

# *Bridging Strategies using Clinical Trial Simulations*

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The 4th Kitasato University-Harvard School of Public Health  
Symposium

Advanced and Global Drug Development Techniques:  
Emerging Trends, Technology Updates and Novel  
Paradigms

28-29th October 2003, Tokyo, Japan

*Phase III data for Aricept was bridged from the US to Japan, based on similar efficacy at 5 mg vs. placebo in both regions.*

Donepezil Hydrochloride (Efficacy)

		ADAS-Jcog -cog	Difference from Placebo
Japan	Placebo	-0.26	
	5mg	-2.70	2.44
USA-1	Placebo	0.39	
	5mg	-2.09	2.48
USA-2	Placebo	1.73	
	5mg	-0.79	2.52

Dr. Yoshinobu Hiroyama. Bridging Guidance. The 1st K-H Symposium on Global Drug Development Techniques

- Similarity for AE's and Global Improvement also demonstrated
- No statistical criteria

*What criteria should be used when the dose-response relationship is dissimilar between regions?*

- **Matsuzawa Y, Kita T, Mabuchi H, Matsuzaki M, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H; J-LIT Study Group.**

**Effects of low-dose simvastatin therapy on serum lipid levels in patients with moderate hypercholesterolemia: a 12-month study. The Simvastatin Study Group.**

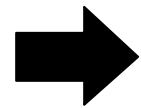
Circulation Journal Vol. 67 (2003) , No. 4 287-294

- Open-labeled simvastatin was given to 51,321 patients at an initial dose of mostly 5 mg/day. After 6 months of the treatment, the average serum total cholesterol (TC) ... were reduced by 18.3% ...
- Low-dose simvastatin therapy of 5 mg/day effectively controlled the serum TC concentration by reducing it by approximately 20% on average ... a reduction that corresponds to the effect of simvastatin 20 mg/day in Western studies.

*The purpose of this presentation is to discuss bridging strategies for compounds with dose-response relationships that differ between regions.*

- According to ICHE5, foreign data may be extrapolated to a new region at a different dose if the safety/efficacy profile are not substantively different.
- Illustrate with a hypothetical HMG-coA reductase inhibitor for cholesterol.
- Evaluate different strategies using simulation
- The simulation model is based on:
  - Slope of dose-response for all statins
  - Typical LDL variability
  - Assumed potencies in Japanese and Westerners.

# *Agenda*

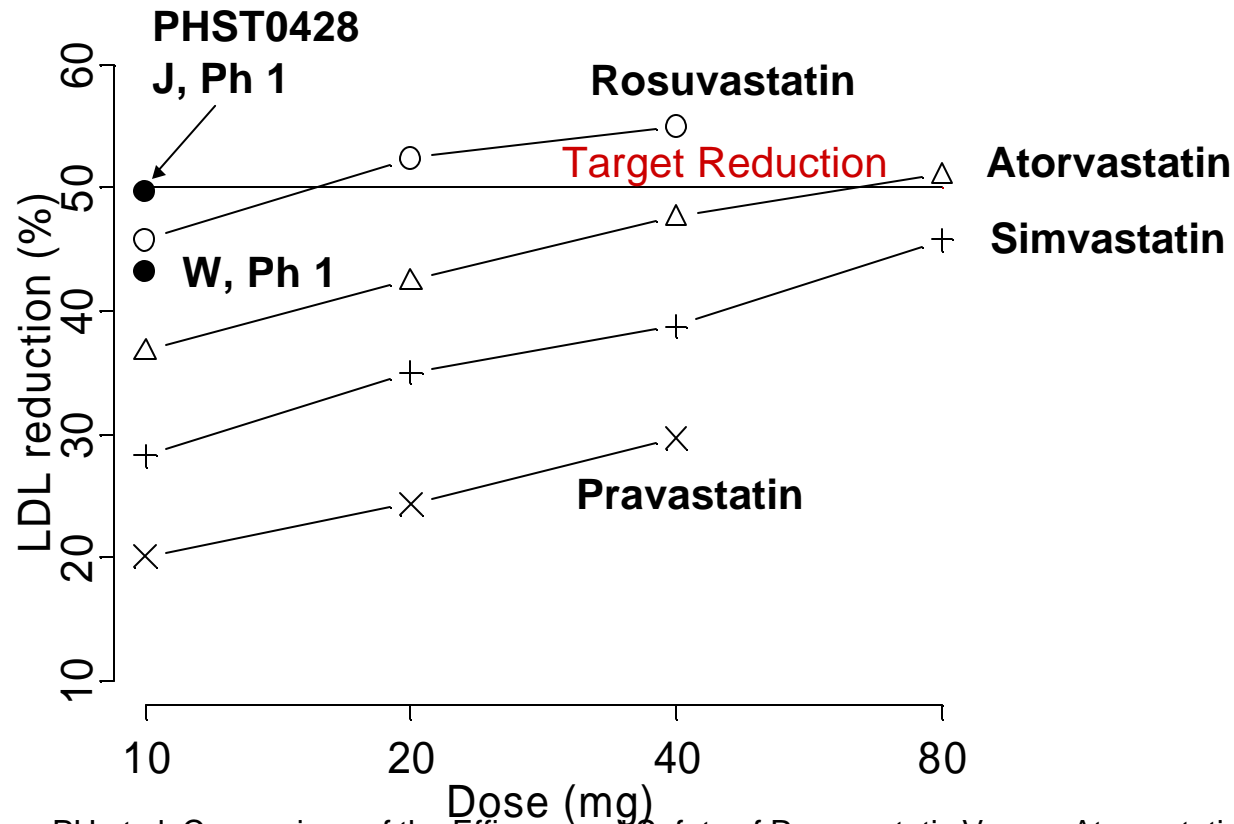


- Development strategy
- Evaluation of Phase II strategies to conclude similarity
- Conclusions

*PHST0428 is a potent NCE in the class of statins entering Phase II.*

- HMGcoA reductase inhibitor
  - More potent than competitors in in-vitro and in-vivo studies
  - Less influenced than competitors by OATP-C transporter variants, therefore anticipate less incidence of myopathy.
- Phase I completed in volunteers, Japanese and Westerners
  - Single dose PK, 1 – 80 mg QD
    - Well-tolerated, dose-linear PK
    - Similar between regions
  - Multiple dose PK, 10 mg QD, 14 days
    - Well-tolerated
    - 50% LDL reduction in Japanese, 43% in Westerners

*The target LDL reduction is selected to be 50%, to be superior to the start dose of 10 mg rosuvastatin.*



Jones PH et al, Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR\* Trial). Am J Cardiol 2003;92:152–160.

- Approximately 160 subjects per dose group, 6-week treatment
- Parallel dose-response curves

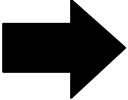
*LDL cholesterol reduction can be demonstrated in Phase II, however the infrequent incidence of myopathy must be evaluated in Phase III.*

- Conduct Phase II dose-response in hypercholesteremic Japanese and Westerners
  - Show dose response
  - Select two doses for Phase III
    - One dose which exceeds the target (50%)
    - The next lower dose
  - Find doses that show similar responsiveness in Japanese and Westerners
- Conduct Phase III in hypercholesteremic Westerners
  - Show acceptable cholesterol reduction vs. competitors for approval
  - Show acceptable safety on myopathy
    - <1% above 5 x ULN CPK
    - <0.1% above 10 x ULN CPK

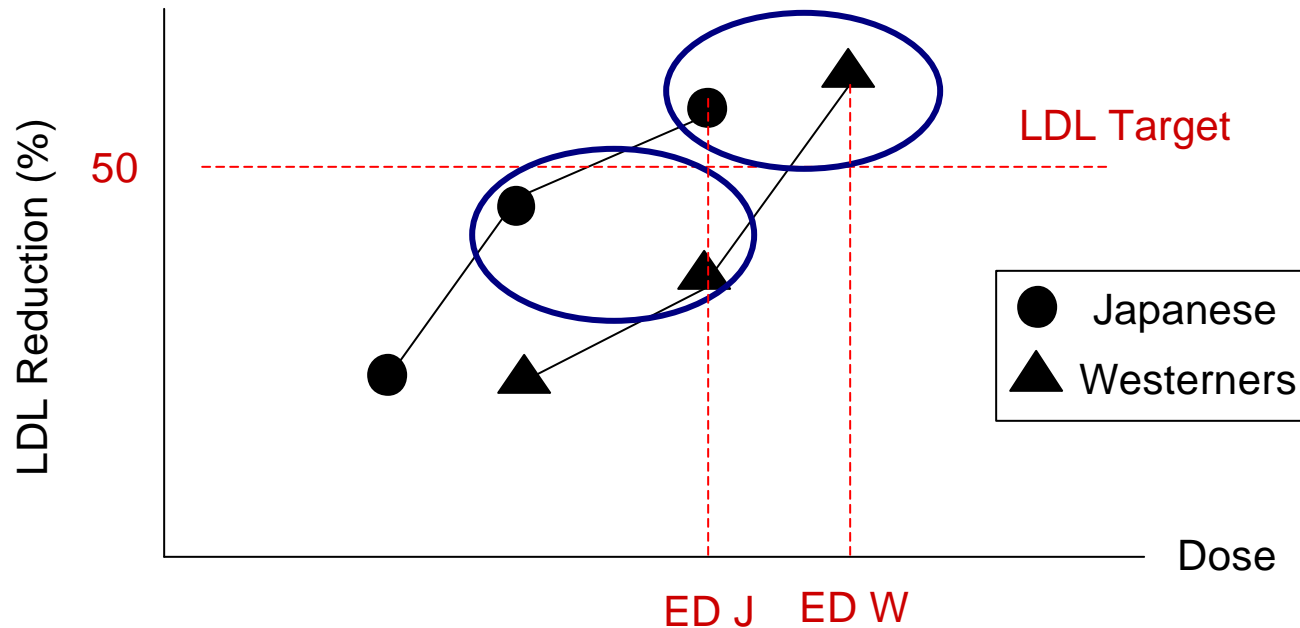
*The Phase II design can use a small number of subjects and a wide dose range, because of the small variability in LDL observed for past statins.*

- Hypercholesteremic, generally total cholesterol above 220 g/dL
- 4-week dietary run-in, 6-week treatment
- 12 patients per dose group will assure more than 80% power
  - Fewer than 10% dropouts
  - Variability on LDL reduction about 10%
  - Effect size of 20%
- Doses in Westerners: Placebo, 5, 10, 20, 40 mg
- Doses in Japanese: Placebo, 2.5, 5, 10, 20 mg
- Primary Analysis
  - Treatment versus placebo, e.g. ANOVA followed by Dunnett's test
  - Dose-response, e.g. Williams test

# *Agenda*

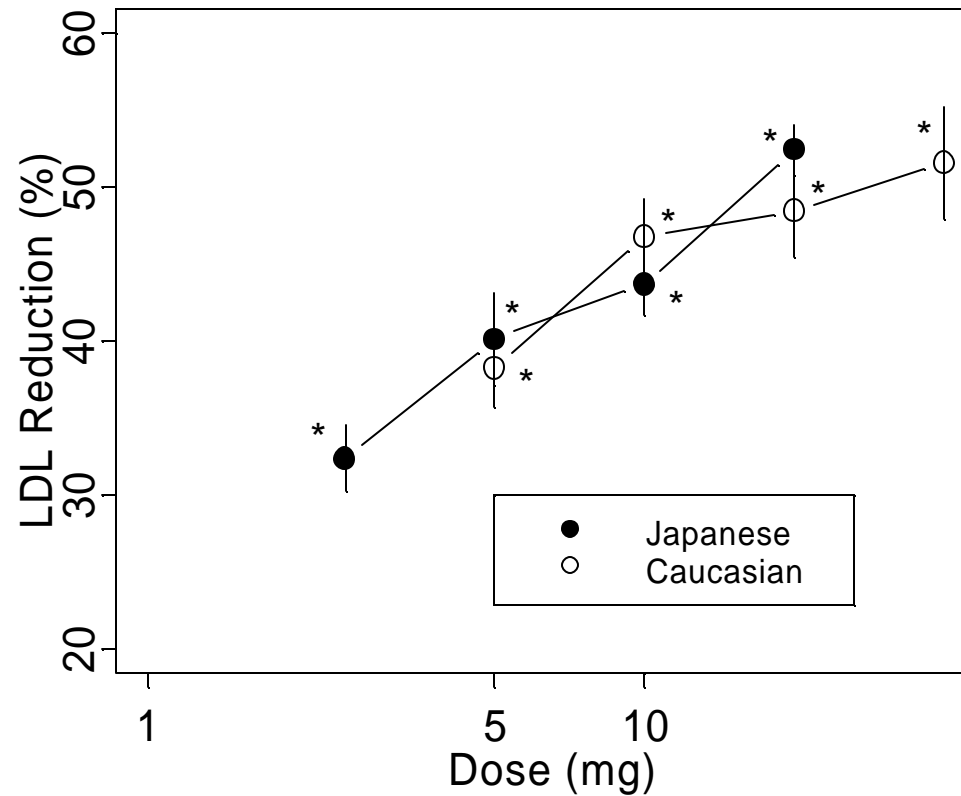
- Development strategy
-  • Evaluation of Phase II strategies to conclude similarity
- Conclusions

*As a first try we find two doses in Japanese and Westerners that meet the target profile and produce similar responses (5% apart).*



- Take effective dose (ED) achieving 50% LDL reduction in Westerners to Phase III in Europe and the US
- Find an Effective dose in Japanese, which achieves a LDL reduction within 5% (absolute percentage) of the Westerners response to the ED.
- Show that the next lower doses also produce similar response.

*To evaluate this strategy, we simulate Phase II trial results.  
Here is example simulation #1.*



\*Significant difference ( $p < 0.05$ ) versus placebo (data not shown) using unpaired t-test. 12 subjects per dose group.

*For simulation #1, dose selection in Japanese and Westerners is straight forward.*

Dose (mg)	LDL Reduction (%)	
	Japanese	Westerners
0	1	-4
2.5	32	
5	40	38
10	44	47
20	52	48
40		52

- 40 mg is the Effective Dose in Westerners
- 20 mg is the Effective Dose in Japanese
- 20 and 40 mg are the doses to take to Phase III in Westerners
- 10 and 20 mg provide similar effect in Japanese (5% diff vs. Westerners)

*Three additional simulations illustrate difficulties in dose selection.*

**Original Phase II simulation #1**

Dose (mg)	LDL Reduction (%)	
	Japanese	Westerners
0	1	-4
2.5	32	
5	40	38
10	44	47
20	52	48
40		52

**New simulation #2**

Dose (mg)	LDL Reduction (%)	
	Japanese	Westerners
0	1	-2
2.5	42	
5	41	39
10	51	43
20	49	49
40		58

**New simulation #3**

Dose (mg)	LDL Reduction (%)	
	Japanese	Westerners
0	2	-2
2.5	37	
5	40	39
10	47	42
20	50	46
40		47

**New simulation #4**

Dose (mg)	LDL Reduction (%)	
	Japanese	Westerners
0	-5	5
2.5	36	
5	39	40
10	45	38
20	49	54
40		51

Need higher doses!

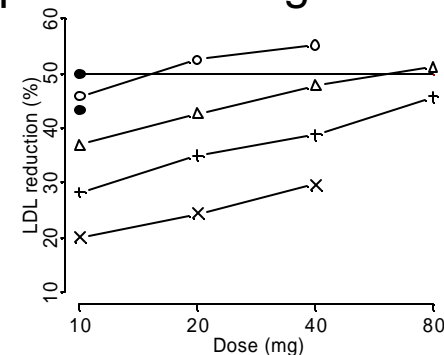
*The likelihood of finding an Effective Dose in Westerners is high. The likelihood to demonstrate similar responses for two doses in each region is 60%.*

Criterion	Likelihood of Similarity
Effective Dose in Westerners	95%
+ Effective dose in Japanese	75%
+ Similar response at next lower doses	60%

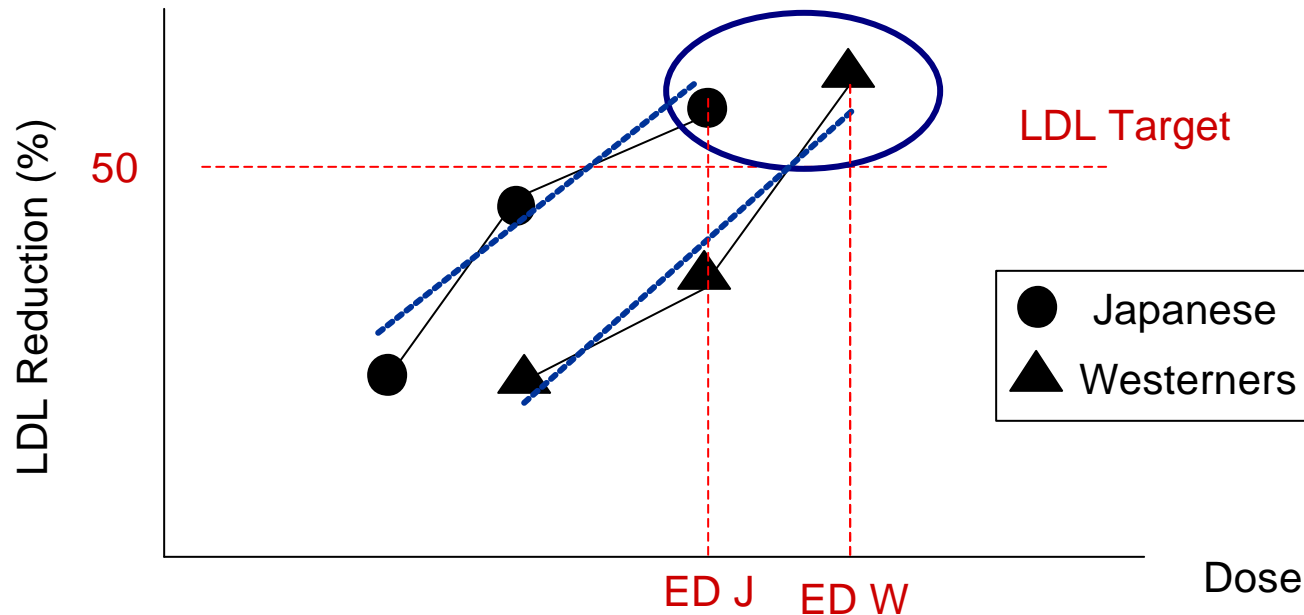
Effective Dose is the minimum dose achieving more than 50% LDL reduction in Westerners. The Equivalent dose is the minimum dose in Japanese achieving LDL reduction within 45 to 55%. The next lower doses (MED/2 and Equivalent dose/2) are matched if they achieving LDL reduction with an absolute 5% of each other. The likelihood of bridging success is the number of simulated programs out of 100 that demonstrate the composite criteria.

## *There are a variety of strategies to improve the likelihood of demonstrating similarity.*

- Different Phase II design
  - Higher doses (80 mg in Westerners, 40 mg in Japanese)
  - Increase n (12 to 16/group)
  - Determine covariates of increased responsiveness and match baseline conditions
- Different criteria for similarity
  - Compare slopes, instead of the response of the second dose
- Add more information
  - More Japanese Phase II studies (High vs. low dose vs. competitor)
  - Include Western Phase III data (High vs. low dose vs. competitor)
  - Competitor dose-response (Incorporate prior knowledge on slope of dose-response in Westerners)



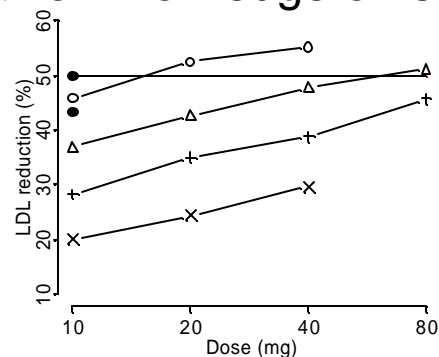
*For the slope similarity criteria, we find a single dose in each of Japanese and Westerners that meet the target profile and produce similar responses (5% apart). Then we match slopes.*



- Take effective dose (ED) achieving 50% LDL reduction in Westerners to Phase III in Europe and the US
- Find an Effective dose in Japanese, which achieves a LDL reduction within 5% (absolute percentage) of the Westerners response to the ED.
- Show that the ratio of the slopes of the response vs. log(dose) relationship is between [0.8, 1.25].

*We return to the previous slide, just to remind us of the different types of options to consider.*

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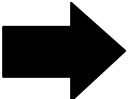
*Adding more information increases the likelihood to demonstrate similar dose-response slopes between Japanese and Westerners.*

Likelihood to demonstrate similarity (%)\*

	Similarity Criteria	
	Two doses	One dose + slope
First Try	60	38
+ Higher doses	73	56
+ Competitor dose-response	75	70
+ More Japanese Phase II	82	92
+ Include Western Phase III	86	94

\*400 trial simulations per scenario

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## *Learnings from this HMG-coA reductase case study.*

- When the dose-efficacy relationship differs between Westerners and Japanese:
  - Finding the Effective Dose and the “next best dose” in Westerners and Japanese is moderately effective.
  - Finding the Effective Dose and comparing the slopes of the dose-response relationship is also moderately effective.
  - Adding more information may benefit the “slope” approach more
    - Phase III studies in Westerners
    - Additional Phase II studies in Japanese.
    - Prior knowledge on slope of dose-response
- Define similarity criteria proactively, because they may affect development strategy.
  - For nth in class NCEs, it may be possible to evaluate criteria after Phase I single-dose PK studies.

