Drug development and evaluation with small clinical Trials from the regulatory point of view

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Outline of the presentation

- Small clinical trials in drug development
- Cases from approved drugs in Japan
- Efforts for Early Approval of Orphan Medicine in the PMDA
- Conclusion
What is Small Clinical Trials?

➤ When the clinical context does not provide a sufficient number of research participants for a trial with adequate statistical power but the research question has great clinical significance, research can still proceed under certain condition.

Small Clinical Trials Issues and Challenges(2001)
What is Small Clinical Trials?

Small Clinical Trials might be warranted for the study of

- Rare diseases
  - Orphan diseases
- Individually tailored therapies
  - Subpopulation of diseases, e.g. specific genetic mutation
- Unique study populations
  - Pediatric diseases
Orphan Drug Development in Japan

As of March 2013

Designated  Approved  In development  Revoked

<table>
<thead>
<tr>
<th>Year</th>
<th>Designated</th>
<th>Approved</th>
<th>In development</th>
<th>Revoked</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>11</td>
<td>8</td>
<td>2</td>
<td>1</td>
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<tr>
<td>2005</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2006</td>
<td>17</td>
<td>13</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2008</td>
<td>16</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>2009</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2010</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>2011</td>
<td>18</td>
<td>9</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>2012</td>
<td>28</td>
<td>0</td>
<td>28</td>
<td>0</td>
</tr>
</tbody>
</table>
Drug development with CoDx in Japan

☑ Point to consider
  – PFSB/ELD Notification No. 0701-10 July 1, 2013

☑ Approved drug
  – Mogamulizumab (POTELIGEO®)
    • CCR4 (C-C chemokine receptor 4)
    • Adult T-cell leukemia
  – Crizotinib (XALKORI®)
    • ALK (anaplastic lymphoma kinase) fusion gene
    • non-small cell lung carcinoma
Analysis of NDA data of approved medicinal products

Number
- Total number of approval including modification
- Number of pediatric approval

year
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012

Number
Points to consider for reviewers in PMDA

- Released in 2008
- In general, more than two RCTs were required for the security of the reliability
- In the area of orphan diseases or severe conditions without therapeutic tools, review should be performed with flexibility

http://www.pmda.go.jp/topics/file/h200417kohyo.pdf
Multiple Sclerosis

- Central nervous system affected
- Inflammatory disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged.
- Rare diseases in Japan, 8-9/100,000
- No curable treatment
Multiple Sclerosis

Atlas: multiple sclerosis resources in the world 2008
Multiple sclerosis international federation/WHO
http://www.msif.org/
Multiple Sclerosis

- **Fingolimod** (Imusera®/Gilenya®)
  - Designated to Orphan drug in 2007
    - (19yaku) No. 203
  - Approved in 2011
  - Sphingosine 1-phosphate receptor modulator, which sequesters lymphocytes in lymph nodes, preventing them from contributing to an autoimmune reaction.
Multiple Sclerosis

Data package

<table>
<thead>
<tr>
<th>Trial</th>
<th>design</th>
<th>Primary Endpoint</th>
<th>Sample Size</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1201 (JAPAN)</td>
<td>DBRCT</td>
<td>MRI</td>
<td>165</td>
<td>6 month</td>
</tr>
<tr>
<td>D2201 (Foreign country)</td>
<td>DBRCT</td>
<td>MRI</td>
<td>240</td>
<td>6 month</td>
</tr>
<tr>
<td>D2301 (Foreign country)</td>
<td>DBRCT</td>
<td>Relapse rate</td>
<td>1248</td>
<td>2 years</td>
</tr>
<tr>
<td>D2302 (Foreign country)</td>
<td>DBRCT</td>
<td>Relapse rate</td>
<td>1275</td>
<td>1 year</td>
</tr>
</tbody>
</table>

Primary Endpoint D1201 (JAPAN)
- MRI gadolinium (Gd)-enhanced lesion
- Patient ratio without Gd-enhanced lesion in 3 and 6 month
## Multiple Sclerosis

### Result

<table>
<thead>
<tr>
<th>D1201 (JAPAN)</th>
<th>Placebo</th>
<th>0.5mg</th>
<th>1.25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients without Gd-enhanced lesion in 3 and 6 month</td>
<td>40.4%</td>
<td>70.0%</td>
<td>86.0%</td>
</tr>
<tr>
<td>P value</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Surrogate endpoint (not validated)**

<table>
<thead>
<tr>
<th>D2301 (Foreign country)</th>
<th>Placebo</th>
<th>0.5mg</th>
<th>1.25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse rate</td>
<td>0.40[0.34, 0.47]</td>
<td>0.18[0.15, 0.22]</td>
<td>0.16[0.13, 0.19]</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**True endpoint**
Multiple Sclerosis

➢ PMDA comment
  – Primary endpoints in Clinical trials for MS should be clinical relapse or progression of disability. MRI was not validated surrogate biomarker.
  – Suggest the effectiveness
    • Severity and rarity of MS
    • Similarity of the result between Japanese and foreign trials
    • Be able to evaluate foreign data
  – Recommend participation on global trial in such rare condition like MS
Churg–Strauss syndrome (Neuropathy)

- Autoimmune medium and small vessel vasculitis
  - Asthma and/or allergic rhinitis
  - Eosinophils (hypereosinophilia), which causes tissue damage, most commonly to the lungs and the digestive tract
  - Vasculitis, which can eventually lead to necrosis and is potentially life-threatening.

- Rare diseases, 1800 in Japan
Churg–Strauss syndrome (Neuropathy)

- **Immunoglobulin (Kenketsu venilon-I®)**
  - Designated to Orphan drug in 2008
    - (20yaku) No. 218
  - Approved in 2012
  - Product contains the pooled immunoglobulin G (IgG) immunoglobulins from the plasma of blood donors
Churg–Strauss syndrome (Neuropathy)

- Data Package
  - Development in Japan
    - GGS-CCS-1(Ph2) Open trial
    - GGS-CCS-2(Ph3) DBRCT
- GGS-CCS-2
  - Trial design: DBRCT
  - Primary endpoint: Change from the baseline in Muscle Manual Test (MMT) score

<table>
<thead>
<tr>
<th></th>
<th>A (n=8)</th>
<th>B (n=8)</th>
<th>C (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1</td>
<td>IVIG</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Period 2</td>
<td>Placebo</td>
<td>IVIG</td>
<td>Placebo</td>
</tr>
<tr>
<td>Period 3</td>
<td>Placebo</td>
<td>Placebo</td>
<td>IVIG</td>
</tr>
</tbody>
</table>
Churg–Strauss syndrome (Neuropathy)

- **Result**
  - **Primary endpoint**: MMT change from the baseline
    \[ 7.13 \pm 9.76 \, [2.91, 11.35] \, (n=23, \, p = 0.002 \, \text{paired t-test}) \]
  - **Secondary endpoint**

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B + C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMT change in Period 1</strong></td>
<td>8.13 \pm 9.49</td>
<td>3.13 \pm 3.52</td>
</tr>
<tr>
<td>Difference [95% C.I.]</td>
<td></td>
<td>4.99 [-0.64, 10.63]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Student t-test)</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Placebo</strong></td>
<td></td>
</tr>
<tr>
<td>MMT change</td>
<td>7.12 \pm 1.59</td>
<td>3.57 \pm 1.12</td>
</tr>
<tr>
<td>Difference [95% C.I.]</td>
<td></td>
<td>3.53 [-0.33, 7.43]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Mixed effect model)</td>
</tr>
</tbody>
</table>
Churg–Strauss syndrome (Neuropathy)
Churg–Strauss syndrome (Neuropathy)

- PMDA comment
  - Difficulty in conducting a double-blind placebo-controlled trial in rare condition like CSS
  - Importance of evaluation for efficacy in double blind trial

- Suggest the effectiveness
  - Severity and rarity of CSS
  - MMT improved after Injection of Immunoglobulin
  - Bigger change compared to placebo
Adult T-cell leukemia

- A rare cancer of the immune system’s own T-cells
- Human T cell leukemia/lymphotrophic virus type 1 (HTLV-1) is believed to be the cause
- Poor prognosis
  - median survival was 7.7 months overall
Adult T-cell leukemia

➢ Mogamulizumab (POTELIGEO®)
  – Designated to Orphan drug in 2012
    • (22yaku) No. 232
  – Approved in 2012
  – Humanized monoclonal antibody targeting CC chemokine receptor 4 (CCR4)
# Adult T-cell leukemia

## Data package

<table>
<thead>
<tr>
<th>Trial</th>
<th>design</th>
<th>Inclusion criteria</th>
<th>Endpoint</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0761-0501 (JAPAN)</td>
<td>open</td>
<td>Recurrent ATL (CCR4 positive)</td>
<td>Safety PK</td>
<td>16</td>
</tr>
<tr>
<td>0761-002 (JAPAN)</td>
<td>open</td>
<td>Recurrent ATL (CCR4 positive)</td>
<td>Efficacy Safety PK</td>
<td>28</td>
</tr>
<tr>
<td>0761-EU-0001 (Foreign country)</td>
<td>DBRCT</td>
<td>Healthy or Seasonal allergic rhinitis</td>
<td>Safety PK</td>
<td>55</td>
</tr>
</tbody>
</table>
## Adult T-cell leukemia

### Result 0761-002 (JAPAN)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Number (%) total N= 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>CRu</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>PD</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>NE</td>
<td>0</td>
</tr>
<tr>
<td>Response rate</td>
<td>13 (50.0)</td>
</tr>
<tr>
<td>[95% C.I. ]</td>
<td>[29.9, 70.1]</td>
</tr>
</tbody>
</table>
Adult T-cell leukemia

➤ PMDA comment
  – Suggest the effectiveness
    • No standardized therapy for recurrent or relapsing ATL
    • Clinical importance in response rate
    • Response dose not necessarily contribute to the survival advantage
Summary

- Before choosing a single-arm, non-randomized, open-label design, traditional method should be considered

  - Patient registries
    - to help in study planning and recruitment
  - Clinical networks
    - to help in study conduct
  - Patient advocacy
    - to be tapped for assistance in recruitment
  - Patient’ motivation
Summary

➢ When the clinical context does not provide a sufficient number of research participants for a trial with adequate statistical power
  – Study design
  – Study conduct
  – Statistical analysis
  – Clinical importance
Major Projects Across Multi-Offices in PMDA

- Microdose Trials Project
- Post-approval Manufacturing Changes Project
- In Vitro Companion Diagnostics Project
- Pediatric and Orphan Drugs Project
  - Pediatric drugs WG
  - Orphan drugs WG
- QbD Assessment Project
- Innovative Statistical Strategies for New Drug Development
- Nanomedicine Initiative Project
- Global Clinical Study Project
- Cardiovascular Risk Evaluation Project
- Omics Project [link](http://www.pmda.go.jp/english/service/projects_am_e.html)
Orphan Drug Working Group

- **Started in November 2011**
- **Our Task is...**
  - To review and analyze the problems surrounding development of orphan drugs
  - To contribute to the further development of orphan drugs

- **PMDA will proactively push forward the Orphan drug development!!**
Orphan Drug Working Group

- Encourage industries and investigators to develop medicinal products for Orphan diseases
- Standardize development of medicinal products for orphan diseases
  - Necessary data for approval
  - Timing of development
- Strengthen collaboration with other regulatory agencies for development of Orphan medicines
Conclusion

- Small Clinical Trials is key issue in the drug development where the clinical context does not provide a sufficient number of research participants.
- Study design, conduct, statistical analysis and clinical importance should be considered.
- Academia, pharmaceutical companies, patients advocacy and regulatory bodies should work together.
Thank you for your attention.

Information
– Email: nakamura-harumasa@pmda.go.jp
– PMDA Homepage (English)
– PMDA Drug Information (Japanese)
  http://www.info.pmda.go.jp/
Backup