Design Challenges in the Elvitegravir Phase 3 Programs

Brian Kearney

Gilead Sciences

Elvitegravir Clinical Development

- Monotherapy dose- and dose-interval ranging
- Tx-experienced subjects
  - Phase 2 dose-ranging
    - 20, 50, 125 mg vs. investigator-selected comparative protease inhibitor (each w/ OBR)
  - ***Phase 3***
    - ***Ongoing single non-inferiority study of EVG QD vs. RAL BID + OBR comprised of fully-active PI/r + one additional agent***
- Tx-naïve subjects
  - Ph 2 and Ph 3 studies as a fixed-dose combination tablet (EVG/COBI/FTC/TDF) vs. NNRTI- (EFV/FTC/TDF FDC) and PI-based (ATV/r + FTC/TDF) regimens
  - Non-inferiority Phase 3 studies

General Design Challenges

- Selection of a non-inferiority margin
  - 10% vs. 12%
  - EU vs. US requirements
  - Statistical methodologies
- Use of TaqMan vs. Amplicor
- Evolution of snapshot vs. TLOVR analyses for primary endpoint

Tx-Experienced Ph 3 Challenges

- Impact of DRV/r, ETV and MVC approvals
  - Not possible to demonstrate benefit of investigational agent over placebo due to overly active OBR
  - EVG tx-experienced Phase 3 study assures two but no more than three active drugs in regimen
- Dwindling numbers of suitable tx-experienced subjects
  - Many subjects already receiving DRV/r + other new agent(s)
  - Heavily-experienced patients with few active ARVs to configure appropriate OBR
  - Consideration given to Phase 3 study in adolescents
- Desire for within-class assessment vs. RAL regulatory status
  - RAL not approved during initial design discussions
  - Consideration given to comparison of EVG vs. MVC

Future Challenges

- Continuing challenges with studying tx-experienced subjects in registrational studies
  - Availability of integrase inhibitors add to challenge

- Switch studies
  - Desire to simplify HAART for as many patients as possible
  - Risk / benefit to patients
  - Unavoidable impact of making any change to an established regimen on primary endpoint
  - Can this approach be used for tx-experienced population?
    - Design (I/E criteria) is critical for successful trial
    - Standardization needed if this approach is used for development path and/or registrational studies