Celerion’s Symposia Series: Bridging the Gap from Phase I to Proof-of-Concept

San Francisco, CA
Tue 8th, Apr 2014
Managing Risk vs Reward in Drug Development

- **Discovery**

- **Preclinical**

- **Full Clinical Development**

- FIH to Clinical Proof-of-Concept (CPoC)

- Where a new drug acquires real value

- Fail fast. Fail early

- The Valley of Death in drug development

- Where translational medicine is applied
# Searching for More Efficient Ways of Managing Risk in Drug Development

## Engineered Process
- Stepwise
- Early studies structured same as later studies – primary objectives and endpoints
- Influenced by “rules-based” regulations

## Preclinical
- Phase I: safety, tolerance, PK (healthy participants)
- Phase II: dose response (small groups of patients)
- Phase III: safety and efficacy (statistically robust)
- Phase IV: post-approval surveillance
- Global filings to each market
- Filings for new indications

## Adaptive Development
- Feedback loops to discovery (Translational Medicine)
- Early studies fused with multiple objectives and endpoints
- Influenced by emerging “risk-based” guidances

## Learn
- Preclinical
  - Human Microdose - PK
  - Early Clinical: safety, tolerance, PK (healthy subjects and patients)
    - Proof-of-Presence
    - Proof-of-Mechanism
    - Proof-of-Concept
  - Dose Response

## Confirm:
- Safety and efficacy (statistically robust)

## Uptake:
- Simultaneous global filings
- Post-approval surveillance
- Filings of new indications
Clinical Pharmacology Impact Areas in Drug Development

**IND/CTA**
- IND Enabling (support IND/CTA)
  - Toxicokinetics
  - Allometric Scaling
  - PK/PD Modeling
  - Novel Biomarker Development
  - Microdosing AMS (Phase 0)

**FIH to CPoC**
- FIH to CPoC (support go/no go decisions)
  - SAD – safety/PK
  - MAD – safety/PK
  - Pilot Food Effect - PK
  - Elderly – safety/PK
  - Robust Cardiac Safety
  - Absolute BA (Microtacer - AMS)
  - Drug Metabolizing Enzyme Probes or Genotyping on PK
  - Early Metabolic Profile (Microtracer – AMS)
  - First-in-Patient - Signal of Effect

**Learn**

**Confirm**

**NDA/MAA**
- NDA Enabling (support product labeling)
  - Drug-Drug Interactions (DDI)
  - Hepatic and Renal Insufficiency on PK
  - Thorough QTc (TQT)
  - Radiolabeled ADME (mass balance)
  - Market-image Bioequivalence (BE)
  - PK or PK/PD in Special Populations
  - PK or PK/PD in Pediatric Populations
  - Population PK or PK/PD from Pivotal Efficacy or Safety Studies

**Product Extension**

- (support new indications)
  - PK in New Patient Populations
  - BE New Formulations
  - BE Generics
  - Population PK

**sNDA/ANDA (US)**

**Uptake**

**IND Enabling**

- Toxicokinetics
- Allometric Scaling
- PK/PD Modeling
- Novel Biomarker Development
- Microdosing AMS (Phase 0)
### Clinical Pharmacology vs. Confirmatory Studies

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<thead>
<tr>
<th>Clinical Pharmacology Studies</th>
<th>Confirmatory Studies</th>
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<tbody>
<tr>
<td>- Small number of participants</td>
<td>- Large numbers of participants</td>
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<tr>
<td>- Few sites, usually single geography</td>
<td>- Many sites, many countries and geographies</td>
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<tr>
<td>- High density sampling</td>
<td>- Low density sampling</td>
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<tr>
<td>- Sampling logistics critical</td>
<td>- Study logistics critical</td>
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<tr>
<td>- Specialized units with subject confinement capabilities</td>
<td>- Hospital or outpatient clinic settings</td>
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<tr>
<td>- Focus on “Proof-of-Presence”, “Proof-of-Mechanism”, “Proof-of-Concept” and specific product labeling needs.</td>
<td>- Focus on pivotal efficacy and safety for regulatory approval and major product labeling claims</td>
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What’s Driving Change in Early Clinical Studies?

- Fail fast in Phase I
  - More information needed for early drug development decisions
- Clinical Pharmacology studies becoming more complex
  - Inclusion of patient cohorts
  - More biomarkers, more sampling
    - Sampling logistics challenges
  - Fusion and adaptive designs
  - More biologic drug candidates – immunogenicity
  - Earlier robust cardiac safety assessment
Bridging Strategy

Start design of CPoC study first

- What is “Proof”? Endpoints?
- What patients? How many?

How to get to CPoC?

- What can I do in healthy participants?
- Are biomarkers available?
- Develop novel biomarkers?
  - Biochemical assays
  - Imaging and imaging agents
  - MicroRNA panels
- Would microtracer studies be valuable?
- Can PK/PD modeling be applied?

What preclinical work is needed to support the early clinical program?
Bridging the Gap From Phase I to Clinical Proof-of-Concept

- Diabetic Drugs – an Example of Learning Early
  - Helmut Steinberg MD: Diabetes and Drug Development
  - Clayton Dehn MS: Techniques to uncover early signals of efficacy

- Cardiovascular Safety – Changing Requirements
  - Joy Olbertz PharmD PhD: Update on QTc Interval Assessments

- Patients Earlier in Clinical Research
  - Fred Pritchard PhD: Evolving Solutions
Questions?