BQP Qualification Program Cover Letter

Date: 3/19/2021

Subject: DDT QUALIFICATION SUBMISSION

DDT Type: Biomarker Qualification

ATTN: CDER-Biomarker Qualification Program

C/O CDER Document Room: Upon receipt notify:
CDER-BiomarkerQualificationProgram@fda.hhs.gov

Biomarker DDT Tracking Number: not assigned yet

Check Here	Submission Type
X	Letter of Intent
	Qualification Plan
	Full Qualification Package
	Update of Above (Check two, this box and one above)
	Other (please specify):

Biomarker Name(s): PE(38:6), PC(38:8), and TG(60:12)

Context of Use: Diagnostic enrichment biomarker, in conjunction with other clinical factors, based on the plasma biomarker level to identify patients with traumatic brain injury appropriate for inclusion in drug-development clinical trials.

Contact Information: Complete contact information including name(s), affiliation, mailing address, email address, phone and fax numbers.

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Purpose Statement: This submission is an initial Letter of Intent submission. The proposed biomarkers are being studied as part of a CERSI Proposal: "Development of diagnostic biomarkers for determination of traumatic brain injury". The purpose of this submission is to solicit feedback from the FDA regarding the potential viability of PE(38:6), PC(38:8), and TG(60:12) as diagnostic biomarkers for traumatic brain injury and the next steps for biomarker development.

Submission Statement: The physical media submission is virus free having been checked with Symantec Endpoint Protection (Definition: Thursday March 18, 2021, r22) antivirus software to check the files for viruses.

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Biomarker Qualification Letter of Intent

Administrative Information

Submission Title: Plasma traumatic brain injury biomarkers as assessed by liquid chromatography-tandem mass spectrometry

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Submission Dates:

LOI submission (original): 3/19/2021

Drug Development Need Statement

More than 1.7 million new cases of traumatic brain injury occur annually in the United States. In addition to immediate mortality, traumatic brain injury leads to high incidence of long-term disability as well as has been proposed as a major risk factor for the development of neurodegenerative disease. Currently, there is a dearth in minimally invasive, quantitative diagnostic biomarkers for traumatic brain injury employed in clinical use. A diagnostic plasma biomarker could determine if a patient has traumatic brain injury and the severity of that injury. Current methods use clinical outcome assessments that are highly subjective both due to patient responses and clinicians' observations. Thus, quantitative blood-based biomarkers could provide additional information and assist in the diagnoses of traumatic brain injury. Additionally, a diagnostic biomarker would have utility in determining which patients would be appropriate for inclusion in clinical trials intended to develop new drugs to mitigate traumatic brain injury.

Biomarker Information and Interpretation

Biomarker name:

1. Biomarker name: PE(38:6)
1-hexadecanoyl-2-(docosahexaenoyl)-sn-glycero-3-phosphoethanolamine
PE(38:6)
PE(16:0/22:6)*

HMDB ID: HMDB0008946; HMDB08946
https://hmdb.ca/metabolites/HMDB0008946
Pubchem ID: 9546799
https://pubchem.ncbi.nlm.nih.gov/compound/9546799
LMID: LMGP02010095
http://www.lipidmaps.org/data/LMSDRecord.php?LMID=LMGP02010095

Biomarker matrix: Plasma
Biomarker type: Molecular
BEST biomarker category: Diagnostic

2. Biomarker name: PC(38:8)
1-a-Linolenoyl-2-eicosapentaenoyl-sn-glycero-3-phosphocholine
PC(38:8)
PC(18:3/20:5)*

HMDB ID: HMDB0008215
https://hmdb.ca/metabolites/HMDB0008215

PubchemID: 52922865
https://pubchem.ncbi.nlm.nih.gov/compound/52922865

LMID: LMGP01011693
https://www.lipidmaps.org/data/LMSDRecord.php?LMID=LMGP01011693

Biomarker matrix: Plasma
Biomarker type: Molecular
BEST biomarker category: Diagnostic

3. Biomarker name: TG(60:12)
1-Oleoyl-2-eicosapentaenoyl-3-docosahexaenoyl-glycerol
TG(60:12)
(18:1/20:5/22:6)*

HMDB ID: HMDB0050239
https://hmdb.ca/metabolites/HMDB0050239
Pubchem ID: 9545994

https://pubchem.ncbi.nlm.nih.gov/compound/9545994
LMID: LMGL03012033
https://lipidmaps.org/data/LMSDRecord.php?LMID=LMGL03012033

Biomarker matrix: Plasma
Biomarker type: Molecular
BEST biomarker category: Diagnostic

**Lipid identification numbers and acyl chain designation for each biomarker are for the most likely lipid isomer based upon the mass spectrometry product ion spectra showing molecular fragmentation. Additional isomeric species for these lipids could exist.*

Analytical methods: Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

Measurement units and limits of detection: Concentrations for PE(38:6), PC(38:8), and TG(60:12) are typically µmol/L. Limit of detection is still being optimized and determined but is typically in the low nmol/L range (e.g., lower limit of quantification for PE(38:6) is 0.655 nmol/L).

Biomarker interpretation and utility:

Post-analytical application/conversion of biomarker raw measure to the applied measure: The raw biomarker measure will be used directly.

Describe rationale for post-analytical elements used as inputs in application or conversion of the raw biomarker measurement: N/A

Clinical interpretive criteria. It is still to be determined what will be used as the cutoff values, or thresholds, or boundaries/limits of the biomarkers to draw an actionable conclusion based on the biomarker result.

Context of Use Statement

Diagnostic enrichment biomarker, in conjunction with other clinical factors, based on the plasma biomarker level to identify patients with traumatic brain injury by blunt mechanism head injury appropriate for inclusion in drug-development clinical trials.

Analytical Considerations

General description of what aspect of the biomarker is being measured: plasma level of biomarker

PE(38:6), PC(38:8) and TG(60:12) are lipids that are present endogenously in brain and in plasma. According to our data, these lipids have a change in abundance after traumatic brain injury (TBI) in both brain and in plasma. PE(38:6) and PC(38:8) are decreased after TBI and TG(60:12) is increased after TBI. The absolute amount of the biomarker molecule will be quantified directly in plasma. The amount of PE(38:6), PC(38:8) and TG(60:12) will be quantified from plasma extracts using liquid chromatography tandem mass spectrometry (LC-MS/MS). Extracts will be prepared with a one-step protein precipitation. LC-MS/MS will use liquid chromatography to separate analytes of interest followed by detection using tandem mass spectrometry (MS/MS) using selected reaction monitoring (SRM) of a pre-defined precursor

ion to product ion transition. LC-MS/MS has high specificity given that analytes must meet the chromatographic retention time, precursor ion mass selection, and characteristic product ion mass selection for detection. Quantification of biomarkers will be determined from a calibration curve constructed with authentic standards and controlled for experimental variation by internal standards. The LC-MS/MS assay yields confident assignment of identity and accurate quantification of targeted lipid species with a 3-order of magnitude linear range. **Attachment 1** has additional information of the targeted LC-MS/MS analysis methodology and **Attachment 2** includes an SOP for the LC-MS/MS assay for PE(38:6). Similar assays are in the process of being developed and validated for PC(38:8) and TG(60:12).

Description of sample source. Sample matrix is plasma. Thirty microliters (30 µL) of plasma is used in the biomarker analysis. Standard plasma preparation methodology where whole blood is collected into an anti-coagulant-treated tube and then centrifuged to remove cells yielding a plasma supernatant is used. Initial assay development has been with plasma prepared with either anticoagulant potassium EDTA or CPD (Citrate-phosphate-dextrose). The effect of anticoagulant additives and biospecimen stability are in the process of being determined. Anticoagulant additive has not shown any effect and is not anticipated to impact the analyses based upon previous experience. The current sample preparation method is detailed in **Attachment 2**.

Description of pre-analytical factors and quality assurance/quality control (QA/QC) plans. An SOP for sample collection is still to be determined. Only plasma samples within the defined biospecimen stability parameters will be evaluated.

Analytical validation plan. The liquid chromatography-tandem mass spectrometry (LC-MS/MS) biomarker assay will be technically validated according to the FDA Guidance on Bioanalytical Method Validation (1). The biomarker assay validation will include definition of accuracy, precision, sensitivity, selectivity, parallelism, range, reproducibility, and stability characteristics. **Attachment 3** includes an SOP describing the plan for analytical method validation. Relevant sections of this SOP will be used to validate the LC-MS/MS biomarker assays for analytical performance. Analytical validation is being carried out in human plasma.

The LC-MS/MS methodology and validation for PE(38:6) has been completed and is in progress for PC(38:8) and TG(60:12). The LC-MS/MS methodology and validation process for PC(38:8) and TG(60:12) is similar to that conducted for PE(38:6). **Attachment 4** includes a summary of the method validation results for PE(38:6). Similar method validation summaries for PC(38:8) and TG(60:12) are currently in progress.

The technically validated biomarker method will be used to perform biomarker measurements in animal model samples and in a human cohort to determine the clinical utility, including establishing and validating normal/reference values, threshold values, useful window of measurement, and potential for severity scaling of biomarker levels and correlation with clinical outcome assessments.

Once the SOP and analytical validation plan is finalized, describe how you will use this process to validate the final version of the measurement tool. The technical validation of the individual biomarkers as well as the clinical utility as determined by the animal and human cohorts (threshold levels and/or severity scaling) will be the basis for the final individual or composite biomarker for qualification. The validated LC-MS/MS biomarker assay will be used to assay plasma samples from patients with traumatic brain injury and healthy controls which have been collected according to the sample collection and processing SOP.

Clinical Considerations

Describe how the biomarker measurement is used to inform drug development. Please provide a decision tree to guide how the biomarker information would be used in drug development or a clinical trial. As a diagnostic enrichment biomarker, the plasma biomarker level of PE(38:6), PC(38:8), and/or TG(60:12) could be used after clinical assessment to identify patients with traumatic brain injury appropriate for inclusion in drug-development clinical trials. PE(38:6), PC(38:8)and TG(60:12) could be used either individually or in combination, with the maximum clinical utility to be determined. A decision tree is provided in **Figure 1** to show how the plasma levels of the biomarker would be used as a diagnostic enrichment biomarker, in conjunction with other clinical factors, to identify patients with traumatic brain injury by blunt mechanism head injury appropriate for inclusion in drug-development clinical trials in accordance with the COU statement.

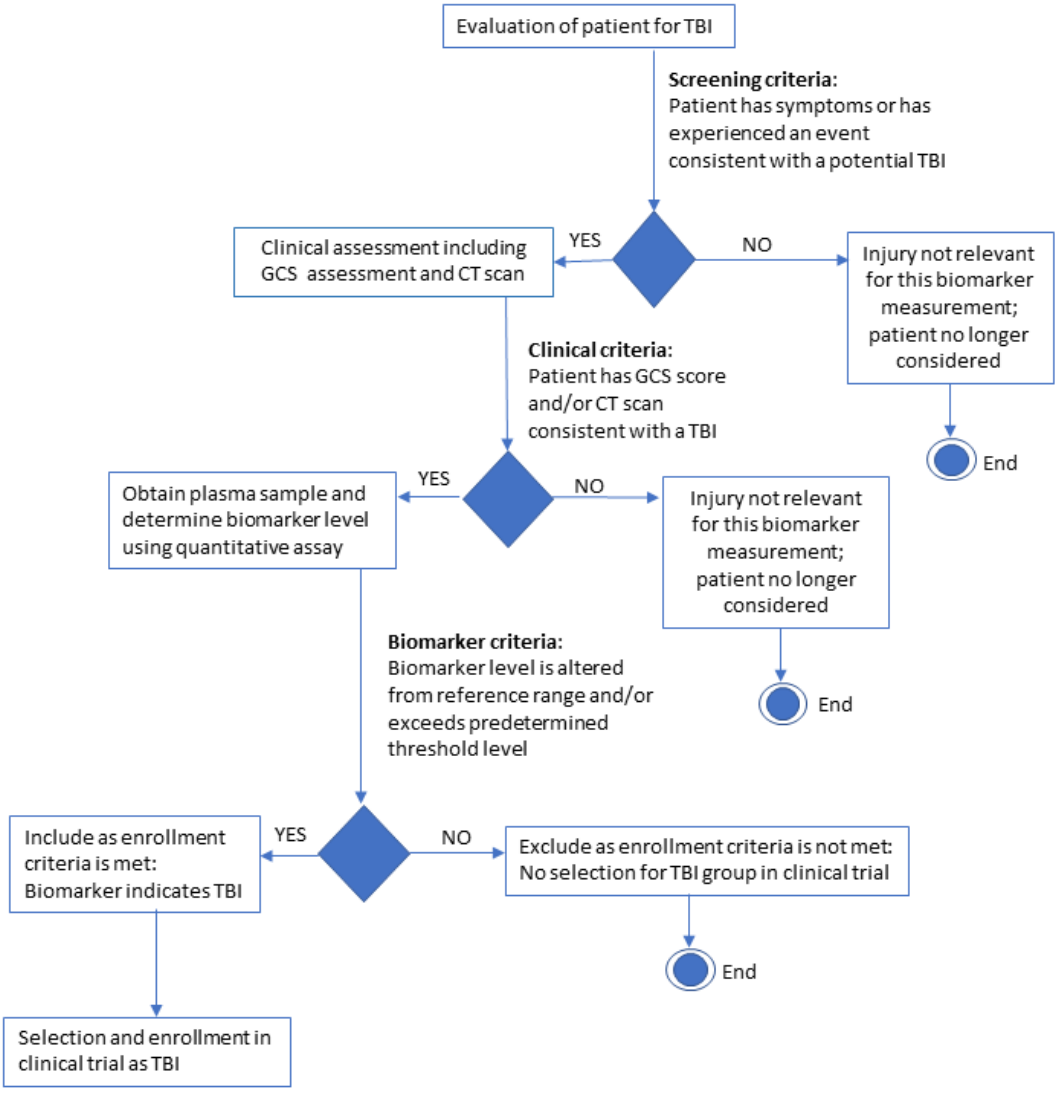

Figure 1. Decision tree for how biomarker information would be used for inclusion in drug development trials. Biomarker to be used as a diagnostic enrichment biomarker in conjunction with other clinical factors to identify patients with traumatic brain injury appropriate for inclusion in drug development trials.

Describe patient population or drug development setting in which the biomarker will be used. Biomarker is intended to be used in patients with a report of a blunt mechanism head injury. The diagnostic biomarker would be used to identify patients with traumatic brain injury, in conjunction with clinical assessments, and identify patients appropriate for inclusion in drug development clinical trials.

Clinical validation: provide information to support biological and clinical relevance of the biomarker as applied in the COU. Describe how normal or other reference values are established, provide study design(s), analytical plan, etc.: To be determined from in-progress study data (see **Attachment 1**). We are currently conducting an animal study in conjunction with a human study where reference values, typical variability, and magnitude change after TBI will be established. The biomarker(s) use is intended as a diagnostic enrichment biomarker(s) in conjunction with clinical assessments to identify patients with traumatic brain injury appropriate for inclusion in drug-development trials.

The animal study is a controlled cortical impact mouse model of traumatic brain injury that is widely used and well-characterized. The animal study is described briefly in the **Supporting Information** (below) and in **Attachment 1, and Attachment 5**. The in-depth understanding of this widely accepted injury paradigm makes the findings very generalizable toward understanding of traumatic brain injury and the development of the proposed diagnostic enrichment biomarkers for traumatic brain injury. The animal model will enable the characterization of biomarker performance under well-controlled conditions in order to enable the determination of metrics that will be applied to patients including biomarker response according to severity, the biokinetics of biomarker response (definition of the useful time window for measurement), and the determination of the CNS specificity by using both TBI and other traumatic injury models (that exclude brain injury).

The human study will be with patients diagnosed with traumatic brain injury from the University of Maryland Shock Trauma Center. Reference values for each biomarker will be determined in plasma from healthy volunteers with no history of head trauma. We will validate the animal model findings in a cohort of human patients where we will analyze de-identified plasma samples from adults aged 18-55 with a positive head CT and traumatic brain injury resulting from blunt mechanism, collected between 12-24h after injury. Patients will be diagnosed with TBI according to clinical outcome assessments. Clinical outcome assessments to establish TBI will be conducted for each patient and will include assessment of a Glasgow Coma Scale (GCS) score and collection of a computed tomography (CT) scan of the brain. GCS is the most common clinical index for assessment of TBI severity (2-4). Most literature relates GCS score to TBI severity as follows: severe TBI at 3-8, moderate at 9-12 and minor at 13-15 (3). GCS assessments are based upon three elements, all of which must be completed to assign a score, including eye opening, verbal response, and motor response (3). Brain CT is the imaging modality of choice to triage TBI patients (4).

Statistical Analysis. The human study objective will be to determine the potential of these markers to serve as diagnostic enrichment biomarkers for TBI in conjunction with clinical considerations.

The sample size of the human study will be determined based upon the magnitude of change observed in the animal model and the typical baseline variability in a healthy human population to have 80% power to detect a significant difference ($p<0.05$) in biomarker levels in TBI patients as compared to healthy uninjured controls. Based upon preliminary baseline levels and the anticipated magnitude change in the biomarker with the smallest change after TBI, we estimate a minimum of 15 patients in each group will

be needed. Power analysis will be revisited as the reference range(s) (normal baseline levels and variability) are further established in healthy human with no history of head trauma.

Threshold values are to be determined and will be established based upon the magnitude of the change in biomarker and the typical variability of the baseline reference range and injured biomarker levels. Correlation analysis will be performed, if possible, with clinical outcome assessments to determine if severity scaling can be established. We will assess sensitivity and specificity of biomarkers for TBI by means of Receiver Operating Characteristic (ROC) curves. We will evaluate the sensitivity and specificity of biomarkers at specific time points to define the utility at various time points after injury. To further evaluate the diagnostic enrichment potential of the biomarkers, positive predictive value and negative predictive value will be calculated. Additionally, we will calculate the false negative rate and the false positive rate. A combination of biomarkers may be included as a panel of multiple diagnostic enrichment biomarkers according to maximization of the area under ROC curve and subsequent calculation of the metrics described above. Bias will be mitigated by blinding all samples to the analyst and randomizing samples during analysis.

Benefits and risks of applying the biomarker in drug development or a clinical trial: The biomarker would provide a quantitative assessment of potential traumatic brain injury, that is currently not available. May help determine mild, moderate, severe traumatic brain injury. (see **Attachment 1**). A benefit of the proposed biomarkers is that they would add an objective measure for diagnostic enrichment of patients with TBI for the purpose of enrollment in drug development trials.

Describe any current knowledge gaps, limitations and assumptions in applying the biomarker in drug development or a clinical trial: (see **Attachment 1**). Specificity of plasma biomarkers for TBI to brain is a current knowledge gap that our animal studies will address using models of TBI and other models of traumatic injuries that do not involve brain (traumatic muscle or bone injuries). Other current knowledge gaps are to determine if biomarkers can inform on injury severity, and to determine the useful time window of measurement after injury. Correlation with clinical outcome assessments are to be determined.

Current clinical outcome assessments for TBI, including the GCS and brain CT, have an element of subjectivity or lack diagnostic utility. The GCS is the most common clinical index for assessment of TBI severity (2-4). The GCS assessment presents a number of challenges for diagnosis of TBI. GCS is a subjective measure that relies on the skill of the observer and discrepancies in scoring have been reported between the various medical personnel that assess GCS (2, 3). GCS assessments are based upon three elements, all of which must be completed to assign a score, including eye opening, verbal response, and motor response (3). It is challenging or impossible to administer the GCS for patients with TBI who have received neuromuscular paralysis or sedation or who have periorbital swelling (2). Additional confounders to GCS assessment include baseline cognition function, ventilatory support, alcohol or drug intoxication, and circadian rhythm (4). An additional limitation of the GCS scale is that the scale is non-parametric, meaning the values at different regions of the scale may not be equally proportionate. For example, the difference between a score of 12 and 13 as compared to the difference between a score of 3 and 4, may not represent the same magnitude difference in injury severity (3). Brain CT is the imaging modality of choice to triage TBI patients. However, it has been found to have low diagnostic potential for the more subtle injuries including mild TBI (4).

Supporting Information

Underlying biological process; evidence of association of the biological process with the biomarker: See **Attachment 1**. A description of the underlying biological process and association of the biomarkers with the biological process is included in CERSI Biomarker Development Proposal: "Development of diagnostic biomarkers for determination of traumatic brain injury". Additional information and supporting references regarding the underlying biological processes and the association of the underlying biological processes with the biomarker are provided in **Attachment 5**.

Summary of existing data to support the biomarker and its COU: See **Attachment 1**. The summary of existing data to support the biomarker development and its COU are detailed in CERSI Biomarker Development Proposal: "Development of diagnostic biomarkers for determination of traumatic brain injury". Additional relevant data to support the biomarker and its COU is provided in **Attachment 6**.

Summary of planned studies to support the biomarker and the COU: See **Attachment 1**. The planned studies to support the biomarker development and its COU are detailed in CERSI Biomarker Development Proposal: "Development of diagnostic biomarkers for determination of traumatic brain injury". Additional studies will be determined, as needed, upon completion of the studies in **Attachment 1**.

Briefly, the animal study will be used to systematically define biomarker performance that will be validated in human subjects. For the animal study, biomarker plasma-tissue correlations will be established by quantifying brain (ipsilateral and contralateral cortex) and plasma biomarker lipids using the described LC-MS/MS methodology at time points of 0, 1, 3, 7, 14, and 28 days after moderate traumatic brain injury. Both male and female mice will be used in separate groups to assess any effect of gender. Plasma biomarker levels will also be quantified for mild and severe traumatic brain injury at the same timepoints after injury to establish biomarker dose response and the useful window of measurement of the biomarker after injury. Biomarker levels in the mouse model will be correlated with molecular, histological, and cognitive outcome assessments. The CNS-specificity of the biomarker response will be determined by analyzing plasma from non-brain traumatic injury models of muscle and bone injury that are likely to be coincident with traumatic brain injury using a critical defect muscle injury model and fibula fracture model in mouse. These animal studies are described in greater detail in **Attachment 1**.

The human study will be with patients diagnosed with traumatic brain injury from the University of Maryland Shock Trauma Center. Reference values for each biomarker will be determined in plasma from healthy volunteers with no history of head trauma. We will validate the animal model findings in a cohort of human patients where we will analyze de-identified plasma samples from adults aged 18-55 with a positive head CT and traumatic brain injury resulting from blunt mechanism, collected between 12-24h after injury. Patients will be diagnosed with TBI according to clinical outcome assessments. Clinical outcome assessments to establish TBI will be conducted for each patient and will include assessment of a Glasgow Coma Scale (GCS) score and collection of a computed tomography (CT) scan of the brain.

Current comparator, current standards, or approaches: There are no biomarkers for traumatic brain injury. Whereas a number of molecules have been investigated as potential biomarkers, there is no molecule that is a definitive biomarker to accurately characterize TBI. Serum or plasma biomarkers represent the vast majority of studies according to a recent review of the literature (>70%) (4). Among the many molecules that have been investigated, cytokines, nerve tissue proteins, and coagulation tests

are the most studied categories (4). S100B, a protein that increases after TBI due to release from damaged glial cells or disruption of the BBB, is the most commonly studied TBI biomarker according to this recent review of the literature (~20% of studies) (4). Whereas its elevation has a 24 h half-life in severe TBI, its very short half-life in mild TBI (4-6 h) limits its biomarker utility (5). Additionally, reviews of the literature have shown contradictory results of S100B as a diagnostic (6, 7). Cytokines are fast responding, but suffer from a lack of specificity (8). Cytokines interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor, alpha (TNF-α), as well as protein neuron-specific enolase (NSE) have all been studied widely as potential biomarkers for TBI but have also displayed a lack of specificity because they can be produced by other injuries, and, therefore, lack diagnostic utility (8-10). Coagulation tests have utility for identifying TBI-induced coagulopathy, but have not been shown to be diagnostic for TBI (4). Lipids represent a small fraction of TBI biomarker studies (~1%) (4) and, therefore, present an opportunity for further biomarker development.

Previous Qualification Interactions

None

Attachments

- **List of publications most relevant to biomarker development proposal**: A list of relevant publications is included in **Attachment 1**, pages 36-39. Additional references are provided in **Attachment 5** and at the **end of this LOI**.

- **Attachment 1:** CERSI Biomarker Development Proposal: "Development of diagnostic biomarkers for determination of traumatic brain injury"

- **Attachment 2: SOP for measurement of PE(38:6).** (*Note: Similar assays are in the process of being developed for PC(38:8) and TG(60:12).*

- **Attachment 3: SOP for analytical method validation.** Relevant sections of this SOP will be used to validate the LC-MS/MS assays for analytical performance.

- **Attachment 4: Summary of method validation results for PE(38:6).** *(Note: Method validation for PC(38:8) and TG(60:12) are currently in progress.)*

- **Attachment 5: Additional information on the underlying biological process and evidence of association of the biological process** with the biomarker for PE(38:6), PC(38:8) and TG(60:12).

- **Attachment 6: Figures 1-4:** Additional biomarker data to support LOI
    - Figure 1: Controlled cortical impact mouse model of traumatic brain injury (TBI) and critical defect mouse model of traumatic muscle injury (TMI) models.
    - Figure 2. Data to support PE(38:6)
    - Figure 3. Data to support PC(38:8)
    - Figure 4. Data to support TG(60:12)

REFERENCES

1. FDA. Guidance for Bioanalytical Method Validation. Guidance for Industry: Bioanalytical Method Validation. 2001.
2. Marion DW, Carlier PM. Problems with initial Glasgow Coma Scale assessment caused by prehospital treatment of patients with head injuries: results of a national survey. J Trauma. 1994;36(1):89-95. doi: 10.1097/00005373-199401000-00014. PubMed PMID: 8295256.
3. Mehta R, trainee GP, Chinthapalli K, consultant n. Glasgow coma scale explained. BMJ. 2019;365:l1296. doi: 10.1136/bmj.l1296. PubMed PMID: 31048343.
4. Edalatfar M, Piri SM, Mehrabinejad MM, Mousavi MS, Meknatkhah S, Fattahi MR, Kavyani Z, Hajighadery A, Kaveh M, Aryannejad A, Ghafouri M, Jamshidi E, Rezwanifar MM, Sadeghi-Naini M, Bari A, Sharif-Alhoseini M. Biofluid Biomarkers in Traumatic Brain Injury: A Systematic Scoping Review. Neurocrit Care. 2021. doi: 10.1007/s12028-020-01173-1. PubMed PMID: 33403583.
5. Thelin EP, Zeiler FA, Ercole A, Mondello S, Buki A, Bellander BM, Helmy A, Menon DK, Nelson DW. Serial Sampling of Serum Protein Biomarkers for Monitoring Human Traumatic Brain Injury Dynamics: A Systematic Review. Front Neurol. 2017;8:300. doi: 10.3389/fneur.2017.00300. PubMed PMID: 28717351; PMCID: PMC5494601.
6. Lugones M, Parkin G, Bjelosevic S, Takagi M, Clarke C, Anderson V, Ignjatovic V. Blood biomarkers in paediatric mild traumatic brain injury: a systematic review. Neurosci Biobehav Rev. 2018;87:206-17. doi: 10.1016/j.neubiorev.2018.02.006. PubMed PMID: 29462640.
7. Papa L, Ramia MM, Kelly JM, Burks SS, Pawlowicz A, Berger RP. Systematic review of clinical research on biomarkers for pediatric traumatic brain injury. J Neurotrauma. 2013;30(5):324-38. doi: 10.1089/neu.2012.2545. PubMed PMID: 23078348.
8. Woodcock T, Morganti-Kossmann MC. The role of markers of inflammation in traumatic brain injury. Front Neurol. 2013;4:18. doi: 10.3389/fneur.2013.00018. PubMed PMID: 23459929; PMCID: PMC3586682.
9. Toman E, Harrisson S, Belli T. Biomarkers in traumatic brain injury: a review. J R Army Med Corps. 2016;162(2):103-8. doi: 10.1136/jramc-2015-000517. PubMed PMID: 26527607.
10. Xiong Y, Mahmood A, Chopp M. Current understanding of neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities. Chin J Traumatol. 2018;21(3):137-51. doi: 10.1016/j.cjtee.2018.02.003. PubMed PMID: 29764704; PMCID: PMC6034172.