Date: January 10, 2018

ATTN: Geoffrey T. Manley, M.D., Ph.D.
Principal Investigator, TBI Endpoints Development (TED) Initiative and TRACK-TBI Study
University of California, San Francisco
1001 Potrero Avenue
Bldg. 1, Room 101
San Francisco, CA 94110

SUBJECT: Biomarker Letter of Support

Dear Dr. Manley:

We are issuing this Letter of Support to the TBI Endpoints Development (TED) Initiative and the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) investigators to encourage the further study of blood levels of glial fibrillary acidic protein (GFAP), a possible biomarker of astrocytic injury, and ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1), a possible biomarker of neuronal injury, as exploratory prognostic enrichment biomarkers to identify patients who are likely to develop persistent disability during the course of mild traumatic brain injury (TBI) clinical trials.

Although most patients with mild TBI have no abnormalities on non-contrast head computed tomography (NCCT), a typical imaging modality used for evaluation of mild TBI, some of these patients develop persistent disabling symptoms despite having a normal NCCT. There is no current standard technique to identify which of these mild TBI patients will experience unfavorable long-term outcomes. Identifying patients with mild TBI who are likely to develop persistent disability within the time frame of a clinical trial could lead to the development of therapies for this condition.

We support the TED Initiative and TRACK-TBI's proposed plan to study GFAP and UCH-L1 as prognostic enrichment biomarkers. Inclusion of patients expected to develop clinically relevant disability over the course of a clinical trial of reasonable duration may enhance the potential to observe clinically meaningful effects of novel therapeutic agents. Such application is consistent with the FDA's draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products."[1] Greater experience with the use of these biomarkers in clinical trials may be useful to more accurately determine their clinical utility for prognostic enrichment, drug development decisions, and study design considerations.

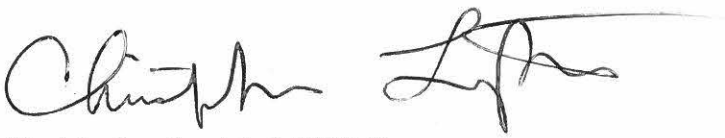
[1] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf

We support the TED Initiative and TRACK-TBI's plan to leverage blood-based biomarker data from multi-center studies, allowing within-study and between-study comparisons to elucidate the prognostic accuracy of blood-based biomarkers. Additionally, we recommend further studies to improve the current understanding of the biological and analytical variations in biomarker levels and to determine optimal biomarker cut points for informing TBI outcome prognostication. Because blood-based biomarkers of TBI may be elevated irrespective of the underlying cause of brain injury and may also be elevated in injuries to the peripheral nervous system, we encourage the conduct of additional studies that will elucidate the role of confounding factors, such as age, polytrauma, gender, and various comorbidities, on blood levels of proposed biomarkers of brain injury. Strong emphasis on applying good scientific and laboratory practices for quality control and validation of the proposed biomarkers is imperative.

We encourage exploration of blood levels of GFAP and UCH-L1 to identify patients with mild TBI who may be more likely to develop persistent disability from their injuries for the purpose of clinical trial enrichment. We will consider data collection on these biomarkers to be exploratory in nature. When including biomarkers in clinical trials, sponsors are encouraged to employ consensus TBI Clinical Data Interchange Consortium (CDISC)[2] standards for data harmonization. We believe data sharing and integration across trials can foster an accelerated path for TBI drug development programs. If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a given Investigational New Drug (IND) development program, they should prospectively discuss the approach to these analyses with the Division of Neurology Products in CDER.

Any groups (academia, industry, and government) that would like to join in this effort or have information or data that may be useful can contact Dr. Geoff Manley (manleyg@ucsf.edu), the TED Initiative and TRACK-TBI point of contact for this project, or view the TED Initiative and TRACK-TBI websites.

Signed:



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[2] https://www.cdisc.org/standards