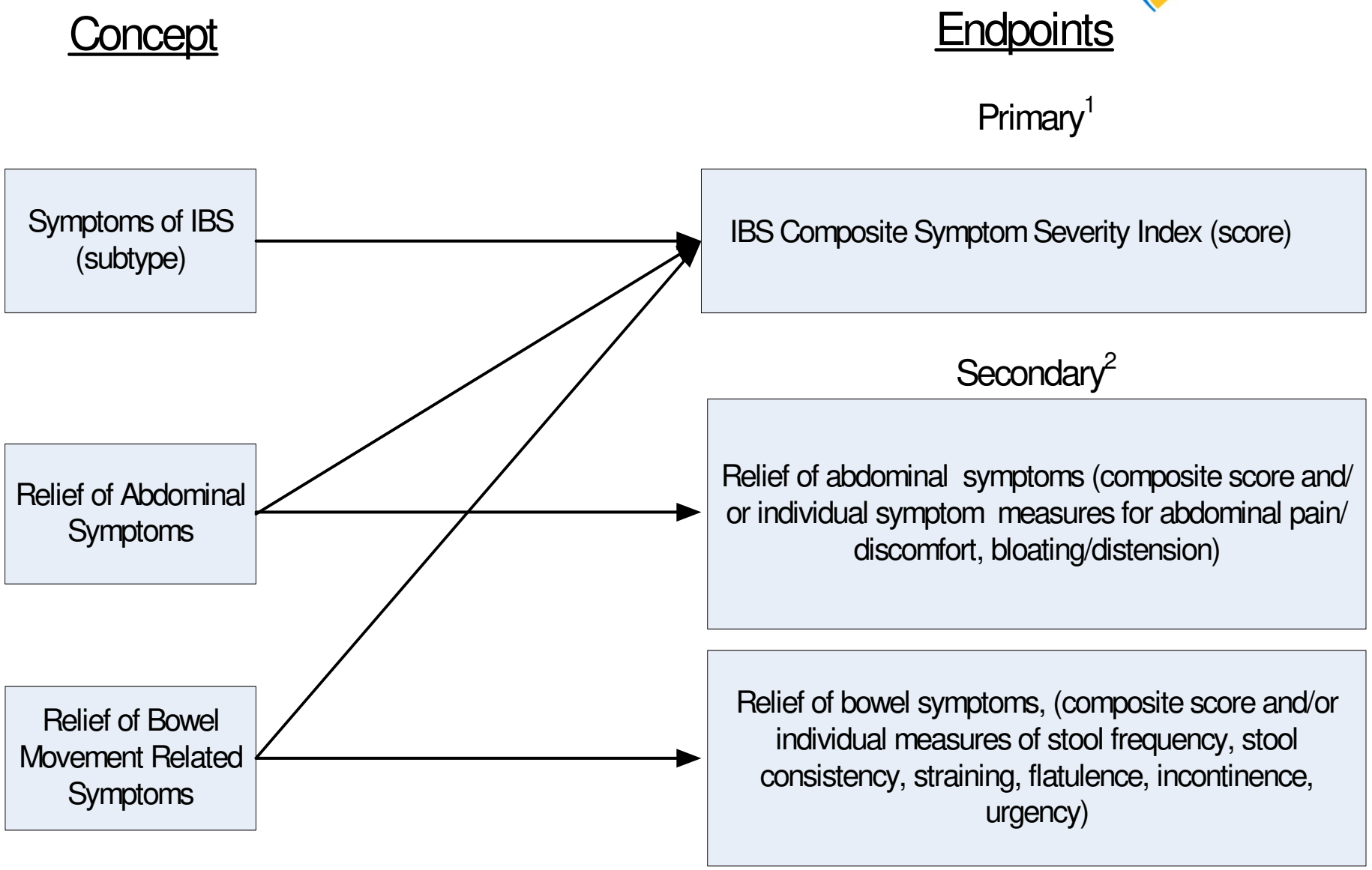
# IBS WG - Conceptual Framework



# IBS WG - Targeted Labeling Language

- Proposed labeling language:
  - As currently conceived, the IBS PRO instrument would provide an indication of improvement in symptom severity (composite score).
    - Treatment with product X results in a clinically meaningful improvement in the symptoms of IBS subtype.
  - Secondary labeling claims around individual concepts/items (e.g., abdominal pain) will require evidence that the concept is adequately measured

# IBS Endpoint Model



# IBS WG - Status

- IBS Working Group to begin Vendor Selection Stage

# Cognition Working Group (WG)

Usha Mallya, PhD

Associate Director, Global Health Economics

and Outcomes Research

Novartis Pharmaceutical Corporation

# Cognition WG - Participants

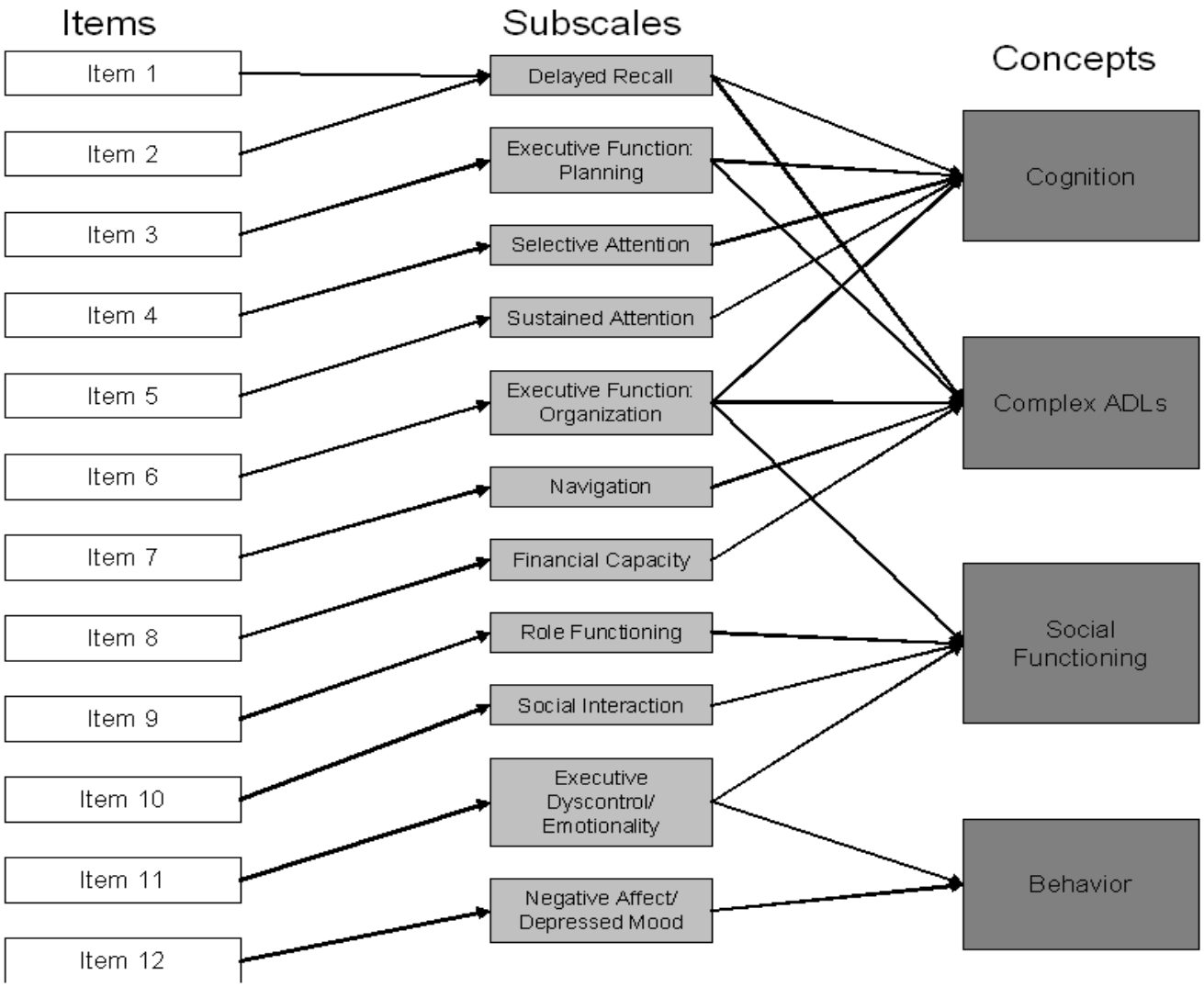
| Company | Name |
|---|---|
| **CO-CHAIRS** | |
| Merck Sharpe & Dohme Corp. | Marc Cantillon |
| Novartis | Usha Mallya |
| **PARTICIPANTS** | |
| Abbott | Nicholas Greco, Steven Hass, Genevieve Laforet, Ramanuj Achari |
| Bristol-Myers Squibb | Leah Burns, Lucinda Orsini |
| Boehringer Ingelheim | Juergen Reess, Andrea Jung |
| Janssen Alzheimer's Immunotherapy R&D | Christopher Leibman, Trent McLaughlin |
| Eisai | Grant Maclaine |
| Merck Sharpe & Dohme Corp. | Julie Chandler, Yi Mo |
| Novartis | Ari Gnanasakthy, Simu Thomas |
| Pfizer | Ming-Ann Hsu |
| Genentech | Nina Hill, Sarah Trease |
| Takeda | Stephen Sainati, Anuja Roy |

# Cognition WG - Overview

- **Objectives**
  - The Cognition Working Group seeks to develop outcome measures that improve upon the measurement of mild levels of cognitive impairment and capture the patient's and informant's perspectives on relevant outcomes.

- **Target Population**
  - A continuum of patients aged ≥ 50 years, meeting inclusion/exclusion criteria, diagnosed with MCI, amnestic subtype, and mild to moderate probable AD and without a diagnosis for Major Depressive Disorder as well as any clinically relevant condition
  - Informant: Family member or friend of a patient meeting inclusion criteria and who has familiarity with the patient's basic and complex Activities of Daily Living

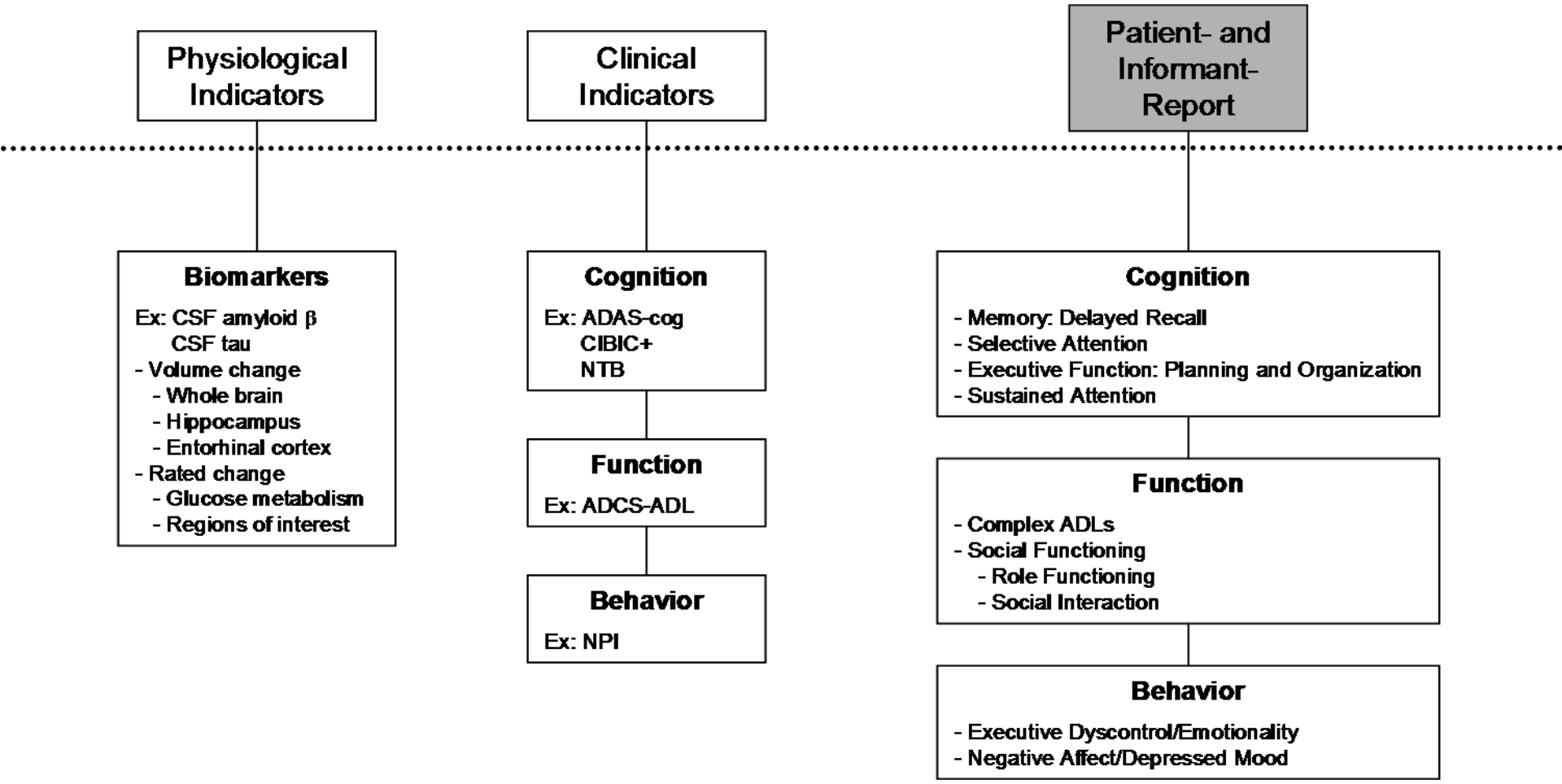
# Cognition WG - Proposed Conceptual Framework for the Patient- and Informant-reported Instrument



# Cognition WG - Targeted Labeling Language

- Cognition:
  - Treatment slows the progression of memory impairment in patients with mild cognitive impairment.
- Functioning:
  - Treatment reduces worsening of Complex Activities of Daily Living functioning in patients with mild cognitive impairment.
- Behavior:
  - Treatment reduces worsening of executive dyscontrol and emotionality in patients with mild cognitive impairment.
  - Treatment reduces worsening of negative affect in patients with mild cognitive impairment.
  - Treatment reduces worsening of emotional dyscontrol as it affects social functioning, represented by appropriate interpersonal interactions and social role functioning and/or occupational functioning, in patients with mild cognitive impairment.

# Cognition WG - Endpoint Model



# Cognition WG - Status

- Cognition Scoping Stage Summary Document submitted to the FDA and EMA on December 22nd, 2009

# Asthma Working Group (WG)

Presenter: Linda Nelsen, MHS

Associate Director, Epidemiology

Merck Sharpe & Dohme Corp.

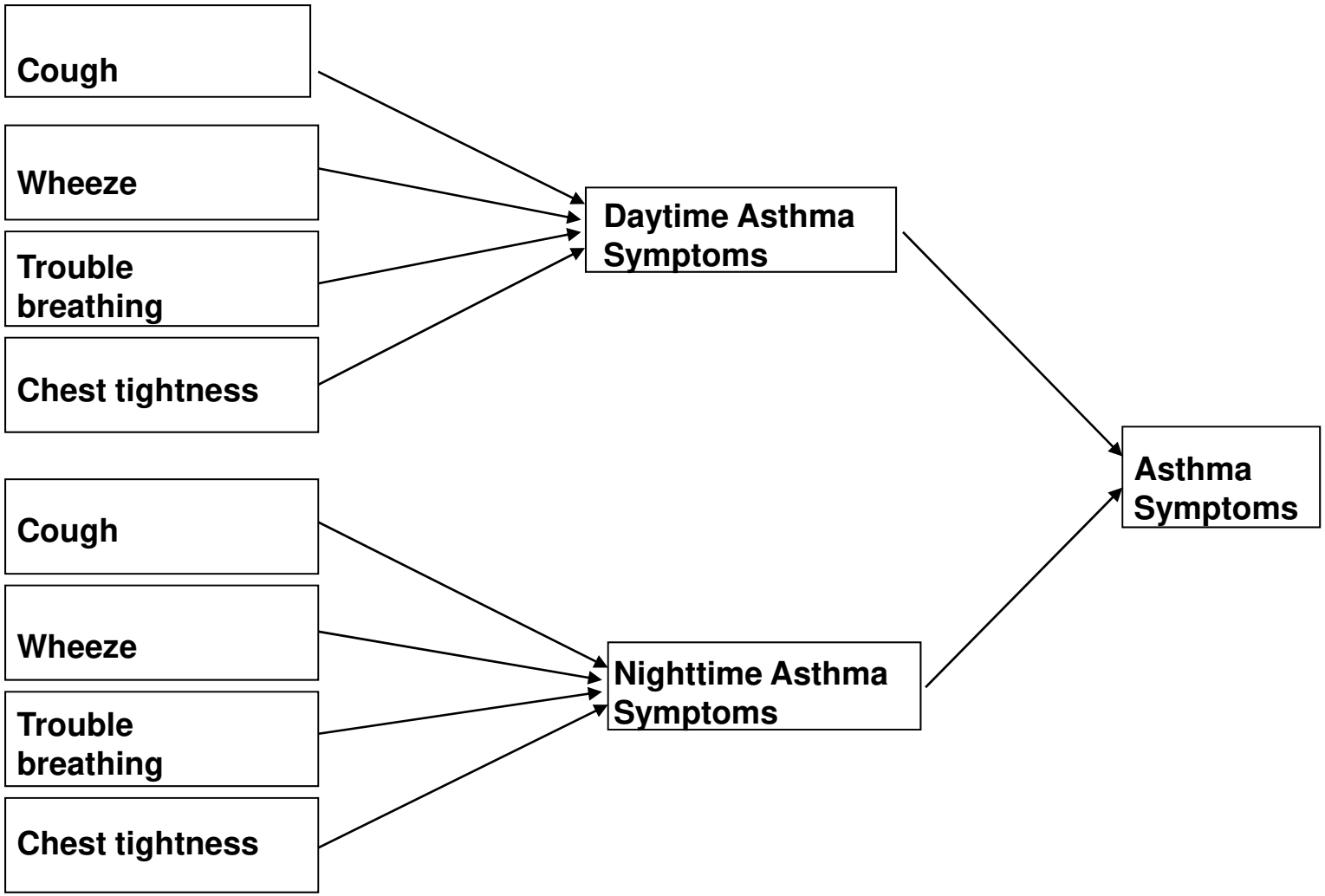
# Asthma WG - Participants

| Company | Name |
|---|---|
| **CO-CHAIRS** | |
| AstraZeneca | Sulabha Ramachandran |
| Merck Sharpe & Dohme Corp. | Linda Nelsen |
| **PARTICIPANTS** | |
| Abbott | Katherine Gooch, Katharina Buesch |
| Actelion | Elke Hunsche |
| Amgen | Fang Chiou, Vasily Belozeroff |
| AstraZeneca | Kim Gilchrist, Niklas Karlsson |
| Boehringer Ingelheim | Michael Engel, Rozsa Schlenker-Herceg |
| Dainippon Sumitomo Pharma America | Vincent Chia |
| Forest | Juliana Setyawan, Michelle Dembiski, Paul Rowe |
| GlaxoSmithKline | Priti Jhingran, Richard Stanford, Margaret Tabberer |
| Ironwood Pharmaceuticals | BJ Lavins, Barbara Lewis |
| Novartis | Andrine Swensen, Jie Zhang, Cat Bui |
| Pfizer | Tara Symonds, Claire Gilbert |
| UCB | Dorothy Keininger, Enkeleida Nikai |

# Asthma WG - Overview

- Objectives
  - To develop a new asthma symptom diary
- Target Population
  - Adolescents and adults aged 12 and older with a clinical diagnosis of persistent asthma with lung function impairment but without fixed airway obstruction

# Asthma WG - Proposed Conceptual Framework for Asthma Symptom Diary



# Asthma WG - Targeted Labeling

**OVERALL**

- Patients treated with X reported significant reductions in asthma symptom [frequency; severity; duration]
- Significantly more patients treated with X reported improvements in asthma symptoms
- Patients treated with X reported significantly fewer days with asthma symptoms

**DAYTIME**

- Patients treated with X reported significant reductions in daytime asthma symptom [frequency; severity; duration]
- Significantly more patients treated with X reported improvements in daytime asthma symptoms
- Patients treated with X reported significantly fewer days with asthma symptoms

**NIGHTTIME**

- Patients treated with X reported significant reductions in overnight awakenings with asthma symptoms
- Patients treated with X reported fewer nights with awakenings with asthma symptoms

**INDIVIDUAL SYMPTOMS**

- Product X improves [intensity, frequency, duration] of cough associated with asthma
- Patients treated with X reported significant improvements in shortness of breath
- Product X reduces the [frequency, intensity, duration] of wheeze

# Asthma WG - Endpoint Model

| 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 |
| Nocturnal awakenings | Number of nights with nighttime awakenings due to asthma symptoms measured in Asthma Symptom Diary |
| Asthma exacerbation | Number of exacerbations |

# Asthma WG - Status

- Asthma Scoping Stage Summary Document submitted to the FDA and EMA on March 2, 2010

# Depression Working Group (WG)

Presenter: Ken LaPensee, PhD, MPH

Director, Health Economics and Outcomes Research

Forest Research Institute

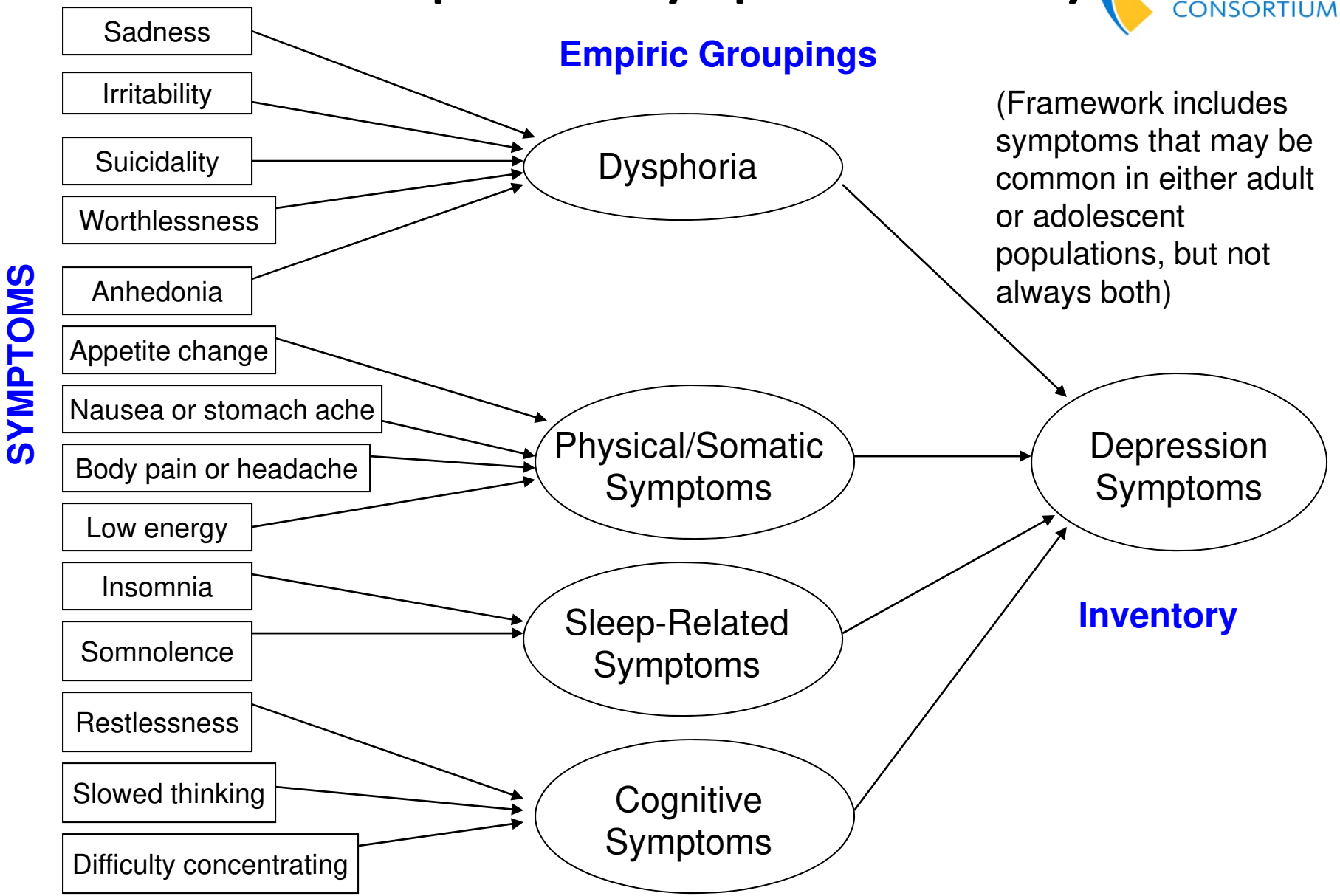
# Depression WG - Participants

| Company | Name |
|---|---|
| **CHAIR** | |
| Forest Research Institute | Ken LaPensee |
| **PARTICIPANTS** | |
| Abbott | Nicholas Greco, Steven Hass |
| AstraZeneca | Mariam Hassan |
| Dainippon Sumitomo Pharma America | Omar Olhaye, Vincent Chia |
| Eisai | Grant Maclaine |
| Eli Lilly & Co | Glenn Phillips |
| Forest Research Institute | Abhilasha Ramasamy, Steven Blum |
| GlaxoSmithKline | Brian Bowers, Sunny Mahajan |
| Ironwood Pharmaceuticals | BJ Lavins |
| Merck Sharpe & Dohme Corp. | Jaime Barnes |
| Sanofi-Aventis US, Inc | Daryl DeKarske |
| Takeda | Stephen Sainati, Anuja Roy |

# Depression WG - Overview

- Objectives
  - Assess adequacy of PRO instruments currently used in major depressive disorder (MDD) studies regarding capture of important symptom information from the patient's perspective
  - If there is an unmet need, either modify an existing instrument or develop a new depression symptom inventory
- Target Population
  - Male & female adolescents and adults aged ≥12 with MDD including patients of all levels of severity from "mild" to "severe" requiring ambulatory or inpatient pharmaceutical, somatic, or cognitive therapy
  - Sponsors may target segments of the depression population based on proposed labeling claim and mechanism of action (e.g., "severe" or "treatment-resistant" depression, adolescents)

# Depression WG - Proposed Conceptual Framework for Depression Symptom Inventory



# Depression WG - Targeted Labeling Language

- **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 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 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 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 symptom inventory

# Depression WG - Endpoint Model


| Concept | Endpoints |
| --- | --- |
| **Indication**<br>•Clinician rated: treatment of symptoms of depression | **Primary**<br>•Total score on the HAM-D, MADRS, QIDS-C |
| OR | |
| **Indication**<br>•Patient reported: treatment of symptoms of depression | **Primary**<br>•Total score on the QIDS-SR |
| OR | |
| **Indication**<br>•Clinician rated: treatment of symptoms of depression<br>•Patient reported: treatment of symptoms of depression | **Co-Primary**<br>•Total score on the HAM-D, MADRS, QIDS-C<br>•Total score on the QIDS-SR |
| OR | |
| **Supportive Concepts**<br>• Patient reported: treatment of symptoms of depression | **Secondary**<br>• Total score on the QIDS-SR |

# Depression WG - Status

- **Completed:**
  - Surveys of depression-related endpoints used in trials (e.g., symptom inventories, HR-QOL, life satisfaction), current PRO labeling language
  - Group consensus that a currently used symptom inventory shows promise as PRO instrument
    - Both PRO and clinician assessments are based on DSM-IV symptom lists
  - Selection of the QIDS-$SR_{16}$ as a candidate for modification to comply with FDA guidance
- **Next steps:**
  - Determine how the patient perspective was incorporated into:
    - QIDS-$SR_{16}$ development
    - DSM-IV/DSM-V diagnostic criteria development
  - Conduct qualitative/quantitative research to support validity and reliability of modified instrument

# Non-Small Cell Lung Cancer (NSCLC) Working Group (WG)

Presenter: Bhash Parasuraman, PhD

Senior Director, Health Economics and Outcomes Research

AstraZeneca

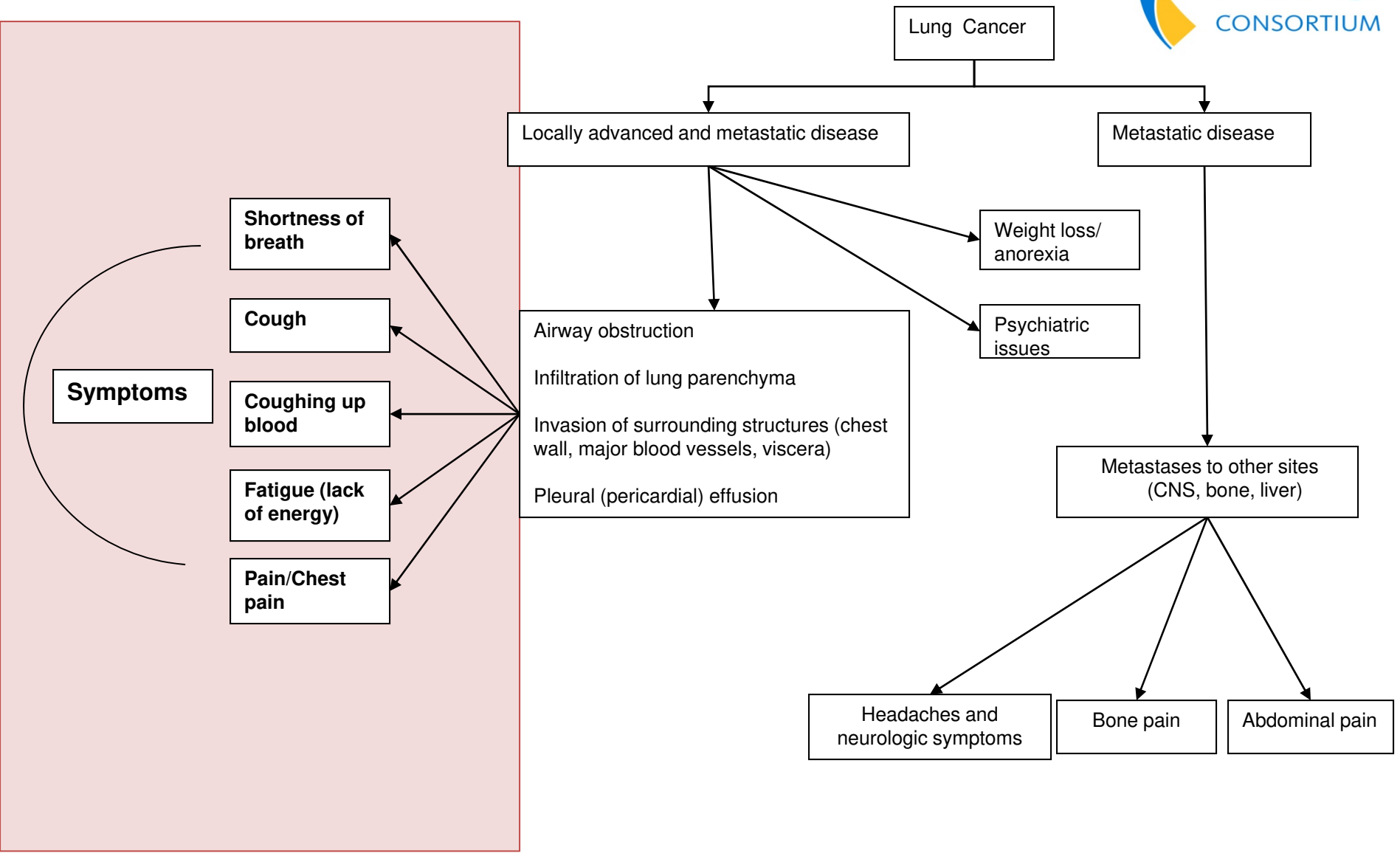
# NSCLC WG - Participants

| Company | Name |
|---|---|
| **CHAIR** | |
| AstraZeneca | Bhash Parasuraman |
| **PARTICIPANTS** | |
| Boehringer Ingelheim | Henrik Finnern |
| Bristol-Myers Squibb | Ben Gutierrez |
| GlaxoSmithKline | Maureen Neary |
| Pfizer, Inc. | Peter Trask |
| Eli Lilly & Company | Astra Liepa |
| Genentech | Sarah Trease |
| Merck Sharp & Dohme Corp. | Jean Marie Arduino |

# NSCLC WG - Overview

- Objective
  - To develop a symptom measure for advanced, metastatic NSCLC, to be included in RCTs for pharmaceutical product development
- Target Population
  - Patients 18 and older with advanced stage (Stage III/IV) NSCLC and with performance status 0-2, regardless of line of therapy

# Lung Cancer WG - Proposed Conceptual Framework for NSCLC



# NSCLC WG - Targeted Labeling Language

Patients treated with Product X reported…

- an improvement in shortness of breath.
  - a delay in the time to deterioration of shortness of breath.
- an improvement in fatigue/lack of energy.
  - a delay in the time to deterioration of fatigue/lack of energy.
- an improvement in chest pain.
  - a delay in the time to the worsening of chest pain.
- an improvement in cough.
  - a delay in the time to the worsening of cough.

# NSCLC WG - Endpoint Model

| Efficacy Endpoint | Measure |
|---|---|
| **Primary Endpoints** | |
| Delay in disease progression | Progression free survival as determined by RECIST criteria |
| Longer life | Overall survival from baseline |
| **Secondary Endpoints** | |
| Improvement or delay in the time to deterioration of shortness of breath | Shortness of breath scale score |
| Improvement or delay in the time to deterioration of fatigue or lack of energy | Fatigue scale score |
| Improvement or delay in the time to deterioration of chest pain | Chest pain scale score |
| Improvement or delay in the time to deterioration of cough (including hemoptysis) | Cough scale score |

# NSCLC WG - Status

- Scoping Stage Summary Document under development

# Advanced Breast Cancer Working Group (WG)

Presenter: Bonnie Teschendorf, PhD

Director, Patient Reported Outcomes

Johnson & Johnson

# Breast Cancer WG - Participants

| Company | Name |
|---|---|
| **CHAIR** | |
| Johnson & Johnson | Bonnie Teschendorf |
| **PARTICIPANTS** | |
| Boehringer Ingelheim | Gerlinde Maas |
| Bristol-Myers Squibb | Lisa Melilli |
| Eisai | Thomas Tencer |
| Eli Lilly & Company | Greg Price, Mark Boye |
| Genentech | Elaine Yu, Sarah Trease |
| GlaxoSmithKline | Mayur Amonkar |
| Merck Sharp & Dohme Corp. | Greg Reardon, Prakash Navaratnam |
| Pfizer, Inc. | Connie Chen |
| sanofi-aventis | Brian Seal, Lei Chen |

# Breast Cancer WG - Overview

- Objective - To prepare a scoping document using state of the science information to guide development of a PRO instrument
- Breast Cancer PRO target population
  - Female breast cancer patients diagnosed with advanced (Stage IIIB or IV) disease. Approximately 99% of breast cancers are diagnosed in females. Male gender or patients with stage I thru IIIA disease are excluded from the target population.
  - May incorporate breast cancer patients with Stage I-III who progress from baseline with tumor induced symptoms
  - Other important planning considerations for subject recruitment in qualitative research
    - Subject characteristics and representativeness: age, ethnicity, socioeconomic groupings
    - Geographic distribution of subjects
    - Disease Characteristics/Classification: Pathology, Histology, disease symptoms, Family history, Genetic profile
    - Treatment History: Type of current therapy, prior therapy type, number of prior therapies, prior therapy side effects, comorbidities, history of adverse events

# Breast Cancer WG - Proposed Conceptual Framework for Symptoms/Side Effects of Treatment


| Items | Concepts | Subscales |
|---|---|---|
| **Pain**<br>Pain at worst<br>Pain right now<br>Pain… | Pain<br>Severity/Frequency | Pain |
| **Tiredness**<br>Tired at worst<br>Tired all time | Tiredness<br>Severity/Frequency | Tiredness |
| **Sleep Loss**<br>Can't go to sleep<br>Restless sleep | Sleep Disturbance | Sleep |
| **Appearance**<br>Alopecia<br>Weight | Appearance Change | Appearance |
| **Depression**<br>Lack motivation<br>Feel disengaged | Mood/Disposition | Mood |
| **Arm Swelling**<br>Large in size<br>Indentation | Lymphedema | Lymphedema |

# Breast Cancer WG - Targeted Labeling Language

1. Subjects treated for advanced breast cancer with Product X demonstrate clinically meaningful delay in time to worsening of pain (e.g., cancer-related; treatment-related, bone pain)

2. Subjects treated for advanced breast cancer with Product X demonstrate clinically meaningful stabilization in symptoms of tiredness (e.g., energy level, sleepiness)

3. Subjects treated for advanced breast cancer with Product X demonstrate clinically meaningful delay in time to worsening of distressing side effects (e.g. alopecia, neuropathy, lymphedema, sleep disturbance)

4. Subjects treated for advanced breast cancer with Product X demonstrate clinically meaningful stabilization in body weight (e.g., appetite)

# Breast Cancer WG - Endpoint Model for the Treatment of Advanced Breast Cancer

| Concept | Endpoints |
| --- | --- |
| **Indication:**<br>Treatment<br>of Advanced Breast Cancer | **Primary:**<br>Stable Disease Progression<br>(non-PRO assessment) |
| **Supportive Concepts:**<br>Stable signs & symptoms<br>Breast cancer | **Secondary (ordered):**<br>Stable/controlled pain<br>(PRO assessment)<br>Improved /No worsening sleep<br>(PRO assessment)<br>Improved /No worsening mood/disposition<br>(PRO assessment)<br>Stable body weight<br>(non-PRO assessment) |

# Breast Cancer WG - Status

- Scoping Stage Summary document in progress
  - Critical concepts identified from literature
  - Further deliberation on symptoms at diagnosis and side effects/symptoms post-treatment
  - Summary tables are complete:
    - PRO-Related Concepts in Current Labeling
    - PRO Measures used in Advanced Breast Cancer
  - Conceptual framework to be refined
  - Endpoint model in progress