



U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

FDA Perspectives on Clinical Trial Design for New HCV Products

Kimberly Struble, PharmD
Medical Team Leader
Division of Antiviral Products
FDA

EATG Meeting
November 20, 2009



FDA Disclaimer

The views in this presentation represent the author's opinion and not necessarily official policy of the Food and Drug Administration

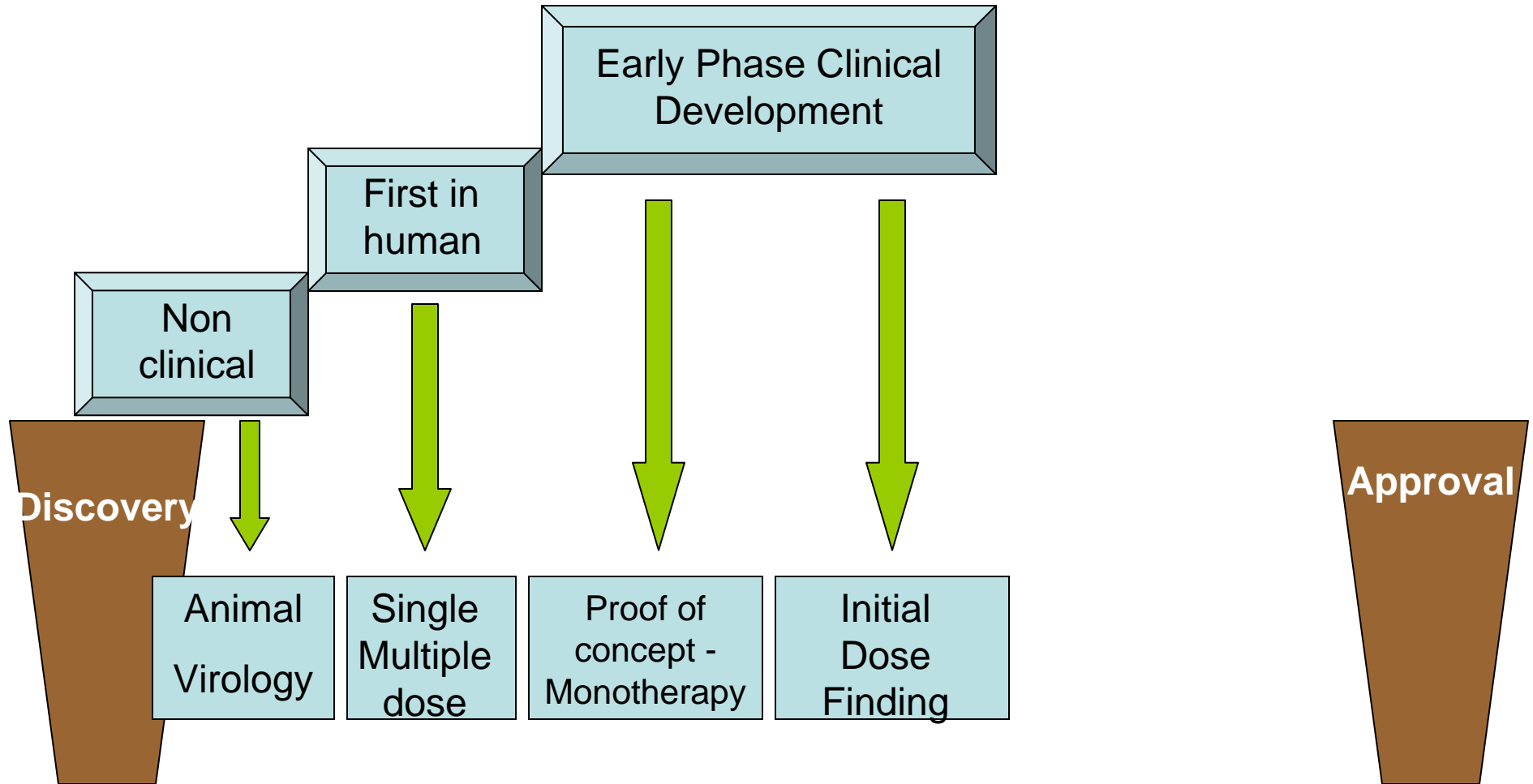


Presentation Outline

- Phases of HCV Drug Development
 - Early Phase Development
 - Phase 2 and 3
- Combination Therapy with Multiple Direct Acting Antiviral Agents Considerations
- Special Populations
 - Hepatic Impairment
 - HIV/HCV Co-infected
 - Decompensated Cirrhosis



Bridging Discovery to Approval





Early Phase Clinical Development Considerations

- Rational plan to provide sufficient data to establish preliminary safety and activity to support Phase 3 trials
- Initial trials in treatment-naïve
- Subsequent trials in treatment-experienced
 - Exceptions made on case-by-case basis depending on characteristics of agent
- Drug Development Population



Drug Development Population

- Include broad population (naïve and experienced)
- Adequate representation for gender, race, age, weight
- Include patients with compensated cirrhosis in phase 2 and 3
- Encourage enrollment of patients in most need for new agents



Proof-of-Concept

- Multiple dose monotherapy trials
 - Up to 3 days in duration to minimize potential development of resistance
 - Collect intensive PK, safety, HCV RNA decay and resistance data

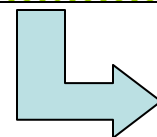
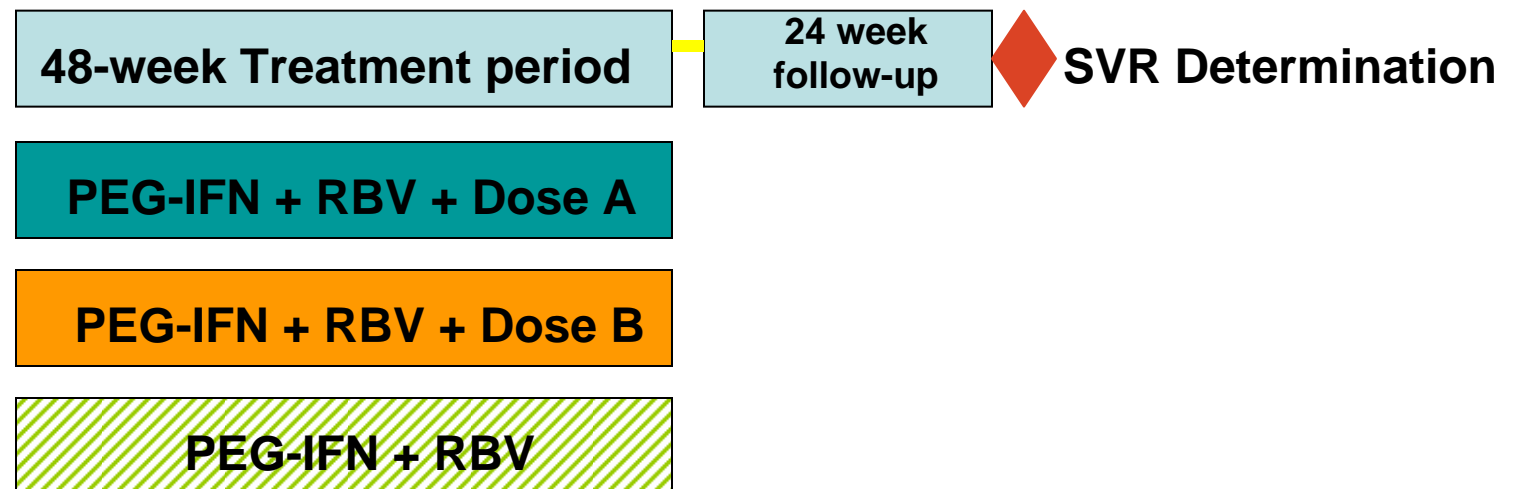


Dose Finding

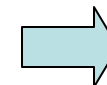
Bridge proof-of-concept phase to phase 2 dose finding trials

Conduct pilot study in treatment-naïve

Choose most active doses from monotherapy trial(s), viral decay, resistance, PK safety and modeling data



Can use Week 12 on-treatment data to design Phase 2 dose finding in larger population



Based on Week 12 data simultaneous Phase 2 trials in naïve and experienced possible

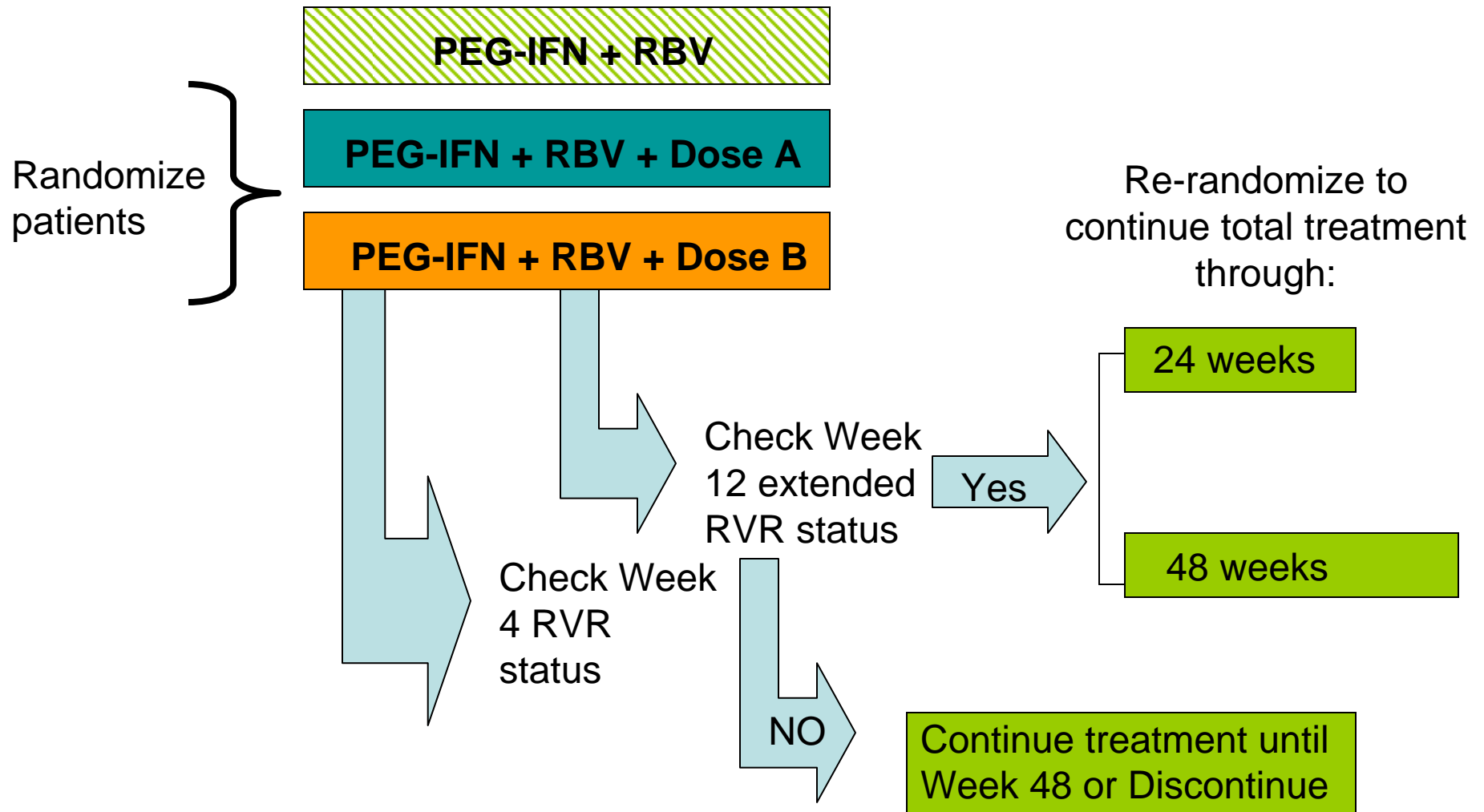


Duration Finding

- Based on sound scientific rationale
- Sufficient nonclinical data to support long term dosing (48 weeks)
 - Unless data to alter risk/benefit
- Recognize utility of shorter duration of treatment
 - Balance between risks of non-response and relapse, development of resistance and safety
 - Alternative treatment strategies

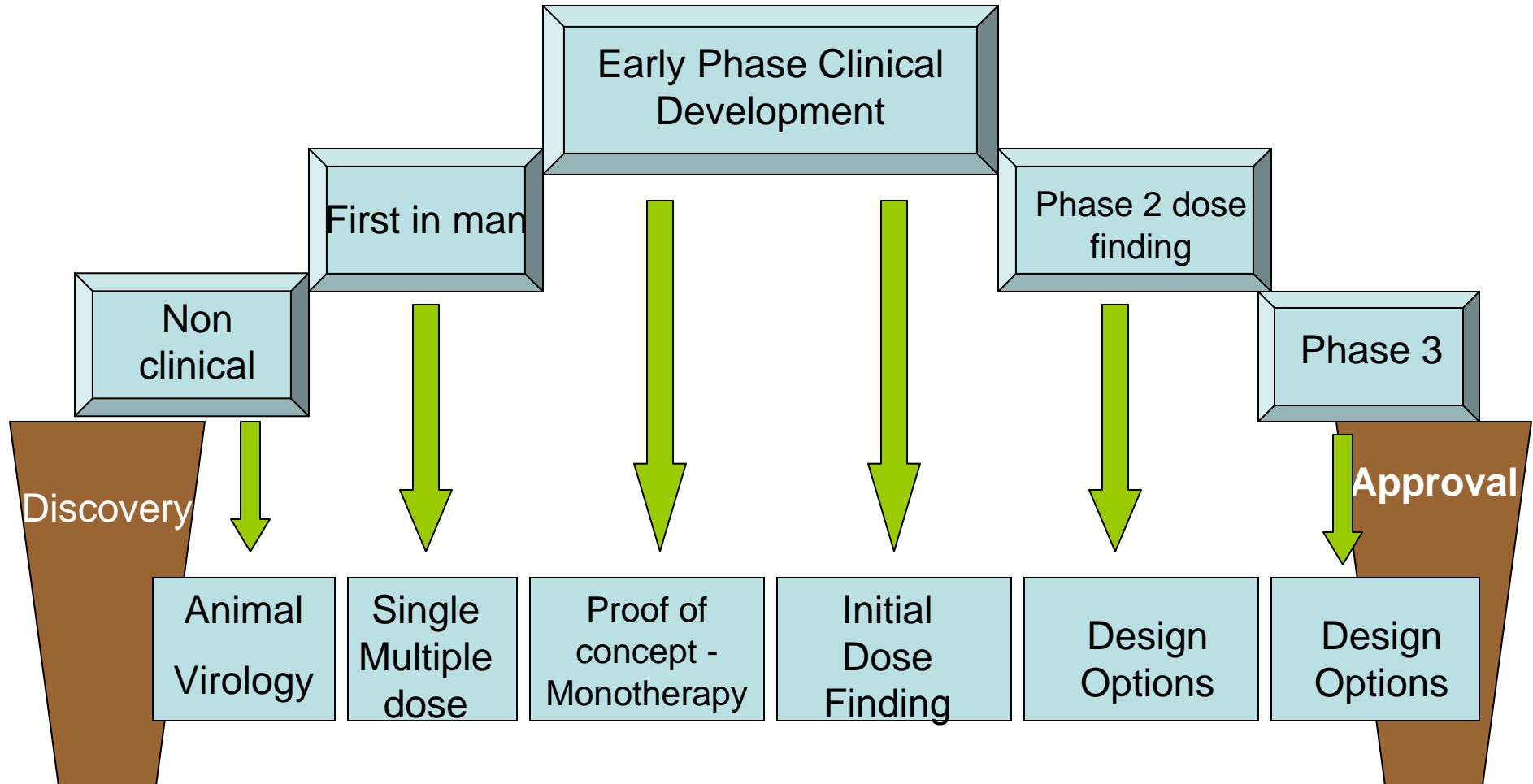


Alternative Strategies





Bridging Discovery to Approval



Phase 2/3 Development

- Numerous strategies for trial designs
 - Dose, duration, lead-in explorations
- Adequate SVR data (SVR₁₂ and SVR₂₄) from phase 2 are needed prior to phase 3
 - ensure on-treatment responses are durable
 - allow for sample size calculations for Phase 3 trials





Long-Term Follow-Up

- Subjects who achieve SVR should be followed for at least 3 years to:
 - Ensure durability of response
 - Determine whether subsequent detection of HCV RNA represents outgrowth of pre-existing virus or re-infection
 - Evaluate development of progressive liver disease or hepatocellular carcinoma



U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Combination Therapy with Multiple Direct Acting Antiviral Agents (DAAs)



Use of Two or More DAAs

- Strongly encouraged throughout development
- Timing
 - Case by Case Basis
 - Depends on available data and risk benefit assessment
- Patient populations to benefit from use of two or more agents
 - SOC Null Responders
 - Patients for whom SOC contraindicated such as decompensated liver disease or severe anemia
 - Patients not able to tolerate SOC
 - Transplant patients and patients with decompensated cirrhosis
 - Genotype 1a/b treatment-naïve or experienced
 - Improve on SVR rates when added to SOC
 - African Americans
 - HIV/HCV co-infected





Use of Two or More DAAs

- Ideally, different mechanism of action
- Data needed on each individual agent prior to combination trials
 - Cell culture combination antiviral activity
 - Resistance and cross resistance
 - Animal data
 - Anti-HCV activity data from clinical trials
 - Some human safety data
 - 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



Potential Designs for 2 or More DAAs

- Short durations (< 2 weeks) of 2 or more agents in treatment-naïve followed by SOC for 24-48 weeks
- Longer durations of 2 or more agents in treatment-naïve or experienced with frequent HCV RNA monitoring and stopping rules for loss or lack of response
 - Can be with or without interferon or ribavirin
- Multiple doses of combination therapy prior to liver transplant
 - evaluate overall antiviral effect prior to transplant
 - evaluate effect on preventing infection of transplanted liver



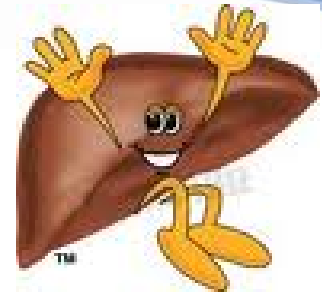
Use of Two or More DAAs

- Need to show contribution of each agent in the regimen
- Factorial designs/modified factorial designs likely
 - PEG-IFN + RBV
 - PEG-IFN + RBV + Drug A
 - PEG-IFN + RBV + Drug B
 - PEG-IFN + RBV + Drug A + Drug B
- Pilot studies recommended to inform decisions for future trials
 - Evaluate drug/dose combinations, +/- SOC (or part of SOC) and different patient population as appropriate
 - Include early decision points to continue with combination of two novel agents or expand cohort





Special Populations



- Prerequisite data are needed to study special populations and are encouraged to be collected early in development

- Transplant
- Decompensated cirrhosis
- Coinfection

Some data in compensated HCV infected patients, pharmacokinetics in hepatic impairment and drug-drug interactions

- Pediatrics



Hepatic Impairment

- Conduct early in development
 - Determine need for dose modifications
 - Allows subjects with hepatic impairment to enroll in Phase 2 and 3 trials
 - Data can support use in pre/post transplant subjects



HIV/HCV Co-Infected

- Strongly encourage initial NDA contain some clinical data on the HIV/HCV co-infected population at time of filing
 - Drug-drug interaction with the most commonly used HIV drugs
 - Safety data on a cohort of co-infected patients receiving the drug for the recommended treatment duration
 - Preliminary efficacy data characterizing, at minimum, on-treatment responses
- Labeling describing drug interactions and preliminary safety data would be appropriate
- To expand indication to HIV co-infected
 - Trial in at least 300 co-infected patients
 - Single arm may be acceptable if HCV mono-infected population shows robust and substantial efficacy of new DAA
 - Endpoint SVR at 24 weeks after end of treatment
 - Safety evaluation includes loss of HIV efficacy



Subjects with Decompensated Cirrhosis

- Treatment with multiple DAA likely needed
- Today single arm trials with at least 2 DAA maybe acceptable design to support indication
 - Because spontaneous resolution of infection is negligible in this population
 - But still need to show clinically significant SVR in trial
 - Single arm trial needs to be supported by efficacy data in subjects with less advanced disease
- SVR primary endpoint
 - Other important endpoints - progression of liver disease, transplantation, mortality
- In the future, trials with multiple arms and factorial type design maybe needed
- Plans for expanded access trials or safety trials should also be considered early in development



Early Access/Treatment IND

- Depends on willingness of pharmaceutical sponsor
- FDA supports concept when sufficient data available to characterize reasonably safe and active dose
- Timing
 - After phase 3 trials are fully enrolled or well underway as to not interfere with development
- Alternatives (these can occur earlier in drug development)
 - Individual patient INDs
 - Treatment access protocols for intermediate size populations (approximately 100 patients or less)
- Can include multiple investigational agents or allow for co-enrollment into several Treatment IND programs simultaneously



FDA Hepatitis List Serve

- Similar to HIV/AIDS List Serve
- Provides late breaking information, as well as an archival record of updates on safety and regulatory issues related to Hepatitis A, B and C including
 - Product approvals
 - Significant labeling changes
 - Safety warnings
 - Notices of upcoming meetings
 - Notices about proposed regulatory guidances

www.fda.gov [type Hepatitis in the search engine]