Enriching Phase I Studies for Better Decision Making

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Overview of Presentation

- What is driving the need for innovation in early clinical research?
- What are considered “game-changing” applications of emerging technology?
- How can these enriching technologies help answer troubling problems encountered in Phase I research programs?
- What are some examples?
- Summary
Clinical Development is Evolving

Traditional Paradigm: Phased Approach

- Test each scarce molecule thoroughly
- Scarcity of molecules from discovery

Emerging Paradigm: POC / Conformation Approach

- Shift attrition earlier
- Abundance of molecules from discovery

Pre-Clinical → Phase I → Phase II → Phase IIb → Phase III

Importance of Proof-of-Concept Studies

Defines Product Value For the First Time

% Chance of Reaching Market

- Preclinical: 0.1-1
- FIH study: 5-10
- POC study: 10-30

Typical Costs ($million)

- IND tox study: 0.5 – 1.0
- FIH study: 0.7 – 1.4
- POC study: 2 - 20
The Pressure is On for Proof-of-Concept!

- Increase in novel new drugs from discovery research
- More difficult disease states to study and treat
- Greater regulatory expectations on clinical trials
- Need for more informed decisions at clinical proof-of-concept
- Increased cost of clinical research
- Regulatory acceptance of adaptive-like study designs
- Expanding universe of new technology applications

Innovation
What is a better decision?

- One made earlier
- With greater confidence
- More efficiently

Better data, faster, cheaper

Game Changing Innovation

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Game Changing Innovation
New Technology Drives Innovation

So Many New Tools in So Little Time

Genomics
Metabolomics
Proteomics
LC-MS/MS
AMS
MALDI/TOF
RIA
EMIT
ELISA
BiaCore
Flow Cytometry
Luminex
Digital Data Handling
PET
SPECT
EEG
ECG
PFT
Gamma Scintigraphy
MRI
CT
Troublesome Problems Encountered in Early Clinical Research

Positive or equivocal signals in preclinical cardiovascular safety assessment

Drugs with potentially poor absorption or unknown hepatic first-pass metabolism

Active metabolites, species-unique metabolites, or disproportionate human vs. tox species metabolite(s).

Establishing if drug gets to site of action

High definition digital ECG collection and analysis

Use of microtracers with Accelerator Mass Spectrometry

Efficacy/Mechanism biomarkers
Photograph of a complete electrocardiograph, showing the manner in which the electrodes are attached to the patient, in this case the hands and one foot being immersed in jars of salt solution.
Holter Monitor

- Developed for Mercury space program
- Evolved far beyond early devices
- Now continuous 12 lead ECG acquisition
- Most TQT studies in ECG Warehouse are collected using Holter monitors

1971 2011
## Comparing ECG Acquisition Modalities

<table>
<thead>
<tr>
<th></th>
<th>Stand alone 12 Lead</th>
<th>Standard Holter</th>
<th>Telemetry System</th>
<th>Blue-tooth Holter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous ECG Collection</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Retrospective data collection</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>View Safety ECG</td>
<td>Yes</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Data capture out of range</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Transportable</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>
The Hybrid Phase I/ECG Core Laboratory

- Phase I focus only
- Single vendor with unified functionality
- Single database
- Single PM, DM, stats

BLUETOOTH HOLTER

- Instant ECG review
- Computer generated date/time stamp
- Preconfigured demographics

HIGHLY AUTOMATED ECG PROCESSING

- Single device to acquire safety ECGs during Holter recording
- 1000 sample/second acquisition
- Up to 48 hours ECG collection

- Automated, optimized ECG extractions from Holter
- Normal ECGs measured automatically providing lower variability—better data

- Cardiologist only review approximately 10-20%
- Faster data turnaround
Digital ECG Reading Enables Overlay of Lead Signals for Better Accuracy in Measurement of Intervals
ECG Extraction: Artifacts Are a Problem
Antares Optimal ECG Extraction: Decreases Variability

Searching for best extraction, noise and HR stability criteria…

OPTIMUM WINDOW

Second extraction
Nominal Timepoint
Third extraction
Best ECG! First extraction

F Badilini, Vaglio, Sarapa, A.N.E 2009;14(Supp1):22-29
ECG Measurement Modalities

- Semi automated: standard process in most labs
  - aka “manually adjudicated”
  - Computer performs measurements
  - Every ECG confirmed by cardiologist

- Fully automated: “Black Box”
  - Machine read only
  - Consistent in normal ECG recordings
  - Recording characteristics can cause inaccurate measurements
  - Moxifloxacin produces abnormal ECGs

- Highly automated
  - Cardiologist reviews only questionable ECGs
  - Decreases variability
# Traditional vs. the Hybrid ECG Core Lab

<table>
<thead>
<tr>
<th>Traditional ECG Core Lab</th>
<th>Hybrid ECG Core Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two contracts (clinic+core lab)</td>
<td>One contract</td>
</tr>
<tr>
<td>Two study teams (clinic+core lab)</td>
<td>One study team</td>
</tr>
<tr>
<td>Large infrastructure supports late stage trials</td>
<td>Supports only Phase I clinics</td>
</tr>
<tr>
<td>Little to no Core lab visibility on clinic conduct</td>
<td>Direct visibility of clinic conduct</td>
</tr>
<tr>
<td>Cardiologist reviews all ECGs</td>
<td>Cardiologist reviews 10-20% of ECGs</td>
</tr>
<tr>
<td>ECG turnaround 4-6 weeks after LPLV</td>
<td>ECG turnaround 2 weeks after LPLV</td>
</tr>
</tbody>
</table>
Optimal client interactions

Data

- Better
- Faster
- Cheaper
  - ~50% decrease in ECG costs
Accelerator Mass Spectrometry

Measures isotope ratios – can detect ultra low levels of $^{14}$C radioactivity

Technology used in carbon dating of antiquities

First biological application in 1989

Applications in Pharmaceutical Research (since 1998)

Preclinical: Special bioanalysis (proteins, monoclonal antibodies, interfering RNA); Phase 0 (subtherapeutic dose) clinical studies

Early Clinical: MIST (Metabolism in Safety Testing) solution, metabolic profiling, absolute bioavailability

Clinical: Bioanalysis of high potency drugs
Isotopic Tracers: Determination of Absolute Bioavailability (F)

Oral dose

IV dose (labelled)

Blood samples over time

LC-MS measures total drug

Providing the $^{14}$C-drug concentration is very small this = oral dose

HPLC-AMS measures $^{14}$C-drug

This = IV dose

$F = \frac{AUC_{po}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{po}}$
Example: Fexofenadine

- Fexofenadine HCl is a histamine H1-receptor antagonist used to treat allergies
- It is a PgP and an OATP substrate
- Fexofenadine is not substantially metabolized
- It has been on the market for over 12 years
- Although fexofenadine is a well established drug, it has never previously been administered intravenously
Study Design

6 healthy male volunteers

Single oral dose 120 mg non-labelled fexofenadine

Simultaneous IV dose of 100 µg, 200 nCi $^{14}$C-fexofenadine

Plasma collected over 24 h

Plasma analysis
Total fexofenadine determined by HPLC-fluorescence
Total $^{14}$C determined by AMS
$^{14}$C-fexofenadine determined by HPLC and AMS

Acknowledgement:
This research study was funded by the European Commission grant number LSHG-CT-2005-018672
Mean data (errors bars are Std Dev)

Confirms fexofenadine undergoes very limited metabolism
Absolute Oral Bioavailability of Fexofenadine

Mean data (errors bars are Std Dev)

Results are dose normalized to 1mg

Mean oral absolute bioavailability 28%
# PK Parameters for Fexofenadine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Microtracer data (%CV, n= 6)</th>
<th>Literature data</th>
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</thead>
<tbody>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>10 (27)</td>
<td>14</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>17 (23)</td>
<td>4.2*</td>
</tr>
<tr>
<td>V (L)</td>
<td>245 (17)</td>
<td>85</td>
</tr>
<tr>
<td>F(%)</td>
<td>28 (26)</td>
<td>? 10*</td>
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</table>

* Minimum based on excretion of unchanged drug in urine
When AMS Provides Enriched Data?

Poor or variable bioavailability
- Is absolute bioavailability too low?
- Is it influenced by formulation?
- Role of gut absorption/metabolism vs. hepatic metabolism and efflux

Different metabolic profiles between species used in toxicology
- Which species reflect human metabolic profile qualitatively and quantitatively?

Exposure in tissues
- Cerebral spinal fluid (CSF) exposure for CNS-acting drugs?
- Systemic exposure for dermal, inhaled, optical, etc. drug delivery

High potency drugs
- Ultra-low concentration measurements
Human Biomarker: a measure of biochemical or physiological function, anatomical structure, genetic characteristics or pharmacological activity primarily used to identify or predict changes in the human body brought on by disease or therapy.

How will the biomarker(s) advance the drug’s development?
- Primary purpose of biomarkers is to enable better decisions.
Plethora of Biomarkers for Diabetes

- Glucose
- Fatty Acids
- C-Peptide
- TGs
- Glucagon
- Insulin
- HbA1c
- Adiponectin
- TCF7L2
- PPARγ (glitazones)
- KCNJ11

Gastric Emptying

- CRP
- TNF-α
- IL-6
- GIP
- GLP-1
- DPP4

IGF

IGFBP

OCT1 (metformin)

OCT2 (metformin)

Adiponectin

TNF-α

IL-6
SAD Study of a Novel DPP-4 Inhibitor in Mild Diabetic Patients

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Patients</th>
<th>Treatment Periods</th>
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<tr>
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<td>1</td>
<td>N = 5</td>
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<tr>
<td>2</td>
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<td>25 mg</td>
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<td>3</td>
<td>N = 5</td>
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<td>P’1</td>
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<td>4</td>
<td>N = 5</td>
<td>PLA</td>
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<tr>
<td>5</td>
<td>N = 5</td>
<td>50 mg</td>
</tr>
<tr>
<td>6</td>
<td>N = 5</td>
<td>50 mg</td>
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</tbody>
</table>
Results of SAD Study in Mild Diabetic Patients: 
Early Evidence of Efficacy

Drug Plasma Concentration

Percent DPP-IV Inhibition

GLP-1 Concentration

Good Activity

Glucose Concentration

F=4-8%

Lower limit of quantitation
Summary

- **Opportunities**
  - New technologies enrich early clinical pharmacology studies by providing better data, faster and cheaper.
  - Regulators are open to new and creative approaches

- **Challenges**
  - Technologies must be effectively deployed and properly validated
  - Study designs and logistics more complex
Q & A