Regulatory and statistical issues of Multi-regional Clinical Trials: "Reference Cases" and current situation in Japan

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Outline

• Introduction
  – “Basic Principles on Global Clinical Trials”
  – Current situation

• “Basic Principles on Global Clinical Trials - Reference Cases”

• Recent examples

• Difference in regulatory requirements
Global drug development

• Purposes of global drug development
  – To prevent unnecessary duplication of clinical trials
  – To make drug development more efficient and cost-effective
  – To enable simultaneous drug submission and approval all over the world
  – To provide effective and safe drug to patients faster

• Multi-Regional Clinical Trial (MRCT) is considered as one of efficient tool for simultaneous global drug development.
Using foreign data for J-NDA

• ICH-E5 guideline, “Ethnic factors in the acceptance of foreign clinical data” (1998)
  – “Bridging strategy” and “bridging study”
• ICH-E5 Q&A No.11 (2006)
  – MRCT for the purpose of bridging
  – Shift to global simultaneous drug development with MRCT
• Japanese guidance document “Basic Principles on Global Clinical Trials” (2007)
• Supplement of original guidance document “Basic Principles on Global Clinical Trials – Reference Cases” (2012)
Contents of “Basic Principles”

- Basic requirements to conduct a Global Clinical Trial (GCT)
- Appropriate timing to participate in global drug development
- Importance of Phase I study prior to a GCT
- Importance of dose-finding study
- Basic points to consider in designing a GCT
- Sample size and proportion of Japanese subjects
- Acceptability of evaluation index which has not been established in Japan
- GCT and a smaller clinical study with identical protocol in Japan
- Control group (use of active control, active control which is not approved in Japan)
- Concomitant medications or therapeutics
- Recommended areas
- Flow chart
### Approved cases based on MRCT in Japan

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Tolterodine, Losartan</td>
</tr>
<tr>
<td>2007</td>
<td>Trastuzumab, Insulin - Glulisine, Tadalafil</td>
</tr>
<tr>
<td>2008</td>
<td>Peramivir, Everolimus, Panitumumab, Travoprost / Timolol, Temsirolimus, Laninamivir, Nilotinib</td>
</tr>
<tr>
<td>2009</td>
<td>Dabigatran, Trastuzumab, Pramipexole, Edoxaban, Everolimus</td>
</tr>
<tr>
<td>2010</td>
<td>Denosumab, Aripiprazole, Olanzapine, Exenatide, Crizotinib, Budesonide / Formoterol, Esomeprazole</td>
</tr>
<tr>
<td>2011</td>
<td>Formoterol, Axitinib, Budesonide / Formoterol, Atomoxetine, Aflibercept, Insulin - Degludec</td>
</tr>
<tr>
<td>2012</td>
<td>Glycopyrronium, Pazopanib, Everolimus, Fesoterodine, Everolimus, Apixaban</td>
</tr>
<tr>
<td>2013</td>
<td>Insulin - Degludec, Aspart, Paclitaxel, Pregabalin, Tofacitinib, Regorafenib</td>
</tr>
</tbody>
</table>

- **Red:** Asian Clinical Trial
- Guidance: “Basic Principles on Global Clinical Trials”
- Guidance RC: “Basic Principles on Global Clinical Trials – Reference Cases”

- **45 applications were approved as of May 1, 2013**
“Reference Cases”

• Based on recently accumulated scientific data and our experiences in consultation meetings and new drug review
• Reflect the outcome of cooperation in clinical trials among the regulatory authorities of China, Korea and Japan
• Purpose of “Reference cases”
  – To promote further understanding of the former “Basic Principles” issued in 2007
  – To ensure Japan’s smooth participation in global drug development activities from an early stage
  – To ensure smooth and appropriate conduct of global clinical trials in East Asia
Contents of “Reference Cases”

- 4 special points to consider for global clinical trial in East Asia
- 13 general points to consider, such as
  - Global drug development strategy plan based on data of interethnic comparison of PK profiles
  - Points to consider in planning clinical development strategies and a protocol of regional study in the trend of globalization of drug development
  - Points to consider in evaluating the results of a global clinical trial
  - Points to consider in participating in a large-scale global clinical trial using a true endpoint such as survival time
Evaluation of the results of GCT

• Evaluation of the results of overall population
  – Patients characteristics, efficacy (primary purpose of the trial in most cases), and safety
  – Ethnic difference (Effect of region)

• Evaluation of the results of individual region
  – Patients characteristics, efficacy, and safety
  – Consistency between overall population and population of the region
Evaluation of the results of GCT

• Population in individual region is sub-population of the overall population.
  – Smaller sample size for statistical tests
  – Necessity of consideration on the variability of the results
  – Necessity of the evaluation of secondary and other endpoints as supportive results
  – Use of overall results for investigating effect of factors (Careful interpretation of subgroup analysis by factors in each region)

• When the results show inconsistency,
  – Possible reason of inconsistency should be reviewed.
  – Possibility of using the results of the GCT for NDA for individual region should be carefully investigated.
Large-scale GCT

• The number of Large-scale GCTs including Japan is increasing, especially in cardiovascular area.
• One region may contribute to establishment of evidence based on the true endpoint by participating in large-scale GCT.
• However, considering number of participating regions, adequate sample size of subjects in individual region may not be achieved.
  – It may be difficult to evaluate the consistency of the results between the overall study population and the population in one region.
Large-scale GCT

• Need special care for small sample size of population in one region
  – Prior investigation of ethnic differences
  – Considering endpoints that were used in earlier phase trials when evaluate consistency
  – Careful interpretation of subgroup analysis results by factors in overall population, even when we consider special population in particular region
  – Possibility of deciding minimum required sample size of each region based on other endpoints that relate closely to primary endpoint
Three examples

• Three approved cases of cardiovascular drugs that have issues of large-scale clinical trial and dose selection
  – Large-scale MRCT including Japanese
    • Dabigatran (Direct thrombin inhibitor)
    • Apixaban (Direct Factor Xa inhibitor)
  – Foreign MRCT not including Japanese and separately performed Japanese trial
    • Rivaroxaban (Direct Factor Xa inhibitor)
      – Strategy which is generally not recommended
      – Example of the case that Japan could not participate in worldwide MRCT
### Three examples

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Prevention of ischemic stroke and systemic embolism in patients with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>non-valvular atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MRCT</strong></td>
<td>RE-LY</td>
<td>ARISTOTLE</td>
<td>ROCKET AF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>J-ROCKET AF</td>
</tr>
<tr>
<td><strong>Design of Trial(s)</strong></td>
<td>PROBE Non-inferiority</td>
<td>Double-Blinded Non-inferiority</td>
<td>Double-Blinded Non-inferiority</td>
</tr>
<tr>
<td><strong>Comparison groups</strong></td>
<td>Dabigatran 150mg</td>
<td>Apixaban 5.0mg**</td>
<td>ROCKET AF: Rivaroxaban 20mg**</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 110mg</td>
<td>Warfarin*</td>
<td>warfarin</td>
</tr>
<tr>
<td></td>
<td>Warfarin*</td>
<td></td>
<td>J-ROCKET AF: Rivaroxaban 15mg**</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>Total: 18113</td>
<td>Total: 18201</td>
<td>ROCKET AF: 14264</td>
</tr>
<tr>
<td></td>
<td>Japan: 326 (1.8%)</td>
<td>Japan: 336 (1.8%)</td>
<td>J-ROCKET AF: 1280</td>
</tr>
</tbody>
</table>

* Different PT-INR criteria for warfarin in Japanese elderly

** Can be reduced to the lower doses depend on patient characteristics, such as, age, weight, and serum creatinine (Apixaban), or creatinine crearance (Rivaroxaban)
Incidence of stroke (including hemorrhagic) and systemic embolism

<table>
<thead>
<tr>
<th></th>
<th>110mg</th>
<th>150mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6015</td>
<td>6076</td>
<td>6022</td>
</tr>
<tr>
<td>Subject-years</td>
<td>11900</td>
<td>12039</td>
<td>11797</td>
</tr>
<tr>
<td>Stroke/SEE (Yearly rate%)</td>
<td>182 (1.53)</td>
<td>133 (1.10)</td>
<td>198 (1.68)</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>0.91 (0.75-1.12)</td>
<td>0.66 (0.53-0.82)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Japanese</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>107</td>
<td>111</td>
<td>108</td>
</tr>
<tr>
<td>Subject-years</td>
<td>145</td>
<td>150</td>
<td>151</td>
</tr>
<tr>
<td>Stroke/SEE (Yearly rate%)</td>
<td>2 (1.38)</td>
<td>1 (0.67)</td>
<td>4 (2.65)</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>0.52 (0.10-2.84)</td>
<td>0.25 (0.03-2.27)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>110mg</td>
<td>150mg</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110mg</td>
<td>150mg</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>6015</td>
<td>6076</td>
</tr>
<tr>
<td></td>
<td>Subject-years</td>
<td>11900</td>
<td>12039</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>318 (2.67)</td>
<td>375 (3.11)</td>
<td>396 (3.36)</td>
</tr>
<tr>
<td>(Yearly rate%)</td>
<td>0.79 (0.68-0.92)</td>
<td>0.93 (0.81-1.07)</td>
<td>—</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.68 (0.55-5.15)</td>
<td>1.02 (0.29-3.51)</td>
<td>—</td>
</tr>
<tr>
<td>(95%CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>N</td>
<td>107</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>Subject-years</td>
<td>145</td>
<td>150</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>8 (5.53)</td>
<td>5 (3.33)</td>
<td>5 (3.31)</td>
</tr>
<tr>
<td>(Yearly rate%)</td>
<td>1.68 (0.55-5.15)</td>
<td>1.02 (0.29-3.51)</td>
<td>—</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95%CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Apixaban: Results (Efficacy)

Incidence of stroke (including hemorrhagic) and systemic embolism

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>N</td>
<td>9120</td>
</tr>
<tr>
<td>Stroke/SEE</td>
<td>212 (1.27)</td>
<td>265 (1.60)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.79 (0.66-0.95)</td>
<td>—</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.79 (0.62-1.00)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Japanese</strong></td>
<td>N</td>
<td>161</td>
</tr>
<tr>
<td>Stroke/SEE</td>
<td>3 (0.87)</td>
<td>6 (1.67)</td>
</tr>
</tbody>
</table>
Apixaban: Results (safety)

Major bleeding

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>9088</td>
<td>9052</td>
</tr>
<tr>
<td>Major bleeding (Yearly rate%)</td>
<td>327 (2.13)</td>
<td>462 (3.09)</td>
</tr>
<tr>
<td><strong>Japanese</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>160</td>
<td>175</td>
</tr>
<tr>
<td>Major bleeding (Yearly rate%)</td>
<td>4 (1.26)</td>
<td>18 (5.99)</td>
</tr>
</tbody>
</table>
## Apixaban: Results (dose)

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>9120</td>
<td>9081</td>
</tr>
<tr>
<td>5.0mg BID</td>
<td>8692 (95.3%)</td>
<td>8678 (95.6%)</td>
</tr>
<tr>
<td>2.5mg BID</td>
<td>428 (4.7%)</td>
<td>403 (4.4%)</td>
</tr>
<tr>
<td><strong>Japanese</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>161</td>
<td>175</td>
</tr>
<tr>
<td>5.0mg BID</td>
<td>151 (93.8%)</td>
<td>161 (92.0%)</td>
</tr>
<tr>
<td>2.5mg BID</td>
<td>10 (6.2%)</td>
<td>14 (8.0%)</td>
</tr>
</tbody>
</table>
## Rivaroxaban: Results of two trials

### ROCKET AF

<table>
<thead>
<tr>
<th></th>
<th>20mg</th>
<th>Warfarin</th>
<th></th>
<th>15mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td><strong>J-ROCKET AF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6958</td>
<td>7004</td>
<td>N</td>
<td>637</td>
<td>637</td>
</tr>
<tr>
<td>Stroke/SS (1/100pat.-y.)</td>
<td>188 (1.71)</td>
<td>241 (2.16)</td>
<td>Stroke/SS (1/100pat.-y.)</td>
<td>11 (1.26)</td>
<td>22 (2.61)</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>0.79 (0.66-0.96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>7111</td>
<td>7125</td>
<td>N</td>
<td>639</td>
<td>639</td>
</tr>
<tr>
<td>Bleeding (1/100pat.-y.)</td>
<td>1475 (14.91)</td>
<td>1449 (14.45)</td>
<td>Bleeding (1/100pat.-y.)</td>
<td>138 (18.04)</td>
<td>124 (16.42)</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.03 (0.96-1.11)</td>
<td></td>
<td>Hazard ratio (95%CI)</td>
<td>1.11 (0.87-1.42)</td>
<td></td>
</tr>
</tbody>
</table>

### Efficacy endpoint: composite of stroke and non-CNS systemic embolism
### Safety endpoint: composite of major and non-major clinical relevant bleeding events
Lessons Learned from 3 cases

• Consistency evaluation of large-scale MRCT
  – Need comprehensive review of efficacy and safety, with reviewing secondary endpoints
  – Post-approval research will be useful
  – Possible effect of PT-INR criteria for warfarin dose adjustment in Japanese elderly

• Different strategy for recommended dose
  – Parallel dose design and one dose group with adjustment
  – Appropriateness of criteria for low dose
  – Possible regional deference of distribution of final dose in strategy with dose adjustment

• Separate trial for Japanese
  – Although there is a possibility that Japan can not participate in MRCT because of dose difference, it is difficult to evaluate results of efficacy in Japanese trial because of lack of power
  – Need thorough investigation for different dose in Japanese
Difference in regulatory requirements

• In some MRCTs, different primary analysis methods are planned for different regulatory agencies respectively.

• Such difference based on the clinical environment or regulatory decision making may be inevitable and understandable in some situations.
Recent Examples

• Apixaban (MRCT including Japanese patients)
  – Significance level for one pivotal trial, 2.5% or 0.5% (one-sided)
  – Non-inferiority margin, 1.44 or 1.38

• Fesoterodine (foreign/global clinical trials which are extrapolated to Japanese by bridging strategy)
  – Different combination of primary and secondary endpoints
    • Urination and incontinence
    • Urination and response rate
  – Order of test for closed testing procedure
Difference in regulatory requirements

• In the example cases, primary analysis method for other regions (including Japan) was not provided.
  – In Japan, we review the trial according to our criteria or guidance document of clinical evaluation of the disease.
  – Which will be the general overall results of the trial?
• Understanding of the situations in the different regions and prior consultation is very important.
• Designing trial to meet regulatory requirements of multiple regions is important for efficient drug development.
Summary and future tasks

• MRCT is one of the tools for efficient drug development in the era of global development.
• In each case, optimal study design including MRCT should be chosen in consideration of development plan, prior information of ethnic difference.
• Innovative and efficient trial designs will be applied to MRCT, and topics may be discussed in combination with ethnic difference.
  – Design and evaluation of dose-response trials
  – Patient selection by biomarkers
• We should share our experience between industry and regulatory agencies.
Reference

- “Basic Principles on Global Clinical Trials”
- “Basic Principles on Global Clinical Trials - Reference Cases”
- Review information (in Japanese)
  - Dabigatran
    - http://www.info.pmda.go.jp/shinyaku/P201100019/530353000_22300AMX00433000_A100_1.pdf
  - Apixaban
    - http://www.info.pmda.go.jp/shinyaku/P201200166/670605000_22400AMX01496_A100_1.pdf
  - Rivaroxaban
    - http://www.info.pmda.go.jp/shinyaku/P201200011/630004000_22400AMX00041_A100_1.pdf