Qualification Plan for the PSYCHS as a COA for Attenuated Positive Symptoms in Patients at Clinical High Risk for Psychosis

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Methodological Issue Being Addressed Drug development for early psychosis intervention depends on identifying patients at Clinical High-Risk for Psychosis (CHR-P) and assessing illness severity over time. The Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) are commonly used semi-structured interviews for both purposes. The U.S. National Institute of Mental Health (NIMH) spearheaded an effort to harmonize them, resulting in the Positive Symptoms and Diagnostic Criteria for the CAARMS Harmonized with the SIPS (PSYCHS). The PSYCHS assesses 15 attenuated positive symptoms.The current work outlines a proposed FDA Qualification Plan (QP) for the PSYCHS as a Clinician-Reported Outcome. The FDA has accepted a Letter of Intent (DDT-COA-000163) and provided funding (U01FD008131) to support this development.

Introduction We report preliminary results to support methodological decisions for the PSYCHS QP. The targeted population is CHR-P, a psychiatric condition in DSM-5 affecting youth and young adults (1.7% in the general youth population) who experience distressing attenuated psychotic symptoms that impair daily functioning but are not full-blown psychosis. The PSYCHS is used in the Accelerating Medicines Partnership Schizophrenia (AMP® SCZ) observational study to prepare for future clinical trials supporting drug registration.

Methods For content validity assessment, we plan for qualitative methods to address concept elicitation, item understanding, expert input, and contextual relevance. Preliminary data from CHR-P individuals, aged 12–35, baseline (BL, n = 381) to 3 months follow-up (3M, n=231 completers) from the AMP SCZ observational study was used to explore item level performance, discriminant and convergent validity, recall bias, PSYCHS scores, and an estimation of a cut-off for clinically meaningful change performed with anchor-based methods using the Patient Global Impression of Severity (PGIS) and the Brief Psychiatric Rating Scale (BPRS). In addition, two ongoing criterion validity studies compare the PSYCHS against the CAARMS and the SIPS.

Results Item analysis identified unusual thoughts, suspiciousness, and auditory and visual perceptual abnormalities as the most frequently endorsed and severe attenuated positive symptoms. High concordance from baseline to three months (ICC = 0.841) suggested strong test-retest reliability, with an overall decrease in severity scores of 24.3%. Convergent validity was supported by significant correlations between PSYCHS and BPRS items, while divergent validity was confirmed by weak correlations with negative symptom items and functioning. Investigation of recall bias, by correlating monthly PSYCHS scores with daily ecological momentary assessments

(EMAs), showed stable correlations over time, supporting a "past month" recall period. A 5-point improvement in PSYCHS total scores at 12 weeks corresponded with a one-category improvement in PGIS, indicating this threshold as clinically meaningful. Criterion validity analyses show high ICCs for symptoms (range 0.856 to 0.943).

Conclusion Pending content validity assessment, these results suggest that the PSYCHS instrument is a reliable and valid tool for assessing attenuated positive symptoms over time in CHR-P. By identifying a clinically meaningful change benchmark, the PSYCHS aids in evaluating treatment efficacy.

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Keywords

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Disclosures Dr. Woods reports that he has received speaking fees from the American Psychiatric Association and from Medscape Features. He has been granted US patent no. 8492418 B2 for a method of treating prodromal schizophrenia with glycine agonists. He is a consultant to and is a partner and owns stock in NW PharmaTech.

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