Asthma Working Group

Presented at the Sixth Annual PRO Consortium Workshop – Silver Spring, MD – April 29-30, 2015

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Asthma Working Group (WG)

- Asthma was defined as an area for development of novel PRO measures to support clinical trials. There is no standard PRO instrument that is qualified by the FDA for the purpose of measuring important patient-experienced aspects of asthma.
- The Asthma WG is working to address this unmet need in close collaboration with regulatory agencies by evaluating and developing PRO instruments for use in clinical trials of asthma therapies in accordance with the FDA PRO Guidance.

Goal of the Asthma WG

- To develop a patient-reported diary to document daily asthma symptoms in adults and adolescents with a clinical diagnosis of mild to severe persistent asthma for use in clinical trials of asthma therapies as a co-primary or secondary endpoint to establish treatment benefit.

Targeted Labeling Language

Overall	Patients treated with [*drug X*] reported significant reduction in asthma symptom severity
Daytime Symptoms	Patients treated with [*drug X*] reported significant reduction in daytime asthma symptom severity Patients treated with [*drug X*] reported significantly fewer days with asthma symptoms
Nighttime Symptoms	Patients treated with [*drug X*] reported significant reduction in nighttime asthma symptom severity Patients treated with [*drug X*] reported significantly fewer nights of awakenings due to asthma symptoms

Milestones

Milestone	Expected Date	Completed Date
Content Validity Stage		
Vendor selection and contracting	Jun2011	Feb2012
Complete background research (Literature Review Report and Expert Panel Meeting)	Jul2012	Sep2012
Draft Instrument: Complete initial qualitative research and generate items (concept elicitation interviews, item generation, expert panel input, and initial round of cognitive interviews)	Aug2013	Aug2013
Submit Qualitative Research Summary Briefing Document to FDA for review and feedback	Oct2013	Nov2013
Submit updates to FDA for review and feedback (round 3 cognitive interviews, final cognitive interview report, expert panel meeting, updated instrument, and quantitative protocol)	Jun2014	Jul2014
Complete documentation of content validity and cross-sectional evaluation of other measurement properties	4Q2015	
Submit exploratory endpoint qualification dossier to FDA	1Q2016	

Content of Interest

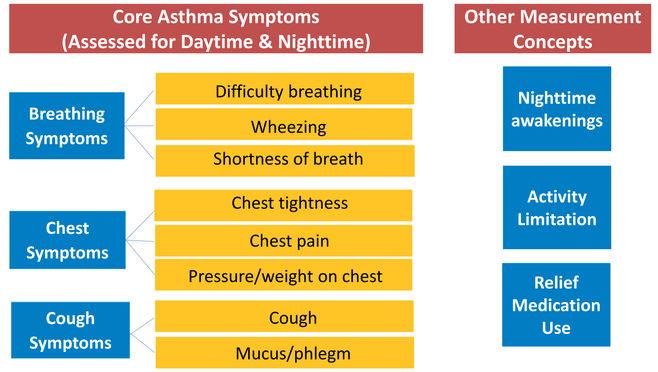
Endpoint Model for Treatment of Asthma

Endpoint Hierarchy	Endpoint Concept(s)	Type of Endpoint
Primary	Improvements in airflow re-obstruction • FEV1 Reduction in asthma symptoms • Asthma total symptom score from Asthma Daily Symptom Diary	COA (PerfO) PRO
Secondary	Daytime Symptoms • Proportion of days without symptoms based on Asthma Daily Symptom Diary (symptom free days) Nighttime Symptoms • Proportion of nights without asthma symptoms based on Asthma Daily Symptom Diary	PRO PRO

Target Population

- Adolescents and adults aged 12 years and older with a clinical diagnosis of asthma with lung function impairment
- Patients will be categorized in the guideline-defined levels of disease severity, which include mild through severe persistent asthma (GINA, 2009)

Revised Hypothesized Conceptual Framework*



*Framework to be finalized after the completion of the quantitative pilot study.

Draft Instrument – Asthma Daily Symptom Diary (ADSD)

Core Items: Eight items were developed to measure the 'core' asthma symptoms identified during concept elicitation. Four additional items were developed to measure other concepts related to asthma (i.e., nighttime awakenings, activity limitations, relief inhaler use, nebulizer use). Based on cognitive debriefing, only seven were retained (mucus/phlegm removed).

Recall Period: Twice daily (morning and evening)

Response Options: Respondents asked to rate each symptom at its 'worst' using a 0-10 numeric rating scale, which is consistent with patients' spontaneous descriptions of symptom severity

Symptom Attribute: Severity was chosen (as opposed to frequency, duration, or bothersomeness) based on patient descriptions of asthma symptom experience

Updates

- Submitted updated briefing document to the FDA including the completion of cognitive interviews , the revised *ADSD*, and the quantitative research protocol (July 2014)
- The FDA provided positive feedback (e.g., completeness, execution and analysis of qualitative research) to the July 2014 submission of qualitative research through cognitive interviews and the draft *ADSD* (February 2015)
- Teleconference with FDA to confirm quantitative protocol and statistical analysis plan (SAP) are acceptable (February 27, 2015)
- FDA endorsed proceeding with quantitative pilot study (March 12, 2015)
- FDA endorsement of SAP is pending further review (2Q2015)
- CRF Health, the selected ePRO system provider, implemented the instrument for use in the upcoming quantitative pilot study

Working Group Plans

Next Steps

- Begin quantitative pilot study – target 2Q2015
- Submit quantitative data to FDA – target 1Q2016
- Identify clinical trial(s) in which to incorporate the *ADSD* as an exploratory endpoint – target 1Q2016

Information Dissemination Plan

- Manuscript on qualitative research written and planned for submission to *Value in Health* – target 2Q2015
- Develop and submit abstract on quantitative pilot study results for 2016 American Thoracic Society International Conference – TBD
- Develop manuscript on quantitative pilot study for submission to *Chest* – target 4Q2016

Working Group Participants

Company/Organization	Name
AstraZeneca AB	Niklas Karlsson, Sean O'Quinn
Boehringer Ingelheim	Dirk Esser, John Downie
Actavis, Inc., an affiliate of Forest Research Institute, Inc.	Sean Sun
Genentech, Inc.	Alison Greene, Kristina Fitzgerald
GlaxoSmithKline , LLC	Linda Nelsen (Co-Chair), Margaret Tabberer, Richard Stanford
Janssen Global Services, LLC	Sarah Fleming (Co-Chair), Renee Pierson
Merck Sharp & Dohme Corp.	Josephine Norquist
Novartis Pharma AG	Luísa Álvares
Pfizer, Inc.	Joel Bobula
Sanofi	Asif Khan, Laurent Eckert
Expert Panel Members	**Affiliation**
Michael Schatz, MD	Kaiser Permanente, UCSD
Jerry Krishnan, MD, PhD	University of Chicago, NHLBI
John Haughney, MB	University of Aberdeen
Stuart Stoloff, MD	Fellow FAAAAI, Family Practitioner
Contract Research Organization	**Research Team**
Adelphi Values	Adam Gater, Rob Arbuckle, Nicola Bonner, Cheryl Coon, Rebecca Hall, Kerry Turner, Hannah Staunton