January 14, 2019

Christopher Leptak, M.D., Ph.D.
Director, CDER Biomarker Qualification Program
Office of New Drugs
Center for Drug Evaluation and Research
CDER Central Document Room
ATTN: Biomarker Qualification Program
5901-B Ammendale Road,
Beltsville, MD 20705-1266

Subject: Status Update for Legacy Biomarker Qualification Project DDTBMQ000037 (Drug-Induced Vascular Injury Biomarkers)

Dear Dr. Leptak:

On November 7, 2016, FDA issued a Letter of Support (LoS) to the Safer and Faster Evidence-based Consortium (SAFE-T) and the Predictive Safety Testing Consortium (PSTC) for the further study and development of safety biomarkers for monitoring drug-induced vascular injury (DIVI) in early clinical drug development.

The SAFE-T consortium was funded by the EU's Innovative Medicines Initiative (IMI). IMI funded projects have a limited lifetime, which is typically five years. SAFE-T was funded from 2009 to 2014, and then was granted a one-year extension up to June 2015 to complete the regulatory submission process.

After the formal end of SAFE-T, the consortium received Letters of Support from FDA and EMA for a subset of new safety biomarkers for drug-induced vascular injury; none of the markers had achieved regulatory qualification at that time.

Towards the end of SAFE-T, plans were made for a follow-up project, aiming at completion of qualification of those biomarkers for which SAFE-T received Letters of Support, expanding the project scope towards additional toxicity areas, as well as the investigation of new biomarkers for safety monitoring.

The proposed plan was submitted by an industry consortium and approved by IMI; the corresponding IMI call for applications was published in November 2017. IMI selected a consortium from among competing applicant consortia in April 2018, and the winning consortium joined the already existing industry consortium under the name TransBioLine, the Translational Safety Biomarker Pipeline. The project is expected to start in early 2019.

In order to align TransBioLine's qualification work with regulatory expectations, the consortium is seeking regulatory input during this planning phase of the project. We would greatly appreciate your advice so that we can address the Agency's concerns and align on a plan that will lead to the successful qualification of DIVI biomarkers.

If you have any questions or need any additional information please contact Lidia Mostovy by telephone (862-778-0854) or email (lidia.mostovy@novartis.com).

Best regards,

On behalf of the TransBioLine DIVI Work Package

Lidia D. Mostovy
Global Program Regulatory Director
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

cc: Beth Walton MBA, PMP, RAC, Regulatory Project Manager, Office of New Drugs (OND), Biomarker Development and Regulatory Science

Legacy Biomarker Qualification Project Status Update[1]

Administrative Information

Requesting Organization

Name: **The Innovative Medicine Initiative, TransBioLine**

Address: Michael Merz, MD
Consortium Coordinator
Clinical Pharmacology and Toxicology
University Hospital Zürich
Raemistrasse 100
CH-8091 Zürich
Phone: +49 151 21237386

Email: Michael.Merz@usz.ch

Primary Contact

Name: **Lidia D. Mostovy**

Address: One Health Plaza, East Hanover, New Jersey

Phone: 862-778-0854

Email: lidia.mostovy@novartis.com

Alternate Contact

Name: **ABX-CRO Advanced Pharmaceutical Services**

Address: Forschungsgesellschaft mbH
Blasewitzer Str. 78-80
D-01307 Dresden
Germany
Phone: +49 351 214440

Email: info@abx-cro.com

Submission Date (MM/DD/YYYY): 01/14/2019

[1] The content you provide in this completed Status Update will be publicly posted as part of the section 507 transparency provisions.

I. Context of Use

A. Biomarker Category

The biomarkers are molecular biomarkers in the blood (plasma or serum) and urine. The primary biomarker category is as a **monitoring** biomarker.

The biomarkers proposed are being developed for use as individual or a panel of biomarkers for monitoring acute vascular injury (VI). The potential for additive statistical approaches, such as a composite measure, will be assessed for the biomarkers to evaluate the potential added value to the individual biomarker performance in monitoring VI.

B. Intended Use in Drug Development

The proposed novel biomarkers, in conjunction with standard endpoints wherein available, can sensitively measure VI caused by disease or medical condition or by exposure to a medical product or an environmental agent. It is planned to qualify these biomarkers for the use in monitoring acute VI in clinical evaluation.

C. Context of Use Statement

The individual or panel of biomarkers of VI, for use in conjunction with the totality of preclinical and/or clinical information, can sensitively and specifically monitor acute VI (vascular endothelial and smooth muscle damage, and inflammation).

II. Drug Development Need

There is a high unmet need for safety biomarkers that could be used to sensitively and specifically monitor VI in drug development. Drug-induced vascular injury (DIVI), characterized by vascular endothelial and smooth muscle damage, and inflammation, is a poorly monitorable and a difficult to predict side effect of new and existing medications from diverse chemical and pharmacological classes. The relevance of DIVI in nonclinical animal toxicology studies to humans is often uncertain. While heart rate and blood pressure can be used as biomarkers of VI for those compounds causing systemic hemodynamic changes, this is not true for compounds with only localized vasoactivity or with a different mode of action. Other circulating biomarkers, like C-reactive protein, are non-specific indicators of some VI. Further, while sporadic occurrences of clinical DIVI have been reported for a large number of drugs, these occurrences manifest as a

vasculitis syndrome that cannot always be differentiated from idiopathic vasculitides. Thus, pharmaceutical companies seldom advance compounds with a nonclinical DIVI liability into clinical trials, especially at or near clinically relevant exposure multiples, because the occurrence of this injury usually cannot be monitored or conclusively ruled out in patients. It is estimated that on average, approximately 2.5% of the typical pharmaceutical company's nonclinical portfolio is affected by DIVI-related safety liability, leading to significant delays or project termination (FDA and EMA LoS SAFE-T biomarkers 2016).

DIVI is most commonly associated with vasoactive compounds. More recently, a smaller group of other compounds is thought to cause injury through other mechanisms at different anatomic sites (e.g., cytostatic agents and large molecules) but with shared histomorphologic outcomes to vasoactive compounds (Engelhardt et al. 2015; Frazier et al. 2015; Mikaelian et al. 2014). Such histomorphologic changes also are shared with a spectrum of systemic vasculitides affecting different vascular sizes and beds, including cutaneous leukocytoclastic vasculitis, anti-neutrophil cytoplasmic antibody-associated (ANCA+) vasculitis, giant cell arteritis and Takayasu's disease, as well as with balloon angioplasty patients. In addition, vascular injury can manifest in the vascular beds in the eye and represent a component of glomerular response due to various insults. As such, better biomarkers based on shared histomorphologic outcomes rather than on mechanism of injury are needed to identify, characterize, and/or monitor DIVI in nonclinical species and patients. These biomarkers would also serve to monitor the disease state and progression of vasculitides (systemic or localized) and the response to treatment in clinical trials, especially if they precede or correlate with standard endpoints.

III. Biomarker Information

The learning phase of this project will identify a subset of the most promising biomarkers across the three categories that will be brought into the confirmatory phase (target of 9 biomarkers).

A. Biomarker Name, Source, Type and Description

Type of Biomarker (Check relevant type(s))			
X	Molecular		Radiologic/Imaging
	Histologic		Physiologic Characteristic
	Other (please describe):		

B. For molecular biomarkers, please provide a unique ID.

Scheme: UniProt (http://uniprot.org/)

Endothelial biomarkers

1. Angiopoietin 2 (ANGP2 O15123) – secreted by endothelial cells. Plasma and urine matrices.
2. P-selectin (SELP P16109) – component of the Weibel-Palade bodies of resting endothelial cells and alpha granules of resting platelets; component of cell membrane of activated endothelial cells and platelets. Plasma and urine matrices.
3. Thrombomodulin (THBD P07204) – component of endothelial cell membrane (receptor). Plasma and urine matrices.
4. Vascular adhesion protein 1 (VCAM1 P19320) – component of cell membrane of activated endothelial cell membrane (receptor). Plasma and urine matrices.

Smooth muscle biomarkers

1. Caldesmon 1(CALD1 Q05682) – component of thin filaments in mature smooth muscle cells and of stress fibers in fibroblasts. Plasma and urine matrices.
2. Calponin 1 (CNN1 P51911) – component of thin filaments in mature smooth muscle cells. Plasma and urine matrices.
3. Smoothelin isoform b variant (SMTNb P53814) – component of vascular smooth muscle cells. Plasma and urine matrices.

Inflammation biomarkers

1. C-reactive protein (CRP P02741) – secreted by hepatocytes as an acute phase protein. Serum matrix.
2. C-X-C motif chemokine 10 (CXL10 P02778) – secreted chemokine by several cell types including monocytes, endothelial cells and fibroblasts. Plasma matrix.
3. Growth regulated alpha protein (GroA P09341) – secreted chemokine by several activated cell types including (leukocytes (macrophages and neutrophils), endothelial cells and fibroblasts. Serum matrix.

4. Interleukin 6 (IL6 P05231) – secreted cytokine by activated leukocytes (T lymphocytes and macrophages), vascular smooth muscle cells, endothelial cells and osteoblasts; secreted myokine by activated skeletal muscle cells. Serum matrix.

5. Interleukin 8 (IL8 P10145) – secreted chemokine by several activated cell types including macrophages and endothelial cells (stored in Weibel-Palade bodies). Serum matrix.

6. Matrix metalloproteinase 3 (MMP3 P08254) – component of extracellular matrix. Plasma and urine matrices.

7. Metalloproteinase inhibitor 1 (TIMP1 P01033) – secreted preferentially by Th17 and Th1 cells. Plasma matrix

8. Neutrophil gelatinase associated lipocalin (NGAL P80188) – secreted by activated leukocytes (neutrophils and macrophages), kidney tubule cells, smooth muscle cells and endothelial cells. Plasma and urine matrices.

9. Pentraxin-related protein (PTX3 P26022) – component of several activated cell types, including monocytes and endothelial cells. Plasma matrix.

Circulating microRNAs

Scheme: miRBase (www.mirbase.org)

1. MicroRNAs (miRNAs) are small non-coding RNA of approximately 22 nucleotides length that control gene expression in all human cells. Currently, approximately 2000 human microRNA genes are known.

C. Rationale for Biomarker

The panel will contain endothelial, smooth muscle, and inflammation biomarkers that will indicate vascular injury irrespective of mechanism or cause of injury. The specificity of certain biomarkers to endothelial cells or (vascular) smooth muscle cells, either in a resting or activated state, will lend specificity of the biomarker panel to VI. The inflammation biomarkers, of which several are associated with vascular components, are anticipated to augment sensitivity of the biomarker panel to VI. The selection of biomarkers in the panel encompasses the breadth of vascular response to injury in pathogenesis and in time, and thus lends itself to being agnostic of the mechanism of injury. Thus, the panel of biomarkers, in an individual or combined statistical approach, should provide a reliable, sensitive and specific means to monitor, diagnose, and evaluate progression of VI.

Endothelial biomarkers:

- Angiopoietin 2 (ANGPT2) – Renders the endothelial barrier responsive to pro-inflammatory cytokines. In the absence of angiogenic inducers, such as VEGF, ANGPT2-mediated loosening of cell-matrix contacts may induce endothelial cell apoptosis with consequent vascular regression. In concert with VEGF, it may facilitate endothelial cell migration and proliferation, thus serving as a permissive angiogenic signal.
- P-selectin (SELP) – Mediates, in addition to intercellular adhesion molecule 1 and E-selectin, the interaction of activated endothelial cells or platelets with leukocytes (rolling and adhesion).
- Thrombomodulin (THBD) – Endothelial cell receptor and cofactor for thrombin, initiating an essential anticoagulant pathway via factor V and VIIIa.
- Vascular adhesion protein 1 (VCAM1) – Expressed on both large and small blood vessels only after the endothelial cells are stimulated by cytokines; mediates the adhesion and signal transduction of lymphocytes, monocytes, eosinophils, and basophils to vascular endothelium.

Smooth muscle biomarkers:

- Caldesmon (CALD1) – Role in contractility through regulation of the actomyosin interactions in smooth muscle and non-muscle cells (fibroblasts), acting as a potential bridge between myosin and actin filaments.
- Calponin 1 (CNN1) – Role in contractility through regulation and modulation of the actomyosin interactions in smooth muscle.
- Smoothelin isoform b variant (SMTNb) – Role in contractility through modulation of contractile properties of vascular smooth muscle cells in association with alpha actin.

Inflammation biomarkers:

- C-reactive protein (CRP) – Acute phase protein associated with host defense, promoting agglutination, bacterial capsular swelling, phagocytosis and complement fixation. Can interact with DNA and histones and may scavenge nuclear material released from damaged circulating cells.
- Neutrophil gelatinase associated lipocalin (NGAL) – Iron-trafficking protein involved in multiple processes such as apoptosis, innate immunity and renal development. In innate immunity, it sequesters iron to limit bacterial growth.
- Interleukin 6 (IL6) – Acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine; osteoblasts secrete IL-6 to stimulate osteoclast formation. Vascular smooth muscle cells and leukocytes produce IL-6 as a potent inducer of the acute phase response. Also plays a role in leukocyte differentiation.

- Interleukin 8 (IL8) – Attracts neutrophils, basophils and T lymphocytes; involved in neutrophil activation (phagocytosis); and a potent promoter of angiogenesis.
- Growth regulated alpha protein (GroA) – Attracts neutrophils and exerts autocrine effect on endothelial cells in angiogenesis and arteriogenesis. Also has a role in spinal cord development by inhibiting the migration of oligodendrocyte precursors as well as in wound healing and tumorigenesis.
- C-X-C motif chemokine 10 (CXL10) - Attracts monocytes, T-lymphocytes, NK cells, and dendritic cells, and promotes T cell adhesion to endothelial cells in response to activated endothelial cells, monocytes and fibroblasts.
- Matrix metalloproteinase 3 (MMP3) – Degrades fibronectin, laminin, gelatins of type I, III, IV, and V; collagens III, IV, X, and IX, and cartilage proteoglycans. Activates procollagenase. In addition, MMP3 can also activate other MMPs such as MMP1, MMP7, MMP9, MMP13, MMP14 and MMP15, rendering it a critical part of a tissue-specific acute response to remodeling stimuli.
- Pentraxin-related protein (PTX3) – Plays a role in the regulation of innate resistance to pathogens, inflammatory reactions and possibly clearance of self-components in response to secretion from endothelial cells and activated leukocytes. Also a role in female fertility
- Metalloproteinase inhibitor 1 (TIMP1) – Inhibits and irreversibly inactivates matrix metalloproteinases, including MMP1, MMP2, MMP3, MMP7, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13 and MMP16, to promote extracellular matrix proliferation (i.e., tissue remodeling). Also functions as a growth factor that regulates cell differentiation, migration and cell death and activates cellular signaling cascades via CD63 and ITGB1, which promotes cell survival, reorganization of the actin cytoskeleton, cell adhesion, spreading and migration, as well as VEGFA signaling and the adhesion of leukocytes onto endothelial cells via regulation of SELP trafficking.

<u>Circulating microRNAs:</u>

- MicroRNAs are small non-coding RNAs of approximately 22 nucleotides length that control gene expression. Out of approximately 2000 known human microRNA genes, several microRNAs are known to exhibit highly tissue-specific transcription patterns. This includes microRNAs that are specifically transcribed in vascular and microvascular endothelial cells (e.g. hsa-miR-126-3p), as well as vascular smooth muscle cells (hsa-miR-133, hsa-miR-143, hsa-miR-145). Active or passive release of microRNAs from cells, specifically upon tissue injury, enables minimal-invasive detection of such microRNAs in the circulation. Hence, we hypothesize that circulating microRNAs might serve as sensitive and specific biomarkers for VI. We will apply next-generation

sequencing as non-targeted analytical platform to select VI microRNA biomarker candidates in the learning phase.

IV. Biomarker Measurement Information

A. General Description of Biomarker Measurement

These proteins originating from vascular endothelium, smooth muscle, leukocytes or other cells in response to inflammatory stimuli are biomarkers in the cascade of response to vascular injury and can be measured in blood (plasma or serum as appropriate). As submitted in the SAFE-T briefing book, we have demonstrated in rats that circulating levels of several of these endothelial and inflammation biomarkers change compared to control rats in response to various vascular toxicants with different mechanisms of injury and correlate with shared histomorphologic outcomes of vascular injury (defined by endothelial apoptosis/degeneration/necrosis; endothelial hypertrophy/hyperplasia; smooth muscle degeneration/necrosis; smooth muscle hypertrophy/hyperplasia; inflammation). The biomarkers measured also return to baseline compared to control rats on recovery from vascular injury as determined by histopathology (defined as reconstitution of the vasculature). Although not measured in blood, the smooth muscle biomarkers demonstrate decreased expression by immunohistochemistry in a pilot rat toxicity study, suggesting that the smooth muscle proteins are released into circulation and thus will be measurable in blood in response to VI. The exploratory data set included in SAFE-T submission for the Letter of Support currently is being augmented by a confirmatory data set in rat toxicology studies and opportunistic large animal toxicology studies.

We infer that the biomarkers correlate to the same histomorphologic endpoints in humans irrespective of mechanism of toxicity or disease pathogenesis as defined by standard endpoints of imaging, functional tests, and/or established circulating biomarkers (wherein available). The exploratory clinical data set using patients with systemic vasculitides generated by SAFE-T to obtain the Letter of Support indicates this inference is likely true. Further, several of the same biomarkers demonstrated a response in clinical trials of patients with systemic vasculitides, either to diagnose and/or indicate response to treatment (Monach 2014; Monach et al. 2013).

Multiple platforms will be evaluated for the measurement of these biomarkers.

B. Test/Assay Information

Indicate whether the biomarker test/assay is one or more of the following:

i. Laboratory Developed Test (LDT) ○ Yes **X No**

ii. Research Use Only (RUO) ○ **Yes X** No

iii. FDA Cleared/Approved. ○ Yes **X No**

If yes, provide 510(k)/PMA #:_____

iv. If the biomarker is qualified, will the test/assay be performed in a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory?

X Yes ○ No

*MLM is a CAP-, CLIA-, ISO15189 accredited lab; Signatope is not a CLIA certified lab but has passed quality inspections by several pharma partners. TAmiRNA is not a CLIA certified lab but conforms to the ISO9001 standard and has passed inspections by pharma partners.

v. Is the biomarker test currently under review by the Center for Devices and Radiological Health or the Center for Biologics Evaluation and Research?

○ Yes **X No** ○ Don't Know

vi. Is there a standard operating procedure (SOP) for sample collection and storage?

X Yes ○ No

vii. Is there a laboratory SOP for the test/assay methodology?

X Yes ○ No

C. Biomarker Measurement

This section can be provided once the assay validation is completed.

i. Quality Control

ii. Quality Assurance

iii. Limits Sources and Quantification of Measurement Error

D. Additional Considerations for Radiographic Biomarkers

Not applicable

V. Assessment of Benefits and Risks

A. Anticipated Benefits

Benefit to the patient is a critical driver in our considerations for clinical qualification of the biomarker of VI. The biomarkers are intended for diverse patient population in disease type and spectrum of severity. However, the biomarkers may be especially

important in patient populations having disease of lesser severity, wherein the risk:benefit of therapy is weighted toward benefit and thus, the potential to monitor for early, mild and reversible VI may reduce the perceived risk, assuming the biomarkers have a low risk for false negative response.

As such, the new biomarker(s) will provide a more sensitive and specific measure of DIVI, and thereby potentially provide an earlier indication of adverse events, providing researchers with greater confidence in a decision to limit dose, or perhaps to discontinue development based on more definitive clinical data; or to continue development of a promising candidate based on the absence of vascular adverse signals during clinical dosing.

This would result in more efficient, safer and potentially faster drug development with reduced frequency of abandoning the development of promising drugs with vascular safety signals in animal studies suspected to be of questionable human relevance or perhaps more importantly, because we did not have the monitoring possibility to safely approach or reach efficacious exposures.

B. Anticipated Risks

The anticipated overall risk to using these biomarkers in clinical trials to inform patient safety is considered low.

A false negative may occur when the biomarker levels observed following treatment by the drug candidate do not exceed a threshold established as “normal” in spite of DIVI and thus, there is false confidence to continue treatment or dose escalate, especially if conventional inflammation or functional markers are not informative. This possibility will be integrated into the evaluation of the totality of information for each program and relative to the strength qualification data to establish conservative thresholds.

A false positive may occur when the biomarker changes observed following treatment by the drug candidate exceed a threshold established as “normal” in the absence of DIVI and thus, clinical trial progression may be halted inappropriately. This possibility would be addressed by assessing individual findings in the totality of the data to assign truism and causality but moreover, progression to the clinic from a nonclinical DIVI finding likely would not have occurred if the biomarkers were not available.

C. Risk Mitigation Strategy

The following approaches could be used to help mitigate the perceived risk to patients.

- Use conventional (inflammatory and organ injury biomarkers) in conjunction with the new biomarkers to place an upper bound on any potential injury derived from a false negative biomarker result.
- The biological qualification of new biomarkers against a breadth of defined morphologic responses that capture multiple mechanisms of injury with large and small molecules and across various vasculitides provides the foundation for the new biomarkers to capture diverse pathologies associated with DIVI and thus mitigate false positive and negative occurrences.
- Demonstrate for each drug candidate that the new biomarkers provide monitorability assurances of vascular safety in animal studies anchored in histopathology that are being conducted with the same exact test agent (or a surrogate for large molecules) that is being proposed for investigation in a clinical trial would mitigate risk for unknown mechanisms of false positive or false negative biomarker responses.
- The initial focus of using the new biomarkers in healthy volunteers (Phase 1 studies), and the exclusion of certain named underlying inflammatory diseases from clinical trial investigations, provides some basis for reducing potential for false positives, and also some understanding for follow-up of potential positive findings that may be suspected of not deriving from a true drug-induced vascular injury event.

D. Conclusions

In light of the unmet need for biomarkers of VI that can be used to monitor for acute VI in a diverse population of patients and the risk mitigation strategy to minimize the possibility for a false negative result, the benefit to patients for biomarkers of VI greatly outweighs potential risk to the patient.

VI. Evaluation of Existing Biomarker Information: Summaries

A. Pre-Clinical Information, as appropriate

Exploratory nonclinical data has been generated by PSTC that supported receipt of the clinical Letter of Support correlating the biomarker response to histopathology (rodent). This data was summarized in the submission package for the Letter of Support.

B. Completed Clinical Information, as appropriate

Exploratory clinical data has been generated by IMI SAFE-T correlating the biomarker response to standard diagnostic determinants of vasculitides with shared histomorphologic outcomes as that evaluated in aforementioned rodent data. This data is summarized in the submission package for the Letter of Support. In addition, published data from clinical trials using similar proteins as exploratory diagnostic and efficacy biomarkers further supports the inference to correlate biomarker response to shared histomorphologic outcomes (Monach 2014, Monach et al. 2013).

C. Summary of Ongoing Information Collection/Analysis Efforts

A second "confirmatory" set of seven rodent vascular toxicity studies and 1 rat balloon angioplasty study is being completed this year by the PSTC and will be published. This includes 6 studies using small and large vascular toxicants across different mechanisms of toxicity in which biomarker performance is evaluated against the same histomorphologic outcomes. A similar, but more consistent study design and the same pathology lexicon was used as in the aforementioned "learning" set of rodent studies that is summarized in SAFE-T's submission that resulted in the Letter of Support.

VII. Knowledge Gaps in Biomarker Development

A. List and describe any knowledge gaps, including any assumptions, that exist in the application of the biomarker for the proposed COU

The assumption is that patients with systemic or localized vasculitides can serve as a surrogate population to demonstrate the performance of the vascular injury biomarkers to detect and monitor drug-induced vascular injury.

The assumption is that the biomarkers will be used as a panel, either through individual or combined biostatistical approaches.

B. List and describe the approach/tools you propose to use to fill in the above-named gaps when evidence is unknown or uncertain, (i.e., statistical measures and models, meta-analysis from other clinical trials).

The biostatistical plan for TransBioLine will be partly informed by approaches tested in the nonclinical "learning" and "confirmatory" studies, as well as on available clinical data in which exploratory vascular injury biomarkers were evaluated.

C. Describe the status of other work currently underway and <u>planned for the future</u> toward qualification of this biomarker for the proposed context of use.

In IMI TransBioLine, the panel of biomarkers will be measured in several populations to:

1) Establish a reference range in healthy subjects for a biomarker subset selected based on the learning phase data, characterizing inter- and intra-subject variability.

2) Establish the performance of the biomarker in blood in the presence of VI (associated with shared histomorphologic outcomes of endothelial and smooth muscle injury and inflammation) and determine their correlation relative to diagnostic determinants of disease state (acute onset / acute flare and quiescent state) in a learning phase

a) Cross sectional and longitudinal studies using patients with systemic vasculitides and balloon angioplasty to identify biomarker subset for subsequent confirmatory phase

b) Cross sectional and longitudinal studies using patients with VI localized to the eye to evaluate feasibility to detect biomarkers in circulation and evaluate performance against more tangible endpoints of ocular imaging

c) Cross sectional and longitudinal studies using patients with VI localized to kidney glomerulus to evaluate feasibility to measure biomarkers in urine as well as in blood and evaluate performance against more tangible endpoints of renal imaging

d) Rat toxicity studies using vascular toxicants with histopathology as a gold standard to analyze sensitivity. Supplement with opportunistic large animal toxicity studies with compound-associated vascular injury.

e) Rat and non-rodent toxicity studies using glomerular toxicant with histopathology as a gold standard and a bio-imaging endpoint to analyze biomarker performance in the urine as well as in blood. This will serve as a bridging study to the human glomerular injury component (#2c)

4) Establish thresholds of the biomarker subset in blood that indicate the presence of VI (as outlined in #2) in a confirmatory phase

a) Cross sectional and longitudinal studies using patients with systemic vasculitides and balloon angioplasty

b) Supplement systemic vasculitides patients as appropriate with vasculitides localized to the eye and/or kidney glomerulus (including in urine) to augment performance evaluation against more tangible endpoints

References

REFERENCES AVAILABLE UPON REQUEST

EMA Letter of Support (Date 11/7/2017): http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/11/WC500238043.pdf

Engelhardt J, Fant P, Guionaud S, Henry SP, Leach M, Louden C, Scicchitano MS, Weaver JL, Zabka TS, and Frazier KS. 2015. Drug-Induced Vascular Injury associated with non-small molecule therapeutics in preclinical development: Part 2. Antisense oligonucleotides. Tox Path: 43(7):935-44.

FDA Letter of Support (Date 11/7/2016): https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM530365.pdf

Frazier KS, Engelhardt J, Fant P, Guionaud S, Henry SP, Leach M, Louden C, Scicchitano MS, Weaver Jl and Zabka TS. 2015. Drug-Induced Vascular Injury associated with non-small molecule therapeutics in preclinical development: Part I. Biotherapeutics. Tox Path: 43(7):915-34.

Mikaelian I, Cameron M, Dalmas D, Enerson B. Gonzalez R, Guionaud S, Hoffman P, King N, Lawton M, Scicchitano M, Smith H, Thomas R, Weaver J, ZabkaTS. 2014. Nonclinical Safety Biomarkers of Drug-Induced Vascular Injury: Current Status and Blueprint for the Future. Tox Path 42: 635-657.

Monach PA. 2014. Biomarkers in Vasculitis. Curr Opin Rheumatol 26:24–30.

Monach PA, Warner RL, Tomasson G, Specks U, Stone JH, Ding L, Fervenza FC, Fessler BJ, Hoffman GS, Ikle D, Kallenberg CGM, Krischer J, Langford CA, Mueller M, Seo P, St. Clair EW, Spiera R, Tchao N, Ytterberg SR, Johnson KJ, Merkel PA. 2013. Serum proteins reflecting inflammation, injury and repair as biomarkers of disease activity in ANCA-associated vasculitis. Ann Rheum Dis 72:1342–1350