Early Global Development from Sponsor’s Point of View

Clinical Research, Pfizer Japan Inc.
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Objective

To discuss points to consider for Japan to join G-FIH (Global First-In-Human) study with Western countries, which will be a base for future global Ph2 and Ph3 development plans.
Agenda

- Strength and Weakness of Japan
- Eligible Study Site for FIH Study
  - Performance
  - Ability of study sites
  - Ability of investigators/staff
  - Extra values
    - Non-clinical work
    - Investigator Initiated Trials (IITs)
- Regulatory Challenges
- Summary
## Strength of Japan

The number of published articles indicate strength in certain DAs

<table>
<thead>
<tr>
<th>Disease Areas</th>
<th>Japan</th>
<th>China</th>
<th>Korea</th>
<th>India</th>
<th>US</th>
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<tbody>
<tr>
<td>Oncology</td>
<td>62</td>
<td>6</td>
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<td>1,446</td>
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<tr>
<td>A&amp;R (Allergy &amp; Respiratory)</td>
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<td>3</td>
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<tr>
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<td>339</td>
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<td>9</td>
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<td>Vaccine</td>
<td>25</td>
<td>11</td>
<td>2</td>
<td>1</td>
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</tbody>
</table>

1. Papers published in either Nature or Science
   Cumulated results from 2005 to 2010 (as of Nov 18, 2010)
Many Japanese researchers are collaborating with global researchers

Japan is a key global player in basic research
Weakness of Japan

Cancer basic research
- Molecular biology
- Cellular biology
- Genome science
- Therapeutics and engineering
- Social science
- Epidemiology

Cancer TR
- Pre-clinical TR
- Clinical TR
- Reverse TR

Cancer clinical research
- Exploratory treatment
- Clinical trial
- Investigator Initiated Trial
  (using unapproved drug)
- Standardization of medicine
- Long term study
- Analysis of side effect
- Personal medicine
- Research of predictor/responsive marker

Establishment of next generation therapy

がん研究の現状と今後のあり方について
（平成22年6月25、ライフサイエンス委員会、がん研究戦略作業部会）改変

10th Anti-Tumor Drug Development Forum, Feb 19th, 2011
Lack of experience in G-FIH study and IITs, coming from / resulting in few TR activities

Japan is not yet a key global player in TR and clinical research
Eligible Study Site for FIH Study (1)

- **Performance**
  - Enrollment speed in various tumor types
    - Constant enrollment throughout the study period
  - CRF data entry (especially AE)

- **Ability of study sites**
  - Handling unexpected AEs (dermatology, cardiology etc)
  - Imaging technology, tissue sampling etc.
  - Acceptance of innovative/flexible study design

- **Ability of investigators/staff**
  - Deep discussion with W-investigators in English
  - In depth knowledge of target molecule
## Enrollment Speed
### -Number of Patients/site in Global Studies-

<table>
<thead>
<tr>
<th>Country</th>
<th>Rank for Enroll</th>
<th>Pts/Site</th>
<th>Rank of Pts/Site</th>
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</thead>
<tbody>
<tr>
<td>US</td>
<td>1</td>
<td>3.2</td>
<td>25</td>
</tr>
<tr>
<td>Japan</td>
<td>2</td>
<td>4.9</td>
<td>13</td>
</tr>
<tr>
<td>Korea</td>
<td>3</td>
<td>9.4</td>
<td>4</td>
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</table>

Source: Pfizer Japan data

(No. of studies = 13)
Enrollment in Japan is competitive in Ph2/3

For FIH study…
Can we enroll various types of tumors?
Can we constantly enroll patients throughout the study period?

Establish a network with affiliate sites
Speed of Data Entry: AE Module
-Median Number of Days in Global Studies-

Data Entry Speed Median (days)

Country

0_All  JAPAN  CHINA  KOREA  HONG KONG  TAIWAN  UNITED STATES

(No. of studies = 13)

Source: Pfizer Japan data
Speed of Data Entry: AE Module
-Median Number of Days and Number of AEs in a Global Ph1-

Country (# of subject)

JAPAN (8)  KOREA (14)

Data Entry Speed (Day)

0  5  10  15  20  25  30  35  40

The number of AEs

0  50  100  150  200  250  300  350  400  450  500

(No. of studies = 1)

Source: Pfizer Japan data

10th Anti-Tumor Drug Development Forum, Feb 19th, 2011
Why Prompt Data Entry is Important?

ALCOA Standard

- Accurate: 正確であること
- Legible: 判読可能であること
- Contemporaneous: 同時であること
- Original: オリジナルであること
- Attributable: 属性を持つこと, 起因性（誰が記載したか, audit trail）

http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.PDF
Data entry, record, and update must happen at the same time.
Data should be recorded once it is generated in order to maintain high quality.
Eligible Study Site for FIH study (2)

- **Performance**
  - Enrollment speed in various tumor types
    - Constant enrollment throughout study period
  - CRF data entry (especially AE)

- **Ability of study sites**
  - Handling of unexpected AEs (dermatology, cardiology etc)
  - Imaging technology, tissue sampling etc.
  - Acceptance of innovative/flexible study design

- **Ability of investigators/staff**
  - Deep discussion with W-investigators in English
  - In depth knowledge of target molecule
If these eligibility criteria are met, Japan can become a player in global studies.

Sites with extra values are selected.
Extra Values: Proactive research

• Proactive involvement in optional tumor sampling and diagnosis assessment (IHC, gene expression profile, etc)

• Conduct of additional non-clinical pharmacology studies for other potential indications and/or treatment concepts
Establish collaborations among clinical site, non-clinical Sites, and Sponsor

Clinical study sites

Science from Japan/Asia

Sponsor

Academia Basic research sites (non-clinical site)
Extra Values: Investigator Initiated Trials (IITs)

- Overseas, IITs are conducted after FIH or POM
- In Japan, examples of IITs using new agents are limited
  - Difficult to get an agreement on IITs from global company
    - Hard for global company (HQ) to understand Japan insurance system and clinical research system
  - Little knowledge of study sites capable of conducting IITs with new agents under ICH-GCP
• Study sites should establish a system for IITs
• PMDA/MHLW and sites should appeal their ability/acceptability of conducting IITs
Regulatory Challenges

Current situation

- Few examples of G-FIH study with Western countries in Japan due to concern on ethnic differences
  - Korea can join G-FIH study with any country
- Data on recommended dose in Japanese is required
  - Concern on safety in Japanese population
- Separate J-IND/Protocol is required when core protocol elements are amended
  - Study objective, design, target population, etc. are frequently modified based on emerging clinical data
Sponsor, study sites, and PMDA should work together for Japan to join G-FIH study
Summary

• Strength and weakness of Japan
  – Japan is a key global player in basic research, but not yet in TR and clinical research

• Eligible study site for FIH study
  – Improvement in performance and ability of study sites/investigators/staff is required to be selected for FIH study site

• Extra values such as non-clinical work and IITs
  – Proactive involvement in optional tumor sampling and diagnosis assessment (IHC, gene expression profile, etc)
  – Conduct of additional non-clinical pharmacology studies for other potential indications and/or treatment concepts
  – Investigator Initiated Trials

• Regulatory challenges
  – Sponsor, study sites, and PMDA should work together for Japan to join G-FIH study
Thank you for your attention!
ご静聴ありがとうございました。
Quality of Data Entry
-Number of Queries in Global Studies-

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(No. of studies = 13)

Source: Pfizer Japan data
Improvement in Perception of Clinical Trials

- **Education of patients**
  - Understand difference between research and treatment
  - Balanced expectation on efficacy and safety
    - In some cases, single agents may not show efficacy

- **Fair message on clinical research from media**