

Combination Therapy with 2 or More DAAs

- **Strongly encouraged**
- **Timing**
 - Case by Case Basis
 - Depends on available data and risk benefit assessment
- **Studies of combinations of DAA in patients who**
 - SOC Null Responders
 - SOC contraindicated such as decompensated liver disease or severe anemia
 - Not able to tolerate SOC
 - Genotype 1a/b treatment-naïve or experienced
 - Improve on SVR rates when added to SOC
 - African Americans
 - HIV/HCV co-infected

Combination Therapy with 2 or More DAAs

- **With and without PEG/RBV**
 - Depending on patient population, provided the rationale for the combination adequately considers safety, pharmacokinetic, and virologic risks and benefits
- **Viral kinetic modeling suggests perhaps as many as three or four DAAs may be needed to achieve optimal SVR rates without IFN and RBV, but at present it is not known whether regimens that do not include IFN can produce SVR at all**

Combination Therapy with 2 or More DAAs General Considerations

- **Ideally, agents with different MOA**
 - Cell culture combination antiviral activity data
 - Resistance and cross resistance patterns
 - Anti-HCV activity data from clinical trials
 - Some human safety data on each agent
 - Justification for proposed doses based on clinical trials or other sources to indicate doses chosen are likely to provide reasonable anti-HCV activity
 - Drug-drug interaction data if the metabolism profile suggests an interaction potential
 - Animal data

Combination Therapy with 2 or More DAAs Preclinical Considerations

- **Nonclinical combination studies may not be useful for safety assessment of combination clinical trials**
 - Review of nonclinical combination studies did not yield new data when compared to data from single agent studies
 - Nonclinical Safety Evaluation of Drug or Biologic Combinations Guidance suggests dosing animals with agents at a comparable human AUC exposure (basically a PK study, not a toxicity study)
 - 3 month repeat dose toxicity in rodent and non-rodent for each to support 90 days in humans
 - Longer-term data on each (up to 6 month rodent and 9 month non-rodent) support longer duration dosing depending on toxicities
- **Combination studies of any duration with PEG-INF/RBV + new agent in animals are not needed**

Combination Therapy with 2 or More DAAs Trial Design Considerations

- **Some potential designs**
 - **<2 weeks in naïves followed by SOC for 24-48 weeks**
 - **Longer duration in naïves or experienced in combo with PEG/RBV with frequent HCV RNA monitoring and stopping rules for loss or lack of antiviral response**
 - **Then longer durations of 2+ molecules with or without PEG and/or RBV could be considered, and could focus on patients with greatest need for treatment that doesn't include PEG or RBV**
 - **Multiple doses of combination prior to liver transplant to study the overall antiviral effect and potentially the effect on preventing re-infection**
- **Once initial proof-of-concept data are available for a combination of 2+ DAAs, many possible approaches moving forward**

Combination Therapy with 2 or More DAAs Virology/Resistance Considerations

- Examples of approaches that are difficult to rationalize, from a resistance perspective, for initial trials in HCV infected patients:
 - Short term duration of 2+ DAAs in previous Peg-IFN/RBV failures
 - Short term duration of 2+ DAAs with no rollover to SOC
 - Long term duration of 2+ DAAs, with neither DAA having long duration experience as a single agent in combination with Peg-IFN/RBV
- For initial trials of 2+ DAAs without Peg-IFN/RBV, consider screening by IL28B polymorphism to include naïve subjects who are most likely to respond to Peg-IFN/RBV rollover
- If combining two agents that target NS5B, characterize resistance in cell culture and conduct extensive cross-resistance characterizations, preferably building on clinical experience for the individual DAAs
- Conduct duration-finding for SVR endpoint trials working backwards: if investigating a shorter than “standard” duration, provide sufficient rationale and include an appropriate arm for direct comparison

Special Populations 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
 - Cell culture combination anti-HIV and anti-HCV activity relationships for drugs with similar mechanisms of action
 - 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**
 - Clinical trial demonstrating efficacy and safety in at least 300 co-infected patients is needed.
 - Evaluate SVR at 24 weeks after end of therapy (primary endpoint)
 - Loss of HIV efficacy (rebounds in HIV viral RNA) (safety)

Special Populations Decompensated Cirrhosis

- **SOC not appropriate for subjects with decompensated cirrhosis or pre or post-liver transplant**
 - Treatment with multiple investigational direct acting antiviral agents are likely needed
- **Single arm efficacy and safety trials with at least two DAAs may be most feasible trial in decompensated cirrhosis. Single arm trials would need to be supported by efficacy data from studies in subjects with less advanced disease**
 - SVR should be the primary efficacy endpoint
 - Other important endpoints include: progression of liver disease, transplantation and mortality
 - SVR is an important endpoint not withstanding disease progression requiring transplantation, because SVR will likely translate into prevention of infection of a newly transplanted liver
- **The contribution of each agent toward overall efficacy of a regimen should be demonstrated, but may be based on information of the individual agents from other clinical trials**
- **Plans for expanded access trials or safety trials should also be considered early in development**

Special Populations Pediatrics

- Early trials of DAAs should enroll adult subjects only, reserving pediatric exposure until the PK, PD, and safety are reasonably well-defined
- Sponsors are encouraged to begin discussions of their pediatric formulation and clinical development plan early in development
 - EMEA PIP (EOP-1)
 - Pediatric clinical trials should be initiated once Phase 2 adult data characterizing the safety profile and initial antiviral efficacy
- If clinical trials in adults have demonstrated no safety concern specific to a histologic stage, liver biopsy not required for entry into pediatric trials

Special Populations Pediatrics

- The pediatric development program should include:
 - **Development of an age appropriate formulation**
 - **Clinical pharmacology trials to assess single or multiple dose PK (as appropriate) across the pediatric age range (3-18 or 21 yrs)**
 - **Clinical trial(s) to assess safety and efficacy of the proposed regimen over the proposed duration of treatment with assessment of SVR as the primary endpoint**
- The pediatric safety database should include approximately 100 patients who have received the drug at the to-be-marketed dose or higher for the proposed length of treatment
- Long-term follow-up after treatment completion to assess growth and development, durability of response, and status of liver disease
 - **Follow-up over a period of at least 5 years**

Expanded Access Programs New Regulations

- New Subpart I consolidates treatment use into a separate subpart of the IND regulations
- New Subpart I contains all necessary information
 - Describes the three categories of (Individual, Intermediate-Size, Treatment IND/protocol)
 - Describes the general criteria applicable to all categories of access and additional criteria that must be met for each access category
 - Describes the submission requirements
 - Describes the safeguards applicable to EAPs (e.g., informed consent, IRB review, reporting requirements)
- Provides for possible access to drugs that have a Risk Evaluation and Mitigation Strategy (REMS) that restricts availability of the drug - for patients who do not meet REMS criteria

How does FDA Weigh Safety and Risk for EAPs? (the general evidentiary standard)

- Evidentiary basis linked to size of exposed population and seriousness of disease
- Sufficient evidence of safety and effectiveness to support the use of the drug
- Reasonable basis to conclude the therapy may be effective and would not expose patients to unreasonable and significant risk – relative to the risk of the disease
- More rigorous requirements with increasing exposure -- makes access risk-benefit analysis analogous to the clinical trial phase 1, 2 and 3 paradigm of growing exposure

Requirements for Individual Patient EAPs 21 CFR 312.310

- Physician determines probable risk from drug does not exceed that from disease
- FDA determines that the patient cannot obtain access under another type of IND
- Procedures for emergency use (where there is not time to make a written IND submission)
- Additional Safeguards
 - Treatment generally limited to one course
 - FDA requires report and may require special monitoring
 - FDA may request consolidation of multiple cases into single, intermediate size patient population IND

Requirements for Intermediate Size Population 21 CFR 312.315

- Drug is
 - Not being developed (e.g., disease rare)
 - Being developed (e.g., patients not eligible)
 - Approved or related (e.g., drug withdrawn)
- Sufficient evidence drug is safe at proposed dose and duration to justify size of exposed population
- Preliminary evidence (clinical or plausible pharmacological) of effect
- Additional Safeguards
 - Require explanation of why drug cannot be developed or why patients cannot be enrolled in clinical trial
 - Annual review to determine whether treatment use should be continued and whether a Treatment IND would be a more appropriate mechanism

Requirements for Treatment IND or Protocol 21 CFR 321.320

- Drug is being investigated in clinical trial designed to support marketing or trials are complete
- Company is actively pursuing marketing approval
- Sufficient evidence of safety and effectiveness
 - Serious disease: evidence from phase 3 or compelling data from phase 2 clinical trials
 - Immediately life-threatening disease: evidence from phase 3 or phase 2 studies, but could be based on more preliminary clinical evidence
- Additional safeguards
 - Monitoring

Human Subject Protections Apply to Expanded Access

Drugs in EAPs are investigational drugs therefore, they are subject to the following requirements from 21 CFR:

- Part 50- Protection of Human Subjects
- Part 56- Institutional Review Board
- Part 312 -including Clinical Holds based on safety and reporting requirements (adverse event reports, annual reports)

Expanded Access - Implementing the Process

- The manufacturer
 - Must be able and willing to provide the product
 - Work with clinicians to provide and monitor use of product
 - Develop mid-size and large scale program protocols and support program infrastructure
 - Administration
 - Monitoring and reporting responsibilities
 - IRB review and continuing review
 - EAPS consume time, energy, and resources – may not be the best use of resources from a commercial perspective
 - There may not be enough capacity to produce an investigational drug to meet the additional demand generated by an EAP
 - Equitable distribution of limited product – lotteries?
 - Logistics of communicating and working with physicians who are outside of research/investigator network
 - Challenge to train individual physicians on regulatory requirements, processes and procedures
 - Liability concerns
 - Concerns about how data might affect application review

Expanded Access - Implementing the Process

- FDA
 - Resource intensive
 - IND paperwork
 - Medical records review
 - Quick turn-around time
 - Assessment of existing data for safety and evidence of effectiveness
 - Assurance of patient protections (IRB review, informed consent)

Expanded Access - Implementing the Process

- IRB
 - Not all IRBs are familiar with expanded access protocols and how to review them (intent is treatment, not clinical research)
 - May overestimate risk
 - Workload and scheduling issues for IRB can delay review
 - Requires entire committee to review (no expedited review procedures at present)
 - Liability concerns
 - Cost concerns and reimbursement for services

Applicability to HCV

- Expanded Access programs could
 - Be coordinated so that a Treatment IND makes available at least TWO DAA drugs from one company
 - Allow co-enrollment in another program from another company
 - Two companies could collaborate in a Treatment IND
- Looking for opinions about when or for what populations would expanded access to a single DAA be appropriate