FDA Perspective on Early Clinical Testing of Novel HCV Antiviral Drugs

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FDA Disclaimer

The views in this presentation represent the author’s opinion and not necessarily official policy of the Food and Drug Administration.
The race is on...
And FDA guidance is trying to stay ahead!
Critical outstanding issues

• Can novel antivirals deliver high rates of SVR without interferon and/or ribavirin?
• If so, how many agents and what combination is needed?
• If not, can we use interferon or ribavirin at lower doses in combination with other antivirals?
• How high of an SVR rate is achievable with DAAs or other novel antivirals?
• Would an IFN or RBV-sparing regimen that provides improved safety/tolerability be acceptable if it results in lower SVR?
• If not all patients can achieve SVR, is chronic suppression with antivirals a viable option?
Critical outstanding issues

• How will we study non-responders to IFN/RBV + PI (or other DAA class)?

• Are there special populations that have more to gain from novel antivirals or combinations?
  – IL28B genotypes CT/TT
  – HIV co-infected
  – African Americans
  – Prior partial and null responders
  – Cirrhotics
  – Liver transplant
  – Decompensated liver disease
Also...

(And improved)

Standard Of Care
Early Phase Clinical Development

• FIH study: SAD and/or MAD in healthy volunteers, unless otherwise unacceptable (e.g. genotoxic compound)
• Initial Phase 1b (proof-of-concept): Multiple-dose, dose-ranging, monotherapy (~ 3 days) in tx-naïve, with intensive PK and HCV RNA data collection
• E/R analyses or mechanistic viral kinetic modeling is used to inform Phase 2 study design
• Assess food effect and biopharm issues early to inform practical dose selection for later studies
Phase 1b/2

- Purpose: characterize optimal dose and duration
- First study in patients is typically in tx-naïve
- Duration selection should be based on clinical rationale
  - Re-randomization to duration based on early response (e.g. eRVR)
- Design should allow for direct comparison between arms
- Earlier analyses (e.g. on-treatment Week 12) may inform design of larger Ph 2b trials or trials in other populations (e.g. tx-experienced)
- SVR is always the primary endpoint
- Stratification by IL28B when combined with Interferon
PK/PD Considerations

- A combination of rich and sparse sampling should be used throughout development, where appropriate
- Obtain PK samples in all subjects at key virologic assessments (Weeks 4, 12, 24, 48)
- Collect PK samples for all agents in regimen (including PegIFN/RBV)
- Data should be utilized in design of Ph 2b or 3 trials using a mechanistic modeling approach
- Simplified E/R analyses may be performed when SVR12 or SVR24 data are available, to support efficacy and dose selection
Antiviral Combinations

• Potential benefit: IFN or RBV-sparing regimens, suppression of resistant variants, synergism/improved potency, greater efficacy in difficult-to-treat populations

• Preliminary data needed before combination trials:
  - Cell culture combination antiviral activity
  - Resistance & cross-resistance data
  - Initial monotherapy, dose-ranging data for individual agents to support initial dose selection for combo
  - Clinical safety data for individual agents
  - +/- DDI study

• Individual or combination clin pharm studies are acceptable, depending on development intent (individual and combo use, or only combo use)
Potential HCV Treatment Combinations

- New Agent + Approved 3-Drug Regimen
- 2 New Agents + PegIFN/RBV
- 2 or 3 New Agents + RBV
- 2, 3 or 4 New Agents (no RBV or PegIFN)
- Others?
Phase 2 Combination Trials

2010 Guidance for Industry: Codevelopment of 2 or More Drugs for Use in Combination

- “Need to demonstrate the contribution of each agent to the extent possible and needed (given available nonclinical and pharmacologic data)”
- “Amount and types of clinical data needed and appropriate study designs will vary depending on the nature of the combination being developed…”
- Most straightforward approach are factorial or modified factorial designs:
  
  E.g.) SOC vs. SOC + A vs. SOC + B vs. SOC + A + B
Phase 2 Combination Trials

- Contribution of both agents may be demonstrated in other ways, depending on the agents and development path
- Other data to support contribution of each agent:
  - Cell culture or early clinical data showing combo prevents resistance
  - Clinical trial data for each component
  - Comparison of viral load reduction of short term monotherapy
- Possible scenarios for Drug A (PI) and Drug B (NS5A inhibitor):
  - **SOC** (P/R + approved PI) vs. **P/R + A** (N.I. to SOC) vs. **P/R + A + B**
    (superior to SOC and P/R + A)
  - **P/R + A** is N.I. to SOC in tx-naives, and **P/R + A + B** demonstrates significant improvement over SOC in null responders
  - **SOC + B** is superior to SOC in tx-experienced, and **RBV + A + B** demonstrates success in an IFN-contraindicated population (e.g. decompensated cirrhotics or post-transplant)
Other Potential Combination Trial Designs

• Short duration (<2 wks): 2 or more agents in treatment-naïve, followed by full treatment course w/ SOC (+/- addt’l agent)

• Longer duration: 2 or more agents (+/- IFN or RBV) in treatment-naïve or -experienced, with frequent HCV RNA monitoring and stopping rules

• Pilot studies (single-arm): evaluate drug/dose combinations (+/- SOC) in difficult-to-treat populations or those without treatment options (e.g. pre-transplant, hepatic decompensation), with early decision points to expand cohort or D/C a combination
Trials in Difficult-to-Treat Subgroups

- FDA encourages trials of novel agents in difficult-to-treat populations or those without treatment options (decompensated cirrhotics, transplant, contraindications to IFN, etc)
- Single-arm, historic control design often acceptable
- Minimum data requirements:
  - Preliminary safety in humans
  - Activity data from HCV patients to support dose selection
  - +/- PK studies (e.g. hepatic impairment trial)
  - +/- DDI studies (e.g. HIV co-infected, transplant)
Resources

- Draft Guidance: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment (Sept. 2010)
  

- Draft Guidance: Codevelopment of Two or More Unmarketed Drugs for Use in Combination (Dec. 2010)
  

- FDA Hepatitis List Serve
  
  http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm151488.htm