GLOBAL CLINICAL TRIALS IN DRUG DEVELOPMENT
- PRINCIPLRS AND CASE STUDIES

Principles and Case Examples in Global/Asian Clinical Trials

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Outline

- Introduction
- Guidance documents in Japan
  - “Basic Principles on Global Clinical Trials”
  - “Basic Principles on Global Clinical Trials – Reference Cases”
- Current situation in Japan
- Selected points from “Basic Principles” and “Reference cases ” with case example
  - Selected points from “Basic Principles”
  - Selected points from “Reference cases ”
- Other issues related to Global Clinical Trials
- Summary

Introduction

- 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
- Global Clinical Trial (GCT) is considered as one of efficient tool for simultaneous global drug development.

Introduction

- History of using foreign data in Japan
  - ICH-E5 guideline, “Ethnic factors in the acceptance of foreign clinical data” (1998)
    - After ICH-E5, foreign clinical trial data have been used in Japan with “bridging strategy” and “bridging study”.
  - ICH-E5 Q&A No.11 (2006)
    - The Q&A clearly mentioned the use of GCT for the purpose of bridging.
    - The strategy for using foreign clinical data shifted to global simultaneous drug development with GCT.

Introduction

- History of using foreign data in Japan (Cont.)
  - Japanese guidance document “Basic Principles on Global Clinical Trials” (2007)
  - Supplement of original guidance document “Basic Principles on Global Clinical Trials – Reference Cases” (2012)

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“Basic Principles on Global Clinical Trials”

- “Basic Principles on Global Clinical Trials” was 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

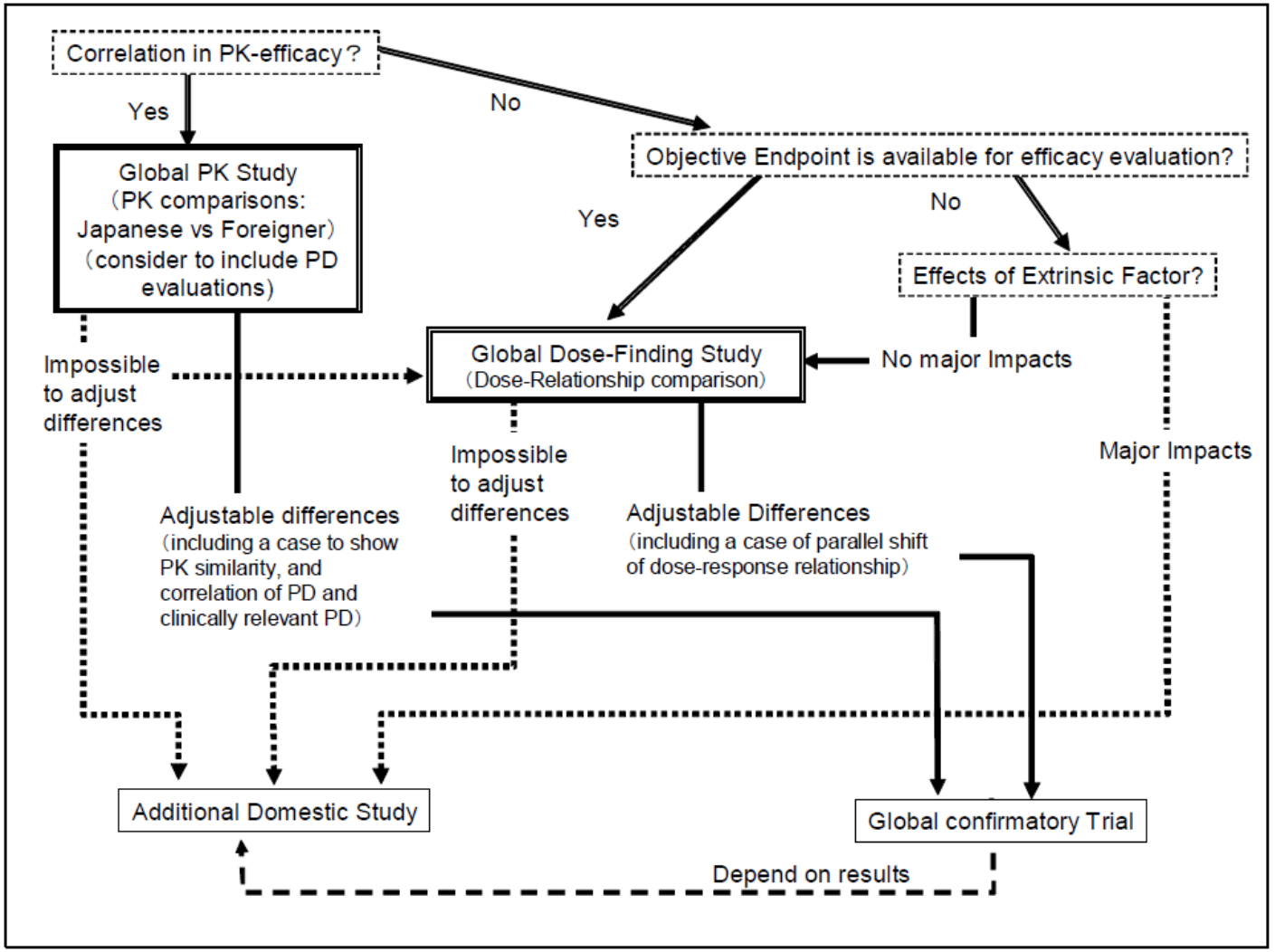
“Basic Principles on Global Clinical Trials”

- 12 Q&As
  - Basic requirements to conduct a 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

“Basic Principles on Global Clinical Trials”

- 12 Q&As (Cont.)
  - 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

Flow chart


Correlation in PK-efficacy?
Yes
No
Global PK Study
(PK comparisons:
Japanese vs Foreigner)
(consider to include PD
evaluations)
Objective Endpoint is available for efficacy evaluation?
Yes
No
Effects of Extrinsic Factor?
Impossible
to adjust
differences
Global Dose-Finding Study
(Dose-Relationship comparison)
No major Impacts
Major Impacts
Impossible
to adjust
differences
Adjustable differences
(including a case to show
PK similarity, and
correlation of PD and
clinically relevant PD)
Adjustable Differences
(including a case of parallel shift
of dose-response relationship)
Additional Domestic Study
Global confirmatory Trial
Depend on results

“Reference Cases”

- There were few approved cases when the original guidance document was issued in Japan.
  - “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 in original guidance.
- 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 China, Korea and Japan

“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

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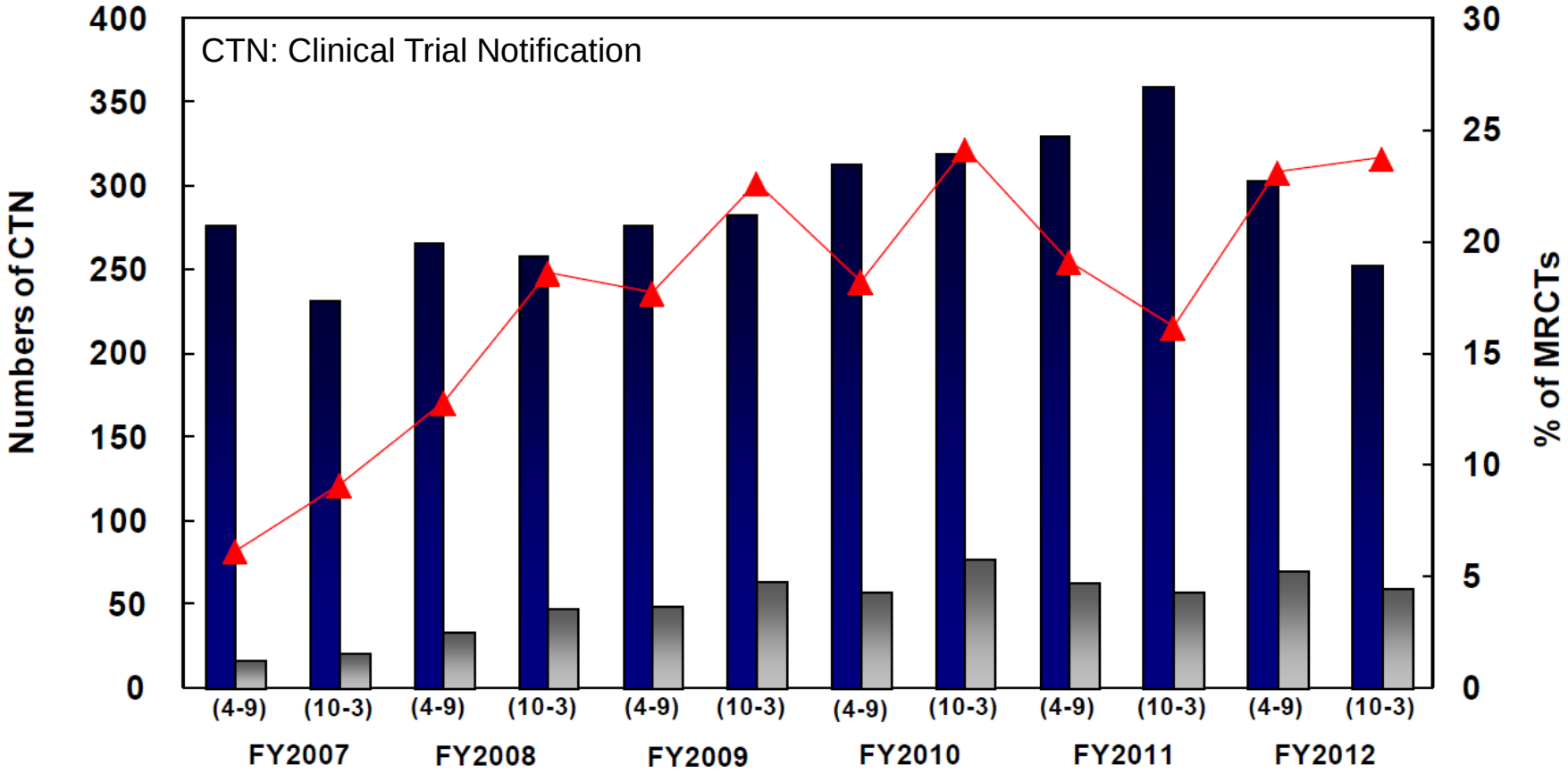
Current situation in Japan

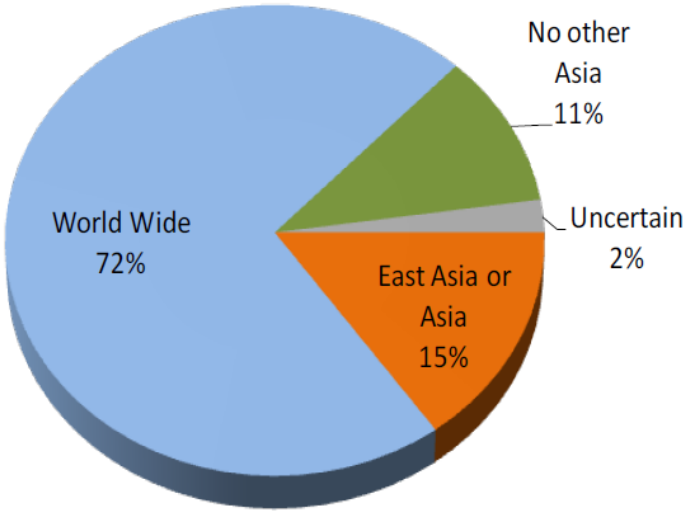
- The proportion of global clinical trials including Japanese subjects is increasing.
- There is a certain number of Asian clinical trials.
- GCT now seems to be a general tool for drug development.
- There are a few cases of bridging strategy.
  - When the development outside Japan is ahead of development in Japan
  - Bridging strategy is still useful in such cases.

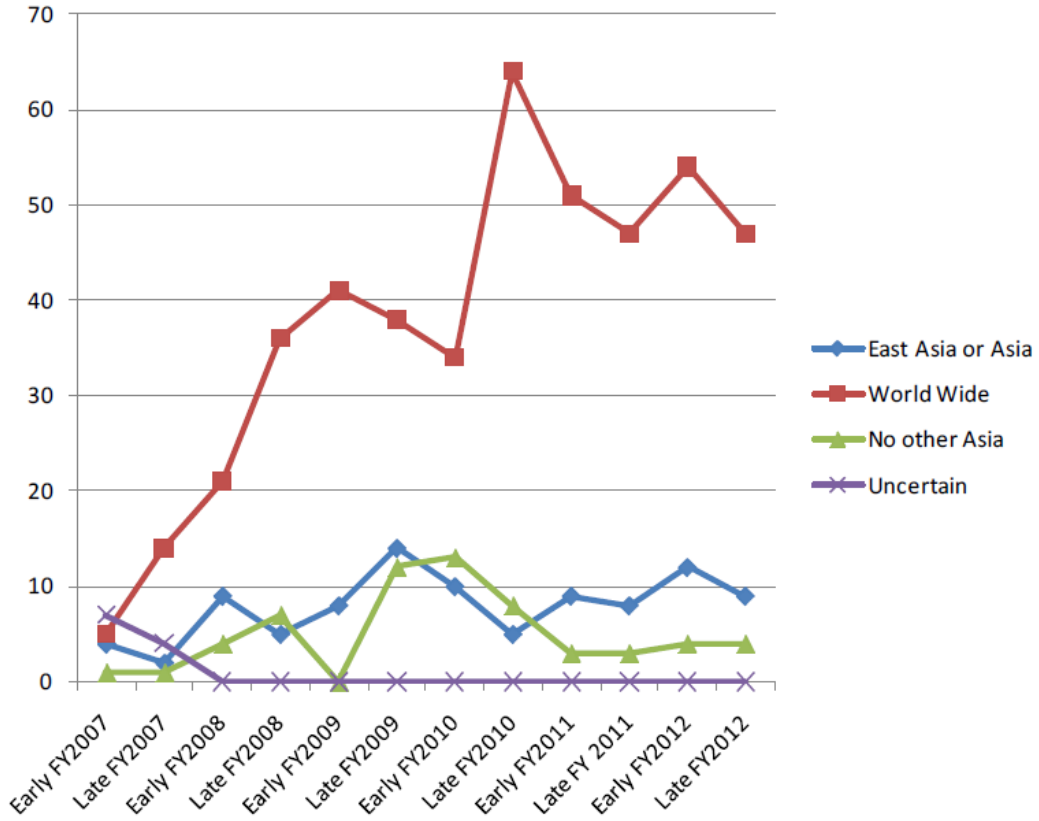
Trend of GCT including Japan



http://www.pmda.go.jp/regulatory/file/RS_data/MRCT/MRCT_FY2007-FY2012.pdf

Regions for conducting GCT





http://www.pmda.go.jp/regulatory/file/RS_data/MRCT/MRCT_FY2007-FY2012.pdf

Approved cases based on GCTs in Japan

2006	2007	2008	2009	2010	2011	2012	2013
Tolterodine		Trastuzumab	Insulin - Glulisine	Peramivir	Dabigatran	Denosumab	Insulin - Degludec
Losartan			Tadalafil	Everolimus	Trastuzumab	Aripiprazole	Glycopyrronium
				Panitumumab	Pramipexole	Olanzapine	Pazopanib
				Travoprost/ Timolol	Edoxaban	Exenatide	Everolimus
				Temsirolimus	Dasatinib	Crizotinib	Fesoterodine
				Laninamivir	Indacaterol	Budesonide/ Formoterol	Everolimus
				Nilotinib	Linagliptin	Esomeprazole	Apixaban
					Gefitinib	Formoterol	Insulin-Degludec+Aspart
					Everolimus	Axitinib	Paclitaxel
						Budesonide/ Formoterol	Pregabalin
						Atomoxetine	Tofacitinib
						Aflibercept	Regorafenib

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 Apr 1, 2013

Current situation in Japan

- The number of approved cases with GCT is rapidly increasing.
- We accumulate experiences in planning and evaluating worldwide and Asian GCTs in Japan.

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Selected points from Japanese guidance document

- Although the guidance was issued for promoting global drug development including Japan, most of the points are useful for other regions.
- Especially when
  - consider participation in global drug development
  - evaluate efficacy and safety of a drug in a region based on the results of GCT

Basic principles

- "Global Clinical Trial (GCT)"
  - A trial designed for a new drug aiming for worldwide development and approval
  - Having multiple countries, regions and medical institutions participating in a single clinical trial
  - Conduct concurrently in accordance with a common clinical trial protocol

Basic principles

- An appropriate timing to participate in global drug development
  - Regarding clinical developments that are globally proceeding, it is recommended to participate as soon as possible.
  - At the latest, participation to the exploratory dose-finding study should be possible.

Phase I study

- Importance of a phase I trial or pharmacokinetic information prior to conduct of a GCT for patients
  - The dosage regimen to be used in the GCT should be confirmed beforehand, so it is important to examine single dose safety and pharmacokinetics of the drug in a region.
  - PK comparison between participating regions is important to determine an appropriate dose for the regions.
  - If safety in the region can be determined from the results of foreign PI trials, a PI in the region is not necessarily required prior to the GCT

Dose-finding study

- Acceptability of participation in a confirmatory PIII GCT without conducting any dose-finding study in the region?
  - PK may be different between regions and it is sometimes difficult to conclude that we can use same dose as a recommended dose for all regions.
  - It is recommended to participate in a dose-finding GCT to identify inter-ethnic difference in dose-response relationship early in clinical development.

Possibility of dose difference

FORUM/REGULATORY SCIENCE

Same Drug, Different Dosing: Differences in Dosing for Drugs Approved in the United States, Europe, and Japan

Henry J. Malinowski, PhD, Agnes Westelinck, Pho and Ting Ong, MS

With globalization of the pharmaceutical industry, newly approved drugs nearly always become available worldwide, including the 3 major pharmaceutical regions: the United States, Europe, and Japan. One might think that these drugs would have the same recommended dosing throughout the world, but this appears not to be true in many instances. The objective of this study was to identify any patterns of differences in labeled dosing. Approved labeling, for the most widely prescribed proprietary drugs in the United States, was used as a basis for this study. Dosing was compared, for common indications, for the United States, Europe, and Ja are numerous approved in all ied, dosing in J States or Euro apparent betwe

Keywords: *Int exp*

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Malinowski, et al., *Journal of Clinical Pharmacology* 2008;48:900-908

Arnold, et al., *Clin Pharmaco Therapeut.*, 2010;87:714-720

ARTICLES

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Exploring Differences in Drug Doses Between Japan and Western Countries

FL Arnold[1], M Kusama[1] and S Ono[1]

Japan is unique among Asian countries in that it requires inclusion of substantial domestic clinical trial data in new drug application data packages. Some question the need for this and call for globalization of approved doses. The current study examines international differences in maximum daily dose of drugs approved in Japan between 2001 and 2007, and for all cardiovascular system (CVS) and central nervous system (CNS) drugs marketed in Japan. For 32% of the drugs approved in Japan between 2001 and 2007, the maximum recommended dose in the United States was ≥2 times higher than the maximum dose approved in Japan. Dose differences were rare for antitumor and antiviral drugs and also for priority-review and orphan drugs. Of all the price-listed CVS drugs currently available in Japan, 65% had maximum doses that were ≥2 times higher in the Netherlands than in Japan; similarly, 57% of the drugs had maximum doses that were ≥2 times higher in the United States than in Japan. For CNS drugs, these figures were 32% (the Netherlands) and 29% (United States). These results underscore the necessity to carry out quantitative analyses to determine the causes of these differences.

Designing GCT

- The basic points to consider in designing a GCT
  - It is necessary to evaluate
    - effects of ethnic factors specific to individual regions on efficacy and safety of the drug
    - efficacy and safety of investigational drugs in region where the GCT will be used for new drug submission
  - The designs and analytical methods for the GCT should be acceptable to all regions.
  - The primary endpoints should be those acceptable to all individual regions
    - If the primary endpoints are different by region, data on all the primary endpoints should be collected in all regions
  - The collecting and assessing method of adverse event information should be standardized as much as possible across all regions

Sample size for a region

- Appropriate sample size (or a proportion) for one region
  - Sufficient statistical power to detect statistically significant results should not necessarily be secured within the subpopulation (population in one region).
  - GCT should be designed so that consistency can be obtained between results from the entire population and that from population in each region.
  - Sample size for each region needs to be determined by considering some factors, including the number of regions, the scale of trial, target disease, and the relevant ratio between the total and each subject numbers.
  - (Two methods as examples)

Sample size for a region

- Method 1:
  - Determine the sample size of Japanese subjects so that DJapan/Dall>0.5 will occur with a probability of 80% or higher. (D: Difference between placebo and study drug)
- Method 2:
  - Determine sample sizes so that D of each region show a similar tendency. For example with three regions, the number of subjects is determined so that each of the D1, D2, and D3 will exceed 0 with a probability of 80 % or higher.

Sample size for a region

- Current situation in Japan
  - Sample size based on Method 1 or Method 2 in the guidance
  - Sample size based on modified Method 1 or 2
    - For non-inferiority trials, hazard ratio
    - At least based on criteria for point estimates of the endpoint with a certain degree of probability
  - Sample size based on the feasibility
    - For orphan type disease, oncology, or large scale trials

Endpoint

- GCT with endpoint which is not established in some regions
  - Conduct of a pilot study in the regions would be needed at as an early stage as possible
    - to confirm whether drug response in the regions is similar to other regions
  - In addition, to minimize possible differences among raters, trial sites, and regions, some measures are needed before the start of the GCT, such as developing and conducting a regionally-common training program.
  - -> Example: Atomoxetine

Separately performed trial

- Foreign GCT and smaller domestic trial that is separately performed using identical protocol
  - They should generally be regarded as separate trials, and it is difficult to conclude that the efficacy and safety are the same between all regions based on the results of these trials.
  - Bridging study with enrollment of enough number of subjects to allow statistical consideration within the region would be recommended.
  - -> Example: Rivaroxaban

Disease areas

- Disease areas where conduct of a GCT is recommended
  - GCT can be performed in any therapeutic areas.
  - Conduct of a GCT should be actively considered for diseases for which conduct of a large confirmatory clinical trial in one region will be difficult
    - E.g., orphan diseases
    - Building clinical evidence based on the more appropriately designed trial
  - Also, participating in GCT should be actively considered for the disease area that take a long time to accumulate a sufficient number of subjects even at global level, such as a large clinical trial with true clinical endpoints.

Example: Tadalafil

- PDE5 inhibitor
- Indication: pulmonary arterial hypertension (PAH)
- GCT:
  - Randomized placebo-controlled trial conducted in Europe, North America, and Japan
  - Objective: To demonstrate efficacy and safety of each dose group of tadalafil compared to placebo
    - Dose groups: 2.5mg, 10mg, 20mg, 40mg
  - Number of patient: 405 (including 26 Japanese)
  - Primary endpoint: 6-minute walk distance change from baseline to week16

http://www.info.pmda.go.jp/shinyaku/P200900050/index.html

http://www.info.pmda.go.jp/shinyaku/P200900050/530471000_22100AMX02266000_A100_1.pdf

Tadalafil: Results

Result of primary endpoint: Mean 6-minute walk distance (m)

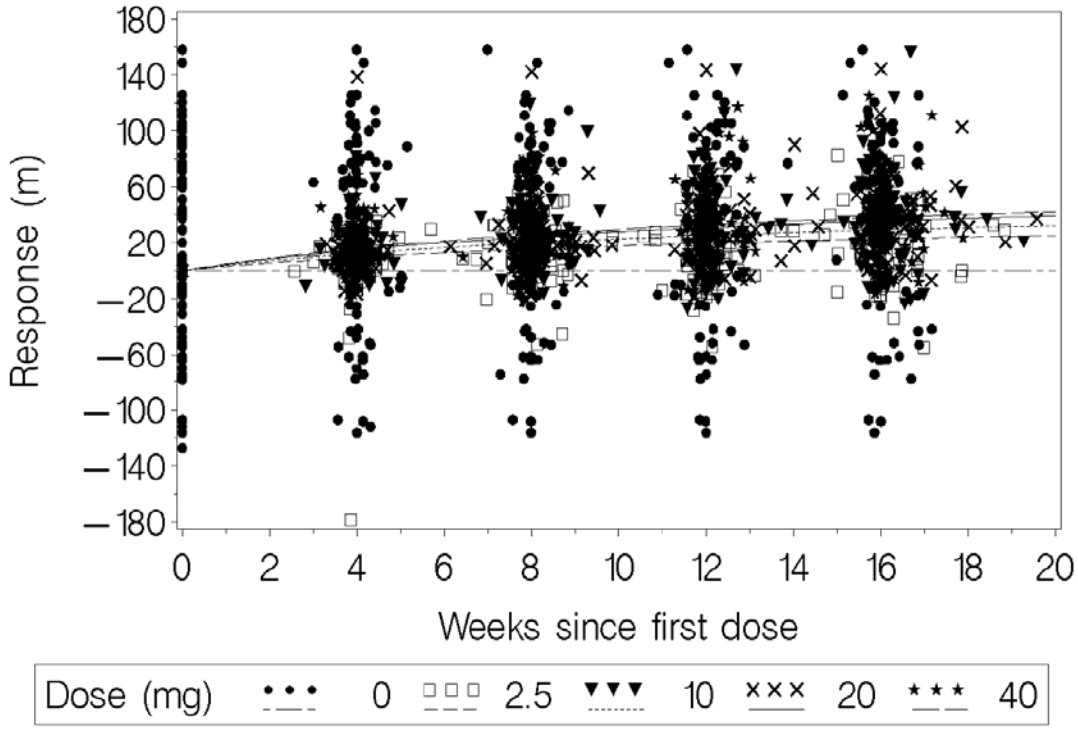
		Placebo	2.5mg	10mg	20mg	40mg
All regions	Baseline	347.49	346.53	340.01	338.26	352.67
	Week 16	356.71	368.32	368.61	374.49	393.80
	Change	9.21	21.79	28.60	36.23	41.14
	N	79	79	78	80	76
Japan	Baseline	313.33	371.08	311.06	370.87	375.20
	Week 16	362.67	398.50	405.62	409.75	459.25
	Change	49.33	27.42	94.56	35.25	63.00
	N	3	6	5	6	4

Tadalafil: Discussion point

- Most of the clinical trials conducted for previously approved drugs for PAH were single arm trials
- General conclusion for this case
  - Sample size of Japanese patients was not sufficient to evaluate consistency.
  - However, there was not a severe discrepancy between all patients results and Japanese results from a comprehensive viewpoint that looks at the total patient data.

Tadalafil: Results

- Selection of recommended dose
  - 6-minute walk distance change from baseline of individual patient and predicted value from PK/PD modeling



Disease areas

- Experiences in Japan
  - In some cases of drugs for orphan type diseases and oncology drugs, the number of Japanese subjects did not seem to be sufficient for efficacy evaluation.
  - Even in such cases, participating in GCT is useful for collecting safety information in target Japanese patients, and is also important for establishing evidence of the drug.

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Selected points from “Reference cases”

- “Reference Cases” includes special points to consider for GCT in East Asia
- Also it includes points to consider based on recent experiences

Points to consider for GCT in East Asia

- Special points to consider for global clinical trial in East Asia
  - The types and frequency of metabolic enzyme polymorphisms and gene profiles are expected to be similar
  - However, 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

Points to consider for GCT in East Asia

- Recommended therapeutic areas
  - 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
  - E.g. gastric cancer, hepatitis

Points to consider for GCT in East Asia

- Global drug development strategy plan based on data of interethnic comparison of pharmacokinetic profiles

Points to consider for GCT in East Asia

- Development plan may depend on the comparison of the PK profile
  - Between East Asian and Caucasian
  - Among East Asian populations
- Based on the results of comparison, most efficient plan should be chosen, such as
  - Worldwide GCT from early exploratory phase
  - East Asian exploratory clinical trial
  - Exploratory study in one region
- 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 clinical development strategies and a protocol of regional study in the trend of globalization of drug development

Development plan

- Key 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

Development plan

- Three major types of clinical development strategies
  - 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 (for East Asian Countries)
- Optimal protocol should be developed for the next phase based on the data available at the moment.

Example: Atomoxetine

- Selective norepinephrine reuptake inhibitor
- Indication: Adult attention-deficit hyperactivity disorder (AD/HD)
  - Already approved in 29 countries including US, Taiwan, and Korea
- Prior information
  - Japanese PII, foreign PII, results in AD/HD in children
- GCT (PIII)
  - Placebo-controlled double-blinded East Asian clinical trial conducted in Taiwan, Korea, and Japan

http://www.info.pmda.go.jp/shinyaku/P201200114/index.html

http://www.info.pmda.go.jp/shinyaku/P201200114/53047100_22100AMX00644_A100_1.pdf

Atomoxetine: results of GCT

Primary endpoint: CAARS-Inv: SV* AD/HD Total Score

*: Conner's Adult AD/HD Rating Scales-Investigator Rated and Scored: Screening Version

	Group	n	Baseline	Post	Change	Difference (95%CI)
All	Placebo	195	33.9±7.5	25.1±11.2	-8.8±9.6	-5.78 (-7.66,-3.91)
	Atomoxetine	191	33.2±7.8	18.9±10.2	-14.3±10.4	
Japan	Placebo	124	32.8±7.6	26.0±10.6	-6.8±8.5	-5.98 (-8.18,-3.77)
	Atomoxetine	123	32.0±7.5	19.5±10.2	-12.6±9.5	
Korea	Placebo	37	33.0±6.5	19.8±10.6	-13.2±8.7	-5.60 (-10.06,-1.15)
	Atomoxetine	34	35.8±7.8	16.0±9.8	-19.8±10.4	
Taiwan	Placebo	34	39.3±6.1	27.6±12.6	-11.6±12.1	-6.13 (-11.92,-0.34)
	Atomoxetine	34	34.9±7.8	19.7±10.7	-15.2±11.9	

Atomoxetine: discussion points

- Prior consideration of ethnic differences
  - There was no major difference in intrinsic factors such as
    - pharmacokinetics between Japanese and other Asian countries
    - Incidence rate
  - AD/HD was not so well recognized and it seemed that there was no major difference in Extrinsic factors such as
    - Diagnostics
    - Standard therapy

Atomoxetine: discussion points

- Study design
  - Diagnostics criterion in the trial
    - Establishment of Japanese version of Conners' Adult AD/HD Diagnostic Interview for DSM-IV (CAADID)
    - Training for evaluation using CAADID
  - Primary endpoint
    - Establishment of Japanese version of CAARS-Inv: SV with validation study
    - Check inter-rater variability in all countries
- Results
  - Consistent between regions
  - No major factors affect the efficacy and safety

Example: Rivaroxaban

- Direct factor Xa inhibitor
- Indication: Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Japan could not participate in worldwide GCT.
  - Rivaroxaban is approved in Japan not based on GCT including Japanese subjects
  - Smaller trial with Japanese subjects, which is basically not recommended, was conducted and evaluated.

http://www.info.pmda.go.jp/shinyaku/P201200011/index.html

http://www.info.pmda.go.jp/shinyaku/P201200011/630004000_22400AMX00041_A100_1.pdf

Example: Rivaroxaban

- Two trials with almost identical protocol
  - GCT not including Japan(ROCKET AF)
    - Randomized double-blinded parallel group trial conducted in 45 countries
    - Objective is to show non-inferiority to warfarin
    - Number of patients: 14264
  - Japanese trial(J-ROCKET AF)
    - Randomized double-blinded parallel group trial conducted in Japan
    - Objective is to investigate safety (non-inferiority) compared to warfarin
    - Number of patients: 1280

Rivaroxaban: Results of two trials

ROCKET AF

		20mg	Warfarin
Efficacy	N	6958	7004
	Stroke/SS (/100pat.-y.)	188 (1.71)	241 (2.16)
	Hazard ratio (95%CI)	0.79 (0.66-0.96)	
Safety	N	7111	7125
	Bleeding (/100pat.-y.)	1475 (14.91)	1449 (14.45)
	Hazard ratio (95%CI)	1.03 (0.96-1.11)	

J-ROCKET AF

		15mg	Warfarin
Efficacy	N	637	637
	Stroke/SS (/100pat.-y.)	11 (1.26)	22 (2.61)
Safety	N	639	639
	Bleeding (/100pat.-y.)	138 (18.04)	124 (16.42)
	Hazard ratio (95%CI)	1.11 (0.87-1.42)	

Efficacy endpoint: composite of stroke and non-CNS systemic embolism
Safety endpoint: composite of major and non-major clinical relevant bleeding events

Rivaroxaban: Discussion points

- Different dose for Japanese
  - Based on the PPK model, simulation
- We could expect that the clinical usefulness shown in ROCKET AF will be shown also in Japanese patients, but the efficacy information in Japanese was limited.
  - Information from J-ROCKET AF is useful, but smaller number of Japanese population was not sufficient for efficacy confirmation.
- -> Contrasted with Example: Apixaban

General points to consider

- Points to consider in evaluating the results of a global clinical trial

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

Example: Insulin Degludec

- Insulin analog
- Indication: diabetes mellitus
- GCT:
  - GCT for Type 1 diabetes
  - Asian trial for Type 2 diabetes
    - Comparing insulin degludec to insulin glarugin

Asian trial of Insulin Degludec

- Information of ethnic factors
  - Possibility of severe impairment in insulin secretion and less insulin resistance in Asian type 2 diabetes compared to Caucasian
  - Age, disease duration, BMI, and HbA1c are almost same among Asian countries based on research results
  - Similar guidance documents based on the worldwide used guidance (e.g. WHO)
  - No major difference in PK among Asian countries

Asian trial of Insulin Degludec

- Check results of all subjects and those of Japanese subjects
  - Primary endpoint: HbA1c
  - Secondary endpoints: blood sugar level, % of patients with HbA1c<7.0%, etc.
  - -> No major difference
- Check patient characteristics
  - -> Difference in sex, age, and concomitant drugs (glucose lowering agents)

Asian trial of Insulin Degludec

- Check effects of factors based on the subgroup analysis of overall population (and Japanese population) by factors
  - Sex: no major effects in overall population (and Japanese population)
  - Age: change from baseline of HbA1c is smaller in age > 65 in both group and there was no effects of age on difference between groups (in overall population and in Japanese population)
  - Concomitant drugs: no effects of on difference between groups in overall population

Large-scale GCT

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

Large-scale GCT

- One region 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 subjects in individual region may not be achieved 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

Example: Dabigatran

- Direct thrombin inhibitors
- Indication
  - Stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Prior information
  - Japanese PII for safety
- GCT: Global PIII (RE-LY)
  - Prospective, randomized, open label, blinded endpoint evaluation (PROBE)
  - Parallel group trial of 150mg, 110mg, and warfarin, to show non-inferiority of Dabigatran to warfarin
  - Number of patients: 18113 (including 326 (1.8%) Japanese patients)

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

http://www.info.pmda.go.jp/shinyaku/P201100019/530353000_22300AMX00433000_A100_1.pdf

Dabigatran: Results (efficacy)

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)	—

Dabigatran: Results (safety)

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)	—

Dabigatran: discussion points

- Design issues
  - PROBE design, non-inferiority margin
  - Acceptance of PT-INR criteria for warfarin dose adjustment 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

Dabigatran: post-marketing

- 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
- Even there was the results of large scale clinical trial, it may be difficult to assume actual use in clinical environment

Example: Apixaban

- Direct factor Xa inhibitor
- Indication
  - Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Prior information
  - Japanese PII for safety
  - Foreign PII in patients with elective knee replacement
  - Foreign PII in patients with deep venous thrombosis

http://www.info.pmda.go.jp/shinyaku/P201200166/index.html

http://www.info.pmda.go.jp/shinyaku/P201200166/670605000_22400AMX01496_A100_1.pdf

Example: Apixaban

- GCT: Global PIII (ARISTOTLE)
  - Randomized double-blinded parallel group non-inferiority trial compared to Warfarin
  - Number of patients: 18201 (including 336 (1.8%) Japanese patients)
  - Dose could be reduced from 5.0mg BID to 2.5mg BID, according to the criteria for patient characteristics
    - Age, weight, and serum creatinine

http://www.info.pmda.go.jp/shinyaku/P201200166/index.html

http://www.info.pmda.go.jp/shinyaku/P201200166/670605000_22400AMX01496_A100_1.pdf

Apixaban : Results (efficacy)

Incidence of stroke (including hemorrhagic) and systemic embolism

		Apixaban	Warfarin
Total	N	9120	9081
	Stroke/SEE (Yearly rate%)	212 (1.27)	265 (1.60)
	Hazard ratio (95%CI)	0.79 (0.66-0.95)	—
	Hazard ratio (99%CI)	0.79 (0.62-1.00)	—
Japanese	N	161	175
	Stroke/SEE (Yearly rate%)	3 (0.87)	6 (1.67)

Apixaban : Results (safety)

Major bleeding

		Apixaban	Warfarin
Total	N	9088	9052
	Major bleeding (Yearly rate%)	327 (2.13)	462 (3.09)
Japanese	N	160	175
	Major bleeding (Yearly rate%)	4 (1.26)	18 (5.99)

Apixaban : Results (dose)

		Apixaban	Warfarin
Total	Total N	9120	9081
	5.0mg BID	8692 (95.3%)	8678 (95.6%)
	2.5mg BID	428 (4.7%)	403 (4.4%)
Japanese	Total N	161	175
	5.0mg BID	151 (93.8%)	161 (92.0%)
	2.5mg BID	10 (6.2%)	14 (8.0%)

Apixaban: Discussion points

- Design issues
  - 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

Apixaban: discussion points

- Information of doses
  - Appropriateness of criteria for low dose
  - sufficiency of information of low dose

Outline

- Introduction
- Guidance documents in Japan
  - “Basic Principles on Global Clinical Trials”
  - “Basic Principles on Global Clinical Trials – Reference Cases”
- Current situation in Japan
- Selected points from “Basic Principles” and “Reference cases ” with case example
  - Selected points from “Basic Principles”
  - Selected points from “Reference cases ”
- Other issues related to Global Clinical Trials
- Summary

Different regulatory requirement

- In some GCTs, 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.

Different regulatory requirement

- Apixaban
  - Significance level for one pivotal trial, 2.5% or 0.5% (one-sided)
  - Non-inferiority margin, 1.44 or 1.38

Different regulatory requirement

- Fesoterodine

  (foreign (but 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 in closed testing procedure

Different regulatory requirement

- 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 are very important.
- Designing trial to meet regulatory requirements of multiple regions is important for efficient drug development.

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Summary and 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
  - Patient selection by biomarkers
- It is important to share our experience between industry and regulatory agency (agencies).

Reference

- Please see the original text of the Japanese guidance documents for details
- “Basic Principles on Global Clinical Trials”
  - http://www.pmda.go.jp/kijunsakusei/file/guideline/new_drug/GlobalClinicalTrials_en.pdf
- “Basic Principles on Global Clinical Trials - Reference Cases”
  - http://www.pmda.go.jp/kijunsakusei/file/guideline/new_drug/GCT-jirei_en.pdf