Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000006: Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)
Full Qualification Package

Executive Summary

Objective measures such as forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) are typically used in clinical studies to determine asthma disease severity. Eradication of or a reduction in the frequency and severity of symptoms is an indicator of asthma control and among the goals of asthma management.[1-4] However, there is a poor correlation between objective measures of disease severity and patients' experience of asthma symptoms.[1-3] Many symptoms of asthma can only be known to patients themselves and as such must be assessed via patient-reported outcome (PRO) measures. To date, however, there is no accepted gold standard PRO measure for the assessment of asthma symptom severity in clinical studies.[4]

To fill this measurement gap, the PRO Consortium's Asthma Working Group at the Critical Path Institute (C-Path) embarked upon the development and qualification of the *Asthma Daily Symptom Diary* (*ADSD*), a self-administered PRO measure designed to assess asthma symptoms in adolescents and adults with mild to severe persistent asthma aged 12 years old and older. The intention is that the *ADSD* will be used to derive co-primary or secondary endpoints for use in clinical research to establish the treatment benefit of novel asthma treatments and support product labeling claims. This briefing document provides details of research conducted to support the qualification of the *ADSD* as a PRO-based endpoint measure for use in clinical trials.

The *ADSD* is a six-item daily measure of asthma symptom severity that assesses three core categories of asthma symptoms: breathing symptoms (Difficulty breathing; Wheezing; Shortness of breath) chest symptoms (Chest tightness; Chest Pain) and cough. The *ADSD* is intended for twice daily completion and comprises a morning diary (for completion upon waking and referring to asthma symptoms during the nighttime) and an evening diary (for completion before going to bed and referring to asthma symptoms during the day). Respondents are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine').

The *ADSD* has been developed in accordance with the US Food and Drug Administration (FDA) PRO Guidance[5], with evidence supporting the validity of the measure generated via a number of qualitative and quantitative research activities including: a review of existing peer-reviewed literature regarding asthma symptomatology (stage 1); concept elicitation interviews (stage 2); cognitive interviews (stage 3); and a quantitative pilot study (stage 4). At each stage of the *ADSD* development process, input was obtained from the Asthma Working Group, C-Path scientists, scientific advisors in the field of pulmonary/respiratory medicine, and representatives of FDA's Center for Drug Evaluation and Research via the formal drug development tool qualification process.[6] Input was also obtained from a linguistic validation specialist to provide insights into the linguistic/cultural adaptability of the *ADSD* and an electronic PRO (ePRO) vendor who provided expertise and assistance regarding the development of formats of the *ADSD* for completion using an electronic handheld device.

Content of the *ADSD* was informed via a review of existing published qualitative research studies conducted in asthma and findings from open-ended concept elicitation interviews conducted with a diverse sample of adolescents and adults (n=55) in the US. Eight 'core symptoms' of asthma were

identified from these sources which were categorized as breathing symptoms (e.g., difficulty breathing, shortness of breath, and wheezing), chest symptoms (e.g., chest tightness, chest pressure, and chest pain) and cough symptoms (including the presence of mucus/phlegm). Subgroup analyses revealed consistency in the relevance of the eight core symptoms and the terms used to describe them across sociodemographic and clinical subgroups.

Informed by findings from the literature review, concept elicitation interviews, input from the scientific advisors, and findings of both an electronic implementation assessment and translatability assessment, it was decided to operationalize the assessment of the eight core symptoms of asthma via a single diary suitable for use in adults and adolescents with asthma aged 12 years or older. A daily diary format was chosen to minimize the impact of recall bias, to account for day-to-day variation in asthma symptoms, and also to facilitate both the calculation of symptom-free days and the assessment of changes in symptom severity over time.

Semi-structured cognitive and usability interviews were conducted with an independent sample of 65 participants in the US with asthma to evaluate the relevance and participant understanding of draft *ADSD* items, instructions, response options, and ease of *ADSD* completion using the handheld electronic device. Findings revealed that the content of the *ADSD* offered sufficient conceptual coverage of participants' asthma symptom experience and was well understood and consistently interpreted across sociodemographic and clinical subgroups of participants. Exit interviews conducted with a subset of participants (n=24) from the quantitative pilot study designed to evaluate the measurement properties of the *ADSD*, also provided further support for the content validity of the *ADSD*.

The performance, reliability, and validity of *ADSD* items and *ADSD* scores were explored using data collected via an observational quantitative pilot study conducted with a diverse sample of adolescents and adults in the US (N=219). Participants in this study completed the *ADSD* (alongside a number of other concurrent measures) for a period of 10 days. The *ADSD* items demonstrated strong item performance, reliability (reproducibility), and construct validity (in terms of the ability of the items to distinguish between known-groups and relationships with other PRO measures of similar concepts). Evidence supported the removal of the *ADSD* item assessing 'chest pressure' due to redundancy with the item assessing 'chest tightness' and poor item performance. This decision was supported by the scientific advisors and FDA during discussions at an instrument review meeting. During this meeting it was agreed that an average score across all seven items ranging from 0 to 10 (no weighting applied so each item contributes equally) would be calculated for both the morning and evening diaries, referred to as the '7-Item *ADSD* Daily Morning Score' and '7-Item *ADSD* Daily Evening Score,' respectively. During subsequent analyses these scores demonstrated good reliability, effectiveness in discriminating between groups of participants (i.e., known-groups construct validity) and correlation with scores from other PRO measures assessing similar concepts (i.e., concurrent construct validity).

Evidence regarding the reliability and validity of the 7-Item *ADSD* scores, documented in the Development of the *Asthma Daily Symptom Diary* Quantitative Pilot Study Report v3_0 (26th August 2016), was provided for FDA review and comment as part of the COA DDT #000006 submission dated October 14, 2016. Following feedback from and discussions with the Qualification Review Team (QRT), the decision was made to remove Item 8 (mucus/phlegm) from the *ADSD* as it was not considered a core asthma symptom and therefore adds "noise" to the *ADSD* as a measure of asthma symptom severity. As such, it was requested that additional analyses to evaluate the reliability and validity of the 6-Item *ADSD* Daily Morning and Evening Scores be conducted. These 6-Item scores demonstrated good reliability, effectiveness in discriminating between groups of participants (i.e., known-groups construct validity) and correlation with scores from other PRO measures assessing similar concepts (i.e., concurrent construct validity).

Collectively, this evidence supports the reliability and validity of 6-Item *ADSD* for use as an endpoint measure to evaluate the efficacy of asthma treatments in clinical studies.

1.1 Introduction and overview

A number of objective methods for determining asthma disease severity exist. Forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF), for example, typically serve as standard measurements of airway function in clinical studies. There is also increasing evidence to support the value of various biomarkers (including fractional exhaled nitric oxide, total Immunoglobin E, and blood eosinophils).[7] Among the goals of asthma management (as highlighted in clinical guidelines), and an indicator of overall asthma control, is eradication of or reduction in asthma symptoms.[8-10] Nevertheless, there is a poor correlation between the aforementioned objective measures of disease severity and patients' experience of asthma symptoms.[1-3] To provide a holistic understanding of patient disease severity and asthma control in clinical research, there is a need for a standardized way of assessing patients' experience of asthma symptoms.

Many symptoms of asthma can be known only to patients themselves and are therefore best reported via patient-reported outcome (PRO) measures. To date, however, there is no accepted gold standard PRO measure for the assessment of asthma symptom symptoms in clinical studies. As recent as 2012, the National Institutes of Health (NIH) stated during an asthma outcomes workshop that "asthma clinical research will highly benefit from standardization of major outcomes in terms of definition and assessment methodology"[11] and concluded that no published asthma symptom diary had sufficient validation information to be chosen as a core asthma outcome measure for use in clinical research sponsored by the NIH.[4] In particular, strong evidence supporting the content validity (the extent to which the PRO measure actually assesses the concept of interest, i.e., asthma symptoms) of existing measures in adolescents and adults with asthma was lacking.

To fill this measurement gap, the PRO Consortium's Asthma Working Group at the Critical Path Institute (C-Path) embarked upon the development and qualification of the *Asthma Daily Symptom Diary*; a daily asthma symptom diary developed according to recommendations in the FDA PRO Guidance to assess severity of asthma symptoms among adolescents (aged 12 to 17 years) and adults (aged 18+) with asthma.

1.2 Concept of Interest for meaningful treatment benefit

The *ADSD* is intended to be used as a co-primary or secondary endpoint measure in asthma clinical trials to assess self-reported asthma symptom severity in adolescent and adults. The *ADSD* assesses six symptoms which, based on extensive qualitative research with patients and consultation with clinical experts, may be considered as 'core' symptoms of asthma.

Product-specific claims and labeling language would be the responsibility of the sponsor and should be based on product attributes, study design and hypotheses, and discussions with the appropriate regulatory agencies. Using the *ADSD*, product-specific claims and labeling language pertaining to the severity of symptom experience and/or the occurrence of symptom free days (SFDs) could be targeted, depending on sponsor-specific clinical trial aims.

1.3 Context of Use

The target population includes adults and adolescents aged 12 years and older with a clinical diagnosis of mild persistent through severe persistent asthma, with lung function impairment (i.e., FEV1 of 45%-90% of predicted normal value) and who demonstrate reversibility consistent with American Thoracic Society (ATS)/European Respiratory Society (ERS) standards for the diagnosis of asthma.[12] This does not include those with other respiratory conditions such as chronic obstructive pulmonary disease (COPD) or upper airway obstructions. The targeted patients require daily asthma controller therapy based on current asthma management guidelines (e.g., Expert Panel Report-3 [EPR-3]).[10]

The *ADSD* has been developed in a sample diverse with respect to gender, ethnic and racial backgrounds, differing levels of educational ability, and differing levels of asthma control and severity. Diversity in clinical characteristics (e.g., asthma control, exacerbations, and medication use) was also ensured during the development of the measure, meaning that the *ADSD* is appropriate for use in clinical trials which have recruited subjects with asthma who have varied demographic and clinical backgrounds. The *ADSD* has been developed and tested in US English.

In regulated pharmaceutical trials, the intention is that the *ADSD* may be used as a co-primary or secondary endpoint measure to facilitate the comparison between either treatment and placebo groups, or different treatment groups. Other clinical measures (e.g., FEV1 or PEF) or clinically relevant events (e.g., exacerbations or rescue medication use) would be expected to serve as primary or co-primary endpoints of disease severity and asthma control alongside the *ADSD* as a measure of symptom severity. In instances where the *ADSD* is employed to derive a secondary endpoint, the clinical trial would need to succeed on the physiologic or clinician-reported endpoint before success could be attained on the secondary endpoint relating to symptom severity, using the *ADSD*.

The specific endpoint selection, positioning, and measurement approach would be determined by the study sponsor in concert with the appropriate regulatory review agencies.

1.4 *ADSD* conceptual framework

The *ADSD* is a 6-item daily assessment of asthma symptom severity. The *ADSD* comprises items assessing three core categories of asthma symptoms: breathing symptoms (difficulty breathing, wheezing, and shortness of breath); chest symptoms (chest tightness and chest pain); and cough symptoms (cough). The *ADSD* is completed twice daily, encompassing a morning diary (completed upon waking and referring to nighttime symptom severity) and an evening diary (completed before going to bed and referring to daytime symptom severity). Other clinically relevant and important concepts (e.g., mucus/phlegm, nighttime awakenings, impact on usual activities, and relief medication use) are also assessed as part of the morning and evening diaries but are not considered as part of the core *ADSD* for which qualification is sought.

A topline conceptual framework for the *ADSD* is presented in Figure 1.

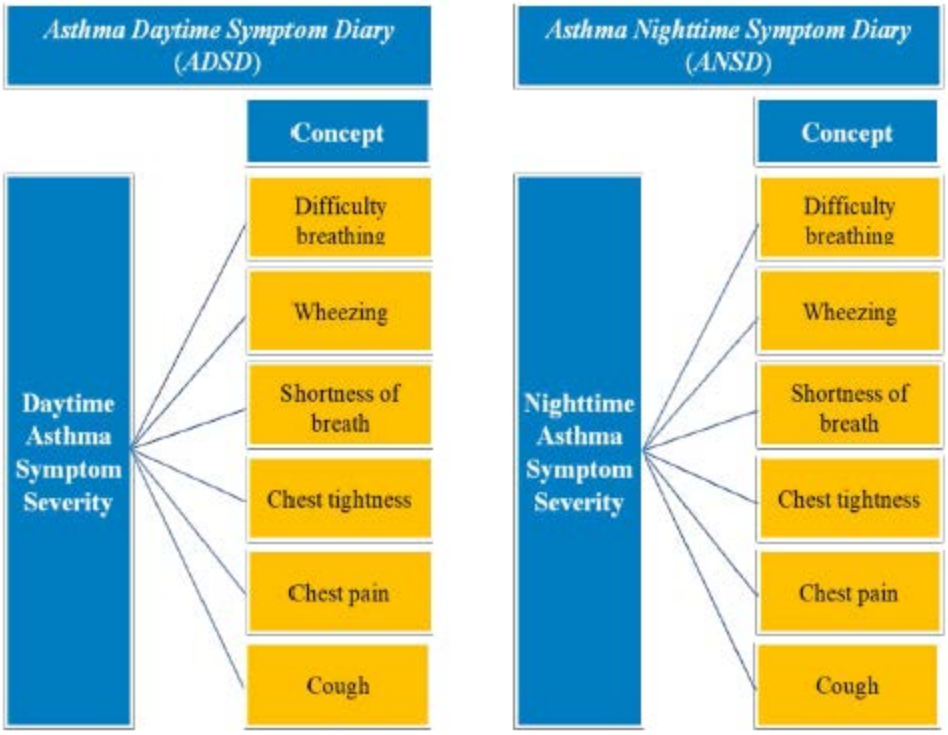

Figure 1. ***ADSD*** **topline conceptual framework**

1.5 Critical details of the measure to the degree known

1.5.1 Patient population

The *ADSD* has been developed as a self-administered PRO measure for use in adults and adolescents (aged 12 years and older) with a clinical diagnosis of mild persistent through severe persistent asthma.

1.5.2 Item content

The *ADSD* is a 6-item PRO measure designed for use in adults and adolescents (aged 12 years and older) diagnosed with asthma to assess self-reported severity of the core, defining symptoms of asthma. The *ADSD* is designed to be completed twice daily. The *ADSD* Morning Diary is to be completed upon waking and asks respondents to rate the severity of asthma symptoms during the night. Conversely, the *ADSD* Evening Diary is to be completed before going to bed and asks respondents to rate the severity of their asthma symptoms during the day. Item wording is consistent between both versions with the only differences being references to the respective recall periods.

The *ADSD* also includes supplementary items designed to assess other measurement concepts including presence of mucus/phlegm, nighttime awakenings (in the *ADSD* Morning Diary only), activity limitations (in the *ADSD* Evening Diary only) and relief medication use. These supplementary items are not included in the core item set for the *ADSD* and are scored separately as individual items.

1.5.3 Modes of administration/data collection

The *ADSD* is a self-administered PRO measure designed to be completed twice daily: once in the morning (upon waking) and once in the evening (before going to bed). The *ADSD* was originally developed and tested in paper and pencil format (round 1 of the cognitive interviews). However, the *ADSD* has been developed with electronic administration in mind using a handheld device such as a smartphone. The *ADSD* was developed and migrated to an electronic handheld device format in accordance with industry best practices.[13-15] Subsequent testing in rounds 2 and 3 of the cognitive interviews confirmed respondent understanding and user acceptance of the *ADSD* in electronic format. The quantitative pilot study also involved data collection via electronic format, using a handheld smartphone device. Future use of the *ADSD* in different data collection modes (e.g., tablet, computer, interactive voice response system [IVRS]) may require additional usability and equivalence testing.

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