3rd Paris NASH Symposium

French-US Meetings

July 6 & 7, 2017

Institut Pasteur - Paris

Organized by

Arun Sanyal & Lawrence Serfaty

Virginia Commonwealth University School of Medicine, Richmond, Virginia, US

Hôpital Saint-Antoine, APHP, Inserm, Université Pierre & Marie Curie, Paris, France

With the partnership of

AFEF Société Française d'Hépatologie

Société Francophone du Diabète

FORUM for Collaborative RESEARCH

3rd Paris NASH Symposium

July 6 & 7 2017 • Institut Pasteur, Paris

SHORTENING TIMELINES AND IMPROVING EFFICIENCY IN DRUG DEVELOPMENT
-Seamless drug development paradigms

Claudia Filozof, MD PhD
Executive Medical Director
Covance

Challenges in Clinical Development in NASH

- No regulatory Guidelines towards approval
- Limitations of preclinical models to replicate the disease in humans
- Long asymptomatic natural history: Time to hard endpoints is long
- No validated non-invasive biomarkers as surrogate endpoints
- Disease progression is bidirectional
- Limitations of liver biopsy as a surrogate marker
  - Sampling variability
  - Intra and Inter-subjects variability in interpretation

Clinically Meaningful Benefit

- Based on how a patient feels:
  - symptoms
  - quality of life
- Based on how a patient functions:
  - functional status (impairment or improvement in ability to lead a normal active life)
- Based on patient morbidity and mortality:
  - survival
  - liver-related outcomes
  - rates of hospitalization (resource utilization)

Surrogate Endpoints: Regulatory Perspective

Generally Accepted

- Substantial body of literature available
- Quality of data is strong
- Surrogate should reflect:
  - Mortality?
  - Other clinical outcomes
- Surrogate should have:
  - Content and face validity
  - Sensitivity to change

Reasonably Likely

- Less amount of data available
- Quality of data not as strong
- Surrogate should have:
  - Reasonable likelihood of reflecting change in health status based on its relationship to biology of disease
  - Sensitivity to change

Rationale for the use of Adaptive Design in NASH

- High unmet need for an approved therapy
- Number of patients with biopsy-confirmed NASH and/or willing to have multiple liver biopsies is very limited
- Disease progression and regression are not well understood
- It may take several years to progress to cirrhosis and generate clinical outcomes
- Currently accelerated/conditional approval involves a 2-step approach

Adaptive Design in NASH: Potential Advantages

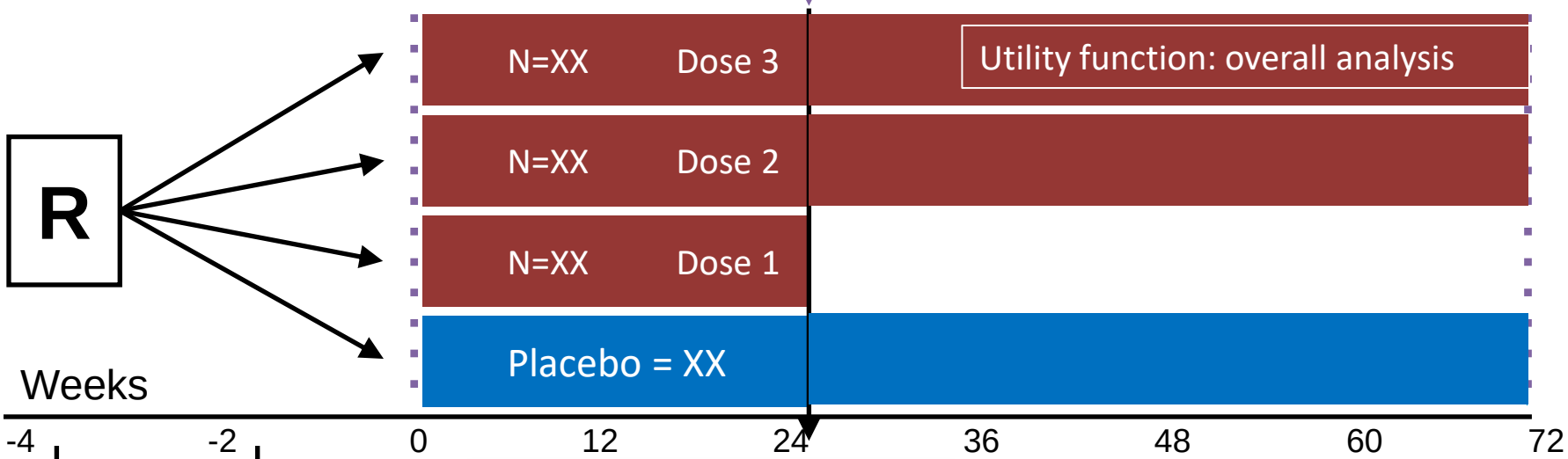
- Provides an opportunity for prospective planning of modifications of one or more aspects of a study
  - Adding or dropping treatment arms
  - Re-estimating sample size
  - Changes in the allocated proportion of subjects in one or more arms
- Allows evaluation of data collected from different stages for a combined analysis
- May help minimize the overall number of patients required during the entire drug development process
- Allows the same subjects to move from one phase to another, reducing the need to find additional subjects willing to undergo multiple biopsies
- May reduce the clinical development process/ overall time to reach marketing approval

Proof of Concept/Dose Ranging Adaptive Trial Design

Population:
- Biopsy-confirmed NASH patients

Randomize Additional Patients

Population:
- Patients at high risk of NASH



Screening period

Run-in

Interim Analysis at Weeks 12 | 16 | 24

Safety stop criteria

Futility/efficacy criteria based on non-invasive biomarkers

Adaptations

Weeks 48 | 52 | 72

Biopsy driven endpoints

Utility function

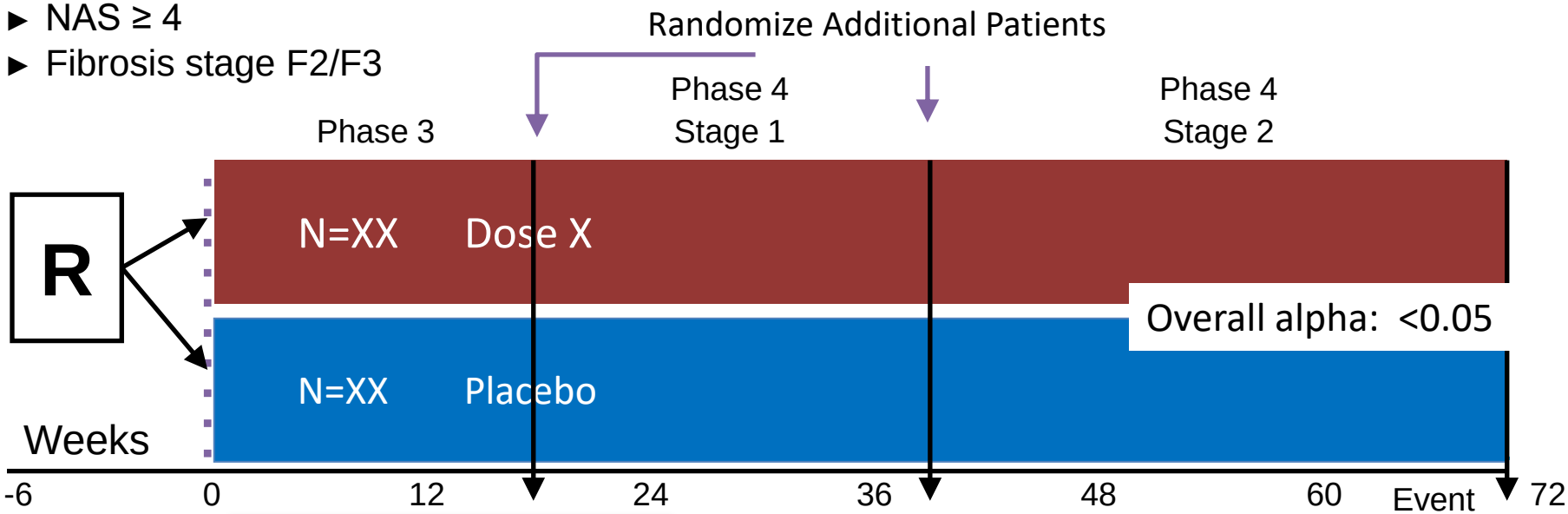
Filozof et al. Hepatology Communications 2017. In press

3rd Paris NASH Symposium

Phase 3/4 Adaptive Design

Population:

- Biopsy confirmed NASH
- NAS ≥ 4
- Fibrosis stage F2/F3



Screening Period Lifestyle Advice

Efficacy Based on Histology may Lead to Accelerated/ Conditional Approval

1. **Resolution of NASH without worsening of fibrosis**
2. **Reduction in fibrosis without worsening of NASH**

Event Rate Confirmation

Safety Evaluation

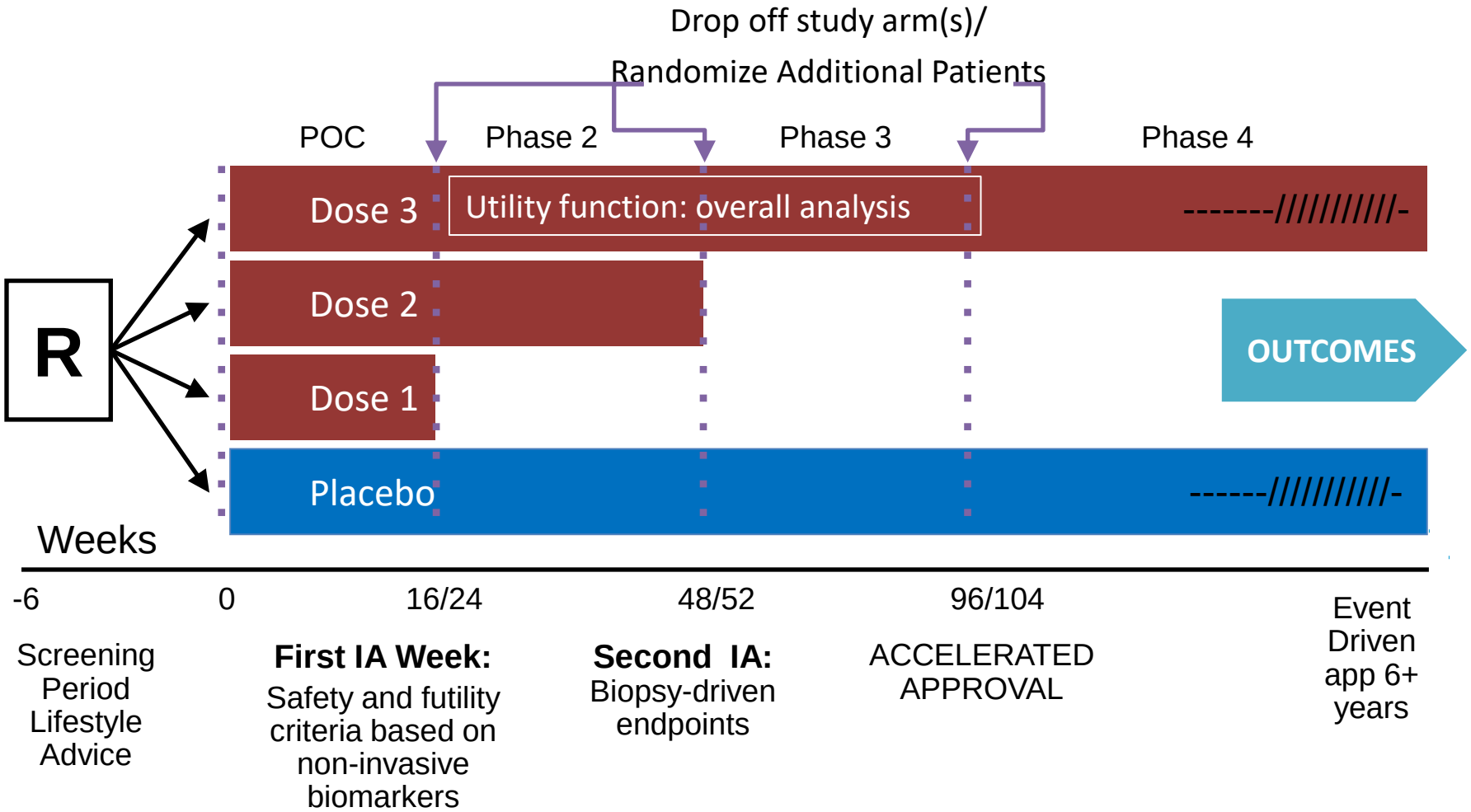
Long Term Composite Endpoint

Progression to cirrhosis (histology)

Overall mortality and liver Clinical outcomes

Filozof et al. Hepatology Communications 2017. In press

Seamless Phase 2/3/4 Adaptive Study Design



Filozof et al. Hepatology Communications 2017. In press

3rd Paris NASH Symposium

Seamless Phase 2/3/4 Adaptive Study Design

- Sample size is often selected to power the study for detecting a meaningful treatment effect at the end of the phase 3.
- Limited power for critical decision making (e.g., for dose selection or dropping arms) .
- A precision analysis is recommended to assure that the selected dose has achieved statistical significance
  - The dose with highest confidence level for achieving statistical significance will be selected
  - The doses with confidence levels for achieving statistical significance less than 75% will be dropped.
- A trend test (e.g. Cochran Amitage test) may be considered
- To protect the trial integrity due to the un-blinding of the interim data, a very small alpha (e.g., 0.0001) is recommended.

Adaptive Design in NASH: Potential Limitations

- Prevent potential operational biases that may arise during the evaluation of the interim data:
  - Identification, minimization and control of sources of bias/variation;
  - Overall type I error control rate at a pre-specified alpha level
  - Maintain the quality, validity and integrity of data: outline roles and responsibilities of a data safety monitoring committee.
- Need for multiple liver biopsies and long term follow-up of phase 2/3/4 seamless trials may limit the number of patients who are willing to participate.
- The need for type 1 error control with a very small alpha increases the total number of patients to allow reasonable power.

Conclusions

- High unmet need of an approved therapy
- Seamless adaptive clinical designs may have several advantages:
  - Reduce the overall number of patients and timelines without compromising the quality of the evidence needed to establish the efficacy and safety of therapeutic agents
  - Flexibility for pre-planned adaptations
  - The use of a utility function may allow all endpoints to be linked for the overall analysis
- But some limitations:
  - Operational complexity
  - Need to control of potential operational bias
  - Need of multiple liver biopsy and long-term follow-up

Thank you

3rd Paris NASH Symposium

French-US Meetings

July 6 & 7, 2017

Institut Pasteur - Paris

Organized by

Arun Sanyal & Lawrence Serfaty

Virginia Commonwealth University School of Medicine, Richmond, Virginia, US

Hôpital Saint-Antoine, APHP, Inserm, Université Pierre & Marie Curie, Paris, France

With the partnership of

AFEF Société Française d'Hépatologie

Société Francophone du Diabète

FORUM for Collaborative RESEARCH