Ethnic Bridging in Phase 1 Clinical Trials:

A Strategy for Enhancing Asset Value and Accelerating Global Drug Development
Agenda

1 Drug Approval Lag in Japan
2 ICH E5 Overview
3 The Ethnic Bridging Paradigm
4 Trends Towards Global Clinical Trials
5 Bridging Trial Acceleration Strategies
6 Summary
Drug Approval Lag in Japan

Lag in 1999

The “Doxil” example

Approved in 75 countries since 1999
Approved in Japan in 2009

Similar examples cited for both new indications as well as 1st approvals
- Both drugs developed in Japan and those developed in other countries
- Viewed as a major public health issue

2004 data for NME launches:

Japan 3.8 Years  U.S 1.3 Years
Drug Approval Lag in Japan

Lag in 1999

The Possible Reasons cited:

- Sluggish drug innovation
  - Rx health insurance reimbursement – lengthy review
  - Prices lowered biennially
  - Created pressure to develop low risk drugs in order to realize the profits with the least upfront investment
    - Immature entrepreneurial environment

Suboptimal environments:

- For clinical trials
  - Expensive (4Xs the cost in EU or US!)
  - Lack of seasoned PIs
- Drug approval process
  - Navigating the system was difficult (language and cultural issues)
    - Accreditation as a foreign manufacturer
    - Marketing approval under the Pharmaceutical Affairs Law
    - All forms in Japanese
    - PMDA Understaffed
Drug Approval Lag in Japan

Lag in 1999

The Plan

Modify Drug Pricing System

- Certain Rxs under patents exempted from biennial price reduction

MHLW identified

- 109 Rxs to receive prompt reimbursement decisions
- 91 NCEs requiring expedited development by Pharma
- 200 Japanese Institutions to prescribe “unlisted” drugs in order to meet identified unmet medical needs

MHLW supported ICH E-5 and Urged Japanese participation in Global Development Programs
# Drug Approval Lag in Japan

**Relative to US FDA**

<table>
<thead>
<tr>
<th>Drug Lag</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-application</td>
<td>1.2</td>
<td>2.4</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Review</td>
<td>1.2</td>
<td>1.0</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2.4</strong></td>
<td><strong>3.4</strong></td>
<td><strong>2.2</strong></td>
<td><strong>2.0</strong></td>
</tr>
</tbody>
</table>

**Pre-application lag**:  
Median years of difference between USA/Japan application for each product

**Post-application Review lag**:  
Median years of difference between review time (USA/Japan) application for each product approved in Japan
Drug Approval Lag in Japan
Official acceptance of GCT in Japan

September 28, 2007
Notification No. 0928010

Attention to:
Commissioner of Prefectural Health Supervising Department

From Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau Ministry of Health, Labour and Welfare

Basic principles on Global Clinical Trials
Up to the present according to “Ethnic Factors in the Acceptability of Foreign Clinical Data” based on ICJ-E5 guideline (Notification. No. 763, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998), utilizing foreign clinical trial data in a new drug application what is called “Bridging” has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a review for regulatory approval where necessary.

Drug Approval Lag in Japan

The Traditional Development Approach

**U.S.**
- IND in the U.S.
- First in Human
- SAD
- MAD
- Phase II
- Phase III
- NDA in the U.S.

**Japan**
- IND in Japan
- First in Human
- SAD
- MAD
- Phase II
- Phase III
- NDA in Japan
Impact of “ethnic factors” on the acceptability of foreign data

- Minimize duplication of clinical data
- Bridging requirements for extrapolation of FCD to new region
- Enhance global development
ICH E5 Overview

Extrapolation/Bridging Requirements

1. Complete Clinical Data package
2. Adequate Characterization of:
   - PK/PD
   - Efficacy and Safety
   - Dose-Response
   - Clinical Disorders evaluated using medical & diagnostic definitions acceptable in the region
3. Determine the requirement of the “Bridging Study”
ICH E5 Overview

“Ethnic” Considerations

Assess product’s sensitivity to “ethnic” factors

- PK, PD → safety, tolerance, efficacy or dose-response
  - Extrinsic (food, climate) culturally or behaviorally determined
  - Intrinsic factors (genetics) greater impact on ability to extrapolate
# ICH E5 Overview

## Ethnic Factors

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Extrinsic</th>
</tr>
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<tbody>
<tr>
<td>Genetic</td>
<td>Physiologic/Pathologic Condition</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Hepatic Function</td>
<td></td>
</tr>
<tr>
<td>Renal Function</td>
<td></td>
</tr>
<tr>
<td>C/V Status</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>ADME</td>
<td></td>
</tr>
<tr>
<td>Receptor sensitivity</td>
<td></td>
</tr>
<tr>
<td>Polymorphic Drug Metabolism</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic Diseases</td>
<td>Disease</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ICH E5 Overview

Specific Drug Properties

- Linear or Nonlinear PK
- Concentration – Effect Curve
- Therapeutic Margin
- Metabolism
  - Polymorphic?
  - Extensive?
- Pro-drug requiring rapid conversion?
- Protein Binding
- Need for co-medications
- Likelihood for inappropriate use
# The Ethnic Bridging Paradigm

## Types of Bridging Studies

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Ethnicity of Region</th>
<th>Medical Practice</th>
<th>Drug Class</th>
<th>Clinical Experience</th>
<th>Bridging Studies?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnically Insensitive</td>
<td>Similar</td>
<td>Similar</td>
<td></td>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>Ethnically Sensitive</td>
<td>Similar</td>
<td>Similar</td>
<td>Sufficient</td>
<td></td>
<td>NO</td>
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<tr>
<td>Ethnically Sensitive</td>
<td>Dissimilar</td>
<td>Similar</td>
<td>Familiar</td>
<td></td>
<td>PD</td>
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<tr>
<td>Doubts about choice of dose</td>
<td>Different</td>
<td>Unfamiliar</td>
<td>Insufficient</td>
<td></td>
<td>CCT</td>
</tr>
</tbody>
</table>
The Ethnic Bridging Paradigm

Management of Development Strategies based on PK-profile

Comparison of PK between Japanese and Caucasian

- Major Difference
- No Major Difference

PK comparison among East-Asian population

- Major Difference
- No Major Difference

Local study in Japan

Regional study in East Asia

Collaboration study in Japan/US/EU

World wide collaboration

Source: Y. Uyama, DIA 7th Annual Conference in Japan for Asian New Drug Development, Tokyo, April 2013
Global Clinical Development

Key Benefits

- Prevention of unnecessary duplication of clinical trials
- Efficient and cost-effective drug development
- Solving the “drug lag” issue with global simultaneous drug development
Trends Towards Global Clinical Development

Development Strategy for Drug Approvals in Japan

Source: Y. Uyama, DIA 7th Annual Conference in Japan for Asian New Drug Development, Tokyo, April 2013
Trends Towards Global Clinical Development

Move toward resolution of Drug Lag

Source: MHLW/PMDA Seminar [data from MHLW], Tokyo, Dec 2012
## Trends Towards Global Clinical Development

### The Potential of Simultaneous Review in EU, US and JP

#### Standard Review

<table>
<thead>
<tr>
<th>Review Period</th>
<th>1</th>
<th>2</th>
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<th>4</th>
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<th>6</th>
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<th>10</th>
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<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
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<tr>
<td><strong>EU</strong> MAA</td>
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<td>D120</td>
<td>D180</td>
<td>D210</td>
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<td></td>
<td><strong>EC decision</strong> 13-15M</td>
<td></td>
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<tr>
<td>(Centralized Procedure for NCE)</td>
<td></td>
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<tr>
<td><strong>US</strong> NDA</td>
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<td></td>
<td></td>
<td><strong>Review by CDER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>JP</strong> NDA</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td><strong>Review by PMDA</strong></td>
<td><strong>12M</strong></td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td><strong>ER</strong></td>
<td>DC</td>
<td>PAC</td>
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</tbody>
</table>

OE: Oral Explanation, AC: Advisory Committee meeting, M: MENDAN meeting, ER: meeting, DC: Drug Committee meeting, PAC: Pharmaceutical Affairs Council meeting
Trends Towards Global Clinical Development

“Basic requirements for Global Clinical Trials”

Concerns about launching a Global Clinical Trial

- What are the basic requirements to conduct a Global Clinical Trial?
- What are the basic points to consider in designing a Global Clinical Trial? What is an acceptable sample size and proportion of
- Japanese/ Asian subjects?
- Management of concomitant medications or therapies in a GCT

No guidance for Global Clinical Trials in Japan  
Utilize PMDA consultation*

*PMDA consultation is not essential in development process
Trends Towards Global Clinical Development

“Basic principle on Global clinical trials ?”

PMDA consultation is potential opportunity

• To get advise from PMDA officially
• To make a “binding” agreement with PMDA prior to GCT

However....

• PMDA consultation is NOT free (approx. 30000-60000USD in each consultation)
• Official request of PMDA consultation "shall be made no later than 2 months prior to meeting" [Not easy]
Trends Towards Global Clinical Development

Asian Global Clinical Trials

Based Clinical Trials in Japan as of Dec 2012

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Indication</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine</td>
<td>Overactive bladder with symptoms of urge urinary incontinence, urgency and frequency</td>
<td>Apr. 2006</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>Diabetes mellitus</td>
<td>Apr. 2009</td>
</tr>
<tr>
<td>Peramivir</td>
<td>Type A and Type B Influenza virus infection</td>
<td>Jan. 2010</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Advanced renal cell carcinoma</td>
<td>Jul. 2010</td>
</tr>
<tr>
<td>Laninamivir</td>
<td>Type A and Type B Influenza virus infection</td>
<td>Sep. 2010</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Prevention of venous thromboembolism after major orthopedic surgery</td>
<td>Apr. 2011</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema</td>
<td>Jul. 2011</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR-positive unresectable or metastatic non-small cell lung cancer (NSCLC)</td>
<td>Nov. 2011</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Manic episodes associated with bipolar disorder</td>
<td>Jan. 2012</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Type II diabetes mellitus (adjunctive to diet, exercise and treatment with SU)</td>
<td>Mar. 2012</td>
</tr>
<tr>
<td>Esomeprazol</td>
<td>Risk reduction of low-dose aspirin-induced gastric or duodenal ulcer</td>
<td>Jun. 2012</td>
</tr>
<tr>
<td>Stratera</td>
<td>Attention-Deficit/ Hyperactivity Disorder in adulthood</td>
<td>Aug. 2012</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>Diabetes mellitus</td>
<td>Sep. 2012</td>
</tr>
<tr>
<td>Insulin degludec/ Insulin aspart</td>
<td>Diabetes mellitus</td>
<td>Dec. 2012</td>
</tr>
</tbody>
</table>

Source: Y. Uyama, DIA 7th Annual Conference in Japan for Asian New Drug Development
### Trends Towards Global Clinical Development

#### GCT Impact on Japanese Drug Lag

<table>
<thead>
<tr>
<th>Drug</th>
<th>Japan</th>
<th>US</th>
<th>Lag (month)</th>
<th>EU</th>
<th>Lag (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>2002.7</td>
<td>2003.5</td>
<td>-10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trastuzumab (Adji, Breast cancer)</td>
<td>2009.1</td>
<td>2006.11</td>
<td>15</td>
<td>2006.5</td>
<td>21</td>
</tr>
<tr>
<td>Everolimus (RCC)</td>
<td>2010.1</td>
<td>2009.3</td>
<td>10</td>
<td>2009.8</td>
<td>5</td>
</tr>
<tr>
<td>Panitumumab (2nd line)</td>
<td>2010.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>2010.7</td>
<td>2007.5</td>
<td>39</td>
<td>2007.11</td>
<td>33</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>2010.12</td>
<td>2010.6</td>
<td>6</td>
<td>2010.12</td>
<td>0</td>
</tr>
<tr>
<td>Trastuzumab (Gastric cancer)</td>
<td>2011.3</td>
<td>2010.10</td>
<td>5</td>
<td>2010.1</td>
<td>14</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>2011.6</td>
<td>2010.10</td>
<td>8</td>
<td>2010.12</td>
<td>6</td>
</tr>
<tr>
<td>Fefitinib (EGFR mut+)</td>
<td>2011.11</td>
<td>-</td>
<td>-</td>
<td>2009.6</td>
<td>0*</td>
</tr>
<tr>
<td>Everolimus (pNET)</td>
<td>2011.12</td>
<td>2011.5</td>
<td>7</td>
<td>2011.8</td>
<td>4</td>
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<tr>
<td>Denosumab</td>
<td>2012.1</td>
<td>2010.11</td>
<td>15</td>
<td>2011.5</td>
<td>8</td>
</tr>
</tbody>
</table>
# Trends Towards Global Clinical Development

## Japanese Sample Size in GCTs

<table>
<thead>
<tr>
<th>Drug Description</th>
<th>Total</th>
<th>Japan</th>
<th>Japan/ Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>210</td>
<td>102</td>
<td>48.6</td>
</tr>
<tr>
<td>Trastuzumab (Adji, Breast cancer)</td>
<td>5090</td>
<td>138</td>
<td>2.7</td>
</tr>
<tr>
<td>Everolimus (RCC)</td>
<td>416</td>
<td>24</td>
<td>5.8</td>
</tr>
<tr>
<td>Panitumumab (2nd line)</td>
<td>1186</td>
<td>20</td>
<td>1.7</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>82</td>
<td>20</td>
<td>24.4</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>846</td>
<td>79</td>
<td>9.3</td>
</tr>
<tr>
<td>Trastuzumab (Gastric cancer)</td>
<td>584</td>
<td>101</td>
<td>17.3</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>519</td>
<td>49</td>
<td>9.4</td>
</tr>
<tr>
<td>Gefitinib (EGFR mut+)</td>
<td>1,217 (233)</td>
<td>261 (56)</td>
<td>21.4 (24.0)</td>
</tr>
<tr>
<td>Everolimus (pNET)</td>
<td>410</td>
<td>40</td>
<td>9.8</td>
</tr>
<tr>
<td>Denosumab (Breast Cancer)</td>
<td>2046</td>
<td>136</td>
<td>6.6</td>
</tr>
</tbody>
</table>
Trends Towards Global Clinical Development

Drug Safety: Everolimus & Temsirolimus

Ethnic Difference?

Indication: Unresectable or metastatic renal cell carcinoma

Incidence rate of Interstitial Lung Disease (ILD)

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Trmsirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Japan</strong></td>
<td>26.7% (4/15)</td>
<td>55.0% (11/20)</td>
</tr>
<tr>
<td><strong>Overseas</strong></td>
<td>12.7% (33/259)</td>
<td>55.2% (16/29)</td>
</tr>
<tr>
<td><strong>Korea</strong></td>
<td>64.3% (18/28)</td>
<td>58.4% (45/77)</td>
</tr>
<tr>
<td><strong>US &amp; EU</strong></td>
<td>29.2% (52/178)</td>
<td></td>
</tr>
</tbody>
</table>
Bridging Trial Acceleration Strategies

Accelerating Japanese Drug Development

**U.S.**
- IND in the U.S.
- First in Human
  - SAD
  - MAD
  - Japanese Bridging
  - Phase IIa
  - Phase III
  - NDA in the U.S.

**Japan**
- First in Human
  - SAD
  - MAD
  - Skip Phase I Studies in Japan
  - Phase IIa
  - Phase III
  - NDA in Japan

**Strategies**
1. Cost down
2. Shorten timeline to NDA
Bridging Trial Acceleration Strategies
Enhanced Design Concept

- Comparative Safety & Tolerance and PK/PD across doses and ethnic groups
- Food Effect

EGs
- Korean
- Chinese
- Japanese
- Philippine
- Asian Indian

Patient Cohorts may be utilized
Bridging Trial Acceleration Strategies
Asian Bridging Concept to FIM

DL-1
• EG-1
• EG-2

DL-1
• EG-1
• EG-2

DL-1
• “EG-1”
• EG-2

PK-PD signal?

NO
• Initiate MD- S, T, PK-PD Study.
• Include same EGs
• Plan for GCT

Yes
• Initiate MD- S, T, PK-PD Study.
• Include same EGs as staggered dose groups?
• Increase “n”
• Plan for GCT but consider regional development

FIM - Rising Single Dose
• Safety, Tolerance, PK
• PK-PD (biomarker)
  ✓ PopPK across EGs
• Asian Bridging
**Bridging Trial Acceleration Strategies**

**Simultaneous Global Drug Development**

**U.S.**
- IND in the U.S.
  - FIH
  - SAD
  - MAD
  - Chinese/Japanese/Korean Bridging Study
  - Phase II
    - In US or global

**Japan, Korea, Taiwan**
- Skip Phase I Studies in Japan, Korea, and Taiwan
  - (1) Cost down
  - (2) Shorten timeline to NDA in Japan, Korea and Taiwan
- Japanese PMDA accepts a NDA as long as approximately 15% of entire patient population in the global study is Asian (Chinese, Japanese, Korean, and Taiwanese).
- IND in Japan, Korea, and Taiwan
  - Phase II
    - In Japan, Korea, and Taiwan
      - Or Global
  - Global Phase III
    - (1) include Chinese, Japanese, Korean, and Taiwanese patients in the strategy

**China**
- Include Chinese NDA in your global strategy without delay
  - (After negotiation with SFDA, it is possible to concurrently conduct a required Chinese Phase I and Global Phase III study in China)
- IND in Japan, Korea, and Taiwan
  - Phase I in China

**NDA in the U.S. & Europe**
- NDA in Japan
- NDA in Korea
- NDA in Taiwan
- NDA in China
Trial Design Strategies to support GCT – Case 1

Ethnic Bridging Case Study #1: Multiple Ethnicities

45 Han Chinese, Japanese, and Caucasian subjects (135 total).
Quick recruitment hastened timelines for completion at a 100% rate

- **Screening Duration**: 35 Days
- **Enrollment Duration**: 17 Days

<table>
<thead>
<tr>
<th>Cohort #</th>
<th>Day 1-7</th>
<th>Day 8-14</th>
<th>Arm 1 (Check-in 16Apr)</th>
<th>Arm 2 (Check-in 03May)</th>
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<tbody>
<tr>
<td></td>
<td>Dose A</td>
<td>Dose A + B</td>
<td>Cauc.</td>
<td>JP</td>
</tr>
<tr>
<td>Cohort 1</td>
<td>Dose A</td>
<td>Dose A + B</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>Dose C</td>
<td>Dose C + D</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>Dose E</td>
<td>Dose E + F</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>Dose G</td>
<td>Dose G + H</td>
<td>5</td>
<td>5</td>
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<td>Dose I + J</td>
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Trial Design Strategies to Support GCT – Case 2

Ethnic Bridging Case Study #2: Ophthalmology Ethnic Bridging

- Ethnic Bridging study with Ocular Assessments
- Completed recruitment of 30 Japanese in a single cohort
- Achieved a 100% completion rate by efficiently locating subsets of Asian patients, ensuring compliance, and narrowing eligibility prior to full screening

Study Design features:

**Screening:** Day -21 to Day -2

**Confinement:** Day -1 to Day 6

**Out-Patient Visit Days (4):** Day 7, Day 8, Day 16, and Day 35

<table>
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<tr>
<th></th>
<th>Start Screen</th>
<th>FSFD</th>
<th>End Screen</th>
<th>LSFD</th>
<th>Total Screening Duration</th>
<th>Subjects Randomized</th>
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<td>FSFD</td>
<td>4/21/2018</td>
<td>LSFD</td>
<td>17 Days (13 actual screening days)</td>
<td>2 Cohorts of 15 planned; Completed in 1 Cohort of 30</td>
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<td>LSFD</td>
<td>4/21/2018</td>
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<tr>
<td><strong>Total Screening Duration</strong></td>
<td>17 Days (13 actual screening days)</td>
<td></td>
<td>2 Cohorts of 15 planned; Completed in 1 Cohort of 30</td>
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<td><strong>Subjects Screened</strong></td>
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<td>Enrollment Duration (FSFD to LSFD)</td>
<td>1 Day; 1 Cohort</td>
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<td><strong>Enrollment Duration</strong></td>
<td>(FSFD to LSFD)</td>
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Trial Design Strategies to Support GCT – Case 3

Multiple Studies to support a Large Global Sponsor

- 22 completed Japanese bridging trials (16 NCEs) over the past 5 years.
- 9 compounds received PMDA approval, to date.
- 2 compounds are currently in Phase 2 development in Japan.
- 5 await sponsor or regulatory action.
Summary

- Increasing Number of Global Clinical Trials
- Industry would feel more comfort if “guidance document” were available
- In recent years, Global Clinical Trials have become quite diversified
  - multi-regional clinical trials among East-Asia
  - More early phase, More large-scale
- Operational and regulatory hurdles are almost overcome, but document translation remains an issue
Mel Affrime, PharmD
President & Chief Scientific Officer