Welcome to Celerion’s Dinner and Discussion Program
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Efficient Clinical Pharmacology Study Designs

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Research & Development (R&D) Process: PhRMA 2013 Profile

- **Pre-Discovery:**
  - Basic Research and Screening
  - 5,000 - 10,000 Compounds
  - 250 compounds
  - 5 compounds

- **Drug Discovery:**
  - IND Submitted

- **Preclinical:**
  - Phase 1: 20 - 100 volunteers
  - Phase 2: 100 - 500 volunteers
  - Phase 3: 1,000 - 5,000 volunteers

- **Clinical Trials:**
  - 3 - 6 years

- **FDA Review:**
  - Scale-Up to Manufacturing
  - Ongoing Research and Monitoring
  - INDEFINITE

- **One FDA-Approved Medicine**
New Drug And Biologics Approvals/R&D Spending

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Phase Transition Rates

Tufts CDSS 2014

Hays 2014

Clinical Phase Transition Probabilities and Overall Clinical Approval Success Rate*

Transition Probability

Phase I-II | Phase II-III | Phase III-NDA/BLA Sub | NDA/BLA Sub-NDA/BLA App | Phase I-NDA/BLA App
---|---|---|---|---
59.52% | 35.52% | 61.95% | 90.35% | 11.83%

*Therapeutic new molecular entities and new therapeutically significant biologic entities first tested in humans, 1995-2007

Phase success

- Phase 1 to phase 2
- Phase 2 to phase 3
- Phase 3 to NDA/BLA
- NDA/BLA to approval
- LOA from phase 1

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Attrition Rate of NME Due to PK/ADME

Nat. Rev. Drug Disc. 2004

NME: New Molecular Entity
PK: Pharmacokinetic
ADME: Absorption, Distribution, Metabolism & Excretion
Characteristics of an Efficient First-in-Human Study

- Establishes drug does not elicit acute, treatment-limiting adverse events
- Characterizes the ADME properties:
  - Peak exposure
  - Overall exposure
  - Half-life
- Identifies influences for future patient exposure
  - Effect of food for oral dosing
  - Site of administration for Subcutaneous (SC)
  - Timing of dose
- Minimizes time and cost to Proof-of-Concept (POC) step
Efficient First-in-Human Designs

- **SAD HS – 1st dose level**
- **SAD HS – 2nd dose level**
- **SAD HS – 3rd dose level**
- **SAD HS – 4th dose level**
- **SAD HS – 5th dose level**
- **MAD HS – 1st dose level**
- **MAD HS – 2nd dose level**
- **MAD HS – 3rd dose level**
- **MAD HS – 4th dose level**
- **MAD HS – 5th dose level**

Simulate exposure using non-compartmental or compartmental approach.

*SAD HS* = Single Ascending Dose – Healthy Subjects

*MAD HS* = Multiple Ascending Dose – Healthy Subjects
What Do We Know/Understand Regarding the Target Population?

CYP1A Substrate, will smokers receive drug in POC?

Will it be likely the POC population will be on conmeds known to perpetrate DDIs?

Indicated in obese patients? Is meal time important?

CYP: Cytochrome P450 Enzyme
POC: Proof-of-Concept
DDI: Drug-Drug Interaction
Integrate Intrinsic/Extrinsic Factors into SAD/MAD

- SAD HS – 1st dose level
- SAD HS – 2nd dose level
- SAD HS – 3rd dose level
- SAD HS – 4th dose level
- SAD HS – 5th dose level

- MAD HS – 1st dose level
- MAD HS – 2nd dose level
- MAD HS – 3rd dose level
- MAD HS – 4th dose level
- MAD HS – 5th dose level

- Patient population?

- Extrinsic factor (e.g. smoking, DDI)
- X-Over Food Effect
- Intrinsic factors (e.g. obese, elderly?)

Simulate exposure using non-compartmental or compartmental approach
Integrate Intensive Electrocardiographic (ECG) Monitoring for Early Cardiovascular Signal

Each Cohort

- ECG Extractions
- Single 24hr Holter monitoring session
- Three triplicate baseline timepoints
- 6-9 triplicate post-dose timepoints
- Proactively plan for extended supine periods
SAD Allows for Evaluation of Potentially Supra-Therapeutic Exposure

\[ \Delta \Delta QTcF \text{ (msec)} \]

\[ \text{Concentration (ng/ml)} \]

**QTcF:** Fridericia corrected QT interval  
**msec:** millisecond  
\( \Delta \): Greek letter ‘Delta’ represents change from baseline, change from placebo
Pros

- Low risk
- Allows for full evaluation of SAD Safety and Exposure prior to designing the MAD

Cons

- Longer duration due to not starting MAD until SAD complete
- Potentially higher cost associated with multiple protocols, CSRs, study start-up, IRB approval

CSR: Clinical Study Report
IRB: Institutional Review Board
Sequential SAD/MAD Under a Single Protocol with PK Pause Between Phases

Approx. No. Weeks From FPFV

0 1 2 3 4 8 9 10

MAD HS– 1st dose level
MAD HS– 2nd dose level
MAD HS– 3rd dose level
Interim PKPD Check To Finalize MAD Plan
SAD HS– 2nd dose level*
SAD HS– 3rd dose level*
SAD HS– 4th dose level*
SAD HS– 1st dose level*

FPFV: First-patient enrolled, first visit
Sequential SAD & MAD protocols with pause between Phases

Pros
- Cost/time savings due to single protocol, analysis plan, study start-up
- Single IRB approval
- Pause between SAD/MAD reduces risk/time/cost of amendments due to study changes based on SAD results (e.g. duration/frequency of dosing based on exposure data)

Cons
- Longer duration than overlapping SAD/MAD
- May require additional amendments relative to sequential discrete SAD/MAD protocols
Overlap SAD MAD with Transition After 3rd SAD Cohort

Approx. No. Weeks From FPFV

0 1 2 3 4 5 6 7 8

MAD HS– 3rd dose level
MAD HS– 2nd dose level
MAD HS– 1st dose level
SAD HS– 5th dose level*
SAD HS– 4th dose level*
SAD HS– 3rd dose level*
SAD HS– 2nd dose level*
SAD HS– 1st dose level*

+/− PK Pause of Interim
To amend MAD Plan
Overlap SAD MAD with Transition After 3rd SAD Cohort

**Pros**
- Cost/time savings due to single protocol, SAP, study start-up
- Single IRB approval
- Allows for faster transition to POC/special populations than sequential SAD/MAD
- Allows for continued exploration of single-dose evaluations while MAD on-going (intrinsic/extrinsic factor testing: elderly, obesity, smoking effects, food-effect)

**Cons**
- Risk is highest when little is known about exposure scaling and/or safety signals apparent in toxicology program
- Typically associated with protocol amendments (but can be mitigated by flexible/adaptive protocol construct
- Amendments may be needed for I/E, additional safety between SAD and MAD
- No true idea regarding MAD PK/Safety if transitioning without interim check
Lessons Learned: Combined SAD/MAD

- Combining is lowest risk when more is known about the NCE
  - PK/exposure well understood and consistent across species
    - If not, definitely recommend interim PK between SAD cohort or at least one pause prior to MAD
- Failure to write protocols adaptively/flexibly results in multiple amendments & additional IRB review
  - Delay in data delivery
  - Additional costs
- Failure to confirm PK prior to MAD
  - More cohorts dosed than necessary
  - Longer duration to POC than necessary
- Desire to combine too many unrelated objectives can delay important milestones and adds risk (e.g. addition of a DDI arm adds risk to a combined SAD/MAD when PK in absence of DDI unknown and safety issues arise)
Efficient Clinical Pharmacology Studies After FIH: Case Study

- Small molecule oncology drug being developed for several indications (including lung cancer)
- In-vitro/cell culture screening implicate CYP1A2 and CYP3A4 mediated metabolism
- IND comments from FDA specified to exclude patients on CYP 1A2 inhibitors (e.g. ciprofloxacin) & 3A4 inhibitors (e.g. clarithromycin, ketoconazole) or test before further patient studies
- Cardiac signal in dog CV study

....how can these objectives be addressed efficiently?

CYP: Cytochrome P450 Enzyme
CV: Cardiovascular
Study 1

- 2-period single-dose x-over in HS
  - Fasted
  - Fed
- Parallel group comparison to HS moderate-heavy cigarette smokers

Study 1: Food-effect + Effect of Smoking (CYP1A induction)

A: Fasted
B: Fed
C: Smoking group

X-over: Crossover Design
HS: Healthy Subjects
Study 2: Parallel Cohort, Fixed-Sequence DDI with Intensive ECG Monitoring

**Study 2**

- **2-distinct parallel cohorts**
  - Fixed-sequence test of itraconazole (strong CYP3A4 inhibitor)
  - Fixed-sequence test of ciprofloxacin (strong CYP1A2 inhibitor)
  - Intensive ECG monitoring on cipro arm to test effect of higher concentrations of substrate on $\Delta QTcF$

*SD: Single-dose  
MD: Multiple-dose  
DDI: Drug-Drug Interaction*
Multiple DDIs Integrated into a Single Cohort

- NCE being developed for CNS indication
- In-vitro testing and PBPK simulations suggests NCE is inhibitor of MATE-2 and OCT transporters
- NCE ~7 days to achieve steady-state
- Objective to test MATE-2 and OCT probe substrates in the same study at steady-state concentrations of NCE
Multiple DDIs, Single Cohort

Legend
Day 1: SD Metformin 500 mg, full PK profile
Day 4: SD Pramipexole 0.25 mg, full PK profile
Day 7-22: NC mg twice daily (last dose is PM dose)
Day 14: PK profile of NCE over AM dosing interval
Day 15: SD Pramipexole 0.25 mg, full PK profile in presence of NCE
Day 21: SD Metformin 500 mg, full PK profile in presence of NCE
Drug-Drug Interaction Studies: Combining Objectives and Panels Under a Single Protocol

2012-2014 at Celerion
Thank You!

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