FDA U.S. FOOD & DRUG ADMINISTRATION

Date: March 31, 2017

ATTN: Geoffrey T. Manley, M.D., Ph.D.
Contact 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 cortical contusions and diffuse axonal injury, as measured by magnetic resonance imaging (MRI), 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 computed tomography (NCCT) of the head, 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 develop these biomarkers. Preliminary data suggest that many mild TBI patients with normal NCCT on acute evaluation have abnormalities on subsequent MRI assessment. Evidence of cortical contusions or diffuse axonal injury on MRI was associated with worsened outcome several months later. 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 Such application is consistent with the FDA's draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products[1]."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 neuroimaging biomarkers in clinical trials may be useful to more accurately determine their clinical utility for prognostic enrichment, drug development decisions, and study design considerations.

We support the TED Initiative and TRACK-TBI's plan to leverage existing MRI data from multi-center studies, which collectively contain several thousand CT and MRI scans, to perform analyses and within-study and between-study comparisons to elucidate the effects of image acquisition hardware and software parameters, as well as imaging protocols, on the

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

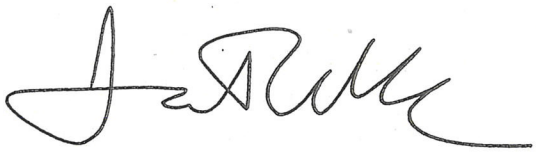
reproducibility of evaluating the association of the candidate biomarkers with clinical outcomes. We also support the development and use of consensus imaging protocols for individuals with TBI and the establishment of protocols for measuring diffuse axonal injury. No specific cortical contusion or diffuse axonal injury image analysis algorithm, validation process, hardware, or manufacturer is endorsed by FDA. Because the analysis algorithm may introduce uncertainty in the measurement of cortical contusions and diffuse axonal injury, strong emphasis on applying good scientific, laboratory, and software development practices for quality control and validation of these proposed biomarkers is imperative. We strongly recommend the adoption of standardized imaging acquisition protocols, imaging interpretations, and data standards to reduce uncertainty and to facilitate future analyses across studies. While protocol standardization plays a vital role in reducing variability in clinical trials, we recognize that innovative imaging techniques may play a role in the development of these biomarkers. We encourage investigators to conduct bridging studies that may allow investigators to leverage retrospective imaging data that does not meet recommended protocol criteria and future imaging data from sites using innovative imaging techniques.

We encourage exploration of cortical contusions and diffuse axonal injury as measured by MRI 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 these 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.

Sincerely,

Janet Woodcock, M.D.



Director, CDER
U.S. Food and Drug Administration

[2] https://www.cdisc.org/standards/therapeutic-areas/traumatic-brain-injury

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10903 New Hampshire Avenue
Silver Spring, MD 10903
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