

## List of Figures

Figure 1 The inhibition of the platelet aggregation is dependent on the concentration of the active metabolites of prasugrel and clopidogrel.....	24
Figure 2 No relationship between dose and major cardiovascular events (MACE - Death+MI+Stroke+CTVT+Recurrent Ischemia at 30-day visit).....	25
Figure 3 Increase in the active metabolite exposures trends to increase in number of bleeding adverse events (NBAE).....	25
Figure 4 Prasugrel LD of 60 mg achieves highest IPA. Maintenance doses of 10 mg and 15 mg achieve significantly greater IPA compared to clopidogrel MD of 75 mg.....	26
Figure 5: Maximum effectiveness is achieved when the loading dose is administered at the start or within 30 min of start of PCI ( <i>Red dots – represent proportion of events corresponding to the midpoints of the octiles; Blue bars – 95% Confidence interval; Black line – Smooth trend line; Green line – is the lowest confidence limit of the extremes</i> ).....	29
Figure 6 Pre-treatment with clopidogrel/prasugrel 6 hrs before the start of PCI results in decreased effectiveness compared to no pre-treatment ( <i>Orange squares – represent proportion of events; Black bars – 95% Confidence interval</i> ) .....	29
Figure 7 The effect of the timing of loading dose relative to the start of PCI is similar across prasugrel and clopidogrel.....	30
Figure 8: The cumulative event rate of the efficacy endpoint is lower when the loading dose is administered at the start of PCI or within 30 minutes of the start of the PCI irrespective ...	30
Figure 9 Cumulative event rate of the efficacy endpoint across quartiles of difference in time of loading dose and start of PCI is similar between clopidogrel (left) and prasugrel (right)....	31
Figure 10 Time course of mean $\Delta\Delta Q_{TcF}$ .....	33
Figure 11 Log concentration- $\Delta\Delta Q_{TcF}$ relationship for R-138727.....	33
Figure 12. The mean concentration vs. time profiles of R-138727, R-95913, R-119251, and R-106583 following a single prasugrel 60-mg LD (left panel) and during 10-mg MD (right panel), Study TAAV. ....	34
Figure 13. PK Parameters of R138727 vs. Prasugrel Dose, Study TAAW. ....	39
Figure 14. Observed AUC <sub>0-tlast</sub> and C <sub>max</sub> of R-138727 vs. body weight following a 60-mg LD or during 10-mg MD of prasugrel.....	40
Figure 15 Risk for TIMI Major bleeding is higher in patients with body weight less than 60 Kg. ....	41
Figure 16 Clearance of R-138727 increases with increase in body weight (Left: Study TAAD; Right: Study TABR) .....	42
Figure 17 <b>Decreased Exposures of R-138727 with increased body weight in Study TAAL.</b> ( <i>Circles represent plasma concentrations 0.75-1.25 h post MD; Blue line is a smooth trend line</i> )e .....	42
Figure 18 <b>Simulation (N=2000) of the proposed dose of 5 mg in patients with body weight &lt; 60kg will result in exposures predominantly corresponding to lower two quartiles of those expected with 10 mg MD in patients with body weight &gt;60 kg.</b> ( <i>The red dashed line represent the concentration range beyond which the bleeding related adverse events were highest from Figure 3). (CL = <math>123 \times (WT/85)^{0.798}</math>; Between-subject variability (%CV) = 24% - Obtained from Reviewer's POPPK analysis of TABR for Simulation)</i> .....	43
Figure 19 Effect of age by gender on observed R-138727 C <sub>max</sub> and AUC <sub>0-tlast</sub> following a 60-mg LD and daily 10-mg MD of prasugrel .....	43

Figure 20: Risk for CVD/Non-fatal MI/ Non-fatal Stroke is high in patients above 75 years of age compared to patients below 75 years. ( <i>The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups</i> ) .....	44
<b>Figure 21 Risk for TIMI Major bleeding is high in patients above 75 years of age compared to patients below 75 years. (<i>The Hazard Ratios are for Prasugrel compared to Clopidogrel in each of the age groups</i>)</b> .....	45
Figure 22 Box plots compare the observed AUC <sub>0-tlast</sub> and C <sub>max</sub> values of R-138727 by ethnic group following 60-mg LD or 10-mg MD of prasugrel .....	46
Figure 23. R138727 Plasma Concentrations vs Time. Food Effect.....	51
Figure 24. Formation of R-95913 by hCE1 (A) and hCE2 (B). The points with the error bars represent the average and standard error, while the lines represent the best model fit of their respective kinetic models. Inset shows the sigmoidicity of the Hill kinetics. ....	64
Figure 25. Formation of R-138727 by expressed CYPs following incubation with 20 $\mu$ M R-95913.....	74
Figure 26. Formation of R-138727 from R-95913 (10 $\mu$ M) with respect to time (A) and with respect to protein (B). ....	77
Figure 27 Formation of isomer sets of R-138727 by expressed CYPs following incubation with 20 $\mu$ M R-95913.....	79
Figure 28. The structures of R-138727 stereoisomers and their relative activity towards inhibition of platelet aggregation.....	81
Figure 29. Mean ( $\pm$ SEM) of the percentages of $^{14}$ C dose eliminated in humans following a single oral 15-mg (100 $\mu$ Ci) dose of $^{14}$ C -CS-747.....	84
Figure 30. Radiochromatogram of the 0.5-hour underivatized plasma (Subject 4503).....	85
Figure 31. Mean plasma concentrations of LY640315 metabolites in plasma following a 15-mg oral dose of [ $^{14}$ C]LY640315, (N = 5).....	86
Figure 32 Radiochromatogram of the pooled 0-24 hour urine of Subject 4503 .....	87
Figure 33 Radiochromatogram of a 0-24 hour fecal extract of Subject 2949 .....	88
Figure 34. R-95913, R-119251, R-106583, and R-138727 arithmetic mean ( $\pm$ SD) plasma concentration versus time profiles after a single oral dose of 15 mg $^{14}$ C -CS-747.....	89
Figure 35. Plasma (upper panel) and whole blood (lower panel) radioactivity arithmetic mean ( $\pm$ SD) concentration versus time profiles after a single oral dose of 15 mg $^{14}$ C -CS-747....	89
Figure 36. Ratio of radioactivity in plasma and whole blood after a single oral dose of 15 mg $^{14}$ C -CS-747. ....	90
Figure 37 Sponsor's plot of the mean plasma concentrations of 3 metabolites of prasugrel after the 2.5 mg dose of prasugrel .....	95
Figure 38 Three metabolites of prasugrel after the 2.5 mg (left) and 75 mg (right) doses of prasugrel.....	96
Figure 39. The sponsor's plots for the assessment of linearity of C <sub>max</sub> and AUC <sub>0-24</sub> . ....	96
Figure 40. Inhibition of platelet aggregation with ADP 5mM in individual subjects after the doses of prasugrel of 2.5, 10, 30, 75 mg and placebo.....	97
Figure 41. R-1006583 plasma concentrations vs time after the dose of 10 mg of CS-747 .....	101
Figure 42. Plasma concentrations (arithmetic mean) of prasugrel's metabolites after single doses. ....	105
Figure 43. Plasma concentrations (arithmetic mean $\pm$ SD) of R-130964 and R-138727 following a single LD (A) and the seventh MD (B) of clopidogrel and prasugrel .....	112

Figure 44. Box plots of MPA response to 20 $\mu$ M ADP following a single 60-mg LD and daily 10-mg MDs of prasugrel.....	113
Figure 45. Box plots of MPA response to 20 $\mu$ M ADP following a single 300 mg (upper panel) or 600-mg (lower panel) LD and daily 75-mg MDs of clopidogrel.....	114
Figure 46. Time profile of least squares mean IPA response ( $\pm$ 90% CI) to 20 $\mu$ M ADP following a single LD of prasugrel and clopidogrel.....	115
Figure 47. Time profile of least squares mean IPA response ( $\pm$ 90% CI) to 20 $\mu$ M ADP following a single LD and daily MDs of prasugrel and clopidogrel.....	115
Figure 48. Time profile of least squares mean (90% CI) VASP phosphorylation following a single LD of prasugrel and clopidogrel.....	116
Figure 49. VASP phosphorylation response at 24 hours following LDs of prasugrel and clopidogrel.....	117
Figure 50. MPA to 20 $\mu$ M ADP vs VASP phosphorylation at 6 hours following LDs of prasugrel and clopidogrel.....	117
Figure 51. Scatter plot of IPA response to 20 $\mu$ M ADP at 24 hours versus AUC(0-tlast) (ng•hr/mL) following LDs of prasugrel and clopidogrel.....	118
Figure 52. Scatter plot of IPA response to 20 $\mu$ M ADP at 24 hours versus AUC(0-tlast) (ng•hr/mL) following the seventh MD of prasugrel and clopidogrel.....	118
Figure 53. IPA with ADP 20mcM vs AUC of clopidogrel and prasugrel. Blue symbols – LD, Red symbols – MD.....	119
Figure 54. Geometric mean plasma concentrations of R-138727.....	123
Figure 55. Geometric mean plasma concentrations of R95913 (upper left), R119251 (upper right), and R106583 (lower panel).....	123
Figure 56. Mean ( $\pm$ SD) plasma R-138727 concentration-time profiles following a prasugrel 60-mg LD (left) and after the fifth daily 10-mg MD (right).....	128
Figure 57. Mean ( $\pm$ SD) plasma R-95913(upper), R-119251 (middle), and R-16583 (lower) concentration-time profiles following a prasugrel 60-mg LD (left) and after the fifth daily 10-mg MD (right).....	129
Figure 58. Mean MPA to 20 $\mu$ M ADP following a single 60-mg LD of prasugrel in subjects with mild and moderate hepatic impairment (Parts 1 and 2) and healthy subjects.....	133
Figure 59. MPA to 20 $\mu$ M ADP at 6 (left) and 24 hours (right) following a single 60-mg LD of prasugrel in subjects with mild and moderate hepatic impairment and healthy subjects... ..	133
Figure 60 Plasma concentrations (arithmetic mean $\pm$ SD) of R-138727 after a single 60-mg LD (A) and after the fifth daily 10-mg MD (B) of prasugrel in healthy subjects and moderate hepatic impairment subjects.....	137
Figure 61 Mean (SD) MPA to 20 $\mu$ M ADP following a 60-mg LD and the fifth daily 10-mg MD of prasugrel in subjects with moderate hepatic impairment and in healthy subjects.....	140
Figure 62 Arithmetic mean ( $\pm$ SD) plasma concentrations-time profiles of R-138727 after a single 5-, 10-, 30- or 60-mg prasugrel dose in healthy subjects and ESRD subjects.....	144
Figure 63 Mean ( $\pm$ SD) MPA to 20 $\mu$ M ADP following a single oral dose of 5-mg (upper panel) and 60 mg (lower panel) prasugrel in subjects with ESRD and healthy matched subjects.....	147
Figure 64. Arithmetic mean ( $\pm$ SD) plasma concentrations-time profiles of R-138727 after a single 60-mg prasugrel dose in healthy subjects, ESRD subjects and moderate renal impairment subjects.....	151

Figure 65. Individual estimates of R-138727 C <sub>max</sub> and AUC(0-t <sub>last</sub> ) Circles represent ESRD subjects (open) with healthy matched subjects (closed); Triangles represent moderate renally impaired subjects (closed) with healthy matched subjects (open).....	152
Figure 66. Mean MPA to 20 $\mu$ M ADP following a 60-mg dose of prasugrel in subjects with ESRD (●), subjects with moderate renal impairment (▲) and healthy matched subjects to each group (○, Δ). .....	153
Figure 67. Arithmetic mean plasma concentration-time profiles of R-138727 following a 60-mg LD of prasugrel on Day 1 (right panel linear with from 0-6 h) .....	157
Figure 68. Individual estimates with arithmetic mean $\pm$ SD of R-138727 C <sub>max</sub> (upper panel) and AUC(0-t <sub>last</sub> ) (lower panel) stratified by ethnic group following a 60-mg LD of prasugrel on Day 1 .....	157
Figure 69. Arithmetic mean plasma concentration- time profiles of R-138727 following 10-mg MDs of prasugrel on Day 8 (right panel linear with inset 0-4 h).....	159
Figure 70. Individual estimates with arithmetic mean $\pm$ SD of R-138727 C <sub>max</sub> and AUC(0-t <sub>last</sub> ) stratified by ethnic group following 10-mg MDs of prasugrel on Day 8 .....	160
Figure 71. Arithmetic mean plasma concentration- time profiles of R-138727 following 5-mg MDs of prasugrel on Day 18 (upper panel linear with inset 0-4 h; lower panel log-linear). .....	162
Figure 72. Individual estimates with arithmetic mean $\pm$ SD of R-138727 C <sub>max</sub> (left panel) and AUC(0-t <sub>last</sub> ) (right panel) stratified by ethnic group following 5-mg MDs of prasugrel on Day 18. ....	162
Figure 73. ....	164
Figure 74. Relationship between R-138727 AUC(0-t <sub>last</sub> ) and MPA to 20 $\mu$ M ADP following 60-mg prasugrel LD (upper panel) and daily 5- and 10-mg prasugrel MDs combined (lower panel).....	165
Figure 75 Prasugrel active metabolite AUC(0-8h) (upper panel) and C <sub>max</sub> (lower panel) after single doses of 10, 20, 40 and 60 mg prasugrel in Chinese subjects (Parts A and B). .....	169
Figure 76 Arithmetic mean plasma concentration-time profiles of R-130964 in Chinese and Caucasian subjects following a single oral 300-mg clopidogrel dose .....	171
Figure 77. Arithmetic mean IPA to 20 $\mu$ M ADP following administration of 60 mg prasugrel and 300 mg clopidogrel in Chinese and Caucasian subjects .....	172
Figure 78. Bleeding time vs. Prasugrel Dose at Baseline (diamonds) and 24 hours post-dose (squares) in Chinese Subjects .....	173
Figure 79. Bleeding Time vs Time post-dose. Period 1 – clopidogrel 300 mg and Period 2 – prasugrel 60 mg.....	173
Figure 80. Arithmetic mean plasma concentration-time profiles of R-138727 after 10 days of 5-mg prasugrel MDs and following an additional 10 days of 10-mg prasugrel MDs in young and elderly subjects in the presence of aspirin.....	177
Figure 81. Arithmetic mean (1-sided SD) MPA to 20 $\mu$ M ADP following 75 mg aspirin MDs, and 5 and 10 mg prasugrel MDs with 75 mg aspirin MD in healthy young and elderly subjects.....	179
Figure 82. Arithmetic mean (1-sided SD) VN-P2Y <sub>12</sub> % inhibition following 75 mg aspirin MDs, and 5 and 10 mg prasugrel MDs with 75 mg aspirin MDs in healthy young and elderly subjects.....	180
Figure 83. Scatter plot of IPA to 20 $\mu$ M ADP (LTA) versus VN-P2Y <sub>12</sub> % inhibition following 5 and 10 mg prasugrel MDs.....	181

Figure 84. Arithmetic mean (1-sided SD) bleeding time ratios following the tenth daily 5 mg prasugrel MDs and tenth daily 10 mg prasugrel MDs in healthy young and elderly subjects.	182
Figure 85. Geometric mean plasma concentrations for the active metabolite of CS-747 (R138727).	186
Figure 86. Time profile of the predicted median IPA (with 90% CI) to 20 $\mu$ M ADP.	187
Figure 87. Plasma concentrations of R-138727 after a 60-mg prasugrel loading dose (left) and after the seventh daily 10-mg prasugrel maintenance dose (right) alone and with ranitidine.	191
Figure 88. Plasma concentrations of R-130964 after a 600-mg clopidogrel loading dose (left) and after the seventh daily 75-mg clopidogrel maintenance dose (right) alone and with ranitidine.	191
Figure 89. Arithmetic mean IPA to 20 $\mu$ M ADP time profile of clopidogrel and prasugrel alone and with ranitidine. LD, Day 1, top panel. MD, Day 8, bottom panel.	193
Figure 90 Light transmission aggregation tracings from pre and post administration of a thienopyridine.	198
Figure 91 The mean plasma concentrations of the active metabolites after a 60 mg loading dose and the final 15 mg maintenance dose of prasugrel (upper plots) and a 300 mg loading dose and the final 75 mg maintenance dose of clopidogrel (lower plots).	199
Figure 92 Time profile of the estimated mean IPA response (with 90% CI) to 20 $\mu$ M ADP.	201
Figure 93 Distribution of IPA response to 20 $\mu$ M ADP on Day 1 at 4 hours after the loading dose.	201
Figure 94 Distribution of IPA response to 20 $\mu$ M ADP predose on Day 6.	202
Figure 95 Distribution of IPA response to 20 $\mu$ M ADP 4 hours postdose on Day 6.	202
Figure 96 Time profiles of predicted median bleeding time ratios.	203
Figure 97 Distribution of bleeding time ratios by treatment group on Day 6 at 4 hours postdose.	203
Figure 98 Plasma concentrations of R-138727 after a 60-mg prasugrel loading dose (A) and after the tenth daily 10-mg prasugrel maintenance dose (B) alone and with atorvastatin.	207
Figure 99 Plasma concentrations of R-130964 after a 300-mg clopidogrel loading dose (A) and after the tenth daily 75-mg clopidogrel maintenance dose (B) alone and with atorvastatin.	207
Figure 100 Mean (SD) IPA to 20 $\mu$ M ADP following a loading dose (Day 1) and maintenance dose (Day 11) of prasugrel and clopidogrel administered alone and with atorvastatin.	210
Figure 101 Mean (SD) VASP (PRI) following a loading dose (Day 1) of prasugrel and clopidogrel administered alone and with atorvastatin.	211
Figure 102 Digoxin serum concentrations for all treatment arms.	214
Figure 103 Individual APTT measurements prior to prasugrel / placebo dosing or prior to UFH / saline administration.	218
Figure 104 Individual ACT measurements prior to prasugrel / placebo dosing or prior to UFH / saline administration.	218
Figure 105 Mean APTT-time profiles following UFH / saline dose.	220
Figure 106 Mean anti-Xa-time profiles following UFH/saline dose.	220
Figure 107 Mean ACT-time profiles following UFH/saline dose.	220
Figure 108 LS mean IPA response to 20 $\mu$ M ADP time profile following UFH administration in the presence of prasugrel.	221



Figure 109 IPA response adjusted for the baseline MPA at the end of aspirin phase. ....	225
Figure 110 Distribution of maximum IPAs on Day 6 (ADP), with the outliers (indicated by the small open boxes), minimum, lower quartile, median, mean (indicated by a plus sign), and maximum. ....	225
Figure 111 Distribution of IPAs at 24 hours post-maintenance on Day 10 (ADP), with minimum, lower quartile, median, mean (indicated by a plus sign), and maximum. ....	225
Figure 112 Time profiles of the predicted median bleeding time ratios. ....	226
Figure 113 Distribution of bleeding time ratios by treatment group on Day 10, 4 hours post-dose. ....	226
Figure 114 Light transmission aggregation tracings from pre and post administration of a thienopyridine. ....	229
Figure 115 Mean rIPA response to 20 $\mu$ M ADP following prasugrel administration in the presence of aspirin. ....	231
Figure 116 Mean bleeding time ratio following administration of prasugrel alone (N=23) and with aspirin (N=21). ....	231
Figure 117 Light transmission aggregation tracings from pre and post administration of a thienopyridine. ....	235
Figure 118 Plasma concentrations of R-warfarin following administration of warfarin alone and with prasugrel. ....	236
Figure 119 Plasma concentrations of S-warfarin following administration of warfarin alone and with prasugrel. ....	236
Figure 120 International normalized ratio following warfarin administration in the presence of prasugrel. ....	237
Figure 121 Prothrombin times after warfarin administration in the presence of prasugrel. ....	238
Figure 122 Least squares mean IPA to 20 $\mu$ M ADP time profile following warfarin administration in the presence of prasugrel. ....	238
<b>Figure 123 Plasma concentrations of bupropion and hydroxybupropion following a single 150-mg dose of bupropion alone or with prasugrel. ....</b>	<b>242</b>
Figure 124 Plasma concentrations of R-138727 and R-95913 following a single 60-mg LD of prasugrel alone and with rifampicin. ....	244
Figure 125 Plasma concentrations of R-138727 and R-95913 after the fifth once daily 10-mg MD of prasugrel alone and with rifampicin. ....	244
<b>Figure 126 Mean IPA to 20 <math>\mu</math>M ADP following administration of prasugrel alone and with rifampicin. ....</b>	<b>246</b>

## 1 EXECUTIVE SUMMARY

Eli Lilly Inc. submitted NDA 22-307 - EFFIENT (Prasugrel Hydrochloride tablets) on December 26, 2007. Prasugrel is proposed for the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes (ACS).

EFFIENT is a novel adenosine diphosphate (ADP) receptor antagonist of the thienopyridine class and an inhibitor of platelet activation and aggregation mediated by the P2Y<sub>12</sub> ADP receptor. EFFIENT was developed in collaboration with Daiichi Sankyo Inc. EFFIENT will be marketed as an oral 5 and 10 mg film coated tablets.

The recommended administration: an initial single oral 60 mg loading dose and then continued at a 10 mg once daily dose. All patients taking prasugrel should also take aspirin (75 mg to 325 mg) daily. Prasugrel may be taken with or without food. Patients weighing less than 60 kg should be given a single 60 mg loading dose and then continued at a 5 mg once daily dose.

The submission included 48 clinical pharmacology studies where the pharmacokinetics and pharmacodynamics of prasugrel were assessed. The sponsor conducted several in vitro studies to assess the metabolism by CYP450, binding to plasma protein and drug-drug interaction studies with drugs that could be possibly co-administered in the clinic. A total of 36 studies were reviewed.

### 1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 22-307. The CPB information provided in NDA 22-307 is acceptable.

#### ***SPECIFIC RECOMMENDATIONS:***

1. The proposed dose adjustment of prasugrel maintenance dose to 5 mg QD for patients with body weight less than 60 Kg is acceptable.
2. The proposed dose adjustment of prasugrel maintenance dose in patients with age  $\geq$  75 y is not acceptable.
3. Pre-treatment of at least 6 hrs for prasugrel or clopidogrel is not necessary to achieve maximum effectiveness. The loading dose for either prasugrel or clopidogrel should be administered at least within 30 minutes of the start of PCI.

The following comments should be properly addressed by the sponsor.

#### ***COMMENTS:***

1. The sponsor should consider lowering the 60/10 dosing regimen of prasugrel in order to decrease the incidence of bleeding.
2. The sponsor should investigate the effects of a CYP2B6 inhibitor on the PK of prasugrel.

3. Not enough information is provided in the study reports in patients with ESRD. The sponsor is requested to provide additional information in order to better evaluate the study results and be able to provide labeling recommendations in this patient population.

4. 

b(4)

5. The labeling comments should be addressed by the sponsor.

## 1.2 PHASE IV COMMINTMENTS:

The sponsor should \_\_\_\_\_

b(4)

\_\_\_\_\_  
Elena Mishina, Ph. D.  
Senior Clinical Pharmacologist

Date \_\_\_\_\_

\_\_\_\_\_  
Sripal Mada, Ph.D  
Clinical Pharmacologist

\_\_\_\_\_  
Raj Madabushi, Ph.D  
Pharmacometrics Reviewer

\_\_\_\_\_  
Yaning Wang, Ph.D  
Pharmacometrics Team Leader

\_\_\_\_\_  
Patrick Marroum, Ph. D.  
Cardio-Renal Team Leader

CPB Briefing was held on May 21, 2008

Attendees: Menon D, Younis I, Burkhart G, Mehta M, Unger E, Rahman A, Huang SM, Uppoor R, Zhang L, Chen TO, Orlof D, Yun X, Iyer G, Dorantes A, Ququan L, Hicks K, Marroum P, Mada S, Mishina E, Madabushi R.

cc list: NDA 22-307, MehulM, MarroumP, MishinaE, UppoorR, HFD 110 BIOPHARM