DDT COA #000110 **REQUEST FOR QUALIFICATION PLAN**

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Dear Dr. Litten,

We have completed our review of the letter of intent (LOI) submission for pDDT #2018-05 received on December 6, 2018.

You have proposed that a reduction in the World Health Organization (WHO) risk drinking levels of alcohol consumption be used as a primary efficacy endpoint in Phase 3 clinical trials targeting patients diagnosed with alcohol use disorder (AUD). We agree to enter this LOI into the COA Qualification Program. However, only complete drug development tools (including standardized assessment AND scoring system) can ultimately receive qualification. As such, the specific version of the Alcohol Timeline Follow-Back (TLFB), the standardized alcohol consumption collection tool from which the proposed WHO risk drinking endpoints can be derived, will also need to be submitted for qualification under DDT COA #000110. In addition, the qualification process will focus on the WHO 2-level risk drinking reductions as this has the potential to be more clinically meaningful to AUD patients than the WHO 1-level risk drinking reductions. The tracking number for this project has been reassigned to DDT COA #000110. Please refer to DDT COA #000110 in all future communications.

Appendix 1 of this letter contains an outline of the content to include in your submission to reach the next milestone (qualification plan). Please contact the COA Staff at COADDTQualification@fda.hhs.gov should you have any questions before the next milestone.

Sincerely,

Elektra J. Papadopoulos -S

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Date: 2019.04.15 11:27:57 -04'00'

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Appendix 1: COA QUALIFICATION PLAN

The COA Qualification Plan should be accompanied by a cover letter and should include the following completed sections. This plan should contain the results of completed qualitative research and the proposed quantitative research plan. If literature is cited, please cite using the number assigned to the source in a numbered reference list.

Note: Sections 1 and 2 will be posted publicly under Section 507 as well as any appendices or attachments referred to in those sections. Section 507 refers to section 507 of the Federal Food, Drug, and Cosmetic Act [FD&C Act] which was created by Section 3011 of the 21st Century Cures Act.

Section 1: Proposed Plan for COA Qualification

1.1 Introduction and overview

- This should include a concise description of the disease and the clinical trial setting in which the COA would be used, the limitations of existing assessments, a brief description of the existing or planned COA, and the rationale for use in drug development.

1.2 Concept of Interest for meaningful treatment benefit

- Describe the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., the specific symptom and/or sign presence or severity or limitations in performance or daily activities relevant in the targeted context of use).

1.3 Context of Use

- Identify the targeted study population, including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, language/culture groups).
- Identify the targeted study design. Most commonly the COA will be used to assess the change (compared to a control) induced by a medical treatment.
- Identify the targeted study objectives and endpoint positioning (i.e., planned set of primary and secondary endpoints with hierarchy). Usually, the COA will serve as a primary or secondary study endpoint measure.

1.4 Critical details of the measure to the degree known

- Reporter, if applicable
- Item content or description of the measure (for existing instruments, the specific version of the instrument and copy of the tool from which quantitative evidence has been or will be derived)
- Mode of administration (i.e., self-administered, interview-administered)
- Data collection method

1.5 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable (i.e., working group, consortia).

Section 2: Executive Summary

- High-level summary of what is included in the Qualification Plan and results to be described in the sections below

Section 3: Qualitative Evidence and Conceptual Framework

- Evidence of content validity (i.e., documentation that the COA measures the concept of interest in the context of use)

3.1 Literature review
3.2 Expert input
3.3 Reporter input (e.g., for PRO measures, concept elicitation, focus groups, or in-depth qualitative interviews to generate items, select response options, recall period, and finalize item content; for PerfO measures, evidence to support that the tasks being performed are representative of the meaningful health aspect of the concept of interest and are relevant to ability to function in day-to-day life)
3.4 Concept elicitation
3.5 Item generation
3.6 Cognitive interviews
3.7 Draft Conceptual Framework (for existing instruments, the final version conceptual framework)

Sections 4, 5, and 6: Proposed Quantitative Analysis Plan

Section 4: Cross-sectional evaluation of measurement properties

4.1 Item Level Description

4.1.1 Item descriptive statistics including frequency distribution of both item response and overall scores, floor and ceiling effect, and percentage of missing response
4.1.2 Inter-item relationships and dimensionality analysis (e.g., factor analysis or principal component analysis and evaluation of conceptual framework)
4.1.3 Item inclusion and reduction decision, identification of subscales (if any), and modification to conceptual framework

4.2 Preliminary scoring algorithm (e.g., include information about evaluation of measurement model assumptions, applicable goodness-of-fit statistics). The scoring algorithm should also include how missing data will be handled.

4.3 Reliability

4.3.1 Test-retest (e.g., intraclass correlation coefficient)
4.3.2 Internal consistency (e.g., Cronbach's alpha)
4.3.3 Inter-rater (e.g., kappa coefficient)

4.4 Construct validity

4.4.1 Convergent and discriminant validity (e.g., association with other instruments assessing similar concepts)
4.4.2 Known groups validity (e.g., difference in scores between subgroups of subjects with known status)

4.5 Score reliability in the presence of missing item-level and if applicable scale-level data
4.6 Copy of instrument
4.7 User manual and plans for further revision and refinement

4.7.1 Administration procedures
4.7.2 Training administration
4.7.3 Scoring and interpretation procedures

Section 5: Longitudinal evaluation of measurement properties (If Known)

5.1 Ability to detect change

Section 6: Interpretation of Score (If Known)

6.1 Evaluation and definition of meaningful within person change (improvement and worsening)

Section 7: Language translation and cultural adaptation (If Applicable)

7.1 Process for simultaneous development of versions in multiple languages or cultures
7.2 Process of translation/adaptation of original version
7.3 Evidence that content validity is similar for versions in multiple languages

Section 8: Questions to CDER

Section 9: References

- References and copies of the most important references that the submitter feels CDER reviewers may want to review.

Section 10: Appendices and Attachments

- Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s))

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