

**CV Safety and COPD Drug Development:
Synopsis of the March 6, 2014 CSRC/FDA Think Tank Meeting**

A CSRC/FDA-sponsored Think Tank was convened at the FDA on March 6, 2014 to discuss issues surrounding COPD drug development and CV safety. The goal was to reach consensus regarding general CV safety issues in COPD drug development as well as thresholds for performing randomized controlled CV outcome studies. Talks focused on the burden of CV disease in COPD population and the unmet medical needs; critical CV safety issues with in depth examination of the potential for ECG effects and arrhythmias, BP increases, HR increases, and atherosclerotic events; how best to optimally assess CV safety issues; and potential thresholds for requiring CV outcome studies. Areas of consensus were arrived at through discussion and, with the potential exception of arrhythmia assessment (which continues to evolve), the general consensus was that drug development for COPD drugs is not inherently different than that for other therapeutic areas with respect to CV safety evaluation and assessment.

General Points of Consensus

- Standardized approach to collecting baseline CV medical history is important to assist in later evaluations, should a potential CV safety signal be identified
- Consider using a specific form to capture CV history (eg, previous history of angina or Afib)
- Targeted prospective capture of CV events of interest, ideally using standardized definitions
- Identify specific diagnosis (Afib vs LBBB vs non-sustained VT instead of 'arrhythmia')
- Robust data collection for individual CV adverse events (eg., ECGs)
- Consider utilizing the CSRC CRF forms or a similar data capture tool
- Blinded adjudication if there is a meaningful safety signal in early development (some may want to prospectively adjudicate all CV events)
- Best to not exclude higher CV risk pts, wherever appropriate. Pts should be receiving appropriate medical care (e.g., not significantly hypokalemic)
- Small imbalance of numbers of events- fraught with difficulty of interpretation and should not be over-interpreted
- Meta-analysis needs to be performed at appropriate standards

Specific Potential CV Risks and COPD Drug Development Implications

- Heart rate increases- there is an absence of data showing an increased CV risk associated with drug-induced HR increases for COPD drugs or other medications
- QTcF/PR/QRS- evaluated in TQT trial; has not been a significant clinical issue; TdP has not appeared to be an clinical issue with COPD medications
- Clinical arrhythmias- the focus should be on clinically meaningful events- Afib, Aflut, Sustained VT, VF, Cardiac Arrest, and not PAC's or PVC's

- Consider examining the current Holter database to determine the yield from sporadic Holter screening in order to better understand the potential role of surveillance Holter monitoring in COPD drug development
- Consider arrhythmia monitoring in higher risk pts if there is a clear arrhythmic signal (likely during Phase 3)
- Ischemia- Clinical events- focus on CV death, ACS/MI, CVA
- BP- has not been a meaningful clinical issue- measured during clinical development has been sufficient unless a drug with a specific signal is identified

Thresholds for CV Outcome Studies

- CV Outcome studies in the context of a clinically meaningful CV safety signal should be considered
- Maximize data collection during clinical development
- Depending on a safety signal effect size (absolute risk), benefit:risk considerations, and underlying risk of the population, post-approval assessments may also be considered. A Sentinel-type approach may be helpful in the future in the post-approval setting. For pharmaco-epidemiology studies, consider having an active comparator and a new-user design
- Without a clinically meaningful CV safety signal, CV outcome studies not usually indicated

