Regulatory perspective to review MRCT data for drug approval: Focusing on ethnic factor evaluation

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Drug Approval Based on Global Clinical Trials

As of Dec
Conduct of MRCT has contributed to decreasing “Drug Lag”

Drug approved in FY2007-FY2012

Recent experiences to review MRCT data for regulatory approval
Suvorexant: Product Overview

- Approval: September 2014
- New active ingredient (an orexin receptor antagonist) indicated for the treatment of insomnia
- Phase II and Phase III was conducted as GCT
  - Phase II:
    • Japan and US, n=254
  - Phase III:
    • 16 countries (Japan, US, Australia, Brazil, Canada, France, Denmark, Germany, Spain etc.)
    • n=1022
Pre-consideration about ethnic factors

- **Intrinsic factors**
  - There was no major differences in PK data between Japanese and other populations

- **Extrinsic factors**
  - Common diagnostic criteria in all regions
  - No major differences on medical treatment for insomnia
  - Training to ensure inter-rater reliability
Efficacy: Phase III trial

sTSO\textsubscript{m} (3M)
Differences from placebo

\begin{align*}
\text{LOW DOSE} & \quad & \text{HIGH DOSE} \\
-5.2 & \quad & -6.5 \\
-3.4 & \quad & -3.4 \\
-4.9 & \quad & -10.3 \\
\end{align*}

Overall: n=915
Japanese: n=226

sTST\textsubscript{m} (3M)
Differences from placebo

\begin{align*}
\text{LOW DOSE} & \quad & \text{HIGH DOSE} \\
10.7 & \quad & 19.7 \\
7.1 & \quad & 11.7 \\
12.5 & \quad & 23.1 \\
\end{align*}

sTSO\textsubscript{m}: Subjective time to sleep onset (min.)
sTST\textsubscript{m}: Subjective total sleep time (min.)

Relatively small effects in Japanese, but improvement tendency was consistently found in all conditions.
• Similar safety profiles
• Different incident rate was observed in some events, but most of them were mild
MRCT Data Review Experiences

- **Extrinsic** ethnic factors such as concomitant therapies sometimes have impacts on data evaluation
- PPK data are useful for ethnic factor consideration
- **Consistency evaluation approach** following to confirming efficacy in overall population is beneficial.
  - limitation in evaluating data when sample size was small
- Differences in **adverse event rate** are not uncommon; partly due to difference on categorization or data collection process of adverse events in GCTs
- Ethnic factor consideration is important even in Asian GCTs
Recent scientific advances on impacts of ethnic factors in drug responses
Ethnic Similarities
Genetic similarities/differences among Asian populations

HLA-B*5801


NAT2
Genetic similarities among East-Asian populations

- The frequencies of 1936 variants representing 225 genes encoding drug-metabolizing enzymes and transporters were determined from 786 healthy participants (448 Korean, 208 Japanese, and 130 Chinese).

- No major ethnic differences among Chinese, Korean and Japanese populations.

Correlation of minor allele frequencies between population

Ethnic differences
Ethnic sensitivities on US-approved drugs

# Example; Ethnic difference on PK and safety -US drug label-

<table>
<thead>
<tr>
<th>Generic name</th>
<th>PK</th>
<th>Efficacy/Safety</th>
<th>Approved dose: US/Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib (NSCLC)</td>
<td>No major difference on PK</td>
<td>Incidence of interstitial lung disease Asian (2.1%) &gt; non-Asians (1.2%).</td>
<td>40mg/40mg</td>
</tr>
<tr>
<td>Eltrombopag olamine (thrombocytopenia)</td>
<td>East Asian 50-55% higher &gt; non-East Asian</td>
<td>A reduction in the initial dose is recommended for East Asian patients More reduced dose in East Asian patients with hepatic impairment.</td>
<td>50mg/12.5mg</td>
</tr>
<tr>
<td>Simeprevir (Anti-viral, HCV infection)</td>
<td>Asian 3.4-fold higher &gt; Caucasians.</td>
<td>Higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity.</td>
<td>150mg/100mg</td>
</tr>
</tbody>
</table>

Effects of Green Tea on β-blocker, nadolol responses


OATP1A2-mediated [3H]-nadolol uptake
Toward Regulatory Harmonization
-ICH E17 guideline-
ICH E17 Guideline: MRCTs

General principle on planning/designing Multi-Regional Clinical Trials

- **E17 EWG**: established in June 2014
- **Rapporteur**: PMDA
- **Provide common points to consider in planning/designing MRCTs and minimize conflicting opinions from regulatory bodies.**
1. INTRODUCTION
   1.1 Objective(s) of the Guideline
   1.2 Background
   1.3 Scope of the Guideline
   1.4 General Principles

2. General recommendations in planning/designing MRCT
   2.1 Strategy-related points
      2.1.1 The value of MRCTs in drug development and regulatory approval
      2.1.2 The basic requirements to conduct a MRCT
      2.1.3 Scientific consultation meeting with regulatory agencies
2. General recommendations in planning/designing MRCT
   2.2 Clinical trial design and protocol-related points
      2.2.1 Pre-consideration of regional variability on efficacy/safety
      2.2.2 Subject selection
      2.2.3 Selection of doses in MRCTs
      2.2.4 Choice of endpoint/index
      2.2.5 Estimation of a sample size and a proportion of each regional subjects in an MRCT
      2.2.6 Collecting and handling efficacy/safety information in MRCTs
      2.2.7 Statistical analysis plans that specifically address the features of MRCTs
      2.2.8 Selection of comparator (where applicable)
      2.2.9 Handling concomitant medications or therapies in a MRCT

3. GLOSSARY
Current Timeline of the E17 guideline

- First face-to-face EWG Meeting in November 2014 in Lisbon
- Discussion by e-mail and web-based conference: 4Q 2014 - 1Q 2015
- Second F2F EWG Meeting in 2Q 2015 for coordinating opinions of all parties and delivering Step 1 document
- Third F2F EWG meeting in 4Q 2015 for adaption of Step 2 document
- Public consultation: 4Q 2015 - 2Q 2016
- Revision of the guideline based on comments: 2Q 2016 - 4Q 2016 (depending on contents of comments recived)
- Fourth face-to-face EWG Meeting for adaption of Step 4 document in 4Q 2016 or 2Q 2017
Conclusion

- More regulatory experiences to review MRCT data facilitate our understanding regarding impacts of ethnic factors on drug efficacy/safety

- More scientific data promote international harmonization on regulatory requirements for drug approval based on MRCT data

**International cooperation for providing more drugs earlier to patients**
Information

- PMDA web site (English)

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Thank you for your attention
Ask