Session 36 - Advances in Multi-regional Clinical Trials

Regulatory and statistical issues of Multi-regional Clinical Trials: "Reference Cases" and current situation in Japan

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Outline

- Introduction
  - "Basic Principles on Global Clinical Trials"
  - Current situation
- "Basic Principles on Global Clinical Trials - Reference Cases"
- Recent examples
- Difference in regulatory requirements

Global drug development

- 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
- Multi-Regional Clinical Trial (MRCT) is considered as one of efficient tool for simultaneous global drug development.

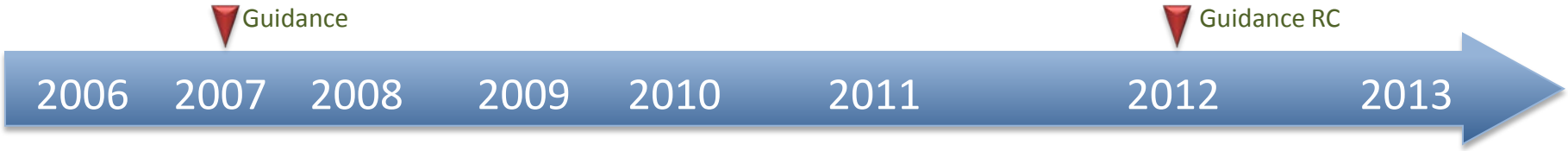
Using foreign data for J-NDA

- ICH-E5 guideline, “Ethnic factors in the acceptance of foreign clinical data” (1998)
  - “Bridging strategy” and “bridging study”
- ICH-E5 Q&A No.11 (2006)
  - MRCT for the purpose of bridging
  - Shift to global simultaneous drug development with MRCT
- Japanese guidance document “Basic Principles on Global Clinical Trials” (2007)
- Supplement of original guidance document “Basic Principles on Global Clinical Trials – Reference Cases” (2012)

Contents of “Basic Principles”

- Basic requirements to conduct a Global Clinical Trial (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
- 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

Approved cases based on MRCT in Japan



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 May 1, 2013

“Reference Cases”

- 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
- 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

Contents of “Reference Cases”

- 4 special points to consider for global clinical trial in East Asia
- 13 general points to consider, such as
  - Global drug development strategy plan based on data of interethnic comparison of PK profiles
  - Points to consider in planning clinical development strategies and a protocol of regional study in the trend of globalization of drug development
  - Points to consider in evaluating the results of a global clinical trial
  - Points to consider in participating in a large-scale global clinical trial using a true endpoint such as survival time

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)
- When the results show inconsistency,
  - Possible reason of inconsistency should be reviewed.
  - Possibility of using the results of the GCT for NDA for individual region should be carefully investigated.

Large-scale GCT

- The number of Large-scale GCTs including Japan is increasing, especially in cardiovascular area.
- One region may contribute to establishment of evidence based on the true endpoint by participating in large-scale GCT.
- However, considering number of participating regions, adequate sample size of subjects in individual region may not be achieved.
  - It may be difficult 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

Three examples

- Three approved cases of cardiovascular drugs that have issues of large-scale clinical trial and dose selection
  - Large-scale MRCT including Japanese
    - Dabigatran (Direct thrombin inhibitor)
    - Apixaban (Direct Factor Xa inhibitor)
  - Foreign MRCT not including Japanese and separately performed Japanese trial
    - Rivaroxaban (Direct Factor Xa inhibitor)
      - Strategy which is generally not recommended
      - Example of the case that Japan could not participate in worldwide MRCT

Three examples

	Dabigatran	Apixaban	Rivaroxaban
Indication	Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation		
MRCT	RE-LY	ARISTOTLE	ROCKET AF J-ROCKET AF
Design of Trial(s)	PROBE Non-inferiority	Double-Blinded Non-inferiority	Double-Blinded Non-inferiority
Comparison groups	Dabigatran 150mg Dabigatran 110mg Warfarin*	Apixaban 5.0mg** Warfarin*	ROCKET AF: Rivaroxaban 20mg**, warfarin J-ROCKET AF: Rivaroxaban 15mg**, warfarin*
Number of patients	Total: 18113 Japan: 326 (1.8%)	Total: 18201 Japan: 336 (1.8%)	ROCKET AF: 14264 J-ROCKET AF: 1280

* Different PT-INR criteria for warfarin in Japanese elderly

** Can be reduced to the lower doses depend on patient characteristics, such as, age, weight, and serum creatinine (Apixaban), or creatinine crearance (Rivaroxaban)

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)	—

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%)

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

Lessons Learned from 3 cases

- Consistency evaluation of large-scale MRCT
  - Need comprehensive review of efficacy and safety, with reviewing secondary endpoints
  - Post-approval research will be useful
  - Possible effect of PT-INR criteria for warfarin dose adjustment in Japanese elderly
- Different strategy for recommended dose
  - Parallel dose design and one dose group with adjustment
  - Appropriateness of criteria for low dose
  - Possible regional deference of distribution of final dose in strategy with dose adjustment
- Separate trial for Japanese
  - Although there is a possibility that Japan can not participate in MRCT because of dose difference, it is difficult to evaluate results of efficacy in Japanese trial because of lack of power
  - Need thorough investigation for different dose in Japanese

Difference in regulatory requirements

- In some MRCTs, 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.

Recent Examples

- Apixaban (MRCT including Japanese patients)
  - Significance level for one pivotal trial, 2.5% or 0.5% (one-sided)
  - Non-inferiority margin, 1.44 or 1.38
- Fesoterodine (foreign/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 for closed testing procedure

Difference in regulatory requirements

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

Summary and future tasks

- MRCT is one of the tools for efficient drug development in the era of global development .
- In each case, optimal study design including MRCT should be chosen in consideration of development plan, prior information of ethnic difference.
- Innovative and efficient trial designs will be applied to MRCT, and topics may be discussed in combination with ethnic difference.
  - Design and evaluation of dose-response trials
  - Patient selection by biomarkers
- We should share our experience between industry and regulatory agencies.

Reference

- “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
- Review information (in Japanese)
  - Dabigatran
    - http://www.info.pmda.go.jp/shinyaku/P201100019/index.html
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