2011 APEC Multi-Regional Clinical Trials Tokyo Workshop

Multi-Regional Clinical Trials in Global Drug Development: Update and Related Issues

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  - MRCT for dose selection
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Introduction: Discussion at last year WS

- Several issues of study design of MRCTs were discussed at the workshop last year
  - How to consider intrinsic and extrinsic factors inter-regionally and intra-regionally
  - Importance of early phase development
  - Design factors
    - Endpoint
    - Region definition
    - Trial quality
    - Sample size
- Practical issues are shown in the recent cases as the mixture of some of them, depending on the development strategy

Recent experience

- Increasing number of the approved NDAs with MRCT including Japanese patients
- Several cases with designing or evaluation of 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
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	Chinese Taipei-Japan
Dasatinib	Chronic myeloid leukemia	Jun. 2011	Global Oncology
Indacaterol	Chronic obstructive pulmonary disease	Jul. 2011	Asian
Linagliptin	Type 2 diabetes	Jul. 2011	Global

MRCT of approved cases

- Oncology area is still the key area that actively using MRCTs for J-NDA
- The number of chronic diseases and Asian trials is also increasing

Experience of MRCTs for dose-response

- Conducting MRCTs to collect sufficient information of ethnic difference in early phase of drug development is recommended
- Increasing experience of evaluating dose-response relationship in each region (country) in the PMDA consultation meetings
  - However, there are cases with different dose-response between the regions

Experience of MRCTs for dose-response

- Consistency of the dose-response relationship between Japanese subjects and total subjects was not shown in the PII MRCT
  - Although possible reasons seemed to be the difference of demographic factors and condition of patients based on the post hoc investigation, but they were unclear
  - Recommended dose for Japanese could not be established based on the results
- Possible reasons of this case
  - Lack of prior information
  - Existence of many factors including dose and Basically based on subgroup analyses and difficulty of pursuing the cause of difference

Difference in dose-response relationship

- Importance of early phase information , such as PK/PD, factors affect on the efficacy and safety
  - To design dose-response MRCT
  - To investigate and exclude the reason of difference
- With consideration of the lack of sample size for each region (country),
  - Investigation of the discrepancy between expected and actual dose-response relationship in each region should be discussed
  - In some cases, there is possibility of the difference by chance

Late phase MRCTs

- In some areas, one large scale MRCTs including many regions may be mainly focused on in the development strategy
- There are several issues related to such strategy
  - Investigation and interpretation or multiple doses in PIII
  - Available information at the time point of approval

Late phase MRCTs - Dabigatran

- Indication: Stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Clinical trials
  - 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 Japanese patients)

Late phase MRCTs - Dabigatran

- 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

Late phase MRCTs - Dabigatran

- 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

Late phase MRCTs - Dabigatran

- Review points
  - 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 Japanese and all 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

Late phase MRCTs - Dabigatran

- Post-marketing phase
  - Reports of adverse events (severe bleeding) especially in the patients with renal impairment and elderly
  - 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

Late phase MRCTs - Dabigatran

重要

—医薬品の適正使用に欠かせない情報です。必ずお読みください。—

安全性速報

プラザキサ®カプセル 75mg
プラザキサ®カプセル 110mg による重篤な出血について

2011 年 8 月
日本ベーリンガーインゲルハイム株式会社

本剤の発売の 2011 年 3 月 14 日から 2011 年 8 月 11 日までの間に、重篤な出血性の副作用が 81 例[注)] 報告されています。そのうち、専門家の評価により、本剤との因果関係が否定できないとされる死亡例が 5 例[注)] 報告されています（発売以降の推定使用患者数約 6 万 4 千人）。このような状況を考慮し、使用上の注意に「警告」を加えて注意喚起することに致しました。

http://www.boehringer-ingelheim.co.jp/com/Home/products/prescription/medicine_data/pxa_cap/blue_letter_201108.pdf

Late phase MRCTs - Dabigatran

- Limited available safety data even in the global drug development with large scale MRCT
  - Although the trial include the large number of patients, safety evaluation may depend on the data from the MRCT at the time point of the approval in many countries
  - Regionally customized safety consideration and globally prompt feedback of the information may be needed in post marketing phase

Role of data monitoring committees

- Guidance for data monitoring committees is now under consideration in Japan
  - Increasing use of interim analysis in Japan
  - Necessity of safety monitoring in various situations
- There are several experts' comments in the discussion related to MRCTs
  - Promotion of proper use of interim analysis is important
  - Appropriate safety monitoring for each region (Japan) in MRCTs should be considered

Role of data monitoring committees

- Role of DMCs for MRCT under the uncertainty of the ethnic difference should be considered
  - Appropriate participants for DMC
  - Possibility of regional DMC

Risk benefit evaluation

- Limitation of the information of the efficacy and safety based on the data from the pre-approval phase
  - Sufficient for the approval based on the data basically from average patients, limited duration
  - Long term efficacy and safety data should be collected after the approval
  - Additional investigation for special population may be useful

Risk benefit evaluation

- In MRCTs, regional conditions will be harder to be reflected
- Reviewing the characteristics of actual patient population regionally may be important
  - For fine-tuning the information provided to the regional patients

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.
- Well-considered data collection from early phase to post approval phase and efficient way of integration of the data from phases and regions should be considered, in addition to consider appropriate information for regionally proper use of the drug.

Thank you for your attention.

- Information
  - Email: ando-yuki@pmda.go.jp
  - PMDA Homepage (English)
    - http://www.pmda.go.jp/english/index.html
  - PMDA Drug Information (Japanese)
    - http://www.info.pmda.go.jp/