TAVI FORUM

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Better Health, Brighter Future

Clinical Trial SHP620-303 Relevant Inclusion Criteria and Definitions

1. The subject must have a documented CMV infection in plasma, with a screening value of ⩾910 IU/mL in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to randomization with the second sample obtained within 5 days prior to randomization. **The same laboratory** and sample type (whole blood or plasma) must be used for these assessments.

2. The subject must have a current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agents.

- Refractory is defined as documented failure to achieve >1 log10 (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a **14 day or longer treatment** period with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir (same agent for this time period)

- Subjects with documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir must also meet the definition of refractory CMV infection.

Challenges with Resistant/Refractory Definitions Used in SHP620-303

- For subjects with resistant CMV infections, refractory definition was also required, despite high viral loads or low probability of success with available treatment(s)
  - Consideration of elimination of refractory requirement for specific mutations that are unlikely to resolve despite a higher dose of gan/valganciclovir or toxicity considerations

- Subjects may have demonstrated “refractory” infection by using another health care center’s assay as first CMV level, but required same lab at investigative site due to assay variability
  - Potential to delay optimal treatment of CMV

- Challenges documenting refractory CMV end organ disease – biopsy may not be feasible due to patient’s medical condition or desire to enroll (change therapy that is not effective or has toxicities)

Considerations with Current Refractory Study Definitions (Chemaly et al)

- Many investigators will not wait to enroll a subject to qualify as refractory (2 weeks of rising CMV titer) prior to changing treatment and/or enrolling patient in a CMV study. So, failure to achieve at least 1 log decrease in viral load after 2 weeks of appropriately dosed therapy is a feasible option (303 study definition). Of note, in 303 study we required the same anti-viral for 2 weeks
- From a practical perspective, a more ideal/less challenging requirement for enrollment with refractory CMV infection definition would shorten the treatment interval to 1 week (ex failure to have at least 1 log decrease after a week of appropriate therapy)
  - Some subjects demonstrate refractory infection or high viral loads prior to referral to investigative site
  - Some physicians prefer to not wait two weeks if viral load is not improving
- Consider a single definition for “refractory CMV infection” criteria. Regulators question differences between refractory and probable refractory and consider a probable refractory CMV infection to be less severe

Other Considerations with CMV Infection and Disease Definitions

- Challenges with obtaining previous source documents of biopsies or other diagnostic tests and/or patient clinical stability to undergo diagnostic procedure(s)

- CMV Syndrome definition is qualitative and challenging to assess if fever, malaise, or fatigue are related to CMV syndrome or other etiology. Regulators question using these characteristics as useful to make CMV syndrome diagnosis

- Recurrent CMV infection is defined as a new CMV infection with previous evidence of CMV infection and has not had virus detected for at least 4 weeks. Is the 4 week interval necessary or would a shorter duration be reasonable?

- Endpoint Adjudication Committee should be considered in R/R clinical trials given the complexity of definitions and challenges associated with accurate classification

Thank you!