Statistical Considerations in Design and Analysis of Bridging and Multi-Regional Trials

Design and Evaluation of Multiregional Clinical Trials: Experience in Japan

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Outline

- Recent experience
  - Trend of approved cases
  - Asian trials in particular therapeutic areas
  - Large-scale MRCT
- New guidance document
- Summary

Recent experience

- Number of the approved NDAs with MRCT including Japanese patients is rapidly increasing
  - 28 cases as of Aug 1st
  - Both global trial and Asian trial
  - In various therapeutic areas
- There have been many cases with designing or evaluating early phase MRCT, such as MRCTs for dose selection, in consultation meetings in the PMDA.

MRCT of approved cases within Japan 1

	Indication	Date of Approval	Note
Tolterodine tartrate	Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	Apr. 2006	Korea-Japan
Losartan potassium	Diabetic nephropathy with proteinuria and hypertension in patients with type 2 diabetes	Apr. 2006	Global (Asian data)
Trastuzumab	Adjuvant therapy for HER2-positive breast cancer	Feb. 2008	Global Oncology
Insulin glulisine	Diabetes mellitus	Apr. 2009	Korea-Japan
Tadalafil	Pulmonary arterial hypertension	Oct. 2009	Global Dose-finding
Peramivir	Type A and Type B Influenza virus infection	Jan. 2010	Asian
Everolimus	Metastatic renal cell carcinoma	Jan. 2010	Global Oncology
Panitumumab	Metastatic colorectal carcinoma with wild-type KRAS tumors	Apr. 2010	Global Oncology
Travoprost/Timolol	Glaucoma	Apr. 2010	BE
Temsirolimus	Advanced renal cell carcinoma	Jul. 2010	Asian Oncology

MRCT of approved cases within Japan 2

	Indication	Date of Approval	Note
Laninamivir	Type A and Type B Influenza virus infection	Sep. 2010	Asian
Nilotinib	Newly diagnosed chronic myeloid leukemia in chronic phase	Dec. 2010	Global Oncology
Dabigatran	Stroke and systemic embolism in patients with non-valvular atrial fibrillation	Jan. 2011	Global
Trastuzumab	HER-2 positive metastatic gastric cancer	Mar. 2011	Oncology
Pramipexole	Parkinson's Disease	Apr. 2011	Global
Edoxaban	Thromboprophylaxis after total hip and knee replacement, hip fracture surgery	Apr. 2011	Taiwan-Japan
Dasatinib	Chronic myeloid leukemia	Jun. 2011	Global Oncology
Indacaterol	Chronic obstructive pulmonary disease (COPD)	Jul. 2011	Asian
Linagliptin	Type 2 diabetes	Jul. 2011	Global
Gefitinib	EGFR-Positive unresectableor metastatic non-small cell lung cancer (NSCLC)	Nov. 2011	Asian

MRCT of approved cases within Japan 3

	Indication	Date of Approval	Note
Everolimus	Progressive neuroendocrinetumors of pancreatic origin (PNET)	Dec. 2011	Global Oncology
Denosumab	Bone complications in patients with multiple myeloma or solid tumourthat has spread to the bone	Jan. 2012	Global Oncology
Aripiprazole	Manic episodes associated with bipolar disorder	Jan. 2012	Asian
Olanzapine	Depression episodes associated with bipolar disorder	Feb. 2012	Asia + US
Exenatide	Type II diabetes mellitus (adjunctive to diet, exercise and treatment with SU)	Mar. 2012	Asian
Crizotinib	Anaplastic lymphoma kinase(ALK)-positive, advanced or metastatic non-small cell lung cancer (NSCLC)	Mar. 2012	Global Oncology
Budesonide/ Formoterol	Asthma (where use of a combination of inhaled corticosteroid and long-acting β2 adrenoceptor agonist is appropriate)	Jun. 2012	Global
Formoterol	Chronic obstructive pulmonary disease (COPD)	Jun. 2012	Global

MRCT of approved cases

- Our experiences in reviewing MRCTs are rapidly increasing.
  - Most of the cases were approved in the last 2-3 years.
- Oncology area is the main area that actively uses MRCTs for J-NDA.
- The number of cases for chronic disease and Asian trials is also increasing.
- MRCT cases for same/similar indications were approved.
  - Type A and Type B Influenza virus infection
  - Bipolar disorder
- One case with large-scale MRCT was approved.

Approved cases in psychiatry area

- Two new indications and dosing for bipolar disorder were approved in early 2012 with MRCTs as main evaluation data.
- Both MRCTs were conducted mainly in Asian countries.
  - Aripiprazole (for manic episodes)
    - Asian MRCT was conducted in Japan, China, Indonesia, Malaysia, Philippines
  - Olanzapine (for depression episodes)
    - MRCT was conducted in Japan, China, Korea, and US

Trial design of MRCTs

- Aripiprazole
  - Placebo controlled randomized double-blinded parallel group trial of placebo and 24mg
  - Number of patients: 256 (FAS: 247, including 79(32.0%) Japanese patients)
  - Primary endpoint: Young Mania Rating Scale (YMRS)
- Olanzapine
  - Placebo controlled randomized double-blinded parallel group trial of placebo and 5~20mg (titration)
  - Number of patients: 514 (including 156(30.4%) Japanese patients)
  - Primary endpoint: Montgomery-Asberg Depression Rating Scale (MADRS) Total Score

Results - Aripiprazole

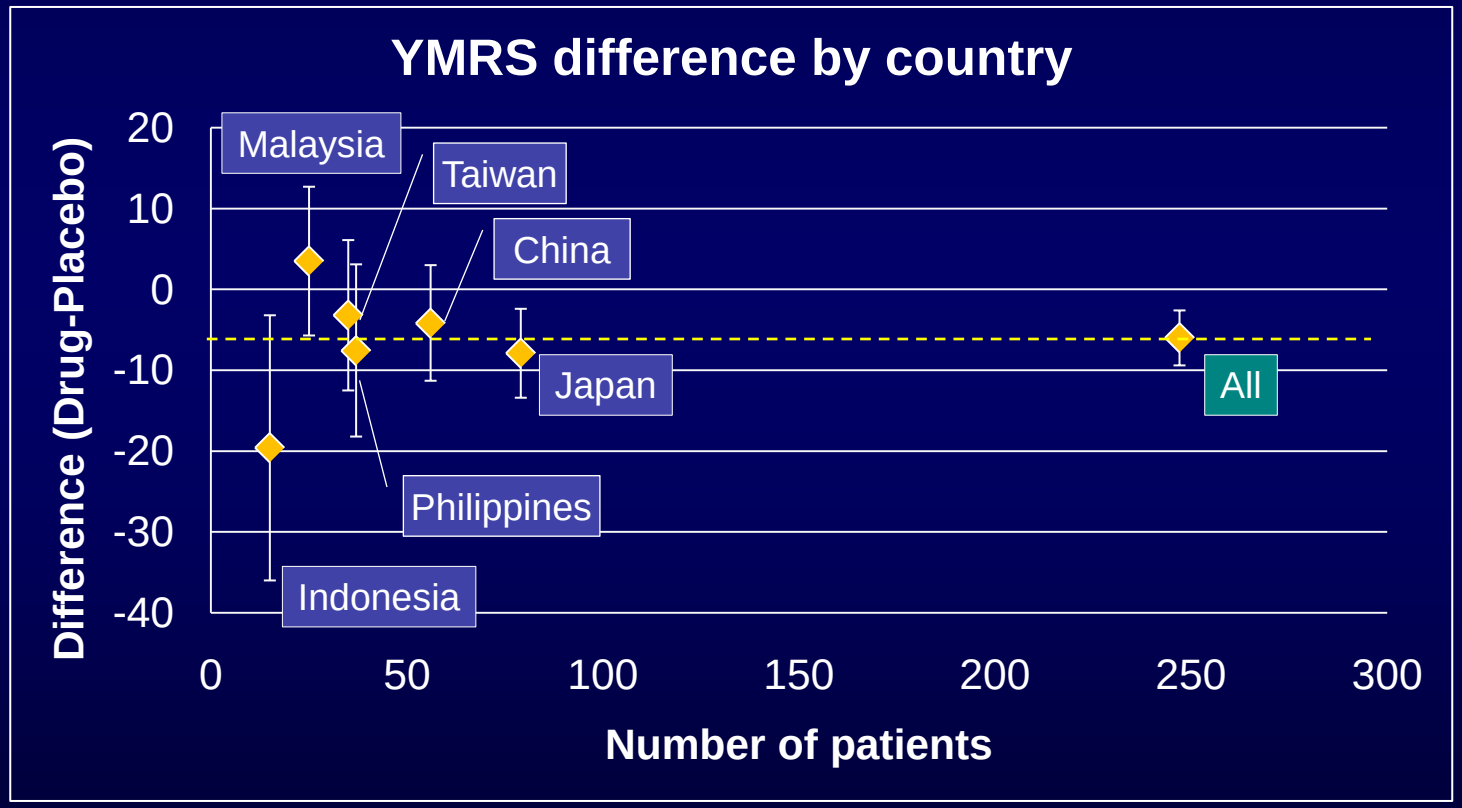
- YMRS change from baseline

		Placebo Mean±SD	Aripiprazple Mean±SD	Difference [95%CI]
All	Baseline Study endpoint Change N	28.0±5.97 22.0±15.23 -6.0±14.4 125	28.3±5.96 16.3±13.37 -12.0±12.9 122	-6.0 [-9.4, -2.6]
Japan	Baseline Study endpoint Change N	27.8±5.76 19.8±13.73 -8.0±13.3 40	29.0±6.80 12.6±11.68 -16.4±11.5 39	-7.9 [-13.4, -2.4]

http://www.info.pmda.go.jp/shinyaku/P201200002/18007800_21800AMZ10013000_A100_1.pdf

Results - Aripiprazole

- Results of primary endpoint by country



Prepared based on
http://www.info.pmda.go.jp/shinyaku/P201200002/18007800_21800AMZ10013000_A100_1.pdf

Results - Olanzapine

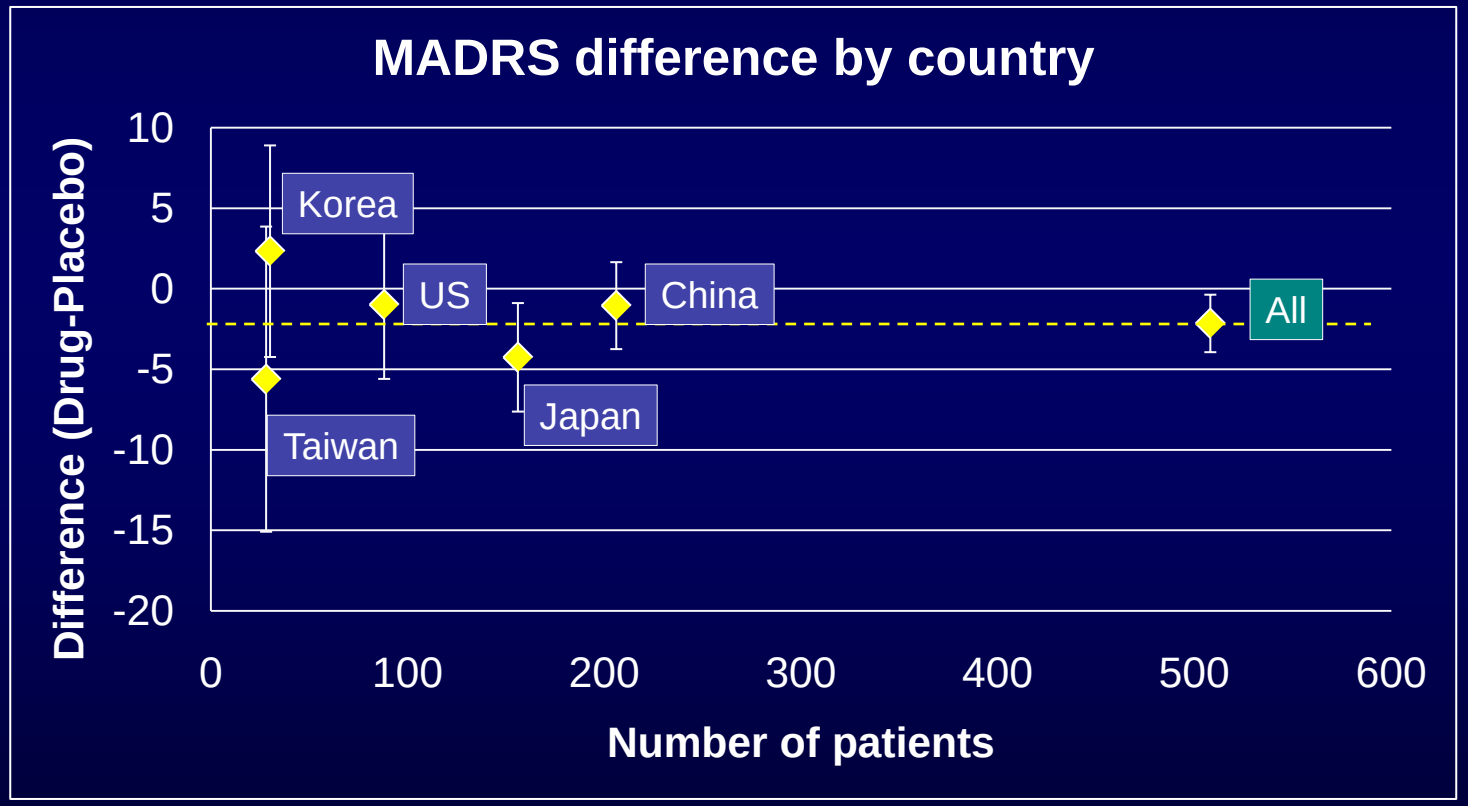
- MADRS change from baseline

		Placebo Mean±SD	Olanzapine Mean±SD	Difference [95%CI]
All	Baseline	28.69±6.33	29.36±5.71	
	Study endpoint	16.98±10.21	15.10±9.79	
	Change	-11.71±11.09	-14.26±9.73	-2.15 [-3.93, -0.36]
	N	169	339	
Japan	Baseline	28.62±8.01	29.00±6.15	
	Study endpoint	18.10±11.59	13.99±9.73	
	Change	-10.52±13.33	-15.01±9.33	-4.26 [-7.63, -0.89]
	N	52	104	

http://www.info.pmda.go.jp/shinyaku/P201200019/53047100_21200AMY00249_A100_1.pdf

Results - Olanzapine

- Results of primary endpoint by country



Prepared based on
http://www.info.pmda.go.jp/shinyaku/P201200019/53047100_21200AMY00249_A100_1.pdf

Review points

- Aripiprazole
  - Design issues such as inpatient/outpatient, training of the clinical evaluation
    - Only inpatients were included in Japan
  - Limitation of interpreting relationship between region and patient characteristics in some regions
- Olanzapine
  - Extrinsic ethnic factors such as approved drugs for the disease
  - Design issues such as training of the clinical evaluation
- The primary efficacy results are consistent between all subjects and Japanese subjects in both cases.
- Although consistency between all subjects and Japanese subjects was discussed, it is also important to consider consistency between countries for Asian trial, in expectation of more efficient drug development in the future.

Large-scale MRCT

- Specifically for cardiovascular drug, one large-scale MRCT including many regions may be the main confirmatory data in development strategy and also in submission data package.
- There are several issues related to such strategies.
  - Investigation and interpretation of drug doses for large-scale MRCT
  - Limited information available in each region at the time point of approval
- One approved case in Japan - Dabigatran

Large-scale MRCT - Dabigatran

- Indication
  - Stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Clinical trials as evaluation data
  - Japanese trial: Safety PII
  - MRCT: Global PIII
    - Prospective, randomized, open label, blinded endpoint evaluation (PROBE)
    - Parallel group trial of150mg, 110mg, and warfarin to show non-inferiority to warfarin
    - Number of patients: 18113 (including 326 (1.8%) Japanese patients)

Results of Dabigatran trial - efficacy

- Primary efficacy endpoint: the incidence of stroke (including hemorrhagic) and systemic embolism

		110mg	150mg	Warfarin
Total	N	6015	6076	6022
	Subject-years	11900	12039	11797
	Stroke/SEE (Yearly rate%)	182 (1.53)	133 (1.10)	198 (1.68)
	Hazard ratio (95%CI)	0.91 (0.75-1.12)	0.66 (0.53-0.82)	–
Japanese	N	107	111	108
	Subject-years	145	150	151
	Stroke/SEE (Yearly rate%)	2 (1.38)	1 (0.67)	4 (2.65)
	Hazard ratio (95%CI)	0.52 (0.10-2.84)	0.25 (0.03-2.27)	–

http://www.info.pmda.go.jp/shinyaku/P201100019/index.html

Results of Dabigatran trial - safety

- Safety endpoint: major bleeding

		110mg	150mg	Warfarin
Total	N	6015	6076	6022
	Subject-years	11900	12039	11797
	Major bleeding (Yearly rate%)	318 (2.67)	375 (3.11)	396 (3.36)
	Hazard ratio (95%CI)	0.79 (0.68-0.92)	0.93 (0.81-1.07)	–
Japanese	N	107	111	108
	Subject-years	145	150	151
	Major bleeding (Yearly rate%)	8 (5.53)	5 (3.33)	5 (3.31)
	Hazard ratio (95%CI)	1.68 (0.55-5.15)	1.02 (0.29-3.51)	–

http://www.info.pmda.go.jp/shinyaku/P201100019/index.html

Review points for Dabigatran

- Design issues
  - PROBE design, non-inferiority margin
  - Acceptance of PT-INR criteria for warfarin in Japanese elderly
- Evaluation of the Japanese data
  - Difficulty of reviewing consistency between all subjects and Japanese subjects due to the Japanese sample size based on the feasibility
  - Need of comprehensive review of efficacy and safety, with reviewing secondary endpoints for them
  - Use of lower dose (110mg)
  - Consideration on special population in Japan

Post-marketing phase of Dabigatran

- Reports of adverse events (severe bleeding) especially in elderly patients
- The blue letter and change of the package insert
  - Importance of consideration for the risk of using dabigatran based on the characteristics of the patients
  - Warning statement for risk of bleeding, lack of neutralizing agents and measurements of bleeding risk
- Emergency statement from the Japanese Circulation Society

Lessons learned from recent cases

- Two new indications and dosing for bipolar disorder
  - Along with the accumulation of the experience, by reviewing cases for same/similar indication, efficient design of MRCT should be well investigated.
- Large-scale MRCT
  - Issues with small proportion of Japanese subjects in large-scale MRCT conducted for rare events
    - Necessity of evaluating several endpoints
    - Sensitivity analysis will be the key in evaluating the variation of Japanese results and relationship of the results between all patients and Japanese patients.
  - Limitation of available safety data at pre-approval phase
    - In many regions, safety evaluation may depend on the data from the large-scale MRCT
    - Regionally customized safety consideration and globally prompt feedback of the information is needed in post marketing phase

Project across multi-offices in PMDA

- In Vitro companion diagnostic devices project
- Pediatric and orphan drugs project
- QbD assessment project
- Innovative statistical strategies for new drug development project
- Nanomedicine initiative project
- Global clinical study project
- Cardiovascular risk evaluation project
- Omics project

http://www.pmda.go.jp/english/service/projects_am_e.html

New guidance document

- "Basic Principles on Global Clinical Trials" was issued in 2007
  - Mainly based on out experience in clinical trial consultation meetings
- "Basic Principles on Global Clinical Trials -Reference Cases-" will be issued soon
  - Based on recent scientific knowledge, review experience of approved cases, and experience in consultation meetings
  - Focused on both special points to consider for GCTs (MRCTs) in East Asia and general points to consider on GCTs

Topics in the new guidance document

- Points to consider for East Asian GCTs
  - Special points to consider in conducting a global clinical trial in East Asia
    - Possible similarity of gene profiles
  - Recommended therapeutic areas
    - Encouraging drug development for diseases with high morbidity in East Asia
  - Interethnic comparison of pharmacokinetic profiles and global drug development strategy
  - Possibility of a GCT as a bridging study
    - Sufficiency of information of ethnic difference

Topics in the new guidance document

- General points to consider
  - Japanese clinical development strategies and study protocols in the trend of globalization
  - Points to consider in evaluating the results of a global clinical trial
  - Evaluating the data of Japanese subjects living outside of Japan enrolled in foreign studies
  - Comparing PK data between different ethnicities
  - Global clinical trial as a First in Human trial
  - Global clinical trial with different drug exposure between Japanese and non-Japanese

Topics in the new guidance document

- General points to consider (cont.)
  - Unapproved drug as a control
  - Difference of recommended dose of control or concomitant drug between Japan and other regions
  - Points to consider in using a competitive registration system
  - Points to consider in participating in a large-scale global clinical trials with true endpoint such as mortality
    - Dabigatran would be one of the cases
  - Required Japanese subjects for evaluating long-term safety

Summary

- MRCT in the global drug development is the key strategy as a way to provide effective and safe drugs to patients in the world.
- Evidence shown by all patients in a MRCT and regional concern should be considered in a stepwise manner in the context of worldwide, simultaneous development strategy
- Along with the accumulation of the experience,
  - Integrated information which is useful for MRCT design in particular area
  - Evaluation methods for particular situation

  should be provided and updated.

Thank you for your attention.

- Information
  - Email: ando-yuki@pmda.go.jp
  - PMDA Homepage (English)
    - http://www.pmda.go.jp/english/index.html
  - Selected review reports translated in English (including peramivir)
    - http://www.pmda.go.jp/english/service/drugs.html