



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

07 November 2017  
EMA/641470/2017  
Executive Director

## Letter of support for drug-induced vascular injury (DIVI) biomarker

Dear PSTC/SAFE-T:

We are issuing this Letter of Support to SAFE-T and PSTC to encourage the further study of soluble biomarkers of endothelial cell injury and inflammation, and potential soluble markers of vascular smooth muscle cell injury, to monitor for drug-induced vascular injury (DIVI) in early clinical drug development. Such translatable biomarkers, alone or in panel(s) (herein referred to as “biomarkers”), may reflect DIVI affecting vascular smooth muscle cells and endothelial cells, as well as the associated inflammatory response, as determined by histomorphologic endpoints in rodents. Further work on bridging biomarker biology across species and shared vascular injury histomorphology in humans as considered by the Consortium are welcomed. These vascular injury biomarkers may eventually be used in healthy volunteers – in addition to usual safety measures - with no concurrent vascular disease to monitor for vascular safety in early clinical trials. These biomarkers should be explored when such injury has been demonstrated to be monitorable by translatable biomarkers in animal studies of similar duration with the same test agent (including small and large molecule therapeutics). Applying the biomarkers in initial single and multiple ascending dose clinical studies could help inform planned dose escalations or continued dosing schedules.

Drug-induced vascular injury in nonclinical animal toxicology studies can cause considerable delays in the drug development process and promising candidate drugs are often terminated as the occurrence of DIVI cannot be monitored or substantiated in healthy volunteer or patient trials due to the absence of specific, sensitive biomarkers.

For this reason, there has been a search for circulating biomarkers that can detect, in a sensitive and specific manner, the onset, progression, and reversibility of DIVI (i.e. monitoring-based biomarkers for safety evaluation). The only currently available biomarkers used to assess the potential for vascular injury in early clinical studies are non-specific markers of inflammation, markers of immune-mediated drug reactions (for large molecules), and for compounds that are systemically “vasoactive” in nonclinical studies, heart rate and blood pressure. Having more sensitive and specific DIVI biomarkers would allow drug development teams to manage DIVI as a monitorable nonclinical finding. With these tools a team could safely advance potential new medicines, including both small molecules and large molecules, which cause nonclinical DIVI into clinical studies at safety margins not previously possible



without such DIVI biomarkers, thus enabling exploration of clinically efficacious doses.

We encourage further exploration in healthy volunteers in early clinical studies if biomarkers have been identified that show changes in their concentrations when vascular smooth muscle or endothelial cells are injured, or when vascular inflammation is detected. The clinical biomarker candidates described herein were selected based on their association with the three main histopathology features involved in nonclinical DIVI: damage to vascular endothelium, damage to smooth muscle, and inflammation. Because nonclinical DIVI typically involves one or more of these features and these features may confer specificity to the vasculature, it is likely that combinations, or panels, of multiple biomarkers will be required for clinical use. Candidate biomarkers could include one or more of the following: endothelial cell proteins (E-Selectin, P-Selectin, sICAM-1, sICAM-3, sVCAM-1, thrombomodulin, and VEGF); smooth muscle cell proteins (calponin, caldesmon); and inflammatory factors (CRP, GRO $\alpha$ , NGAL, IL-6, IL-8, IP-10, I-TAC, MCP-1, MIG, SAA, MIP-1 $\alpha$ , and TIMP-1). Of note, assays for the smooth muscle proteins were not technically feasible to design or did not meet validation requirements for human specimens.

To ensure that the biomarkers associated with vascular injury are translatable across species, including humans, we appreciate that SAFE-T and PSTC have collaborated to provide both clinical and nonclinical data that underpin this Letter of Support using a morphologic-based, mechanism-independent approach to qualifying biomarkers of DIVI. We expect that considerable similarities in the morphologic characteristics of vascular injury in animals and in humans, including the early-stage events of endothelial cell degeneration/necrosis and hypertrophy, smooth muscle cell degeneration/necrosis and inflammation, and the later-stage events of vascular wall hypertrophy and hyperplasia can be leveraged for the selection of biomarkers.

We encourage further nonclinical and exploratory clinical analyses to evaluate the translational relevance of changes in identified non clinical DIVI biomarkers. We believe data sharing and integrating data across trials can foster an accelerated path for biomarker qualification to support numerous drug development programs.

Sincerely,

Guido Rasi  
Executive Director