Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000110: WHO Risk Drinking Levels of Alcohol Consumption
Letter of Intent

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Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities).

For many individuals, AUD is a chronic relapsing disease where maintaining abstinence is often difficult. However, significant improvement in drinking, short of full abstinence, can have many health, social, and economic benefits. Analyses done by a Public-Private Partnership workgroup, the Alcohol Clinical Trials Initiative (ACTIVE), herein demonstrate that a reduction in a relatively new metric of alcohol harm reduction, the World Health Organization (WHO) risk drinking level, has validity in real-world settings and could be a viable AUD clinical trial endpoint. For example, we show that individuals drinking at WHO very high-risk levels, who subsequently reduce their WHO risk drinking level, report clinically significant improvements in how they feel and function. These improvements include a lower risk for alcohol dependence, less severe alcohol-related consequences, reduction in health care costs, improved mental health, improved quality of life, improved liver function and lower systolic blood pressure. In addition, the WHO risk drinking level endpoint is as sensitive or, in some instances, more sensitive than the standard

FDA guided "total abstinence" and "percent of subjects with no heavy drinking" endpoints in detecting differences between an experimental medication and placebo in alcohol treatment clinical trials. Moreover, this endpoint identifies more individuals as improved compared to "full abstinence" or "percent subjects with no heavy drinking". Finally, the WHO risk drinking reduction endpoint appears to maintain its efficacy in predicting improved function after extended periods of time (at least 1 year for function and up to 3 years for health costs). Furthermore, this outcome displays considerable stability by the third or fourth month of clinical trial participation, suggesting that a clinical trial length of 3-4 months might be an adequate duration for AUD phase three clinical trials using this outcome as a primary endpoint.

International publicly-available data suggest that reducing drinking from very high levels to more moderate levels can reduce long-term mortality and overall disease burden. Also, the use of the same outcome by regulatory agencies in the United States and Europe, where a 2-level reduction in WHO risk drinking is accepted, would harmonize regulatory requirements and provide efficiency in medication development for this undertreated disorder. In addition, the WHO risk drinking level outcomes capture reductions in drinking, the preferred goal of most patients, and are more readily achieved as a measure of success than "abstinence" or "no heavy drinking days". Substantial reductions in drinking, if agreed upon as a suitable goal of alcohol treatment, could increase the desirability and acceptability of treatment to patients and caregivers, and enhance the drug development process by providing additional outcomes for clinical trials of this underserved and costly disorder.

See attached report for more detail.

Provide a conceptual framework for the COA(s)

Alcohol use disorder (AUD), previously called alcohol dependence, is a devastating brain disease that causes a myriad of medical, psychological, social, and economic problems, affecting over 15 million adults and over 620,000 adolescents in the United States (U.S.) (https://pubs.niaaa.nih.gov/publications/AlcoholFacts&Stats/AlcoholFacts&Stats.htm). It estimated that over 88,000 Americans die from alcohol-related causes annually, costing society over $249 billion a year in medical, economic, and social costs. Moreover, 3.3 million deaths, or 5.9 percent of all global deaths annually are attributable to alcohol consumption, one of the highest ranked causes of death. Globally, alcohol misuse is the fifth leading risk factor for premature death and disability. Heavy alcohol use is known to increase heart disease, stroke, cancer, gastrointestinal problems, and is the leading cause of liver transplantation. In the U.S. and elsewhere, heavy alcohol consumption contributes to many social problems such as accidental injury, domestic violence, rape, assaults, and murders, while more than 10 percent of children live with a parent with identifiable alcohol problems. Despite this immense burden of disease and associated social costs, and despite the advanced neuroscience identification of pharmacological targets, there are a limited number of FDA approved medications to treat AUD.

Currently, only 3 medications have been approved by the FDA for "alcohol dependence": disulfiram, oral and injectable long-acting naltrexone, and acamprosate (Litten et al., 2016), and as seen in the table below the last one being over 12 years ago.

COMMERCIAL NAME	GENERIC NAME	DATE OF FDA APPROVAL
ANTABUSE	Disulfiram	08/28/1951
REVIA	Naltrexone, oral	11/20/1984

Campral	Acamprosate	07/29/2004
VIVITROL	Naltrexone for extended-release injectable suspension	04/13/2006

However, partially because of the heterogeneity of AUD, these medications are not universally effective, especially when applying the conservative "success criteria" of "total abstinence" or "no heavy drinking days" currently recommended by the FDA. Since developing new and more effective medications is a priority for the National Institute on Alcohol Abuse and Alcoholism (NIAAA), in conjunction with the ACTIVE workgroup, it has engaged in an effort to evaluate better ways to evaluate the effectiveness of novel medications, including evaluating methods to measure and validate a new efficacy outcome of drinking harm reduction, a reduction in the WHO risk levels of alcohol consumption.

To date, the FDA recommends 2 primary dichotomous outcomes for defining a successful response to treatment in Phase 3 alcohol pharmacotherapy trials: a) total abstinence and b) the percent of subjects with no heavy drinking days (where a heavy drinking day is defined as 5 or more drinks for men and 4 or more drinks for women) (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM433618.pdf). These 2 measures are excellent at capturing incidences of abstinence and low risk-drinking; however, they fail to capture large numbers of individuals with AUD who might achieve significant clinical benefit from lesser, but potentially clinically meaningful, reductions in drinking.

Currently, less than 10 percent of individuals with AUD seek treatment for their drinking problems (Grant et al., 2015), and the majority of individuals with AUD who do not seek alcohol treatment report not wanting to stop drinking as the primary reason for not seeking treatment (Figure 25 in https://www.samhsa.gov/ data/sites/default/files/NSDUH- DR-FRR3-2014/NSDUH-DR-FRR3-2014/NSDUH-DR-FRR3-2014.htm). Many individuals with AUD who do not initially accept an abstinence goal may find treatment more appealing if it is focused on reductions in drinking (Probst et al., 2015; van Amsterdam and van den Brink, 2013). This is partially based on the perception/anticipation that a reduction in drinking will lead to a reduction in alcohol-induced harm. Recent evidence suggests that reduction in drinking is an important goal for many individuals with AUD. In 3 recent AUD multisite pharmacotherapy clinical trials, individuals seeking participation who had a non-abstinence goal of drinking reduction ranged from 72 to 91 percent (Falk et al., 2018; Litten et al, 2013; Ryan et al., 2017). Additionally, many individuals with AUD report fear of the "stigma" associated with being identified as having AUD and are therefore reluctant to stop drinking completely (Probst et al., 2015) since abstinence is often interpreted by others has having an alcohol problem. Moreover, AUD is a chronic relapsing disorder for many people, whereby focusing on the reduction of harmful drinking can be an important aspect of disease management (Maremmani et al., 2015) similar to the management of other chronic diseases like diabetes, obesity, and hypertension where objective measures of reduced-harm (e.g. lowered blood sugar, weight, and blood pressure) are acceptable goals. Indeed, there are numerous benefits to reductions in drinking, including decreases in morbidity and mortality (Laramee et al., 2015), lower healthcare costs (Kline-Simon et al., 2014), decreased alcohol-related consequences (Falk et al., 2010; Witkiewitz, 2013), and improved psychosocial functioning (Kline-Simon et al., 2013; Witkiewitz, 2013).

Given the perceived utility and need for an alcohol consumption reduction measure for clinical trials, the objective of this meeting is to discuss a new endpoint for alcohol medications development that we believe successfully identifies individuals with AUD whose reductions in drinking are associated with clinically meaningful improvements in how they feel and function. Through careful research, NIAAA in conjunction

with ACTIVE has conducted a series of analyses to validate the World Health Organization (WHO) risk levels of alcohol consumption as a clinically meaningful indicator of drinking reduction for AUD clinical trials. The WHO risk drinking levels include very high-risk drinking, high-risk drinking, moderate-risk drinking, and low-risk drinking based on grams of ethanol consumed per day (see below).

Table 1.	WHO risk drinking levels (grams of alcohol consumption)
Risk level	Definition of each level, in grams and US standard drinks
Very high	>100 g (>7.1 drinks) for men; >60 g (>4.3 drinks) for women
High	60–100 g (4.3–7.1 drinks) for men; 40–60 g (2.9–4.3 drinks) for women
Moderate	40–60 g (2.9–4.3 drinks) for men; 20–40 g (1.4–2.9 drinks) for women
Low	1–40 g (<2.9 drinks) for men; 1–20 g (<1.4 drinks) for women

The European Medicines Agency (EMA) currently endorses a 2-level reduction in WHO risk drinking levels as one potential outcome in the regulatory evaluation of new drug applications for AUD pharmacotherapy trials. Based on our work, we propose that the FDA also consider adding a reduction in the WHO level as a primary endpoint to the existing endpoints of total abstinence and the percent of subjects with no heavy drinking days in their guidance offered for regulatory approvals of AUD trials.

In the following attachment below, we demonstrate and discuss the following topics: 1) how drinking is measured; 2) how reductions in the WHO risk drinking level results in improvements in how individuals with AUD feel and function; 3) how reductions in WHO risk drinking level translates to long-term reduction in health care costs; 4) how this drinking endpoint performs and compares to the current primary drinking endpoints in several prominent AUD pharmacotherapy trials; and 5) the degree to which this drinking endpoint remains stable during AUD pharmacotherapy trials.

See attached report for more detail.

Context of Use for COA Qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups).

The targeted study population include individuals diagnosed with an Alcohol Use Disorder (AUD). Many of these patients may also suffer from a comorbid psychiatric disorder and Substance Use Disorder (SUD).

***Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate*).**

In addition to the shift in the WHO risk drinking level endpoint, we would also express drinking in the following outcomes: drinks/day, drinks/drinking days, percent days abstinent, number of heavy drinking days, abstinence, and percent subjects with no heavy drinking.

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***
- ***Other study setting specifics (e.g., inpatient versus outpatient)***

This WHO endpoint can be used in any geographic location and any study treatment settings.

COA Type: PRO

References:

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