Berkeley School of Public Health

EASL European Association for the Study of the Liver

Forum for Collaborative HIV Research

Regulatory Perspective Updates

Regulatory Considerations

Liver Forum #5

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Disclaimer

The views and opinions expressed here are my own and do not represent the FDAs views or policy

I have nothing to disclose

Types of Endpoints That Can be Used for Approval of Drugs

- Clinical Benefit
- Validated Surrogates
- Surrogates reasonably likely to predict clinical benefit
- Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics

  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Clinical Benefit - Regular Approval

- How a patient feels, functions or survives
- Example of clinical benefit in NASH:
  - Reduction in all-cause mortality
  - Prevention of liver transplant
    - MELD increase to 15 from ≤ 12 (listing for transplant)
  - Prevention or reduction of decompensation events

Surrogates Reasonably Likely to Predict Clinical Benefit

- Potential Examples for NASH:
  - Complete resolution of steatohepatitis and no worsening of liver fibrosis
  - At least 1 point improvement in fibrosis (Brunt/Kleiner scale) and no worsening of steatohepatitis (no increase in ballooning or inflammation on NAS score)
  - The acceptability of surrogates is evaluated for each drug and disease combination

Validated Surrogate

- Can be used for Regular Approval
  - For a specific disease setting and class of interventions
  - Recognized as validated by definitive studies
  - There are no validated surrogate endpoints for NASH

Accelerated Approval

- Based on a surrogate reasonably likely to predict clinical benefit
- For a specific disease setting and class of interventions
- Acceptability of a surrogate is determined for each drug/disease combination on an individual basis

Verification Trials under Accelerated Approval

- Two potential ways to perform verification trials:
  - An entirely new trial/trials
  - Seamless phase 3/4 design in which patients are rolled over from phase 3 to phase 4

Requirements for One Phase 3 Trial to be Persuasive

- "Generally limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible"

- FDA Guidance for Industry: Providing Clinical Evidence and Effectiveness for Human Drug and Biologic Products accessible at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf.

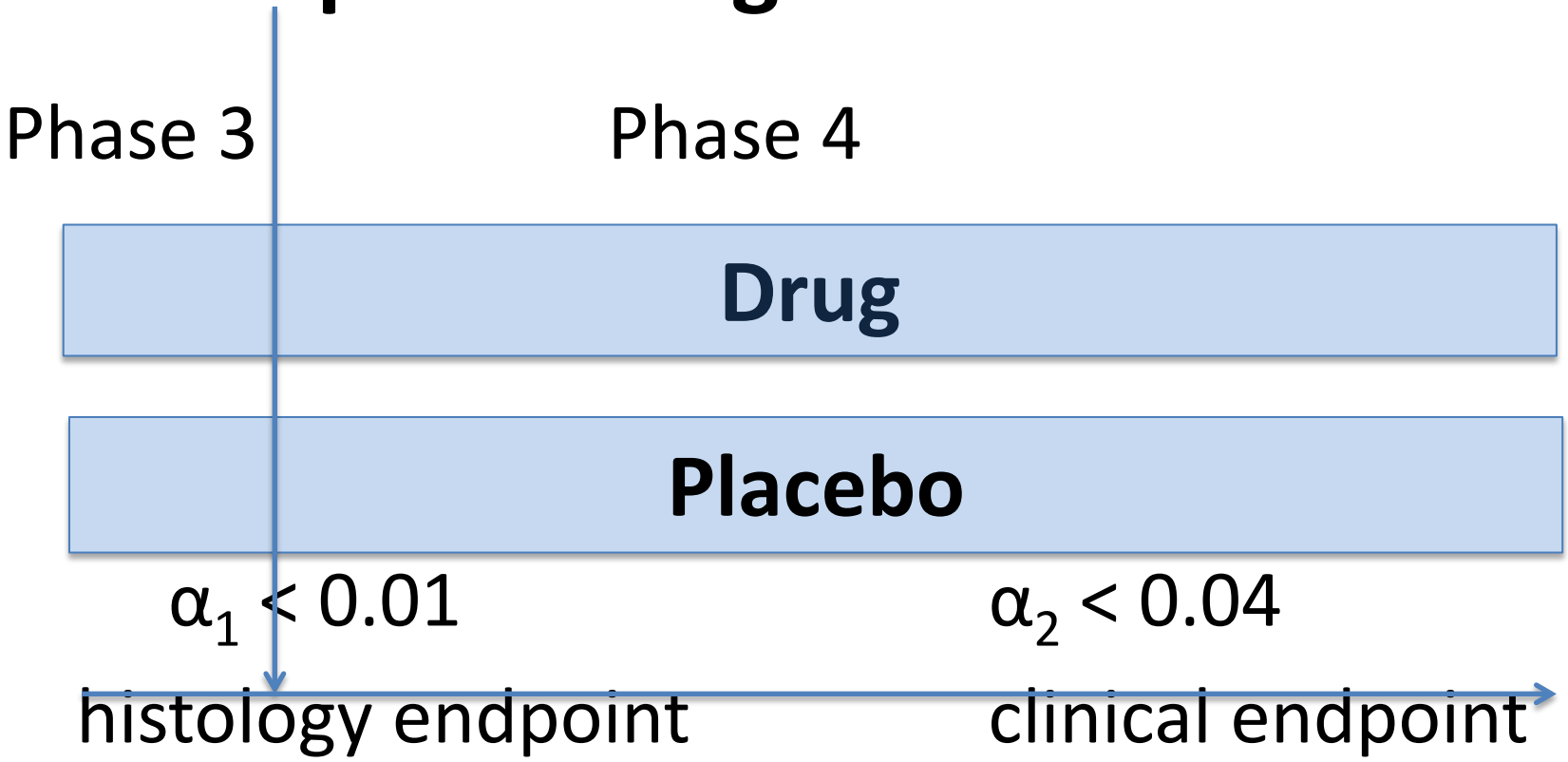
Requirements for One Phase 3 Trial to be Persuasive (2)

- Large, multicenter trials
- Internal consistency across study subsets and sites
- Evidence of an effect on multiple endpoints
- Statistically very persuasive efficacy results

Accelerated Approval Trials
Splitting Alpha for Seamless Phase 3/4 Designs (1)

- If planning **two** seamless phase 3/4 trials:
  - Alpha must be controlled at or below 0.05 for each phase 3/4 trial
  - Example: 0.01 for phase 3 and 0.04 for phase 4
    - Other alpha spending strategies may be acceptable.

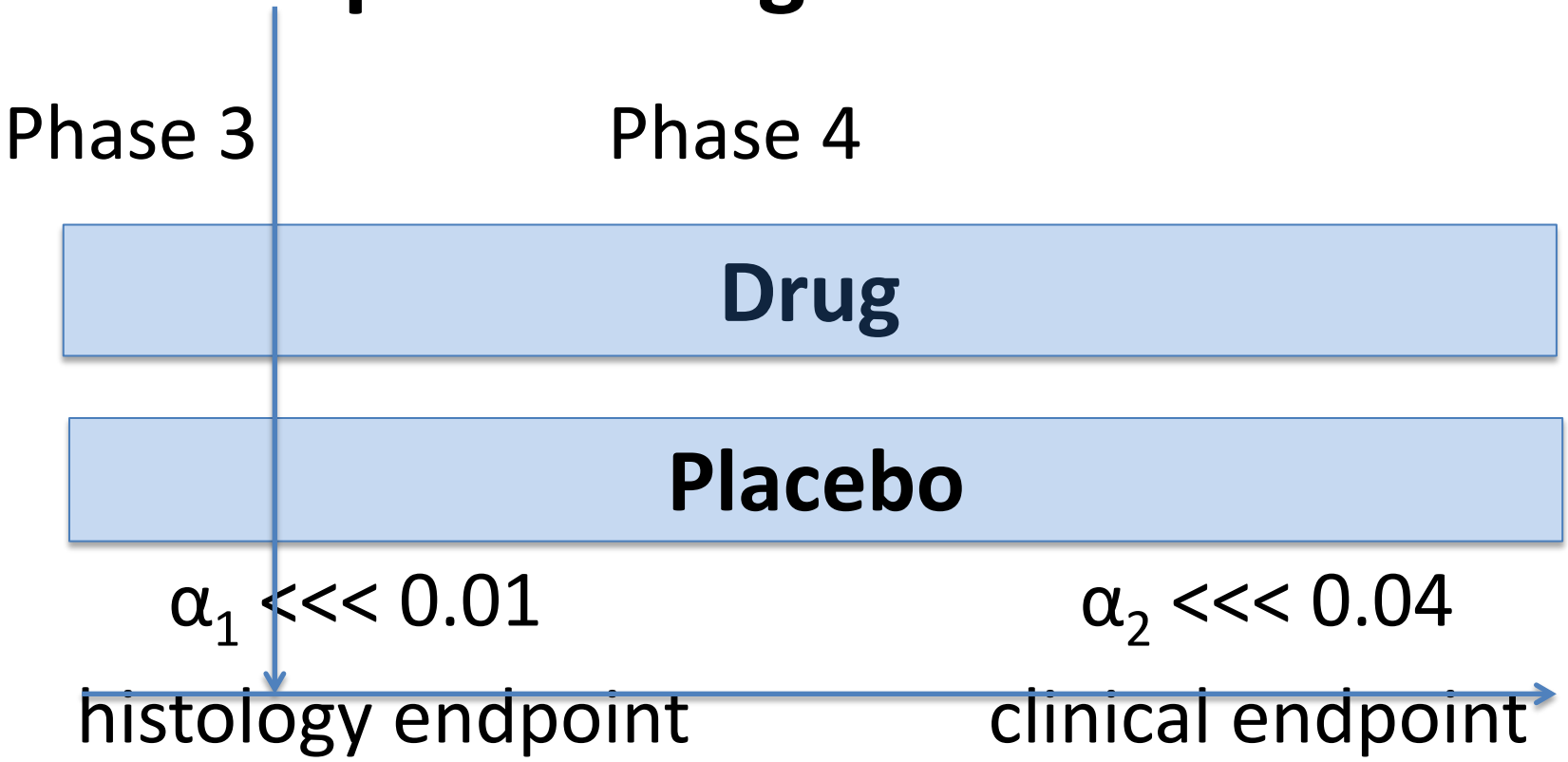
Proposed Phase 3/4 Seamless Adaptive Design – Two Trials



Accelerated Approval Trials
Splitting Alpha for Seamless Phase 3/4 Designs (2)

- If planning **one** seamless phase 3/4 trial:
  - A much smaller over-all alpha, less than 0.05, will need to be applied
  - The alpha will need to be split

Proposed Phase 3/4 Seamless Adaptive Design – One trial



Questions?