2.5 General Biopharmaceutics

The significant, unresolved issues related to in vitro dissolution or in vivo BA and BE

Is the HCL salt formulation of prasugrel bioequivalent to the prasugrel base formulation?

The sponsor investigated the extent of conversion of the salt to the base in 2 bioequivalence studies where lots with high extent of conversion (70%), intermediate extent of conversion (58%) and low extent of conversion (5 %) were compared with and without the coadministration of 30 mg lansoprazole. The low medium and high extent of conversion lots were found to be bioequivalent to each other. However, when given with lansoprazole, the low medium and high extent of conversion were found to be bioequivalent to each other with respect to AUC but not to CMAX. There was on average a 29% difference (90% confidence interval 0.62-083) in CMAX between the low conversion and the high conversion lot. The difference between the medium and high conversion lot was less pronounced (10% with a 90 % CI of 0.77-1.04). This difference between these lots translated into differences in mean IPA of greater than 10% at 0.5 and 1 hour post dose. These differences can be potentially clinically significant. This difference can be attributed to difference in dissolution characteristics at higher pH between the base and the salt form. At higher pH the dissolution of the HCL salt is faster than the prasugrel base resulting in faster absorption rates explaining the 30% difference in CMAX.
The sponsor was made aware of the Agency's concern with regards of not being able to control the amount of conversion from the salt form to the base resulting in highly variable peak plasma concentrations from lot to lot. In a teleconference held on April 23, 2008, the ——— b(4)

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Does the particle size of prasugrel have an effect on bioavailability?

The effect of particle size on the bioavailability of prasugrel was tested in a bioequivalence study where : ——— : were b(4)
compared after coadministration with 30 mg lansoprazole. The results show that the difference in surface area did not have any effect on the extent of absorption as measured by AUC but had a slight effect on the rate of absorption as measured by CMAX as the 90% CI were slightly outside the 80-125% limits on the lower side (79-114% for the low and high surface area ratio and 78-112% for the medium to high surface area ratio). This slight difference in CMAX is not expected to be clinically significant.

What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation of prasugrel was used in the pivotal Study TAAL. The table below lists the prasugrel formulations used in the clinical studies, including TAAL.

Table 7 Summary of Formulations Used in Clinical Studies

Formulation Used	Study Alias
Prasugrel base tablets	148-007, S001, S002, S003, S004, TAAA, TAAC, TAAD, TAAE, TAAF, TAAH
Commercial Tablet: Prasugrel.HCl tablets	TAAF, TAAI, TAAJ, TAAK, TAAL, TAAN, TAAO, TAAP, TAAQ, TAAR, TAAS, TAAT, TAAU, TAAV, TAAW, TAAX, TAAZ, TABF, TABL, TABM, TABN, TABR, TABS, TABV, TABW, TABX, TABZ, TACF, TACG, TACJ, TACK, TACR, TACS
Prasugrel.HCl tablets used in Japan studies	J101, J102, J103, J105, J106, J201
Radiolabeled Prasugrel base Solution	TAAB

What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Except for Studies S002 (pilot study, 6 subjects) and TAAF, clinical pharmacology and pivotal TAAL studies were conducted in fasted subjects. In Study TAAF, coadministration of a single 15-mg prasugrel dose with a high-fat high-calorie meal Cmax was reduced by nearly half, tmax was delayed from 0.5 to 1.5 hours but not the extend of absorption. The figure below shows the effect of food on the kinetics of R138727.

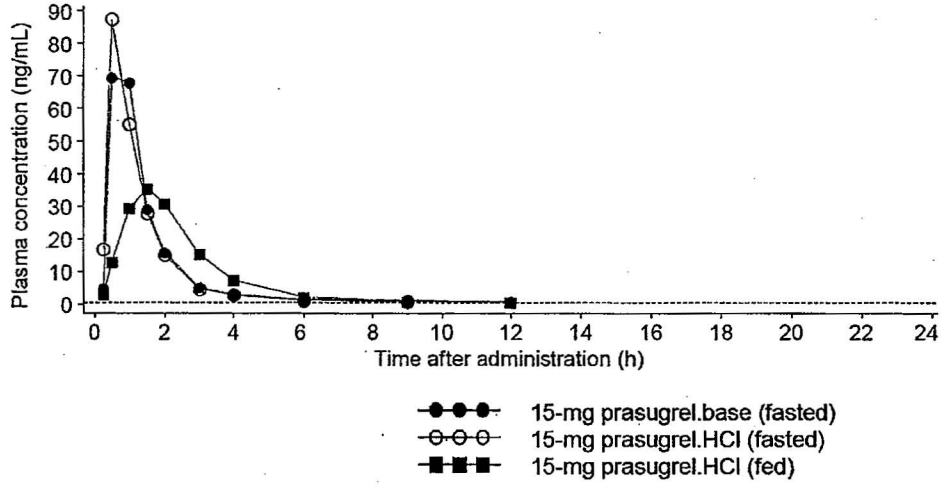

Figure 23. R138727 Plasma Concentrations vs Time. Food Effect

Table 8. Fed vs Fasted PK Parameters for Prasugrel Metabolites

Metabolites	PK Parameter (unit)	Geometric mean[a] (90% CI) [CS-747.HCl (Fed)]	Geometric mean[a] (90% CI) [CS-747.HCl (Fasted)]	Ratio of Geometric mean[a] (90% CI) [CS-747.HCl (fed) vs CS-747.HCl (fasted)]
R-138727	AUC (0-∞) (ng·h/ml)	122 (108, 138)	129 (114, 146)	0.949 (0.893, 1.01)
	AUC (0-t_{last}) (ng·h/ml)	118 (105, 134)	124 (110, 141)	0.952 (0.890, 1.02)
	C_{max} (ng/ml)	63.6 (53.7, 75.4)	124 (105, 147)	**0.512 (0.428, 0.612)[b]**
R-95913	AUC (0-∞) (ng·h/ml)	144 (127, 163)	117 (103, 133)	**1.23 (1.13, 1.34)[b]**
	AUC (0-t_{last}) (ng·h/ml)	133 (117, 151)	107 (93.8, 121)	**1.25 (1.14, 1.36)[b]**
	C_{max} (ng/ml)	50.4 (43.8, 58.1)	62.8 (54.5, 72.4)	**0.803 (0.680, 0.948)[b]**
R-119251	AUC (0-∞) (ng·h/ml)	69.0 (59.9, 79.4)	75.1 (65.4, 86.3)	0.918 (0.849, 0.993)
	AUC (0-t_{last}) (ng·h/ml)	63.4 (54.9, 73.1)	70.8 (61.3, 81.7)	0.896 (0.827, 0.970)
	C_{max} (ng/ml)	27.3 (23.1, 32.3)	53.6 (45.3, 63.4)	**0.510 (0.427, 0.609)[b]**
R-106583	AUC (0-∞) (ng·h/ml)	789 (686, 907)	741 (645, 852)	1.06 (1.02, 1.11)
	AUC (0-t_{last}) (ng·h/ml)	691 (604, 791)	660 (577, 755)	1.05 (0.998, 1.10)
	C_{max} (ng/ml)	98.2 (86.0, 112)	121 (106, 139)	**0.810 (0.741, 0.885)[b]**

When prasugrel was administered with a high fat food breakfast, the disposition of all prasugrel metabolites changed (Table above).
For the inactive metabolite R-95913, food intake increased AUC(0-∞) between 13% and 34% (90% CI) and similarly for AUC(0-tlast). For the active and other inactive metabolites measured (R-119251 and R-106583), both AUC(0-∞) and AUC(0-tlast) are bioequivalent in the fed and fasted conditions. For all metabolites, food intake decreased the Cmax values, and increased median tmax from 0.5 to 1.5 hours.
Because PCI is usually performed in the fasted state, the food effect may be not clinically relevant and therefore, prasugrel can be administered with or without food.

How the elevated gastric pH affect the prasugrel bioavailability?

Prasugrel's dissolution in vitro is faster at pH 1 than at pH 6.8 and is intermediate at pHs in between. Therefore, treatment with drugs that increase gastric pH could slow the rate and/or extent of dissolution and absorption of a prasugrel dose. Treatment with such gastric pH modifiers is common in patients with ACS. In Study TAAL, 41% of subjects took a PPI and 15% took a H2-receptor antagonist through 3 days after the LD. Therefore, any effect occurring when given with prasugrel could be clinically relevant.
The different classes of gastric pH modifiers had different magnitudes of effect on the rate of prasugrel absorption.

Effect of PPIs: Lansoprazole given with a prasugrel LD or MD reduced the Cmax of prasugrel's active metabolite by nearly 30%, did not change tmax and did not affect the AUC(0-8) of prasugrel's active metabolite (Study TAAI).
It is likely that the lower Cmax with PPIs will delay the onset of platelet inhibition when prasugrel is given to a patient taking a PPI, but will not affect the level of platelet inhibition during MD.

Since a 30% differences in Cmax for the active metabolite of prasugrel did not change the PD response, this differences probably would not of clinical significance, and no dose adjustment of prasugrel is required when administered with lansoprazole.

Effect of H2 Antagonists: Oral ranitidine was studied with a prasugrel LD or MD (Study TABS). Ranitidine reduced the rate of absorption, the Cmax of prasugrel's active metabolite decreased by 14%, although it did not change tmax and did not affect the AUC(0-tlast) of prasugrel's active metabolite. This effect on active metabolite Cmax was less than that measured during treatment with lansoprazole. The platelet aggregation assessments included early time points that were lacking in the PPI Study TAAI. The assessment of ranitidine interaction in Study TABS showed no statistically significant difference in IPA at any time point except for 0.5 hours after the prasugrel LD + ranitidine. The reduction in IPA at 0.5 hours was 12 percentage points, which was associated with a 9 percentage point increase in MPA to 20 μM ADP. Prasugrel can be coadministered with or without a H2-receptor antagonist.

2.6 Analytical section

How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma samples collected in clinical studies were analyzed for prasugrel active (R-138727) and/or inactive (R-119251, R-106583, and R-95913) metabolites using validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) methods. The methods for quantifying prasugrel metabolites in human plasma were first developed at Lilly Laboratory for Bioanalytical Research (LLBR). The methods were transferred to Advion BioServices, and the LLBR and Advion methods were successfully cross-validated.
In the drug-drug interaction studies, the assay validations for all measured moieties were provided.

What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The lower limit of quantitation was 0.5 ng/mL for R-138727 and 1 ng/mL for R-119251, R-106583, and R-95913. The upper limit of quantitation was 250 ng/mL for R-138727 and 500 ng/mL for R-119251, R-106583, and R-95913. Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range.
The sponsor described each method used in the clinical studies, their cross-validation methods, as well as the validated standard curve range, intra/inter-assay precision, and intra/inter-assay accuracy for each method. Storage conditions and freeze/thaw stability data for prasugrel are also summarized in this appendix.
Derivatization of R-138727 in blood with 2-bromo-3-methoxyacetophenone within 30 seconds after collection was required to ensure the stability of the active metabolite during sample processing and storage.
The LC/MS/MS method used R138727-MP-d4 (3'-methoxyphenacyl derivative of deuterated R138727) as an internal standard for R-138727. Due to these difficulties, it was not possible to determine the plasma concentrations of the prasugrel active metabolite in the pivotal study TAAL which was performed at the multiple centers. The sponsor instead determined the inactive

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metabolites plasma concentrations and used plausible pharmacokinetic modeling to predict the concentrations of the active metabolite.

What analytical methodologies were used to assess pharmacodynamic action?

Many of the studies that evaluated the PK of prasugrel's metabolites also evaluated the effect of prasugrel on platelet function. The primary method used to determine the PD response to prasugrel was light transmittance aggregometry (LTA) using 20 μM ADP as the agonist; 5 μM ADP was also used. Prasugrel administration results in inhibition of the platelet aggregation response to ADP, a result that may be reported as either a change in MPA, which decreases with increasing PD response, or inhibition of platelet aggregation (IPA), which increases with increasing PD response. Duplicate determinations of MPA were included in Studies TAAD, TAAJ, and TACJ, permitting the reproducibility of the LTA assay to be assessed. In addition to LTA, the PD response to prasugrel was also explored with additional assays as described in the sponsor's Table APP.2.7.1.5. They were VASP (platelet reactivity index) phosphorylation, serum thromboxane B2, activated partial thromboplastin time, factor Xa inhibition and activated clotting time values of anti-Xa.

The bleeding time assessment using a modified Ivy technique is a standard test. A pressure of 40 mmHg was applied using a blood pressure meter cuff inflated around the subject's arm. Three punctures were made on the subject's forearm at 5 second intervals using an Accu-check Softclix lancing device (Roche). A single sheet of filter paper was used to dab the outer perimeter of the three puncture wounds every 15 seconds. Bleeding time was recorded as the time from puncture to when a small clot formed.

Were the validation characteristics of the assays acceptable?

Yes. In all studies the assays have their validation reports, they are acceptable. See individual study reviews.

What is the overall conclusion regarding NDA 22-307?

Overall the Clinical Pharmacology and Biopharmaceutics section is acceptable.

3 DETAILED LABELING RECOMMENDATIONS

GENERAL

The Agency considered that the overall information regarding Clinical Pharmacology provided in the original NDA 22-307 was appropriate.

CLINICAL PHARMACOLOGY LABELING COMMENTS

Highlights Section:

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4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

X Draft Labeling (b5)

_____ Deliberative Process (b5)

4 APPENDIX II:

4.1 Individual In Vitro Study Reviews

4.1.1 In Vitro Protein Binding of Metabolites OF CS-747 (Report No. ATR-151-053)

Investigator: Atsushi Kurihara, Ph.D., Drug Metabolism and Pharmacokinetics Research Laboratories, Sankyo Co., Ltd., 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, Japan
Date of completion: June 27 2005

Objectives	To determine the extent of the protein binding ratios of inactive metabolites of CS-747, i.e., R-95913, R-106583, R-100932, R-119251 in plasma and R-138727 in 4% Human serum albumin (HAS)
Methods	Unbound fractions of the main metabolites of CS-747 in plasma, R-95913, R-119251, R-100932 and R-106583, were measured by an ultracentrigufation method. Rat, dog and human plasma at the concentrations of 50, 100 and 500 ng/mL or 100, 500 and 1,000 ng/mL Each mixture (final volume: 1 mL) was incubated at 37°C for 5 min. Then, centrifuged and ultracentrifuged at 436,000 g for 140 min at 15°C The protein-containing fraction (lower layer), protein-free fraction (middle layer) and lipoprotein-containing fraction (upper layer) separated. [redacted] (for R-95913, R-100932, R-106583 and R-138727 assay) or [redacted] (for R-119251 assay) as the internal standard. The mixtures were vortexed and centrifugated at 14,000 rpm for 3 min at 4 °C. The protein binding ratio in rat, dog and human plasma was calculated. HSA solution at 4% was prepared with sodium phosphate buffer (pH 7.4). R-138727 was mixed with 4% HSA at concentrations of 50, 100 and 500 ng/mL, and then each mixture (final volume: 1 mL) was incubated at 37°C for 5 min. After the incubation, the protein-free fraction and total concentration of R-138727 were measured as described above for the other four inactive metabolites.
Assay	LC-MS for the total plasma concentrations of R-95913, R-106583, R-100932, R-119251. Unbound fraction of R-138727 (active metabolite of CS-747) in 4% HSA was also measured by the ultracentrifugation method.

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Results
The protein binding ratios of R-119251, R-100932, R-106583 and R-95913 are shown in Tables 3, 4 and 5. The result of binding with HSA of R-138727 are also summarized in Table 6. In plasma of each species, the protein binding ratios of R-95913, R-106583 and R-100932 were more than 80% at concentrations of 50, 100 and 500 ng/mL. Binding ratio of R-119251 was 71-77% in rat, 26-36% in dog and 76-77% in human plasma at 100, 500 and 1000 ng/mL. To

evaluate the plasma protein binding of the active metabolite, R-138727, commercially available purified HSA was used since this metabolite has been reported to be unstable in the plasma of each species.3) As a result, R-138727 was proved to be bound to 4% HSA with a binding ratio of 98% at concentrations of 100 and 500 ng/mL.

Table 9. Protein binding ratios of R-95913, R-100932, R-106583 and R-119251 in rat (left panel) and dog (right panel) plasma

<R-95913>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	86.95	86.65	85.98
No. 2	89.20	87.52	84.84
No. 3	86.69	86.90	84.54
Mean	**87.61**	**87.02**	**85.12**
S.D.	1.38	0.45	0.76

<R-95913>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	89.14	88.58	88.25
No. 2	93.07	93.27	92.53
No. 3	85.58	87.42	84.57
Mean	**89.26**	**89.76**	**88.45**
S.D.	3.75	3.10	3.98

<R-100932>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	93.57	92.14	92.13
No. 2	92.87	92.69	91.92
No. 3	92.15	92.61	92.10
Mean	**92.86**	**92.48**	**92.05**
S.D.	0.71	0.30	0.11

<R-100932>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	84.94	85.17	79.35
No. 2	88.56	87.13	83.61
No. 3	81.89	77.86	76.69
Mean	**85.13**	**83.39**	**79.88**
S.D.	3.34	4.89	3.49

<R-106583>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	85.13	82.48	83.63
No. 2	82.84	82.81	82.30
No. 3	81.54	82.77	82.94
Mean	**83.17**	**82.69**	**82.96**
S.D.	1.82	0.18	0.67

<R-106583>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	83.93	84.87	80.07
No. 2	86.51	84.74	82.24
No. 3	83.61	80.66	79.85
Mean	**84.68**	**83.42**	**80.72**
S.D.	1.59	2.39	1.32

<R-119251>

	Protein binding ratio (%)		
	100 ng/mL	500 ng/mL	1000 ng/mL
No. 1	68.78	76.82	76.39
No. 2	71.21	76.38	77.51
No. 3	73.06	75.80	77.60
Mean	**71.02**	**76.33**	**77.17**
S.D.	2.15	0.51	0.67

<R-119251>

	Protein binding ratio (%)		
	100 ng/mL	500 ng/mL	1000 ng/mL
No. 1	32.46	28.12	26.53
No. 2	33.21	21.50	21.86
No. 3	40.95	31.37	30.70
Mean	**35.54**	**27.00**	**26.36**
S.D.	4.70	5.03	4.42

Table 10 Protein binding ratios of R-95913, R-100932, R-106583 and R-119251 in human plasma

<R-95913>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	93.60	93.72	94.19
No. 2	94.12	94.15	96.26
No. 3	95.42	93.70	96.31
Mean	**94.38**	**93.86**	**95.59**
S.D.	0.94	0.25	1.21

<R-100932>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	94.98	91.21	91.40
No. 2	93.45	89.51	89.70
No. 3	93.52	92.32	90.89
Mean	**93.98**	**91.01**	**90.66**
S.D.	0.86	1.42	0.87

<R-106583>

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	N.A.	96.79	95.28
No. 2	N.A.	94.15	94.26
No. 3	N.A.	95.88	94.27
Mean	N.A.	**95.61**	**94.60**
S.D.	N.A.	1.34	0.59

<R-119251>

	Protein binding ratio (%)		
	100 ng/mL	500 ng/mL	1000 ng/mL
No. 1	74.67	75.29	78.23
No. 2	76.54	75.74	74.89
No. 3	75.32	76.41	76.03
No. 4	78.50	77.07	78.29
Mean	**76.26**	**76.13**	**76.86**
S.D.	1.68	0.78	1.68

Table 11 Protein binding ratios of R-138727 in 4% HSA

	Protein binding ratio (%)		
	50 ng/mL	100 ng/mL	500 ng/mL
No. 1	N.A.	97.96	98.06
No. 2	N.A.	97.96	97.91
No. 3	N.A.	97.95	97.99
Mean	N.A.	**97.96**	**97.99**
S.D.	N.A.	0.01	0.08