Welcome to Celerion’s Dinner and Discussion Program
Tokyo, Japan
Apr 2, 2015
Fast to Patient: The Push For Earlier Signals of Efficacy in Clinical Research

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Vice President, Global Drug Development
Questions

- How is early clinical research changing?
- What are some challenges and strategies for engaging patients in early clinical studies?
- What are some challenges in conducting early clinical research studies in patients?
- Why is there increasing attention to Asia-Pacific region in early clinical research?
- What innovations are making early clinical research more efficient and effective?
Changing Paradigm

Traditional Paradigm: Phased Approach

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

Scarcity of molecules from discovery

Test each scarce molecule thoroughly

Emerging Paradigm: POC / Confirmation Approach

- Learn
- Decide
- Confirm

- Pre-Clinical
- Proof of Concept
- Confirmation

Abundance of molecules from discovery

Shift attrition earlier

Regional and Ethnic Differences

Translational Medicine

What’s Driving Evolution of New Paradigm?

**Clinical Proof-of-Concept is where a new drug acquires real value**

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

**Innovation**
Important “Proofs” in Early Clinical Research

- **Proof-of-Presence**
  - Does the drug get to its site of action?
  - Value Add: $

- **Proof-of-Mechanism**
  - Does the drug affect the biological target as it was designed?
  - Value Add: $$$

- **Proof-of-Concept**
  - Is there a sufficient signal that the drug favorably impacts the disease with acceptable risk of toxicity that would stimulate further investment in the drug?
  - Value Add: $$$$$
Early Signals of Clinical Safety and Efficacy are the Key to Applied Translational Medicine

To get an early sense that a drug is working in humans as it was designed, you need:

**Patients**
- Small number
- Stable disease
- Minimal confounding treatments
- Appropriately motivated

**Investigators / Clinical Trial Centers (CTCs)**
- Small number of sites
- Scientifically / medically robust
- Controlled study setting
- Follow global Good Clinical Practice (GCP) standards
- Ethical conduct
Access to Patient/Special Populations and Specialists

Special Populations
- Renal Impairment
- Hepatic Impairment
- Elderly
- Women
- Pediatric/Adolescent

Patient Populations
- Diabetes Mellitus
- Asthma
- Chronic Obstructive Pulmonary Disease (COPD)
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus (SLE)
- Psoriasis
- Alzheimer’s Disease
- Schizophrenia
- Depression
- Cancer
- Hypertension
- Hyperlipidaemia
- Infectious Diseases
The Challenge of Recruiting Patients to Early Clinical Studies

Disease Prevalence

Alternative Treatments

Benefit-Risk to the Patient

Otherwise Healthy Patient

- Usually no drug benefit
  - Not dosed long enough
  - Optimal dosing not established

- Risks to patient unknown

- Can negatively impact health insurance coverage for their disease

- Financial compensation
  - Sometimes allowed like HS studies

- Appeal to altruism

- Single disease

- Withdrawal from current treatment

- Number and type of co-medications

- Gender, age, race and ethnicity
Early Clinical Research Requires Resources Dedicated to Research
Complex sample collection schedules and processing procedures

**Example:** First-in-Patient study – 14 tests, 7 labs

- **Lab A**
  - LC-MS/MS assay
  - parent drug and metabolites
  - Freeze

- **Lab B**
  - Clinical chemistry
  - Add stabilizer

- **Lab C**
  - LC-MS/MS assay
  - pathophysiological substrate and product
  - Add stabilizer

- **Lab D**
  - Pharmacogenomic assay

- **Lab E**
  - Target enzyme assays

- **Lab F**
  - Stimulated cell assay

- **Lab G**
  - Future proteomics

- **Lab B**
  - Urinalysis
  - Freeze

WBCs: Whole Blood Cells
### A Perfect Scenario for Fast-to-Patient Strategy

- Single Ascending Dose (SAD) Study
- Novel Dipeptidyl Peptidase-4 (DPP4) Inhibitor in Mild Diabetic Patients
- No other drugs

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<thead>
<tr>
<th>Sequence</th>
<th>Patients</th>
<th>Treatment Periods</th>
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<td>P1</td>
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<tr>
<td>1</td>
<td>N = 5</td>
<td>PLA</td>
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<tr>
<td>2</td>
<td>N = 5</td>
<td>25 mg</td>
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<tr>
<td>3</td>
<td>N = 5</td>
<td>25 mg</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>
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<tr>
<td>6</td>
<td>N = 5</td>
<td>50 mg</td>
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</table>

**PLA:** Placebo
Results of SAD Study in Mild Diabetic Patients: Early Evidence of Efficacy

Drug Plasma Concentration

Percent DPP4 Inhibition

Glucagon-Like Peptide-1 Concentration

Glucose Concentration

F=4-8%

Good Activity

Lower limit of quantitation

Lower limit of quantitation

25 mg  
50 mg  
75 mg  
100 mg  
200 mg  
300 mg  
Placebo
Global Clinical Pharmacology Unit Networks

- Most patient needs in early clinical research cannot be met by a single center
- Increasing the number of sites has its own challenges
- Need to evolve similar partnering and alliance models among groups of clinical pharmacology units
  - Work to same quality standards (undergo common systems Quality Assurance audits)
  - Coordinate through a group which also brings in other study services as protocol preparation, bioanalysis, pharmacokinetics, data management and statistics, clinical study report preparation
## Examples of networks and therapeutic clusters

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Celerion Site</th>
<th>External Site Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes / Obesity</td>
<td>Phoenix, Lincoln</td>
<td>Supporting networks in North America, Europe, South Korea and Singapore</td>
</tr>
<tr>
<td>Respiratory and Inflammatory (asthma, COPD, cystic fibrosis)</td>
<td>Belfast</td>
<td>Strong network in UK and Germany (therapeutic cluster)</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Belfast, Phoenix</td>
<td>Strong network in UK and Germany (therapeutic cluster)</td>
</tr>
<tr>
<td>Cardiovascular (hypertension, hypercholesterolemia, hyperlipidemia, thrombosis)</td>
<td>Belfast, Phoenix</td>
<td>Strong networks in Europe and Korea (therapeutic cluster)</td>
</tr>
<tr>
<td>Oncology (blood, breast, colon, prostate, lung, pancreatic, ovarian, skin)</td>
<td></td>
<td>Strong networks in Korea (therapeutic cluster)</td>
</tr>
<tr>
<td>Renal or Hepatic Insufficiency</td>
<td></td>
<td>Strong network in US and Europe</td>
</tr>
</tbody>
</table>

**COPD**: Chronic Obstructive Pulmonary Disease
### Examples of networks and therapeutic clusters

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<tr>
<th>Patient Population</th>
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<th>External Site Network</th>
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</thead>
<tbody>
<tr>
<td>Rheumatoid Diseases (RA, OA, SLE)</td>
<td>Belfast</td>
<td>Strong networks in Korea and in Europe (therapeutic cluster)</td>
</tr>
<tr>
<td>CNS /Neurology (Alzheimer’s, schizophrenia, anxiety, depression, pain, Parkinson’s, convulsion)</td>
<td></td>
<td>Collaborative neuroscience network in US Good access in Europe and Korea</td>
</tr>
<tr>
<td>Infectious Disease (HIV, HCV, HSV, influenza, bacterial)</td>
<td></td>
<td>HCV – Europe and Korean sites (Asian phenotypes), Influenza/bacterial: access in Europe and Korea</td>
</tr>
</tbody>
</table>

**RA:** Rheumatoid Arthritis  
**OA:** Osteoarthritis  
**SLE:** Systemic Lupus Erythematosus  
**CNS:** Central Nervous System  
**HIV:** Human Immunodeficiency Virus  
**HCV:** Hepatitis C Virus  
**HSV:** Herpes Simplex Virus
The Importance of Asia-Pacific Region in Early Clinical Research
Growth in Asia in Biomedical R&D Spending

<table>
<thead>
<tr>
<th>Country</th>
<th>Compound Annual Growth Rate (%)</th>
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<tbody>
<tr>
<td>Canada</td>
<td>-2.6</td>
</tr>
<tr>
<td>United States</td>
<td>-1.9</td>
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<tr>
<td>Europe</td>
<td>-0.4</td>
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<tr>
<td>Taiwan</td>
<td>5.2</td>
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<tr>
<td>Japan</td>
<td>5.7</td>
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<tr>
<td>India</td>
<td>6.7</td>
</tr>
<tr>
<td>Australia</td>
<td>6.9</td>
</tr>
<tr>
<td>Singapore</td>
<td>10.0</td>
</tr>
<tr>
<td>South Korea</td>
<td>11.4</td>
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<tr>
<td>China</td>
<td>32.8</td>
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</tbody>
</table>


The compound annual growth rate was calculated on the basis of total inflation-adjusted biomedical R&D expenditures in U.S. dollars for 2007 and 2012.

J. Chakma et al. NEJM 370(1)3-6, 2014
Reasons for Performing Clinical Pharmacology Studies in Asia-Pacific Region

Market Drivers

1. Access to patients for early clinical assessment of safety, PK and signals of efficacy and dose response
2. Bridging PK and PK/PD studies to support registrations of drug products in Asian markets
3. Support First-in-Human assessments of drugs discovered and developed in Korea, Singapore, China, Japan and other Asian nations

Operational Factors

1. Modern, well equipped clinical trial centers at major medical centers with ready access to many patient populations
2. Some regulatory environments similar to North America and Europe
3. Well-trained scientific and medical staff that can communicate in English

Needs

1. Pharma companies need studies to support products for Asian markets
2. Asian clinical trial centers need access to global pharma study opportunities and best operating practices for running efficient operations

PK/PD: Pharmacokinetics / Pharmacodynamics
# Regulatory Environment in Five Asia/Pacific Countries

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>China</th>
<th>South Korea</th>
<th>Singapore</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory Review Time</strong></td>
<td>No queries – 30 days after CTN submission</td>
<td>11 Months</td>
<td>30-60 Days</td>
<td>15-30 Days</td>
<td>No approval for healthy subject studies</td>
</tr>
<tr>
<td><strong>Ethics / IRB Review Time</strong></td>
<td>Variable</td>
<td>60 Days</td>
<td>2-4 Weeks</td>
<td>1-4 Weeks</td>
<td>12-16 Weeks (patients)</td>
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<tr>
<td><strong>Parallel or Sequential</strong></td>
<td>Parallel</td>
<td>Sequential</td>
<td>Parallel</td>
<td>Parallel</td>
<td>Clinical Trial Notification acknowledged in days</td>
</tr>
<tr>
<td><strong>Clinical Trial Centers</strong></td>
<td>Hospital and CRO-owned</td>
<td>SFDA-accredited CTCs</td>
<td>15 Hospital-based CTCs</td>
<td>1 Pharma-owned and 3 Hospital CTCs</td>
<td>5 Academic hospital clinics</td>
</tr>
<tr>
<td><strong>Other Comments</strong></td>
<td>Government funding new CTCs</td>
<td>Difficult to ship samples out of China</td>
<td>MFDS built on US FDA model</td>
<td>Translational medicine focus</td>
<td>Less CMC and preclinical safety</td>
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**IRB:** Institutional Review Board  
**CTN:** Clinical Trials Notification  
**CMC:** Chemistry, Manufacturing and Controls
## Audit Results of 7 Asian CTCs
### 2013-2014

<table>
<thead>
<tr>
<th>Phase 1 CTC (facilities)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td><strong>Clinical Processing/Sample Management</strong></td>
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<td><strong>Study Set Up, Execution, Logistics</strong></td>
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<td><strong>PI Oversight</strong></td>
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<td><strong>IRB</strong></td>
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<td><strong>Pharmacy (including Security)</strong></td>
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<td><strong>Data Management</strong></td>
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<td><strong>Quality Control (inc. Documents)</strong></td>
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<tr>
<td><strong>Equipment (Calibration, Maintenance)</strong></td>
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<td><strong>Computer System Validation</strong></td>
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<td><strong>Information Technology</strong></td>
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<td><strong>Archives / Document Storage (Security)</strong></td>
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<td><strong>CTC Facility and Security</strong></td>
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<td><strong>BCP/DCP and Testing</strong></td>
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<tr>
<td><strong>Quality Systems (SOPs &amp; Policies)</strong></td>
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<td><strong>Controlled Document Process</strong></td>
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<td><strong>Quality Assurance (QA/QI)</strong></td>
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<td><strong>CAPA Process</strong></td>
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<td><strong>CTC Organizational Chart</strong></td>
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<td><strong>Staff Qualification Records (CVs, JDs)</strong></td>
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<td><strong>Staff Training and Records</strong></td>
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<td><strong>Vendor Management</strong></td>
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<td><strong>Regulatory Inspection History</strong></td>
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- Red: Inadequate or missing
- Yellow: Work needed to pass global audit
- Green: Some changes needed to pass global audit
- Light Green: Acceptable for global audit

**BCP/DCP**: Business Continuity Plan/ Data Continuity Plan  
**SOPs**: Standard Operating Procedures  
**CAPA Process**: Corrective and Preventive Action  
**CVs**: Curriculum Vitae  
**JDs**: Job Descriptions  
**PI**: Principal Investigator
Quality

- Most sites never had a full systems audit against global standards/expectations
- Variability across sites in areas of strength and weakness
- Strengths
  - Across all sites: Phase I CTC facility and Security, PI Oversight and IRB or Ethics Committee.
- Weaknesses:
  - Staff Qualification records (6 of 7 sites)
  - IT and Computer System Validation (4 of 7 sites),
  - QA (4 of 7 sites)
  - Vendor Management (4 of 7 sites)
  - Staff Training Records (4 of 7 sites)
  - Pharmacy (3 of 7 sites)
  - CAPA process (3 of 7 sites)
Innovations in Early Clinical Research

- New Biomarkers of drug action and effect
  - Imaging (SPECT, functional MRI/PET), microRNAs, tracking genetic changes in tumors or microbiome, digital high resolution EEGs and ECGs

- Patient Recruitment
  - Social media tools to recruit patients
  - Electronic patient records to quickly assess impact of inclusion and exclusion criteria on recruitment and suitability of patients for a study

- Data Acquisition
  - Digital capture of data – real-time review and monitoring for quality
  - Video for remote viewing of study conduct in real time
  - Tablets and smart phones to capture patient data
  - Electronic tracking to confirm study compliance

- Data Analysis
  - Data repositories that allow comparison across studies and advanced modelling to predict drug response in specific patient settings

SPECT: Single-Photon Emission Computed Tomography
Brief Answers to Questions

- How is early clinical research changing?
  - Focus on Clinical Proof-of-Concept – fail early

- What are some challenges and strategies for engaging patients in early clinical studies?
  - Regional differences, patient networks

- What are some challenges in conducting early clinical research studies in patients?
  - Access to biomarkers, specialty equipment and specialist researchers
  - Sample logistics

- Why is there increasing attention to Asia-Pacific region in early clinical research?
  - Access to patients, modern clinical trial centers, educated staff, rapidly emerging biotechnology industry, large market

- What innovations are making early clinical research more efficient and effective?
  - Digital communications, real-time acquisition and access to data, apply complex analysis and modeling, new biomarkers
Thank You!

ありがとうございます。