Background and outline of "Basic Principles on Global Clinical Trials (Reference Cases)"

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Outline

- “Basic Principles on Global Clinical Trials” and current situation
- Background of “Reference Cases”
- Selected contents of “Reference Cases”
- Summary

Please see the original text of the guidance document for details

- Japanese: http://www.pmda.go.jp/regulatory/file/guideline/new_drug/GCT_jirei.pdf
- English: http://www.pmda.go.jp/regulatory/file/english_guideline/new_drug/GCT-jirei_en.pdf

“Basic Principles on Global Clinical Trials”

- “Basic Principles on Global Clinical Trials” issued on Sep 28, 2007.
  - To encourage Japan’s participation to GCTs from an early stage of drug development
  - To provide points to be considered in GCTs
  - To promote conducting GCTs more appropriately in consideration of ethnic factors
  - Based on accumulated experiences mainly in PMDA consultation meetings

Approved cases based on GCTs

2006	2007	2008	2009	2010	2011	2012	
Tolterodine	Losartan	Trastuzumab	Insulin - glulisine	Peramivir	Dabigatran	Denosumab	
			Tadalafil	Everolimus	Trastuzumab	Aripiprazole	
				Panitumumab	Pramipexole	Olanzapine	
				Travoprost/ Timolol	Edoxaban	Exenatide	
				Temsirolimus	Dasatinib	Crizotinib	
				Laninamivir	Indacaterol	Budesonide/ Formoterol	Atomoxetine
				Nilotinib	Linagliptin	Esomeprazole	Aflibercept
					Gefitinib	Formoterol	Insulin - degludec
					Everolimus	Axitinib	Glycopyrronium
						Budesonide/ Formoterol	Pazopanib

Red: Asian GCT

- 36 applications were approved as of Nov 1, 2012

“Basic Principles on Global Clinical Trials”

- There were few approved cases when previous guidance document was issued.
  - General cases were assumed.
    - Ex. Example of a few hundred subjects of study in the explanation of sample size of Japanese population
  - Points to be considered for evaluating the results of GCT were not provided.
- Number of conduct of Asian trials have been increased and East Asian contribution has been recognized.

“Reference Cases”

- “Basic Principles on Global Clinical Trials (Reference Cases)” was issued on Sep 5, 2012.
  - 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 Japan, China, and Korea

“Reference Cases”

- 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
- 17 Q&As
  - 4 points to consider for global clinical trials in East Asia
  - 13 general points to consider on global clinical trials

Points to consider for GCT in East Asia

- Special points to consider for global clinical trial in East Asia[1)]
- Recommended therapeutic areas[2)]
- Global drug development strategy plan based on data of interethnic comparison of pharmacokinetic profiles[3)]
- Points to consider for East Asian clinical trial as a bridging study[4)]

Points to consider for GCT in East Asia

- Data from well-designed and conducted GCTs in East Asia is acceptable.
- GCTs in East Asia need to be designed and conducted based on prior evaluation of ethnic difference.
- Further accumulation of experience will lead to improvement of the efficiency and quality of clinical development in East Asia.
- Although GCTs in East Asia can be performed for any target disease area, they may contribute to the improvement of the efficiency and quality of development of drugs especially for diseases with high morbidity in East Asia .

Points to consider for GCT in East Asia

- Development plan may depend on the comparison of the PK profile between
  - Japanese and Caucasian
  - Japanese and other East Asian populations
- Based on the results of comparison, most efficient plan should be chosen, such as
  - GCT in Japanese and Caucasian populations from the early exploratory phase
  - East Asian exploratory clinical trial
  - Exploratory study only in Japanese subjects
- Possibility of confirmatory GCT trial is based on
  - The result of prior exploratory studies
  - PK profiles, effects of ethnic factors

General points to consider

- Points to consider in planning Japanese clinical development strategies and a protocol of a Japanese study in the trend of globalization of drug development[5)]

Planning Japanese development

- Important points
  - To develop a long term and overall plan
  - To optimize the development process and protocols for subsequent phases during the course of drug development based on evaluation of data available so far
  - To cooperate with relevant foreign sections from an early stage, and share and understand up-to-date data of the drug and development program

Planning Japanese development

- Three major types of clinical development strategies in Japan or multiple countries including Japan
  - Single-country development
  - Bridging development to which foreign data are extrapolated
  - Global development including confirmatory global clinical trials.
    - World-wide development
    - East Asian global development
- Optimal protocol should be developed for the next phase based on the data available at the moment.

General points to consider

- Points to consider in evaluating the results of a global clinical trial[6)]

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 Japanese population
  - Patients characteristics, efficacy, and safety
  - Consistency between overall population and Japanese population
    - Comparison of the point estimates of primary endpoint results is not sufficient, even when sample size of Japanese population was estimated based on the comparison of point estimate (Method 1 or 2).

Evaluation of the results of GCT

- Japanese population 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 Japanese population)
- Inconsistency?
  - Possible reason of inconsistency and possibility of using the results of the GCT for Japanese NDA should be carefully investigated.

General points to consider

- Data of Japanese subjects living outside of Japan enrolled in foreign studies[7)]
- General points to consider in comparing pharmacokinetic data between different ethnicities[8)]
- Points to consider in conducting a FIH trial as a global clinical trial[9)]
- Possibility of using the drug as combined treatment in a GCT, with only a monotherapy study data in Japanese[10)]
- How many Japanese patients will be required for evaluating the long-term safety[17)]

General points to consider

- Points to be consider for conducting GCT with a certain difference between Japan and other regions in
  - Blood concentration of the investigational drug [11)]
  - Approval of active control for reference[12)]
  - Dosage regimen or formulation of active control[13)]
  - Indications or dosage regimen of the drug used in combination with the investigational drug[14)]

When sample size is not achieved

- Points to be considered when the target sample size of Japanese subjects is not achieved[15)]

When sample size is not achieved

- To achieve the originally determined sample size of Japanese subjects,
  - Thorough assessment should be made in advance.
  - Appropriate actions should be taken as necessary based on careful monitoring of study progression.
- If the target sample size cannot be achieved despite every possible action, the sponsor should review
  - The action taken
  - The reason for the failure
  - Whether the consistency is demonstrated
- A separate study may be required in some cases
  - Extremely small number of enrolled Japanese subjects
  - Inconsistent results suggesting ethnic differences and other concerns

Large-scale GCT

- Points to consider in participating in a large-scale global clinical trial using a true endpoint such as survival time[16)]

Example: Dabigatran

- Indication
  - Stroke and systemic embolism in patients with non-valvular atrial fibrillation
- GCT: 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)

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

Large-scale GCT

- Japan may contribute to establishment of evidence based on the true endpoint by participating in large-scale GCT.
- Considering number of participating regions, adequate sample size of Japanese subjects may not be achieved to evaluate the consistency of the results between the overall study population and the Japanese population.

Large-scale GCT

- Need special care for small sample size of Japanese population
  - 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 Japan
  - Possibility of deciding minimum required sample size of Japanese population based on other endpoints that relate closely to primary endpoint

Future tasks

- GCT is one of the tools for efficient drug development in the era of global development .
- In each case, optimal study design including GCT should be chosen in consideration of development plan.
- Innovative and efficient trial designs will be applied to GCT, and many topics with GCT may be discussed.
  - Design and evaluation of dose-response trials
  - Active use of interim analysis
  - Patient selection by biomarkers
- It is important to share our experience between industry and regulatory agency (agencies).