Bridging the Data Gap: From Discovery to Approval HCV Drug Development Overview

Guidance for Industry
Chronic Hepatitis C Virus Infection:
Developing Direct Acting Antiviral Agents for Treatment
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf

Outline for Slide Set

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Pharmacology/Toxicology Development Considerations

- Not feasible to conduct animal studies for all potentially relevant combinations
  - DAA + SOC and other DAAs
- Combination toxicology studies not needed
  - More useful to have studies with individual agents at multiple and higher doses
- To support human trials for up to 90 days for 2+ DAAs:
  - For each DAA need:
    - Need minimum of 3 months repeat dose noncinical toxicity studies in rodent and non rodent 6 month rodent, 9 month nonrodent can support longer duration combination trials, depending on toxicity profile
- Nonclinical studies of DAA + SOC no needed unless data suggest potential for increased or synergistic toxicity with approved agents

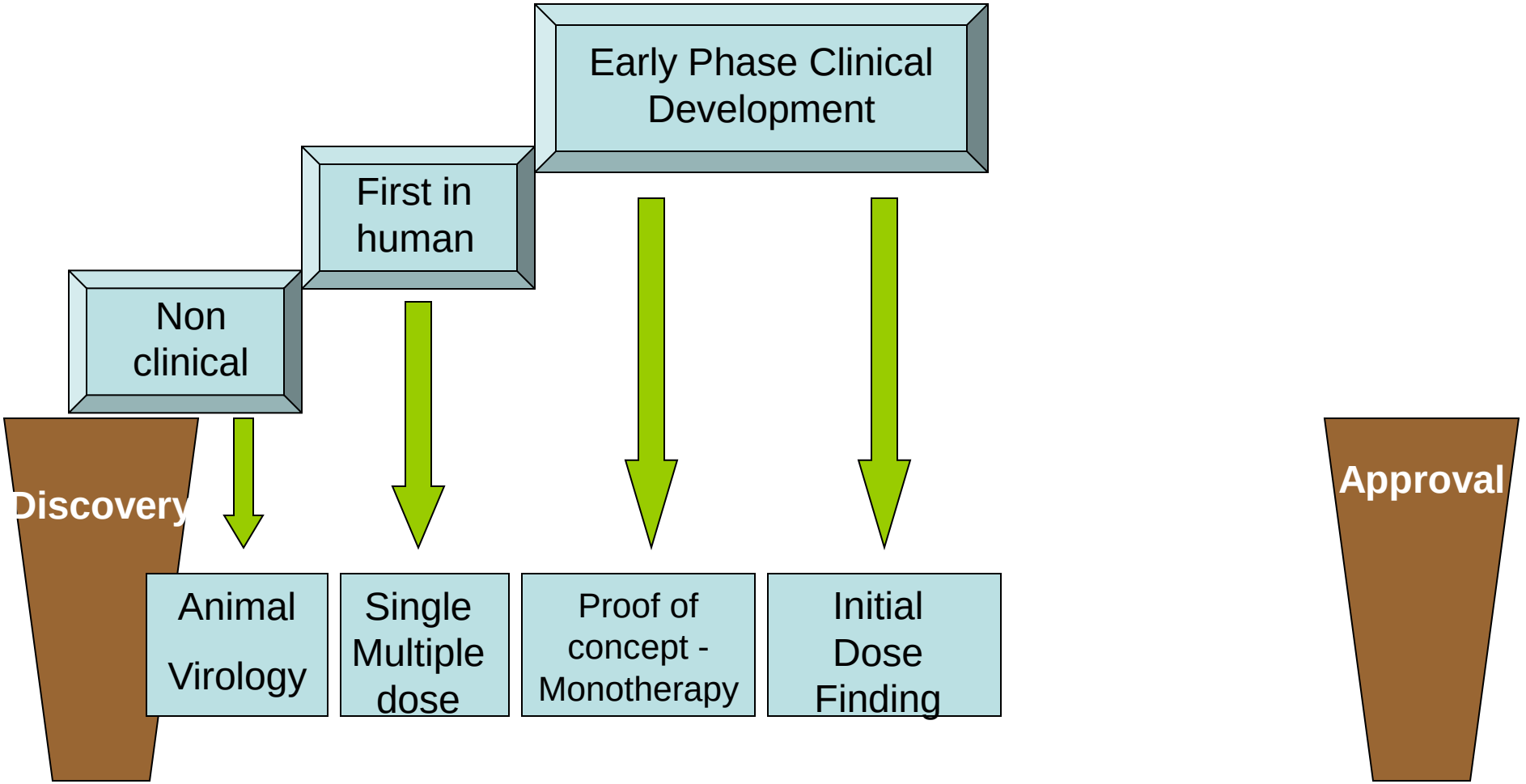
Nonclinical Virology Development Considerations

- See Guidance for Industry: Antiviral Product Development – Conducting and Submitting Virology Studies to the Agency
  - Mechanism of action
  - Antiviral activity in cell culture
  - Resistance and cross-resistance
  - Combination antiviral activity
    - Combination antiviral activity relationships for HIV and HCV agents with similar mechanism of action should be assessed before HIV/HCV co-infected patient trials
  - Activity in animal models
    - Not needed
    - If done include HCV genotype/subtype used, time course plots for viral load, assessment of reistance development

Drug Development Population

- Include broad population (naïve and experienced)
- Adequate representation for gender, race, age, weight
  - Race and ethnicity known to affect response rates to INF based regimens – impt sufficient diversity in trial to conduct meaningful analyses of such groups
- Include patients with compensated cirrhosis in phase 2 and 3 (target @ 20%)
- Encourage study of combinations of DAAs in patients in most need for new agents
  - INF intolerant or contraindicated
  - Transplant
  - 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
- First-in-human trials
  - In general: single and/or multiple ascending dose trials in healthy adult subjects
  - Can also be done in HCV (eg if nonclinical data suggest drug is genotoxic)

Early Phase Clinical Development Considerations

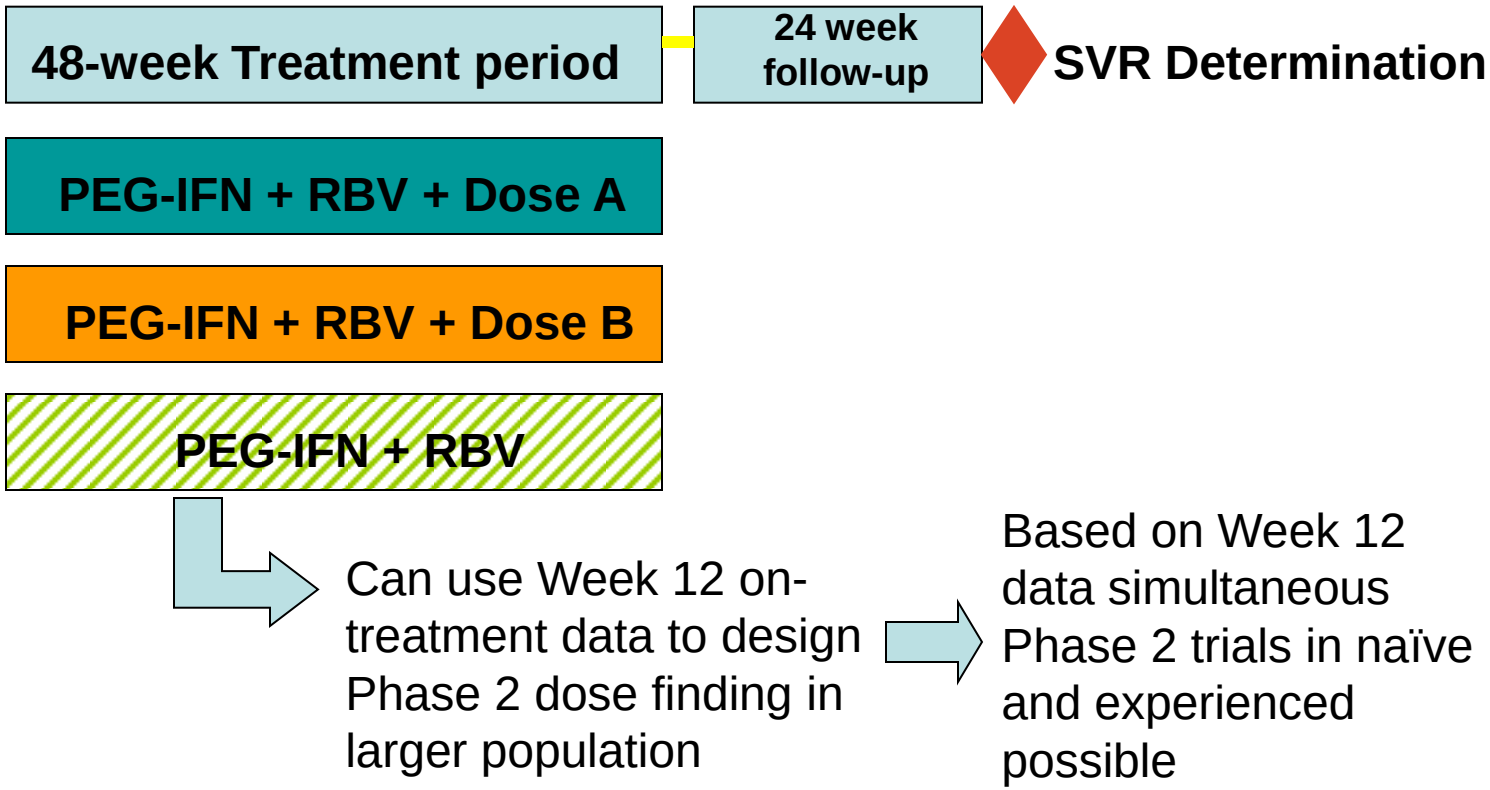
- Phase 1b (proof-of-concept)
  - HCV infected treatment-naïve patients with minimal fibrosis and no significant co-morbidities
  - Repeat-dose, randomized, dose-ranging monotherapy trial
    - Up to 3 days in duration to minimize potential development of resistance (longer duration considered on case-by-case basis depending on characteristics of agent)
    - Collect intensive PK, safety, HCV RNA decay and resistance data
    - Conduct mechanistic modeling of concentration-viral kinetics and concentration-safety to choose doses for early phase 2 trials

Dose Finding

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

Conduct pilot study in treatment-naive

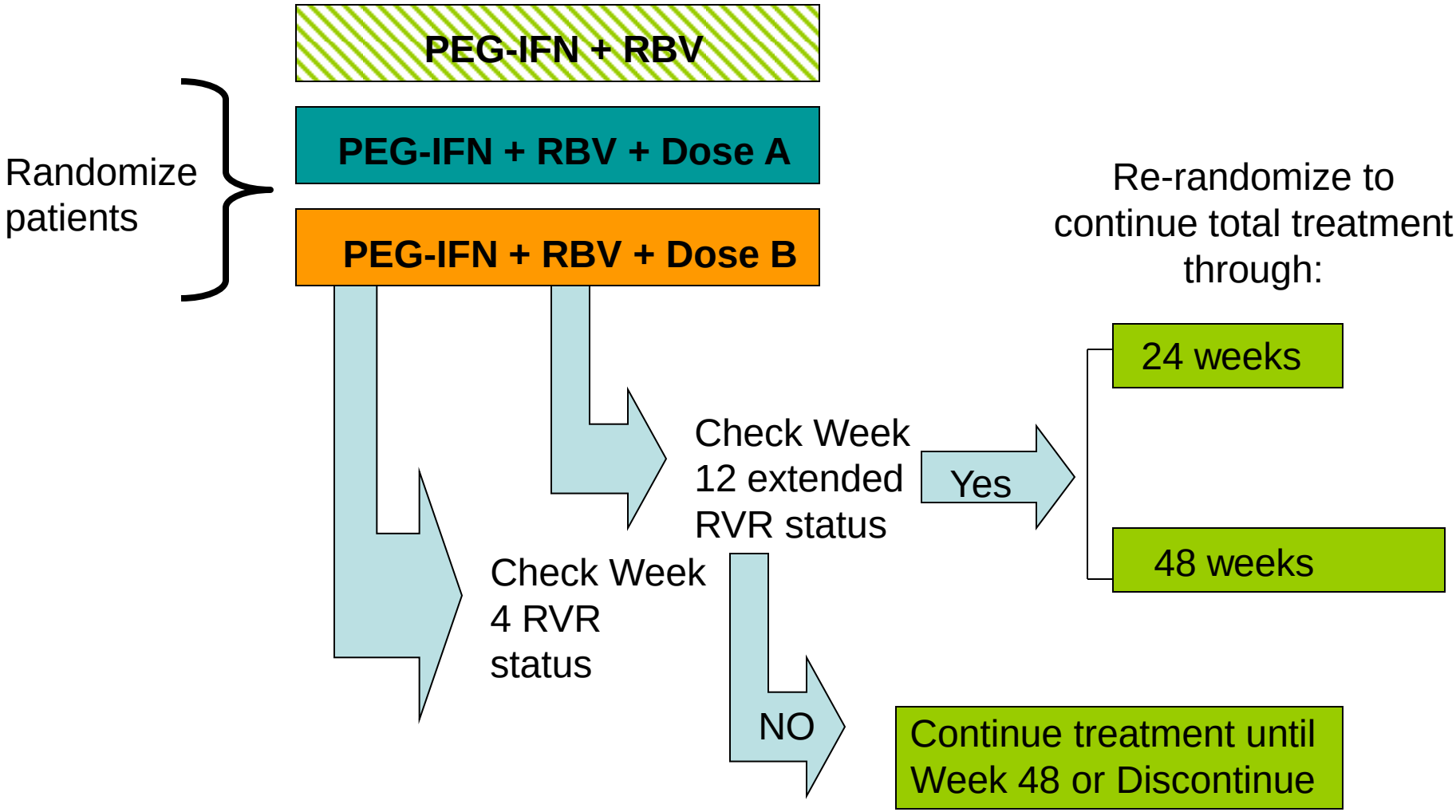
Choose most active doses from monotherapy trial(s), viral decay, resistance, PK safety and modeling data



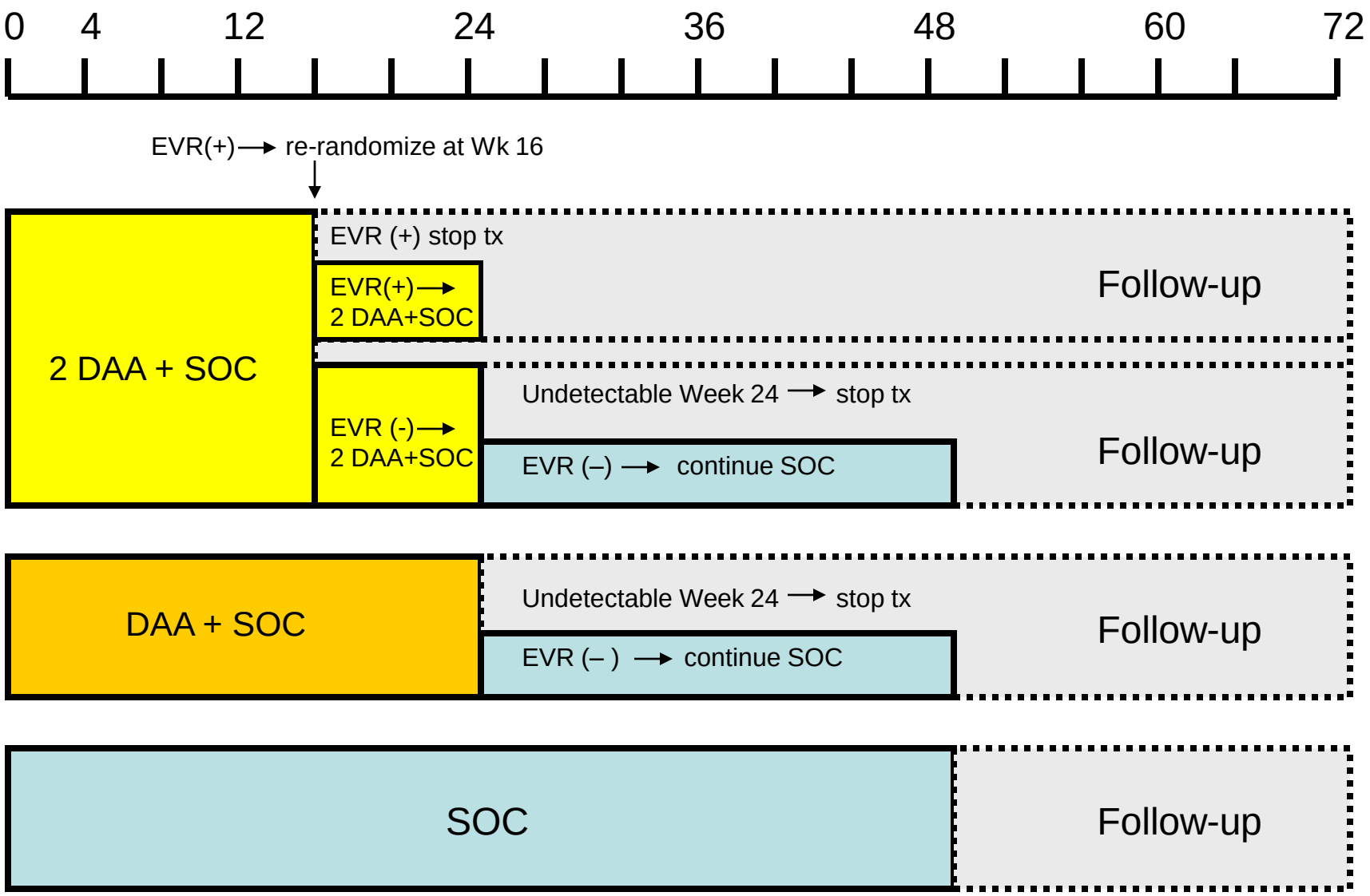
Duration Finding

- Based on sound scientific rationale and not function of the amount of long-term animal toxicology studies that have not been completed
- Optimal duration of dosing of third drug with SOC is not known and likely to vary on characteristics of new drug and treatment population
- Phase 2 trials to generally include at least 1 treatment arm that evaluates 48-weeks of treatment of all components of regimen
  - Unless activity or safety data support rationale for shorter duration
- 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

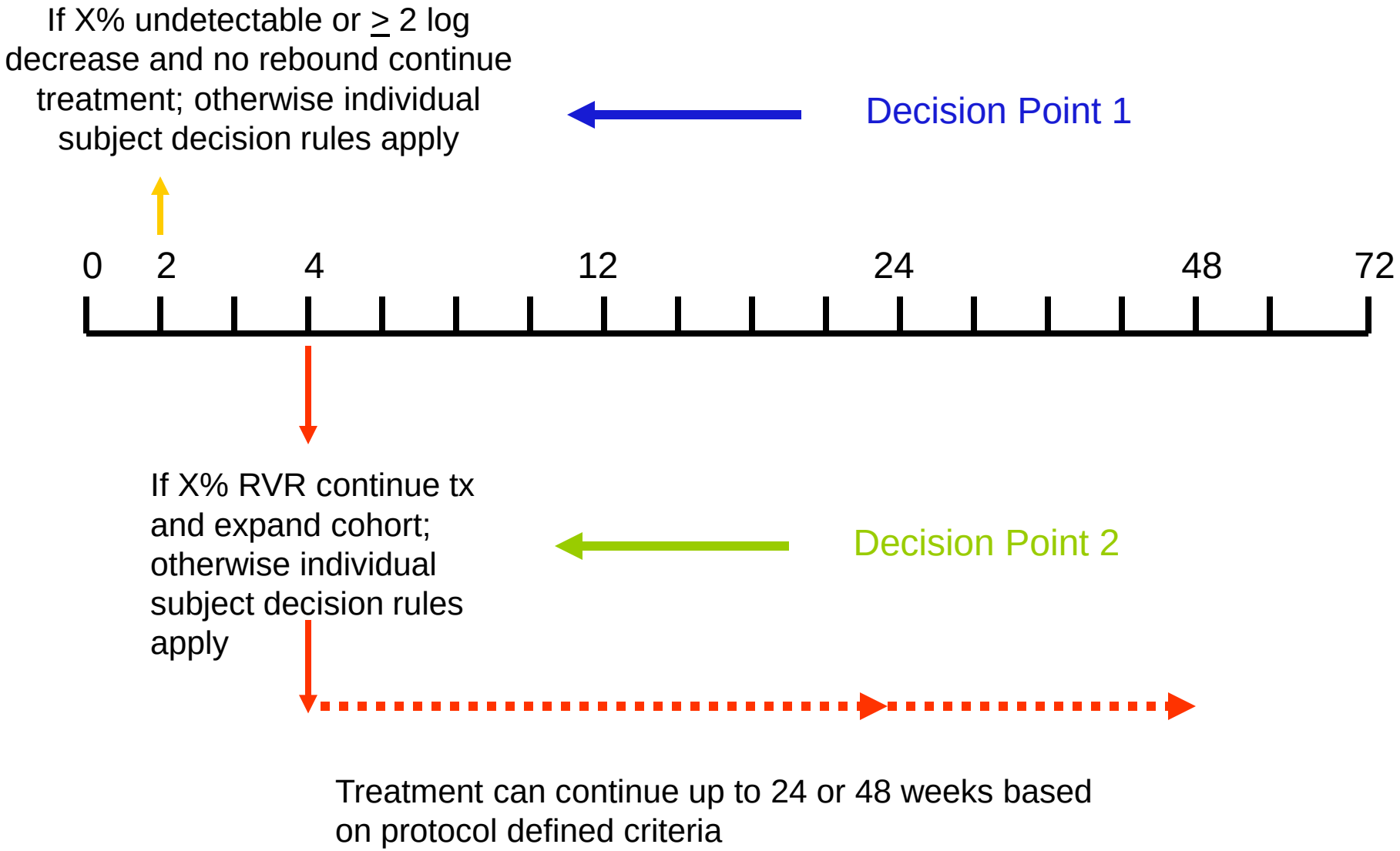


Response Guided Treatment Design Options for Combo DAAs and/or DAA + SOC vs SOC



Null Responders:

Pilot Group randomized: 2 DAA vs 2 DAA + SOC



Phase 2 Trial Considerations

- First Phase 2 combination trial (DAA + SOC)
  - Conduct in treatment-naïve patients
    - Suboptimal doses for treatment-experienced patients can further increase emergence of resistance and could jeopardize future treatment regimens
  - SVR is primary endpoint
  - Week 12 on treatment data can be used to design larger phase 2b dose comparison trials in both treatment-naïve and treatment-experienced patients
  - Designs should allow for direct comparison between treatment arms with respect to dose, strategy and duration
    - If two doses are evaluated then both treatment doses should be evaluated for the same duration
  - Stratify based on IB-28b status when DAA combined with SOC

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

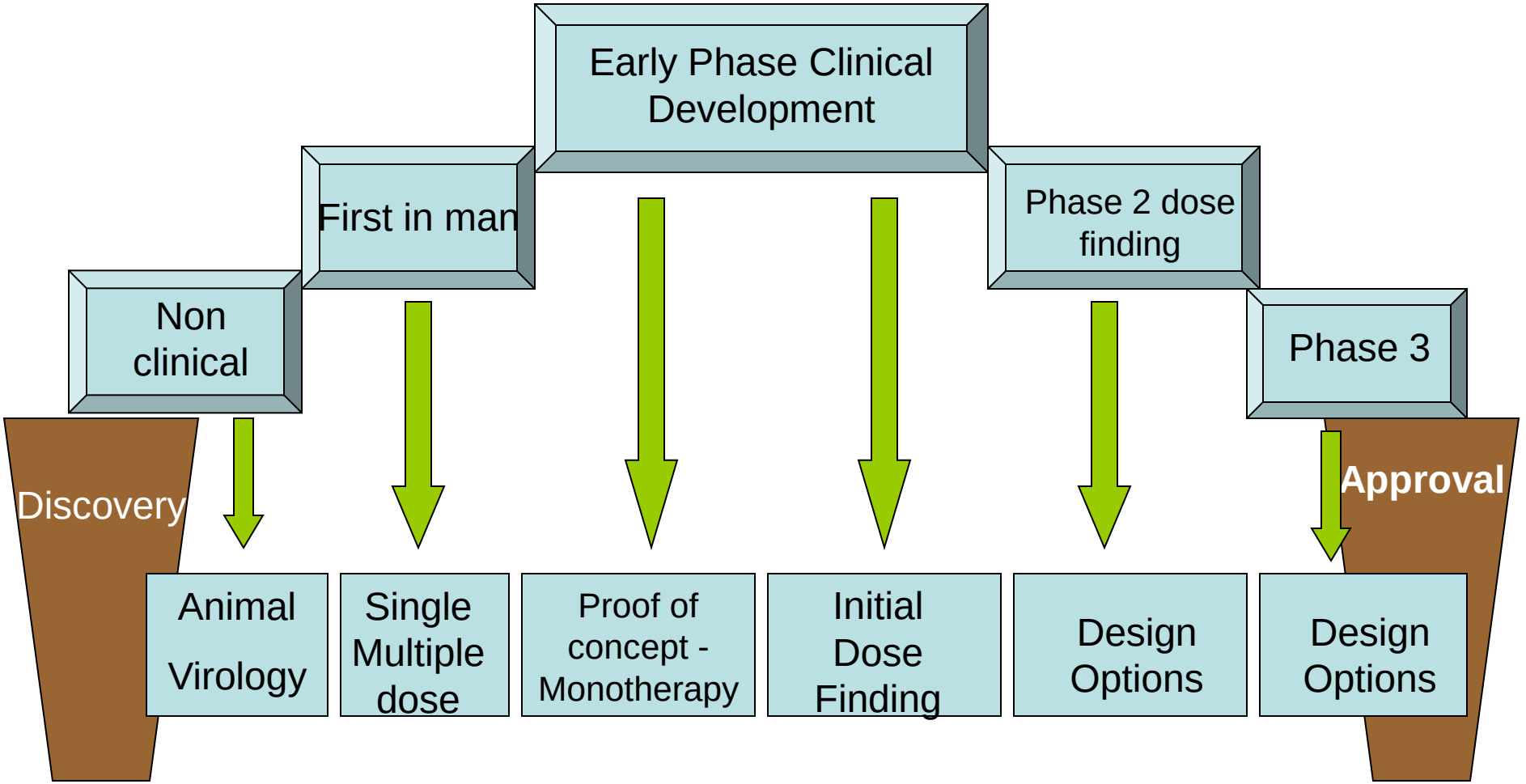
Potential Designs for 2 or More DAAs

- Short durations (< 2 weeks) of 2 or more agents in treatment-naïve followed by a course of SOC either with or without one or more DAAs evaluated in the first two 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
- 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

Other Phase 2 Trial Design Considerations

- Include detailed rationale for alternative dosing strategy with phase 2 protocol submission
- Example
  - Lead in with SOC before initiation of new DAA
  - Explore in Phase 2 and confirm in Phase 3

Bridging Discovery to Approval



Phase 2/3 Development

- Numerous strategies for trial designs
  - Dose, duration, lead-in explorations
- Adequate SVR data (SVR_{12} and SVR_{24}) from phase 2 are needed prior to phase 3
  - ensure on-treatment responses are durable
  - allow for sample size calculations for Phase 3 trials

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
- Alternative to factorial design sponsors can show DAA's contribution toward efficacy of a multiple DAA combo regimen using other types of data
  - Cell culture/early phase 2 showing DAA combos prevent or reduces emergence of resistance
  - Clinical trial data with each DAA + SOC
  - Comparisons of viral load reductions of short term monotherapy
  - Consult 21 CFR 300.50

Safety Considerations

- Initial marketing application for CHC patients without decompensated cirrhosis
  - 1,000-1,500 patients exposed to the proposed dose and duration of treatment
  - If safety signal emerges safety database may need to be increased or specific safety trials may be needed
- Initial marketing application for decompensated cirrhosis or patients with high risk of morbidity and few if any treatment options
  - Approximately 500 patients exposed to the proposed dose and duration of treatment
- Need for controlled and comparative safety data
  - Data from uncontrolled protocols or treatment IND is supportive but lacks degree of detailed reporting and casuality assessment is more difficult

Specific Efficacy Trial Design Considerations

- Until first DAA is approved: recommended design
  - Superiority: DAA + SOC vs SOC
- Future Designs:
  - Active controlled noninferiority trial design
    - New DAA + SOC vs approved DAA + SOC
    - Need to define stringent noninferiority margin
- If achieve SVR in larger phase 2 and 3 trials:
  - Follow for at least 3 to:
    - Ensure durability of response
    - Determine if subsequent detection of HCV RNA represents outgrowth of pre-existing virus vs re-infection
    - Evaluate development of progressive liver disease and/or HCC

Trial Population

- Patient enrollment definition:
  - Positive for anti-HCV antibody, HCV RNA, or an HCV genotype at least 6 months before screening, and positive HCV RNA and anti-HCV antibody at time of screening; or
  - Positive for anti-HCV antibody and HCV RNA at time of screening with liver biopsy consistent with chronic HCV infection (or evidence of CHC disease, such as fibrosis)
- Treatment-experienced patients should also have complete documentation of prior treatment history:
  - compliance with previous therapy and
  - reasons for discontinuation

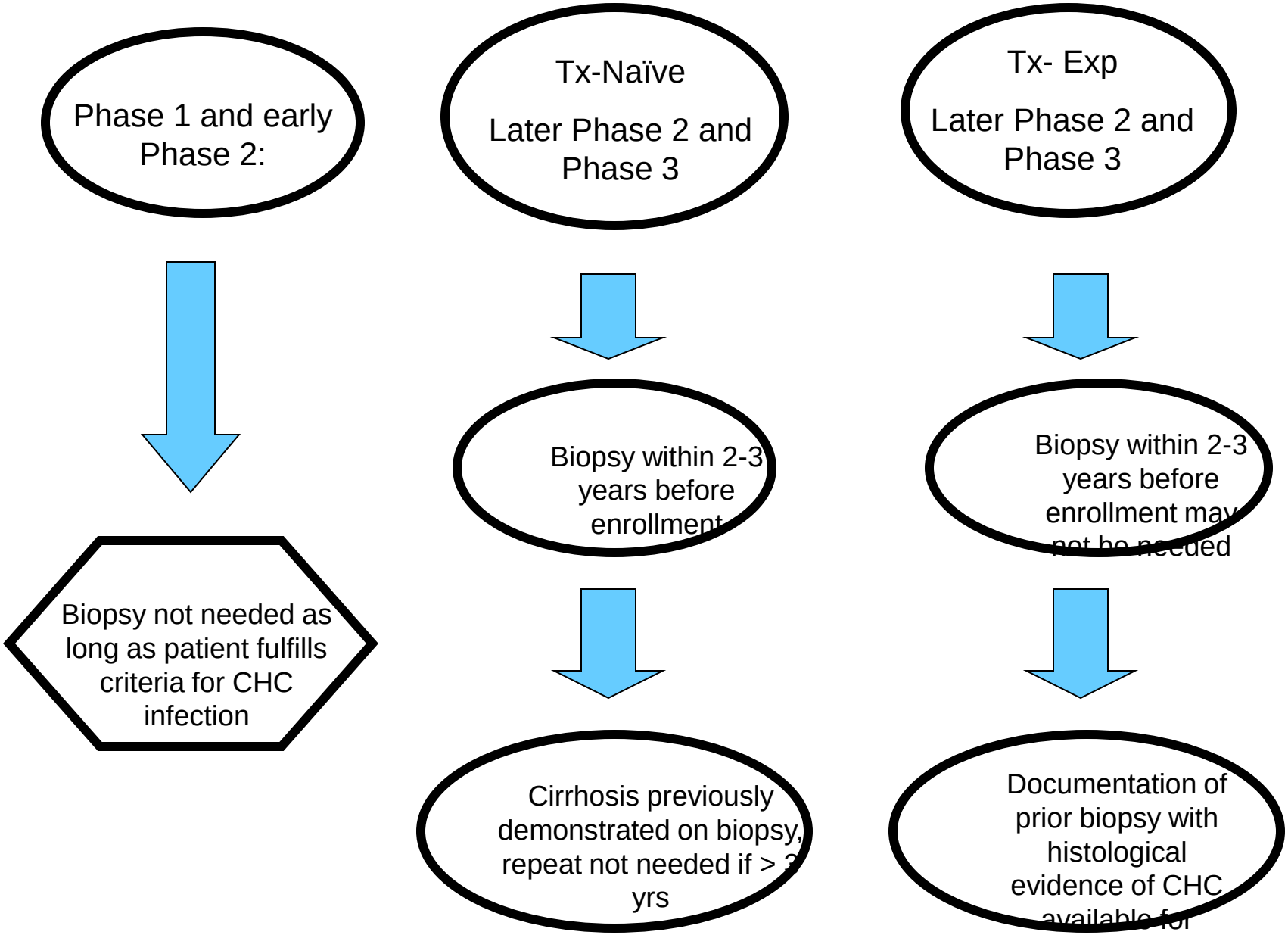
Trial Enrollment Definitions

- **Naïve:** received no prior therapy for HCV (including interferon or pegylated interferon monotherapy)
- **Null Responder:** < 2 log reduction in HCV RNA at Week 12 of Peg-Interferon/RBV
- **Partial Responder:** ≥ 2 log reduction in HCV RNA at Week 12, but not achieving HCV RNA undetectable at end of treatment with Peg-Interferon/RBV
- **Responder Relapser:** HCV undetectable at end of treatment with Peg-Interferon/RBV, but HCV RNA detectable within 24 weeks of treatment follow-up

Patient Enrollment Biopsy Considerations

- Baseline biopsies:
  - Help establish CHC diagnosis
  - Useful to make correlations between amount of baseline fibrosis and treatment outcome (SVR or AE)
  - Need sufficient number of baseline biopsies throughout development to explore correlations between fibrosis and outcomes
    - Biopsies not mandated for all patients such as patients with bleeding disorder
    - Inability to do liver biopsy should not exclude patients from trial
- Noninvasive measures such as biochemical or scanning measurements are not considered validated and should not be substitute for histological information yielded by liver biopsy

Biopsy Considerations

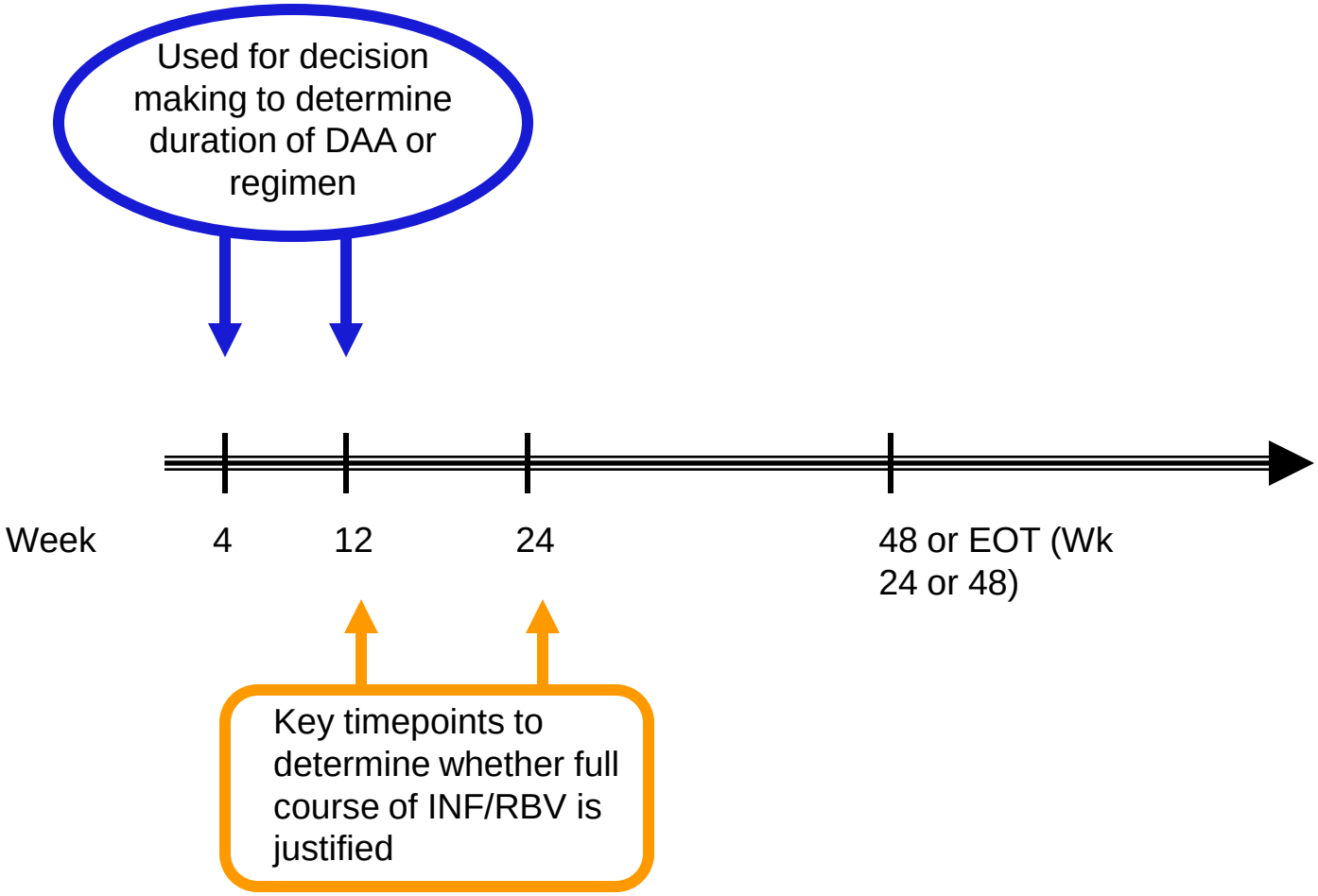


Stratification and Blinding

- Stratify on important baseline factors
  - IB-28B
  - Viral load (high or low)
  - HCV genotype/subtype
  - Cirrhosis
- Double-blind whenever feasible
  - Include matching placebo

Trial Procedures and Timing of Assessments

- Key time points for measuring HCV RNA



Efficacy Analyses

- **Primary endpoint**: SVR24 after completing protocol defined treatment course
  - Adjusted for at least one or two of the most important covariates: (IL-28b, screening HCV RNA, baseline HCV genotype, etc)
  - Subgroup analyses for important demographic and baseline characteristics (region, sex, race, age, HCV genotype, screening HCV RNA, Il-28B, weight, BMI, baseline: ALT, liver histology, fibrosis, and prior INF/RBV experience)
    - Need adequate representation from null and partial responders and responder relapser for meaningful subgroup analyses
- **Secondary endpoints:**
  - Normalization of ALT
  - Proportion with RVR (undetectable HCV RNA after 4 weeks)
  - Proportion with cEVR (undetectable HCV RNA after 12 weeks)
  - Proportion undetectable EOT and SVR12
  - Relapse rates at 12 and 24 weeks EOT

Handling of Missing Data

- Failure if:
  - Discontinue before end of scheduled 24 week follow-up period
  - Missing HCV RNA at end of scheduled 24 week follow-up
- Minimize loss to follow-up
- Conduct various sensitivity analyses
- Collect detailed data on drug-adherence and confirmation of reasons for discontinuation

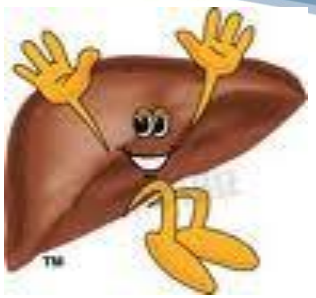
Clinical Virology Considerations

- Resistance testing:
  - Virologic breakthrough (≥ 1 log increase in HCV RNA above nadir, or detectable HCV RNA, while on treatment, after initial drop to below detection
  - Incomplete response (detectable HCV RNA EOT)
  - Slow or plateau viral load decay phase
  - Virologic relapse after treatment cessation
- Phenotypic analyses
- Follow-up
  - Patients with detectable resistance associated substitutions EOT or follow-up should be followed for at least 1 year to assess persistence

PK/PD Considerations

- Combination of rich and sparse sampling may be used throughout development
  - Rich sampling in monotherapy trials
  - Sparse sampling for longer term trials
    - Samples obtained at time of key virologic assessments (Weeks 4, 12, 24 and 48)
  - PK samples for evaluation of INF/RBV or any other agent in the regimen should be collected to assist in exposure-response analyses
- Characterize relationship between exposure and viral kinetics or virologic success:
  - (1) aid in design of phase 2b or 3 with respect to dose and regimen choice – mechanistic approach relating exposure and viral kinetics
  - (2) When sufficient SVR12 and SVR24 available conduct simplified analyses relating proportion of virologic successes with exposure (Cmin or AUC) can be used to support evidence of effectiveness and justify dose selection

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 (can be mix of tx-naïve and tx-exp)
    - 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

Pediatric Populations

- Initiate trials once phase 2 adult data characterizing safety profile and initial antiviral efficacy are available
- If adult trials do not show safety concern specific to histologic stage, then biopsies not needed in children for enrollment
- Trials to be conducted in children ages 3-18

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]