Clinical Pharmacology

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Goals

• Approval

• High quality instructions for use: individualization of dose

• Avoid post-marketing requirements / commitments
Developmental Milestones

- First-in-Human Trial
- Phase 2 Trial
- End-of-Phase 2 Meeting
- Phase 3 Trial
- Pre-NDA/BLA meeting
Safety = hold issues, recommendation to allow trial to proceed, microdose can make non-relevant add sub-bullets

- Entry criteria – e.g., renal impairment
- Monitoring of cardiac safety – e.g., QT<sub>C</sub>
- Drug-drug interactions (DDI) – drug as substrate/victim most often the concern
- Food effect (not relevant for IV)
First-in-Human Trial, 2 of 2

Efficacy = non-hold issues, recommendations for trial design

• **Goal** is “near optimal” dose regimen and imaging conditions (timing, machine) prior to confirmatory trials
  – Process is completed in Phase 2, but begins in first trial
  – Superior images to alternatives which have been studied
    • Assured only when ≥ 3 doses and ≥ 3 imaging windows
    • Accuracy and precision impacts Phase 2 design / success

• Sufficient PK sampling

• DDI / food
Pharmacokinetics

- Useful for drug development goals, not only package insert
- Phase 1/Phase 2: improve selection of imaging timing, timing of repeat dosing, and amount of repeat dose
- Eventual goal is to correlate concentrations with clinical outcomes: collect information in Phase 3
- Bioanalytical Method Validation
- Topicals
  - PK needed to correlate with safety outcomes
    - Demonstration of “non-absorption” may include acquiring PK in Phase 3
Phase 2 Trial

- **Safety** = hold issues, recommendation to allow trial to proceed
  - Same as Phase 1 trial, but informed by Phase 1 information including use of PK for dose adjustments

- **Efficacy** = non-hold issues, recommendations for trial design
  - Completion of discovery of “near optimal” dose and imaging conditions for use in Phase 3
  - Sufficient PK sampling
    - linearity: issue for later specific population studies
End-of-Phase 2 Meeting, 1 of 2

• Near Optimal Dose: efficacy as well as safety
  – Food Effect (not relevant for IV)

• Acquire Agency input on data to address Specific Populations in NDA/BLA

Q.: What to measure in future studies?
Info: Identity of major active (imaging, toxicity for non-microdose) metabolites

Q. What data in subjects with organs impairment are needed?
Info: Route of elimination and excretion of parent and major active metabolites
• Acquire Agency input on data to address Specific Populations in NDA/BLA

Q. What in vivo drug interaction studies with new drug as victim are needed?
Info: parent and major metabolites as substrates (e.g., CYP enzymes and transporters)

Q. What future in vivo drug interaction studies with new drug as perpetrator are needed?
Info: Parent and major metabolites as inhibitors and inducers (CYP enzymes and transporters, not applicable to microdose)
Phase 3 Trial, 1 of 2

Safety = hold issues, recommendation to allow trial to proceed

- Same as Phase 2 trial, but informed by Phase 2 information including use of PK for dose adjustments
Phase 3 Trial, 2 of 2

Efficacy = non-hold issues, recommendations for trial design

• Evaluate if dose is near optimal (e.g., review EOP 2 meeting)

• Sufficient PK sampling to inform dose adjustment during or at end of trial; sampling all patients maximizes information (PK-imaging and PK-safety)
  – Adjust dose for “typical patient”
  – Adjust dose for specific population, or determine dose-adjustment not needed
Pre-NDA/BLA Meeting

- Review of data acquired to fulfill recommendations made at the End-of-Phase 2 meeting
- Review of organization of future application: study reports, datasets
Clinical Pharmacology Guidance Page
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

- This list is not comprehensive (e.g., pregnancy, pharmacogenomics, pediatrics)
  - Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications
  - Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling
  - Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling
  - Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations
Biopharmaceutics Guidance Page

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm

Below not comprehensive; biopharmaceutics often not relevant to IV

• Bioanalytical Method Validation
  – relevant to all PK

• Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations
  – case-by-case relevance for IVs

• Food-Effect Bioavailability and Fed Bioequivalence Studies Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling
  – not relevant for IVs
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End

• END
Dose Adjustment Example

No dose change needed for renal impairment