HCV trials in the post-approval era of telaprevir and boceprevir--the way forward

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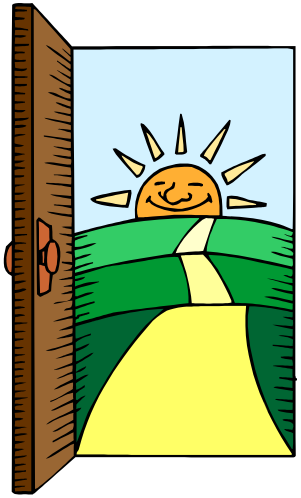

FDA Role in Meeting

- Offered input on agenda and questions
- Participating today as one of several collaborators in discussions
- Not here to offer authoritative guidance
- Looking for ideas and areas of consensus on current issues
- Meeting will be helpful for revision of Draft Guidance and future discussions with sponsors

Prior Activities Related to HCV Drug Development

- Draft Guidance Released-Sept 2010
  - "Chronic HCV Infection: Developing DAAs for Treatment"
- HCV Forum Meeting Dec. 6, 2010
  - "Advancing HCV Drug Development: A Collaborative Approach"
- EMA Guidelines Feb. 2011:
  - Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C.
- Multiple HCV DRAG meetings/telecons

Recent Breakthroughs

- Results of Phase 3 Studies with PR+DAA
- DAA Approvals in U.S.
  - boceprevir—May 2011
  - telaprevir—May 2011

Sessions 1 and 3

- Proof of Concept that DAAs alone can achieve SVR—EASL 2011
  - BMS-790052 (NS5A inhibitor) + BMS-650032 (NS3 Protease Inhibitor)
  - other press releases

Session 2

Draft FDA Guidance Statements that Require Revisions

- “It is not known whether regimens that do not include interferon can produce SVR”
- “Until the first DAA is approved, the recommended, and most straight-forward, design for initial registration of a DAA is demonstration of superiority as an add-on to SOC, PegInterferon/RBV, in a blinded comparison to placebo plus SOC.”
- “... recommend that phase 2 trials include at least one treatment arm that evaluates 48 weeks of treatment with all components of a regimen”
- “The primary analysis endpoint should be SVR24”

Draft FDA Guidance
Sections relevant to DAA-only trials

Statements still relevant but should be revisited:

1. Pre-Clinical/Clinical data requirements
2. Demonstrating each component contributes toward efficacy and is a necessary part of the regimen

DAA Combination Trials (1) Preclinical/Clinical Prerequisites

- Ideally, different mechanisms of action
- Data needed on each individual agent prior to combination trials
  - Cell culture combination antiviral activity
  - Resistance and cross resistance
  - Animal data (combo studies not necessary, but 3 months of toxicology data on each individually)
  - Anti-HCV activity data and safety data from clinical trials
  - Dose rationale based on clinical trials or other sources to select doses likely to provide reasonable anti-HCV activity
  - Drug-Drug interaction studies might be considered if metabolism profile of drugs suggests interaction potential

DAA Combination Trials (2)
Showing Component Contribution

- Use Factorial Designs in Clinical Trials
- Complete factorial designs may not be appropriate due to resistance. Alternative approaches include:
  - Cell culture data showing DAA combinations reduce resistance compared to single agents
  - Clinical trial data showing the efficacy of each new DAA in combination with PR
  - Comparisons of HCV reductions of monotherapy (e.g., 3-day trials) with HCV reductions of combination therapy in the same trial or across other short trials. In this example, HCV reductions in patients given combination therapy with two DAAs should be greater than that observed in patients given the single agents.
  - Early phase 2 clinical trial data showing DAA combinations reduce emergence of resistance.

Additional Progress in Knowledge Relevant to HCV Trial Design

- Difference between LOD/LOQ
  - discussed at HCV DRAG telecon
  - achieving LOD vs. LOQ (detectable) at various early time points appears to confer higher SVR rates
  - For SVR measurements LOQ appears sufficient
- SVR 12 vs. SVR 24 (AASLD Latebreaker #28)
  - sufficient data to use SVR12 as the primary endpoint with SVR 24 as secondary and commitment for longer term follow-up
  - based on data from 10,062 subjects 15 Phase 2 and 3 trials of six drug development programs including PR alone and PR with DAAs

Conclusions

- The field is rapidly evolving
- New findings will change our approach
- Need ideas and consensus on how to move forward
- Expect significant revisions to current guidance.