Pediatric Asthma Working Group

Presented at the Ninth Annual PRO Consortium Workshop – Silver Spring, MD – April 25-26, 2018

Background

Rationale for Pediatric Asthma Working Group (WG)

- Pediatric asthma has been identified as an area in need of novel clinical outcome assessment (COA) tools for evaluating treatment benefit in clinical trials.
- The Asthma Working Group (WG) is developing a patient-reported outcome (PRO) measure (i.e., *Asthma Daily Symptom Diary* [*ADSD*]) for assessing asthma symptom severity in adolescents and adults. The U.S. Food and Drug Administration (FDA) requested that the Asthma WG consider developing COA tools to cover a broader range of asthma patients (i.e., < 12 years old).
- Merck, a sponsor of the Asthma WG, contributed draft versions of a PRO measure (for completion by children ages 8 to 11 years old) and an observer-reported outcome (ObsRO) measure (for completion by parents of children ages 4 to 11 years old) developed for use in pediatric asthma trials.
- The Asthma WG decided to focus its efforts on FDA qualification of the *ADSD,* so a separate Pediatric Asthma WG was formed to examine Merck's research and assess the adequacy of the two draft measures as candidates for qualification.

Goal of the Pediatric Asthma WG

- To pursue FDA qualification of COA measures for the assessment of asthma signs and symptoms: the primary measure would be the ObsRO measure for parents/caregivers of the entire age range. The observer would also consider input from other informants (e.g., siblings, teachers, babysitters, spouses) regarding observable asthma signs or impacts. The PRO measure for children aged 8 to 11 years old would be a supportive measure.

Targeted Labeling Language

- Patients treated with [*Drug X*] experienced a significant reduction in severity of asthma signs and symptoms.

Milestones

Milestone	Target Date	Completed Date
Reanalysis of Merck's qualitative data to evaluate data and identify gaps suggested by FDA that required additional research.		SEP 2016
Letter of Intent submitted to FDA		DEC 2016
Review documentation, recommendations for changes to the measure and recommendations for future research		FEB 2017
FDA Response to Letter of Intent and request for Initial Briefing Package (IBP) received		JUNE 2017
Feasibility study protocol submitted to FDA		AUG 2017
Verbal feedback from FDA on protocol recommending separate ObsRO and PRO measures instead of co-completion		JAN 2018
Complete qualitative research on modified ObsRO measure	TBD	
Submit IBP to FDA	TBD	
Submit Qualification Plan to FDA	TBD	
Submit Full Qualification Package to FDA for use of the COA tools as exploratory endpoint measures	TBD	

Highlights

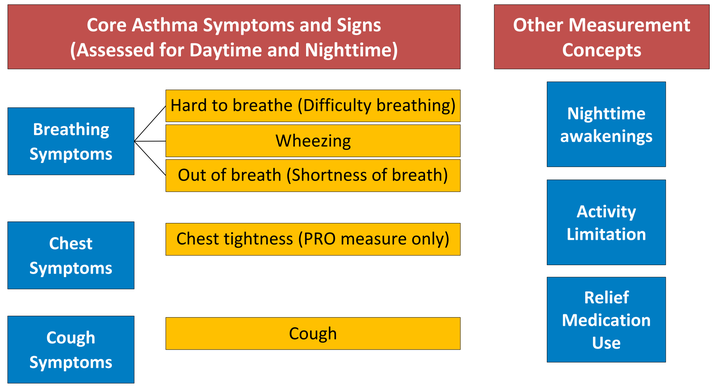
Example Endpoint Model for Treatment of Pediatric Asthma

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Improvements in airflow obstruction • FEV_1 Reduction in asthma symptoms and signs • Total asthma severity score from measure (TBD)	PerfO ObsRO
Secondary	Daytime Symptoms – Symptom Free Days Proportion of days without asthma symptoms or signs based on measure (TBD) Night-time Symptoms – Symptom Free Nights Proportion of nights without asthma symptoms or signs based on measure (TBD)	PRO/ObsRO PRO/ObsRO

Target Population

- Children 4 to 11 years old with a clinical diagnosis of mild to severe persistent asthma requiring a daily long-term control medication

Hypothesized Conceptual Framework



Draft Measures – PRO measure and ObsRO measure

- Concerns about complete and consistent coverage of asthma symptoms for younger ages led to use of Merck's draft ObsRO (for all ages of children) and PRO measures (for older children).
- Recommendations for use of the self-reported PRO measure for children ages 8 to 11 years old and the ObsRO measure to be completed by parents (for children ages 4 to 11 years old) are being considered to allow the child's voice to be heard.
- Instructions will be drafted for the parent to follow when completing the ObsRO measure to standardize the observer-reported process across respondents.

Working Group Updates

Unique Issues for the Working Group

- The age range for this target population is particularly challenging because of the wide range in cognitive development, ability to reliably report symptoms and understand timeframes (e.g., last night; since you woke up this morning), and ability to read and understand the diary items.
- In addition, asthma is a symptomatic condition for which key symptoms such as chest tightness are not easily observed by others and therefore rely heavily on self-report.
- The approach used in the Merck research, where children 8 to 11 years old complete a PRO measure on their own while parents completed an ObsRO measure for all ages, may be problematic because of the limitations of observability of nighttime symptoms (as parents would also be sleeping) and of daytime symptoms (because parents may not be with the child for enough time during the day to reliably report their observations).
- The Pediatric Asthma WG has decided to pursue Merck's approach despite these limitations
- Questions to be addressed include how best to incorporate what the child has said about symptoms as well as input from other informants (e.g., siblings, teachers, babysitters, spouses) regarding observable asthma signs and impacts.

Next Steps

- Modify the two Merck measures (if needed) based on WG and FDA feedback
- If the WG supports moving forward, issue an RFP for the additional qualitative research needed to support the development and submission of an Initial Briefing Package
- Continue to explore alternatives for assessing sleep/night-time awakenings (e.g., actigraphy)

Working Group Participants

Company/Organization	Representatives
AstraZeneca AB	Sean O'Quinn, MPH
GlaxoSmithKline , LLC	Linda Nelsen (formerly); Robyn Von Maltzahn
Novartis Pharma AG	Jessica Marvel, MPH; Luísa Álvares
Affiliation	**Consultant**
TBD	TBD