U.S. FOOD & DRUG ADMINISTRATION

Date: November 7, 2016

ATTN: Safer and Faster Evidence-based Translation (SAFE-T) Consortium
Angelika Hoenlinger, Novartis
Michael Lawton, Pfizer

Predictive Safety Testing Consortium (PSTC)
Tanja Zabka, Genentech
Brad Enerson, Pfizer
John-Michael Sauer, Critical Path Institute

Subject: Letter of Support for Drug-Induced Vascular Injury (DIVI) Biomarker(s)

Dear SAFE-T Consortium and PSTC,

We are issuing this Letter of Support to the Safer and Faster Evidence-based Translation (SAFE-T) Consortium and the Predictive Safety Testing Consortium (PSTC) to encourage the further study and development of soluble biomarkers of endothelial cell injury and inflammation as exploratory safety biomarkers for monitoring drug-induced vascular injury (DIVI) in early clinical drug development. The candidate clinical biomarkers are: endothelial cell proteins (E-Selectin, P-Selectin, sICAM-1, sICAM-3, sVCAM-1, thrombomodulin and VEGF) and inflammatory factors (CRP, GROa, IL-6, IL-8, IP-10, I-TAC, MCP-1, MIG, SAA and MIP-1a).[1]

When DIVI occurs in nonclinical animal toxicology studies, it can cause considerable delays in the drug development process. In many cases, promising candidate drugs are terminated because the occurrence of vascular injury cannot be monitored or conclusively ruled out in patients due to the lack of specific and/or sensitive biomarkers. It is estimated that on average, approximately 2.5% of nonclinical studies are affected by DIVI-related safety concerns that can lead to significant delays or project termination. For this reason, there is a need for non-invasive biomarkers that can detect the onset, progression, and reversibility of DIVI. The only currently available biomarkers used to assess the potential for DIVI in early clinical studies are non-specific markers of inflammation, markers of immunopathic vascular injury (such as ANCAs and AECAs) and, for compounds that are systemically vasoactive in preclinical studies, heart rate and blood pressure. Successful development of these candidate safety biomarkers would allow DIVI to become a monitorable finding and would allow potential new medicines that cause nonclinical DIVI to advance into clinical studies at safety margins not previously possible.

We support the histomorphologic-based, mechanism-independent approach that you used to identify the candidate biomarkers of DIVI given the similar histopathology seen with diverse vasculotoxic insults. The strategy of using morphological similarities as the basis for forecasting has been discussed with FDA in several previous briefing meetings. Preliminary data appear to support the development of these safety biomarkers, alone or as part of a panel, as potential indicators of endothelial cell injury and associated

[1] Reference numbers for all biomarkers listed in the letter are provided in the appendix to ensure clarity and allow for consistency in future studies.

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vasculitis, based on clinical presentation rather than biopsies and histopathology. Because nonclinical DIVI variably involves components of the vessel wall and inflammatory processes, it is likely that combinations, or panels, of multiple biomarkers that are vascular-specific will be required for clinical use.

The candidate clinical safety biomarkers show promise for monitoring DIVI in early clinical studies in healthy volunteers with no concurrent vascular disease when nonclinical safety biomarkers have identified DIVI in nonclinical studies of similar duration with the same test agent. Clinical studies were conducted in vasculitic patients presenting with histopathologic lesions that are morphologically similar in type or vascular compartment to nonclinical DIVI. To cover most of the histopathologic features found in nonclinical DIVI, patients presenting with vasculitides that variably affect the mural wall components, and are characterized by different localization and cell type of inflammatory infiltrates, were selected. These included Takayasu's arteritis, Behçet's disease, mixed cryoglobulinemia, Sjogren's disease, giant cell arteritis and patients undergoing balloon angioplasty with acute mechanical injury to the vessel wall and endothelium.

To study the candidate DIVI biomarkers and the translation potential between nonclinical and clinical biomarkers, we support your planned nonclinical studies to evaluate vascular injury in rats using new compounds, select repeat compounds, and balloon angioplasty. We also encourage additional testing with compounds that do not impact the vasculature, but cause injury in other organs. To evaluate the translational ability of the candidate biomarkers, we support your plan to develop analytically validated assays, perform retrospective analysis of archived clinical samples and perform prospective nonclinical studies in dogs and in monkeys. In addition, we encourage you to study smooth muscle cell proteins, such as calponin and caldesmon, as potential clinical safety biomarkers for monitoring DIVI, as assays become available.

No specific test system or assay validation process is endorsed for the above listed biomarkers. The analytical assay performance characteristics (e.g., quantitative range, limits of detection, precision, reproducibility, linearity, interference) should be established in advance of use. The sample stability for each of the biomarkers proposed herein should be validated for its intended storage, shipping and use conditions.

We encourage additional use of these biomarkers to characterize their potential role for monitoring DIVI in early clinical drug development. We will consider data collection on these biomarkers to be exploratory in nature. We believe data sharing and integrating data across trials can foster an accelerated path for numerous drug development programs. If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a given IND drug development program, they should prospectively discuss the approach with the appropriate regulatory review division in CDER.

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Michael Lawton (michael.lawton@pfizer.com), Tanja Zabka (zabka.tanja@gene.com), Brad Enerson (bradley.e.enerson@pfizer.com), or John Michael Sauer (jsauer@c-path.org), or visit the PSTC biomarker qualification website (http://c-path.org/programs/pstc/regulatory-successes/) or the IMI SAFE-T Consortium website (http://www.imi-safe-t.eu/) .

Sincerely,

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration

I. Appendix

References for listed biomarkers

Gene/ Target Symbol	Gene/Target Name and other symbols/names	UniProt Accession Number[2]
GROa	Cytokine- induced neutrophil chemoattractant-1 (KC, Cinc, CXCL1)	P09341
IL-6	Interleukin 6	P05231
IL-8	Interleukin 8	P10145
CRP	C-reactive protein	P02741
IP-10	Interferon gamma induced protein 10 / CXCL10	P02778
I-TAC	Interferon-Inducible T-Cell Alpha Chemoattractant / CXCL11	O14625
MCP-1	Monocyte chemotactic protein 1 / CCL2	P13500
MIG	Monokine induced by gamma interferon / CXCL9	Q07325
SAA	Serum amyloid A	P0DJI8
MIP-1A	Macrophage inflammatory protein 1 alpha / CCL3	P10147
SELE	E-selectin	P16581
SELP	P-selectin	P16109
sICAM-1	Soluble Intercellular adhesion molecule 1	P05362
sICAM-3	Soluble Intercellular adhesion molecule 3	P32942
sVCAM-1	Soluble Vascular cellular adhesion molecule 1	P19320
THBD	thrombomodulin	P07204
VEGF	Vascular endothelial growth factor	P15692

[2] UniProt (Universal Protein Resource) is a catalog of information on proteins: http://www.uniprot.org/