

### **5.1.2 Relative Bioavailability of Stored Compared to Newly Manufactured Tablets after a 60 mg Prasugrel Loading Dose in Healthy Subjects taking a Proton Pump Inhibitor**

Technical Report no: H7T-EW-TACS.

Investigator and site:

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**Study Objectives:**

To determine the effect of salt conversion to base during storage of prasugrel tablets on the pharmacokinetics of the prasugrel's active metabolite in healthy subjects taking lansoprazole 30 mg once daily. The secondary objectives were to assess the effect of salt conversion to base during storage of prasugrel tablets on the time course of maximum platelet aggregation (MPA) after a 60 mg loading dose of prasugrel in healthy subjects taking lansoprazole 30 mg once a daily for at least 1 week and to assess the safety and tolerability of prasugrel in healthy subjects.

Study Design:

This was a three treatment three period, open label, randomized crossover study in which subjects taking 30 mg lansoprazole once daily for at least one week received 60 mg prasugrel tablets with low, intermediate and high extent of conversion of prasugrel.HCl to prasugrel base. 34 subjects between the ages of 18 and 65 taking 30 mg lansoprazole received study treatment out of which 30 completed the study. 2 subjects were withdrawn after completion of the lansoprazole lead in phase and prior to the first dose of prasugrel and one subject was withdrawn after receiving the first dose of prasugrel. One further withdrawn subject was given lansoprazole doses although it was not known if these were administered and this subject did not receive prasugrel.

Prasugrel was administered orally as a single 60 mg dose provided as 10 mg tablets. Lansoprazole was administered orally as daily 30 mg doses provided as 30 mg capsules. The prasugrel formulations were as follows: low extent of conversion of prasugrel.HCl (5 %), intermediate (58 %) or high extent of conversion (70 %)

Subjects received each of the treatments with a washout period of at least 7 days between doses. Subjects had a 7 day lead in phase of once a day 30 mg lansoprazole before the first dose of prasugrel and continued taking lansoprazole until the last dose of prasugrel was given. Blood samples for the determination of plasma concentrations of prasugrel's active metabolite R-138727 were collected pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9 12 and 24 hours post dose administration.

Test Drug:

10 mg high surface area prasugrel tablets batch # CT530045  
10 mg medium surface area prasugrel tablets batch # CT53047  
10 mg low surface area prasugrel tablets batch # CT530568  
30 mg Prevacid capsules lot #478272E80.

Assay:

Plasma samples were analyzed for the determination of plasma concentrations of prasugrel's active metabolite at Advion Bioservices using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS)

Data Analysis

Pharmacokinetic parameters were determined for R-138727 by non-compartmental techniques. The 90% confidence intervals were constructed by the two one-sided tests procedure to assess bioequivalence.

The inhibition of platelet aggregation using LTA was assessed by the MPA and the inhibition of platelet aggregation (IPA) to 20  $\mu$ M ADP.

MPA to 20  $\mu$ M ADP was the primary pharmacodynamic parameter. The secondary pharmacodynamic parameter, IPA to 20  $\mu$ M ADP, was calculated using the equation:

$$IPAt = 100\% \times (1 - MPAt / MPA0)$$

where IPAt is the IPA at time t, MPAt is the observed MPA at time t, and MPA0 is the baseline (predose) MPA.

Results:

Figure 1 shows the plasma concentration time profiles while Table 1 gives the summary of the relevant PK parameters. Table 2 gives the statistical comparison for the relative bioavailability of the low, medium and high surface area tablets.

The results show that after pre-treatment with 30 mg lansoprazole, the low, intermediate and high rate of conversion tablets are not bioequivalent to each other as the CMAX fails to meet the 90 % confidence interval criteria of 80-125.

The extent of prasugrel salt to base conversion did not affect the time to or the magnitude of the peak effect on MPA. No statistically significant differences in MPA were detected between treatments except at 0.5 and 1 hour post dose when MPA following the high conversion tablet was significantly higher than both after the intermediate and low conversion tablets. The difference in MPA at the 0.5 hour was greater than 10 % and therefore clinically significant.

Conclusion:

The high, intermediate and low conversion tablets were found to be bioinequivalent in healthy volunteers pre-treated with 30 mg lansoprazole. This difference in plasma levels translated into differences in mean platelet aggregation which potentially can be clinically significant.

**Table TACS.7.1. Summary of Geometric Mean (CV%) Pharmacokinetic Parameter Estimates of R-138727 for the Low, Intermediate, and High Extents of Conversion of Prasugrel.HCl after a 60-mg Dose of Prasugrel on a Background of 30-mg Lansoprazole Once-Daily**

| Parameter                              | Geometric Mean (%CV)             |                                  |                                  |
|--|----------------------------------|----------------------------------|----------------------------------|
|  | 60-mg prasugrel<br>L-C<br>(N=35) | 60-mg prasugrel<br>M-C<br>(N=36) | 60-mg prasugrel<br>H-C<br>(N=36) |
| C <sub>max</sub><br>(ng/mL)            | 327<br>(67)                      | 299<br>(61)                      | 235<br>(51)                      |
| t <sub>max</sub> <sup>a</sup><br>(h)   | 0.75<br>(0.25-3.00)              | 0.75<br>(0.50-3.00)              | 0.89<br>(0.50-2.00)              |
| AUC(0-t <sub>last</sub> )<br>(ng•h/mL) | 465<br>(42)                      | 468<br>(42)                      | 406<br>(40)                      |

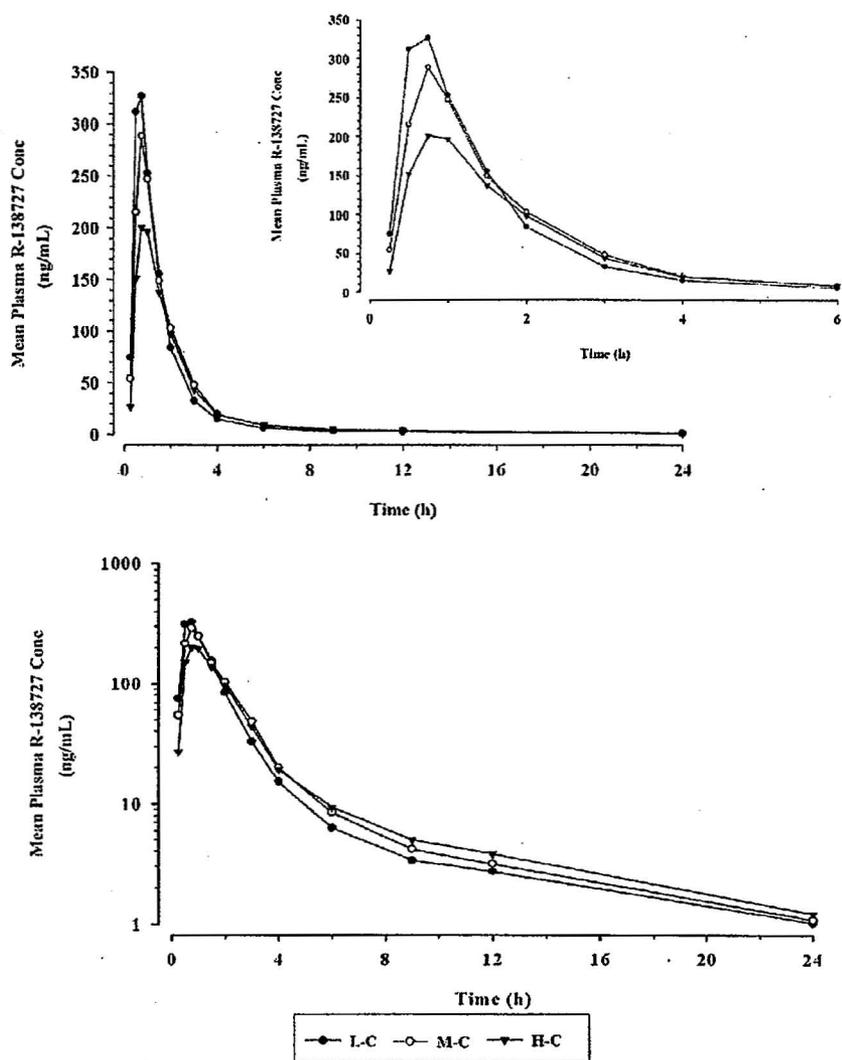
Abbreviations: CV - coefficient of variation; AUC(0-t<sub>last</sub>) - area under the plasma concentration-time curve from time zero through the sampling time of the last quantifiable concentration; C<sub>max</sub> - maximum observed plasma concentration; N = Number of subjects; t<sub>max</sub> - time of C<sub>max</sub>.

<sup>a</sup> Median (range)

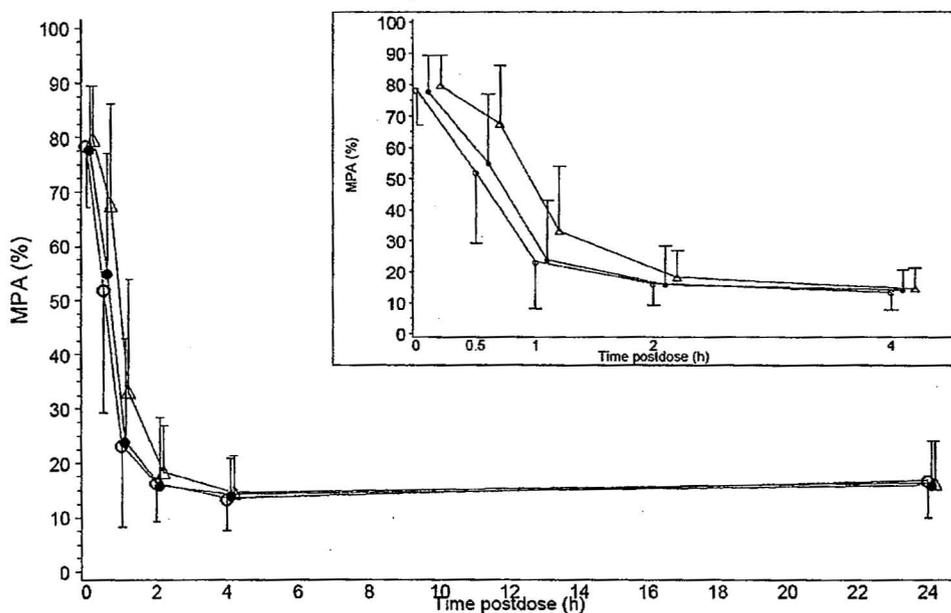
**Table TACS.7.2. Statistical Comparison of the Relative Bioavailability of R-138727 Between the Low, Intermediate, and High Extents of Conversion of Prasugrel.HCl after a 60-mg Dose of Prasugrel on a Background of 30-mg Lansoprazole Once-Daily (L-C as Reference)**

| Parameter<br>(units)                   | Geometric LS means (90% CI) |                           |                           | Ratio of geometric LS means (90% CI) |                      |                      |
|--|-----------------------------|---------------------------|---------------------------|--------------------------------------|----------------------|----------------------|
|  | 60-mg<br>prasugrel<br>L-C   | 60-mg<br>prasugrel<br>M-C | 60-mg<br>prasugrel<br>H-C | M-C/<br>L-C                          | H-C/<br>L-C          | H-C/<br>M-C          |
| AUC(0-t <sub>last</sub> )<br>(ng•h/mL) | 470<br>(424, 522)           | 467<br>(421, 518)         | 409<br>(368, 454)         | 0.99<br>(0.93, 1.06)                 | 0.87<br>(0.82, 0.93) | 0.88<br>(0.82, 0.93) |
| C <sub>max</sub><br>(ng/mL)            | 331<br>(285, 384)           | 297<br>(257, 344)         | 236<br>(204, 274)         | 0.90<br>(0.77, 1.04)                 | 0.71<br>(0.62, 0.83) | 0.80<br>(0.69, 0.92) |

Model: Log(PK) = SUBJECT(SEQUENCE) + TREATMENT + PERIOD + SEQUENCE + RANDOM ERROR



**Figure TACS.7.1.** Arithmetic mean plasma concentration-time profiles of R-138727 following a 60-mg dose of prasugrel containing a low (L-C), intermediate (M-C), or high (H-C) extent of conversion of prasugrel.HCl to prasugrel base, on a background of 30-mg lansoprazole once-daily (upper panel linear; lower panel log-linear).



○ = L-C (Low extent of conversion of prasugrel HCl)  
 ● = M-C (Intermediate extent of conversion of prasugrel HCl)  
 △ = H-C (High extent of conversion of prasugrel HCl)

T + or - Standard Deviation

**Table TACS.7.5. Statistical Comparison of MPA to 20 μM ADP Following a 60-mg Dose of Prasugrel Containing Low, Intermediate, or High Extents of Conversion of Prasugrel.HCl, on a Background of 30-mg Lansoprazole Once-Daily**

| Time                 | LS means MPA (90% CI) |                   |                   | Difference of LS means (90% CI) [p-value] |                               |                              |
|----------------------|-----------------------|-------------------|-------------------|---|-------------------------------|------------------------------|
|                      | L-C                   | M-C               | H-C               | (M-C) - (L-C)                             | (H-C) - (L-C)                 | (H-C) - (M-C)                |
| Predose <sup>a</sup> | 79.0 (76.0, 82.0)     | 77.7 (74.8, 80.7) | 79.9 (77.0, 82.9) | -1.3 (-4.7, 2.2)<br>[0.539]               | 0.9 (-2.6, 4.4)<br>[0.662]    | 2.2 (-1.3, 5.7)<br>[0.294]   |
| 0.5 h                | 51.0 (47.1, 54.8)     | 55.0 (51.2, 58.7) | 67.0 (63.2, 70.8) | 4.0 (-0.7, 8.7)<br>[0.165]                | 16.0 (11.3, 20.8)<br>[<0.001] | 12.0 (7.4, 16.7)<br>[<0.001] |
| 1 h                  | 22.8 (18.9, 26.6)     | 24.1 (20.3, 27.9) | 32.6 (28.8, 36.4) | 1.3 (-3.4, 6.1)<br>[0.645]                | 9.8 (5.1, 14.5)<br>[<0.001]   | 8.5 (3.8, 13.2)<br>[0.003]   |
| 2 h                  | 15.9 (12.1, 19.7)     | 15.9 (12.0, 19.7) | 17.9 (14.1, 21.6) | 0.0 (-4.8, 4.7)<br>[0.993]                | 2.0 (-2.8, 6.7)<br>[0.495]    | 2.0 (-2.7, 6.7)<br>[0.489]   |
| 4 h                  | 13.1 (9.3, 17.0)      | 14.2 (10.4, 18.0) | 14.1 (10.3, 17.9) | 1.1 (-3.6, 5.8)<br>[0.710]                | 1.0 (-3.7, 5.7)<br>[0.735]    | -0.1 (-4.8, 4.6)<br>[0.973]  |
| 24 h                 | 16.3 (12.5, 20.2)     | 16.1 (12.2, 19.9) | 15.8 (12.0, 19.6) | -0.3 (-5.0, 4.5)<br>[0.927]               | -0.5 (-5.2, 4.2)<br>[0.852]   | -0.3 (-5.0, 4.4)<br>[0.925]  |

<sup>a</sup> Model: MPA = Subject + Treatment + Random Error

Model: MPA = MPA at Day 1, Predose + SUBJECT + SUBJECT\*TIME + SUBJECT\*TREATMENT + TREATMENT + TIME + TREATMENT\*TIME + RANDOM ERROR

**5.1.3 The effect of Active Pharmaceutical Ingredient Surface Area on the Relative Bioavailability of a 60 mg Prasugrel Loading Dose in Healthy Subjects Taking a Proton Pump Inhibitor**

Technical Report no: H7T-EW-TACK.

Investigator and site:

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Study Objectives:

To assess the effect of active pharmaceutical ingredient surface area on the pharmacokinetics of prasugrel's active metabolite in healthy subjects taking lansoprazole 30 mg once daily. The secondary objective was to assess the safety and tolerability of prasugrel in healthy subjects taking a proton pump inhibitor.

Study Design:

This was a three treatment three period, open label, randomized crossover study. 34 subjects between the ages of 18 and 65 taking 30 mg lansoprazole received study treatment out of which 30 completed the study. 2 subjects were withdrawn after completion of the lansoprazole lead in phase and prior to the first dose of prasugrel and one subject was withdrawn after receiving the first dose of prasugrel. One further withdrawn subject was given lansoprazole doses although it was not known if these were administered and this subject did not receive prasugrel.

Prasugrel was administered orally as a single 60 mg dose provided as 10 mg tablets with high surface area

Lansoprazole was administered orally as daily 30 mg doses provided as 30 mg capsules extent of conversion of prasugrel.HCl (5 %), intermediate (58 %) or high extent of conversion (70 %)

Subjects received each of the treatments with a washout period of at least 7 days between doses. Subjects had a 7 day lead in phase of once a day 30 mg lansoprazole before the first dose of prasugrel and continued taking lansoprazole until the last dose of prasugrel was given. Blood samples for the determination of plasma concentrations of prasugrel's active metabolite R-138727 were collected pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9 12 and 24 hours post dose administration.

Test Drug:

- 10 mg high surface area prasugrel tablets batch # CT530045
- 10 mg medium surface area prasugrel tablets batch # CT53047
- 10 mg low surface area prasugrel tablets batch # CT530568
- 30 mg Prevacid capsules lot #478272E80.

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Assay:

Plasma samples were analyzed for the determination of plasma concentrations of prasugrel's active metabolite at Advion Bioservices using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS).

The inter assay accuracy expressed as % relative error) ranged from 3 to 14.8 % and the inter assay precision (5 relative standard deviation was <2.8 %. Intra assay accuracy ranged from 1.9 % to 18.4 % and the intra assay precision was <2.6 %.

b(4)

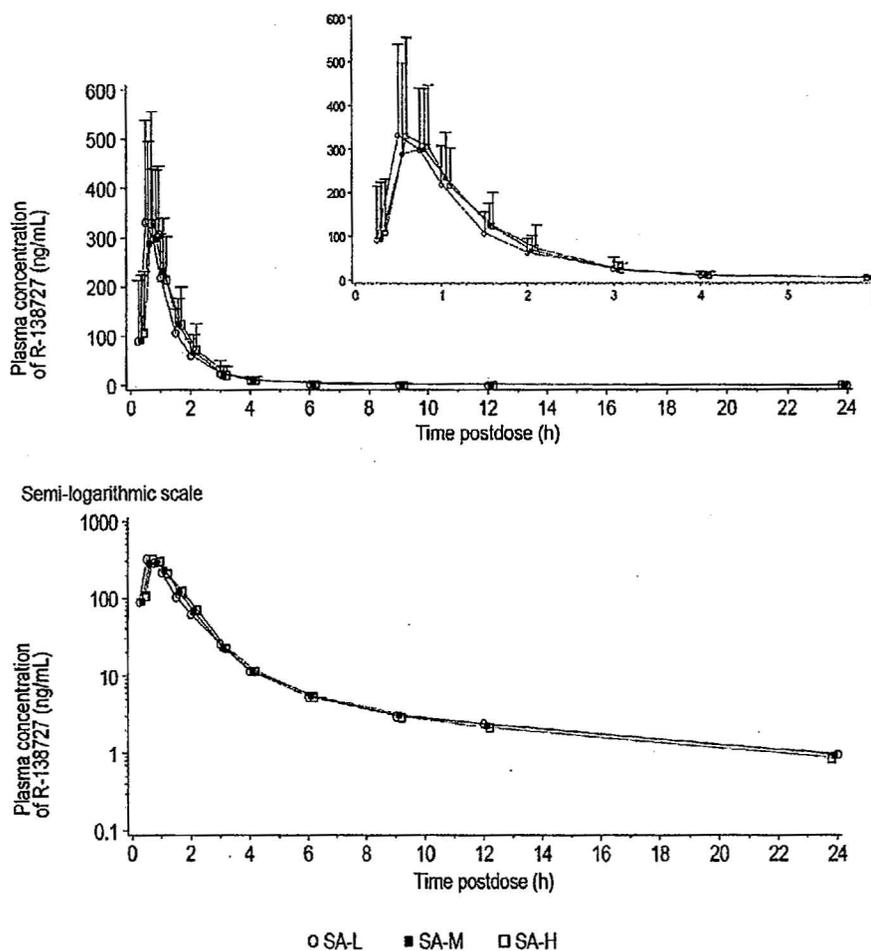
Data Analysis

Pharmacokinetic parameters were determined for R-138727 by non-compartmental techniques. The 90% confidence intervals were constructed by the two one-sided tests procedure to assess bioequivalence.

Results:

Figure 1 shows the plasma concentration time profiles while Table 1 gives the summary of the relevant PK parameters. Table 2 gives the statistical comparison for the relative bioavailability of the low, medium and high surface area tablets.

The results show that both the low and medium surface area tablets are not bioequivalent to the high surface area since the CMAX is outside slightly outside the 80 to 125 % 90 % confidence limits. In terms of exposure (AUC) both the low and medium surface area tablets are bioequivalent to the high surface area.



Error bars on Cartesian plot represent standard deviations

**Figure TACK.7.1. Arithmetic mean plasma concentration-time profiles of R-138727 following the low (SA-L), medium (SA-M), and high (SA-H) API surface areas of 60-mg prasugrel on a background of 30-mg lansoprazole (upper panel linear; lower panel log-linear).**

**Table TACK.7.1. Summary of Geometric Mean (CV%) Pharmacokinetic Parameters of R-138727 for the Low (SA-L), Medium (SA-M), and High (SA-H) API Surface Areas of 60-mg Prasugrel on a Background of 30-mg Lansoprazole**

| Parameters                             | 60 mg prasugrel            | 60 mg prasugrel            | 60 mg prasugrel            |
|--|----------------------------|----------------------------|----------------------------|
|  | SA-L<br>(N=31)             | SA-M<br>(N=30)             | SA-H<br>(N=29)             |
| AUC(0-t <sub>last</sub> )<br>(ng•h/mL) | 425<br>(29.0)              | 426<br>(35.2)              | 420 <sup>b</sup><br>(31.1) |
| AUC(0-∞)<br>(ng•h/mL)                  | 442 <sup>b</sup><br>(29.1) | 455 <sup>c</sup><br>(30.9) | 445 <sup>d</sup><br>(27.8) |
| C <sub>max</sub><br>(ng/mL)            | 336<br>(61.0)              | 328<br>(48.7)              | 348<br>(60.6)              |
| t <sub>max</sub> <sup>a</sup><br>(h)   | 0.517<br>(0.250-3.00)      | 0.750<br>(0.250-1.50)      | 0.750<br>(0.500-2.00)      |

N = Number of subjects

<sup>a</sup> Median (range)

**Table TACK.7.2. Statistical Comparison of Relative Bioavailability of R-138727 Between the Low (SA-L), Medium (SA-M), and High (SA-H) API Surface Areas of 60-mg Prasugrel on a Background of 30-mg Lansoprazole**

| Parameters<br>(units)                  | Geometric LS means<br>(90% CI) |                         |                         | Ratio of geometric LS means<br>(90% CI) |                      |
|--|--------------------------------|-------------------------|-------------------------|---|----------------------|
|  | 60 mg prasugrel<br>SA-L        | 60 mg prasugrel<br>SA-M | 60 mg prasugrel<br>SA-H | SA-L/ SA-H                              | SA-M/ SA-H           |
| AUC(0-t <sub>last</sub> )<br>(ng.h/mL) | 425<br>(386, 467)              | 423<br>(384, 466)       | 425<br>(386, 469)       | 0.99<br>(0.91, 1.09)                    | 0.99<br>(0.91, 1.08) |
| AUC(0-∞)<br>(ng.h/mL)                  | 442<br>(404, 484)              | 449<br>(410, 493)       | 451<br>(411, 494)       | 0.98<br>(0.91, 1.05)                    | 0.99<br>(0.93, 1.06) |
| C <sub>max</sub><br>(ng/mL)            | 334<br>(285, 390)              | 328<br>(280, 384)       | 350<br>(298, 411)       | 0.95<br>(0.79, 1.14)                    | 0.93<br>(0.78, 1.12) |

Model: Log(PK) = SUBJECT(SEQUENCE) + TREATMENT + PERIOD + SEQUENCE + RANDOM ERROR

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. In the submission, Table APP.2.7.1.4 lists the prasugrel formulations used in the clinical studies, including TAAL.

**Table APP.2.7.1.1. 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:<br>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<br>used in Japan studies | J101, J102, J103, J105, J106, J201   |
| Radiolabeled Prasugrel<br>base Solution        | TAAB   |