The Japanese Pharmacokinetic (PK) Study of Sirolimus-Coated Bx VELOCITY™ Balloon-Expandable Stent in Patients With de novo Coronary Artery Lesions

- The Japan PK Study -

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Study Background

RAVEL → CE Mark

SIRIUS → FDA Approval

SIRIUS → Equal? → MHLW(Japan)

Bridging Study

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PK Study

Purpose

First Japanese Study to Evaluate the pharmacokinetic characteristics of Sirolimus released from CYPHER®Stent implanted in Japanese patients with de novo lesion in native coronary artery for bridging the efficacy and safety data provided from SIRIUS study for Japanese patients

Study Design

Prospective, non-randomized study

De novo Native coronary artery

18mm x 3mm stent only

1 stent / patient (n=10)

2 stent / patient (n=10)

Phase 1

7days

Phase 2

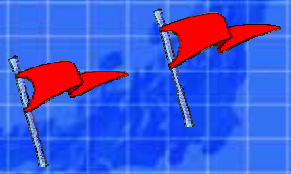
~ 5Year Follow up

Pharmacokinetic

(PK Study)

Safety monitoring

Including 8M angiographic Follow up



Two enrollment sites:

Toho University Ohashi Hospital

National Cardiovascular Center

Concomitant Medical Therapy

cypher
Sirolimus-eluting Coronary Stent

Pre-procedure

Aspirin	81~200mg starting at least 24 hours prior to the procedure.
Ticlopidine	Loading dose of 200~300 mg within 3 days prior to the procedure.

During Procedure

Heparin	Initial bolus IV with additional boluses to maintain an ACT≥250 seconds

Post-Procedure

Aspirin	81~200 mg qd
Ticlopidine	200 mg bid

After Discharge

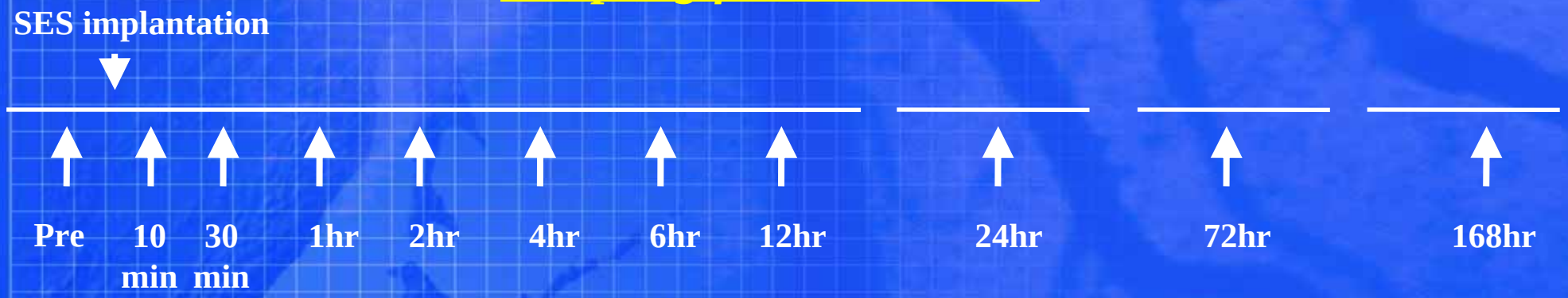
Aspirin	81~200 mg qd
Ticlopidine	200 mg bid for 12 weeks

*Patients were required to use the drug as described in the drug labeling.

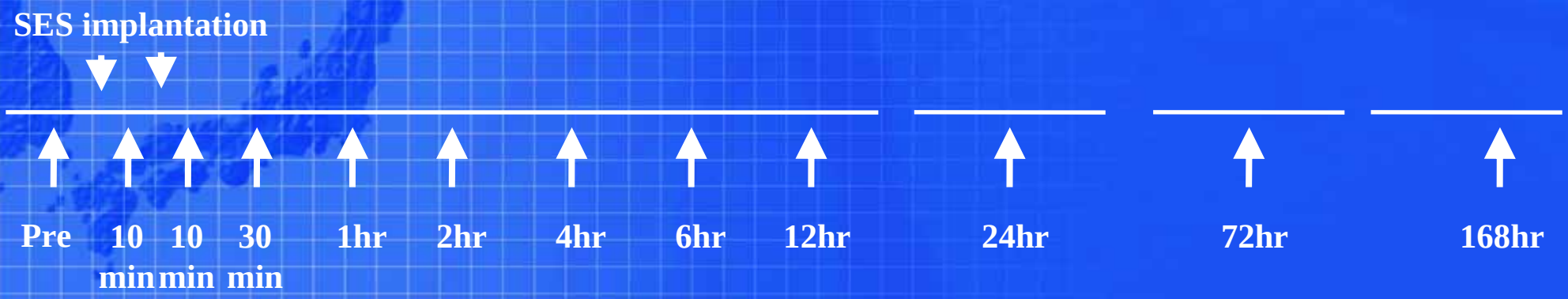
Pharmacokinetic Sampling Schedule

cypher
Sirolimus-eluting Coronary Stent

Sampling for Treatment I



Sampling for Treatment II



Laboratory Analysis

Collected Whole Blood are.....

Mitsubishi Bio-Clinical Laboratories, Inc. (MBC)

Sample A

Sample B

Laboratory:
Taylor Technology, Inc.
Princeton, NJ U.S.A.

Analytical Method

1.Extraction

Whole Blood 1.0 mL

Methanol 50 μL
Internal standard[1)] methanol solution 100 μL
1−chlorobutane 7 mL

Organic Layer

Water Layer

Evaporated under N_2 Gas
Reconstituted in a 70:30 methanol:water solution

HPLC Samples

1) 32-Desmethoxyrapamycin

2. C/MS/MS

Column : BetaBasic C4 (Keystone)

Ionization : Atmospheric Pressure Chemical Ionization

Quantitation Range : 0.1-100ng/mL

Baseline - Patient Characteristics -

Patient Characteristics	N=20 Patients	[95%C.I.]
Male	80.0% (16/20)	[62.5% 97.5%]
Age（year）		
Mean±SD	64.2±9.9	
(Min , Max)	(37, 78)	
Height（cm）		
Mean±SD	166.3±7.9	
(Min , Max)	(153.5 , 182.0)	
Body Weight（kg）		
Mean±SD	66.1±11.1	
(Min , Max)	(45 , 90)	
Obesity	35.0% (7/20)	[14.1% 55.9%]
Diabetes Mellitus	60.0% (12/20)	[38.5% 81.5%]
Hyperlipidemia	55.0% (11/20)	[33.2% 76.8%]
Hypertension	80.0% (16/20)	[62.5% 97.5%]
Smorking	65.0% (13/20)	[44.1% 85.9%]

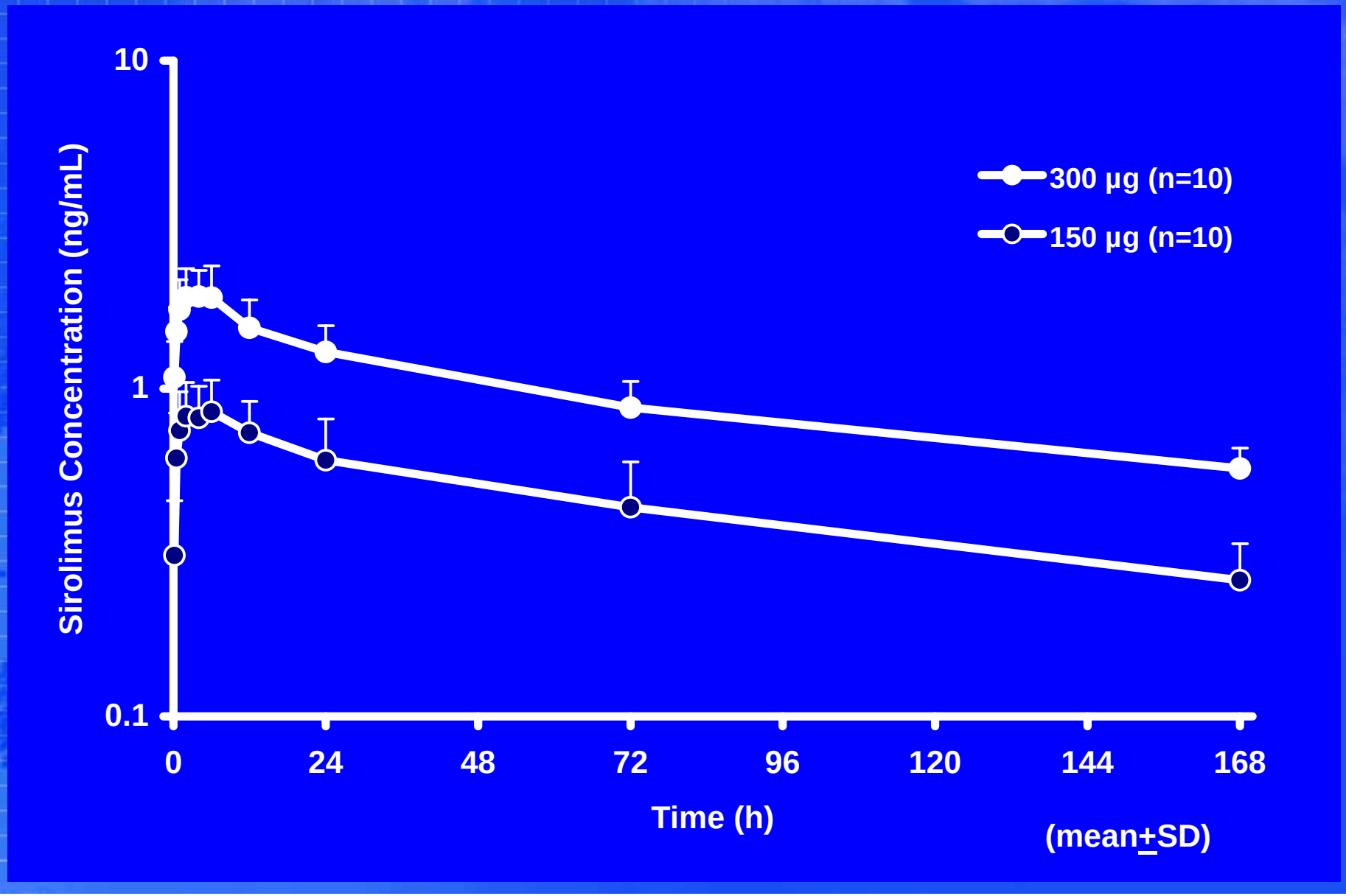
Baseline - Patient Characteristics Cont.-

Patient Characteristics	N=20 Patients	[95%C.I.]
History of		
MI	15.0% (3/20)	[0.0% 30.6%]
PCI	35.0% (7/20)	[14.1% 55.9%]
CABG	0.0% (0/20)	[0.0% 0.0%]
GI Bleeding	0.0% (0/20)	[0.0% 0.0%]
CVA or TIA	15.0% (3/20)	[0.0% 30.6%]
Congestive Heart Failure	0.0% (0/20)	[0.0% 0.0%]
Renal Insufficiency	0.0% (0/20)	[0.0% 0.0%]
Peripheral Vascular Disease	5.0% (1/20)	[0.0% 14.6%]
Ejection Fraction (%)		
Mean±SD	61.0±11.2	
(Min , Max)	（38, 81）	

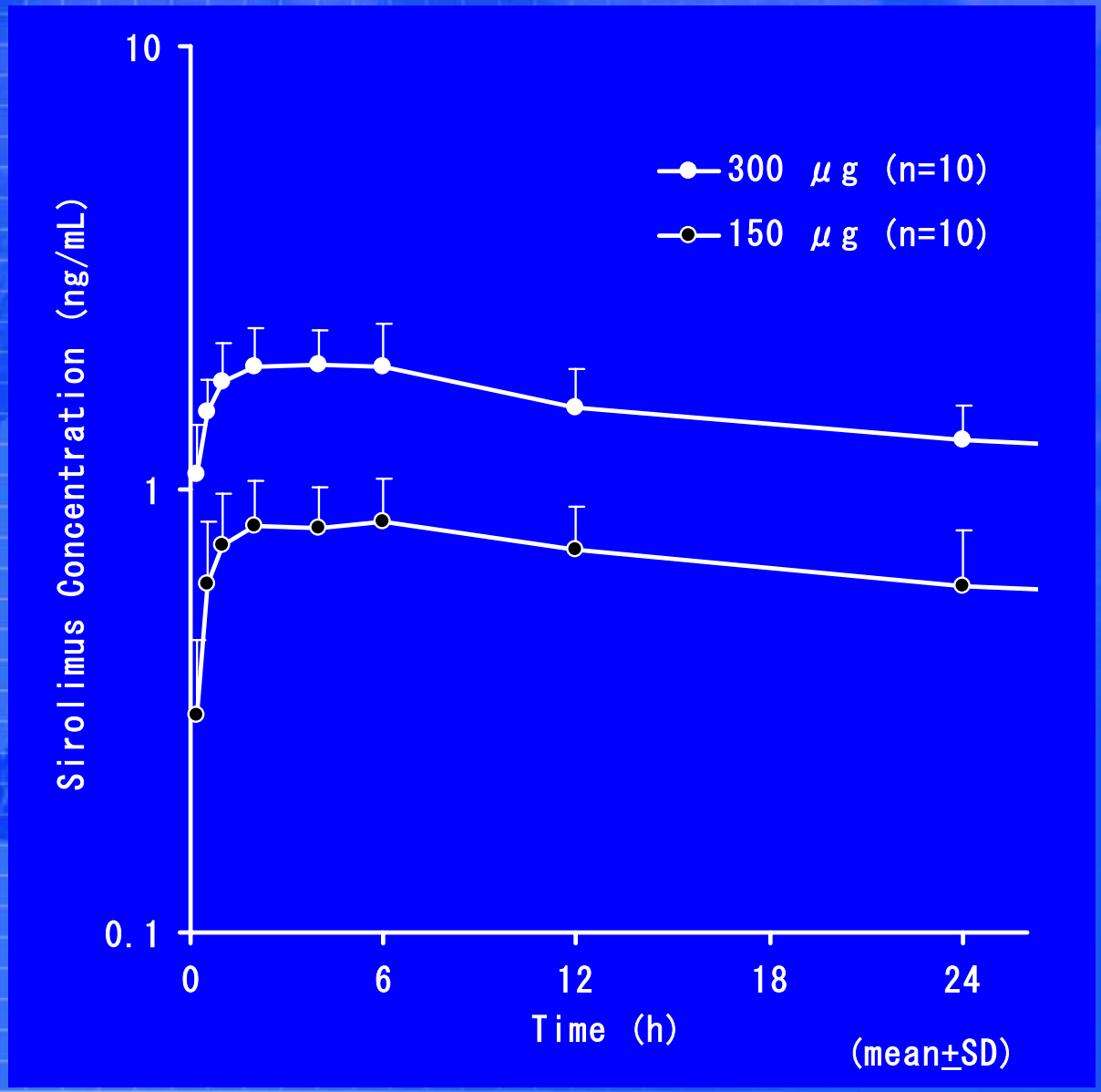
Baseline - Lesion Characteristics -

Lesion Characteristics	20 Patients (n=30 Lesions)	[95%C.I.]
Target Vessel		
RCA	40.0% (12/30)	[22.5% 57.5%]
LAD	40.0% (12/30)	[22.5% 57.5%]
LCX	20.0% (6/30)	[5.7% 34.3%]
Lesion type		
Eccentric	30.0% (9/30)	[13.6% 46.4%]
Irregular	26.7% (8/30)	[10.9% 42.5%]
Calcification	40.0% (12/30)	[22.5% 57.5%]
Bend(>45°)	10.0% (3/30)	[0.0% 20.7%]
Tortuosity	6.7% (2/30)	[0.0% 15.6%]
Ostial	0.0% (0/30)	[0.0% 0.0%]
Bifurcation	0.0% (0/30)	[0.0% 0.0%]
ACC/AHA		
A	56.7% (17/30)	[39.0% 74.4%]
B1	23.3% (7/30)	[8.2% 38.4%]
B2	20.0% (6/30)	[5.7% 34.3%]
C	0.0% (0/30)	[0.0% 0.0%]

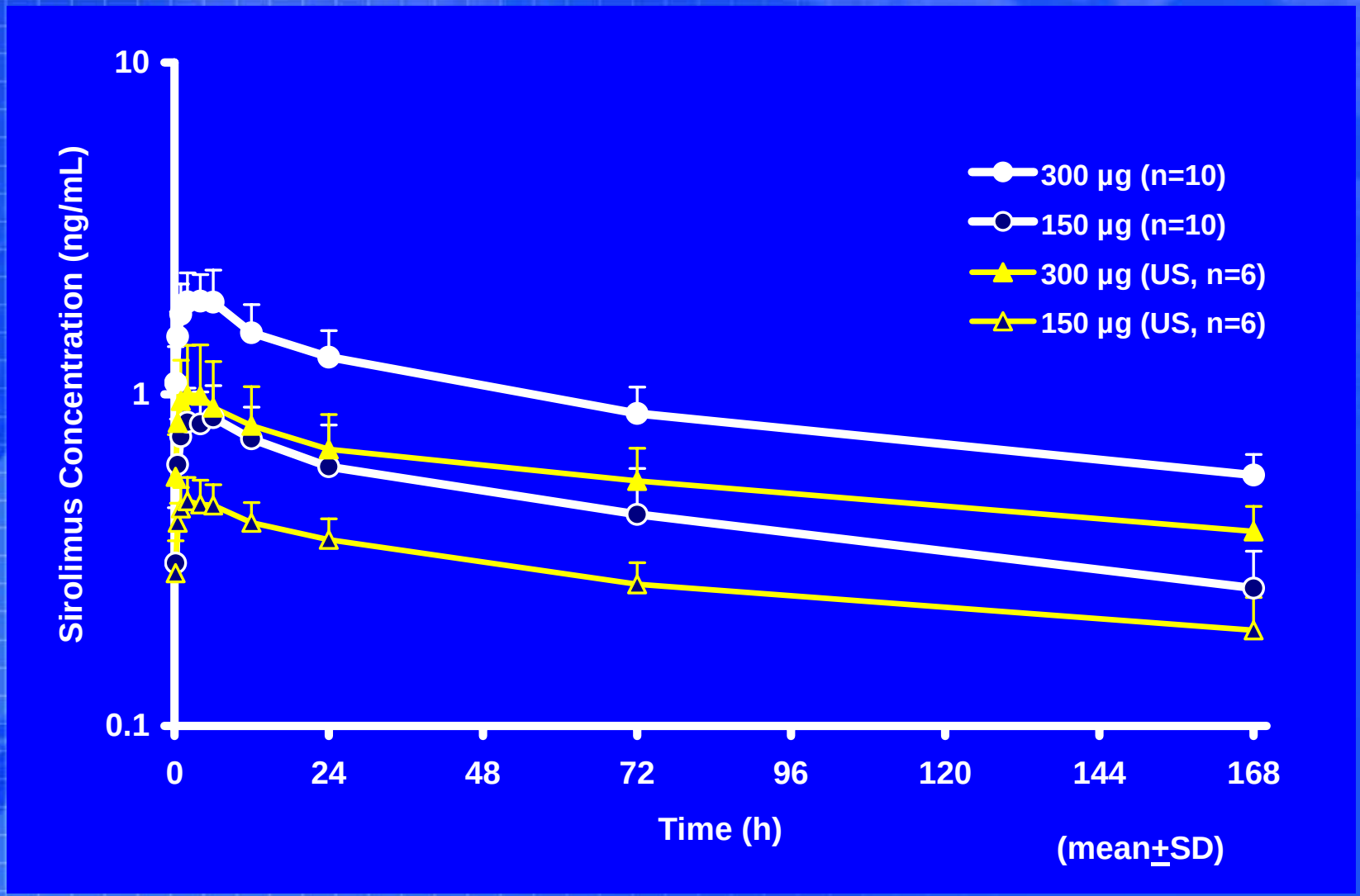
Sirolimus Concentration in blood - Japanese -



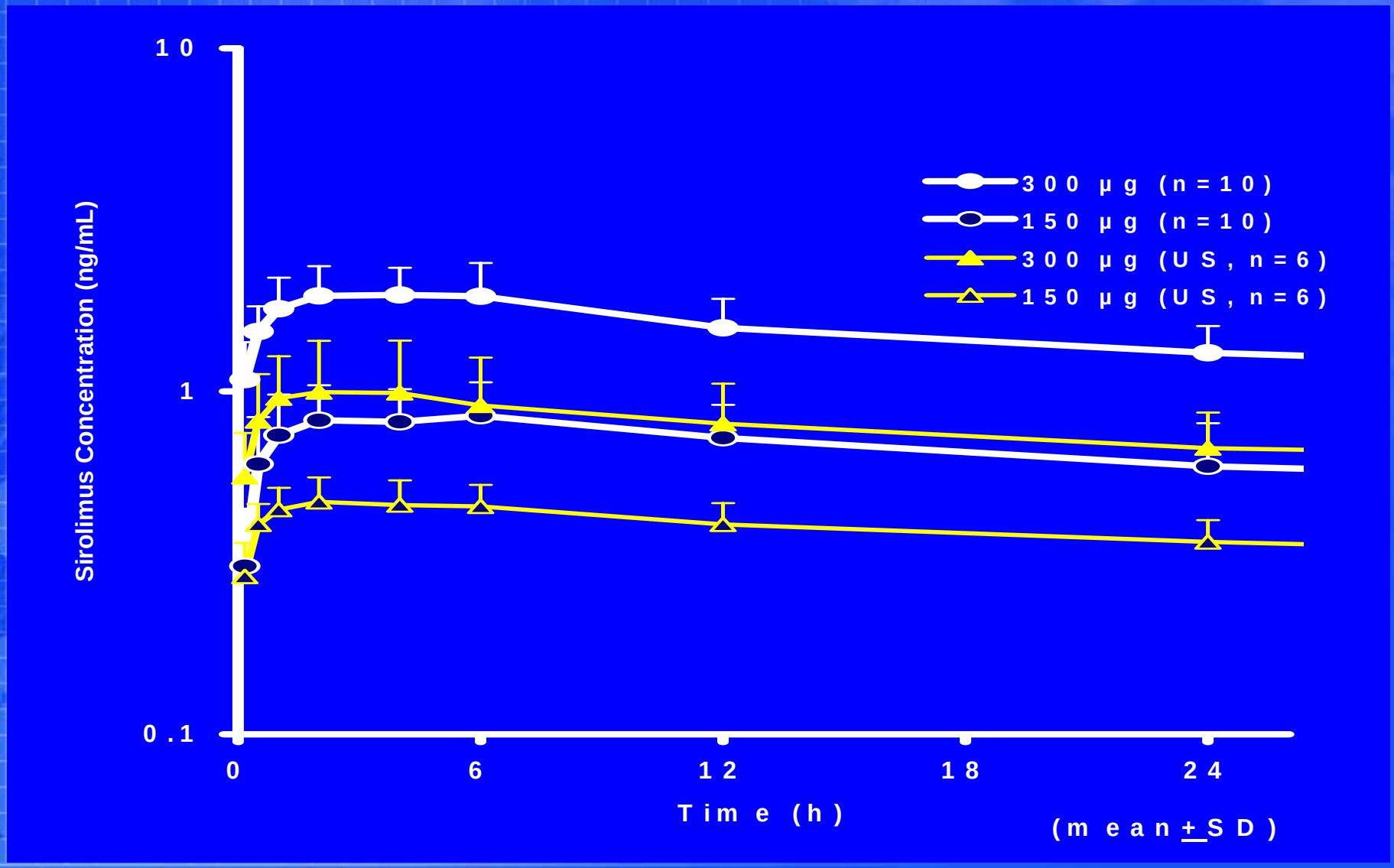
Sirolimus Concentration in blood - Japanese
0~24hr -



Sirolimus Concentration in blood vs. US Data



Sirolimus Concentration in blood
vs. US Data 0~24hr

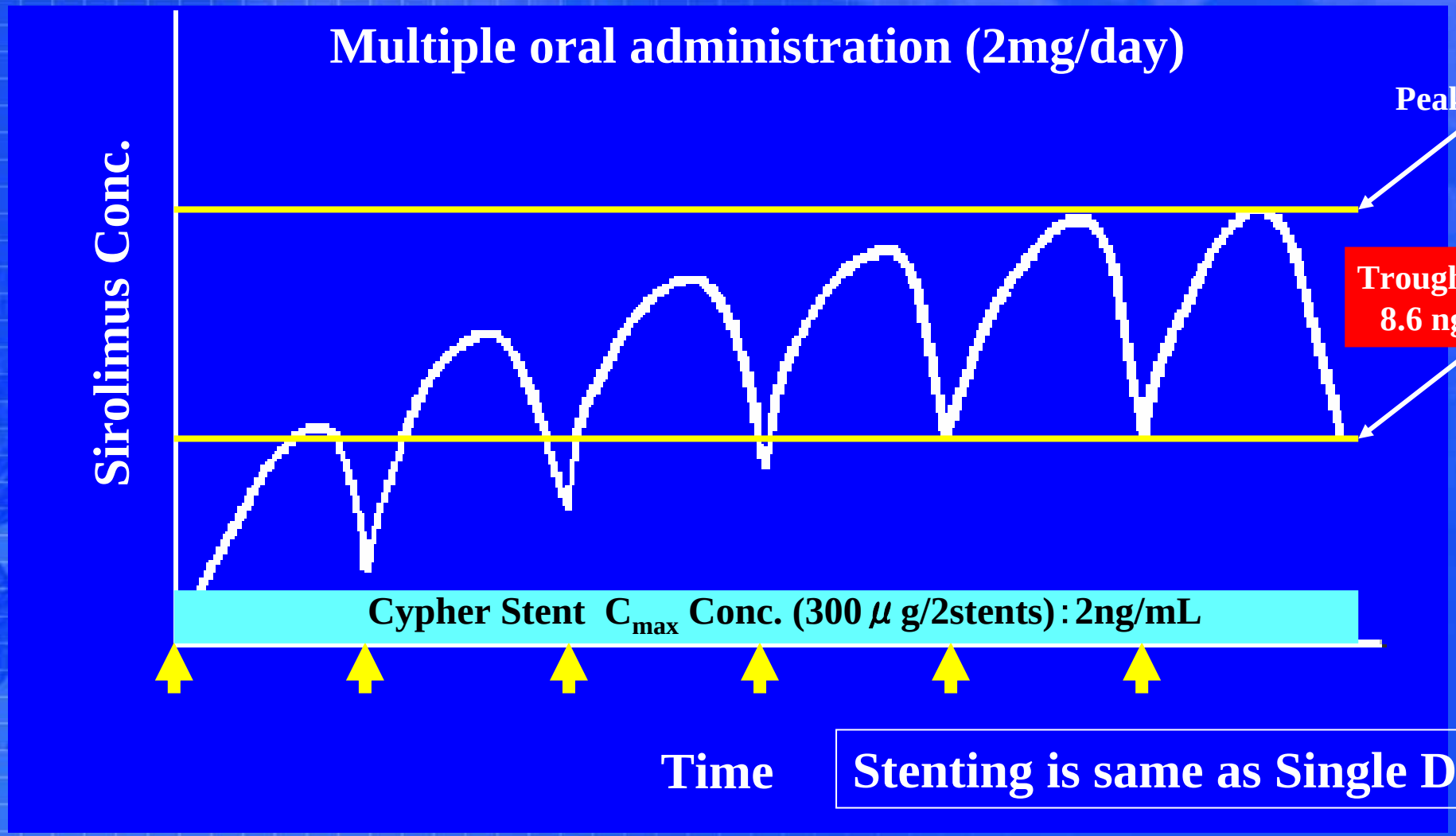


Mean pharmacokinetic parameters

		JAPAN (#JJ-CRD02-1)		US (part of #P01-6305)	
Dose	(µg)	150 (n=10)	300 (n=10)	150 (n=6)	300 (n=6)
Body Weight	(kg)	66.1 ± 11.7 17.7	64.6 ± 14.6 22.6	78.7 ± 11.9 15.1	84.1 ± 16.7 19.9
C_{max}	(ng/mL)	0.86 ± 0.22 25.1	2.00 ± 0.43 21.4	0.50 ± 0.07 13.1	1.03 ± 0.39 38.1
t_{max}	(h)	4.2 ± 1.8 42.0	3.7 ± 1.9 50.5	3.3 ± 2.3 70.1	1.8 ± 1.2 63.7
$t_{1/2}$	(h)	120 ± 19 15.7	119 ± 26 21.8	161 ± 48 29.7	216 ± 137 63.5
CL	(L/h)	1.34 ± 0.36 26.7	1.21 ± 0.30 24.6	1.71 ± 0.53 30.9	1.53 ± 0.51 33.3
Vd	(L)	230 ± 67 29.1	203 ± 38 18.9	371 ± 54 14.5	423 ± 144 34.0

(Mean±SD, CV%)

Cmax Peak blood concentration, ng/mL
Tmax Time peak concentration occurs, h
$t_{1/2}$ Terminal-phase elimination half-life, h
CL Apparent oral clearance, L/h
Vd Apparent oral volume of distribution in the terminal phase, L


Multiple oral administration (2mg/day)
Sirolimus Conc.
Peak Conc.
Trough Conc.
8.6 ng/mL
Cypher Stent C_{max} Conc. (300 μg/2stents) : 2ng/mL
Time
Stenting is same as Single Dose

Adverse Events (1 year F/U)

Event	#Case
MACE	1
Death	0
MI	0
CABG	0
Recurrent AP	0
TLR	2
TVR	1
Subcutaneous Bleeding	2
Hemostatiss Dificulty	4
Other	47

Conclusions

- C_{max} (0.86 with one stent and 2.00 ng/mL with two stents) in Japanese patients with Sirolimus coated BX VELOCITY stent is lower than the whole blood sirolimus concentration (8.6 ng/mL) after multiple oral administration (2mg/day) of sirolimus using for renal transplant patients.

- MACE was 5.0%(n=1) at one year follow up, No serious adverse event, No stent thrombosis was observed

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