# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022433Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Appendix I: Individual Studies Review

**This appendix is an addendum to the clinical pharmacology review checked in DARRTS on 06/17/2010.**

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**Analytical Methods:** wherever it is mentioned throughout the appendix that the performance of the analytical method is acceptable, it implies that the method used met the below requirement:

| | |
|---|---|
| ▪ Study samples were analyzed within the established stability period: | ☑ Yes ☐ No |
| ▪ Quality control samples range is acceptable | ☑ Yes ☐ No |
| ▪ Internal standard was used | ☑ Yes ☐ No |
| ▪ Method was validated prior to use | ☑ Yes ☐ No |
| ▪ Chromatograms were provided | ☑ Yes ☐ No |
| ▪ Calibration range samples accuracy and precision are acceptable | ☑ Yes ☐ No |
| ▪ Quality control samples accuracy and precision are acceptable | ☑ Yes ☐ No |
| ▪ Quality control samples precision is acceptable | ☑ Yes ☐ No |
| Method overall performance is acceptable | ☑ Yes ☐ No |

# Appendix I Table of Content

# CLINICAL PHARMACOLGY

## I. ADME-In Vitro Studies

### 1. Absorption

**Study #** DMY10
**Title:** AZD6140: Investigation of P-glycoprotein-mediated transport of AZD6140 and its active metabolite AR-C124910 using MDCK cells expressing human MDR1 P glycoprotein

- Objective: To determine whether ticagrelor and its active metabolite AR-C124910XX are substrates for P-gp.
- Procedure: A monolayer-based transport assay using MDCK cells over expressing human MDR1 P-gp was run in both basolateral to apical (B.→A) and apical to basolateral (A→.B) directions. GF120918 was used as an inhibitor of P-gp. Erythromycin (10 µM) and propranolol (10 µM) were used as positive and negative controls, respectively.
- Results: Significant unidirectional transport which indicates that both compounds are mainly transported by P-gp.

| Compound | Flux Ratio (B→A/A→B) | |
|---|---|---|
| | No Inhibitor | With inhibitor |
| Ticagrelor 1 µM | 33.9 | 1 |
| Ticagrelor 10 µM | 9.5 | 1.2 |
| ARC-124910XX 1 µM | 14.2 | 1.9 |
| ARC-124910XX 10 µM | 9.9 | 0.9 |
| Erythromycin | 17.6 | ND |
| Propranolol | 0.9 | ND |

- Conclusion: Both compounds are P-gp substrates

**Comment:** Mass recovery was low (<50%) and hence flux ratios may be underestimated.

**Study #** 6140DMY14
**Title:** AZD6140: Effect of AZD6140 and its metabolite AR-C124910 on P-glycoprotein-mediated transport of digoxin

- Objective: To determine whether ticagrelor and its active metabolite AR-C124910XX inhibits P-gp mediated digoxin transport in vitro.
- Procedure: Transport of 5 µM $^{3}$H-digoxin in MDR1-MDCK monolayer was determined in both basolateral to apical (B.→A) and apical to basolateral (A→.B) directions in the presence and absence of ticagrelor and AR-C124910XX (10 µM). GF120918 was used as an inhibitor of P-gp. Ketoconazole (10 µM) and propranolol (50 µM) were used as positive and negative controls, respectively. Effect of both compounds on digoxin transport was further evaluated at concentrations ranging from 0.1 to 50 µM.
- Results: Both compound inhibited digoxin transport in dose dependant manner with $IC_{50}$ of 7.8 ± 2.6 µM. and 9.9 ± 5.1. µM for ticagrelor and AR-C124910XX, respectively.

| Compound | Flux Ratio (B→A/A→B) | |
|---|---|---|
| | Control | Compound |
| Ticagrelor | 19.5 | 3.1 |
| ARC-124910XX | 22.8 | 2.4 |
| Ketoconazole | | 1.4 |
| Propranolol | | 14.1 |

- Conclusion: Ticagrelor and AR-C124910XX are inhibitors of Pgp mediated digoxin transport.

**Comment:** Mass recovery was low (<50%) and hence flux ratios may be underestimated.

## 2. Distribution

**Study #** SC-103174
**Title:** In vitro binding of [$^3$H]-ARC126532XX to the plasma proteins and blood cells of rat, dog, marmoset, rabbit, mouse, and man.

- Objective: To determine the blood association and plasma protein binding of ticagrelor in different species.
- Method: Radioactivity was determined by liquid scintillation
  - Protein Binding: $^3$H-Ticagrelor in plasma (10, 200, 4000 ng/mL) was analyzed by equilibrium dialysis for 3 h (pH 7.4, 37°C).
  - Blood Association: Blood samples containing were spiked with $^3$H-ticagrelor (final concentration (10, 200, 4000 ng/mL) and incubated at 37°C for 30 minutes.
- Results

| Species | Average Plasma Protein Binding | |
|---|---|---|
| | Protein Binding | Blood Association |
| Human | 99.4 | 16.3 |
| Rat | 99.4 | 24.5 |
| Dig | 99.0 | 47.7 |
| Marmoset | 99.1 | 33.3 |
| Rabbit | 99.2 | 39.8 |
| Mouse | 99.3 | 41.2 |

**Study #** YAT/116
**Title:** AZD6140: An in-vitro study to assess the free fraction of AR-C124910XX and AR-C1333913XX in human, marmoset, rat, mouse and rabbit plasma.

- Objective: To determine the plasma protein binding of ticagrelor metabolites (AR-C124910XX and AR-C1333913XX) in different species.
- Method: Both compounds were incubated with plasma (final concentration of 0.1, 0.5, and 1 µg/mL) for 1 h at 37°C prior to equilibrium dialysis analysis for 24 h (pH 7.4, 37°C). Both the diasylate and plasma retenate were assayed by LC-MS/MS.
- Results

| Species | Average Plasma Protein Binding | |
|---|---|---|
| | AR-C124910XX | AR-C133913XX |
| Human | 99.9 | 52.4 |
| Marmost | 99.6 | 52.0 |
| Rat | 99.6 | 48.2 |
| Mouse | 98.1 | 0.767 |
| Rabbit | 99.7 | 46.7 |

## 3. In vitro Metabolism

**Study #** 6140DMN9
**Title:** In vitro metabolism of [$^{14}$C]-AZD6140 in human and animal liver preparations

- Objective: To examine the metabolism of [$^{14}$C]-ticagrelor in:
  1. Hepatocytes: Rat, dog, and cryopreserved from human liver tissues.
  2. Liver Microsomes: Mouse, rat, dog, marmoset, cynomolgus monkey, and human
  3. Liver S9 fraction: Aroclor induced rat liver.
- Procedure: [$^{14}$C]-7-Ethoxycoumarin was used as positive control. Ticagrelor (20 µM , ~10.5 µg/mL) was incubated with:
  1. Hepatocytes (2 x $10^6$ cell/mL) for 0, 1, or 4 h.
  2. Liver microsomes (0.5 mg/mL protein) for 0, 30, or 60 minutes.
  3. Liver S9 fraction: for 0, 1, or 4 h (10, 20, and 80 µM ticagrelor)
- Results:
  1. No human specific metabolite was detected.
  2. A total of 19 metabolites were detected
  3. The majority of ticagrelor metabolism is oxidative and the main metabolites are AR-C124910XX (loss of the hydroxy-ethyl side chain) and AR-C133913XX (loss of the difluorophenyl-cyclopropyl group).

**Study #** DMX12
**Title:** Determination of the human cytochrome P450 enzymes involved in AR-C133913 formation and AR-C124910 formation and elimination (amendment 1)

- Objective: To determine CYP450 enzymes involved in the metabolism of ticagrelor to AR-C124910XX & AR-C133913
- Procedure:
  1. Ticagrelor (3 µM) and AR-C124910XX (1 µM) were incubated with human liver microsomes (0.5 mg/mL), in the presence and absence of CYP450 (1A2, 2C9, 2C19, 2D6, 3A4) inhibitors for 30 and 60 minutes.
  2. Ticagrelor (3 µM) and AR-C124910XX (1 µM) were incubated with human cDNA-expressed enzymes (1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 3A4, 3A5) for 30 and 60 minutes.
  3. Ticagrelor (1-50 µM) was incubated with cDNA-expressed human CYP3A4 and CYP3A5 to determine the enzyme kinetics of metabolite formation.
- Results:
  1. Selective CYP inhibitors: The formation of the two metabolites was inhibited approximately 98% by 1 µM ketoconazole (CYP3A inhibitor) and 30-40% by 50 µM omeparzole (CYP2C9 inhibitor) and 10-18% by 10 µM furafylline (CYP 1A2 inhibitor).

2. cDNA-expressed enzymes: AR-C124910 is primarily formed by CYP 3A4 and 3A5 (slightly higher by 3A4). AR-C133913 is primarily formed by CYP3A4, small amounts were produced by CYP 3A5. Other enzymes did not contribute to the formation of either metabolite.
3. Enzyme Kinetics: Parameters for metabolite formation is shown below:

| | ARC124910XX | | | ARC133913XX | | |
|---|---|---|---|---|---|---|
| | 3A4 | 3A5 | HLM | 3A4 | 3A5 | HLM |
| $V_{max}$ (µL/min/pmol) | 2.17 | 0.38 | 730 | 2.22 | 0.37 | 417 |
| $K_m$ (µM) | 11.0 | 5.36 | 27 | 41 | 127c | 39 |
| $Cl_{int}$ ($V_{max}/K_m$) | 0.197 | 0.071 | 27 | 0.054 | <0.007 | 11 |

## 4. In vivo Metabolite Identification

**Study #** 208066
**Title:** Investigation into the identity of radiolabeled metabolites present in urine, plasma, and feces collected from human volunteers following a single oral dose administration of [$^{14}$C]-AZD6140

- Objective: To profile ticagrelor metabolite following the administration of $^{14}$C-ticagrelor to healthy volunteers.
- Study Design: refer to report # D5130C00013 (mass balance study)
- Analysis: All samples and sample extracts were analyzed by HPLC using on-line radio detection (urine and feces) or fraction collection/LSC (plasma). The 0-24 h pooled urine sample, pooled fecal extract sample and 3 h pooled plasma sample were analyzed by LC-MS to identify the structure of the peaks.
- Results:
  1. Feces: Ticagrelor and AR-C124910XX accounted for > 85% of the total radioactivity recovered at 48 h, 72 h, and 96 h collection time point. Approximately 8% of the total feces radioactivity was lost during sample preparation.
  2. Urine: Most of the radioactivity in the urine was accounted for as shown in the table below, values represents average (n=6)

| | % Recovered Radioactivity | | | | | | |
|---|---|---|---|---|---|---|---|
| **Time** | **Unknown** | **M1 +M2** | **M3** | **M4** | **AR-C133913XX** | **M6+ M9 + M10** | **Lost Dose** |
| 0-6 h | 19.8 | 5.9 | 3.2 | 27.1 | 38.0 | 6.5 | 0.5 |

  3. Plasma: Ticagrelor, AR-C124910XX, and AR-C133913XX accounted for most the recovered radioactivity in plasma (Figure 1)

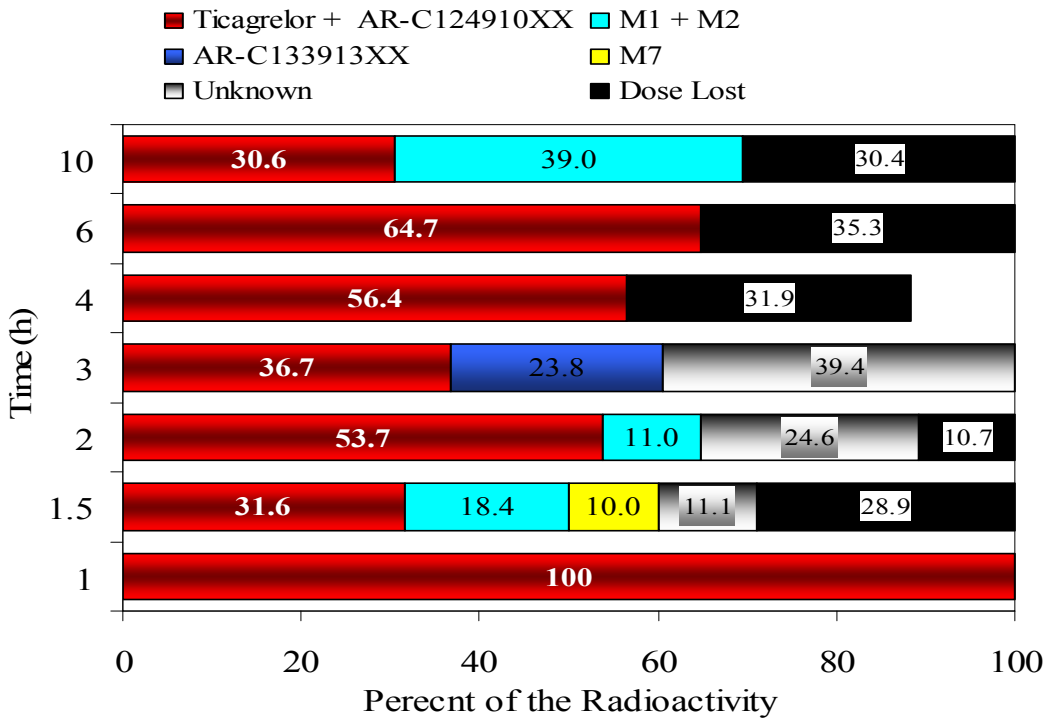


**Figure 1.** Ticagrelor plasma radioactivity profiling. Values represent average (n=6).

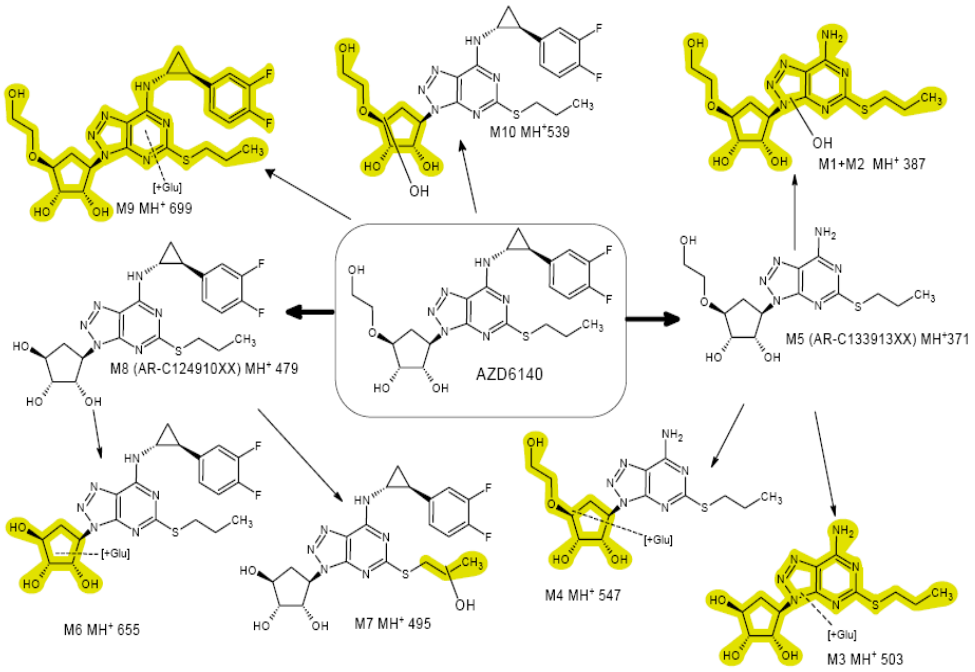


**Figure 2.** Proposed metabolic profile of ticagrelor.

**Comment:** Ticagrelor and AR-C124910XX eluted under the same peak (Rt= 43 min) when subject's plasma samples where analyzed. However, when the pure standard of both compounds were run the retention time was 37.5 min for AR-C124910XX and 41.8 min for ticagrelor.

## 5. Enzyme Inhibition

**Study #** SC-103408
**Title:** An in vitro study examine the effect of AR-C126532XX on human hepatic drug metabolizing enzyme activity

- Objective: to investigate the effect of ticagrelor on human CYP450 enzyme activities.
- Procedure: Incubations contained ticagrelor (1, 2.5, 5, 10, 25, 50 µM), specific CYP enzyme substrate, and human liver microsomes. Positive control incubation used selective CYP inhibitor. Effect of ticagrelor pre-incubation was also evaluated.
- Results:

| CYP | Substrate | | Positive Control | | Ticagrelor Inhibition |
|---|---|---|---|---|---|
| | Reaction | Conc. (µM) | Compound | Conc. (µM) | |
| 1A2 | EthoxyresorufinO-dealkylation | 5 | Furafylline | 10 | None |
| 2C9 | Tolbutamide.4-hydroxylation | 100 | Sulphaphenazole | 10 | Moderate |
| 2C19 | S-Mephenytoin 4-hydroxylation | 200 | Omeprazole | 10 | None |
| 2D6 | Bufuralol 1.-Hydroxylation | 60 | Quinidine | 0.5 | Moderate |
| 2E1 | Chlorzoxazone 6-hydroxylation | 100 | Diethyldithiocarbamate | 10 | None |
| 3A4 | 1. Testosterone 6β-hydroxylation<br>2. Midazolam 1- -hydroxylation<br>3. Midazolam 4-hydroxylation<br>4. Nifedipine oxidation | 150<br>5<br>5<br>25 | Ketconazole | 0.5 | Weak<br>None<br>Strong<br>None |

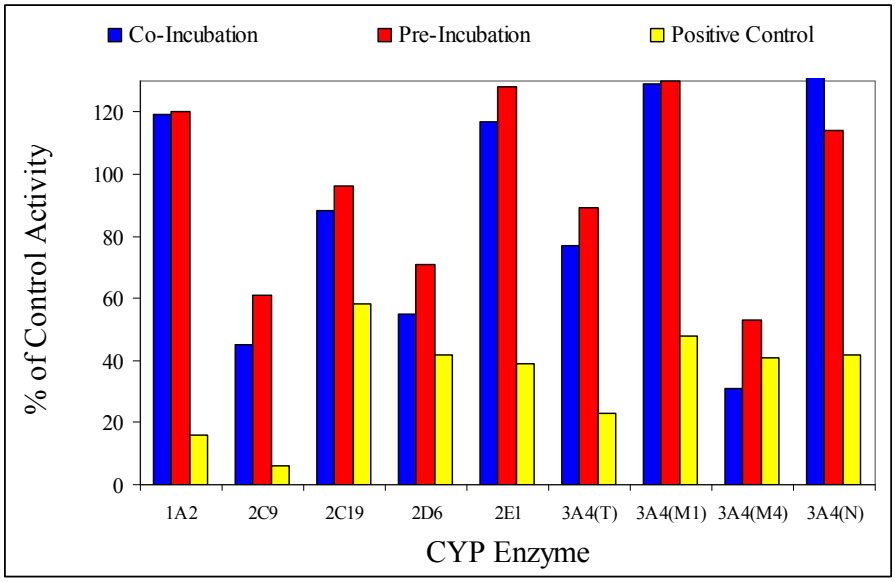


**Figure 1.** Percent remaining of human liver microsomes activity following the incubation with 50 µM ticagrelor

**Study #** DMX22
**Title:** AstraZeneca AZD6140: In vitro human cytochrome P450 (CYP2D6, 2C9, 3A4 and A5) inhibition

- Objective: To further understand the potential of ticagrelor to inhibit CYP 2C9, 2D6, and 3A4/5.
- Procedure:
  - Ticagrelor (0.07 – 50 µM, 7 concentrations) was co-incubated with human liver microsomes and CYP probe substrate. Selective CYP inhibitors were used as positive controls.
  - Ticagrelor (0.07 – 50 µM) was incubated with cDNA expressed CYP 3A4 and CYP3A5 in the presence of midazolam.
- Results: Ticagrelor non-specifically bound to microsomal protein with 80.1% and 79.1% bound at 2 and 10 µM. * indicates values obtained after adjusting to non-specific binding

| CYP | Substrate | | Positive Control | | **Ticagrelor $IC_{50}$** |
|---|---|---|---|---|---|
| | Reaction | Conc. (µM) | Compound | $IC_{50}$. (µM) | |
| 2C9 | Diclofenac 4-hydroxylation | 5 | Sulphaphenazole | 0.28 | 10.5/2.1* |
| 2D6 | Dextromethorphan o-demethylation | 5 | Quinidine | 0.05 | 26.7/5.3* |
| 3A4/5 | Midazolam 1- -hydroxylation<br>Midazolam 4-hydroxylation | 3 | Ketoconazole<br>Ketoconazole | 0.012<br>0.014 | No Inhibition<br>8.2 |
| 3A4 | Midazolam 1- -hydroxylation | 3 | None | | No inhibition |
| 3A5 | Midazolam 4-hydroxylation | 3 | None | | 1.8 |

- Conclusion: Ticagrelor is a moderate inhibitor of CYP 2D6, 2C9, and 3A5. Ticagrelor does not appear to inhibit CY3A4.

**Study #** D5130
**Title:** AZD6140 and AZD11879328: Effect of AZD6140 and AZD11879328 (AR-C124910XX) on human cytochrome P450 enzyme activity

- Objective: To investigate the inhibition potential of ticagrelor and AR-C124910XX on CYP 2C8 and 2B6
- Procedure: Ticagrelor was co-incubated was human liver microsomes and CYP probe substrate. Selective CYP inhibitors were used as positive controls.
- Results

| CYP | Substrate | | Positive Control | | **Ticagrelor $IC_{50}$** | **AR-C124910XX** |
|---|---|---|---|---|---|---|
| | Reaction | Conc. (µM) | Compound | $IC_{50}$. (µM) | | |
| 2C8 | Bupropion hydroxylation | 70 | Tranylcypromine | 4.0 | 40 | 33 |
| 2B6 | Paclitaxel 6α-hydroxylation | 10 | Quercetin | 3.3 | >50 | 43 |

- Conclusion: Neither ticagrelor nor AR-C124910XX is an inhibitor of CYP 2C9 and 2B6.

**Study #** DMX23
**Title:** AstraZeneca AZD6140: In vitro human cytochrome P450 inhibition study of the metabolite, AR-C124910

- Objective; to investigate the inhibition potential of AR-C124910XX on CYP enzymes.
- Procedure:
  - AR-C124910XX (0.07 – 50 µM, 7 concentrations) was co-incubated with human liver microsomes in the presence of CYP probe substrate. Specific CYP enzymes (7 concentrations) inhibitors were used as positive control.

- AR-C124910XX (0.07 – 50 µM, 7 concentrations) was co-incubated was cDNA expressed CYP 3A4 and 3A5 in the presence of midazolam (3 µM)

- Results: AR-C124910XX showed ~ 80% non-specific binding to microsomal protein at 2 and 10 µM. * indicates values obtained after adjusting to non-specific binding

| CYP | Substrate | | Positive Control | | **AR-C124910XX $IC_{50}$** |
|---|---|---|---|---|---|
| | Reaction | Conc. (µM) | Compound | $IC_{50}$. (µM) | |
| 1A2 | Phenacetin O-dealkylation | 20 | Furafylline | 1.3 | >50 |
| 2C9 | Diclofenac 4-hydoxylation | 5 | Sulfaphenazole | 0.3 | 6.9/1.4* |
| 2C19 | S-mephenytoin 4-hydroxylation | 20 | Tranylcypromine | 1.8 | 11.7/2.3* |
| 2D6 | Dextromethorphan o-demethylation | 5 | Quinidine | 0.05 | >50 |
| 3A4/5 | Midazolam 1- -hydroxylation<br>Midazolam 4-hydroxylation | 3 | Ketoconazole | 0.15<br>0.14 | ND<br>7.6/1.5* |
| 3A4 | Nifedipine | 15 | Ketoconazole | 0.024 | >50 |
| 3A4 cDNA | Midazolam 1-hydroxylation | | | | ND |
| 3A5 cDNA | Midazolam 4-hydroxylation | | | | 2.8 |

- Conclusion: AR-C124910 is a strong inhibitor of CYP 3A5 moderate inhibitor of CYP 2C9 and 2C19.

**Study #** 6140DMX28
**Title:** 6140DMX28: Differential interaction between midazolam and AZD6140 in CYP3A4 and CYP3A5.

- Objective: To investigate the influence of Cyt-b5 concentration on the complex activation/inhibition pattern between ticagrelor and midazolam.
- Procedure: Ticagrelor (0.07 – 50, 7 concentrations) was co-incubated with human cDNA expressed CYP3A4 and 3A5, midazolam (3 µM), and various concentrations of Cyt-b5 (0, 150, 500 pM and denaturated 150 pM).
- Results:

| Cyt-b5 (pM) | **CYP3A4** $IC_{50}$ (µM) | | **CYP3A5** $IC_{50}$ (µM) | |
|---|---|---|---|---|
| | 1'-hydroxylation | 4-hydroxylation | 1'-hydroxylation | 4-hydroxylation |
| 0 | >50 | 26.7 | >50 | 5.2 |
| 1:150 | Apparent activation | 36.9 | >50 | 3.1 |
| 500 | Apparent activation | 22.8 | >50 | 3.7 |
| Denaturad 150 | >50 | 9.2 | >50 | 6.3 |

**Study #** 6140DMX30
**Title:** AZD6140: Determination of the time-dependant inactivation of human cytochrome P450 2B6 by AZD6140 using bupropion as probe substrate.

- Objective: To investigate the potential of ticagrelor to cause time dependant inhibition of CYP 2B6.
- Procedure: Ticagrelor or prasugrel (10 µM) were pre-incubated with human liver microsomes for 0, 3, 10, 20, and 30 minutes, before the addition of bupropion (120 µM). Ticlopidine (1 µM) was used as a positive control.

- Results: Ticagrelor did not demonstrate time dependent inhibition of CYP2B6 activity. Prasugrel and ticlopidine exhibited an inactivation rate of 0.086 an 0.082 minutes-$^{1}$.

**Study #** DMX26
**Title:** AstraZeneca AZD6140: Determination of the time-dependent inactivation of human cytochrome P450 CYP3A by AZD6140, AR-C124910, AR-C133913 using midazolam as probe Substrate

- Objective: To investigate the potential of ticagrelor and its metabolites (AR-C124910XX and AR-C133913) to cause time dependant inhibition of CYP 3A4.
- Procedure; Each compound (3 µM) was pre-incubated with pooled human liver microsomes for various times (0-30 min), followed by incubation with midazolam 5 minutes. Verapamil (10 µM) was used as a positive control. Midazolam 1-hydoxylation was evaluated.
- Results: The inactivation rate of all 3 compounds showed no difference compared to the solvent vehicle. The inactivation rate of verapamil was 0.04 min$^{-1}$.

**Study #** D5130
**Title:** AstraZeneca The effect of AZD1640 on testosterone intrinsic clearance in human liver microsomes

- Objective: Ti investigates the effect of ticagrelor on the intrinsic clearance of testosterone in human liver microsomes.
- Procedure: Ticagrelor (2.2, 6.7, 20 µM) was co-incubated with testosterone (10 µM) and human liver microsomes for 0,7,15, 20, and 30 minutes. Testosterone disappearance was monitored.
- Results: ticagrelor inhibits testosterone $Cl_{int}$ (IC50 of 23 µM) in a pool of human liver microsomes from 33 female or male donors.

## 6. Enzyme Induction

**Study #** 6140DMX24
**Title:** 6140DMX24: In vitro induction of cytochrome P450 enzymes by AZD6140 and AR-C124910XX in human hepatocytes

- Objective: To investigate the induction potential of ticagrelor and AR-C124910XX on CYP enzymes in human hepatocytes.
- Procedure: Ticagrelor, AR-C124910 (0.1, 1, 10 µM both), or positive control were dosed to the hepatocytes for 3 consecutive days. Hepatocytes were then incubated with selective CYP probe substrate.

| CYP | Substrate | | Positive Control | |
|---|---|---|---|---|
| | Reaction | Conc. (µM) | Compound | Conc. (µM) |
| 3A4 | Midazolam 1-hydroxylation | 5 | Rifampin | 10 |
| 1A2 | Phenacetin O-dealkylation | 15 | β-naphthoflavone | 25 |
| 2C9 | Dicolfenac 4-hydroxylation | 25 | Rifampin | 10 |

- Results: Midazolam 1'OH levels were below the control level which may indication inhibition potential. Both compounds appear to induce CYP 2C9 and have no induction effect of CYP 1A2.

| CYP | Ticagrelor | AR-C124910XX | Positive Control |
|---|---|---|---|
| 1A2 | 0 | 0 | 17 |
| 2C9 | 2.3 | 1.6 | 1.6 |
| 3A4 | BC | BC | 6.5 |

**Study #** 300841082
**Title:** 300841082: Evaluation of induction potential of cytochrome P450 1A2, 2B6, 2C9, and 3A4 by AZD6140 and AR-C124910 in cultured human hepatocytes

- Objective: To investigate the induction potential of ticagrelor and AR-C124910XX on CYP enzymes in human hepatocytes.
- Procedure:
  - Ticagrelor (0.2, 2, 20 µM), AR-C124910 (0.1, 1, 10 µM both), or positive control were dosed to the hepatocytes for 3 consecutive days.
  - Effect of both compounds on hepatocytes viability was determined using MTT assay and tamoxifen (50 µ) as a positive control.
  - Hepatocytes were then used to prepare microsomes which were evaluated for their protein content, mRNA expression, and immunoreactive protein content.
  - Microsomes were then incubated with selective CYP probe substrate.

| CYP | Substrate | | Positive Control | |
|---|---|---|---|---|
| | Reaction | Conc. (µM) | Compound | Conc. (µM) |
| 1A1 | Phenacetin O-dealkylation | 5 | β-naphthoflavone | 20 |
| 2B6 | Bupropion hydroxylation | 15 | Phenobarbital | 2000 |
| 2C9 | Dicolfenac 4-hydroxylation | 25 | Rifampin | 20 |
| 3A4 | Teststerone | | Rifampin | 20 |

- Results:
  - Both compound exhibited little or no cytotoxicity on hepatocytes.
  - Effect on CYP enzyme activity:

| CYP | Fold increase in Enzyme Activity | | |
|---|---|---|---|
| | Ticagrelor | AR-C124910XX | Positive Control |
| 1A1 | 0.31 – 0.97 | 0.97 – 1.39 | 5.17 – 56.3 |
| 2B6 | 1.4 – 2.9 | 1.4 – 1.5 | 19 – 30.6 |
| 2C9 | 1.2 – 5.0 | 1.3 – 3.6 | 5.0 -18.3 |
| 3A4 | 0.2 - 1.0 | 0.9 – 1.2 | 14.7 -84.0 |

  - Effect on mRNA expression

| CYP | Fold increase in Enzyme Activity | | |
|---|---|---|---|
| | Ticagrelor | AR-C124910XX | Positive Control |
| 1A1 | ≤ 1.7 | ≤ 2.2 | 11.6 -24.0 |
| 2B6 | ≤ 3.1 | ≤ 2.4 | 14.1 – 89.3 |
| 2C9 | ≤ 1.7 | ≤ 2.2 | 2.2 -20.7 |
| 3A4 | ≤ 15.4 | ≤ 7.15 | 33.2 - 6756 |

- Conclusion: Both compound have low potential to induce CYP 2C9 and 2B6 and has no potential to induce CYP 1A2 and 3A4.

**Study #** D5130
**Title:** Evaluation of induction potential of cytochrome P450 1A1 by AZD6140 in cultured human hepatocytes.

- Objective: To investigate the induction potential of ticagrelor on CYP 1A1 enzymes in human hepatocytes.
- Procedure: Ticagrelor (0.2, 2, 20 μM) was dosed to human hepatocytes for 3 consecutive days. mRNA expression was then determined to evaluate enzyme induction. β-naphthoflavone was used as a positive control.
- Result: Ticagrelor did increase CYP1A1 activity and β-naphthoflavone caused 8.9-fold increase in CYP1A1 activity.

**Study #** 1961KV
**Title:** In vitro CYP1A1 induction in human hepatocytes

- Objective: To investigate the induction potential of ticagrelor on CYP 1A1 enzymes in human hepatocytes compared to several prototypical 1A1 inducers.
- Procedure: Cultured human hepatocytes were treated with several prototypical CYP1A1 inducers (3-methycholanthrene, Omeprazole (OMP), β-napthoflavone, Benzo-a-pyrene, TCDD, indole-3-carbinol, Phenobarbital, Rifampicin) and ticagrelor (several concentrations) for 48 hours with fresh compound added at 24 h. mRNA expression of CYP1A was evaluated

Results: Ticagrelor did not generate a potent transcriptional response for CYP1A1 compared to μM 3-methycholanthrene.

# II. Pharmacokinetics

## 1. Mass Balance Study

| **Report #** D5130C00013 | **Study Period:** 09/27/2004- 11/01/2004 | EDR Link |
|---|---|---|
| **Title** | An absorption-distribution-metabolism-excretion (ADME) study of oral [$^{14}$C] AZD6140 in healthy male subjects | |

- **Objectives:** To provide information about ADME, metabolite identification, and tolerability and safety of ticagrelor
- **Test Drug:** [$^{14}$C]-Ticagrelor oral suspension (20 mg/g) containing (b) (4) (Batch P7058)
- **Study Design:** This was an open-label, single-dose (200 mg oral), single center, non-randomized, study in six healthy male volunteers. The subjects remained in the clinic for 7 days following the dose.
- **PK Sampling Times**

Plasma: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 72, 96, 120, 144, 168 h.
Urine & feces:-12-0, 0-6,6-12,12,24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168

- **Analytical Method:** Performance of the analytical method during study samples analysis is acceptable
- **Study Population:** A total of 6 male subjects were enrolled in the study with a median age of 45 years (range 41-54).

**Results**

On average 84% of the radioactivity was recovered, most of the radioactivity was recovered from feces as shown in the table below:

| % Dose Excreted | Mean | %CV | Min | Max |
|---|---|---|---|---|
| Urine | 26.5 | 15 | 21.6 | 31.75 |
| Feces | 57.8 | 8 | 50.1 | 61.76 |
| Total | 84.3 | 7 | 77.5 | 89.5 |

In the terminal phase of the concentration-time curve, concentrations of [$^{14}$C] plasma of ticagrelor and its metabolite decreased monoexponentially (Figure 1), and were undetectable for most volunteers after 12 and 20 hours post-dose in blood and plasma, respectively. Ticagrelor plasma/ whole blood ratio was 1.6 ± 0.4. Less than 1% of the ticagrelor was excreted unchanged in the urine. Most of the radioactivity in plasma is from ticagrelor (mean AUC ticagrelor/ AUC total = 0.6 ± 0.7), while AR-C124910XX (active metabolite) accounted for ~ 24% of the plasma radioactivity (mean AUC AR-C124910XX / AUC total = 0.24 ± 0.0.6). Ticagrelor and AR-C124910XX pharmacokinetics parameters are shown in the table below:

| Parameter | Ticagrelor | AR-C124910XX |
|---|---|---|
| $T_{max}$ (hr)* | 1.5 (1.0 - 3.0) | 3.0 (2.0 - 3.0) |
| $C_{max}$ (ng/mL) | 971 (35.6) | 270 (21.9) |
| $AUC_{0-t}$ (ng.h/mL) | 7113 (44.8) | 2562(28.37) |
| AUC (ng.h/mL) | 7202.8 (44.7) | 2625 (28.4) |
| $t_{1/2}$(h) | 8.4 (24.9) | 11.5 (37.4) |
| CL/F (L/hr) | 32.3 (44.8) | - |
| Ae(∞) (µg)** | 41.5 (84.8) | 81.3 (28.3) |
| $CL_R$ (L/hr) | 0.00584 (65.3) | - |
| Met:par $C_{max}$ ratio | | 0.29 (23.5) |
| Met:par AUC ratio | | 0.40 (37.3) |

* Median & Range, ** Amount Excreted in Urine

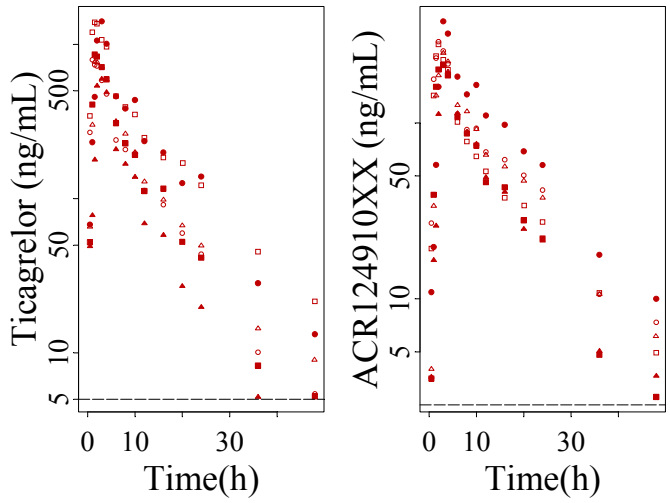


**Figure 1.** Plasma concentration profile of ticagrelor and its metabolite, dashed line represent limit of quantification.

## Conclusions

1. Ticagrelor is rapidly absorbed with median $T_{max}$ of 1.5 hour.
2. Ticagrelor is extensively metabolized and less than 1% of the ticagrelor dose is excreted unchanged in the urine.
3. AR-C124910XX appears to be the major metabolite of ticagrelor and together with the parent accounted for ~ 90% of the plasma radioactivity.

## Comments:

1. The protocol synopsis on page 193 talks about two period cross over study using an IV arm, which is not discussed in the results of this study.

2. The sponsor did not provide justification for < 90% recovery of the total radioactivity, especially in the two subjects with recovery less than 80%.
3. The PK parameters match those obtained following a single dose which validates the results of the study.
4. The accuracy of the lower end of the calibration curve in urine was 31% and 20.4% for ticagrelor and AR-C124910XX, respectively. Both values are unacceptable. The LLQ should be 2.5 ng/mL for ticagrelor and 5.94 ng/mL for AR-C124910XX. This will not alter the conclusion of the study since < 1% of the dose is excreted unchanged in the urine.
5. For metabolic profiling please refer to review of study # 208066.

## 2. Single Ascending Dose (1)

| **Report #** SC-532-5169 | **Study Period**: 04/04/2000- 06/16/2000 | EDR Link |
|---|---|---|
| **Title** | A double-blind, single ascending dose, randomized, placebo-controlled study of the safety, tolerability, activity and pharmacokinetics of oral P2T receptor antagonist AR-C126532XX | |

- **Objectives:** To assess safety, tolerability, PK, and PD following a single oral dose in the dose range 0.1 – 100 mg
- **Test Drug:** Ticagrelor oral suspension, 10 g or 30 g suspension per single unit dose.
- **Study Design:** This was a randomized, double-blind, placebo-controlled, single ascending dose study in healthy volunteers Eight subjects were planned to be studied at each dose level (0.1, 0.3, 1, 3, 10, 30 and 100 mg) in a fasted state. Each subject was to receive a maximum of 3 doses as follows:
  1. Group A: 0.1, 3, and 100 mg.
  2. Group B: 0.3, 10, and 100 mg.
  3. Group C: 1, 30, and 30 mg.
- **Sampling Times:**

PK: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36 h post-dose.
PD: 0, 2, 4, 12, 24 h post-dose.

- **Analytical Method:** LC/MS with calibration range of 1-500 mg/mL. The method performance and validation are acceptable.
- **Study Population:** Healthy Volunteers

| | Group A | Group B | Group C | Total |
|---|---|---|---|---|
| **N** | 8 | 9 | 8 | 25 |
| **Male/Female** | 6/2 | 9/0 | 6/2 | 21/4 |
| **Age (yr)** | | | | |
| Median (Range) | 31 (19-49) | 26 (21-38) | 35 (20-51) | 29 (19-51) |

### Results

**I. Pharmacokinetics**

Ticagrelor plasma levels appear to decline in a mono-exponential way. Concentrations following the 0.1 and 0.3 mg were below the limit of quantification (1 ng/mL). PK parameters were deemed estimable following the administration of 1.0 mg in one subject and were not reported in the table below.

| Parameter | | Ticagrelor Dose (mg) | | | |
|---|---|---|---|---|---|
| | | **3.0** | **10.0** | **30.0*** | **100.0** |
| N | | 6 | 6 | 10 | 5 |
| $AUC_{0-\infty}$ (ng h/mL) | Av. | 109 | 322 | 1105 | 3548 |
| | %CV | 19 | 26 | 32 | 21 |
| $C_{max}$ (ng/mL) | Av. | 15 | 37 | 143 | 510 |
| | %CV | 31 | 34 | 20 | 30 |
| $T_{max}$ (h) | Median | 1.75 | 2 | 1.5 | 1.5 |
| | Range | (1.0-2.0) | (1.5-3.0) | (1.0-3.0) | (1.0-4.0) |
| $t_{1/2}$ (h) | Av. | 6.3 | 7.6 | 7.8 | 8.3 |
| | %CV | 19 | 13 | 25 | 15 |
| CL/F (mL/min/kg) | Av. | 7 | 7 | 7 | 7 |
| | %CV | 17 | 38 | 45 | 26 |

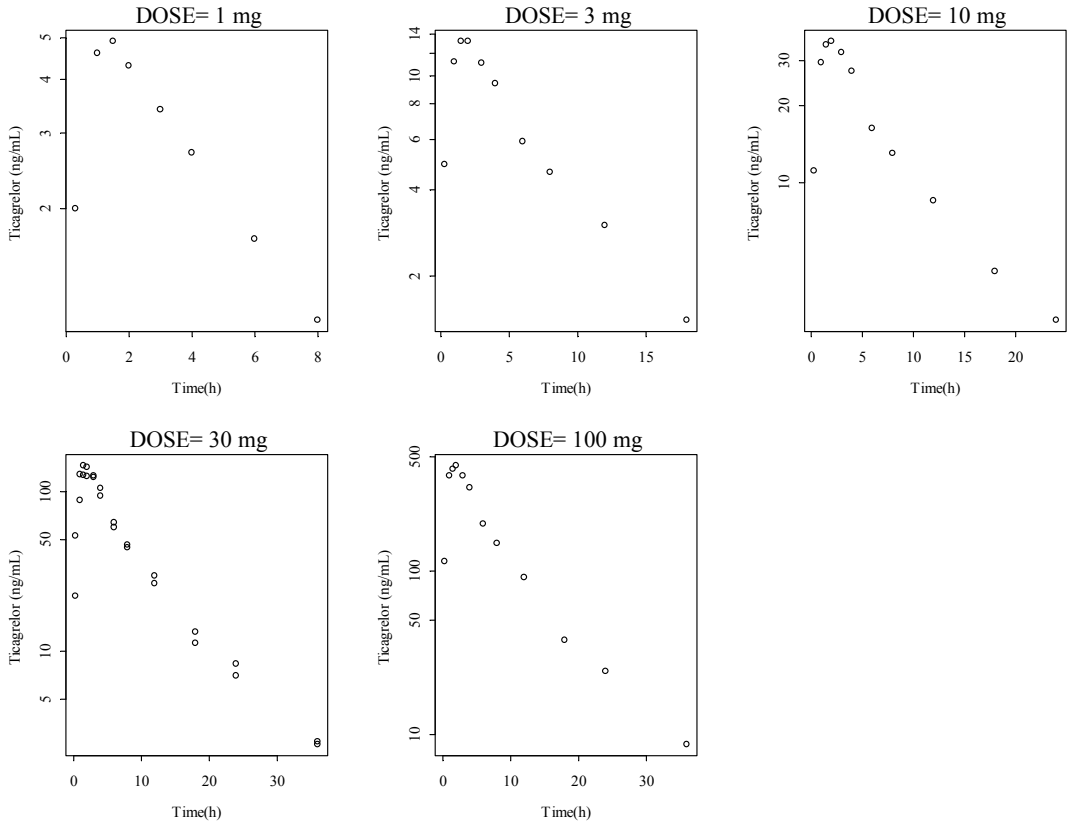


**Figure 1.** Ticagrelor plasma concentrations vs. time profiles following a single oral dose. Values represents mean.

Ticagrelor $AUC_{0-\infty}$ and $C_{max}$ was dose proportional as shown in the table below:

| Parameter | Dose Proportionality | SE | 95% CI l |
|---|---|---|---|
| $AUC_{0-\infty}$ (ng.h/mL) | 1.06 | 0.029 | (1.00, 1.13) |
| $C_{max}$ (ng/mL) | 1.04 | 0.042 | (0.95, 1.13) |

**II. Pharmacodynamic**

1. Platelet Inhibition (PI): PI was measured using impedance aggregometry and residual platelets count at different ADP concentrations. There were no notable differences in %PI for doses of up to 10 mg. Mean %PI peaked at 2 hours post-dose and the effect was fully diminished in 12 hours and returned to baseline in 24 hours.
2. Lancet Bleeding Time: There was no notable difference in bleeding time up to 30 mg dose of ticagrelor. Following the 100 mg dose, mean bleeding time peaked at 2 hours post-dose and nearly returned to baseline at 12 hours post-dose.

**Safety**

No death or serious adverse events were observed.

**Conclusions**

1. The pharmacokinetics of ticagrelor appeared to decline mono-exponentially following the administration of a single dose of ticagrelor with a half-life of ~ 7 hours.
2. Peak plasma concentrations were observed within 2 hours of the dose administration.
3. The pharmacokinetics of ticagrelor was linear over the dose range 3 to 100 mg.
4. Ticagrelor does not affect platelet inhibition or bleeding time up to 10 mg doses.
5. Percent platelet inhibition and bleeding times peaked at 2 hours following the administration of 30 and 100 mg doses of ticagrelor. The effect was diminished in 12 hours post-dose and increased with increasing dose.

**Comments:**

There is a discrepancy in the percent of platelet inhibition obtained using impedance aggregometry and residual platelet count. The sponsor acknowledged the problem, but did not perform a formal analysis to identify the issue.

## 3. Single Ascending Dose (2)

| **Report #** SC-532-5171 | **Study Period**: 10/04/2000- 12/20/2000 | EDR Link |
|---|---|---|
| **Title** | A double-blind, single ascending dose, randomized, placebo-controlled Study to further investigate the safety, tolerability, activity and pharmacokinetics of oral $P_{2T}$ receptor antagonist AR-C126532XX | |

- **Objectives:** To assess safety, tolerability, PK, and PD of ticagrelor and the PK of the active metabolite (AR-C124910XX) following a single oral dose in the dose range 30 – 500 mg
- **Test Drug:** Ticagrelor oral suspension, 10 g or 30 g suspension per single unit dose containing: 30, 100, 200, and 300 mg of ticagrelor.
- **Study Design:** This was a randomized, double-blind, placebo-controlled, single ascending dose study in healthy volunteers. Nine subjects were randomized to receive active treatment: 100, 200, 300, 400, and either 500 or 30 mg. Four subjects were randomized to placebo.
- **Sampling Times:**

PK: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36 h.

PD: 0, 2, 4, 12, 24 h (24 h measurement was not collected in 100 & 200 mg cohorts).

- **Analytical Method:** The performance and validation of the bioanalytical method is acceptable.
- **Study Population:** A total of 13 healthy subjects (9 males/ 4 females) were enrolled in the study with a median age of 35 years (range 24-55). Eleven subjects completed the study.

**Results**

**Pharmcokinetics:** Ticagrelor and AR-C124910XX AUC and $C_{max}$ was slightly more than dose proportional in the dose range 30 – 400 mg as shown in the table below:

| | Parameter | Dose Proportionality(95% CI) |
|---|---|---|
| Ticagrelor | AUC (ng.h/mL) | 1.11 (1.07, 1.15) |
| | $C_{max}$ (ng/mL) | 1.07 (0.99, 1.14) |
| AR-C124910XX | AUC (ng.h/mL) | 1.10 (1.06, 1.15) |
| | $C_{max}$ (ng/mL) | 1.07 (1.0, 1.14) |

| **Ticagrelor Pharmacokinetic Parameters, Mean (%CV)** | | | | | | |
|---|---|---|---|---|---|---|
| **Dose (mg)** | **N** | **$C_{max}$ (ng/mL)** | **$T_{max}$(h)** Median (range) | **AUC (ng h/mL)** | **$t_{1/2}$ (h)** | **CL/F (mL/min/kg)** |
| **30** | 7 | 161 (20.5) | 1.5 (1-2) | 1005 (14.3) | 7.77 (13.0) | 6.72 (17.7) |
| **100** | 9 | 586 ( 28.8) | 1.5 (1-4.1) | 3683 (20.4) | 7.30 (18.9) | 6.52 (22.4) |
| **200** | 8 | 1295 (32.2) | 1.49 (1-3) | 8213 (25.7) | 8.09 (14.1) | 5.71 (24.0) |
| **300** | 8 | 1746 (18.2) | 1.5(1-3.05) | 13170 (22.6) | 7.57 (14.0) | 5.31 (23.5) |
| **400** | 7 | 2711 (21.0) | 1.5 (1-2) | 18547 (23.8) | 7.88 (13.2) | 5.03 (25.8) |

| **AR-C124910XX Pharmacokinetic Parameters, Mean (%CV)** | | | | | | |
|---|---|---|---|---|---|---|
| **Dose (mg)** | **N** | **$C_{max}$ (ng/mL)** | **$T_{max}$(h)** Median (range) | **AUC (ng h/mL)** | **$t_{1/2}$ (h)** | **CL/F (mL/min/kg)** |
| **30** | 7 | 42.1 (31.7) | 2.0 (1.03-3) | 376 (26.1) | 9.39 (22.5) | 18.25 (15.5) |
| **100** | 9 | 166 (27.2) | 3.0(1.5-4.1) | 1460 (27.9) | 8.63 (19.9) | 16.71 (21.8) |
| **200** | 8 | 367 (34.9) | 1.5(1.5-3) | 3722 (44.8) | 10.05 (17.7) | 13.10 (23.9) |
| **300** | 8 | 462 (32.2) | 2.49 (1.5-4) | 4611 (25.4) | 8.54 (17.3) | 14.99 (16.7) |
| **400** | 7 | 713 (21.8) | 1.97 (1.47-3) | 6577 (32.3) | 8.77 (15.1) | 14.13 (18.2) |

**Platelet Inhibition (PI):** PI was determined by measuring ADP induced platelet aggregation using whole blood impedance aggregometry, residual platelet count, and platelet-rich plasma optical aggregometry. Maximum PI was obtained within 2 hours post-dose, and the effect lasted for at least 12 hours post-dose at doses ≥ 100 mg. Depending on the technique used, a close to 100% PI was observed with doses ≥ 100 mg. Scatter plot of ticagrelor plasma concentrations vs. %PI shows that maximum inhibition is obtained at plasma level ~ 200 ng/mL.

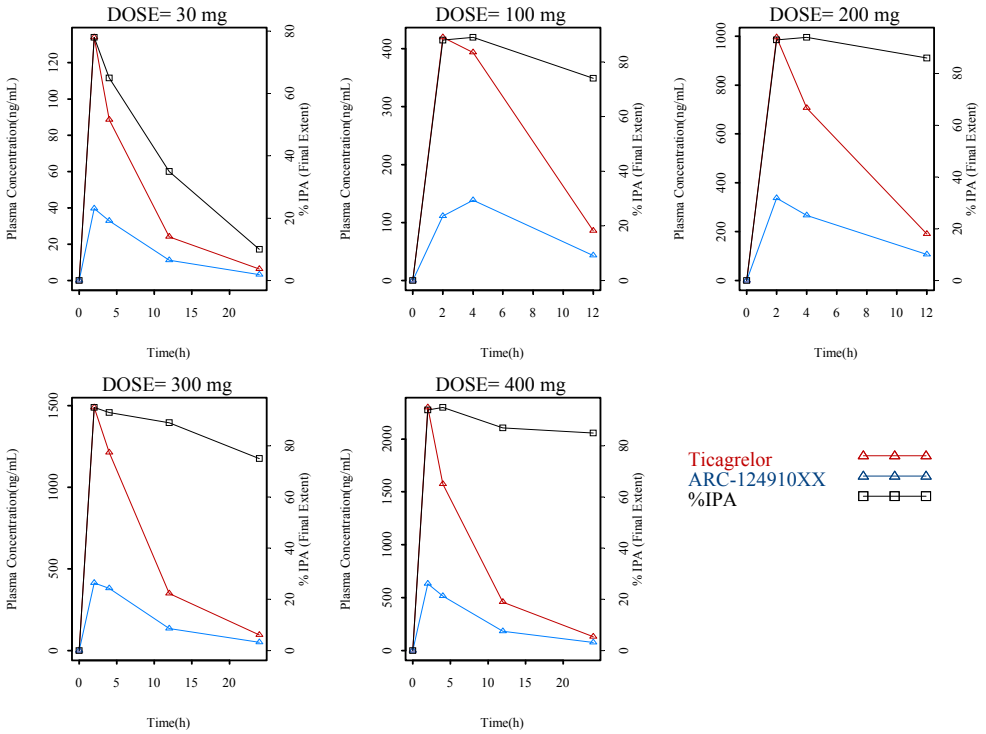


**Figure 1.** Mean plasma profile and percent inhibition in platelet aggregation (20 µM ADP induced) following a single dose of ticagrelor.

**Bleeding Time (BT):** BT increased with increasing dose. Maximum values observed within 2 hours post-dose, after which BT shortens. BT measurements planned at 12 and 24 h were not obtained at all dose levels as the lancet failed to puncture the skin of the subjects. Bleeding times >30 minutes were observed for 2 subjects at 2 and 4 hours post the 300 mg dose. There were no relationship between ticagrelor or AR-C124910XX plasma concentration and bleeding time.

**Safety**

- No death or serious adverse events were observed.
- Two subjects were prematurely discontinued from the study following randomization:

1. One subject reached the individual stopping rule regarding excessive bleeding time (>30 minutes at 2 or more consecutive post-dose time points) after receiving 300 mg of ticagrelor.
2. One subject discontinued due to sever syncope reported 10 days after the administration of the 100 mg dose.

**Conclusions**

1. The pharmacokinetics of ticagrelor and its active metabolite(AR-C124910XX)appeared to decline mono-exponentially following the administration of a single dose of ticagrelor with a half-life of ~ 8 and 9 h, respectively.
2. Peak plasma concentrations were observed within 1.5 for ticagrelor and 2-3 hours for AR-C124910XX.
3. The pharmacokinetics of ticagrelor and AR-C124910XX was linear over the dose range 30 to 400 mg.
4. Percent platelet inhibition (PI) peaked at 2 hours following the administration of ticagrelor. PI effect lasted for at least 12 hours following doses ≥ 100 mg. Maximal PI was achieved with ticagrelor plasma levels of 200 ng/mL.

5. Bleeding times peaked at 2 hours following the administration of ticagrelor in a dose dependant manner. There was no obvious relation between plasma concentration and bleeding times.

**Comments**

- Metabolite to parent ratio were as follow (calculated by Reviewer):

| Dose (mg) | Metabolite/Parent | |
|---|---|---|
| | Cmax | AUC |
| 30 | 26 | 38 |
| 100 | 29 | 40 |
| 200 | 28 | 46 |
| 300 | 26 | 36 |
| 400 | 27 | 36 |

## 4. Single Ascending Dose (3)

| **Report #** D5130C00049 | **Study Period**: 04/5/2006- 05/12/2006 | EDR Link |
|---|---|---|
| **Title** | A randomized, double-blind, single ascending dose, placebo-controlled study to further assess the safety, tolerability, pharmacokinetics and pharmacodynamics of AZD6140 in healthy volunteers age 18 to 45 years | |

- **Objectives:** To assess safety, tolerability, PK, and PD of ticagrelor and the PK of the metabolites (ARC124910XX and AR-C133913XX) following a single oral dose in the dose range 900, 1260, and 1620 mg.
- **Test Drug:** Ticagrelor 180 mg tablets (Batch #05-004497AZ)
- **Study Design:** This was a randomized, double-blind, placebo-controlled, single ascending dose study in healthy volunteers. The study consisted of 2 dose cohorts (900 and 1260 mg) each composed of eight subjects of whom two were randomized to placebo. The 1620 mg planned cohort was not randomized due to GI disturbances at the 1260 mg dose that halted the study.
- **Sampling Times:**
- PK: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 h.
- Bleeding Time: Pre-dose and at 48 and 72 h post-dose.
- Pulmonary Functions: Pre-dose and at 4 and 8 h post-dose.
- **Analytical Method:** The performance of the analytical method is acceptable.
- **Study Population:** A total of 16 subjects (10 males and 6 females) were enrolled in the study with a median age of 25.5 years (range 19-41).

## Results

**Lancet Bleeding Time (BT):** BT increased with increasing dose. Bleeding times > 20 minutes were observed in 3 patients at 72 h post 1260 mg dose, as shown in the table below:

| Ticagrelor Dose | 900 mg (n=6) | 1260 mg (n=6) |
|---|---|---|
| Pre-Dose | 4.6 (3.0-4.9) | 6.0 (4.6-9.1) |
| 48 h post-dose | 10.3 (3.7-20) | 20 (14.5-20) |
| Subjects with BT ≥20 min | 2 | 5 |
| 72 hours post-dose | 5.9 (3.5-8.8) | 14.8(7-20) |
| Subjects with BT ≥20 min | 0 | 3 |
| Values represent median (range) | | |

**Pharmacokinetics:**

| PK Parameter | Dose (mg) | N | $C_{max}$ (ng/mL) | $T_{max}$ (h) | AUC (ng h/mL) | $t_{1/2}$ (h) | % M/P Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | $C_{max}$ | AUC |
| **Ticagrelor** | 900 | 6 | 5513 (41.9) | 1.3 (1-4) | 41486 (36.8) | 12.5 (16.4) | | |
| | 1260 | 6 | 5937 (23.9) | 2.8 (1-6) | 58801 (34.0) | 18.2 (39.2) | | |
| **AR-C124910XX** | 900 | 6 | 1435 (22.6) | 3.0 (1.5- 4) | 19002 (28.3) | 11.2 (10.7) | 28 | 47 |
| | 1260 | 6 | 1640 (29.5) | 4.0 (2-6) | 26096 (10.6) | 16.8 (9.8) | 28 | 52 |
| **AR-C133913XX** | 900 | 6 | 546 (29.1) | 3.0 (1.5-4) | 4480 (22.0) | 10.3 (23.1) | 10 | 12 |
| | 1260 | 6 | 592 (27.4) | 4.0 (1.5-6) | 6819 (29.3) | 19.1 (26.9) | 10 | 12 |
| Values represent mean (%CV), except for Tmax median (range), M/P: Metabolite/Parent | | | | | | | | |

**Pulmonary Functions:** Pulmonary functions did not change following the administration of ticagrelor compared to pre-dose values. Also there was no notable difference in pulmonary functions between the 900 and 1260 mg dose except for mean and peak inspiratory pressure which we higher in 1260 mg cohort.

**Safety**

- There were no deaths, significant AEs, or discontinuations due to AEs.
- This study was stopped after the completion of Cohort B (1260 mg dose) because stopping criteria for GI disturbances were met. Three volunteers who received 1260 mg ticagrelor experienced moderate GI disturbance events. No volunteer who received placebo had a moderate GI AE of nausea or vomiting.
- In addition, there was a SAE of sinus arrest, high grade AV block, and ventricular escape rhythm associated with syncope, as well as an AE of dyspnea in the 1260 mg cohort.

**Conclusions**

Ticagrelor is not tolerated at 1260 mg dose. Ticagrelor 900 mg dose is considered the maximum tolerated dose.

## 5. Multiple Ascending Dose

| **Report #** D5130C05239 | **Study Period**: 03/15/2002- 07/09/2002 | EDR Link |
|---|---|---|
| **Title** | A single-blind, placebo-controlled, parallel group, randomized study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamic properties of multiple ascending doses of AZD6140 compared to clopidogrel in healthy volunteers | |

- **Objectives:** To assess the safety and tolerability of multiple ascending doses of ticagrelor and to compare the PK and PD properties with clopidogrel. The effect of food on ticagrelor PK was also investigated.
- **Test Drug**: 1. Ticagrelor IR tablet (50 mg Lot #, 100 mg Lot#. P6424)
  2. Clopidogrel: 75 mg over-encapsulated IR tablets (Lot #. P6444)
- **Study Design**: This was a single-centre, single-blind, placebo-controlled, parallel group, randomized study. Study schema is shown below, in ticagrelor groups 7 subjects were randomized to receive treatment either QD or BID (Total 14/group). Clopidogrel group ran in two subgroups which ran parallel to group A and group B.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ticagrelor | Group A | Day 1-5 | Day 6-10 | Day 11-15 | Day16 | Treatment | Placebo |
| | | 50 mg QD | 100 mg QD | 200 mg QD | 200 mg QD FED | 5 | 2 |
| | | 50 mg BID | 100 mg BID | 200 mg BID | 200 mg BID FED | 5 | 2 |
| | Group B | Day 1-5 | Day 6-10 | Day 11-15 | Day16-20 | | |
| | | 200 mg QD | 300 mg QD | 400 mg QD | 600 mg QD | 5 | 2 |
| | | 50 mg BID | 100 mg BID | 200 mg BID | 300 mg BID | 5 | 2 |
| Clopidogrel | Group C | Day1 | Day2-14 | | | | |
| | | 300 mg | 75 mg | | | 7/7 | 1/1 |

- **Sampling Times:**

| | Group A | | | Group B | | | Group C | | |
|---|---|---|---|---|---|---|---|---|---|
| Day | PK | IPA | BT | PK | IPA | BT | PK | | |
| 1 | | | | | | | | | |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
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| 16 | | | | | | | | | |
| 17 | | | | | | | | | |
| 18 | | | | | | | | | |
| 19 | | | | | | | | | |
| 20 | | | | | | | | | |

| | | | |
|---|---|---|---|
| IPA: Inhibition of Platelet Aggregation | | | |
| BT: Bleeding Time | | | |
| | Pre-Dose | | |
| | 0,0.5,1,1.5,2,3,4,6,8,12 h | | |
| | 0,0.5,1,1.5,2,3,4,6,8,12,24 h | | |
| | 0,0.5,1,1.5,2,3,4,6,8,12,24,36,48 h | | |
| | 0,4,8,12 h | | 0,4,8,11 h |
| | 0,4,8,12, 24 h | | 11 h |
| | 0,4,8,12,24,36,48 h | | |

- **Analytical Method:** The performance of the analytical method is acceptable.
- **Study Population:** A total of 48 healthy subjects (43 males and 5 females) were enrolled in the study with a median age of 34 years (range 20-64).

**Results**

**Pharmacokinetics:** Steady state was achieved within 2-3 days as shown in Figure 1. Accumulation was higher in the BID group compared to the QD group, as shown in the table below:

| Treatment | Accumulation Ratio | | | |
|---|---|---|---|---|
| | N | Mean | Median | Range |
| 50 mg QD | 7 | 1.4 | 1.3 | 1 -1.9 |
| 200mg QD | 7 | 1.4 | 1.4 | 1.1 -1.5 |
| 50mg BID | 14 | 2.0 | 1.9 | 1.1 -2.6 |

The PK at steady state was slightly more than dose proportional for both QD and BID mode of administration, as shown in the table below:

| | Parameter | Administration Mode | Point Estimate | 95% CI |
|---|---|---|---|---|
| Ticagrelor | $AUC_{\tau}$ | QD | 1.27 | 1.18-1.37 |
| | (ng h/mL) | BID | 1.23 | 1.13-1.33 |
| | $C_{max}$ | QD | 1.2 | 1.08-1.32 |
| | (ng/mL) | BID | 1.21 | 1.06-1.35 |
| AR-C124910XX | $AUC_{\tau}$ | QD | 1.25 | 1.18-1.32 |
| | (ng h/mL) | BID | 1.24 | 1.12-1.37 |
| | $C_{max}$ | QD | 1.14 | 1.02-1.27 |
| | (ng/mL) | BID | 1.2 | 1.05-1.36 |

| Ticagrelor PK parameters | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Treatment | N | AUCτ (ng h/mL) | | $C_{max}$ (ng/mL) | | $T_{max}$ (h) | | CL/F (L/h) | |
| | | | Mean | %CV | Mean | %CV | Median | Range | Mean | %CV |
| **QD** | 50mg | 7 | 1961 | 30.7 | 233 | 34.9 | 3 | 2-4 | 43.59 | 34.8 |
| | 100mg | 7 | 4585 | 36.3 | 609 | 43.3 | 2.71 | 1.5-4 | 41.9 | 46.0 |
| | 200mg | 14 | 8648 | 43.3 | 1109 | 39.1 | 2.43 | 1.5-4 | 46.58 | 46.6 |
| | 300mg | 7 | 11066 | 32.1 | 1384 | 22.6 | 1.71 | 1.5-2 | 49.02 | 29.5 |
| | 400mg | 6 | 15342 | 23.4 | 1873 | 12.0 | 1.58 | 1-2 | 45.81 | 27.2 |
| | 600mg | 6 | 25111 | 30.4 | 3072 | 27.3 | 2 | 1-3 | 43.42 | 34.2 |
| **BID** | 50mg | 14 | 1771 | 33.2 | 264 | 34.5 | 2.82 | 1-4 | 54.03 | 35.1 |
| | 100mg | 13 | 4455 | 44.9 | 687 | 48.7 | 2.69 | 1-6 | 44.14 | 43.3 |
| | 200mg | 13 | 9781 | 25.3 | 1487 | 26.1 | 2.62 | 1.5-4 | 37.97 | 35.6 |
| | 300mg | 7 | 15754 | 46.7 | 2263 | 56.9 | 3.14 | 2-4 | 41.97 | 47.9 |
| τ = 24 h for QD and 12 h for BID | | | | | | | | | | |

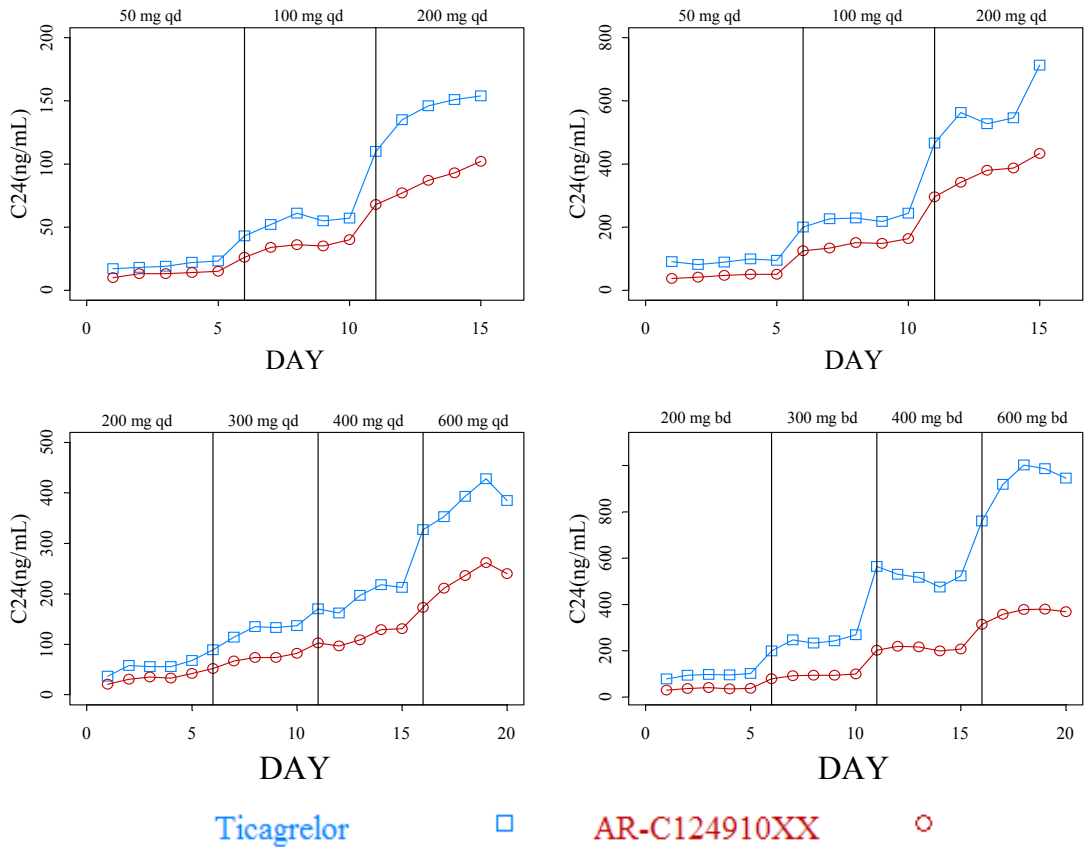



**Figure 1.** Ticagrelor trough concentration following the administration of multiple ascending doses.

| AR-C124910XX PK parameters | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Treatment | N | AUCτ (ng h/mL) | | $C_{max}$ (ng/mL) | | $T_{max}$ (h) | |
| | | | Mean | %CV | Mean | %CV | Median | Range |
| QD | 50mg | 7 | 799 | 46.6 | 77 | 48.1 | 4 | 3-6 |
| | 100mg | 7 | 2026 | 44.5 | 189 | 54.8 | 3.43 | 2-4 |
| | 200mg | 14 | 3371 | 50.1 | 319 | 45.7 | 3.01 | 2-4.12 |
| | 300mg | 7 | 4061 | 27.6 | 377 | 31.5 | 1.93 | 1.5-3 |
| | 400mg | 6 | 5792 | 30.6 | 513 | 14.7 | 2.33 | 2-3 |
| | 600mg | 6 | 9376 | 32.7 | 819 | 27.9 | 2.42 | 1.5-3 |
| BID | 50mg | | | | | | | |
| | 100mg | 14 | 666 | 34.8 | 84 | 30.1 | 3.25 | 1.5-6 |
| | 200mg | 13 | 1894 | 59.5 | 247 | 61.7 | 3.12 | 1.5-6 |
| | 300mg | 13 | 4152 | 61.9 | 514 | 55.7 | 3.19 | 1.5-6 |
| τ = 24 h for QD and 12 h for BID | | | | | | | | |

**1. Platelet Inhibition:** At steady state, full (100%) platelet inhibition was observed at 4 h post-dose. The percent inhibition was lower at 24 h for the QD administration, while the effect was

maintained with the BID administration at 24 h. In general, % platelet inhibition increased with increasing ticagrelor plasma concentration.

**2. Bleeding Time:** As shown in Figure 2, median bleeding time increased with increasing dose for the QD administration up to 400 mg. The BID administration produced a higher median bleeding time than the QD administration for the 50 and 100 mg dose, the median bleeding time was comparable between the BID and QD administration at 200 and 400 mg dose.

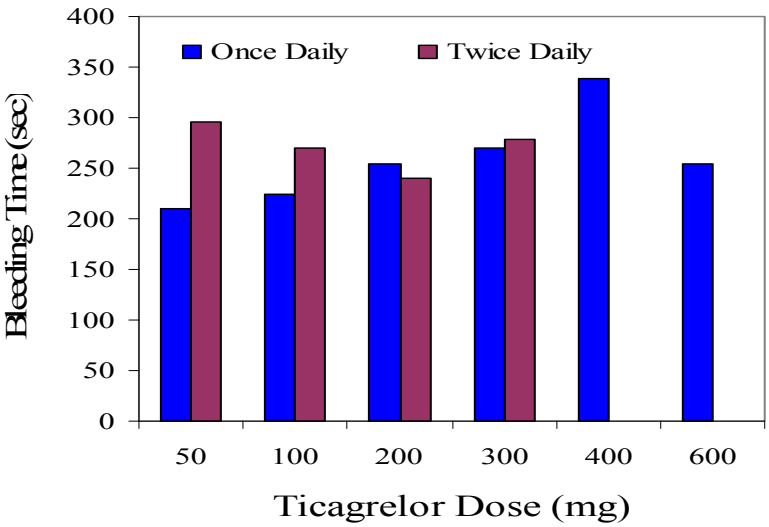



**Figure 2.** Bleeding time following the administration of ticagrelor. Measurements were done at 11 h on Day 4 post-dose, except for the 600 mg QD and the 300 mg BID where the measurement was done on Day 5 post-dose.

**Safety**

- There were no deaths or other serious adverse events during the study.
- Two subjects discontinued the study due to AEs as follows:
  1. One subject in the 50 mg BID group due to asthma and bronchitis
  2. One subject in the 300 mg QD group due to increased transaminases.

**Conclusions**

1. The systemic exposure of ticagrelor at steady state is slightly more than dose proportional in the dose range 50-600 mg QD and 50-300 mg BID.
2. Substantial platelet inhibition was observed with all administered doses and peaked within 4 h. The effect was maintained up to 24 h with the BID administration and was better than the QD administration especially at the 50 and 100 mg doses.
3. Bleeding times were modestly increased with increasing the dose, but did not appear to be related to ticagrelor plasma concentrations.

**Comments:**

1. The mean metabolite to parent ratio in terms of AUCτ was 39.7 ± 15 for all the administered doses irrespective of the administration mode (calculated by the reviewer).
2. The food effect component and the comparison to clopidogrel were not reviewed since dedicated studies to address theses issues were conducted and will be reviewed later.

# III. Specific Population

## 1. Renal Impairment

| **Report #** D5130C00015 | **Study Period**: 02/28/2007 – 29/29/2008 | EDR Link |
|---|---|---|
| **Title** | A single dose, non-randomized, open-label, parallel group study comparing the pharmacokinetics, pharmacodynamics, safety, and tolerability of AZD6140 in patients with renal impairment to volunteers with normal renal function. | |

**Study Design**

| Single-Dose | Non-Randomized | | Open-Label | | Parallel | Multi-Center |
|---|---|---|---|---|---|---|
| No. of Groups | **2** | ☑Normal | ☐Mild | ☐Moderate | ☑Severe | ☐ESRD |
| No. of Subject /Completed | **20** | 10/10 | | | 10/10 | |
| Males/Females | **12/8** | 6/4 | | | 6/4 | |
| Age, Mean(range) | | 63.2 (33-72) | | | 66.9 (41-80) | |
| Dose | | 180 mg | | | 180 mg | |

- **Sampling Times:**

PK, plasma: Pre-dose, 0.5,1,2,3,4,6,8,12,18,24,36,48,72 h post-dose.
PD, plasma: Pre-dose, 2, 4, 8, 12, 24, 48, 72 h post dose.

- **Treatment:** Ticagrelor 90 mg IR tablets (Lot #. 06-009508AZ)
- Renal function classification is consistent with FDA Guidance: ☑ Yes ☐ No
- Renal function was determined via ☑ G-C formula ☐ MDRD formula
- Renal function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body weight
- The selected dose is acceptable ☑ Yes ☐ No
- Protein Binding: ☐All ☑Limited (in all subjects)
  Sampling Times: Pre-dose, 0.5, 1, 2, 2, 4, 6, 8, 12
  Method: Equilibrium Dialysis
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The performance of the analytical method is acceptable: ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No

**Results**

There was no relation between creatinine clearance and ticagrelor and AR-C124910XX AUC or Cmax. Ticagrelor and AR-C124910XX pharmacokinetic parameters are shown in the tables below:

**Ticagrelor PK Parameters**

| | Renal Function | |
|---|---|---|
| | Normal | Severe |
| N | 10 | 10 |
| $CL_{cr}$* (mL/min) | 90.3 (77.2-115) | 25.3 (17.3-36.5) |
| $C_{max}$ (ng/mL) | 1417[34.6] (742 – 2250) | 1266[54.7] (1085 – 2210) |
| $T_{max}$** (h) | 2 (1-4) | 2 (2-4) |
| AUC◊ (ng h/mL) | 10100[35.5] (6106-16549) | 9115[56.6] (2605-16747) |
| $t_{1/2}$ (h) | 18.8 (8.6-24.9) | 14.2 (9.2-20.5) |
| %Fu | <1% | <1% |

Values represent mean [%CV] and (range), * Estimated on day -2,
** Median (range), ◊ % Extrapolated is less than 15% ☑ Yes ☐ No

**AR-C124910XX PK Parameters**

| | Renal Function | |
|---|---|---|
| | Normal | Severe |
| N | 10 | 10 |
| $CL_{cr}$* (mL/min) | 90.3 (77.2-115) | 25.3 (17.3-36.5) |
| $C_{max}$ (ng/mL) | 355[37.2] (206-669) | 377[35.2] (227-556) |
| $T_{max}$** (h) | 3 (2-4) | 3 (2-4) |
| AUC◊ (ng h/mL) | 3611[28.9] (2257-5421) | 4799[61.1] (1526-10954) |
| $t_{1/2}$ (h) | 15.5 (10.5-26.1) | 12.9 (9.8-19.1) |
| % Met. Ratio | | |
| $AUC_{0-\infty}$ | 37(24-47) | 61(25-143) |
| $C_{max}$ | 26(16-33) | 35(14-57) |
| % Fu | <1% | <1% |

Values represent mean [%CV] and (range)
* Estimated on day -2
** Median (range)
◊ % Extrapolated is less than 15% ☑ Yes ☐ No

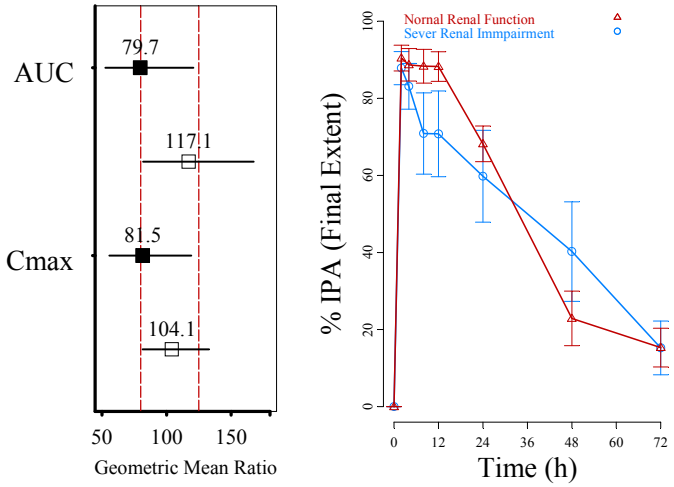



**Figure 1.** Left Panel: Statistical analysis of the pharmacokinetics parameters of ticagrelor (■) and AR-C124910XX (□). Right Panel: % inhibition of platelet aggregation in normal and severe renally impaired subjects, values represent mean ± SE.

**Safety**

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

**Conclusions**

1. There is no relationship between creatinine clearance and ticagrelor or AR-C124910XX systemic exposure.
2. In severe renal impairment subjects, ticagrelor AUC and $C_{max}$ were significantly ~ 20% lower than healthy volunteers.
3. Unbound fraction to plasma protein is slightly higher in severe renal impairment patients for both ticagrelor and AR-C1249010XX. In general the unbound fraction is <1% for both compounds.
4. The formation of AR-C124910XX was faster in subjects with severe renal impairment.
5. Inhibition of platelet aggregation was lower in severe renal impairment subjects.
6. There is no need to adjust ticagrelor dose in patients with sever renal impairment.

**Comments**

Five patients under sever renal impairment had CLcr >30 mL/min at screening or day -2 as shown in the table below:

| | **CLcr (mL/min)** | |
|---|---|---|
| Subject ID | Estimated Day -2 | Measured at Screening (Day -21—3) |
| 4103 | 25.88 | 36.25 |
| 4104 | 22.87 | 31.51 |
| 4602 | 26.52 | 42.99 |
| 4605 | 36.49 | 18.12 |
| 4401 | 28 | 38.71 |

## 2. Hepatic Impairment

| **Report #** D1530C00016 | **Study Period**: 01/31/2007 – 03/26/2008 | EDR Link |
|---|---|---|
| **Title** | A single dose, non-randomized, open-label, parallel group study comparing the pharmacokinetics, pharmacodynamics, safety, and tolerability of AZD6140 in patients with mild hepatic impairment to matched healthy volunteers | |

| **Study Design** | | | | | | |
|---|---|---|---|---|---|---|
| Single-Dose | Non-Randomized | | Open-Label | Parallel | Single-Center | |
| No. of Groups | **2** | ☑Normal | ☑Mild | ☐Moderate | ☐Severe | Total |
| No. of Subject /Completed | **20** | 10/10 | 10/10 | | | 20/20 |
| Males/Females | **12/8** | 4/6 | 4/6 | | | 8/12 |
| Age, Mean(range) | | 58 (42.7-78.3) | 56.7 (41.1-74.5) | | | |
| Dose | | 90 mg | 90 mg | | | |

- **Treatment:** Ticagrelor 90 mg IR tablets (Lot #. 06-009508AZ)
- Screening: Day -21 to Day -2
- Sampling Times:
- ➢ PK, plasma: Pre-dose, 0.5,1,2,3,4,6,8,12,18,24,36,48,72 h post-dose.
- ➢ PD, plasma: Pre-dose, 2, 4, 8, 12, 24,, 48, 72 h post dose.
- ➢ Protein Binding: ☐All ☑Limited (in all subjects)
  Sampling Times: Pre-dose, 0.5, 1, 2, 2, 4, 6, 8, 12 h post-dose
  Method: Equilibrium Dialysis
- . Classification of hepatic function is consistent with the FDA Guidance : ☑ Yes ☐ No
- Hepatic function was determined via Child-Pugh classification ☑ Yes ☐ No
- Hepatic function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body Weight ☑ Smoking Status ☑ Race
- The selected dose is acceptable ☑ Yes ☐ No
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The performance of the analytical method is acceptable: ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No

**Results**

**Ticagrelor PK Parameters:** Values represent mean [%CV] and (range)

| | **Normal Hepatic Function** | **Mild Hepatic Impairment** |
|---|---|---|
| N | 10 | 10 |
| $C_{max}$ (ng/mL) | 607[32.1] (337–897) | 730[55.1] (278–1340) |
| $T_{max}$(h)** | 2.0 (1-3) | 2.0 (1-4) |
| AUC (ng h/mL) | 3929[41.1] (1649-5991) | 5921[64.5] (2316-15235) |
| $t_{1/2}$ (h) | 13[36.8] (8-23) | 20[86.4] (7-48) |
| %Fu | <1% | <1% |

* Estimated on day -2, ** Median (range)

**AR-C124910XX PK Parameters:** Values represent mean [%CV] and (range)

| | Normal Hepatic Function | Mild Hepatic Impairment |
|---|---|---|
| N | 10 | 10 |
| $C_{max}$ (ng/mL) | 162[21.4] (112-209) | 198[38.0] (106-315) |
| $T_{max}$ (h) ** | 2.0 (2-4) | 2.0 (2-4) |
| AUC (ng h/mL) | 1324[18.4] (1046-1799) | 2414[51.7] (1175-4924) |
| $t_{1/2}$ (h) | 10[206] (7.6-14.3] | 19.3[15.9] (7.4-59) |
| % Met. Ratio | | |
| $AUC_{0-\infty}$ | 38(21-66) | 45(30-63) |
| $C_{max}$ | 29(16-51) | 30(22-44) |
| %Fu | <1% | <1% |

* Estimated on day -2, ** Median (range)

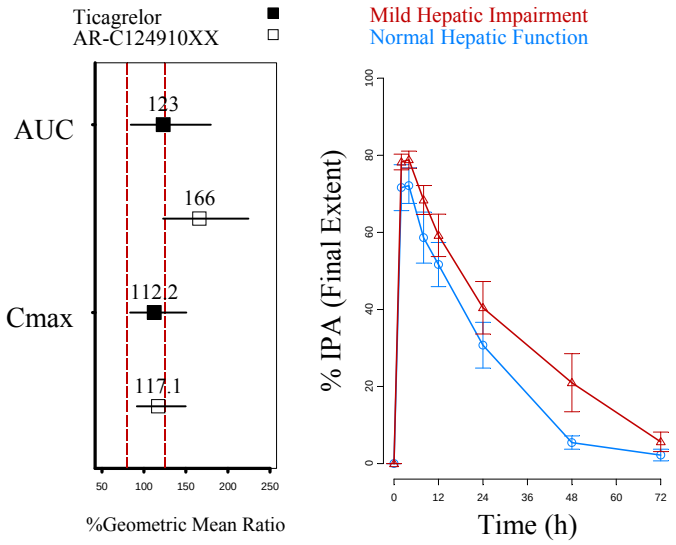



**Figure 1.** Left Panel: Statistical analysis of the pharmacokinetics parameters of ticagrelor (■) and AR-C124910XX (□). Right Panel: % inhibition of platelet aggregation in normal and mild hepatic impairment subjects, values represent mean ± SE.

**Safety**

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

**Conclusions**

1. In subjects with mild hepatic impairment relative to healthy subjects:
   - Ticagrelor AUC and $C_{max}$ were significantly higher by 23% and 12%, respectively.
   - AR-C124910XX AUC and $C_{max}$ were significantly higher by 66% and 17%, respectively.
   - % inhibition of platelet aggregation is lower in mild hepatic impairment subjects relative to healthy volunteers.
2. Ticagrelor and AR-C124910XX unbound fraction to plasma protein is <1% in mild hepatic impairment patients and healthy volunteers.
3. There is no need to adjust ticagrelor dose in patients with mild hepatic impairment.

**Comments**

The sponsor should have included moderate and sever hepatic impairment patients. Since higher exposure is expected in moderate and severe hepatic impairment patients, ticagrelor should not be used in these.

## 3. Age/Gender

| **Report #** D1530C00014 | **Study Period**: 01/28/2003 – 03/08/2003 | EDR Link |
|---|---|---|
| **Title** | An open, non-randomized, parallel group study to assess the effects of age and gender on the pharmacokinetics, pharmacodynamics, safety and tolerability of a single oral dose (200 mg) of AZD6140 in healthy male and female volunteers. | |

### Study Design

| Single-Dose | Non-Randomized | | Open-Label | Parallel | | Multi-Center |
|---|---|---|---|---|---|---|
| No. of Groups | **4** | Young Males | Young Females | Elderly Males | Elderly Females | Total |
| No. of Subjects /Completed | **20** | 10/10 | 10/9 | 10/10 | 10/10 | 40/39 |
| Males/Females | **20/20** | 10/0 | 0/10 | 10/0 | 0/10 | 20/20 |
| Age, Mean(range) | | 29.0 (22-43) | 40.4 (29-45) | 67.5 (65-73) | 70.1 (66-75) | |
| Dose | | 200 mg | 200 mg | 200 mg | 200 mg | |
| No. of Drop outs | **1** | | | | | |

- -Treatment: Ticagrelor 100 mg IR tablets( Lot #. P6424)
- Overnight Fasting: ☑ Yes ☐ No
- Concomitant Medications Prohibited: Aspirin (Day-15)
- Screening: Day -21 – Day -1
- Sampling Times:
- PK, plasma: Pre-dose, 0.5,1,2,3,4,6,8,12,18,24,36,48,72 h post-dose.
- PD , plasma:
  1. Platelet Aggregation: Day -1, Pre-dose, 2, 4, 8, 12, 24, 48, 72 h post dose.
  2. Bleeding Time: Pre-dose, 4 & 24 h post-dose
- Protein Binding: 2 & 4 h post-dose , Method: Equilibrium Dialysis
- The selected dose is acceptable ☑ Yes ☐ No
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The analytical method is acceptable. ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No

### Results

- Unbound fraction was < 1% in all groups.

| **Time point** | **Bleeding Time (min)** | **Age and gender group** | | | |
|---|---|---|---|---|---|
| | | **Young males** | **Young females** | **Elderly males** | **Elderly females** |
| Pre-Dose | Mean | 5.0 | 4.9 | 5.3 | 5.5 |
| | Range | 3.3 - 7.3 | 3.3 - 7.3 | 4.0 - 8.0 | 4.3 - 8.0 |
| 4 h post-dose | Mean | 24.8 | 26.9 | 27.9 | 30.0 |
| | Range | 10.0 - 30.0 | 9.3 - 30.0 | 16.0 - 30.0 | 30.0 - 30.0 |
| 24 h post-dose | Mean | 7.9 | 12.9 | 13.4 | 17.2 |
| | Range | 5.3 - 16.5 | 3.3 - 26.0 | 2.8 - 30.0 | 6.5 - 30.0 |

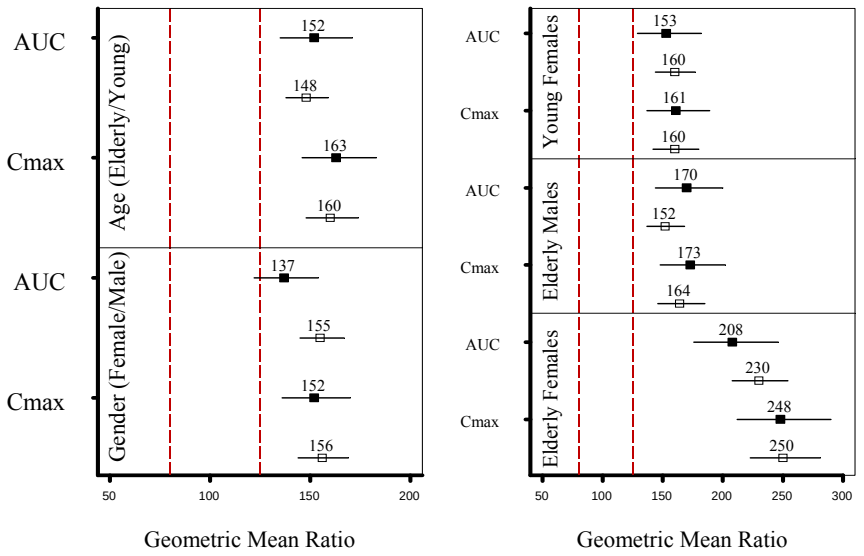



**Figure1**. Ticagrelor (■) and AR-C124910XX (□) systemic exposure geometric mean ratios by gender, age, and gender age interaction.

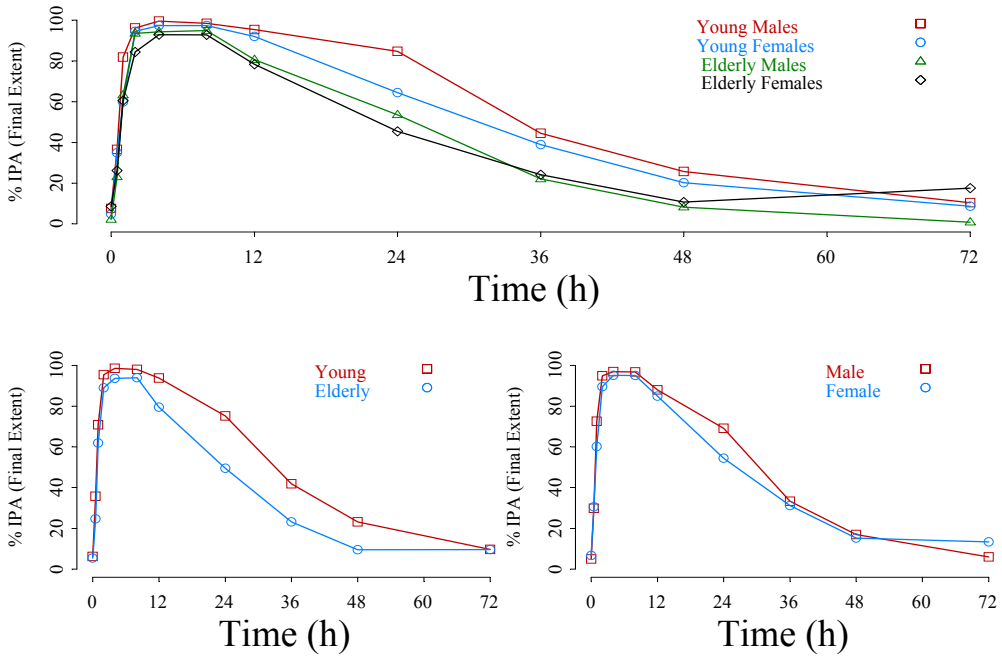



**Figure 2.** % inhibition of platelet aggregation (20 µM ADP, Final Extent) by gender, age, and gender age interaction.

## Safety

- There was no death or serious adverse events.
- One subject (young female) discontinued the study due to vasovagal syncope

## Conclusions

1. Ticagrelor AUC and $C_{max}$ were 52% and 63% higher in elderly subjects compared to young subjects.
2. Ticagrelor AUC and $C_{max}$ were 37% and 52% higher in female subjects compared to male subjects.
3. ARC124910XX systemic exposure was higher in elderly and female subjects compared to young and male subjects, respectively.
4. All bleeding time measurements were > 30 minutes in elderly females at 4 h post-dose.

**Comments**

- The use of 200 mg dose does not allow the evaluation of the effect of age and gender on % IPA. The higher exposure from the 200 mg dose (which is double the final dosing recommendations of 90 mg BID) led to ~100% IPA in 2 h post-dose and the effect lasted till ~ 12 h post-dose before it starts declining.
- Elderly females should be monitored for bleeding when administering ticagrelor.

## 4. Japanese/Caucasian (Single Dose)

| **Report #** D1530C05266 | **Study Period**: 06/02/2003– 10/23/2003 | EDR Link |
|---|---|---|
| **Title** | A randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single ascending oral doses of AZD6140 tablets in healthy male and female Japanese and Caucasian subjects. | |

**Study Design**

- **Objective:** To investigate thee safety, tolerability, PK, and PD of a single ascending oral doses of ticagrelor administered to Japanese and Caucasian subjects.
- **Treatment:** Ticagrelor IR tablets (50 mg Lot #. P6421), 100 mg Lot. # P6426)
- This was a double-blind, randomized, placebo-controlled, single-center study in healthy subjects.
- Subjects in Cohort A received single oral doses of 50, 200, and 400 mg of ticagrelor or placebo. Subjects in Cohort B received single doses of 100, 300, and 600 mg ticagrelor or placebo. There was a minimum 5 days washout period between doses. Each cohort consisted of two groups, Japanese and Caucasian. In each group 8 subjects were randomized to ticagrelor and 2 to placebo.
- **Sampling Times**

| Day | 1 |
|---|---|
| PK | P, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48 |
| PA | P,2,4,12,24 |
| BT | P, 4.5, 24 |
| PA; Platelet Aggregation, BT: Bleeding Time using Simplate II® Method | |

- **Analytical Method:** The performance of the analytical method is acceptable
- **Study Population:** The two groups are balanced.

| | Japanese | Caucasian |
|---|---|---|
| Randomized | 20 | 20 |
| Discontinued<br>Due to AE | 1<br>0 | 1<br>0 |
| Completed | 19 | 19 |
| Age [Median (range)] | 35.0 (21-44) | 32.0 (24-48) |
| Male/Female | 36/0 | 36/0 |

## Results

**Pharmacokinetics:** Ticagrelor systemic exposure was higher and statistically significant in Japanese relative to Caucasian at all doses. Ticagrelor exposure increased in a more than dose proportional in both Japanese and Caucasian as shown in the table below.

| | | Caucasian | | Japanese | |
|---|---|---|---|---|---|
| | **N** | **Slope** | **90% CI** | **Slope** | **90% CI** |
| $C_{max}$ (ng/mL) | 16 | 1.24 | 1.16, 1.32 | 1.23 | 1.16 - 1.31 |
| $AUC_{0-\infty}$ (ng h/mL) | 16 | 1.23 | 1.19, 1.28 | 1.23 | 1.18 - 1.27 |

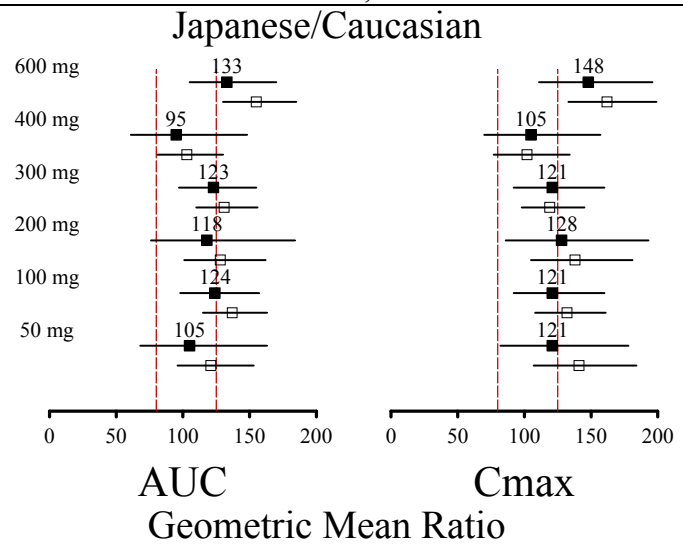



**Figure 1.** Ticagrelor (■)and AR-C124910XX (□)AUC and $C_{max}$ geometric mean ratios (Japanese /Caucasian) and the corresponding 95% CI.

**Pharmacodynamics:** %IPA increased with increasing the dose and was generally slightly higher in Japanese. Bleeding time increased with increasing the dose and was comparable between the two groups (Figure 3). There appeared to be no relationship between ticagrelor or AR-C124910XX plasma concentration and prolongation in bleeding time.

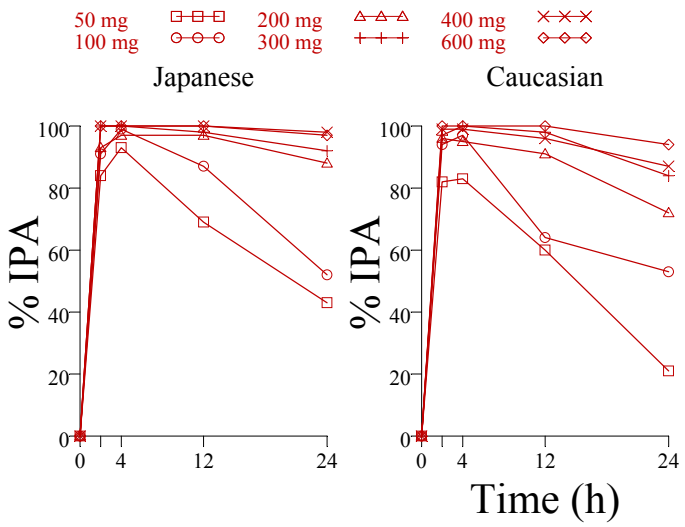



**Figure 2.** %IPA following the administration of ticagrelor in Japanese (left panel) and Caucasian (right panel). Values represent mean.

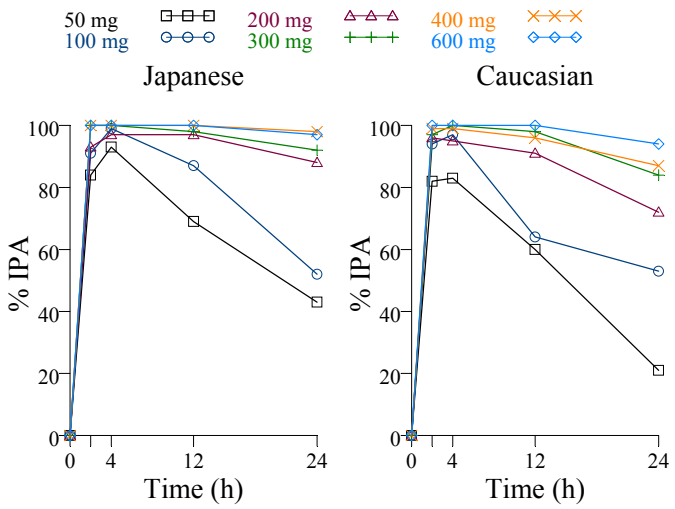



**Figure 3.** Bleeding Time following the administration ticagrelor in Japanese and Caucasian. Values represent mean.

**Safety:** There were no deaths or SAEs in the study.

## Conclusions

1. Ticagrelor systemic exposure is significantly higher (by median ~ 20%) in healthy Japanese compared to healthy Caucasian following the administration of a single dose (50 -600 mg).
2. %IPA is slightly higher in healthy Japanese.
3. Bleeding time is comparable between healthy Japanese and Caucasian.

## Comments

There is no need to adjust ticagrelor dose in Japanese.

## 5. Japanese/Caucasian (Multiple Dose)

| **Report #** D1530C05267 | **Study Period**: 02/17/2004– 06/02/2004 | EDR Link |
|---|---|---|
| **Title** | A single-blind, randomized, placebo-controlled phase I study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple oral doses of AZD6140 in healthy Males and Caucasian volunteers. | |

**Study Design**

- **Objective:** To investigate the safety, tolerability, PK, and PD of a multiple oral doses of ticagrelor administered to Japanese and Caucasian male subjects.
- **Treatment:** Ticagrelor 100 mg IR tablets (Lot #. 300480AP6748)
- This was a single-blind, randomized, placebo-controlled, study in two centers, one in the US and one in Japan, in healthy male subjects.
- In each ethnic group, 36 healthy male subjects were divided into 2 sequential cohorts of 18 subjects. Within each cohort, 15 subject received ticagrelor and 3 subjects received placebo.
- Subjects received a single ticagrelor or placebo dose on Day 1, then they were evaluated by the principal investigator and if allowed they started daily BID multiple doses through Days 4-10. Subject only received the morning dose on Day 10.
- Sampling Times

| Day | 1 | 4 | 6-9 | 10 |
|---|---|---|---|---|
| PK | P, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48 | P | P | P,0.5,1,2,3,4,6,8,12,18,24,36,48,72 |
| PA | P,2,4,12,24 | | | P, 2,4,8,24,48,72 |
| BT | P, 4, 24 | | | P,4,24,48 |
| PA; Platelet Aggregation, BT: Bleeding Time using Simplate® Method | | | | |

- **Analytical Method:** The performance of the analytical method is acceptable.
- **Study Population:** The two groups are balanced.

| | Japanese | Caucasian |
|---|---|---|
| Randomized | 36 | 36 |
| Discontinued<br>Due to AE | 1<br>1 | 2<br>1 |
| Completed | 35 | 34 |
| Age [Median (range)] | 25.0 (20-44) | 22.0 (20-28) |
| Male/Female | 36/0 | 36/0 |

**Results**

**Pharmacokinetics:** Ticagrelor systemic exposure was higher and statistically significant in Japanese relative to Caucasian. The exposure was higher in the 100 mg dose (Figure 1).

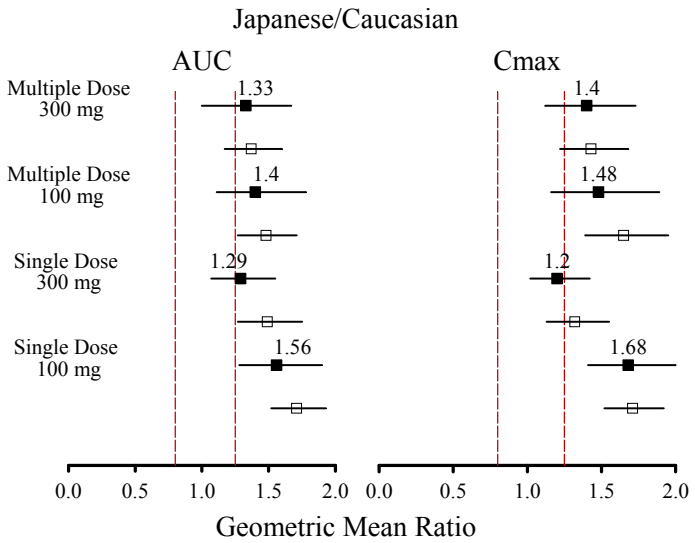



**Figure 1.** Ticagrelor (■) and AR-C124910XX (□) AUC and $C_{max}$ geometric mean ratios (Japanese /Caucasian) and the corresponding 95% CI. AUC is $AUC_{0-\infty}$ for single dose and $AUC_{ss,\tau}$ for multiple dose.

**<u>Pharmacodynamics:</u>** Japanese had higher %IPA than Caucasian following ticagrelor administration. The difference is less pronounced following the 300 mg dose.

Bleeding time was higher in Japanese than Caucasian at both doses (Figure 3). 14 subjects had 60 bleeding time measurement > 60 min in Japanese (30 mg cohort) while 8 subjects had 11 bleeding time measurement > 60 min in Caucasian (7 in 100 mg and 4 in 300 mg cohorts, respectively).

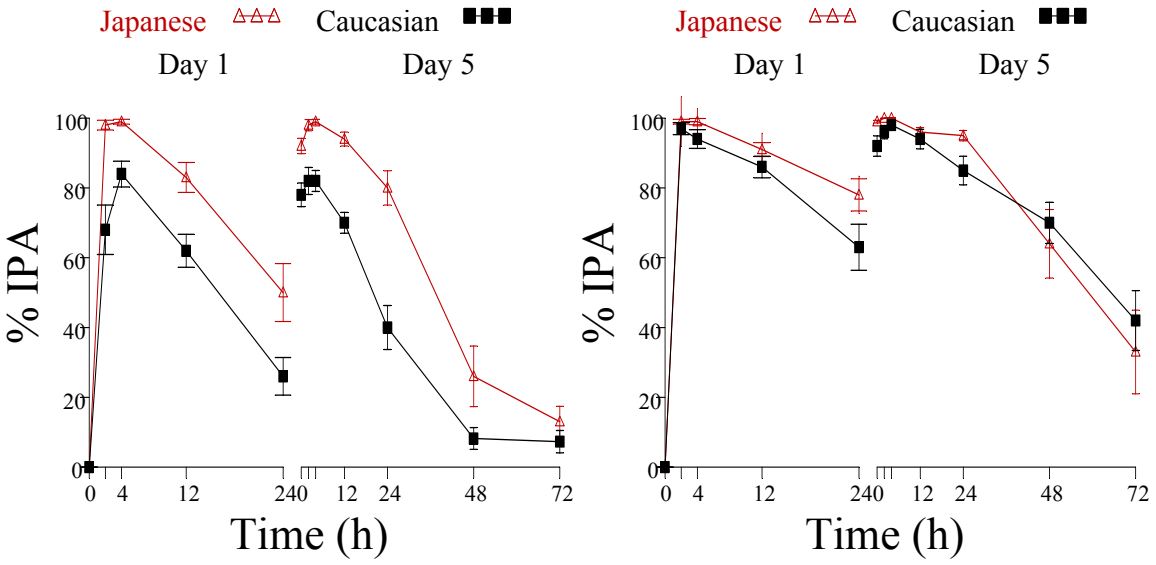



**Figure 2.** %IPA following the administration of 100 mg (left panel) and 300 mg (right panel) ticagrelor. Values represent mean ± S.E.

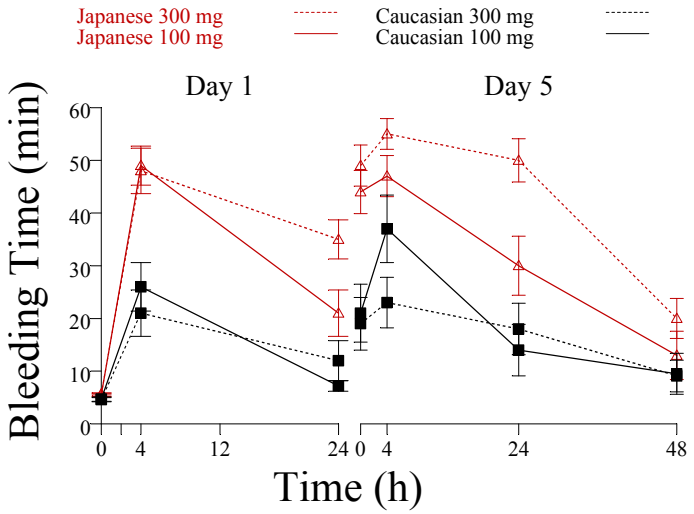



**Figure 3.** Bleeding Time following the administration of 100 mg and 300 mg ticagrelor. Values represent mean ± S.E.

**Safety**

There were no deaths or SAEs in the study. One Japanese subject (300 mg cohort) discontinued the study due to tonsillitis, and 1 Caucasian (300 mg cohort) discontinued due to dysuria reported prior to the start of study drug.

**Conclusions**

- Ticagrelor systemic exposure is 20% higher in healthy Japanese males compared to healthy Caucasian males. %IPA is higher and bleeding time is longer in healthy Japanese males.
- There is no need to adjust ticagrelor dose in Japanese subjects.

## 5. Chinese

| **Report #** D5130C00054 | **Study Period**: 07/02/2008– 08/11/2008 | EDR Link |
|---|---|---|
| **Title** | A two-cohort, open-label, single and multiple dose pharmacokinetic study of 90-mg and 180-mg doses of AZD6140 in healthy Chinese volunteers living in China | |

**Study Design**

- **Objective:** To characterize the PK, safety, and tolerability of ticagrelor and its active metabolite AR-C124910XX after single and multiple (twice-daily) doses of ticagrelor 90 mg and 180 mg in healthy Chinese volunteers
- **Treatment:** Ticagrelor 90 mg IR tablets (Lot #. 07-011183AZ)
- This was a single center, 2-cohort, open-label, single- and multiple-dose PK study in healthy Chinese volunteers with sequential cohorts, cohort A (90-mg dose) and cohort B (180-mg dose). Ticagrelor was dosed as follow:

| Day | Ticagrelor Dose | PK Sampling Times |
|---|---|---|
| 1 | AM only | P, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48,72 |
| 2, 3 | No Drug | |
| 4-9 | AM, PM | P starting on Day 5 |
| 10 | AM only | P, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48,72 |

- **Analytical Method:** The performance of the analytical method is acceptable.

- **Study Population:** The two groups are balanced.

| Cohort | 90 mg | 180 mg |
|---|---|---|
| Randomized | 12 | 14 |
| Discontinued<br>Due to AE | 2<br>2 | 0<br>0 |
| Completed | 10 | 14 |
| Age [Median (range)] | 32.0(24-44) | 29.0(21-33) |
| Male/Female | 8/4 | 11/3 |

**Results**

**Pharmacokinetics:** The variability of PK parameters was <50% and was slightly higher in the 180 mg dose. Steady state was attained following the second day of the multiple dosing periods (Figure 1). AR-C124910XX /ticagrelor mean ratios are shown in the table below. Median $T_{max}$ for ticagrelor and AR-C124910XX was 2 and 2.5 h, respectively. Average $t_{1/2}$ was 13.5 h and 10 h for ticagrelor and AR-C124910XX, respectively.

| | Ticagrelor Dose (mg) | Day 1 | Day 10 |
|---|---|---|---|
| $C_{max}$ Ratio | 90 | 31 | 34 |
| | 180 | 29 | 26 |
| $AUC_{0-\infty}$ Ratio | 180 | 47 | 49 |
| | 180 | 39 | 36 |

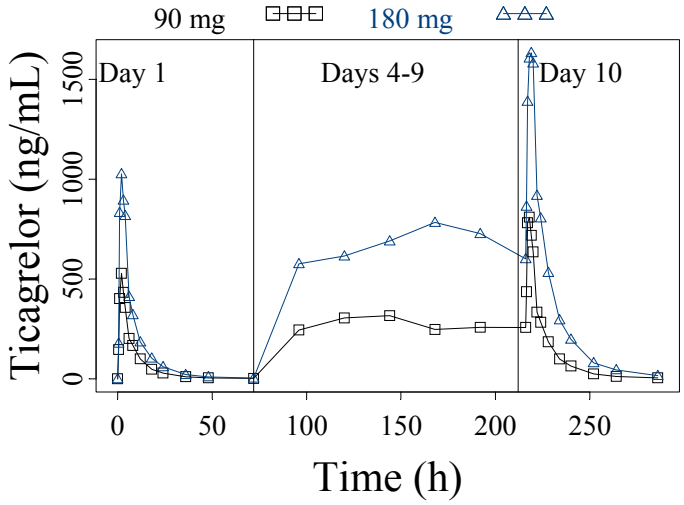



**Figure 1.** Ticagrelor plasma concentration vs. time profile in healthy Chinese subjects. Values represent mean.

**Safety**

There were no deaths or SAEs in the study. Two subjects in the 90 mg cohort discontinued the study due to abnormal hepatic function. The event lasted 10 days and was moderate in intensity.

**Comments**

It appears that the systemic exposure in Chinese is comparable to that obtained in Caucasian. Figure 2 displays boxplot of Ticagrelor $C_{max}$ and $AUC_{0-\infty}$ in Chinese (data from the current study) and Caucasian (data from study D1530C00016 for 90 mg, and D1530C00015 for 180 mg dose, 10 subjects each).

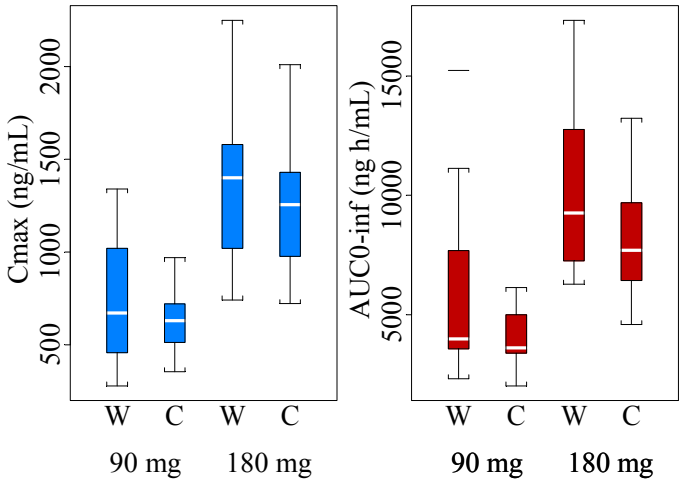



**Figure 2.** Ticagrelor systemic exposure in Caucasian and Chinese.

Analysis of the geometric mean ratio assuming parallel design results are shown in the table below:

| Dose | | AUC Ratio | 95% CI | Cmax Ratio | 95% CI |
|---|---|---|---|---|---|
| 90 mg | Ticagrelor | 77.7 | 51.7 – 116.6 | 92.42 | 63.7 – 134.1 |
| | | | | | |
| 180 mg | Ticagrelor | 80.7 | 61.1 – 106.7 | 89.3 | 68.0 – 117.3 |
| | AR-C124910XX | 86.3 | 68.7 – 108.4 | 102.42 | 80.1 – 131.0 |

# IV. Drug-Drug Interactions

## 1. Ketoconazole

| **Report #** D1530C00022 | **Study Period** 09/17/2004 – 11/09/2004 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | A randomized, open-label, 2-period cross over single center study to assess the effect of ketoconazole (Nizoral®) on the pharmacokinetics of a single oral 90 mg dose of AZD6140 in healthy male and female volunteers |

**Study Design**

**Rationale:** Ticagrelor is primarily metabolized by CYP3A4/5. Ketoconazole is a potent inhibitor of CYP3A4.

Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** ≥14 days |
|---|---|
| **Period 1/2** | 12 days (Ketoconazole) or 9 days (Ticagrelor), inpatient stay ☑Y ☐ N |

| **Sequence** | **A** | **B** |
|---|---|---|
| | ▪ Ketoconazole 200 mg BID for 10 days<br>▪ Ticagrelor 90 unframg QD on Day 4 | ▪ Ticagrelor 90 mg QD on Day 1 |

**Treatments:**
- Ticagrelor: 90 mg IR tablets (Lot # 2000065517)
- Ketoconazole: (Nizoral®) 200 mg tablets (Lot# 3GG043)

▪ **Sampling Times (PK, plasma)**
- Ticagrelor and AR-C124910XX: 0, 0.5,1,2,3,4,6,8,12,18,24,36,48,72,96,120,144,168
- Ketoconazole: Day 3 (Pre AM dose), day 4 (Pre AM dose, Pre PM dose)

**Analytical Method:**

| Analyte | Ticagrelor | AR-C124910XX | Ketoconazole |
|---|---|---|---|
| Method | LC-MS/MS | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma | Plasma |
| Range | 5 - 5000 ng/mL | 2.5-2500 ng/mL | 10 – 5000 ng/mL |
| Performance | Acceptable | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 16/14/2 |
| Age [Median (range)] | 27.5 (20-45) |
| Male/Female | 13/3 |
| Race (Caucasian/Black/Asian/Hispanic) | 12/3/1/0 |

**Results**

▪ Mean % metabolite/parent ratio was 32% and 49% for $C_{max}$ and AUC, respectively. In the presence of ketoconazole the ratio was 1% and 3% for $C_{max}$ and AUC, respectively.
▪ Ketoconazole (N=14) steady state was attained as shown in the table below:

| Ketoconazole (ng/mL) | Day 3 Pre AM Dose | Day 4 Pre AM Dose | Day 4 Pre PM Dose |
|---|---|---|---|
| Geometric mean (%CV) | 1322.7 (54.9) | 1410.0 (72.9) | 1271.1 (84.2) |
| Range | 427 - 3690 | 396 - 3540 | 334 - 4150 |

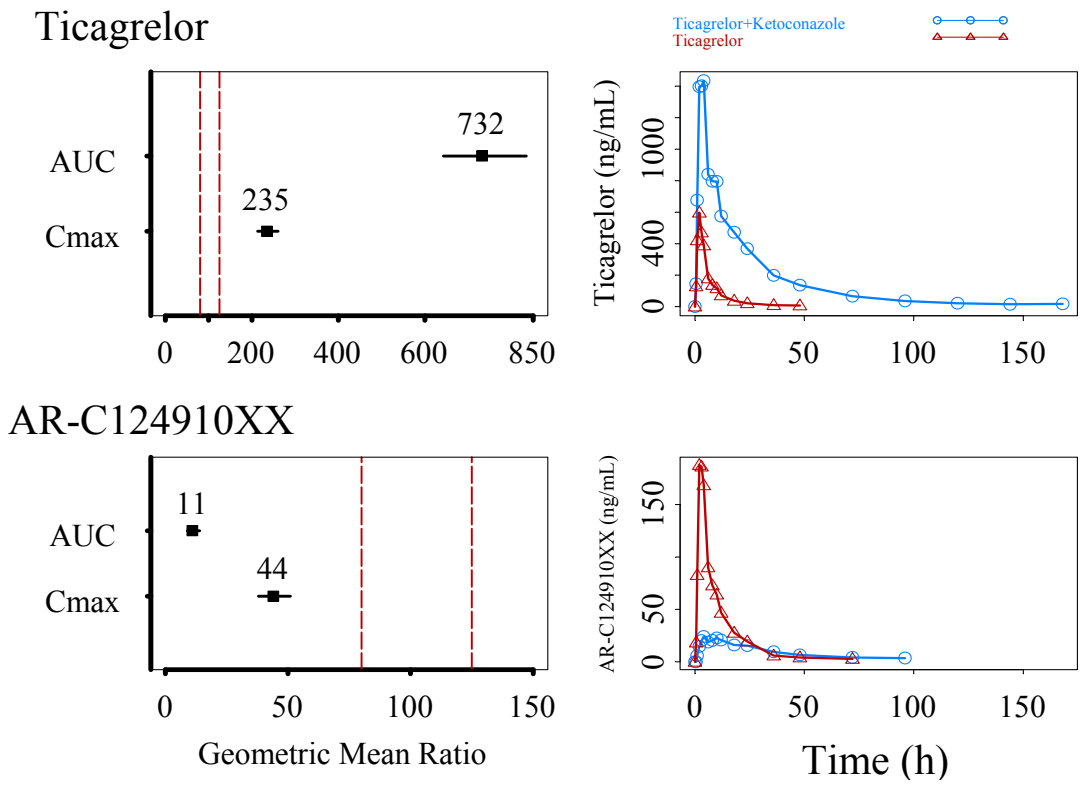



**Figure 1.** Ticagrelor and AR-C124910XX geometric mean ration and corresponding 90% CI (left panel) and plasma profile (right panel) in the presence and absence of ketoconazole.

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- There were 2 mild bleeding related adverse events.
- One subject (26-year-old male Caucasian) was withdrawn from the study because of right bundle branch block of mild intensity after receiving Ticagrelor + ketoconazole treatment during Period I of the study. The volunteer was lost to follow-up. This AE was determined by the investigator to be unrelated to treatment.

**Conclusion**

- The co-administration of ketoconazole significantly increases ticagrelor AUC by 7.32 fold and $C_{max}$ by 2.35.
- The co-administration of ketoconazole significantly decreases AR-C124910XX AUC by 56% and $C_{max}$ by 89%.

**Comments**

Ketoconazole and other potent CYP3A4 inhibitors should not be co-administered with ticagrelor.

## 2. Diltiazem

| **Report #** D1530C00040 | **Study Period** 04/18/2005 – 06/20/2005 | EDR Link |
|---|---|---|

| **Title** | A randomized, open-label, 2-way crossover single center study to assess the effect of Diltiazem (Cardizem®LA), a CYP3A inhibitor, on the pharmacokinetics of a single oral 90 mg dose of AZD6140 in healthy male and female volunteers |
|---|---|

**Study Design**

**Rationale:** Ticagrelor is primarily metabolized by CYP3A4/5. Diltiazem is a moderate inhibitor of CYP3A4.

Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** ≥14 days |
|---|---|
| **Period 1/2** | 16 days (Diltiazem) or 8 days (Ticagrelor), inpatient stay ☑Y ☐ N |

| **Sequence** | **A** | **B** |
|---|---|---|
| | ▪ Diltiazem 240 mg QD x 14 days<br>▪ Ticagrelor 90 mg QD on Day 8 | ▪ Ticagrelor 90 mg QD on Day 1 |

**Treatments:**
- Ticagrelor: 90 mg IR tablets (lot # P6973)
- Diltiazem: (Cardizem®LA) 240 mg tablets (Lot# 05C006P)

▪ **Sampling Times (PK, plasma)**
- Ticagrelor/AR-C124910XX: 0, 0.5,1,2,3,4,6,8,12,18,24,36,48,72,96,120,144,168 h)
- Diltiazem: Day 1-15 (Pre-dose), day 7,8 (0,0.5,1,2,3,4,6,8,10,12,16,20,24 h)

**Analytical Method**

| Analyte | Ticagrelor | AR-C124910XX | Diltiazem |
|---|---|---|---|
| Method | LC-MS/MS | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma | Plasma |
| Range | 5 - 5000 ng/mL | 2.5-2500 ng/mL | 1 – 250 ng/mL |
| Performance | Acceptable | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| Randomized/Completed/ Discontinued Due to AE | 18/17/0 |
|---|---|
| Age [Median (range)] | 33.0 (18-44) |
| Male/Female | 14/4 |
| Race (Caucasian/Black/Asian/Hispanic) | 0/0/0/18 |

**Results**

▪ Mean % metabolite/parent ratio was 30% and 40% for $C_{max}$ and AUC, respectively. In the presence of diltiazem the ratio was 10% for $C_{max}$ and AUC.
▪ Diltiazem (N=14) steady state was attained as shown in the Figure 1.

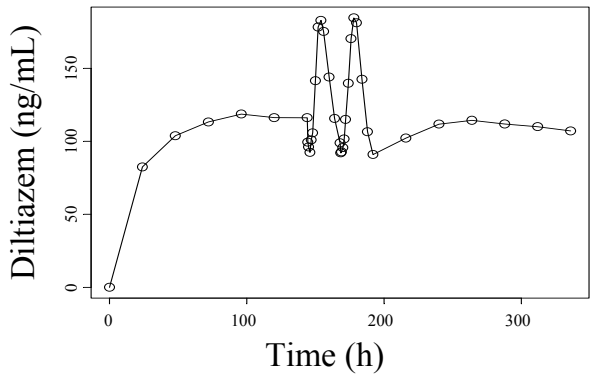



**Figure 1.** Diltiazem plasma concentration-time profile. Values represent mean.

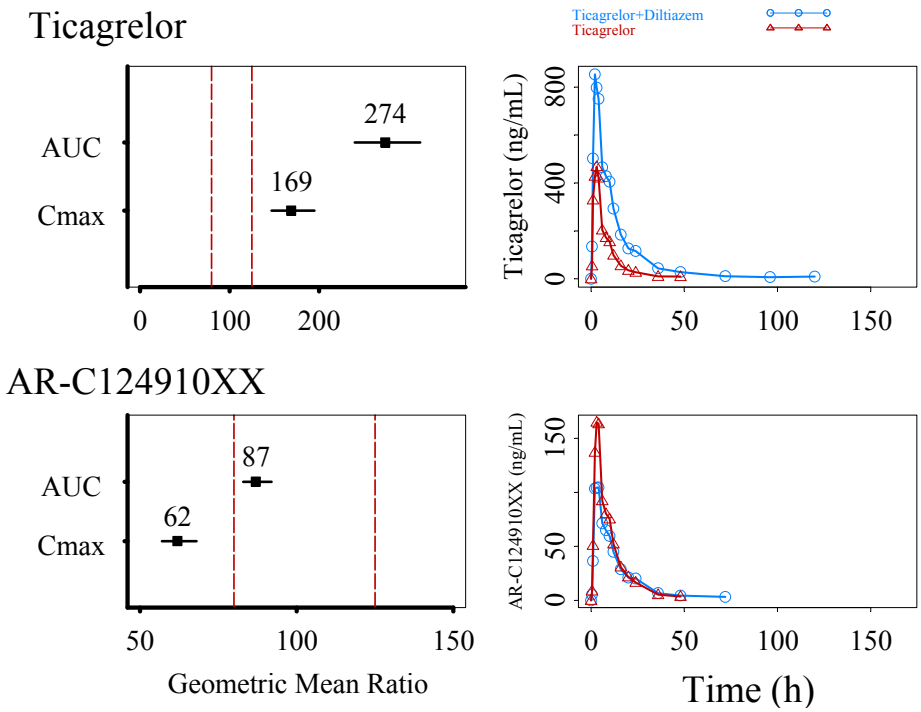



**Figure 2.** Ticagrelor and AR-C124910XX geometric mean ration and corresponding 90% CI (left panel) and plasma profile (right panel) in the presence and absence of diltiazem.

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

**Conclusion**

- The co-administration of diltiazem significantly increases ticagrelor AUC by 2.74 fold and $C_{max}$ by 1.69.
- The co-administration of diltiazem decreases AR-C124910XX AUC by 13% and significantly decreases $C_{max}$ by 38%.

**Comments**

Ticagrelor plasma profile following the administration of 90 mg BID and 90 mg QD+ diltiazem were simulated using parameters obtained by fitting mean profiles obtained in the

study using a two compartment model with 1st order absorption. The results have shown that at steady state AUC ration of [ticagrelor 90 mg QD +diltiazem]/ticagrelor 90 mg BID= 1.19, while Cmax ratio = 2 (Figure 3). Therefore, ticagrelor should be administered once daily and not twice daily when administered with moderate 3A4 inhibitors.

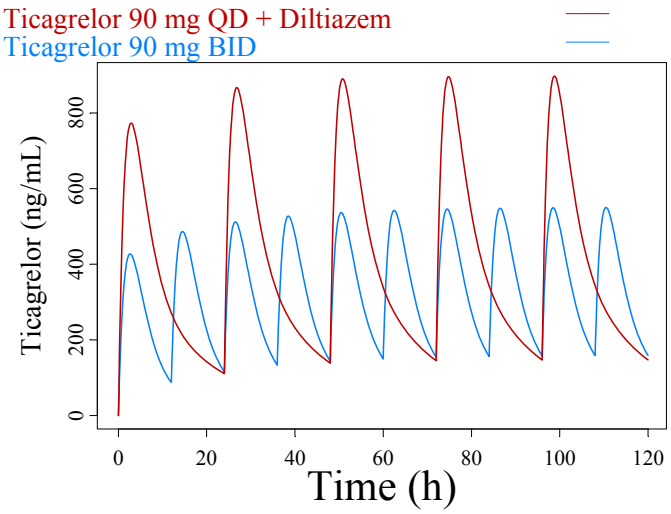



Figure 2. Simulated ticagrelor plasma profiles following the administration of ticagrelor 90 mg QD with ditilazem and 90 mg BID alone.

## 3. Rifampin

| **Report #** D1530C00039 | **Study Period** 10/18/2006 – 12/19/2006 | EDR Link |
|---|---|---|
| **Title** | An open-label study to assess the effect of rifampin, a CYP3A inducer, on the pharmacokinetics of a single oral 180 mg dose of AZD6140 in healthy male and female volunteers | |
| **Study Design** | | |
| **Rationale:** Ticagrelor is primarily metabolized by CYP3A4/5. Rifampin is strong inducer of CYP 3A4 and Pgp. | | |
| Single-Dose Non-Randomized Open-Label Sequential Single-Center 1-Period Healthy Vonuteers | | |
| **Screening:** 28days | **Washout**: Not applicable | |
| **Period** | 18 days<br>Inpatient stay ☑Y ☐ N : Day -1-4, Day 14-18 of each treatment period | |
| **Sequence** | ▪ Day 1: Ticagrelor 180 mg QD<br>▪ Day 4-17: Rifampin 600 mg QD<br>▪ Day 15 Ticagrelor 180 mg QD | |
| **Treatments:**<br>– Ticagrelor: 90 mg IR tablets (Lot # 06-009508AZ)<br>– Rifampin: 150 mg capsle (Lot # Not available) | | |
| ▪ **Sampling Times (plasma)** | | |

– **PK:** Ticagrelor/AR-C124910XX:
Day 1/15: 0,0.5,1,2,3,4,6,8,10,12,18,24,36,48,72 h.
– **PD (20 µM ADP induced platelet aggregation)**
Day 1/15: 0, 2,4,8,12,24 h.

**Analytical Method**

| Analyte | Ticagrelor | AR-C124910XX |
|---|---|---|
| Method | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma |
| Range | 5 - 5000 ng/mL | 2.5-2500 ng/mL |
| Performance | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 18/4/2 |
| Age [Median (range)] | 34.0 (24-45) |
| Male/Female | 15/3 |
| Race (Caucasian/Black/Asian/Hispanic) | 4/14/0/0 |

**Results**

- Mean % Metabolite/parent ratio was32% and 54% for $C_{max}$ and AUC, respectively. In the presence of rifampin the ratio was 120% for $C_{max}$ and 210%AUC.

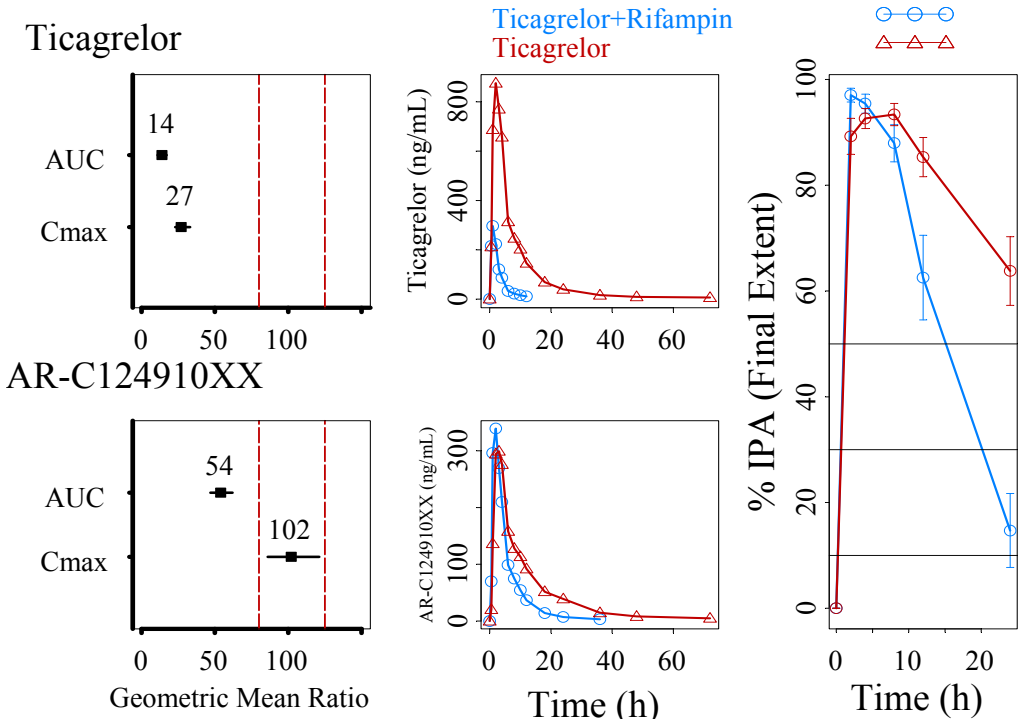



**Figure 1.** Ticagrelor and AR-C124910XX geometric mean ration and corresponding 90% CI (left panel), mean plasma profile (middle panel), and %IPA (right panel, mean ± S.E.) in the presence and absence of rifampin.

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- Two subjects discontinued the study due to AE. One subject under rifampin treatment discontinued due to mild urticaria. One subject under ticagrelor treatment discontinued due to mild blurred vision.

**Conclusion**

- The co-administration of rifampin significantly decreases ticagrelor AUC by 86% and $C_{max}$ by 73%
- The co-administration of rifampin significantly reduces AR-C124910XX AUC by 46% and does not affect $C_{max}$.
- %IPA is the comparable up to 8 h following the administration of ticagrelor and ticagrelor + rifampin.

**Comments**

- Patients taking ticagrelor with strong CYP3A inducers should not use ticagrelor since even with 180 mg dose the resultant ticagrelor exposure in the presence of rifampin (strong CYP 3A4 inducer) is lower than that observed with 90 mg dose in healthy volunteers, as shown in Figure 2.

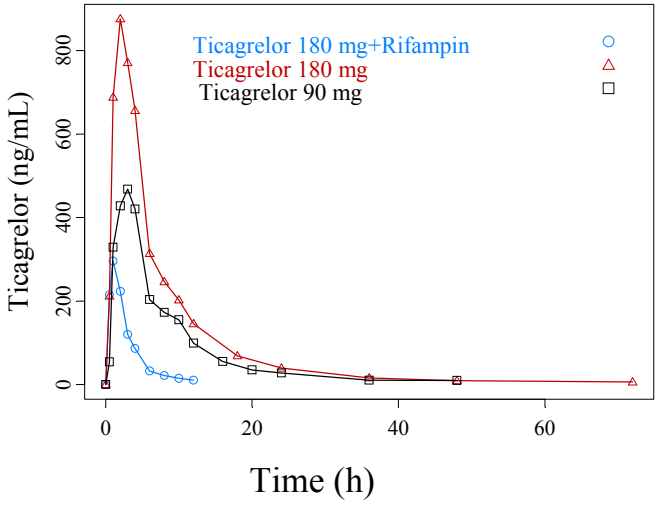



**Figure 2.** Ticagrelor plasma profile following the administration of a single ticagrelor dose of 90 mg (data obtained from study D1530C00016), 180 mg, and 180 mg with rifampin. Values represent mean.

- There was no PK data for rifampin, while one can assume that SS was attained based on the dosing information, it was not confirmed. Also, the subject spent most of the time outside the clinic, so there is a potential for not taking the drug

## 4. Aspirin

| **Report #** D1530C00005 | **Study Period** 12/16/2002 – 02/26/2003 | EDR Link |
|---|---|---|
| **Title** | A phase I, open label, randomized, 2-way crossover study to compare the effects of acetyl salicylic acid on low (50 mg bd) and high (200 mg bd) doses of AZD6140 administered to steady state in healthy male and female volunteers. | |

**Study Design**

**Rationale:** Ticagrelor will be used in combination with aspirin (ASA) in patients with acute coronary artery disease.

Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** ≥ 10 Days |
|---|---|
| **Period 1/2** | 10 days<br>Inpatient stay ☑Y ☐ N : 14 days at each treatment period |

| **Sequence** | **A** | **B** |
|---|---|---|
| | ▪ Day 1-5: Ticagrelor 50 mg BID<br>▪ Day 6-9: Ticagrelor 200 mg BID<br>▪ Day 10: Ticagrelor 200 mg BID | ▪ Same as A + ASA 300 mg QD (Day 1 -10) |

**Treatments:**
– Ticagrelor: 50 mg IR tablets (lot # P6589), 200 mg IR tablets (Lot # P6426)
– ASA: 300 mg tablets (Lot# X1418)

▪ **Sampling Times (plasma)**
– **PK:** Ticagrelor/AR-C124910XX:
Day 1,4,6,9: Pre-dose/Day 9: 4 h/ Day5: 0: 0,0.5,1,2,3,4,6,8,12 h /Day10: 0: 0,0.5,1,2,3,4,6,8,12,24,36,48,72 h
– **PD (20 µM ADP induced platelet aggregation)**
Day 1: pre-dose/Day 5:0,4,8,12 h/Day 10: 0,2,4,8,12,24,36 h
– **Bleeding Time (BT, Simplate®)**
Day 1: Pre-dose/Day 4,9: Pre-dose, 4 h

**Analytical Method**

| Analyte | Ticagrelor | AR-C124910XX |
|---|---|---|
| Method | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma |
| Range | 1 - 500 ng/mL | 2.5-2500 ng/mL |
| Performance | | |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 16/3/3 |
| Age [Median (range)] | 36.0 (21-54) |
| Male/Female | 14/2 |
| Race (Caucasian/Black/Asian/Hispanic) | 15/1/0/0 |

**Results**

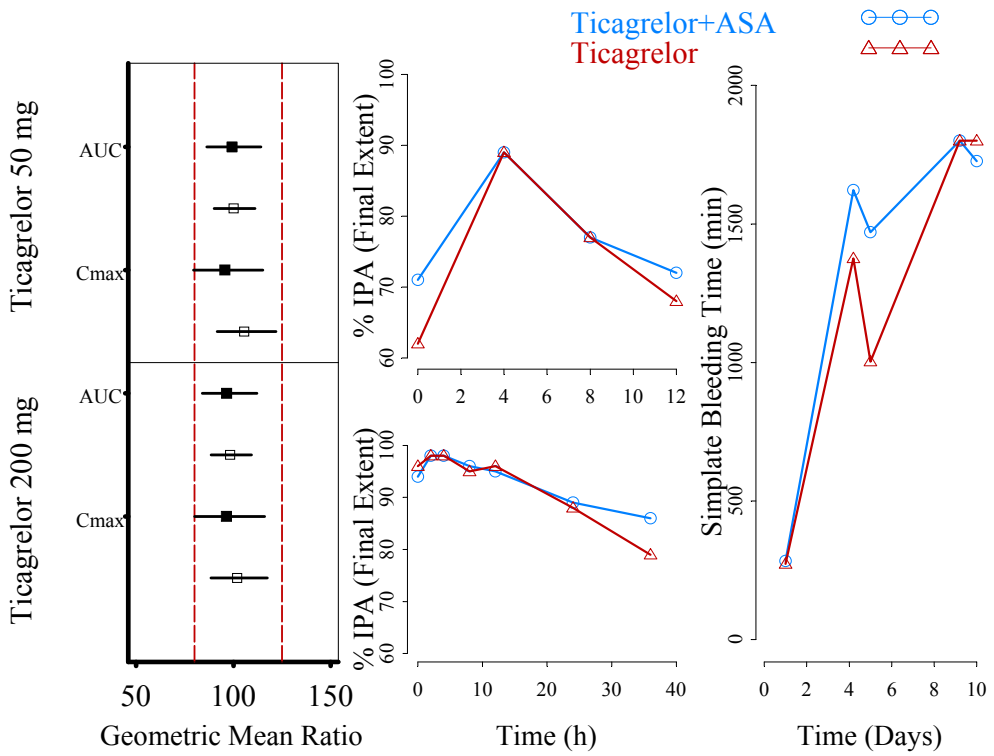



**Figure 1.** Ticagrelor and AR-C124910XX geometric mean ration and corresponding 90% CI (left panel), mean %IPA (20 µM ADP, Final Extent) time profile (middle panel), and mean Simplate® bleeding time (right panel) in the presence and absence of ASA.

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- Three subjects discontinued from the study due to AE related to study drugs as follows:

1. Ticagrelor + ASA group: One subject was withdrawn due to 2 consecutive bleeding times of ≥ 30 minutes and associated bleeding events (epistaxis). The other subject was withdrawn due to haematoma, petechiae and urticaria.
2. Ticagrelor group: One subject was withdrawn due to gingivitis

**Conclusion**

- The co-administration of ASA does not alter the pharmacokinetics of ticagrelor and AR-C124910XX. Also it does not alter 20 µM ADP induced %IPA and simplate® bleeding time.

**Comments**

- Report of the bioanalysis of the study samples was not submitted.

## 5. Desmopressin

| **Report #** D1530C00026 | **Study Period** 06/13/2005 – 10/09/2005 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | A double-blind, randomized, two-period crossover study to assess the effects of desmopressin on AZD6140 pharmacodynamic in healthy male and female volunteers. |

**Study Design**

**Rationale:** To assess whether desmopressin can be used to treat bleeding events associated with ticagrelor

Multiple-Dose Randomized Double-Blind Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** ≥ 7 days, outpatient |
|---|---|

| **Period 1/2** | 7 days, inpatient stay ☑Y ☐ N | |
|---|---|---|
| **Sequence** | **A**<br>▪ Ticagrelor (open label)<br>– Day 1: 270 mg AM + 180 mg PM<br>– Day 2-4: 180 mg BID<br>– Day 5: 180 mg AM<br>▪ Desmopressin:<br>– Day 5: 0.3 µg/Kg IV infusion 2 h post ticagrelor AM dose. | **B**<br>▪ Ticagrelor (open label)<br>– Day 1: 270 mg AM + 180 mg PM<br>– Day 2-4: 180 mg BID<br>– Day 5: AM dose<br>▪ Normal Saline:<br>– Day 5: IV infusion 2 h post ticagrelor AM dose. |

**Treatments:**
- Ticagrelor: 200 mg IR tablets (lot # 05-000353AZ)
- Desmopressin: 4 µg/mL in 1 mL single-dose ampule (Ferring AB) (Lot# Not Available)

- **Sampling Times (PK, plasma)** Ticagrelor and AR-C124910XX:
Days 2,3,4: Pre-dose/Day 5: 0, 0.5, 1 , 2, 2.5 ,3, 4, 6, 8, 10, 12, 24 h
- **PD (PA, PFA-100™,vWFA),** Day 5: 0,2, 2.5,4,8,12,24 h
- **PD(Bleeding Time)** Day 1: Pre-dose, Day5: 0.5, 2, 4, 8, 12, 24 h

**Analytical Method**

| Analyte | Ticagrelor | AR-C124910XX |
|---|---|---|
| Method | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma |
| Range | 5 -5000 ng/mL | 2.5 – 2500 ng/mL |
| Performance | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 21/18/0 |
| Age [Median (range)] | 27.0 (20 – 43) |
| Male/Female | 17/4 |
| Race (Caucasian/Black/Asian/Hispanic) | 4/7/0/10 |

**Results**

- Platelet aggregation, as measured by %IPA, was not affected by co-administration of desmopressin.
- Results obtained with ristocetin cofactor are similar to those obtained with Von

Willebrand (vWF) factor.

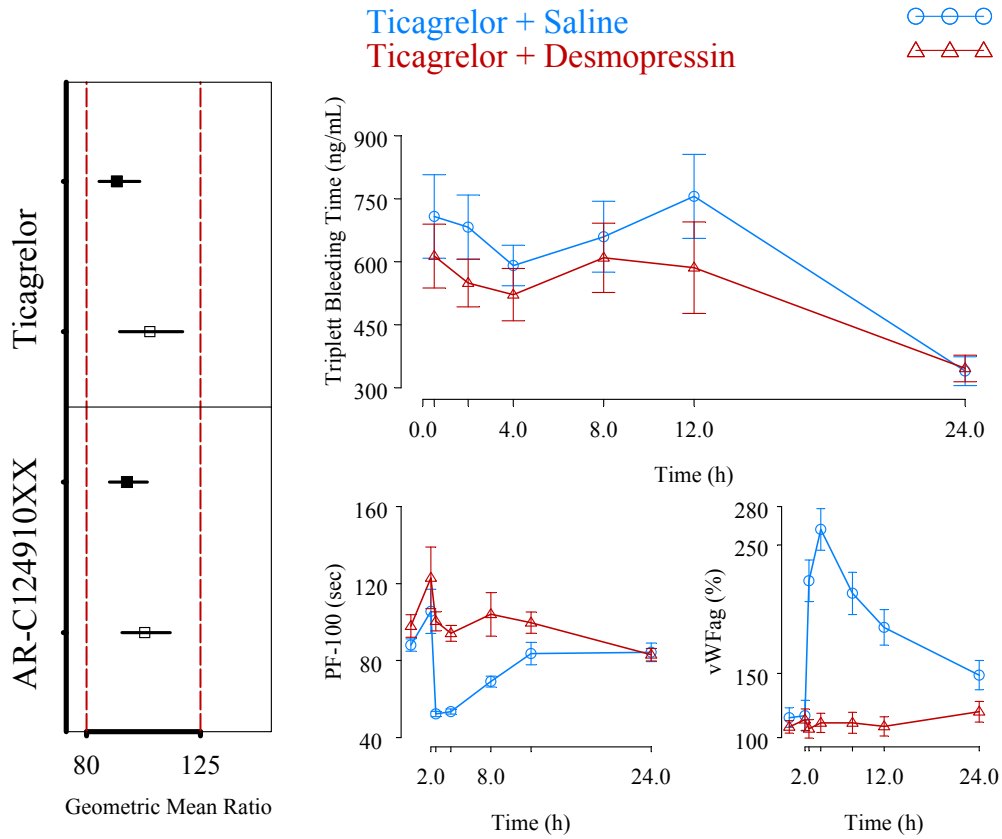



**Figure 1.** Ticagrelor and AR-C124910XX geometric mean ration and corresponding 90% CI (left panel, ■ $AUC_{ss}$ □ $C_{ss,max}$), Triplett™ Bleeding Time (upper panel, mean ± SE), effect on shear induced haemostasis (middle lower panel, mean ± SE ), and vWF factor (right lower panel, mean ± SE) following the administration of ticagrelor for 5 days in the presence and absence of desmopressin.

**Safety**

- Was there any death or serious adverse events? ☐Yes ☑No ☐ NA

**Conclusion**

The co-administration of desmopressin with ticagrelor:

- Does not alter the steady state systemic exposure of ticagrelor and AR-C124910XX.
- Reduces Triplett™ bleeding time, although the reduction is not statistically significant.
- Produces a more rapid haemostasis as measured by PF-100™.
- Significant increases vWFAg factor and ristocetin cofactor

**Comments**

- -Reduction in Triplett™ bleeding time is not expected to be clinically significant. Therefore, desmopressin is not expected to treat ticagrelor related bleeding events.
- Results for vWFAg and ristocetin cofactor indicate the expected pharmacologic effect of desmopressin.

## 6. Heparin

| **Report #** D1530C00006 | **Study Period** 03/26/2007 – 07/25/2007 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | An open-label, randomized, 3-period crossover study to compare the effects of 180 mg (2 x 90 mg) single-dose AZD6140 with and without unfractionated heparin (100 IU/kg) in healthy male and female volunteers. |

**Study Design**

**Rationale:** Ticagrelor and heparin are used in regimens for ACS in settings such as PCI. Therefore, it is important to understand whether co-administration of both drugs could either potentiate or inhibit the anti-coagulant activity of either drug.

Single-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** ≥ 5 days, outpatient |
|---|---|
| **Period 1/2/3** | 5 days, inpatient stay ☑Y ☐ N: CPU |

| **Sequence** | **A** | **B** | **C** |
|---|---|---|---|
| | Ticagrelor 180 mg Single Dose | Unfractionated heparin (100 IU/kg) IV bolus | A+B |

**Sampling Times** (Sequence A & C)

- **(PK, plasma)** Ticagrelor and AR-C124910XX:

Day 1: 0, 0.5, 1 , 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72 h

- **PD (PA),** Day 1: 0,2, 2.5,4,8,12,24, 48, 72 h
- **PD(aPTT, ACT)** Day 1: 0, 2, 3, 4, 6, 8,12,24 h

**Treatments:**

- Ticagrelor: 90 mg IR tablets (lot # 05-000353AZ)
- Heparin Natrium: 250000 ratiopharm (Ratiopharm GmbH&Co, NDC # 0008-0277-01)

**Analytical Method**

| Analyte | Ticagrelor | AR-C124910XX |
|---|---|---|
| Method | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma |
| Range | 5 -5000 ng/mL | 2.5 – 2500 ng/mL |
| Performance | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 30/28/0 |
| Age [Median (range)] | 38.0 (19 -45) |
| Male/Female | 27/3 |
| Race (Caucasian/Black/Asian/Hispanic) | 30/0/0/0 |

**Results**

- The difference of $\%IPA_{max}$ was statistically significantly lower by 3.6% when heparin was co-administered with ticagrelor, also $AUEC_{2-12}$ and $AUEC_{2-72}$.
- When ticagrelor was co-administered with heparin aPTT $AUEC_{2-24}$ was higher and statistically significant, while ACT $AUEC_{0-24}$ was higher but not statistically significant.

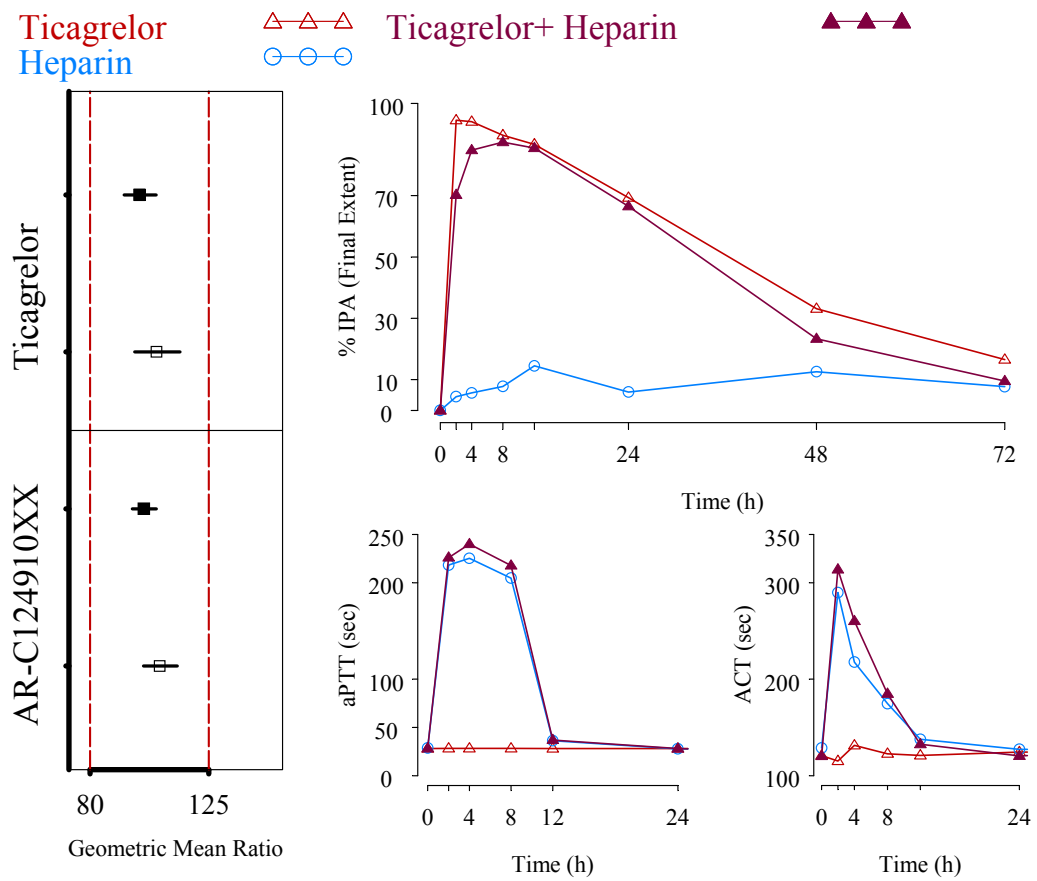



**Figure 1.** Ticagrelor and AR-C124910XX geometric mean ration and corresponding 90% CI (left panel, ■ AUC □ $C_{,max}$), mean 20 µM ADP induced % IPA (Upper panel), mean activated partial thromboplastin tume (middle lower panel), and mean activated coagulation time (right lower panel) following the administration of a single dose of ticagrelor, heparin, and a combination of both.

**Safety**

- Was there any death or serious adverse events? ☐Yes ☑No ☐ NA

**Conclusion**

- The co-administration of heparin does not alter the systemic exposure of ticagrelor, but significantly reduces ADP induced %IPA.
- The co-administration of ticagrelor with heparin significantly increases aPTT $AUEC_{0-24}$ but not ACT $AUEC_{0-24}$.

**Comments**

Although the PD effect of both drugs on each other is statistically significant, the magnitude is small that it bears no clinical significance.

## 7. Enoxaprin

| **Report #** D1530C00007 | **Study Period** 02/23/2007 – 06/27/2007 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | An open-label, randomized, 3-period crossover study to compare the effects of 180 mg (2 x 90 mg) single-dose AZD6140 with and without enoxaprin (1 mg/kg) in healthy male and female volunteers. |

**Study Design**

**Rationale:** Ticagrelor and enoxaprin are used in regimens for ACS in settings such as PCI. Therefore, it is important to understand whether co-administration of both drugs could either potentiate or inhibit the anti-coagulant activity of either drug.

Single-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** ≥ 5 days, outpatient |
|---|---|
| **Period 1/2/3** | 5 days, inpatient stay ☑Y ☐ N: CPU |

| **Sequence** | **A** | **B** | **C** |
|---|---|---|---|
| | Ticagrelor 180 mg Single Dose | Enoxaprin (1 mg/kg) SC injection | A + B (2 h post A dose) |

**Sampling Times** (Sequence A & C)

- **(PK, plasma)** Ticagrelor and AR-C124910XX:

Day 1: 0, 0.5, 1 , 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72 h

- **PD (PA),** Day 1: 0,2, 2.5,4,8,12,24, 48, 72 h
- **PD(Anti-factor Xa)** Day 1: 0, 2, 3, 4, 6, 8,12,24 h

**Treatments:**

- Ticagrelor: 90 mg IR tablets (lot # 05-000353AZ)
- Enoxaprin Na: 100 mg/mL in 10 mL vial (Clexane® multiodose, lot # Not Available)

**Analytical Method**

| Analyte | Ticagrelor | AR-C124910XX |
|---|---|---|
| Method | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma |
| Range | 5 -5000 ng/mL | 2.5 – 2500 ng/mL |
| Performance | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 30/30/0 |
| Age [Median (range)] | 34.0 (22 – 45) |
| Male/Female | 29/1 |
| Race (Caucasian/Black/Asian/Hispanic) | 2/1/1/0 |

**Results**

- The difference of $\%IPA_{max}$, $AUEC_{2-12}$ and $AUEC_{2-72.}$ were not statistically significantly enoxaprin was co-administered with ticagrelor, also
- When ticagrelor was co-administered with enoxaprin anti-factor Xa $AUEC_{2-24}$ was higher and statistically significant, while ACT $AUEC_{0-24}$ was lower and statistically significant.

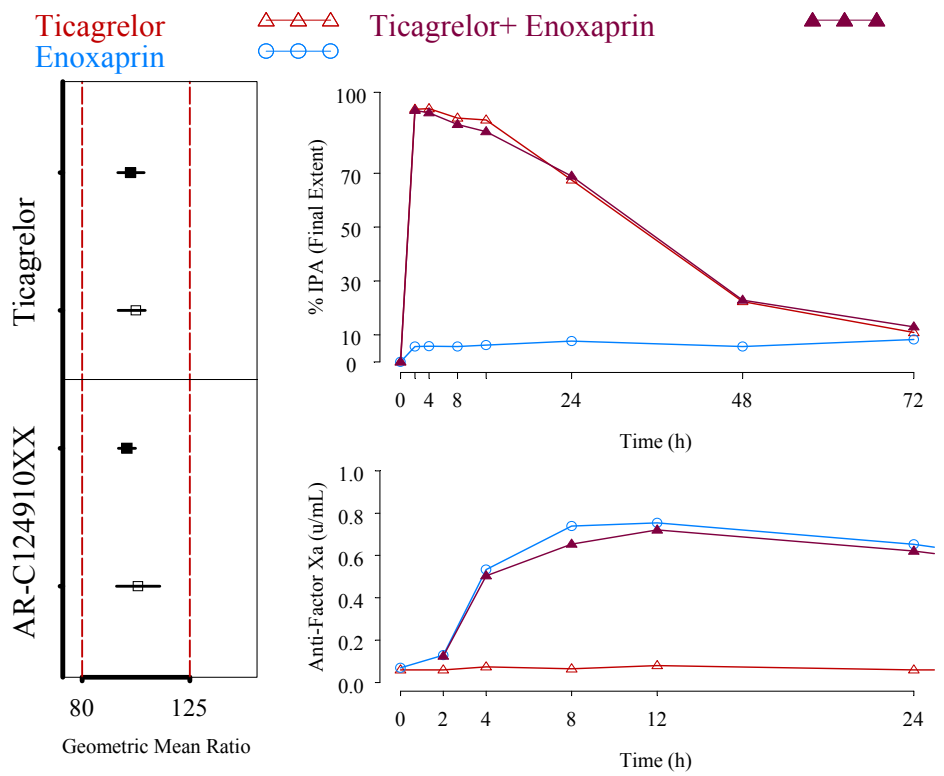



**Figure 1.** Ticagrelor and AR-C124910XX geometric mean ration and corresponding 90% CI (left panel, ■ AUC ☐ $C_{,max}$), mean 20 µM ADP induced % IPA (Upper right panel) and mean anti-factor Xa (right lower panel) following the administration of a single dose of ticagrelor, enoxaprin, and a combination of both.

**Safety**

- Was there any death or serious adverse events? ☐Yes ☑No ☐ NA

**Conclusion**

- The co-administration of enoxaprin does not alter neither the systemic exposure of ticagrelor nor ADP induced %IPA.
- The co-administration of ticagrelor with enoxaprin significantly decreases anti-factor Xa $AUEC_{0-24}$.

**Comments**

Although the effect of enoxaprin on anti-factor Xa $AUEC_{0-24}$.was statistically significant, the magnitude is so small that it does not have any clinical significance.

## 8. Digoxin

| **Report #** D1530C05265 | **Study Period** 09/18/2003 – 11/17/2003 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | A randomized, double-blind, two-period crossover study to assess safety, tolerability, and pharmacokinetics following repeated doses of AZD6140 (400 mg od) and digoxin (0.25 mg od) in healthy male and female volunteers. |

**Study Design**

**Rationale:** Digoxin is a known P-Pgp transporter substrate, while ticagrelor is a substrate and inhibitor of P-gp. Digoxin has a narrow therapeutic window and is likely to be prescribed with ticagrelor in ACS population.

Multiple-Dose Randomized Double-Blind Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** ≥ 14 days, outpatient |
|---|---|

| **Period 1/2** | 16 days, inpatient stay ☑Y ☐ N | |
|---|---|---|
| **Sequence** | **A** | **B** |
| | ▪ Ticagrelor<br>– Day 1-16: 400 mg QD<br>▪ Digoxin: (open label)<br>– Day 6: 0.25 mg BID<br>– Day 7-14: 0.25 mg QD | ▪ Placebo of Ticagrelor<br>– Day 1-16: QD<br>▪ Digoxin: (open label)<br>– Day 6: 0.25 mg BID<br>– Day 7-14: 0.25 mg QD |

**Treatments:**
- Ticagrelor: 200 mg IR tablets (lot # P6661)
- Digoxin: 0.25 mg tablets (Lot# 3ZP0745)

▪ **Sampling Times (PK, plasma)**

| Day | Ticagrelor | Digoxin |
|---|---|---|
| 1,4,12, 13 | Pre-Dose on Day 1,4 | Pre-Dose on Day 1, 12, 13 |
| 5 | 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 h | |
| 14 | 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72 h | |

**Analytical Method**

| Analyte | Digoxin | Ticagrelor | AR-C124910XX |
|---|---|---|---|
| Method | Radioimmunoassay | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma | Plasma |
| Range | 0.1 – 8.0 ng/mL | 1 -500 ng/mL | 2.5 – 500 ng/mL |
| Performance | Acceptable | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 20/16/1 |
| Age [Median (range)] | 44.5 (22–59) |
| Male/Female | 10/10 |
| Race (Caucasian/Black/Asian/Hispanic) | 3/1/0/16 |

**Results**

▪ Steady state of ticagrelor was attained prior to the administration of digoxin dose.

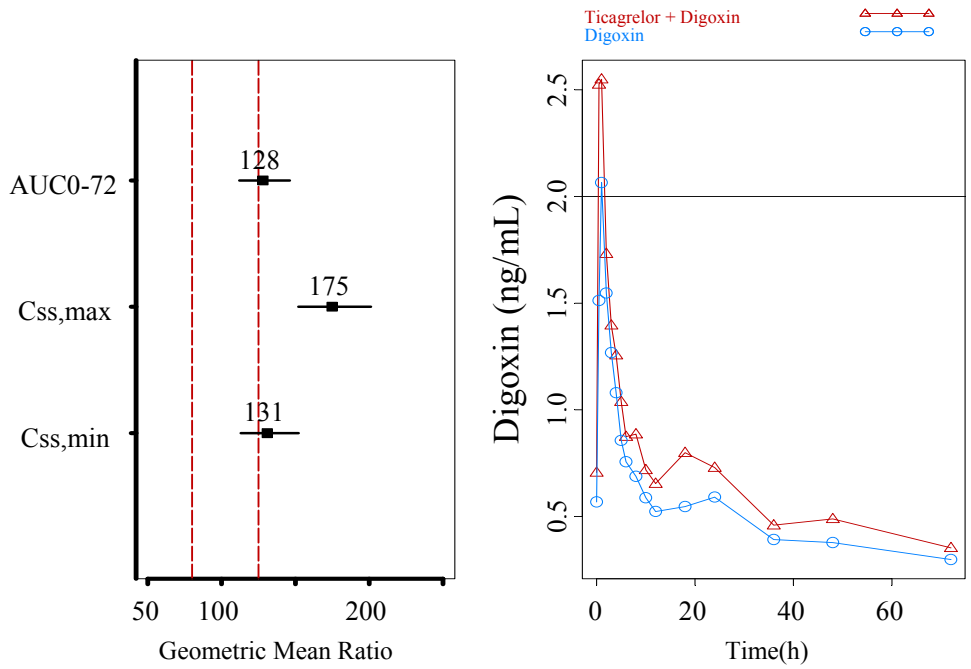



**Figure 1.** Digoxin geometric mean ration and corresponding 90% CI (left panel) and mean plasma profile (right panel) in the presence and absence of ticagrelor.

**Safety**

- Was there any death or serious adverse events? ☐Yes ☑No ☐ NA
- One subject discontinued from study treatment due to an AE of pruritus and raised erythematous on trunk and extremities after receiving the fifth dose of ticagrelor in Study Period 1 (Day 5); the rash resolved by Day 7. On Day 8 the pruritus recurred and the subject was administered.

**Conclusion**

- The co-administration of ticagrelor significantly increases digoxin acid $AUC_{0\text{-}72}$, $C_{ss,max}$, and $C_{ss,\ min}$ by 28%, 75% and 31%, respectively.

**Comments**

Mean $C_{ss,max}$ observed is higher than 2 ng/mL above which of the observed clinical toxicities occurred. Therefore, digoxin levels should be monitored frequently when ticagrelor is co-administered.

## 9. Simvastatin

| **Report #** D1530C00024 | **Study Period** 09/09/2004 – 12/27/2004 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | An open-label, randomized, two-way crossover single center study to compare the safety, tolerability, pharmacokinetics and pharmacodynamic profile of simvastatin alone and in combination with AZD6140 in healthy volunteers age 18 to 48 years |

**Study Design**

**Rationale:** Ticagrelor is a moderate inhibitor of CY3A5 and simvastatin is metabolized by CYP3A4/5.

Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** ≥7 days |
|---|---|

| **Period 1/2** | 5 days (Sequence A) or 9 days (Sequence B), inpatient stay ☑Y ☐ N | |
|---|---|---|
| **Sequence** | **A**<br>▪ Simvastatin:<br>Day 1: 80 mg QD | **B**<br>▪ Ticagrelor<br>Day 1: 270 mg AM<br>Day 1: 180 mg PM<br>Day 2-7: 180 mg BID<br>▪ Simvastatin<br>Day 5: 80 mg QD |

**Treatments:**
- Ticagrelor: 90 mg IR tablets (lot # P7046)
- Simvastatin(Zocor®) 80 mg tablets (Lot# Not Available)

▪ **Sampling Times (PK, plasma)**
- Simvastatin and simvastatin acid:

Day 1 & 5: 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, and 72 h post-dose.
- Ticagrelor and AR-C124910XX:

Day 1 & 4: 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12
Day 3: Pre-dose
Day 5: 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 (Day 6), 36, 48 (Day 7), 60, 72 (Day 8)

**Analytical Method**

| Analyte | Simvastatin | Simvastatin Acid | Ticagrelor | AR-C124910XX |
|---|---|---|---|---|
| Method | LC-MS/MS | LC-MS/MS | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma | Plasma | Plasma |
| Range | 0.25 - 250 ng/mL | 0.25 - 250 ng/mL | 5 -5000 ng/mL | 2.5 – 2500 ng/mL |
| Performance | Acceptable | Acceptable | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 24/20/1 |
| Age [Median (range)] | 27.5 (18-45) |
| Male/Female | 18/6 |
| Race (Caucasian/Black/Asian/Hispanic) | 14/10/0/0 |

**Results**

▪ Steady state of ticagrelor was attained prior to the administration of simvastatin dose.

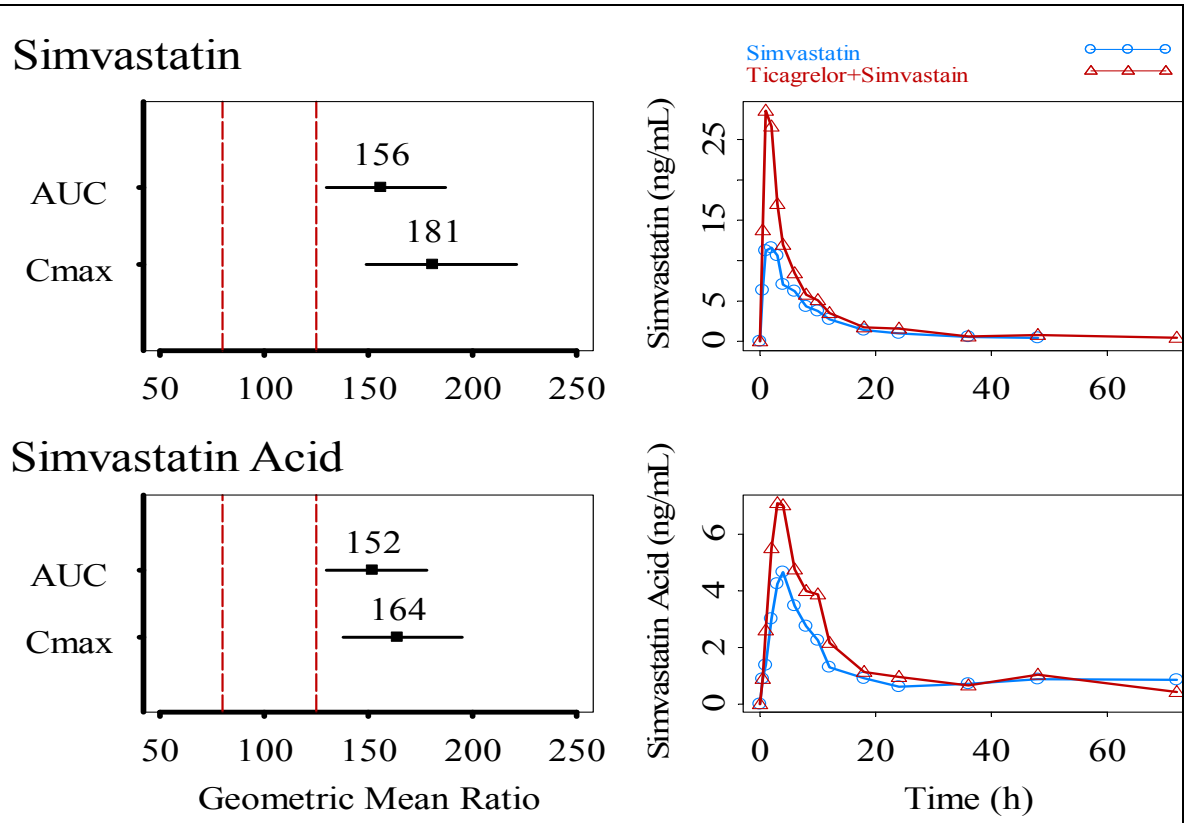



**Figure 1.** Simvastatin and simvastatin acid geometric mean ration and corresponding 90% CI (left panel) and mean plasma profile (right panel) in the presence and absence of ticagrelor.

**Safety**

- Was there any death or serious adverse events? ☑ Yes ☐No ☐ NA
- One volunteer experienced mediastinitis after completing the study. The subject was hospitalized 12 days after the last dose in Period 2, and was re-hospitalized another time after discharge. The investigator judged that the SAE was of moderate intensity and not considered related to study drug.
- One subject had syncope on Day 5 of simvastatin/ticagrelor treatment period. The subject fell to the ground hitting his head causing subsequent nausea, headache and cephalhaematoma, which occurred shortly after the episode of syncope.
- One subject discontinued the study due to atrial fibrillation 3 hours after receiving one dose of ticagrelor (270 mg).

**Conclusion**

- The co-administration of ticagrelor significantly increases simvastatin AUC by 56% and $C_{max}$ 81%.
- The co-administration of ticagrelor significantly increases simvastatin acid AUC by 52% and $C_{max}$ by 64%.

**Comments**

The interaction between simvastatin and ticagrelor is not considered clinically significant. This conclusion has been reach upon consultation with the division of Metabolism and Endocrinology.

## 10. Atorvastatin

| **Report #** D1530C00025 | **Study Period** 05/05/2005 – 06/27/2005 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | An open-label, randomized, two-way crossover single study to compare the safety, tolerability, pharmacokinetics and pharmacodynamic profiles of AZD6140 and atorvastatin Calcium (Lipitor®) administered alone and in combination to healthy volunteers age 18 to 45 years |

**Study Design**

**Rationale:** Ticagrelor interact with CYP3A4, ranging from activation through partial or full inhibition depending on the substrate and specific metabolites measured. Atorvastatin is metabolized by CYP3A4 and is a frequently used statin.

Single-Dose Randomized Double-Blind Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** 21 days | **Washout:** 7 - 10 days, outpatient |
|---|---|
| **Period 1/2** | 9 days, inpatient stay ☑Y ☐ N |

| | **A** | **B** |
|---|---|---|
| **Sequence** | ▪ Ticagrelor<br>– Day 1: 270 mg AM + 90 mg PM<br>– Day 2-7: 90 mg BID<br>▪ Atorvastatin: (open label)<br>– Day 5: 80 mg QD | ▪ Placebo of Ticagrelor<br>– Day 1: 270 mg AM + 90 mg PM<br>– Day 2-7: 90 mg BID<br>▪ Atorvastatin: (open label)<br>– Day 5: 80 mg QD |

**Treatments:**
- Ticagrelor: 90 mg IR tablets (lot # P7046)
- Atorvastatin Calcium (Lipitor®): 80 mg tablets (Lot# Not Available)

▪ **Sampling Times (PK, plasma)**
– Atorvastatin and Metabolites:
Day 5: 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, and 72 h post-dose.
– Ticagrelor and AR-C124910XX:
Day 1 & 3: Pre-dose
Day 4 & 5: 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12

**Analytical Method**

| Analyte | Atorvastatin/Atorvastatin Lactone/ 2-OH Atorvastatin/4-OH Atorvastatin | Ticagrelor | AR-C124910XX |
|---|---|---|---|
| Method | LC-MS/MS | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma | Plasma |
| Range | 0.25 - 250 ng/mL | 5 -5000 ng/mL | 2.5 – 2500 ng/mL |
| Performance | Acceptable | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population:**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 24/21/0 |
| Age [Median (range)] | 34.5 (18–44) |
| Male/Female | 19/5 |
| Race (Caucasian/Black/Asian/Hispanic) | 1/5/0/18 |

**Results**

- Steady state of ticagrelor was attained prior to the administration of atorvastatin dose.

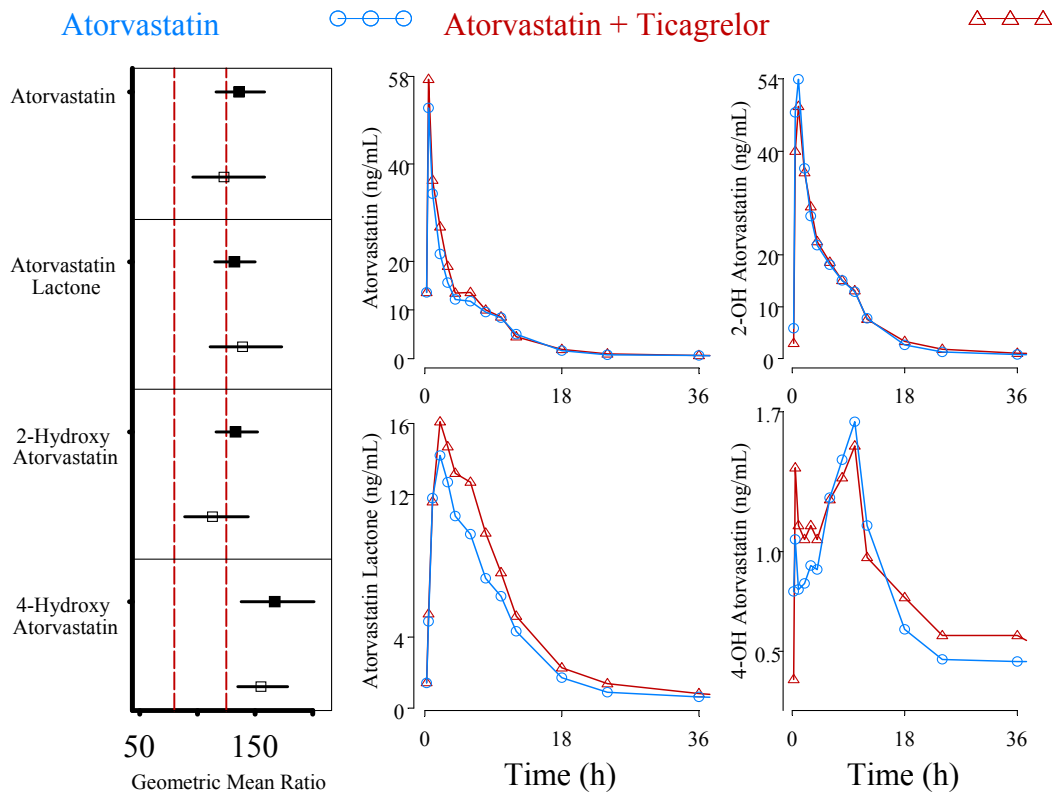



**Figure 1.** Atorvastatin and its metabolites geometric mean ration and corresponding 90% CI (left panel, ■AUC ☐Cmax) and mean plasma profile (middle & right panel) in the presence and absence of ticagrelor.

**Safety**

- Was there any death or serious adverse events? ☐Yes ☑No ☐ NA

**Conclusion**

- The co-administration of ticagrelor significantly increases atorvastatin acid AUC 36% and $C_{max}$ 23%.
- The co-administration of ticagrelor significantly increases atorvastatin lactone AUC 32% and $C_{max}$ 39%.
- The co-administration of ticagrelor significantly increases 2-OH atorvastatin AUC 33% and $C_{max}$ 13%.
- The co-administration of ticagrelor significantly increases 4-OH atorvastatin AUC 67% and $C_{max}$ 55%.

**Comments**

There is no need to adjust atorvastatin dose in the when co-administered with ticagrelor.

## 11. Oral Contraceptive

| **Report #** D1530C00042 | **Study Period** 04/21/2008 – 10/04/2008 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | A randomized, double-blind, two-way crossover study to determine the effects of co-administration of AZD6140 and Nordette® (combination of levonorgestrel and ethinyl estradiol) after multiple oral doses in healthy female volunteers. |

**Study Design**

**Rationale:** Ticagrelor is a substrate, mild inhibitor, and activator of CYP3A4/5. CYP3A4 is involved in the hydroxylation of ethinyl estradiol (EE).

Multiple-Dose Randomized Double-Blind Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** 30 days | **Washout:** 7 days (Day 22-28), outpatient, Nordett®placebo |
|---|---|

| | | |
|---|---|---|
| **Period 1/2** | 22 days, inpatient stay ☑Y ☐ N: Days 19-22<br>▪ There was a 2-month run in/stabilization period in which the subjects came to the clinic every week to determine compliance wit h the use of Nordet® | |
| **Sequence** | **A**<br>▪ Nordette ®: QD x 21 days<br>▪ Ticagrelor: 90 mg BID x 21 days | **B**<br>▪ Nordette ®: QD x 21 days<br>▪ Placebo: BID x 21 days |

**Sampling Times** (Sequence A & C)

- **(PK, plasma)** Ticagrelor / AR-C124910XX/ EE/Levonorgestrel (LN)

[Day 1, 2, 14: Pre-dose][Day 21: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, (EE/LN only)16, 24 h]

- **PD(Progesterone/17-β-estradiol/LH/FSH/SHBG)** Day 1, 7, 14, 21: Pre-Dose

**Treatments:**

- Ticagrelor: 90 mg IR tablets (lot # 07-010829AZ)
- Nordett®: 0.03 mg EE+0.15 mg LN (Duramed Pharmaceuticals, Lot #. 51285-0091-58)

**Analytical Method (**Matrix: plasma**)**

| Analyte | Method | Range | Performance |
|---|---|---|---|
| Ticagrelor | LC-MS/MS | 5 -5000 ng/mL | Acceptable |
| AR-C124910XX | LC-MS/MS | 2.5 – 2500 ng/mL | Acceptable |
| Ethinyl Estradiol | LC-MS/MS | 2 – 1000 pg/mL | Acceptable |
| Levonorgestrel | LC-MS/MS | 0.1- 50 ng/mL | Acceptable |
| 17-β-Estradiol | LC-MS/MS | 2 – 2000 ng/mL | Acceptable |
| Follicle Stimulating Hormone (FSH) | cELISA | 0.05 – 40 mIU/mL | Acceptable |
| Luteinizing Hormone (LH) | cELISA | 0.1- 50 mIU/mL | Acceptable |
| Progesterone | LC-MS/MS | 20 – 2000 pg/mL | Acceptable |
| Sex Hormone Binding Globulin (SHBG) | CIA | 4.0 & 77.0 nM | Acceptable |

**Notes:**

- SHBG assay used only two points for the CC to run study samples, however validation of the method used 5 different concentrations.
- CIA: Chemiluminescent Immunometric Assay.

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period,

and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 26/22/0 |
| Age [Median (range)] | 32.5 (19 – 26) |
| Male/Female | 0/26 |
| Race (Caucasian/Black/Asian/Hispanic) | 20/6/0/0 |

**Results**

- Attainment of ticagrelor steady state was confirmed.
- There was no statistically significant difference between endogenous hormone (FSH,LH, progesterone, 7-β-E, SHBG) at any measurement.

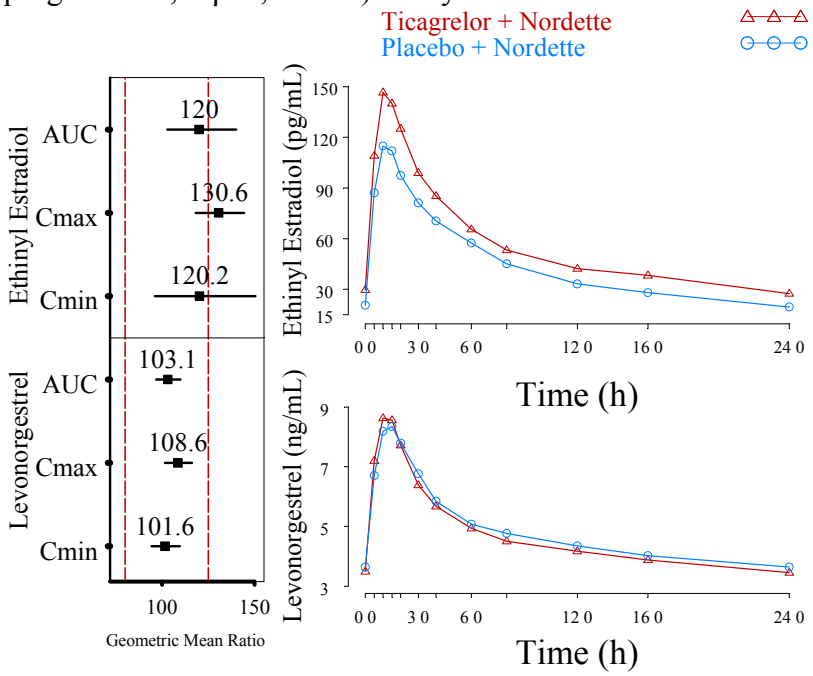



**Figure 1.** EE and LN geometric mean ration and corresponding 90% CI and mean plasma profile (right panel) following the administration of ticagrelor and Nordette® and placebo and Nordette® for 21 days.

**Safety**

- Was there any death or serious adverse events? ☐Yes ☑No ☐ NA

**Conclusion**

- The co-administration of ticagrelor significantly increases ethinyl estradiol AUC, $C_{max}$, and $C_{min}$ by 20%, 30.6%, and 20.2%, respectively.
- The co-administration of ticagrelor does not alter the systemic exposure of levonorgestrel.

**Comments**

Although, ticagrelor increased the systemic exposure of EE, it does not have any effect on the endogenous hormones. Therefore, ticagrelor can be administered safely with oral contraceptive products containing EE and LN.

## 12. Midazolam

| **Report #** D1530C00032 | **Study Period** 12/21/2004 – 05/26/2005 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | An open-label, randomized, 4-period, crossover study to assess safety, tolerability, and pharmacokinetics following co-administration of AZD6140 (180 mg) BID and single intravenous (2.5 mg) and oral dose of midazolam (7.5 mg) in healthy male and female volunteers |

**Study Design**

**Rationale:** Ticagrelor and AR- have been shown in vitro to affect CYP3A4/5 mediated metabolism by activation of 1-OH midazolam formation and inhibition of 4-OH midazolam formation. Midazolam is a substrate marker for CYP3A4/5.

Single-Dose Randomized Open-Label Cross-Over Single-Center 4-Period Healthy Vonuteers

| **Screening:** ≤ 21 days | **Washout:** ≥7 days, outpatient |
|---|---|

| | |
|---|---|
| **Period 1/2/3/4** | 9 days(A & B), 3 days (C & D)<br>Inpatient stay ☑Y ☐ N: |

| | A | B | C | D |
|---|---|---|---|---|
| **Sequence** | Ticagrelor<br>Day 1: 270 mg AM+ 180 mg PM<br>Day 2-7: 180 mg BID<br>Midazolam<br>Day 1, 7: 7.5 mg Oral AM dose | Ticagrelor<br>Day 1: 270 mg AM+ 180 mg PM<br>Day 2-7: 180 mg BID<br>Midazolam<br>Day 1, 7: 2.5 mg IV over 2 minutes AM dose | Midazolam<br>7.5 mg Oral<br>Single Dose | Midazolam<br>2.5 mg IV over 2 minutes<br>Single Dose |

**Treatments:**
- Ticagrelor: 90 mg IR tablets (lot # P7046)
- Midazolam: 7.5 mg oral tablets (Roche, Switzerland, Lot #. X1553)
- Midazolam: 2 mg/2mL ampule (Antigen Pharmaceuticals, Ltd, Ireland, Lot #. NA)

▪ **Sampling Times (PK, plasma)**
- Ticagrelor and AR-C124910XX,

Day 4, 5: Pre-Dose / Day 1,6,7: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 h
- Midazolam IV, Day 1 & 7: 0, End of IV, 10 min, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24 h
- Midazolam oral, Day 1 & 7: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24 h

**Analytical Method**

| Analyte | Ticagrelor | AR-C124910XX | Midazolam<br>1'-Hydroxymidazolam<br>2'-Hydroxymidazolam |
|---|---|---|---|
| Method | LC-MS/MS | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma | Plasma |
| Range | 5 - 5000 ng/mL | 2.5-2500 ng/mL | 0.1 – 100 ng/mL |
| Performance | Acceptable | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 28/25/1 |
| Age [Median (range)] | 23.5 (18 – 45) |
| Male/Female | 27/1 |
| Race (Caucasian/Black/Asian/Hispanic/other) | 21/5/1/0/1 |

**Results**

- Ticagrelor steady state was attained, and metabolite to parent ratio were comparable before and after the administration of midazolam.

| Metabolite/Parent | | Ticagrelor | Ticagrelor + Midazolam |
|---|---|---|---|
| $AUC_{ss,\tau}$ | Oral | 49 | 43 |
| | IV | 43 | 46 |
| $C_{ss,max}$ | Oral | 35 | 35 |
| | IV | 35 | 38 |

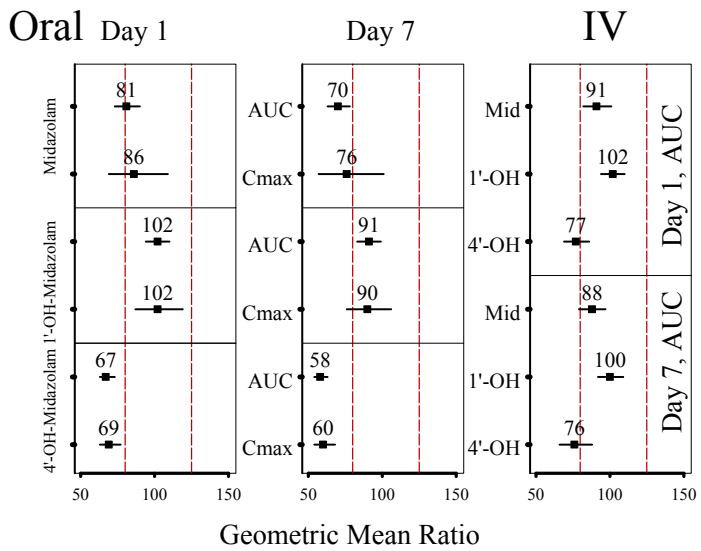



**Figure 1.** Midazolam and its metabolites geometric mean ration and corresponding 90% CI in the presence and absence of ticagrelor.

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- One subject discontinued the study due to 2 episodes of mild genital haemorrhage (vaginal bleeding). The first episode occurred after receiving ticagrelor + IV midazolam, and the second occurred after receiving oral midazolam. The 2 events were judged by the investigator to be unrelated to treatment.

**Conclusion**

- The co-administration of ticagrelor significantly reduces oral midazolam AUC by 10%, and 4'-OH-midazolam by 42%, but does not alter 1'-OH- midazolam AUC.
- The co-administration of ticagrelor does not alter the systemic exposure of IV midazolam and 1'-OH-midazolam, and significantly reduces 4'-OH- midazolam systemic exposure by ~ 23%.

**Comments**

The obtained results are consistent with in vitro findings. Ticagrelor and AR-C124910XX appear to be moderate inhibitors of CYP 3A5 and not CYP 3A4.

## 13. Tolbutamide

| **Report #** D1530C00051 | **Study Period** 01/26/2007 – 03/26/2007 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | A randomized, double-blind, 2-period crossover study to assess the effect of steady-state AZD6140 on the pharmacokinetics of a single oral 500-mg dose of tolbutamide , a substrate of CYP2C9, in healthy male and female volunteers. |

**Study Design**

**Rationale:** Ticagrelor inhibits CYP 2C9 in vitro at high concentration. Tolbutamide is a substrate marker for 2C9.

Single-Dose Randomized Double-Blind Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** ≤ 21 days | **Washout:** ≥14 days |
|---|---|

| **Period 1/2** | 11 days, inpatient stay ☑Y ☐ N | |
|---|---|---|
| **Sequence** | **A**<br>▪ Ticagrelor: 180 mg BID x 9 days<br>▪ Tolbutamide (open label): 500 mg QD on Day 5 | **B**<br>▪ Placebo: BID x 9 days<br>▪ Tolbutamide (open label):: 500 mg QD on Day 5 |

**Treatments:**
- Ticagrelor: 90 mg IR tablets (lot # FDN334)
- Tolbutamide: 500 mg tablets (NDC# 0378-0215-01)

▪ **Sampling Times (PK, plasma)**
- Ticagrelor and AR-C124910XX, Day 2-10: Pre-Dose/
  Day4,5: 0, 0.5, 1, 2, 3, 4, 6, 8 , 10, 12 h
- Tolbutamide, Day 5: 0, 0.5, 1, 2, 3 ,4 ,6 ,8, 10, 12, 18,24,36,48,72, 96, 120 h

**Analytical Method**

| Analyte | Ticagrelor | AR-C124910XX | Tolbutamide<br>4-OH-tolbutamide |
|---|---|---|---|
| Method | LC-MS/MS | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma | Plasma |
| Range | 5 - 5000 ng/mL | 2.5-2500 ng/mL | 10 – 5000 ng/mL |
| Performance | Acceptable | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 23/21/2 |
| Age [Median (range)] | 30.0 (21 – 39) |
| Male/Female | 21/2 |
| Race (Caucasian/Black/Asian/Hispanic) | 9/11/1/0/2 |

**Results**

▪ Ticagrelor steady state was attained, and metabolite to parent ratio were comparable before and after the administration of tolbutamide.

| Metabolite/Parent | Ticagrelor | Ticagrelor + Tolbutamide |
|---|---|---|
| $AUC_{ss,\tau}$ | 48.9 | 53.9 |
| $C_{ss,max}$ | 38.7 | 40.7 |

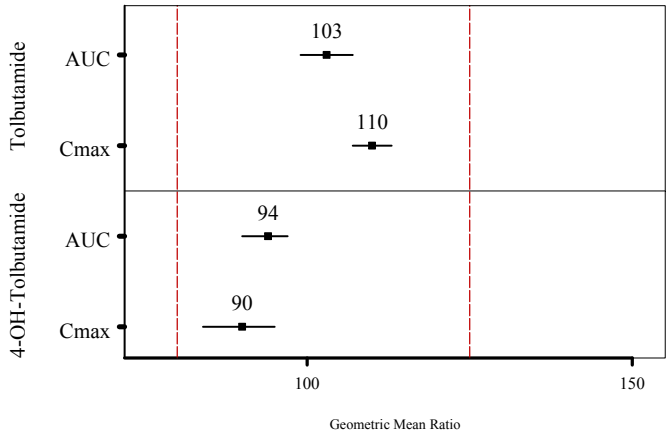



**Figure 1.** Tolbutamide and 4-OH-tolbutamide geometric mean ration and corresponding 90% CI in the presence and absence of ticagrelor.

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- Two subjects discontinued the study; one after receiving placebo due to rash and the second after receiving placebo + tolbutamide due to hypertension.

**Conclusion**

- The co-administration of ticagrelor does not alter the systemic exposure of tolbutamide

**Comments**

Ticagrelor in the current dosing schema (180 mg BID) can be co-administered with other drugs that are metabolized by CYP 2C9

# V. Biopharmaceutics

## 1. Absolute Bioavailability

| **Report #** D5130C00038 | **Study Period**: 03/23/2007 - 05/18/2007 | EDR Link |
|---|---|---|

| **Title** | An open-label, single –center, randomized, two-period, cross-over study to determine the absolute bioavailability of AZD6140 in healthy male and female volunteers |
|---|---|

**Study Design**

| ☐ Bioequivalence | ☑ Bioavailability |
|---|---|

Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers

| **Screening:** ≤ 28 days | **Washout:** ≥7 days, outpatient |
|---|---|
| **Period 1/2** | 4 days, Inpatient stay ☑Y ☐ N: |

**Treatments:** (Active Ingredient: Ticagrelor)

| | **Test** | **Reference** |
|---|---|---|
| Dosage Form | Tablet | IV infusion |
| Dosage Strength | 90 mg | 15 mg |
| Batch #. | 2000106212 | 2000106342 |
| Administration | Once-daily | 30 min infusion (0.1 mg/mL at 300 mL/h) |

**Sampling Times (PK, plasma)**

- Oral: 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 72 h
- IV: Pre-dose, 0.25, 0.5 (end of infusion), 0.67, 0.83, 1, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 72 h.

**Analytical Method:** The performance of the analytical method is acceptable. Yes ☑ No ☐

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 12/1/0 |
| Age [Median (range)] | 31.5(22-45) |
| Male/Female | 12/0 |
| Race (Caucasian/Black/Asian/other) | 1/9/0/2 |

**Results**

The absolute bioavailability of ticagrelor is 36% (range 25.4-64.0) as shown in the table below:

| | N | IV | Oral | Mean Ratio | 95% CI |
|---|---|---|---|---|---|
| Dose-Normalized AUC (ng h/mL mg) | 11 | 70.6 | 20.1 | 0.36 | 0.3 – 0.42 |

AR-C124910XX/ ticagrelor percent ratio is shown in the table below:

| | Oral | IV |
|---|---|---|
| AUC | 53.0 | 17.3 |
| Cmax | 35.6 | 3.7 |

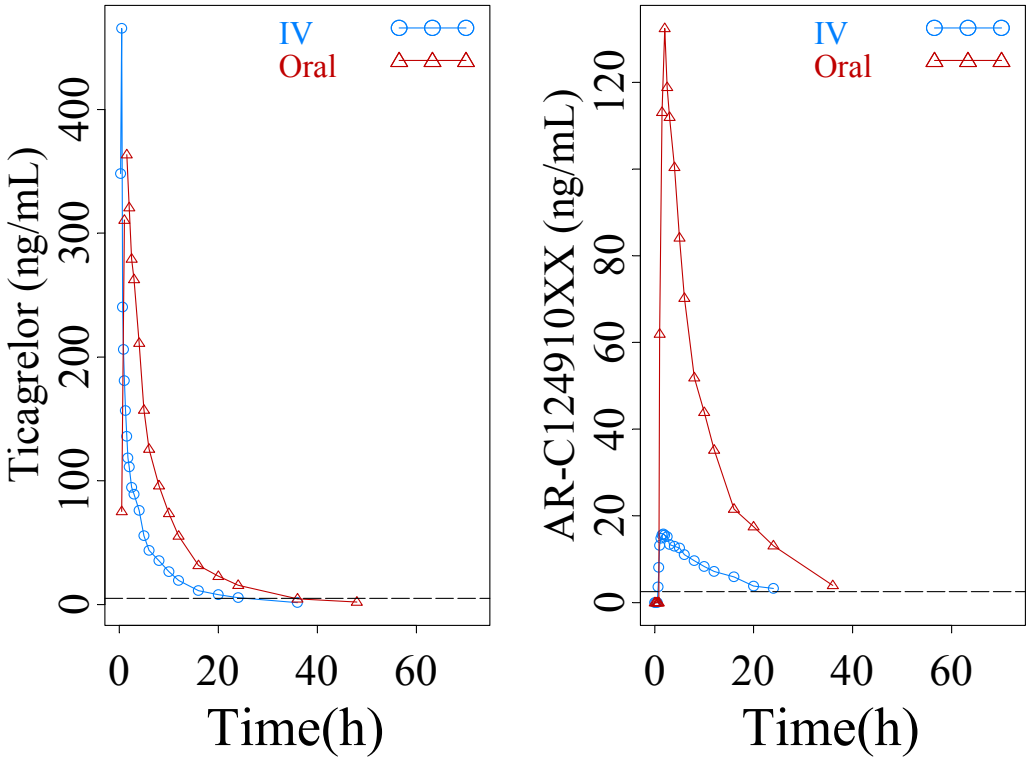



**Figure 1.** Plasma concentration profile of ticagrelor and its metabolite, dashed line represent limit of quantification. Values Represent mean (n =11).

| **Site Inspected** | |
|---|---|
| **Requested:** Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☐ |
| **Safety** | |
| ▪ Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA | |
| **Conclusion** | |
| ▪ Ticagrelor absolute BA is 36%.<br>▪ Ticagrelor undergoes extensive first order metabolism | |
| **Comments** | |
| Three subjects have shown secondary peak for both ticagrelor and AR-C124910XX as shown in the Figure 2, which is suggestive of enterohepatic recirculation of ticagrelor. | |

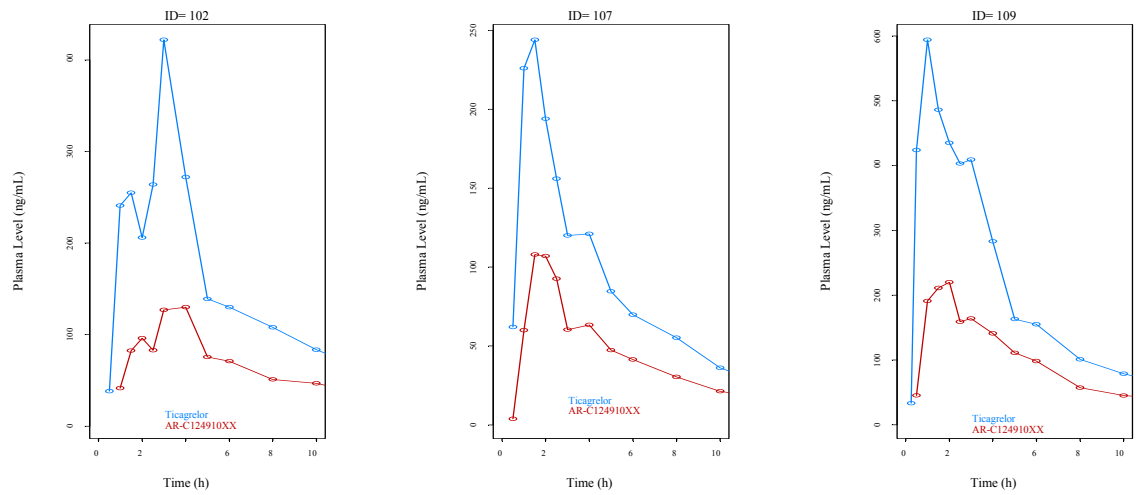



**Figure 2.** Plasma profile of ticagrelor and AR-C124910XX in 3 subjects with secondary peak.

## 2. Food Effect

| **Report #** D1530C00033 | **Study Period**: 03/08/2005 – 04/23/2005 | EDR Link |
|---|---|---|

| | |
|---|---|
| **Title** | An open-label, randomized, two-cohort, two-period, cross-over study to assess the effect of food on phase 3 tablets containing non-micronized and micronized AZD6140 in healthy male and female volunteers |

**Study Design**

☑ Food Effect

Single-Center Single-Dose Randomized Open-Label Cross-Over 2-Period 2-Cohort Healthy Vonuteers

| | |
|---|---|
| **Screening:** ≤ 21 days | **Washout:** ≥7 days, outpatient |
| **Period 1/2** | 4 days, Inpatient stay ☑Y ☐ N: |

**Treatments:** (Active Ingredient: Ticagrelor)

| Formulation | **FDN319** (Micronized) | **FDN318** (Non-Micronized) |
|---|---|---|
| Dosage Form/Strength | Tablets (90 mg) | Tablets (90 mg) |
| Dose Used in the Study | 270 mg (3 x 90 mg) | 270 mg (3 x 90 mg) |
| Batch #. | 05-000363AZ | 05-000358AZ |
| To be Marketed Formulation | Yes ☑ No ☐ | Yes ☑ No ☐ |
| Highest Strength Available | Yes ☑ No ☐ | Yes ☑ No ☐ |

Meal used meets the FDA Guidance Recommendations: Yes ☑ No ☐

**Sampling Times (PK, plasma)**
Pre-dose, 0.5, 1,1.5,2,2.5,3,4,5,6,8,10,12,18,24,36,48,72 h

**Analytical Method:** The performance of the analytical method is acceptable Yes ☑ No ☐

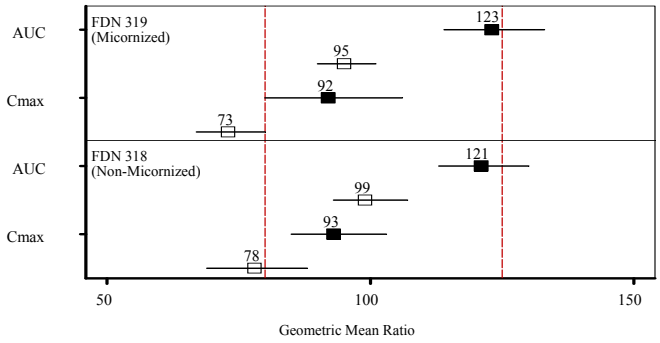
**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| Formulation | **FDN319** | **FDN318** |
|---|---|---|
| Randomized/Completed/ Discontinued Due to AE | 26/24/0 | 26/22/0 |
| Age [Median (range)] | 32.0 (18-45) | 38.0 (21-45) |

| | | |
|---|---|---|
| Male/Female | 19/7 | 23/3 |
| Race (Caucasian/Black/Asian/other) | 2/5/0/19 | 2/2/0/22 |

**Results**




**Site Inspected**

| | |
|---|---|
| **Requested:** Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☑ |

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

**Conclusion**

When administered with food:

1. Ticagrelor AUC significantly increased by 23% and 21% for the micronized and non-micronized formulations, respectively.
2. Ticagrelor $C_{max}$ significantly decreased by 7% and 8% for the micronized and non-micronized formulations, respectively.
3. AR-C124910XX AUC was not affected, however, Cmax was significantly reduced by 27% and 22% for the micronized and non-micronized formulations, respectively.

**Comments**

Ticagrelor can be administered with and without food.

## 3. Clopidogrel BE

| | | |
|---|---|---|
| **Report #** D1530C00020 | **Study Period** 05/21/2004 – 10/06/2004 | EDR Link |
| **Title** | An open label, randomized, three-way crossover study in healthy volunteers to assess the bioequivalence of over-encapsulated European clopidogrel (Plavix®) tablets and European and US source plain, intact clopidogrel (Plavix®) tablets to support blinded comparator studies with AZD6140 | |

**Study Design**

| | |
|---|---|
| ☑ Bioequivalence | ☐ Bioavailability |

Multiple-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Vonuteers

| | |
|---|---|
| **Screening:** ≤ 21 days | **Washout:** ≥14 days, outpatient |
| **Period 1/2/3** | 7 days, Inpatient stay ☑Y ☐ N: |

**Treatments:** (Active Ingredient: Clopidogrel " Plavix®")

| | Test 1 | Test 2 | Reference |
|---|---|---|---|
| Dosage Form | Over-encapsulated Tablets European Source | Tablets US Source | Tablets European Source |
| Dosage Strength | 75 mg | 75 mg | 75 mg |
| Batch #. | P6945 | P6941 | P6981 |
| Administration | Day 1: 4 x 75 mg clopidogrel dosage form<br>Day 2-6: 1 x 75 mg clopidogrel dosage form | | |

**Sampling Times (PK, plasma)**
Day 6: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24 h

**Analytical Method**

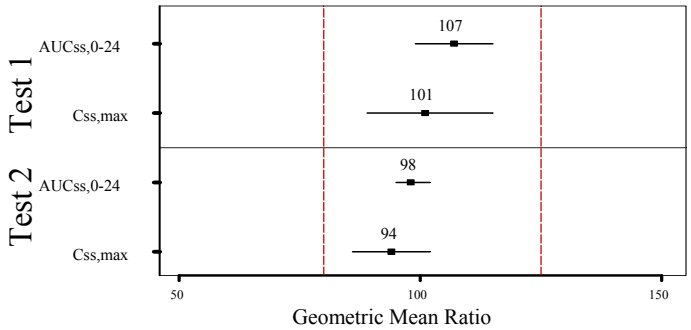
| Analyte | Method | Matrix | Range | Performance | Validation |
|---|---|---|---|---|---|
| Clopidogrel Carboxylic Acid Metabolite | LC-MS/MS | Plasma | 5 – 5000 ng/mL | Acceptable | Acceptable |

**Statistical Method:** ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

**Study Population :**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 54/51/ |
| Age [Median (range)] | 27.0 (18 -45) |
| Male/Female | 54/0 |
| Race (Caucasian/Black/Asian/Hispanic/other) | 40/12/1/0/1 |

**Results**




**Site Inspected**

**Requested:** Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☐

**Safety**

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- One subject discontinued from the study because of tonsillitis of mild intensity while receiving the over-encapsulated tablet during Period 2.

**Conclusion**

- The over-encapsulated clopidogrel tablets and USA source clopidogrel tablets are equivalent to the European source clopidogrel tablet.

**Comments**

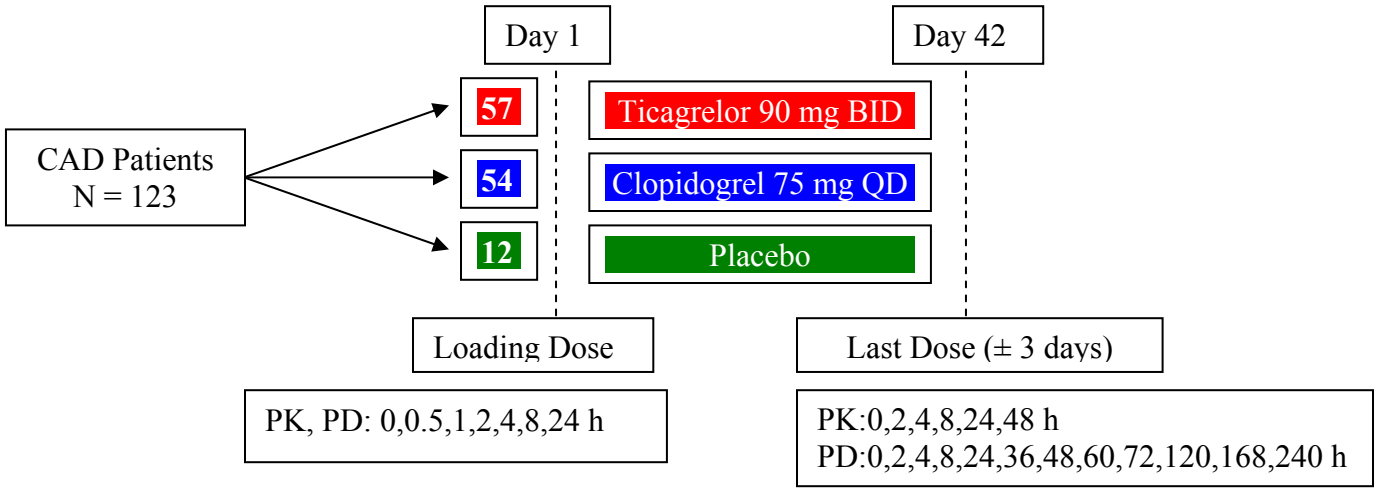
This study confirms the validity of using over-encapsulated clopidogrel tablets in other studies to comply with blinding studies requirement.

# VI. Pharmacodynamics

## 1. Onset Offset

| **Report #** D5130C00048 | **Study Period** 10/17/2007 – 03/05/2009 | EDR Link |
|---|---|---|
| **Title** | A multi-center, randomized, double-blind, double-dummy parallel group study of the onset and offset of the antiplatelet effects of AZD6140 compared with clopidogrel and placebo with aspirin as background therapy in patients with stable coronary artery disease with additional detailed assessment of cardiopulmonary function. | |

- **Objective:** To determine the onset and offset of antiplatelet effect of ticagrelor compared to clopidogrel on ASA background.
- **Study Design:** This was a multi-centre, double-blind, double-dummy, randomized, parallel groups in patients with stable coronary artery disease (CAD).




Loading Dose: Ticagrelor 180 mg in the morning and 90 mg in the evening; clopidogrel 600 mg in the morning. All patients were on ASA background of 75-100 mg. Patients only took the morning dose on the last day of the study.

- **Treatments**
  1. Aspirin: 75 mg IR tablets.
  2. Ticagrelor: 90 mg IR tablets (Lot #. 06-010163AZ, KA511, KD517).
  3. Clopidogrel: 75 mg IR tablets over-encapsulated (Lot #. A06317, A07340, A08025)
- **Study Population:**
  - Stable CAD population
  - Patients with a history of congestive heart failure, COPD, asthma, interstitial lung disease, known pulmonary diseases, and taking strong CYP 3A inhibitors were excluded.
  - The treatment groups were balanced.

| Treatment Group | Ticagrelor | Clopidogrel | Placebo |
|---|---|---|---|
| N/ Completed/ Discontinued due to AE | 57/52/4 | 54/51/0 | 12/11/1 |
| Age, Median (Range) | 64(41-79) | 65(42-83) | 64.5(44-79) |
| Male/Female | 43/14 | 40/14 | 10/2 |
| Race (White/Black/Asian/Other) | 51/4/1/1 | 48/5/1/0 | 9/3/0/0 |

## Results- Pharmacokinetics

| Parameter | Ticagrelor Day 1 | Ticagrelor Day 42 | AR-C124910XX Day 1 | AR-C124910XX Day 42 |
|---|---|---|---|---|
| $T_{max}$ (h) * | 2.0(0.92-23.92) | 2.0 (0.00-4.17) | 2.0 (0.92-24.17) | 2.1 (0.00-8.00) |
| $C_{max}$ (ng/mL) | 1197 (39.5) | 733 (57.8) | 243(40.2) | 210(45.7) |
| $AUC_{0-8}$ (ng.h/mL) | 5539(36.8) | 4130(59.4) | 1254(39.3) | 1325(42.4) |
| $t_{1/2}$(h) | | 9.8 (5.6-16.5) | | 12.4(7.3-22.8) |
| Metabolite: parent $C_{max}$ ratio *◊ | | | 21(15.5-26) | 30(21.4-37.3) |

Values represents geometric mean (%CV), * Median (range), ◊ Reviewer Calculated

## Results- Pharmacodynamic-Onset

- The **onset** of effect was evaluated by comparing % inhibition of platelet aggregation (%IPA) (final extent) induced by 20µM ADP at 2-hours after 1st dose.
- **Statistical Analysis:**
  - Time point comparison: Wilcoxon rank sum test
  - Parameter comparison: ANCOVA model with fixed-effect terms for treatment, centre, centre by- treatment interaction, and baseline platelet aggregation as covariates.

Figure 1 depicts the %IPA (final extent) vs. time for the three treatment groups. Ticagrelor % IPA was statistically significant ($p < 0.0001$, Wilcoxon rank sum test) from clopidogrel at all time points. Similar results ($p < 0.05$) were obtained with 20 µM ADP %IPA (maximum extent), 5 µM ADP %IPA (maximum and final extent), and 2 µg/mL collagen induced IPA (maximum and final extent).

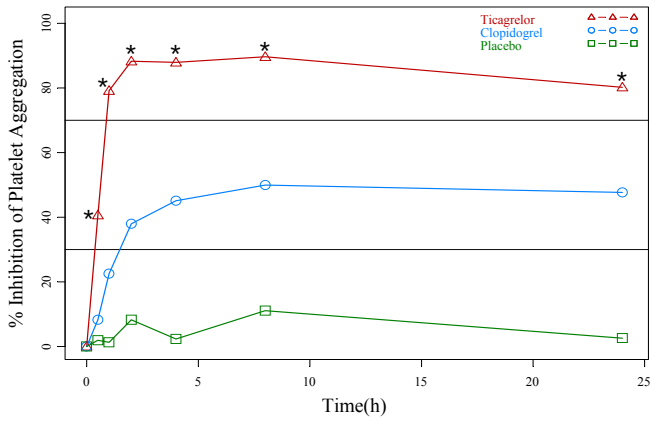



**Figure 1.** %IPA (Final Extent) induced by 20 µM ADP following the administration of ticagrelor, clopidogrel, and placebo on ASA background. Values represent mean. * indicates significant difference ($p < 0.0001$) using Wilcoxon sum rank test.

$\%IPA_{max}$ was greater in the ticagrelor group compared to clopidogrel group. Time to $\%IPA_{max}$ ($TIPA_{max}$) was shorter in the ticagrelor group compared to clopidogrel. The differences were statistically significant except for the $TIPA_{max}$ maximum extent difference.

| | | Ticagrelor | | Clopidogrel | | Ticagrelor-Clopidogrel | |
|---|---|---|---|---|---|---|---|
| | Extent | N | LS Mean | N | LS Mean | Estimate | 95 % CI |
| **20 µM ADP induced Platelet Inhibition** | | | | | | | |
| $\%IPA_{max}$ | Final | 54 | 95.20 | 50 | 60.39 | 34.8 | 25.7 – 43.9 |
| | Maximum | | 73.46 | | 39.93 | 33.5 | 25.7 – 41.3 |
| $TIPA_{max}$ (h) | Final | 54 | 3.96 | 50 | 8.80 | -4.8 | -7.3 – -2.4 |
| | Maximum | | 6.19 | | 7.36 | -1.2 | -3.7 – 1.39 |

**Notes:**

1. The sponsor definition of onset (%IPA at 2 hours post-dose) reflects the magnitude of %IPA and not the time to effect. In both ticagrelor and clopidogrel groups, IPA was observed at 0.5 h which indicates both starts exerting effect on platelets at the same time, although the %IPA is higher and statistically significant in the ticagrelor group.
2. $TIPA_{max}$ which better reflects the onset of effect was statistically significant between the two groups at final extent and not at maximum extent. To resolve the conflicting results a Wilcoxon Sign-Rank test was performed to evaluate the difference between 2, 4, and 8 measurements within each treatment group (final and maximum extent). In ticagrelor group, the three measurement where not statistically significant from each other (final and maximum extent) while in the clopidogrel the three measurement were statistically significant from each other. This indicates that ticagrelor reaches its maximum effect on PA within 2 hours of administration where clopidogrel takes longer time.
3. To further confirm the conclusion, the %IPA measurements (0, 0.5, 1, 2, 4, and 8 h) at onset were fitted to the following equation $\%IPA=100\ T/(TIPA_{50}+T)$, where T is time in hours, TIPA50 is time to reach 50% of maximum effect. Results have shown that TIPA50 are significantly different between the two groups as shown in the table below.

| | Final Extent | | Maximum Extent | |
|---|---|---|---|---|
| | **Ticagrelor** | **Clopidogrel** | **Ticagrelor** | **Clopidogrel** |
| $IPA_{50}$ | 0.5 | 4.3 | 1.3 | 10.0 |
| 95% CI IPA50 | 0.38 to 0.54 | 3.5 to 5.0 | 1.1 to 1.4 | 8.5 to 11.6 |

**Results-Pharmacodynamic-Offset**

- **Importance:** Patients taking antiplatelet agents must frequently undergo elective surgical procedures (e.g. PCI), requiring adequate platelet function to decrease risk of bleeding events related to the procedure. Thus, an antiplatelet agent with a faster offset (and greater or equal platelet inhibition) will provide a clear clinical benefit.
- **Offset** of effect was evaluated based on the slope of IPA (20µM ADP induced, Final Extent) effect curve between 4 and 72 hours post the last dose.
- **Statistical Analysis:** A random coefficients model, which included terms for treatment, time, centre, treatment-by-time interaction, centre-by-treatment interaction, and random effects for patient and patient-by-time interaction. Difference of the slopes and 95% CIs for primary comparisons of interest (ticagrelor versus clopidogrel) were calculated

I. 20 μM ADP induced platelet aggregation

Figure 2 depicts the mean %IPA following the administration of the last dose of the test drug. There was a statistically significant difference ($p \leq 0.0001$ in Wilcoxon rank sum test, 95% CI of the difference (ticagrelor-clopidogrel) does not contain zero in ANCOVA) between ticagrelor and clopidogrel groups in %IPA at the first four measurements (pre-dose, 2, 4, and 8 h post-dose) with higher %IPA observed in the ticagrelor group (Final and Maximum extent). In Wilcoxon test, clopidogrel group produced statistically significant higher % IPA at the 120 h measurement (final extent) and 120 h and 168 h measurement (Maximum Extent). In ANCOVA analysis, ticagrelor produced statistically significant higher %IPA at 24 h (Maximum Extent), and statistically significant lower %IPA at the 72 h measurement (Final Extent) and the 120 h measurement (Final and Maximum extent).

Analysis of the offset curve (4h -72h) showed statistically significant difference in the mean slope between ticagrelor and clopidogrel groups, as shown in the table below. Results are based on the random coefficient linear model with terms for treatment, time, centre, treatment-by-time interaction, and centre by treatment interaction, and random effects for patient and patient-by-time interaction.

| | **Ticagrelor (N=54)** | | **Clopidogrel (N=50)** | | **Difference of mean slope** | | |
|---|---|---|---|---|---|---|---|
| | **Intercept** | **Slope** | **Intercept** | **Slope** | **Estimate** | **95% CI** | **P-value** |
| Final extent | 94.00 | -1.037 | 71.84 | -0.482 | -0.555 | -0.705- -0.404 | < 0.0001 |
| Maximum extent | 59.78 | -0.735 | 41.66 | -0.289 | -0.446 | -0.599 - -0.239 | < 0.0001 |

The mean $IPA_{max}$ was higher and the $TIPA_{max}$ was shorter in the ticagrelor group than the clopidogrel group after 6 weeks of multiple dosing. The differences were statistically significant except for TIPAmax (final extent) as shown in the table below (values represent LS means).

| | **Extent** | **Ticagrelor** | **Clopidogrel** | **Ticagrelor-Clopidogrel** | **95%CI** |
|---|---|---|---|---|---|
| $IPA_{max}$ (%) | Final | 92.4 | 71.7 | 20.7 | 11.2 - 30.3 |
| | Maximum | 70.4 | 46.4 | 24.0 | 15.8 - 32.2 |
| $TIPA_{max}$ (h) | Final | 3.0 | 7.3 | -4.3 | -6.7 - 1.9 |
| | Maximum | 3.9 | 8.4 | -4.5 | -7.13 - -1.8 |

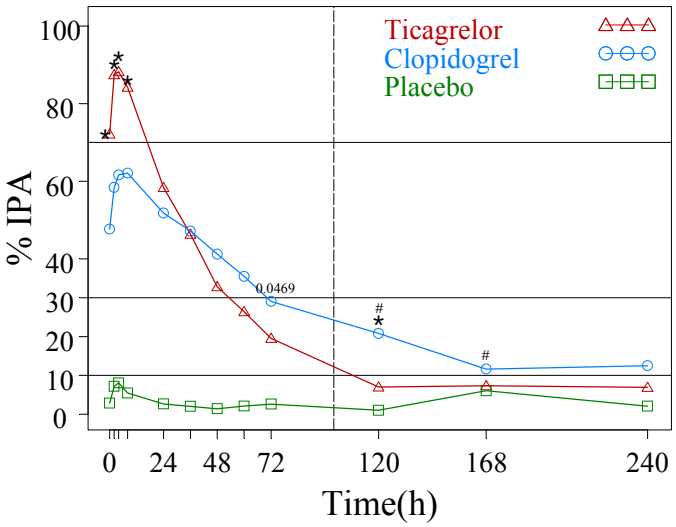



**Figure 2.** %IPA induced by 20 µM ADP following the administration of the last dose of ticagrelor, clopidogrel, and placebo on ASA background. Values represent mean. * indicates significant difference ($p < 0.05$) comparing ticagrelor to clopidogrel. Points in the ticagrelor and clopidogrel groups left to the dashed lines are significantly different from placebo ($p < 0.05$). Points to the right of the dashed lines are not significantly different from placebo unless designated by #.

**Note:** %IPA in the ticagrelor and placebo group were not statistically significant starting on Day 5, while %IPA was statistically significant from placebo at all measurement except for Day 10 measurement (life span for the platelet is 10 days). The data suggest a faster offset of effect in the ticagrelor group.

II. 2 µg/mL collagen induced platelet inhibition (IPA)

Analysis of the offset curve (4h -72h) showed no statistically significant difference in the mean slope between ticagrelor and clopidogrel groups. ANCOVA analysis showed no statistically significant difference between the two treatment groups at all points except the pre-dose measurement with higher %IPA in the ticagrelor group.

## Safety

There was no death or serious adverse events. The most common adverse events (>10%) were dyspnea (35.1%), increased tendency to bruise (15.8%), and contusion (10.5%) for ticagrelor group; and dyspnea (11.1%) for clopidogrel group. The majority of AEs were of mild or moderate intensity. Bleeding-related AEs occurred more frequently in the ticagrelor group (28.1%) than in the clopidogrel (13.0%) and placebo (8.3%) groups. All of the bleeding events were classified as minor (1 event in the ticagrelor group) or minimal bleeds. No major bleeding events were reported.

Three out of the four patients in the ticagrelor group discontinued due to dyspnea and one due to sleep disorders. One patient in the placebo group discontinued due to allergic dermatitis.

## Conclusions

1. Ticagrelor is rapidly absorbed following the administration of the LD and maintenance dose, with rapid conversion to the active metabolite in CAD patients. $T_{max}$ and $C_{max}$ are comparable to those in healthy volunteers following the same dose.
2. The onset of action measured by 20 µM ADP induced %IPA is faster in ticagrelor compared to clopidogrel group.
3. The rate of offset of effect is faster in the ticagrelor group compared to clopidogrel group.
4. Patients missing one dose of ticagrelor (24 hours post-dose) will have IPA similar to patients on clopidogrel 24 hours post dose.

## Comments

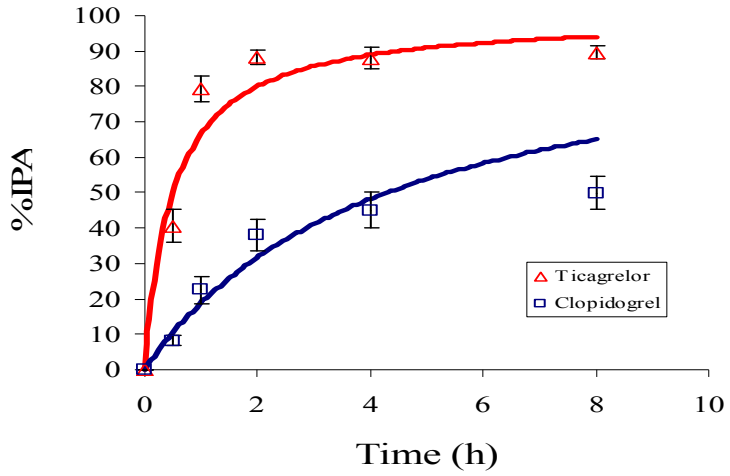
- The over-encapsulated clopidogrel tablets are bioequivalent to clopidogrel tablets (refer to review of study report #. D1530C00020).
- The analytical method used performance during study samples analysis is acceptable.

## Appendix-Re-analysis of onset data

- Wilcoxon Sign-Rank Test Analysis, values represent p-values for %IPA measurement Comparison.

| | Extent | 2 h – 4 h | 2h – 8h | 4h – 8h |
|---|---|---|---|---|
| Ticagrelor | Final | 0.3616 | 0.7440 | 0.7732 |
| | Maximum | 0.119 | 0.3602 | 0.0860 |
| Clopidogrel | Final | 0.0037 | 0.0002 | 0.0508 |
| | Maximum | 0.0211 | 0.0002 | 0.0046 |

- Onset data (0 – 8 h) were fit to the following equation %IPA=100 T/(TIPA$_{50}$+T), where T is time in hours, TIPA50 is time to reach 50% of maximum effect. The Figure below depicts the best fit lines, symbols represent mean ± S.E.



## 2. RESPOND

| **Report #** D5130C00030 | **Study Period** 05/19/2008 – 03/25/2008 | EDR Link |
|---|---|---|
| **Title** | A randomized, double-blind, outpatients, cross-over study of the anti-platelet effects of AZD6140 compared with clopidogrel in patients with stable coronary artery disease previously identified as clopidogrel non-responders or responders [Respond] | |

- **Objectives:**
  1. To investigate the effect of ticagrelor in clopidogrel non-responders
  2. To investigate the effects of switching directly between clopidogrel and ticagrelor (or vice versa) without a washout period in both clopidogrel responders and non-responders.
- **Study Design:**
- This was a multi-center (10 sites), double-blind, double-dummy, randomized, crossover study in patients with stable coronary artery disease (CAD). Treatment schemata are displayed in Figures 1 and 6. All patients were on a background of ASA (75-100 mg qd).
- Patients were classified as clopidogrel responders and clopidogrel non-responders based on platelet aggregation (PA) measurement (Maximum Extent using 20 µM ADP as agonist) at pre-dose ($PA_{Pre}$) measurement and at 6 and 8 h post ($PA_{post}$) a 300 mg single dose of clopidogrel 2 to 4 weeks prior receiving the first dose of the study drug.

  If $|PA_{pre}-PA_{post}| \leq 10\%$ ➔ Non-Responders

  If $|PA_{pre}-PA_{post}| > 10\%$ ➔ Responders
- All patients received a loading dose (LD) on Day 1 of each treatment period. Ticagrelor LD was 180 mg and clopidogrel LD was 600 mg.
- **Study Population:** The two groups were comparable in terms of gender, race, ethnic group, age, height, weight, BMI, baseline creatinine, HTN, diabetes mellitus, dyslipedemia, and concomitant medications. There were more current smokers (26.4%) in the responder group compared to the non-responder group (4.9%).

| Treatment Group | Non-Responder | Responder |
|---|---|---|
| N/ Completed/ Discontinued due to AE | 41/34/5 | 57/54/1 |
| Age, Median (Range) | 66(45-81) | 64(45-85) |
| Male/Female | 28/13 | 48/9 |
| Race (White/Black/Asian/Other) | 48/5/1/0 | 51/4/1/1 |

- **Treatments:**
  1. Ticagrelor: 90 mg IR tablets (Lot # KDN509, KDN516, KDN518).
  2. Clopidogrel: 75 mg IR over-encapsulated tablets (Lot #. A07316, A07165)

### Non-Responders

**I. Design**

Study schema in non-responders is displayed in Figure1. The numbers represents the number of patients who were enrolled in each arm.

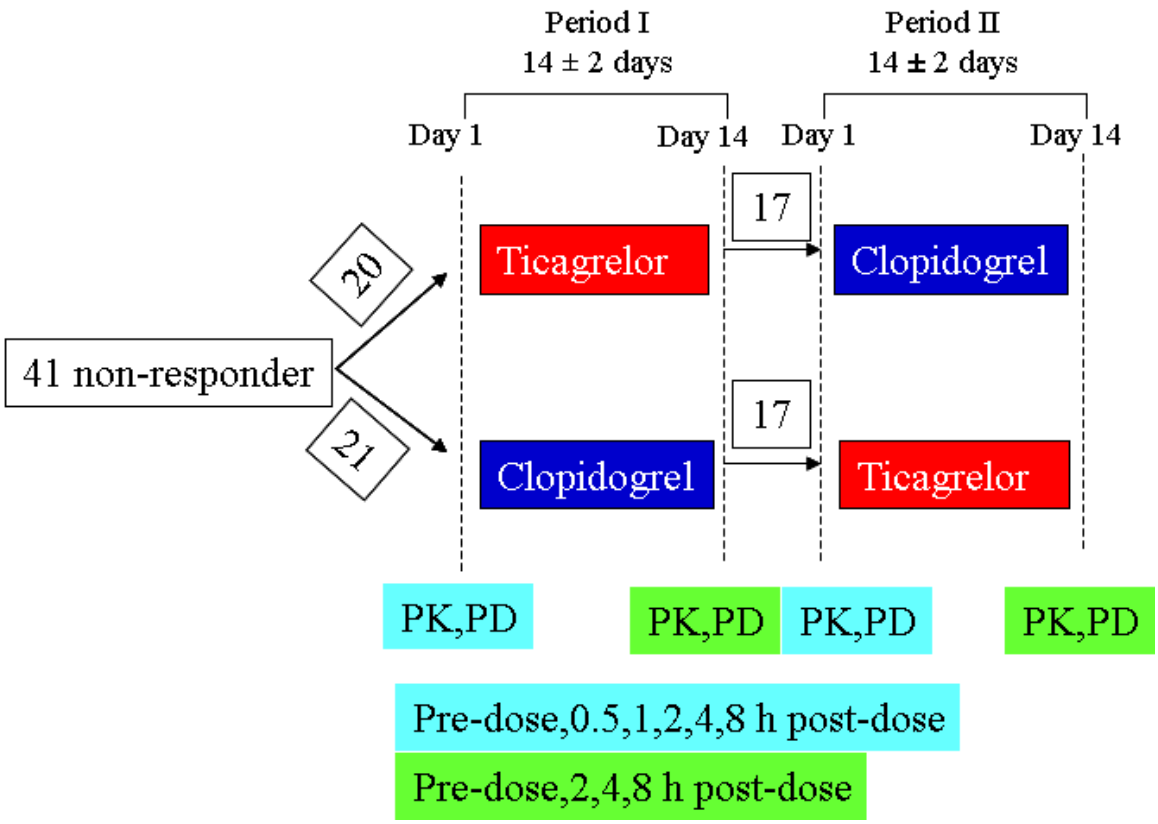



**Figure 1.** Study schema in clopidogrel non-responders.

**II. Pharmacokinetics**

Ticagrelor and AR-C124910XX pharmacokinetic parameters are not altered by prior administration of clopidogrel as shown in Figures 2 and 3.

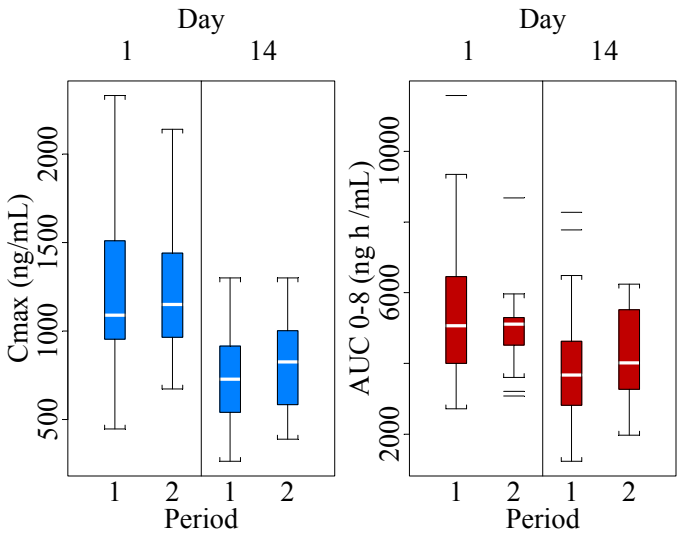



**Figure 2.** Ticagrelor PK parameters in clopidogrel non-responder group.

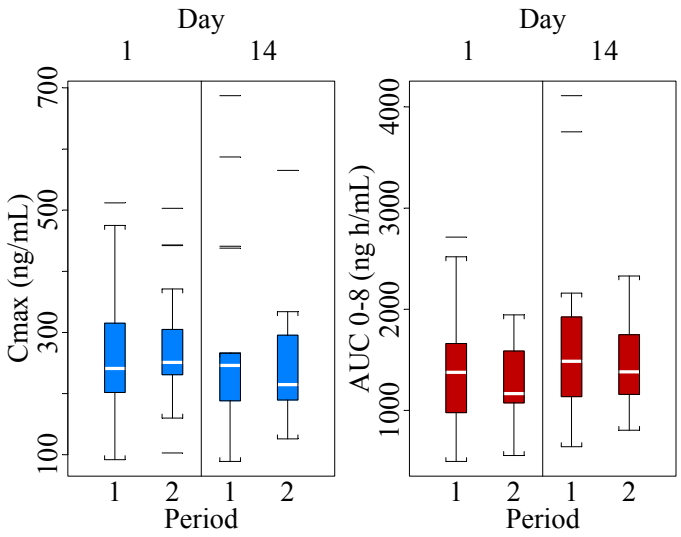



**Figure 3.** AR-C124910XX PK parameters in clopidogrel non-responder group.

**III. Pharmacodynamic**

Sponsor pre-specified statistical analysis was to conduct McNemar's test to compare the proportion of patients who responded to ticagrelor or clopidogrel following steady-state dosing based on IPA measurements (20 µM ADP final extent) taken 4 hours after their last dose (following 14 days of dosing). In the analysis, each patient was treated as a matching pair for each treatment. Summary of analysis of %IPA on Day 14-4 h (Period 1 and 2) is shown in the table below. There is no statistically significant difference in the proportion of patients, classified as clopidogrel non-responders, who responded to ticagrelor or clopidogrel treatment after 14 days of steady-state treatment.

| Response | Ticagrelor (N=32) | | | Clopidogrel (N=32) | | | T-C | | McNemar's Test | |
|---|---|---|---|---|---|---|---|---|---|---|
| Criteria | N | % | 95%CI | N | % | 95%CI | % | 95%CI | N (Pairs) | p-value |
| %IPA>10% Final Extent | 32 | 100 | 89.1-100 | 30 | 93.8 | 79.2-99.2 | 6.1 | -5.4-17.5 | 31 | 0.157 |

**Note:** Non-responders to clopidogrel treatment classification was based on PA ≤10% (Maximum Extent), while the response to treatment analysis was based on %IPA >10% (Final Extent). When the statistical analysis was done using maximum extent data the difference (~ 15%) is statistically significant. Also the sponsor performed a post-hoc analysis to look at proportion of patients with > 30% and 50% increase in %IPA when switched form clopidogrel to ticagrelor. The table below displays analysis of %IPA and PA on Day 14-4 h in the non-responder group.

| Response Criteria | Difference (T-C) % | 95% CI | McNemar's Test N (pairs) | p-value |
|---|---|---|---|---|
| **20uM ADP Final Extent %IPA** | | | | |
| %IPA > 10% | 6.1 | -5.4 - 17.5 | 31 | 0.157 |
| %IPA > 30% | 36.4 | 17.6 - 55.1 | 31 | <.001 |
| %IPA > 50% | 54.5 | 34.3 - 74.8 | 31 | <.001 |
| **20uM ADP Maximum Extent %IPA** | | | | |
| %IPA > 10% | 15.2 | 0.8 -29.6 | 31 | 0.025 |
| %IPA > 30% | 66.7 | 48.7 - 84.6 | 31 | <.001 |
| %IPA > 50% | 48.5 | 29.6 - 67.3 | 31 | <.001 |
| **20uM ADP Final Extent PA** | | | | |
| Decrease from baseline > 10% | 12.1 | -1.4 - 25.7 | 31 | 0.046 |
| Decrease from baseline > 30% | 48.5 | 28.0 - 69.0 | 31 | <.001 |
| Decrease from baseline > 50% | 48.5 | 29.0 - 68.0 | 31 | <.001 |
| **20uM ADP Maximum Extent PA** | | | | |
| Decrease from baseline > 10% | 24.2 | 8.0 -40.5 | 31 | 0.005 |
| Decrease from baseline > 30% | 60.6 | 41.8 - 79.4 | 31 | <.001 |
| Decrease from baseline > 50% | 12.1 | 1.0 -23.3 | 31 | 0.046 |

The sponsor pre-specified analysis was not appropriate since half of the patients classified as responders will not be classified as though if the final extent measurement was used, as shown in Figure 4. The reviewer agrees with the sponsor (see table below) conclusion that clopidogrel non-responders will respond to anti-platelet therapy when switched to ticagrelor.

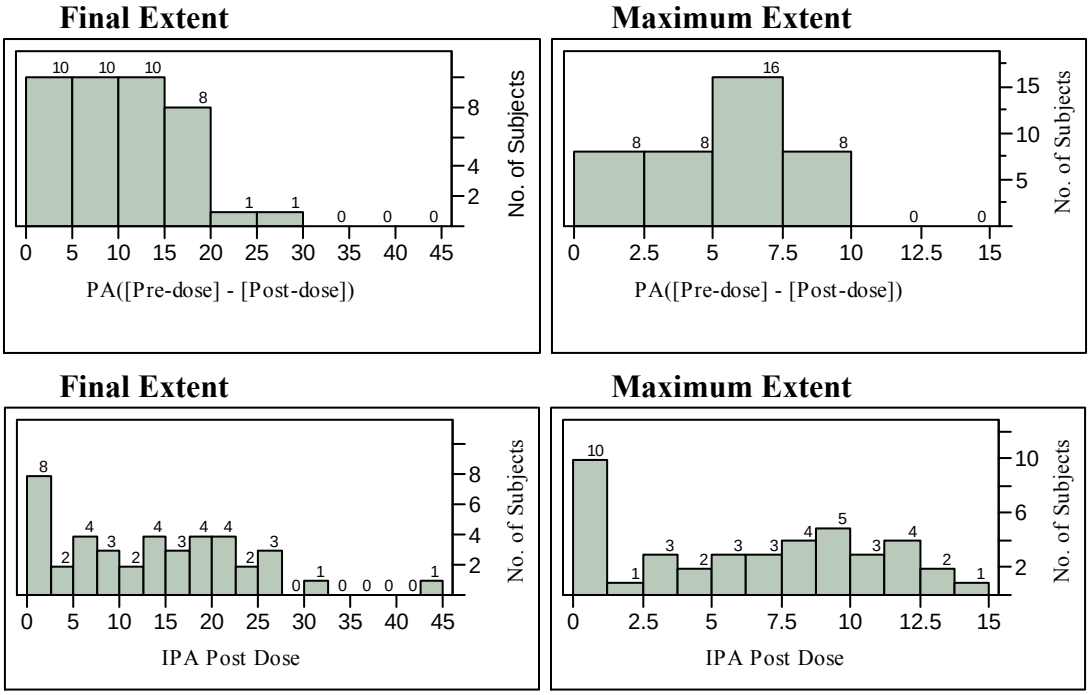



**Figure 4.** Distribution of clopidogrel non-responders at screening.

| Day 14 | Ticagrelor-Clopidogrel | |
|---|---|---|
| Time | LS mean | 95% CI |
| 0 hours | 33.4 | 26.7–40.2 |
| 2 hours | 36.6 | 29.8–43.4 |
| 4 hours | 34.5 | 27.7–41.3 |
| 8 hours | 26.6 | 19.9–33.3 |

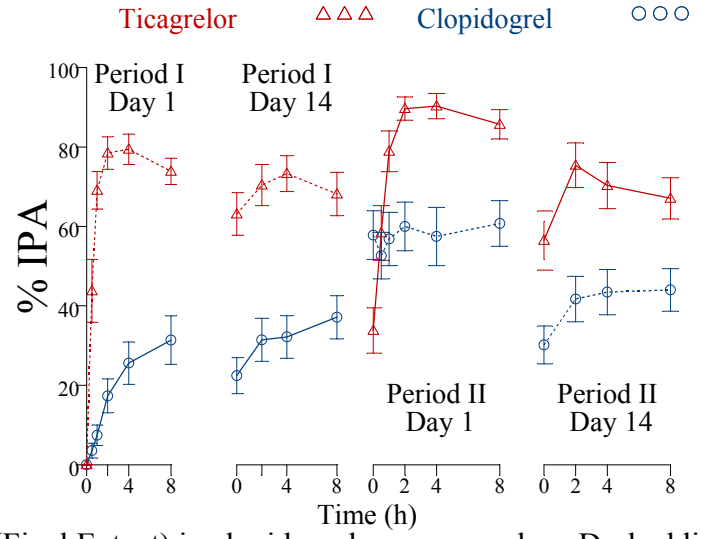



**Figure 5.** %IPA (Final Extent) in clopidogrel non-responders. Dashed lines represent ticagrelor to clopidogrel sequence, while solid lines represent clopidogrel to ticagrelor sequence.

**Responders**

## I. Design

Study schema in responders is displayed in Figure 6. The numbers represents the number of patients who were enrolled in each arm.

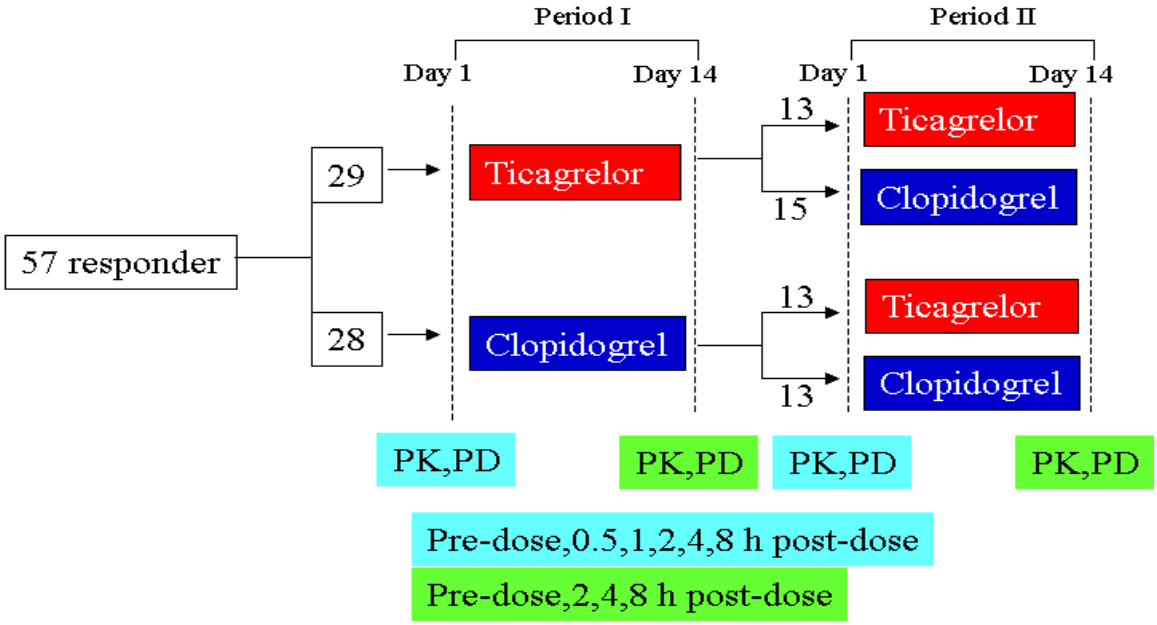



**Figure 6.** Study schema in clopidogrel responders.

## II. Pharmacokinetics

Clopidogrel administration for 14 days prior to ticagrelor administration did not alter the pharmacokinetics parameters of ticagrelor and AR-C124910XX (Figures 7 and 8). Period 1 data represent subjects who started ticagrelor therapy, while period 2 data represent subjects who were switched to ticagrelor after 14 days of clopidogrel therapy.

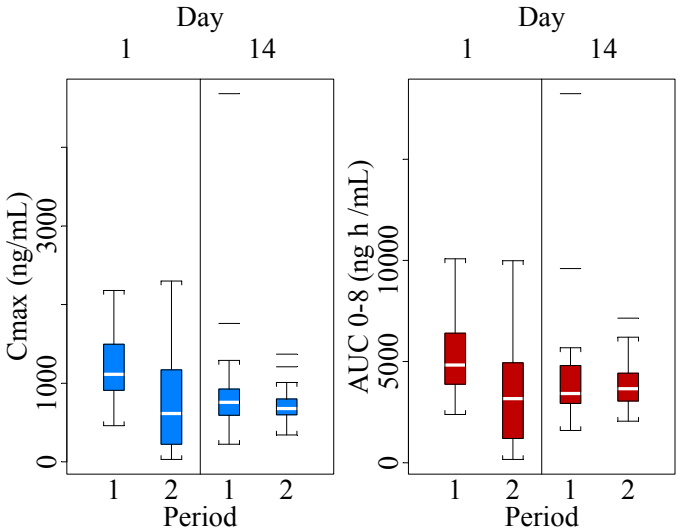



**Figure 7.** Ticagrelor PK parameters in clopidogrel responder group.

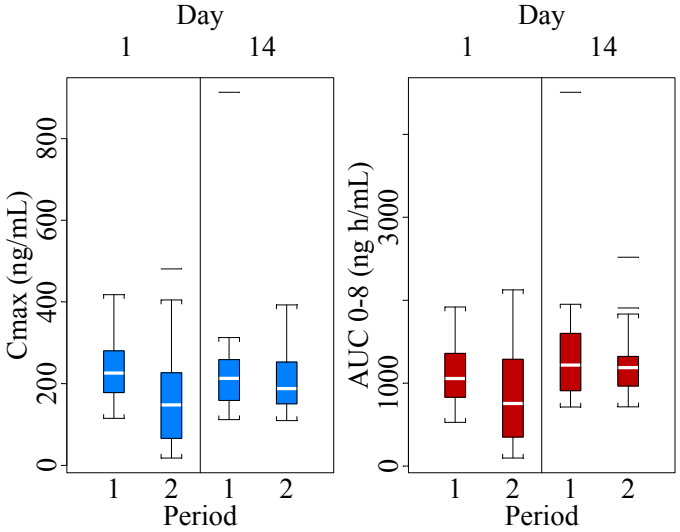



**Figure 8.** AR-C124910XX PK parameters in clopidogrel responder group.

## III. Pharmacodynamic

<u>I. ADP-induced platelet inhibition (IPA)</u>

Statistical Analysis: ANCOVA was applied to analyze PD parameters with a single outcome (i.e., 1 result per patient given a treatment). The effect of switching from one study drug to another study drug on an outcome was conducted using an ANCOVA model including a fixed-effect for centre (2 groups of study centers identified during blinded review), treatment, and

steady state result following the treatment in Period 1 as a covariate (baseline). The contrast of interest was ticagrelor-clopidogrel.

In the responder group and at 4 hours post-dose, patients switched from clopidogrel to ticagrelor showed a 17% increase in ADP induced %IPA at steady state, while patients switched from ticagrelor to clopidogrel showed a 30% reduction in ADP induced %IPA at steady states. Theses differences were statistically significant (Table below).

| | | Time(h) | T-C | 95% CI | | |
|---|---|---|---|---|---|---|
| CC vs. CT | Day 1 | 0 | 7.6 | -5.8 | - | 21 |
| | | 0.5 | 28.7 | 15.3 | - | 42 |
| | | 1 | 44.1 | 30.7 | - | 57.5 |
| | | 2 | 34.3 | 20.9 | - | 47.7 |
| | | 4 | 46 | 32.6 | - | 59.4 |
| | | 8 | 43.8 | 30.4 | - | 57.2 |
| | Day 14 | 0 | 9.1 | -4.7 | - | 23 |
| | | 2 | 14.7 | 0.7 | - | 28.8 |
| | | 4 | **16.8** | 2.9 | - | 30.7 |
| | | 8 | 19.3 | 5.4 | - | 33.3 |
| TT vs. TC | Day 1 | 0 | 20.5 | -2.2 | - | 43.1 |
| | | 0.5 | 12.7 | -10.1 | - | 35.5 |
| | | 1 | 4.1 | -18.8 | - | 27 |
| | | 2 | 5 | -17.6 | - | 27.7 |
| | | 4 | 1.4 | -21.3 | - | 24 |
| | | 8 | -1.6 | -24.2 | - | 21.1 |
| | Day 14 | 0 | 17.1 | -3.1 | - | 37.3 |
| | | 2 | 25.3 | 5.3 | - | 45.3 |
| | | 4 | **29.4** | 9.2 | - | 49.5 |
| | | 8 | 21.3 | 1.2 | - | 41.3 |

T: Ticagrelor, C: Clopidogrel, T-C: LS mean difference,

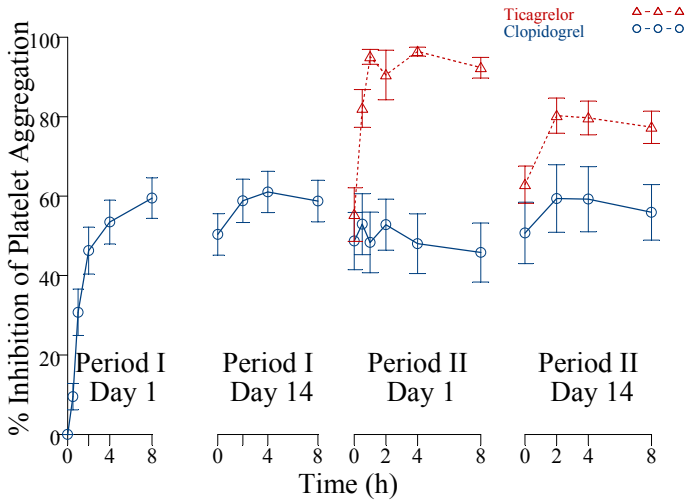



**Figure 9.** %IPA following the administration of ticagrelor in period 1. In period 2 half of the patients were switched to ticagrelor and half remained on clopidogrel.

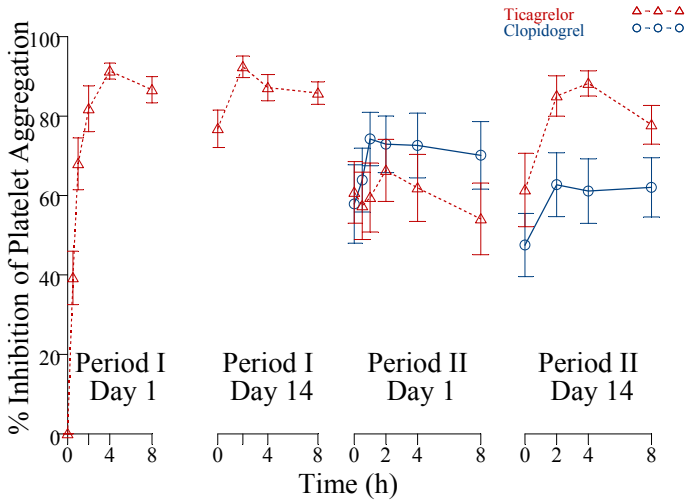



**Figure10** %IPA (final extent) following the administration of ticagrelor in period 1 in responder group. In period 2 half of the patients were switched to clopidogrel and half remained on ticagrelor. Values represent mean ± SE.

**Notes:**

1. Per sponsor, the drop in %IPA for patients in the TT sequence in likely due to a dip in plasma concentrations on Day 1 of Period 2 as they were administered placebo in the morning instead of ticagrelor (design fault).
2. When the pre-dose measurements on day 14 are compared, there is no statistically significant difference in the LS mean, this indicates that ticagrelor is superior to clopidogrel within the first 8 hours only.

**Safety**

Serious adverse events (SAE) occurred in four patients, 2 non-responders, and 2 responders:

- One death (non-responder) occurred on day 30 of follow-up after ticagrelor treatment and was not related (per sponsor) to study treatment.
- Four serious adverse events (myocardial infarction, hypotension, atrial fibrillation, and bradycardia) occurred during ticagrelor therapy.
- Four patients in the responder group discontinued the study due to GI hemorrhage, hypotension, dyspnea, and ECG T-wave inversion.
- One patient on the responder group discontinued the study due to sever bradycardia.

Bleeding: One major (non-responder) and 3 minor (1 non-responder, 2 responder) bleeding events occurred during ticagrelor treatment, and no bleeding events occurred during clopidogrel treatment.

Dyspnea: Two non-responder patients had dyspnea during switching of treatment. Most dyspnea episodes occurred early in the study, resolved without intervention, and did not result in discontinuation. The most common adverse events are summarized in the table below, n represents the number of patients:

| | **Ticagrelor (n)** | **Clopidogrel(n)** |
|---|---|---|
| **Non-Responder** | – Dyspnea (7)<br>– Increased tendency to bruise(3) | – Dyspnea (4)<br>– Dizziness(3) |
| **Responder** | – Dyspnea (6)<br>– Epistaxis(3) | – Dyspepsia (0)<br>– Nausea (4). |

## Conclusions

1. The PK of ticagrelor and its metabolite is not affected by prior administration of clopidogrel in both clopidogrel non-responder and responder groups.
2. Ticagrelor improves ADP induced %IPA in clopidogrel non –responders.
3. There is an apparent increase in ADP induced %IPA when responders are switched from clopidogrel to ticagrelor and an apparent decrease in ADP induced % IPA when responders are switched from ticagrelor to clopidogrel.
4. Switching between clopidogrel and ticagrelor did not produce any major adverse events.

## Comments

- The over-encapsulated clopidogrel tablets are bioequivalent to clopidogrel tablets (refer to review of study report #. D1530C00020).
- The analytical method used performance during study samples analysis is acceptable.
- Two patients (2.7%) in the non-responder group were indentified as poor CY2C19 metabolizer, 9 (32.1) as intermediate and 17 (60.7%) as extensive metabolizer. Due to the low number of poor metabolizer, a genomic oriented analysis was not performed.

## 3. Ticagrelor + ASA vs. Clopidogrel + ASA

| **Report #** D5130C05261 | **Study Period** 06/17/2003 – 09/09/2003 | EDR Link |
|---|---|---|
| **Title** | A double-blind, double-dummy, randomized, two-way crossover study to compare the pharmacodynamic effects of AZD6140 plus acetylsalicylic acid versus clopidogrel plus acetylsalicylic acid at steady state in healthy make and female volunteers | |

- **Objective:** To compare the extent of inhibition of platelet aggregation (IPA), prolongation of bleeding time, safety, and tolerability between ticagrelor with ASA and clopidogrel with ASA at steady state.
- **Study Design:** This was a single-centre, double-blind, double-dummy, randomized, 2-way crossover study in healthy volunteers.

| Group | Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| I | A (mg) | 300◊ | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| | T (mg) | | | | 200 | 200 | 200 | 200 | 200 | 200* |
| Washout Period: 14 days | | | | | | | | | | |
| II | A (mg) | 300◊ | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| | C (mg) | | | | 300◊ | 75 | 75 | 75 | 75 | 75 |

A: Aspirin QD, T: Ticagrelor BID, C: clopidogrel QD
*: AM dose only,◊: Loading Dose

- **Treatments:**
  3. Aspirin: 75 mg IR tablets (Lot #. X1468)
  4. Ticagrelor: 100 mg IR tablets (Lot #. P6426)
  5. Clopidogrel: 75 mg over-encapsulated tablets (Lot #. P6772)
- **Sampling Times:** All measurements are post AM dose. (P: Pre-dose)

| Day | <-2 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| PA | P | P | | 2 | P,2,4,12 | | | | | P,2,4,12,24 |
| BT | P | P | | 4 | P,4 | | | | | P,4,24 |
| PK | | | | | P,0.5,1,2,3,4,6,8,10,12 | | | P | P | P,0.5,1,2,3,4,6,8,10,12,18,24 |

PA: Platelet Aggregation, BT: Bleeding Time, PK: Pharmacokinetics

- **Study Population:** Healthy volunteers

| Treatment Group | |
|---|---|
| N/ Completed/ Discontinued due to AE | 16/16/0 |
| Age, Median (Range) | 33.5 (18 – 53) |
| Male/Female | 15/1 |
| Race (White/Black/Asian/Other) | 15/0/1/0 |

- **Analytical Method** (Study Samples Analysis)

| Analyte | Ticagrelor | AR-C124910XX |
|---|---|---|
| Method | LC-MS/MS | LC-MS/MS |
| Matrix | Plasma | Plasma |
| Performance | Acceptable | Acceptable |

## Results-Pharmacodynamic

I. ADP-induced platelet inhibition (IPA)

**Note:** Platelet aggregation (PA) was assessed using ADP (20 µM) or collagen (4 µg/mL). Both methods produced comparable results and only data from ADP-induced PA are presented in this review.

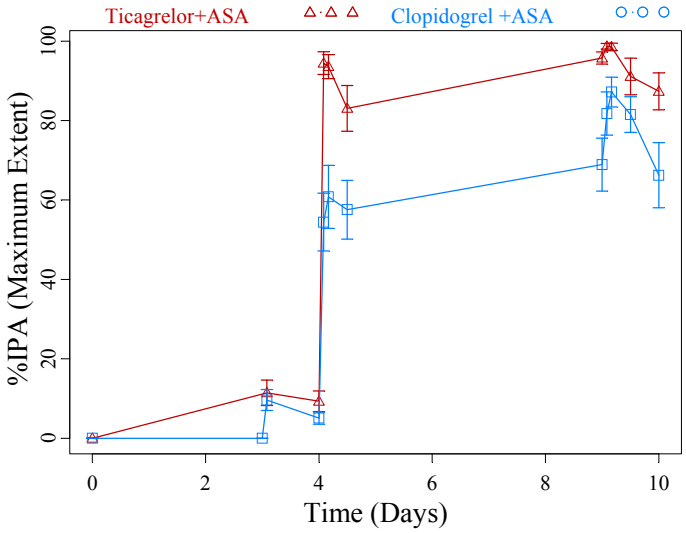



**Figure 1.** Mean ADP-induced platelet aggregation with ticagrelor clopidogrel on aspirin background. Values represent mean ± S.E.

II. Bleeding Time

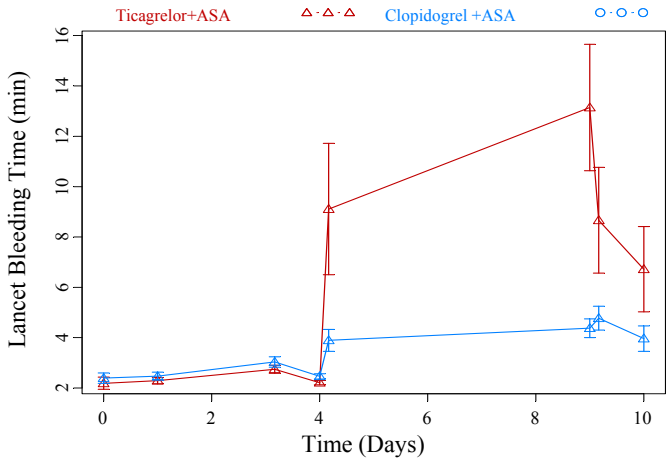



**Figure 2.** Individual lancet bleeding time vs. plasma concentration for ticagrelor and its metabolite.

## Safety

There was no death or serious AEs in the study.

## Conclusions

1. Ticagrelor plus ASA produced statistically significantly greater inhibition of ADP- and collagen-induced platelet aggregation relative to clopidogrel plus ASA.
2. Clopidogrel plus ASA did not prolong lancet bleeding time relative to ASA alone.
3. Ticagrelor plus ASA prolonged lancet bleeding time relative to ASA alone or clopidogrel plus ASA. Ticagrelor effect on bleeding time was higher at steady state compared to the first dose.
4. There is no apparent relationship between ticagrelor and AR-C1249010XX plasma concentration and lancet bleeding time.

## Comments

1. Ticagrelor dose used (200 mg bid) is more than twice the proposed 90 mg bid dose.
2. Subjects were not genotyped for there CYP2C9 metabolic status. Since the PD effect of clopidogrel depends on the formation of the active metabolite, the inclusion of poor metabolizers in the clopidogrel group will lead to lower observed %IPA.
3. The over-encapsulated clopidogrel tablets are bioequivalent to clopidogrel tablets (refer to review of study report #. D1530C00020).

# 4. Loading Dose

| **Report #** D5130C00029 | **Study Period** 09/03/2004 – 11/11/2004 | EDR Link |
|---|---|---|
| **Title** | A double-blind, randomized, 3-period cross-over study to compare the pharmacodynamics of 2 AZD6140 loading doses (270mg and 540 mg) with clopidogrel (Plavix®) 600 mg loading dose in healthy males anmd female subjects | |

- **Objective**: To compare ADP-induced platelet aggregation after 270 and 540 mg loading doses of ticagrelor 600 mg loading dose of clopidogrel.
- **Study Design**: This was single center, double-blind, randomized, 3-period crossover study in healthy volunteers with washout period of ≥ 14 days. The three treatment arms were:
  1. Ticagrelor 270 mg single dose.
  2. Ticagrelor 540 mg single dose.
  3. Clopidogrel 600 mg single dose.
- **Sampling Times**
  - PK: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 h post-dose.
  - PD: Pre-dose, 0.5, 1, 2, 4, 12, 24, 48, and 72 h post-dose
- **Treatments**
  1. Ticagrelor: 90 mg IR tablets (Lot #. 2000065918)
  2. Clopidogrel: 75 mg IR tablets ((Lot #. Not Available)
- **Study Population:** Healthy Volunteers

| N/ Completed/ Discontinued due to AE | 24/23/0 |
|---|---|
| Age, Median (Range) | 53.0 (25 – 62) |
| Male/Female | 9/15 |
| Race (White/Black/Asian/Other) | 2/0/0/22 |

## Results

Figure 1 displays 20 µM ADP induced %IPA following the administration of ticagrelor and clopidogrel. Ticagrelor produced higher $\%IPA_{max}$ at both doses than clopidogrel. The difference was statistically significant as see in the table below. The difference in $IPA_{max}$ between 540 mg ticagrelor and 270 mg ticagrelor was 1.5% (95%CI -0.4-3.5) and was not statistically significant.

| Ticagrelor Dose | N | $\%IPA_{max}$ (Ticagrelor-Clopidogrel) | |
|---|---|---|---|
| | | LS mean Difference | 95% CI |
| 270mg | 23 | 10.3 | 5.0-15.6 |
| 540 mg | 23 | 11.9 | 6.5-17.2 |

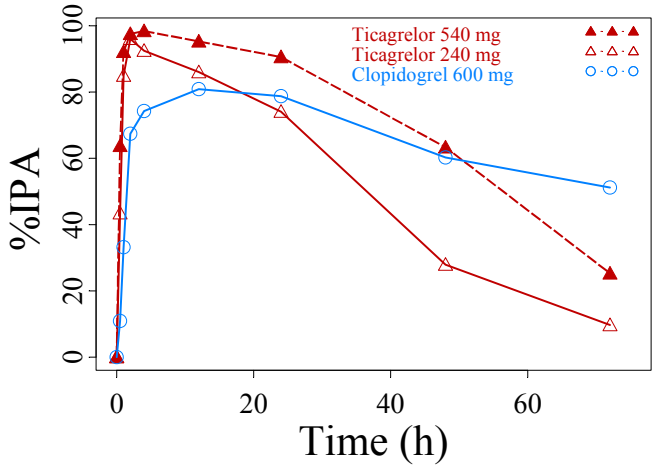



**Figure 1.** %IPA (20 µM ADP, Final Extent) following the administration of ticagrelor and clopidogrel in healthy volunteers. Values represent mean.

## Safety

There were no deaths or SAEs.

## Conclusions

1. Ticagrelor loading doses (270 and 540 mg) produced approximately 10% higher %IPA than clopidogrel loading doses (600 mg).
2. $IPA_{max}$ is comparable among ticagrelor 270 mg an d540 mg doses.

## Comments

- Pharmacogenomic data were collected but it is not clear whether an analysis was carried or not. This should not affect the conclusion of the study since most the subjects are Hispanic (n=22) who has less variation in CYP2C9 than Caucasian.
- PK data were obtained but were not included in this review since PK data in healthy volunteers were generated in other studies.
- The performance of the analytical methods is acceptable.

## 5. Uric Acid

| **Report #** D5130C00050 | **Study Period** 05/27/2008 – 07/08/2009 | EDR Link |
|---|---|---|
| **Title** | A randomized, double-blind, two-period, cross-over study to assess the effect of AZ1640 on uric acid levels in healthy male volunteers | |

- **Objective**: To evaluate the effect of ticagrelor on serum uric acid levels and excretion of uric acid in the urine.
- **Study Design**: This was single center, double-blind, randomized, 2-period, 2-way cross-over study in healthy volunteers. Subjects were admitted to the clinic 4 days before the first dose until the completion of the study procedure (Day 24). During the study, volunteers were required to maintain a standardized diet and to drink a predetermined volume of water per day to standardize urine output. Pre-dose assessment period was used to standardize the diet for purine and sodium content. Study schema is shown below:

| Day | 1-4 | 5 | 6 | 7 | 8 | 9 | 10-12 | 13-16 | 17 | 18 | 19 | 20 | 21 | 22-24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-Dose Ass. | Ticagrelor 90 mg BID | | | | | Post Dose Proc. | Pre-Dose Ass. | Placebo BID | | | | | Post-Dose Proc. |
| | | Placebo BID | | | | | | | Ticagrelor 90 mg BID | | | | | |
| PK | | | | | | | | | | | | | | |
| Uric Acid | | | | | | | | | | | | | | |
| Xanthine | | | | | | | | | | | | | | |
| Hypoxanthine | | | | | | | | | | | | | | |

| | |
|---|---|
| | Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18 h post-dose. |
| | Pre-dose |
| | Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12 |
| | Pre-dose, 2, 3, 4, 8, 12 |
| | Same time of the day as Pre-dose for each day |

- **Treatment:** Ticagrelor 90 mg IR tablets (Lot #. 07-010829AZ)
- **Study Population:** Healthy Volunteers

| | |
|---|---|
| N/ Completed/ Discontinued due to AE | 24/24/0 |
| Age, Median (Range) | 34.5 (22 – 45) |
| Male/Female | 24/0 |
| Race (White/Black/Asian/Other) | 19/5/0/0 |

### Results- Pharmacodynamics

As shown in Figure 1, uric acid serum levels are significantly higher in ticagrelor group starting on 8 h measurement on Day 1 and up to at least 36 h post the last dose on Day 5. The median percent difference between ticagrelor and placebo is 8.5% (range 3.5% to 9.8%). In general, average serum uric acid levels decreased as average ticagrelor plasma level decreased (Figure 2). However, there was no apparent relationship between ticagrelor or AR-C124910XX and serum

uric acid levels. Uric acid clearance was lower but not statistically significant in the ticagrelor group relative to placebo group.

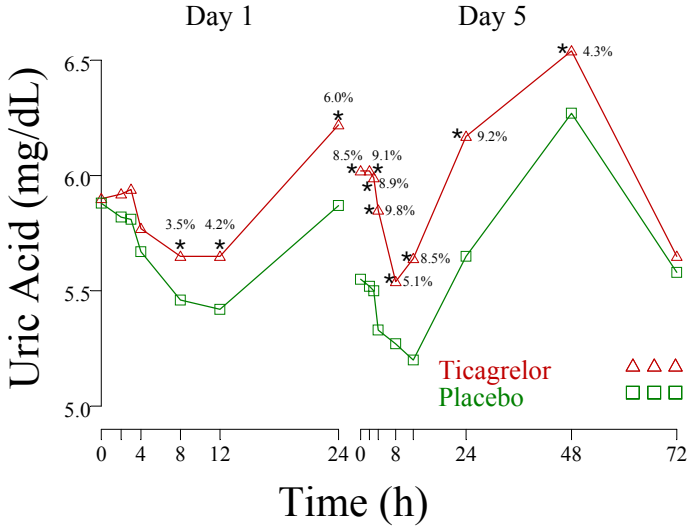



**Figure 1.** Uric acid serum levels following the administration of ticagrelor 90 mg BID and placebo. * indicates significant difference ($p < 0.05$, ticagrelor-placebo). Numbers represent average percent difference at each measurement.

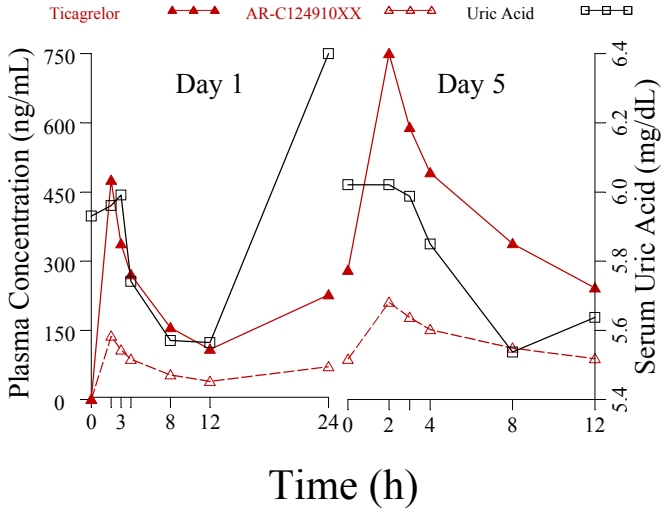



**Figure 2**. Ticagrelor, AR-C124910XX, and uric acid plasma and serum profile.

There were no apparent differences in the FE of sodium and potassium between the ticagrelor and placebo treatments, and the placebo-adjusted FE of sodium was similar for Day 5 and Day 1. Xanthine and hypoxanthine serum levels are generally higher in ticagrelor group relative to placebo group. However, the difference is statistically significant only at the 12 h measurement on Day 5. The average difference at Day 5 12 h measurement is 20.2% and 25.4% for Xanthine and hypoxanthine, respectively.

6-β-hydroxyl cortisol/cortisol ratio is higher (~ 15% on Day 5 pre-dose) in ticagrelor group relative to placebo group. However, the difference is not statistically significant. This indicates that ticagrelor does not affect CYP 3A metabolism.

**Safety**

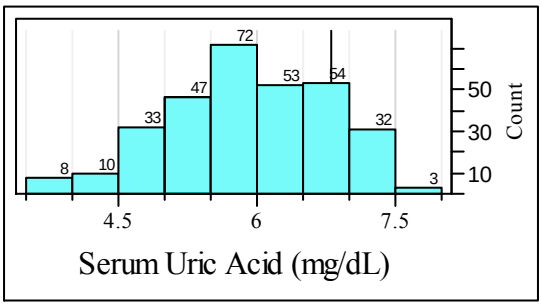
There were no deaths, serious AEs, or AEs leading to discontinuation.

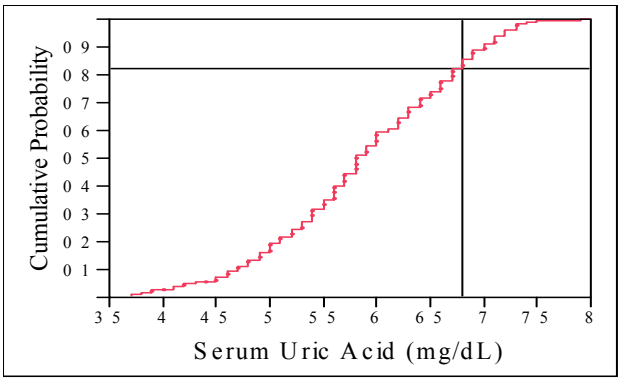
**Conclusions**

1. Ticagrelor increases serum uric acid by 10% in healthy volunteers. This can be attributed to increase in production and decrease in clearance.
2. There is no clear relationship between ticagrelor, AR-C124910XX and serum uric acid.

**Comments**

1. 18% of the observed serum uric acid measurments were ≥ the upper end of the normal range (Hyperuricemia) which is 6 6.8 mg/dL for men and 3.0 mg/dL for women as shown in the Figures below:




2. The sponsor did not provide details of the analytical method used to assay uric acid
3. Xanthine and hypoxanthine were assayed in plasma using an HPLC method with UV detection. Calibration range was 0.05-10.0 µg/mL for xanthine and 0.1-10.0 µg/mL for hypoxanthine. The method validation is acceptable. Method performance during study samples analysis is acceptable.
4. Females were excluded because of known variability of uric acid during the female hormonal cycle.
5. A standard, low-purine, low-sodium (4-mg) diet was provided to volunteers during each study period to minimize the effects of diet on uric acid production and catabolism.
6. Obese volunteers were excluded because of possible predisposition to gout, as well as increased possibility of greater amounts of total body uric acid accumulation.
7. The performance of ticagrelor bioanalytical method is acceptable.

## 6. Respiratory Parameters

| Report # | Study Period | EDR Link |
|---|---|---|
| D1530C00028 | 01/07/2005 – 03/22/2005 | Healthy Elderly |
| D5130C00034 | 05/31/20005 – 02/22/2006 | Asthma & COPD |

**Note:** These two studies were performed at two different sites. However they have the exact design with different population. The aim of both studies is to assess the effect of ticagrelor on respiratory parameters in healthy elderly (study # D1530C00028) and mild asthma and COPD patients (study # D1530C00034)

**Study Design**

Single-Center Multiple-Dose Randomized Double-Blind Cross-Over 2-Period

**Screening:** ≤ 21 days | **Washout:** ≥7 days, outpatient

**Period 1/2** 6 days, Inpatient stay ☑Y ☐ N:

| | A | B |
|---|---|---|
| **Treatments** | Ticagrelor<br>– Day 1: 450 mg AM + 180 mg PM<br>– Day 2,3: 180 mg BID<br>– Day 4: 180 mg AM | Matching Placebo<br>– Day 1,2,3: BID<br>– Day 5: AM only |

**Treatment:** Ticagrelor: 90 mg IR tablet (lot # P7046)

**Sampling Times (PD)**

MV: Minute Ventilation, RRATE: Respiratory Rate, TV: Tidal Volume, MBS: Modified Borg Scale, BDI: Bidirectional Dyspnea Index, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, PEF: Peak Expiratory Flow

| Day | 1 | | | | | | 2 | | | 3 | | | 4 | | | | | | | 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time (h) | 0 | 2 | 3 | 4 | 8 | 12 | 0 | 3 | 12 | 0 | 3 | 12 | 0 | 2 | 3 | 4 | 6 | 8 | 12 | 24 |
| MV/RRATE/TV/MBS/BDI | | | | | | | | | | | | | | | | | | | | |
| FEV1,FVC, PEF | | | | | | | | | | | | | | | | | | | | |
| Pulse Oximetry | | | | | | | | | | | | | | | | | | | | |

**Study Population**

| | D1530C00028 | D5130C00034 | |
|---|---|---|---|
| Population Type | Healthy Elderly | Asthma | COPD |
| N/Completed/Discontinued due to AE | 12/12/0 | 11/11/0 | 7/5/? |
| Age [Median (range)] | 61.0 (55 – 74) | 45.0 (35 – 58) | 55 (55-62) |
| Male/Female | 6/6 | 4/7 | 5/2 |
| Race (Caucasian/Black)) | 11/1 | 8/3 | 5/2 |

**Results**

Figure 1 shows the mean primary respiratory parameters following the administration of ticagrelor and placebo. Similar results were obtained with the other measured respiratory parameters.

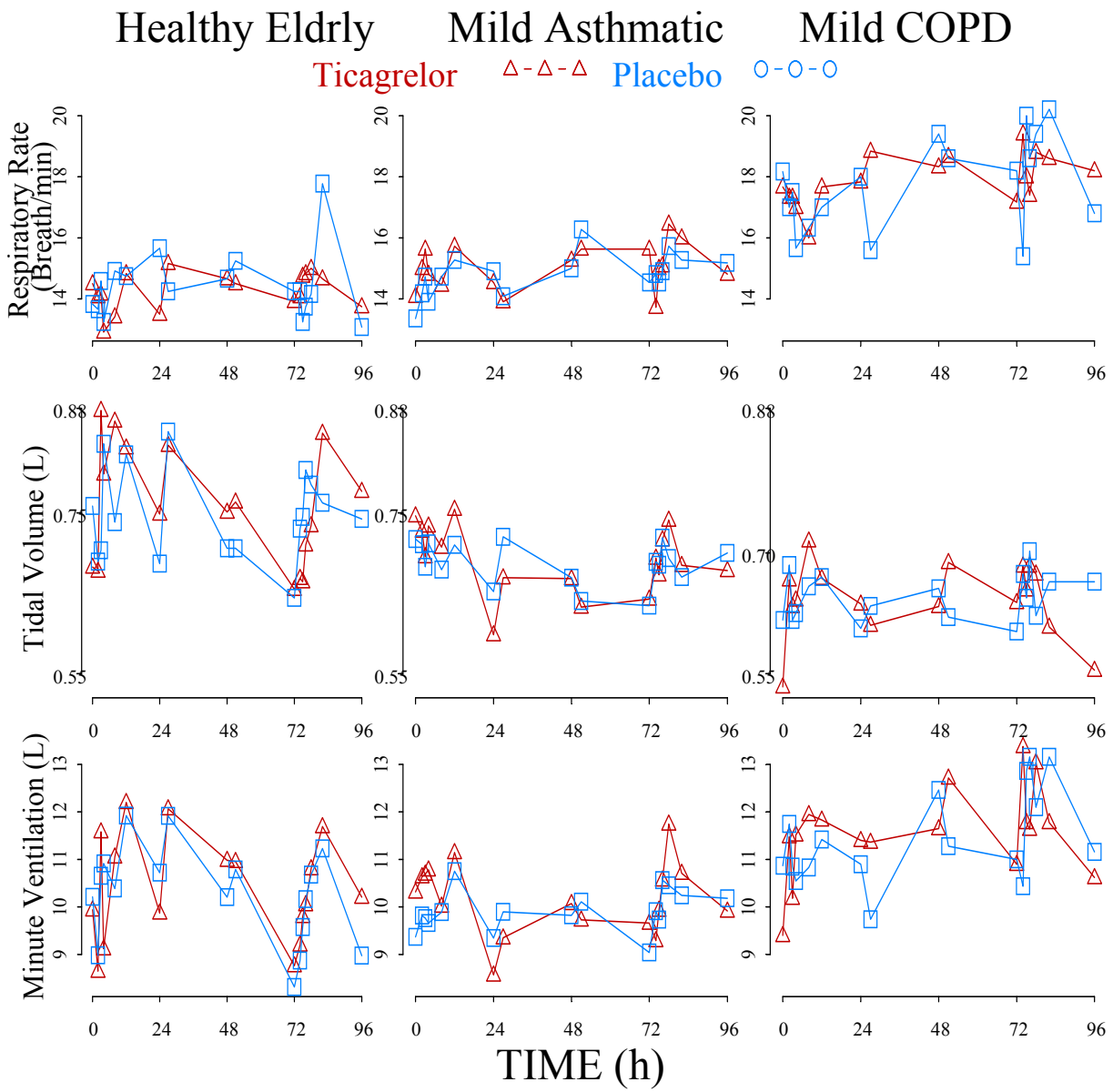



**Figure 1.** Respiratory parameters following the administration of ticagrelor and placebo.

| **Safety** |
|---|
| There was no death or serious adverse events. |
| **Conclusion** |
| ▪ Ticagrelor did not appear to affect respiratory rate, minute ventilation, or tidal volume.<br>▪ Ticagrelor did not cause bronchospasm as assessed by spirometry.<br>▪ Ticagrelor had no effect on exercise performance, caused no worsening in sensation of breathing or change in perception of breathlessness as measured by the Modified Borg Scale and Bidirectional Dyspnea Index, and had no effect on pulse oximetry. |
| **Comments** |
| Ticagrelor related dyspnea can not be attributed to changes in respiratory parameters. |

# PHARMACOMETRICS

## I. Population Pharmacokinetics

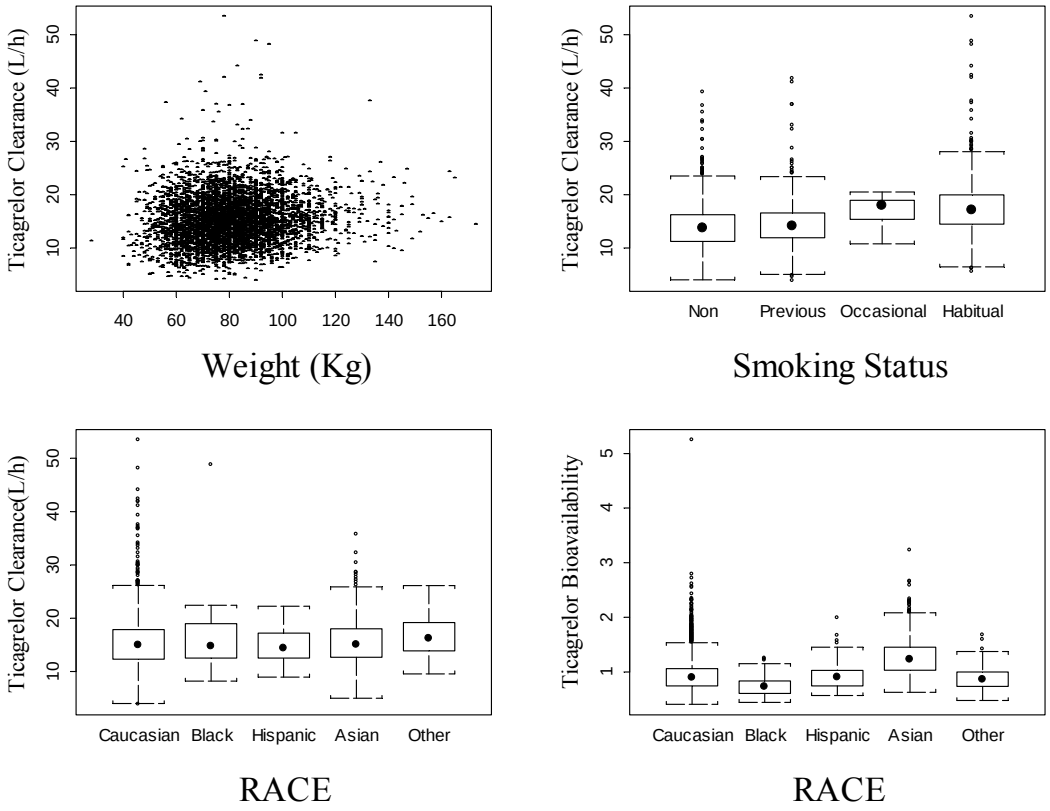
**Summary Of Findings**
**1.1 Key Review Questions**
The purpose of this review is to address the following key question:

**1.1.1 Does the population pharmacokinetic analysis support the sponsor's proposed labeling claims regarding the effects of body weight, ethnicity and smoking on ticagrelor and AR-124910XX exposure?**

Of the 32 pre-specified covariates accounting for demographics, clinical chemistry, disease status, biomarkers, and 7 classes of concomitant medicines, covariates displayed in the table below displayed a significant effect on ticagrelor clearance and bioavailability and AR-C124910XX clearance. Body weight did not alter ticagrelor clearance.

| Covariate | Effect | Magnitude | 95% CI |
|---|---|---|---|
| Effect on Ticagrelor Clearance | | | |
| Smoking | ↑ | 22% | 19% - 25% |
| Moderate CYP3A4 inducer | ↑ | 110% | 52% - 192% |
| Moderate CYP3A4 inhibitors | ↓ | 64% | 39% - 73% |
| Effect on Ticagrelor Bioavailability | | | |
| Race Asian | ↑ | 39% | 33% – 46% |
| Race Black | ↓ | 18% | 6% -28% |
| Effect on AR-C124910XX Clearance | | | |
| Visit | ↓ | 18% | 17% - 19% |
| Gender | ↓ | 31% | 30% - 33% |
| Smoking | ↑ | 28% | 25% - 30% |
| CYP3A4 inducers | ↑ | 99% | 77% - 124% |

**Figure 1**. Relationship between ticagrelor clearance and bioavailability with covariates of interest.




## 1.2 Recommendations:

## 1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font

(b) (4)

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## 2 Pertinent Regulatory Background

Ticagrelor (Brilinta™) is a new molecular entity indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS who are to be either managed medically or invasively with PCI. The application was first submitted to the agency under IND 65,808 on April 28th, 2003. NDA 022433 was submitted on December 15th, 2009 and was granted a standard review status on January 15th, 2010. The goal date for the review is September 16th, 2010 and Advisory Committee Meeting is scheduled for July 28th, 2010.

## 3 Results of Sponsor's Analysis

Per sponsor, the primary goal of the analysis was to assess the effect of various covariates, such as demographic, concomitant therapies, and disease state on the PK of ticagrelor and AR-C124910XX and to predict the steady-state exposure of ticagrelor and AR-C124910XX for the subsequent exposure-response modeling.

### 3.1 Data sets used for model development

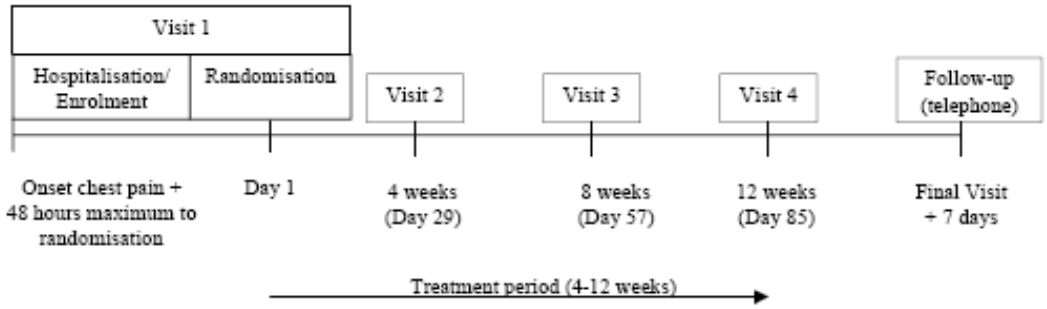
Plasma samples from the following two studies were used in the analysis:

**I. <u>DISPERSE II:</u>**

- A phase II double-blind, double-dummy, parallel group randomized dose confirmation and feasibility in patients with non-ST segment elevation ACS. Patients were randomized to one of the following treatment groups (330/group), all patients were on a background of ASA (75-100 mg):
  1. Ticagrelor 90 mg BID
  2. Ticagrelor 180 mg BID

  A loading dose (LD) of 270 mg was given as the first dose to half of the patients in group 1 and 2 (165/group)
  3. Clopidogrel 75 mg QD: A LD of 300 m g clopidogrel was given as the first dose unless the patient was already on a maintenance dose of clopidogrel, or received a LD of clopidogrel as part of their local clinical care prior to randomization.

**Figure 2.** DISPERSE II flow chart.



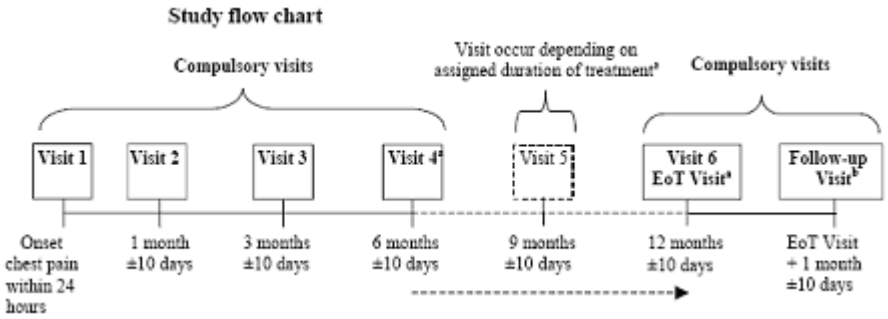

- Sampling Times (90 patients were assigned to the PK/PD sub-study)

1. PK/PD sub-study: Pre-dose, 2, 4, 8 and 12 h post-dose on visits 1, 2, 3, and 4 plus an additional sample 24 h post-dose on visit 4.
2. Remaining Patients:
   - Visit 1: pre-dose sample and a sample within 72 hours of first dose
   - Visits 2, 3, and 4: One sample at each visit at anytime post AM or PM dose.

**II. PLATO**

- Phase III registration trial in which males and females patients (~9000/ group) with either a non-ST or ST segment elevation ACS were followed for up to 12 months after being randomized to either:
  1. Ticagrelor: 90 mg BID either with or without a 180 mg LD.
  2. Clopidogrel 75 mg QD either with or without a 30 mg LD.

**Figure 3.** PLATO study flowchart.




- Sampling Times (One sample /visit)
  1. Visit 1: on Day 4 post-enrolment (anytime 6 hours post AM dose and before PM dose) or at discharge from the hospital, whichever occurred first.
  2. Visit 2: any time after either AM or PM dose.

**Table 1:** The number of available plasma concentrations for the pop PK analysis.

| Study Source | Total number of valid plasma concentration | | |
|---|---|---|---|
| | N(Patients) | Ticagrelor | AR-C124910XX |
| DISPERSE2 | 609 | 1967 | 1965 |
| PLATO | 6381 | 10818 | 10825 |

## 3.2 Model Development

### 3.2.1 Ticagrelor

The basic model was developed initially using ticagrelor concentration in DISPERSE II and was refined later with the addition of data from PLATO.

#### 3.2.1.1 Ticagrelor Population PK model

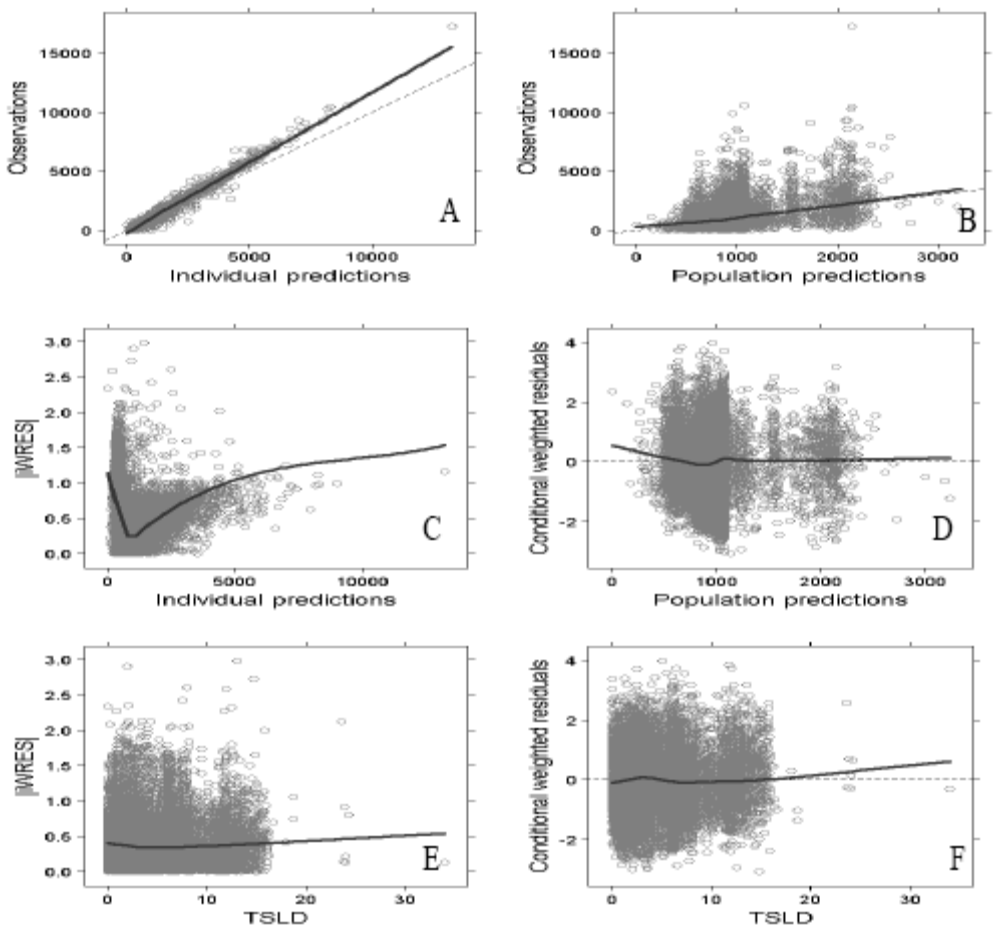
- Model Structure: one-compartment disposition model with first order absorption.
- Residual error model (σ): proportional and additive (with different residual error model parameters between the DISPERSE2 and PLATO studies)
- Inter-individual error (ω) model: Log-normal distribution for CL, V, Ka, and a covariance of CL and V.
- Log-normal distribution of inter-visit random effect (IOV) on the relative bioavailability (F1).

Ticagrelor basic population PK model goodness-of-fit plots are displayed in Figure 4 and parameters estimate are displayed in Table 2.

**Table 2.** Ticagrelor basic population PK model parameter estimates

| Parameter | Mean estimate | % RSE | 95% CI |
|---|---|---|---|
| CL (L/h) | 16.5 | 0.9 | (16.2, 16.8) |
| V (L) | 273 | 7.1 | (235, 311) |
| Ka ($h^{-1}$) | 0.997 | 6.4 | (0.872, 1.12) |
| $\omega_{CL}$ | 0.152 | 4.7 | (0.138, 0.166) |
| $\omega_{CL,V}$ | 0.089 | 18.2 | (0.057, 0.121) |
| $\omega_{v}$ | 0.281 | 29.3 | (0.119, 0.443) |
| $\omega_{Ka}$ | 2.85 | 27.8 | (1.30, 4.40) |
| $\omega_{IOVF1}$ | 0.173 | 4.5 | (0.158, 0.188) |

**Figure 4.** Ticagrelor basic population PK model basic goodness-of-fit plots.




*Reviewer's Comment: The parameter estimates and goodness of fit plots indicate an adequate performance of the model to describe ticagrelor pharmacokinetics*

### 3.2.1.2 Ticagrelor covariate model

Thirty-two covariates were evaluated on F1, CL, and V. Covariates were added by stepwise forward selection followed by stepwise backward elimination using ticagrelor population PK model mentioned above. The effect of each covariate was modeled as an exponential function. Effect of covariates on Ka was not evaluated due to the inadequate number of plasma samples during the absorption phase. Inclusion/exclusion of a covariate effect was determined by the following criteria: physiological relevance, statistical significance based on p=0.01 (or a change of 6.63 units in OFV with 1 degree of freedom), and clinical relevance (defined as a 20% change in population mean parameter estimates).

- Model Structure: Same as ticagrelor population PK model.
- Effect of body weight on the CL was less than 20% and was considered insignificant.
- The following covariates were deemed significant:
  - Visit 1, race Black, and race Asian on F1

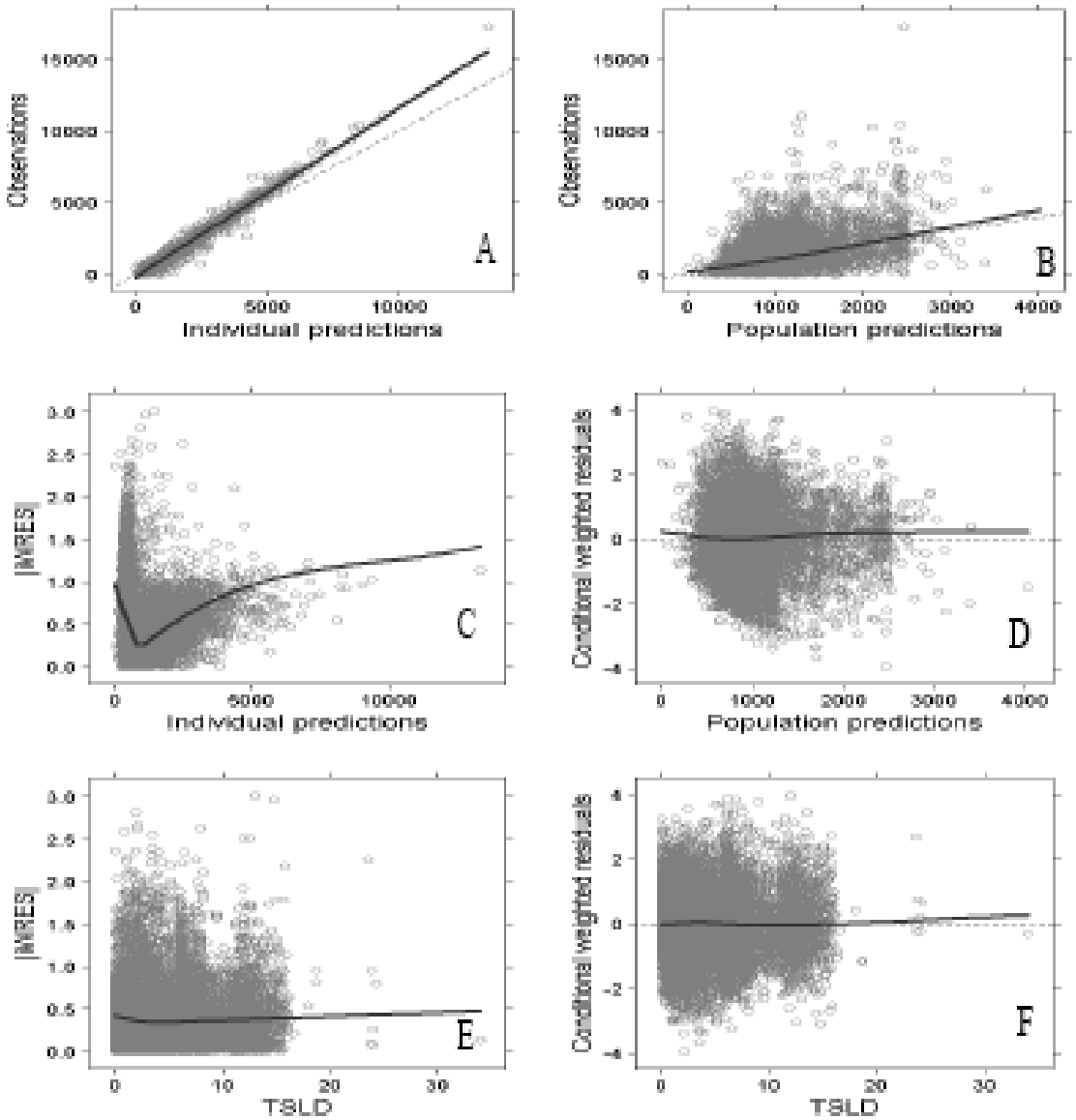
- Smoking (SMKH), moderate 3A4 inhibitors (MINH) and moderate 3A4 inducers (MIND) on CL.

Ticagrelor full covariate model goodness-of-fit plots are displayed in Figure 5 and parameters estimate are displayed in Table 3.

**Table 3.** Ticagrelor covariate model parameter estimates

| Parameters | Mean estimate | % RSE | 95% CI |
|---|---|---|---|
| CL (L/h) | 14.0 | 1.1 | (13.7, 14.3) |
| V (L) | 221 | 4.6 | (201, 241) |
| Ka ($h^{-1}$) | 0.676 | 8.7 | (0.56, 0.79) |
| VISIT 1 effect on F1 | -0.230 | 4.4 | (-0.25, -0.21) |
| Race Black effect on F1 | -0.195 | 33.6 | (-0.32, -0.067) |
| Race Asian effect on F1 | 0.330 | 7.4 | (0.28, 0.38) |
| Smoking effect on CL | 0.199 | 7.0 | (0.17, 0.23) |
| Moderate 3A4 inhibitors effect on CL | -0.439 | 12.6 | (-0.55, -0.33) |
| Moderate 3A4 inducers effect on CL | 0.742 | 22.4 | (0.42, 1.1) |
| $\omega_{CL}$ | 0.144 | 4.6 | (0.13, 0.16) |
| $\omega_{CL,V}$ | 0.244 | 20.7 | (0.16, 0.34) |
| $\omega_{v}$ | 1.97 | 20.7 | (1.2, 2.8) |
| $\omega_{Ka}$ | 0.089 | 13.3 | (0.07, 0.11) |
| $\omega_{IOVF1}$ | 0.150 | 4.9 | (0.14, 0.17) |

**Figure 5.** Ticagrelor full covariate model basic goodness-of-fit plots




*Reviewer's Comment: The sponsor proposed ticagrelor full covariate model is acceptable.*

### 3.2.2 AR-C124910XX

The same approach implemented for ticagrelor model development was utilized using the combined ticagrelor and AR-C124910XX concentration data. All PK parameters related to the ticagrelor were fixed at their values estimated from the ticagrelor PK model. However, the total apparent clearance of ticagrelor was split into two pathways: one through biotransformation to AR-C124910XX (22%), a mean value derived from the [$^{14}$C]-ticagrelor human mass balance study, and the second through all other elimination pathways (78%).

#### 3.2.2.1 AR-C124910XX Population PK model

- Model Structure: One-compartment disposition model with first order absorption for ticagrelor and one compartment disposition model for AR-C124910XX with first order input from ticagrelor compartment.
- Residual error model (σ): proportional and additive
- Inter-individual error (ω) model: Log-normal distribution for CL. (due to long computing time IIV on volume and biotransformation of ticagrelor to AR-C124910XX were not included)

AR-C124910XX basic population PK model goodness-of-fit plots are displayed in Figure 6 and parameters estimate are displayed in Table 4.

**Table 4.** AR-C124910XX basic population PK model parameter estimates

| Parameters | Mean estimate | % RSE | 95% CI |
|---|---|---|---|
| CL (L/h) | 8.26 | 0.6 | (8.17, 8.35) |
| V (L) | 16.9 | 6.4 | (14.8, 19.0) |
| $\omega_{CL}$ | 0.115 | 3.1 | (0.108, 0.122) |

#### 3.2.2.2 AR-C124910XX covariate model

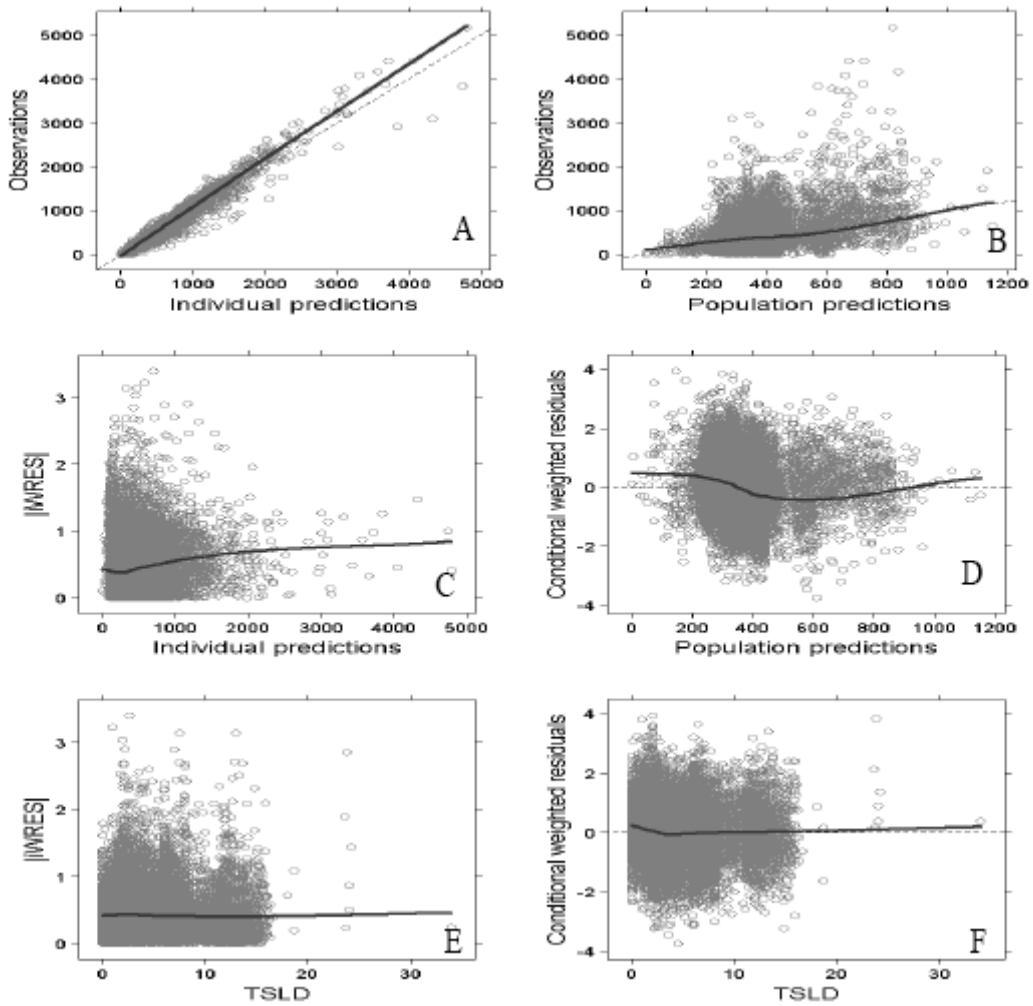
- Thirty-two covariates were evaluated on CL.
- Model Structure: Same as AR-C124910XX population PK model.
- Sex(C1), smoking (C2), and moderate 3A4 inducers (C3), and Visit 1(FLGV1), covariates were deemed significant:

AR-C124910XX full covariate model goodness-of-fit plots are displayed in Figure 7 and parameters estimate are displayed in Table 5.

**Table 5.** AR-C124910XX covariate model parameter estimates

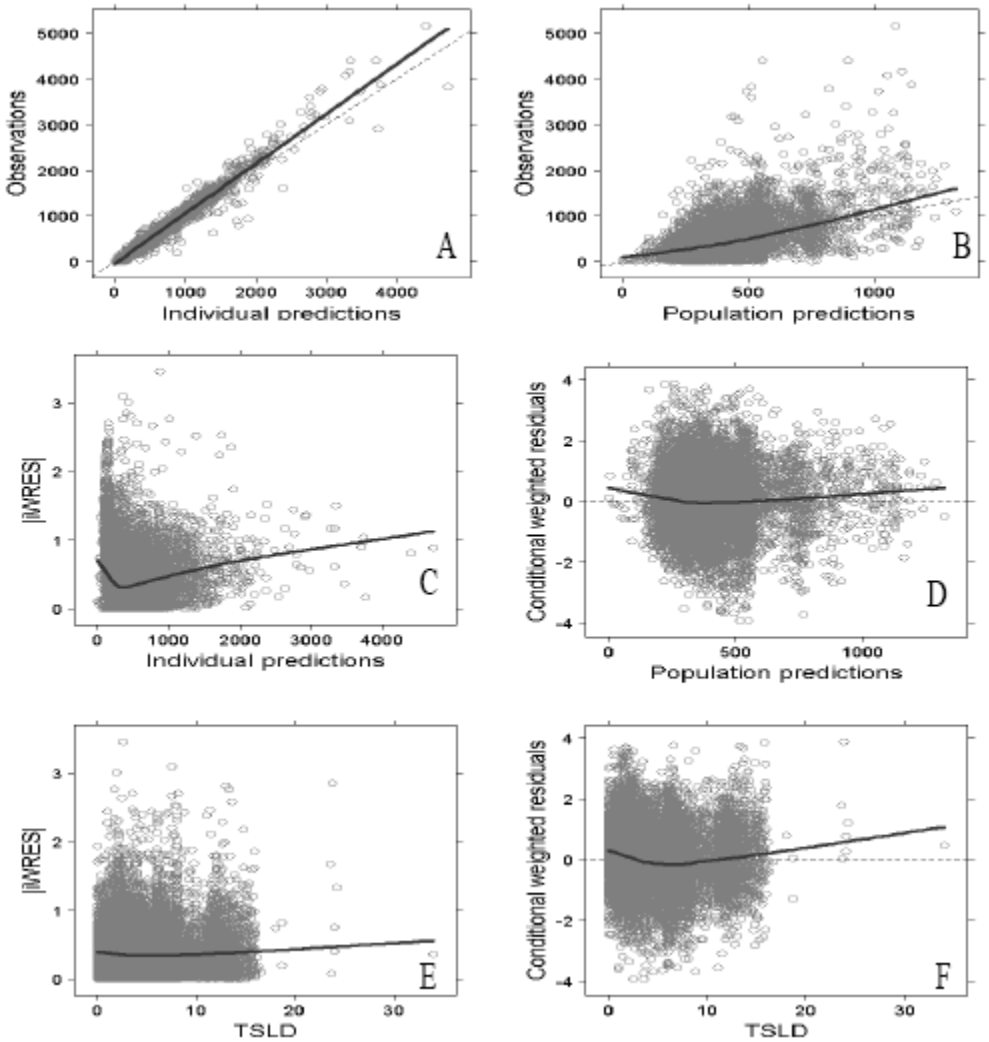
| Parameters | Mean estimate | % RSE | 95% CI |
|---|---|---|---|
| CL (L/h) | 9.06 | 0.9 | (8.9, 9.2) |
| V (L) | 13.1 | 10.6 | (10.4, 15.8) |
| $\omega_{CL}$ | 0.0567 | 5.5 | (0.05, 0.06) |
| Sex effect on CL | -0.374 | 2.8 | (-0.40, -0.35) |
| Smoking effect on CL | 0.244 | 4.1 | (0.23, 0.26) |
| Moderate 3A4 inhibitors effect on CL | 0.688 | 8.8 | (0.57, 0.81) |
| VISIT 1 effect on CL | -0.200 | 3.5 | (-0.20, -0.20) |

**Figure 6.** AR-C124910XX population PK model basic goodness-of-fit plots.




*Reviewer's Comment: The parameter estimates and goodness of fit plots indicate an adequate performance of the model to describe AR-C124910XX pharmacokinetics*

**Figure 7.** AR-C124910XX full covariate model basic goodness-of-fit plots.




*Reviewer's Comment: The sponsor proposed AR-C124910XX full covariate model is acceptable*

**Reviewer Comments**

- The reviewer was able to reproduce the sponsor's analysis. Although the model underestimates higher concentrations, it was deemed acceptable as the sponsor have evaluated different absorption models including first-order, zero-order, and sequential and parallel (combined first- and zero-order) absorption.
- The lower bioavailability at the beginning of the treatment (Visit 1) with ticagrelor compared to later visits (Visit 2 and later) can be associated to the initial stabilizing process of the disease status in patients since visit 1 is confined within 48 hours of onset of chest pain.

# II. Exposure Response

## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

#### 1.1.1 Is there evidence of exposure-response for effectiveness?

An exposure-response relationship could not be established for the composite efficacy endpoint of cardiovascular death, myocardial infarction and stroke in the pivotal PLATO trial. The most likely explanation is that only one dose was studied in PLATO and exposures observed at this dose are at the plateau of the exposure-response relationship.

#### 1.1.2 Is there evidence of exposure-response for safety?

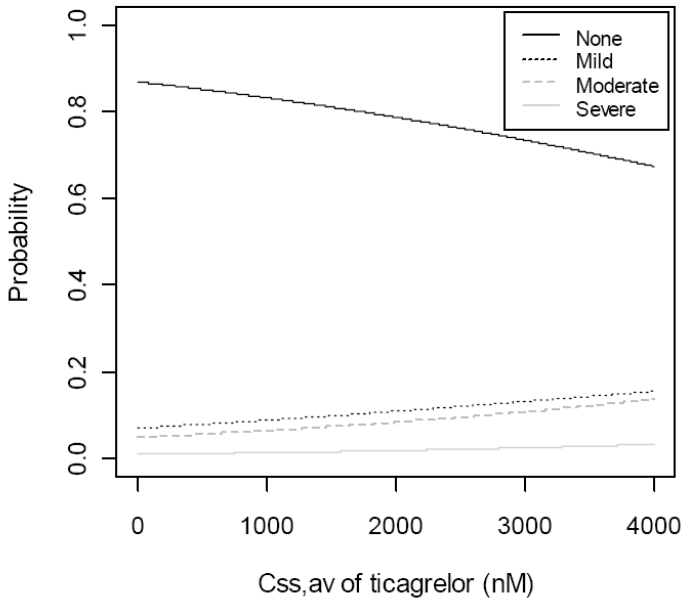
##### 1.1.2.1 Major Bleeding

A shallow relationship between ticagrelor exposure and major bleeding was established. Given the 10-90$^{th}$ percentiles of total exposure in PLATO at Visit 1 in a patient 62 years of age, the probability of major bleeding was 2.8-3.2% (without coronary artery by-pass grafting (CABG) or percutaneous coronary intervention (PCI)), 58-63% (with CABG) and 0.6% (with PCI).

##### 1.1.2.2 Dyspnea

A shallow relationship between ticagrelor exposure and dyspnea was established. The predicted probability of having a dyspnea event (mild, moderate or severe) given the 10-90$^{th}$ percentile of ticagrelor exposure at Visit 1 was 2.2-2.8% in a patient with no risk factors. The relationship in a patient with all risk factors (diabetes, COPD, chronic renal disease, STEMI or NSTEMI index event, female sex, ex-smoker and early enroller in PLATO ) is illustrated in **Error! Not a valid bookmark self-reference.**.

**Figure 1. Predicted probability of dyspnea versus ticagrelor exposure in a patient with all risk factors**




*Source: Sponsor's Exposure-Response Modelling Report Safety Endpoints Fig 40, page 94.*

**1.1.2.3 Ventricular Pauses**

Ventricular pauses were noted in earlier clinical trials so PLATO included a dedicated Holter sub-study. An exposure-response relationship could not be established between ticagrelor exposure and occurrence of ventricular pauses ≥ 3 or ≥ 5 seconds.

**1.1.3 Is there evidence of effectiveness in the U.S. population?**

In PLATO, ticagrelor was superior to clopidogrel in reducing the rate of the primary efficacy endpoint (hazard ratio 0.84 (95% CI 0.77, 0.92) p=0.0003). The hazard ratio for the primary efficacy endpoint within the USA, however, was 1.27 (95% CI 0.92, 1.75) compared to 0.81 (95% CI 0.74, 0.90) for the non-USA region, suggesting a benefit of clopidogrel over ticagrelor in the USA. Several potential explanatory factors were explored, including: compliance, statin exposure, low ticagrelor exposure and a fructose-hyperuricemia relationship. None of these factors satisfactorily explained the observed benefit of clopidogrel over ticagrelor in the USA. Assuming no difference between clopidogrel and ticagrelor, the probability of finding a hazard ratio of 1.27 or higher in the USA was calculated to be 5.8%, which suggests it is unlikely for this to be a chance finding. In the sponsor's multivariate analysis, aspirin dose explained the largest treatment-by region effect, although aspirin dose was highly unbalanced, with most high-dose aspirin use (>300 mg) occurring in the USA. Furthermore, there are no pharmacokinetic or pharmacodynamic interactions that would predict an undesired effect at high aspirin doses.

## 1.2 Recommendations

- Ticagrelor provides acceptable efficacy and safety in the overall population and should be approved. Several factors, including aspirin use, statin use, compliance, chance and differences in ticagrelor exposure were investigated but do not explain the differential effectiveness of ticagrelor between US and non-US patients.

## 2 Pertinent regulatory background

Ticagrelor is an oral reversible adenosine diphosphate receptor antagonist which binds to the $P2Y_{12}$ platelet ADP receptor and is being developed to reduce the risk of fatal and nonfatal vascular events following acute coronary syndromes (ACS). The proposed dosing regimen consists of a 180 mg loading dose followed by 90 mg twice daily maintenance therapy. The current submission includes the results of a single pivotal efficacy and safety trial (PLATO) comparing ticagrelor to clopidogrel.

## 3 Results of Sponsor's Analysis

The sponsor performed exposure-response analyses to explore potential relationships between ticagrelor and its active metabolite (AR-C124910XX) and selected efficacy and safety endpoints. The data used in these analyses originated from a single study (PLATO).

## 3.1 Studies

**PLATO (Study D5130C05262) Exposure/Response Data**

PLATO randomized 18624 patients with ACS encompassing unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI) whether intended for percutaneous coronary intervention (PCI), coronary artery by-pass grafting (CABG) surgery or medical management. Patients were randomized within 24 hours of the index event to either ticagrelor (N=9333) or clopidogrel (N=9291) for 6 to 12 months. Patients treated with ticagrelor received a 180 mg loading dose (with an additional 90 mg if PCI occurred >24 hours after randomization) followed by 90 mg twice daily. Patients treated with clopidogrel received a 300 mg loading dose (with an additional 300 mg at PCI at the investigator's discretion) followed by 75 mg once daily. The primary composite efficacy endpoint was comprised of cardiovascular (CV) death, myocardial infarction (MI) and stroke. Key safety endpoints included major and minor bleeds, dyspnea and ventricular pauses.

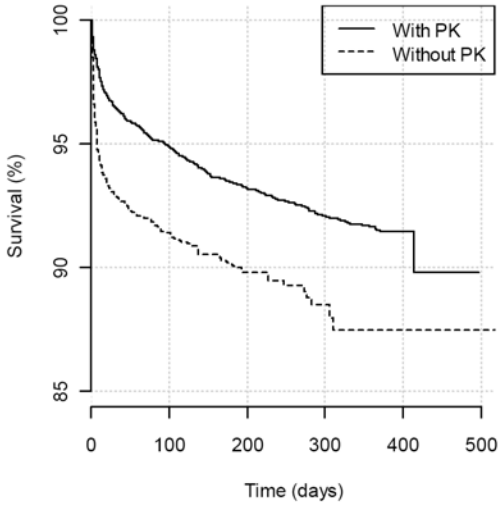
The protocol specified that a blood sample for determination of ticagrelor and AR-C124910XX concentrations would be collected in the first 9000 patients randomized at Visit 1 (discharge/day 4) and Visit 2 (1 month). Population pharmacokinetic models were used to predict individual average steady-state concentrations ($C_{ss,av}$) of ticagrelor and AR-C124910XX at Visit 1 and Visit 2 to be used as indices of exposure in the exposure-response analyses. The **risk factor** data set was defined as comprising all patients randomized to ticagrelor who had received at least one dose (N=9236). The **exposure-response** data set was made up of all patients for whom there were PK samples available for both ticagrelor and AR-C124910XX (N=6366).

## 3.2 Exposure-Efficacy Analysis

Exploratory analysis revealed a difference in survival probabilities between patients with and without PK measurements (**Error! Not a valid bookmark self-reference.**). A possible explanation proposed by the sponsor is that all subjects who experienced an event or dropped out

before the first scheduled PK measurement (Day 4 or discharge) automatically became part of the subgroup without PK measurements. To address this finding, three additional risk factors were evaluated in the risk factor analysis: final diagnosis of index event, number of days between randomization of the first patient in the study and randomization of individual patients thereafter and treatment approach at randomization.

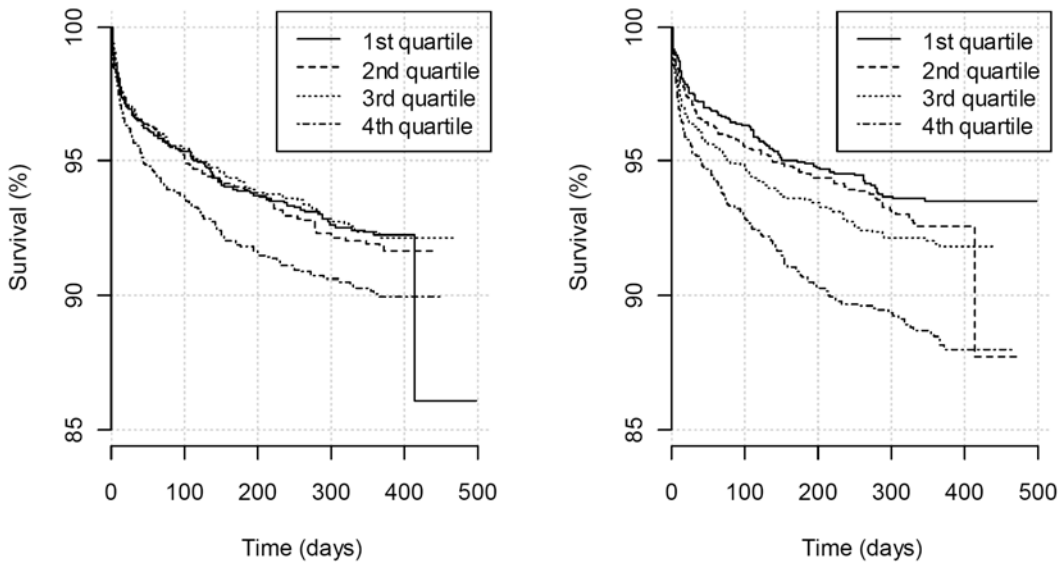
**Figure 2: Kaplan-Meier survival curves for composite efficacy for patients receiving ticagrelor with or without PK measurements**




*Source: Sponsor's Exposure-Response Modelling Report Efficacy Endpoints Fig1, page 23.*

A second exploratory analysis examined the survival curves for composite efficacy divided into subgroups corresponding to quartiles of ticagrelor and AR-C124910XX exposure (**Error! Not a valid bookmark self-reference.**). Unexpectedly, higher exposures of ticagrelor and AR-C124910XX were associated with lower survival curves. The sponsor noted that the characteristics of the patients in the four quartiles were not balanced. For example, patients in the highest quartile of exposure tended to be older, lighter, more likely to be female and non-smokers. Some of these patient characteristics, such as age would be expected to increase the likelihood of efficacy outcomes.

**Figure 3. Kaplan-Meier survival curves for composite efficacy divided into quartiles of exposure of ticagrelor (left) and AR-C124910XX (right)**




*Source: Sponsor's Exposure-Response Modelling Report Efficacy Endpoints Fig 4, page 27.*

In the first step of the formal exposure-efficacy analysis, the risk factor dataset (without exposure data) was used to identify a risk factor model. In the second step, these risk factors, together with exposure indices from the exposure-response data set were used to derive the final exposure-response model. Efficacy endpoints were analyzed using a time-to-event analysis. Proportional hazards were assumed and the hazard was modeled over time as:

$h(t) = h_0(t) \cdot e^{\beta_1 \cdot X_1 + \beta_2 \cdot X_2 + \ \beta_n \cdot X_n + \beta_{\exp} \cdot C}$ where $\beta_n$ is the coefficient describing risk factor $X_n$ and $\beta_{exp}$ is the coefficient describing the exposure relationship (C). The results for the risk factor model for composite efficacy are presented in Table 1. For continuous risk factors, the hazard ratio is the ratio of hazards corresponding to the 75$^{th}$ and 25$^{th}$ quartiles of the factor. For categorical risk factors, the hazard is the ratio of hazards corresponding to different categories of the factor.

**Table 1. Estimates with 95% confidence intervals for hazard ratios in the risk factor model for composite efficacy**

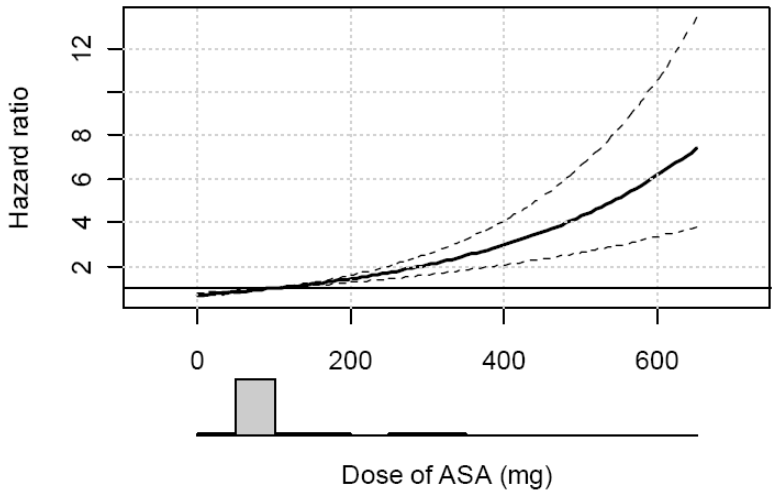
| Risk factor | Estimate | Lower bound | Upper bound |
|---|---|---|---|
| log(NT-proBNP) (log(pmol/L)) | 1.734 | 1.532 | 1.950 |
| Dose of ASA (mg) | 1.095 | 1.063 | 1.125 |
| Diabetes | 1.422 | 1.204 | 1.665 |
| Age (years) | 1.269 | 1.119 | 1.439 |
| log(Creatinine) (log(µmol/L)) | 1.164 | 1.072 | 1.263 |
| Previous stroke or TIA | 1.578 | 1.228 | 1.950 |
| Previous MI | 1.316 | 1.119 | 1.560 |
| BMI (kg/m^2) | 0.867 | 0.784 | 0.959 |
| Hypertension | 1.270 | 1.062 | 1.541 |
| Final diagnosis of index event: Unstable angina pectoris vs non-STEMI | 0.809 | 0.639 | 1.008 |
| Final diagnosis of index event: STEMI vs non-STEMI | 1.125 | 0.951 | 1.334 |
| Final diagnosis of index event: Other vs non-STEMI | 1.254 | 0.694 | 1.969 |
| Peripheral artery disease | 1.295 | 1.007 | 1.634 |

ASA Acetylsalicylic acid; BMI Body mass index; MI Myocardial infarction; NT-proBNP N-terminal pro b-type natriuretic peptide; non-STEMI Non ST-elevation myocardial infarction; STEMI ST-elevation myocardial infarction; TIA transient ischaemic attack.

*Source: Sponsor's Exposure-Response Modelling Report Efficacy Endpoints Table 8, page 31.*

Dose of aspirin (lowest recording dose in each individual) was identified as a significant risk factor. For doses higher than 100 mg, the hazard ratio increases sharply, but the confidence intervals are wide.

**Figure 4. Hazard ratio for the dose of ASA relative to the median (100 mg) with 95% confidence interval**




*Source: Sponsor's Exposure-Response Modelling Report Efficacy Endpoints Fig 6, page 32.*

For the exposure-response model, different exposure indices of ticagrelor and AR-C124910XX were added to the risk factor model using only the exposure-response dataset. No exposure relationships were found to be significant at the 5% level. Therefore, an exposure response relationship could not be established for the composite efficacy endpoint.

This two-step modeling procedure was repeated for the three components of the primary endpoint (CV death, MI and stroke). A summary of the significant risk factors identified for the efficacy endpoint components is provided in Table 2. Three risk factors were associated with higher risk of event for all efficacy endpoints: diabetes, previous stroke or TIA and increasing levels of NT-proBNP.

For the exposure-response models, ticagrelor $C_{ss,av}$ at Visit 2 was positively associated with an increased incidence of CV death and AR-C124910XX $C_{ss,av}$ was positively associated with an increased incidence of MI. The sponsor did not retain indices of exposure in the final model because a positive relationship contradicts the mechanism of action. Two possible explanations of this unexpected finding are that exposures were already on the plateau of the exposure-response curve and the existence of potential correlation between risk factors and exposure so what patients with higher exposure tended to have more risk factors (including those that were not included in the final risk factor model because they described a marginal clinical effect). No exposure-response relationship was found for incidence of stroke.

**Table 2. Significant risk factors identified in the risk factor model for efficacy endpoints**

| | Efficacy endpoints | | | |
|---|---|---|---|---|
| Risk factors | Composite efficacy | CV Death | MI | Stroke |
| Age | X | X | - | X |
| Body mass index | X | - | - | - |
| Carotid stenosis | - | - | | - |
| Coronary artery disease | - | - | X | |
| Days between randomisation of the first patient in the study and randomisation of individual patients thereafter | - | X | - | - |
| Diabetes | X | X | X | X |
| Dose of ASA | X | X | X | - |
| Dyslipidaemia | - | X | - | - |
| Family history of coronary heart disease | - | - | - | - |
| Final diagnosis of index event | X | X | X | - |
| Hypertension | X | - | X | - |
| Peripheral artery disease | X | - | - | |
| Previous MI | X | - | X | - |
| Previous stroke or TIA | X | X | X | X |
| Race | - | - | - | - |
| S-creatinine | X | X | - | - |
| S-high-sensitivity Troponin I | - | X | - | |
| S- | X | X | X | X |
| Sex | - | - | - | - |
| Smoker status | - | - | - | - |
| Treatment approach at randomisation | - | X | - | - |

ASA Acetylsalicylic acid; MI Myocardial infarction; S-NT-proBNP Serum N-terminal pro b-type natriuretic peptide; TIA transient ischaemic attack.

[a] X: significant; - : not significant; grey cell: risk factor not tried

*Source: Sponsor's Exposure-Response Modelling Report Efficacy Endpoints Table 15, page 55.*

*Reviewer's Comments: The sponsor's exposure-efficacy analysis is acceptable, although any interpretation of potential exposure-response relationships is confounded by the observation that the survival probabilities were different in patients with and without PK measurements. The difference between these groups could not be explained by the three additional risk factors tested by the sponsor. The reviewer agrees with the sponsor that the lack of an observed exposure-response relationship can be partially attributed to the relatively limited range of exposure. Only one dose level (90 mg) was studied in PLATO. In addition, only one or two PK samples were taken per individual, resulting in shrinkage of exposure estimates to the mean. The finding of an increased risk of CV death or MI with increased exposure is likely to be a statistical artifact*

*possibly due to correlation between certain risk factors and exposure. A positive relationship was not observed for the composite efficacy endpoint.*

## 3.3 Exposure-Safety Analysis

### 3.3.1 Bleeding Endpoints

The risk of bleeding events was modeled with a similar approach to that used for efficacy events. The model was modified to include time varying CABG and PCI risk factors where the hazard increased at the time of the procedure up until 7 days post procedure. The final risk factor model for major bleeds included age, CABG and PCI. In the exposure-response model, $C_{ss,av}$ of the sum of both ticagrelor and AR-C124910XX at Visit 1 was found to be a statistically significant descriptor of time to major bleed. The results are presented in Table 3.

**Table 3. Parameter estimates of the final major bleeding risk factor**

| Parameter | Estimate[23] | 90% C.I.[24] | Hazard ratio[25] |
|---|---|---|---|
| λ | 0.00021 | 0.000094-0.00030 | - |
| γ | 0.815 | 0.751-0.938 | - |
| CABG | 8.23 | 7.98-8.70 | 3752 |
| PCI | 3.20 | 2.71-3.81 | 24.5 |
| AGE | 0.0179[26] | 0.00132-0.0185 | 1.02[27] |
| $C_{ss,av}$ SLOPE | 0.000108[28] | 0.000091-0.00037 | 1.00[29] |

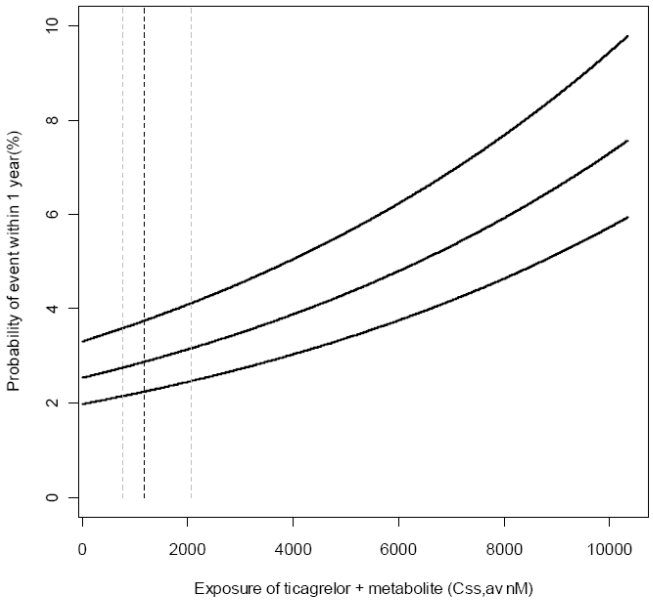
CABG Coronary artery bypass grafting; $C_{ss,av}$ Average plasma concentration at steady state; λ Scale factor of the Weibull distribution; γ Shape factor of the Weibull distribution; PCI Percutaneous coronary intervention.

[23] The estimates of the risk factors are parameterised as log hazard ratio
[24] C.I. confidence interval obtained by bootstrapping
[25] Estimates of risk factors are transformed to hazard ratio
[26] Increase in the logarithmic hazard ratio with every 1 year. Covariate centered around median of 62 years.
[27] Increase in the hazard ratio with every 1 year. Covariate centered around median of 62 years.
[28] Increase in the logarithmic hazard ratio with every 1 nM of sum of Css,av of ticagrelor and AR-C124910XX at Visit 1
[29] Increase in the hazard ratio with every 1 nM of sum of Css,av of ticagrelor and AR-C124910XX at Visit 1

*Source: Sponsor's Exposure-Response Modelling Report Safety Endpoints Table 10, page 52.*

The exposure response relationships for patients with or without CABG or PCI are visualized in **Error! Not a valid bookmark self-reference.**, Figure 6 and Figure 7. Given the 10-90$^{th}$ percentiles of total exposure at Visit 1 in a patient 62 years of age, the probability of major bleeding is 2.8-3.2%, 58-63% and 0.6% for a patient without CABG or PCI, with CABG and with PCI, respectively.

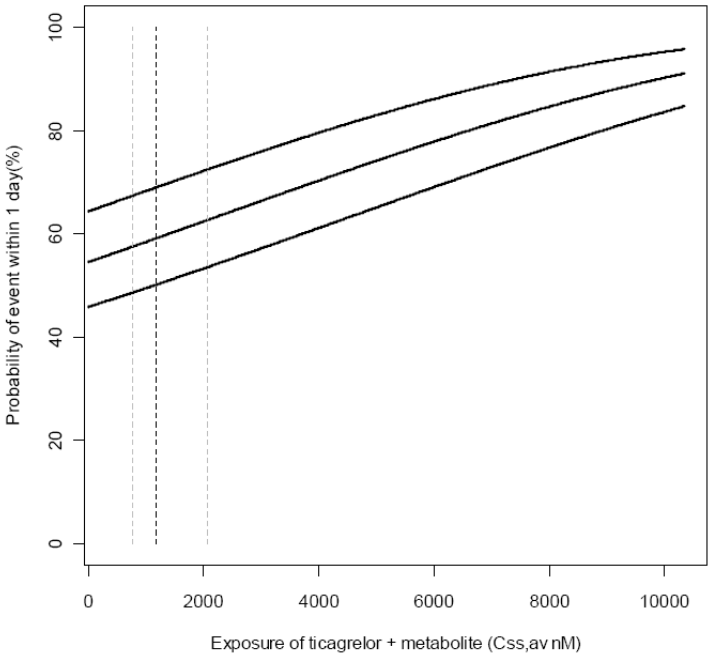
**Figure 5. Probability of major bleeding event within 1 year in patient without CABG or PCI with age of 48, 62 and 72 years vs. total $C_{ss,av}$ ticagrelor and AR-C124910XX at Visit 1.**




Note: The black vertical dashed line gives the median total exposure level. The grey vertical dashed lines give the 10-90% percentile of total $C_{ss,av}$ ; CABG Coronary artery bypass grafting; $C_{ss,av}$ Average plasma concentration at steady state; PCI Percutaneous coronary intervention.

*Source: Sponsor's Exposure-Response Modelling Report Safety Endpoints Fig 17, page 59.*

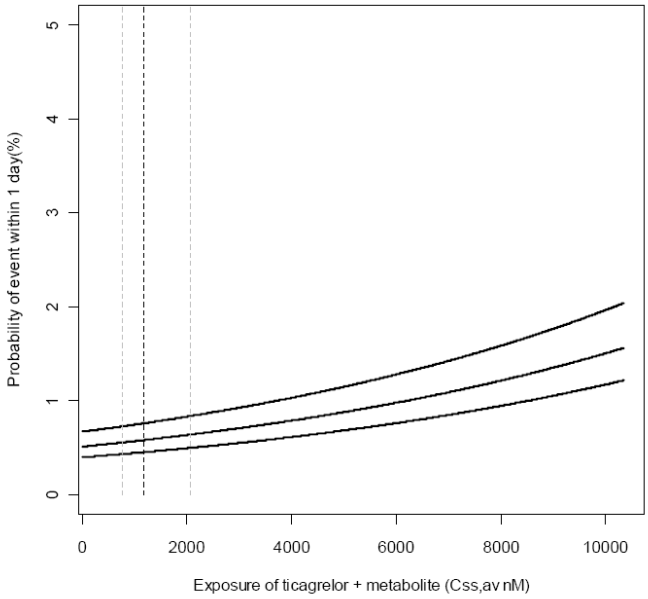
**Figure 6. Probability of major bleeding event within 1 year in patient with CABG but without PCI with age of 48, 62 and 72 years vs. total $C_{ss,av}$ ticagrelor and AR-C124910XX at Visit 1.**




Note: The black vertical dashed line gives the median total exposure level. The grey vertical dashed lines give the 10-90% percentile of total C*ss,av*; CABG Coronary artery bypass grafting; C*ss,av* Average plasma concentration at steady state; PCI Percutaneous coronary intervention.

*Source: Sponsor's Exposure-Response Modelling Report Safety Endpoints Fig 18, page 60.*

**Figure 7. Probability of major bleeding event within 1 year in patient with PCI but without CABG with age of 48, 62 and 72 years vs. total $C_{ss,av}$ ticagrelor and AR-C124910XX at Visit 1.**




Note: The black vertical dashed line gives the median total exposure level. The grey vertical dashed lines give the 10-90% percentile of total $C_{ss,av}$; CABG Coronary artery bypass grafting; $C_{ss,av}$ Average plasma concentration at steady state; PCI Percutaneous coronary intervention.

*Source: Sponsor's Exposure-Response Modelling Report Safety Endpoints Fig 19, page 61.*

*Reviewer's Comments: The exposure-response analysis of major bleeds is acceptable. The absence of a strong relationship between exposure and major bleeds may be due to the same factors described previously.*

### 3.3.2 Dyspnea

Dyspnea was reported in PLATO as no (0), mild (1), moderate (2) or severe (3) at each visit. A proportional odds model for ordered categorical data was used to analyze the data. The dyspnea event rate was found to change over time, so clopidogrel data were used to establish a disease progression model (assuming clopidogrel treatment does not have an effect on occurrence of dyspnea). The best model had a constant probability of a dyspnea event over the first 90 days followed by an increase in the probability of not having a dyspnea event over time. The risk factor model identified the following factors to confer an increased risk of dyspnea: diabetes, COPD, chronic renal disease, STEMI or NSTEMI index event, female sex, ex-smoker and early enroller in PLATO. The final exposure-response model included a linear association with ticagrelor $C_{ss,av}$ up to day 88. The predicted probability of having a dyspnea event (mild, moderate or sever) given the 10-90$^{th}$ percentile of ticagrelor exposure at Visit 1 was 2.2-2.8% in a patient with no risk factors. The relationship in a patient with all risk factors is illustrated in A shallow relationship between ticagrelor exposure and dyspnea was established. The predicted probability of having a dyspnea event (mild, moderate or severe) given the 10-90$^{th}$ percentile of ticagrelor exposure at Visit 1 was 2.2-2.8% in a patient with no risk factors. The relationship in a patient with all risk factors (diabetes, COPD, chronic renal disease, STEMI or NSTEMI index

event, female sex, ex-smoker and early enroller in PLATO ) is illustrated in **Error! Not a valid bookmark self-reference.**.
Figure 1.

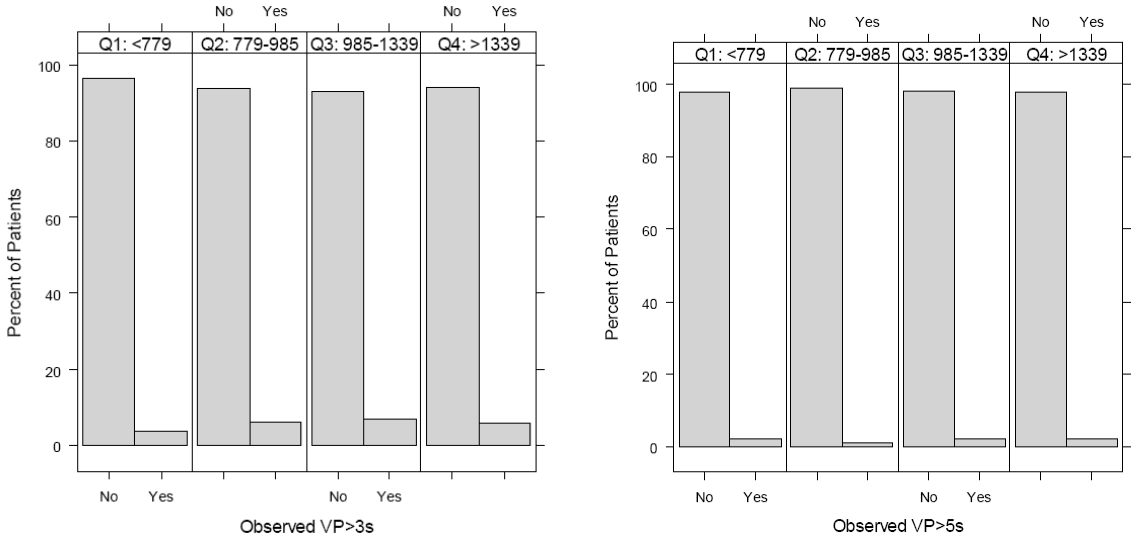
*Reviewer's Comments: The exposure-response analysis of dyspnea is acceptable. The absence of a strong relationship between exposure and dyspnea may be due to the same factors described previously.*

### 3.3.3 Ventricular Pause (VP)

**A subset of patients in the PLATO study was included in a Holter sub-study where ECGs were obtained at Visit 1 with repeat Holter monitoring at Visit 2. There were 1470 and 1282 patients included in the risk factor and exposure-response datasets, respectively. Logistic regression was used to model the relationship between risk factors, including ticagrelor exposure, and the occurrence of ventricular pauses. The observed occurrence of VP ≥ 3 and ≥ 5 seconds versus ticagrelor exposure is displayed in**

Figure 8.

**Figure 8. Oberved VP ≥ 3 (left) and ≥ 5 (right) seconds versus quartiles of ticagrelor exposure at Visit 2**




*Source: Sponsor's Exposure-Response Modelling Report Safety Endpoints Figs 4&7, pages 41&44.*

Only unstable angina pectoris was included in the risk factor model for both VP ≥ 3 and ≥ 5 seconds. No exposure-response relationship could be identified.

*Reviewer's Comments: The exposure-response analysis of ventricular pause is acceptable. The absence of a strong relationship between exposure and ventricular pause may be due to the same factors described previously. In addition, the sample size was smaller for the Holter sub-study and the incidence was lower (<6%), making it more difficult to capture a potential relationship.*

# 4 REVIEWER'S ANALYSIS

## 4.1 Introduction

In PLATO, ticagrelor was superior to clopidogrel in reducing the rate of the primary efficacy endpoint (hazard ratio 0.84 (95% CI 0.77, 0.92) p=0.0003). The hazard ratio for the primary efficacy endpoint within the USA, however, was 1.27 (95% CI 0.92, 1.75) compared to 0.81 (95% CI 0.74, 0.90) for the non-USA region, suggesting a benefit of clopidogrel over ticagrelor in the USA (Figure 9). A multivariate analysis of potential factors conducted by the sponsor suggested a possible role of aspirin dose to explain this finding (Figure 10). In the non-US population receiving aspirin doses greater than 300 mg, the hazard ratio favored clopidogrel over ticagrelor (1.21), but the sample size is very small. In the US population, where most patients received >300 mg aspirin, a similar finding was observed (hazard ratio = 1.68, favoring clopidogrel over ticagrelor). Bleeding rates were similar in ticagrelor and clopidogrel treated patients in the USA. A total of 14.1% of clopidogrel patients and 15.5% of ticagrelor patients experienced major or minor bleeds.

**Figure 9. Survival curves for composite efficacy for all patients (left) and only those patients in the USA**

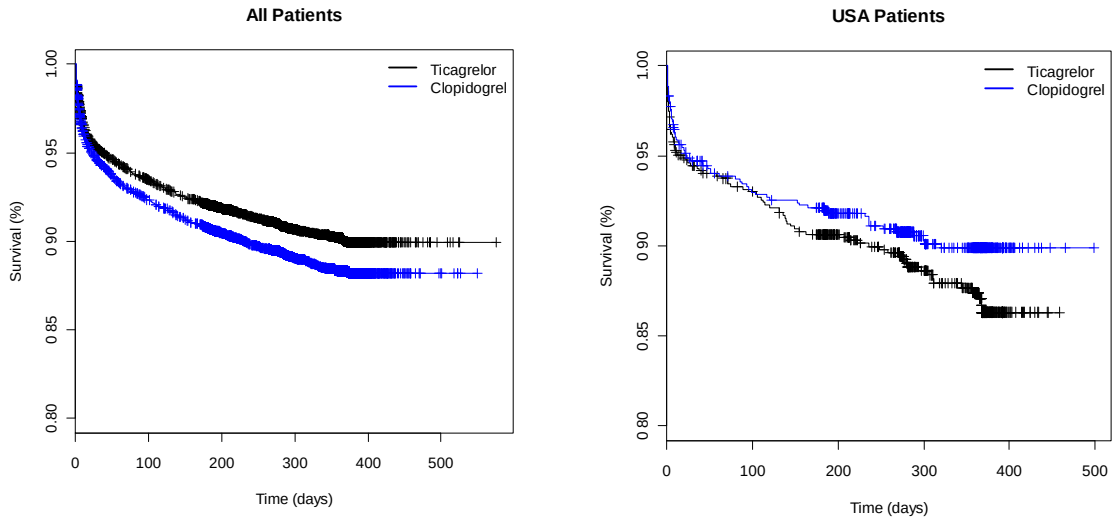
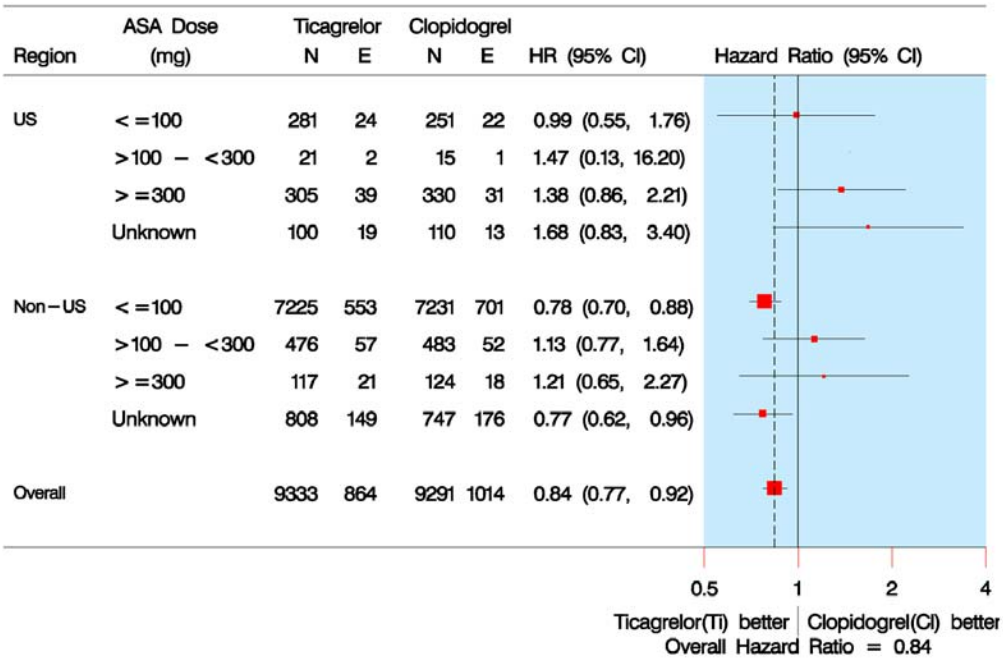


**Figure 10: Primary efficacy endpoint by aspirin dose category and treatment for USA and non-USA**




## 4.2 Objectives

Analysis objectives are:

1. Explore possible explanations for the subgroup analysis showing a benefit of clopidogrel over ticagrelor in the USA population

### 4.2.1 Data Sets

Data sets used are summarized in Table 4.

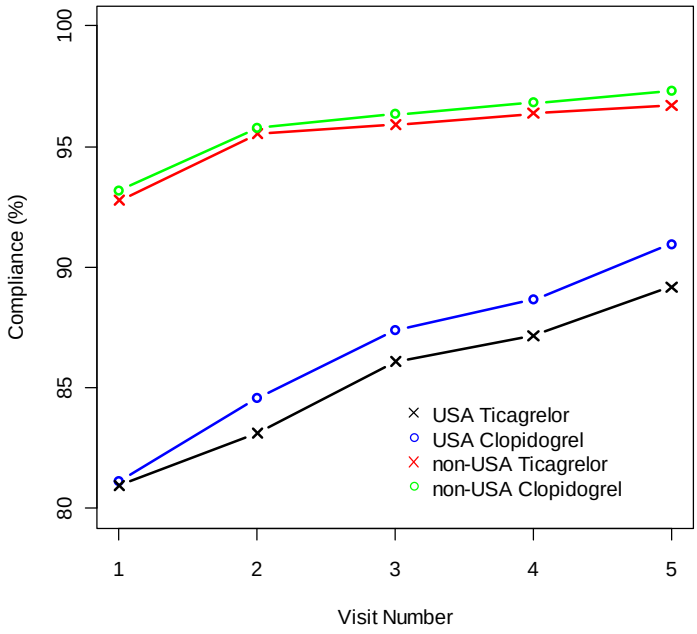
**Table 4. Analysis Data Sets**

| Study Number | Name | Link to EDR |
|---|---|---|
| D5130C05262 (PLATO) | aana.xpt | \\Cdsesub1\evsprod\NDA022433\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets |
| D5130C05262 (PLATO) | alabc.xpt | \\Cdsesub1\evsprod\NDA022433\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets |
| D5130C05262 (PLATO) | aevtlog.xpt | \\Cdsesub1\evsprod\NDA022433\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets |
| D5130C05262 (PLATO) | afdadata.xpt | \\Cdsesub1\evsprod\NDA022433\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\datasets |
| D5130C05262 (PLATO) | vit.xpt | \\Cdsesub1\evsprod\NDA022433\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-coronary-syndromes\5351-stud-rep-contr\d5130c05262\crt\tabulations |

### 4.2.2 Software
Analysis and plotting were performed in R Version 2.10.0.

### 4.2.3 Compliance
A possible explanation for the finding in the USA population is that ticagrelor patients were less compliant to study medication than clopidogrel patients. Patients in PLATO were asked to return unused investigational products and empty packages to the clinic at each visit. If the patient had taken study medication for more than 80% of the days between each visit the patient was regarded by the investigator as compliant. The time course of compliance is presented in **Error! Not a valid bookmark self-reference.**. Two findings from this plot are: (1) non-USA patients were more compliant than USA patients and (2) ticagrelor patients had the same level of compliance as clopidogrel patients. Together, these findings do not explain the discordant efficacy results in the USA population.

**Figure 11. Compliance to ticagrelor and clopidogrel in USA and non-USA in PLATO**

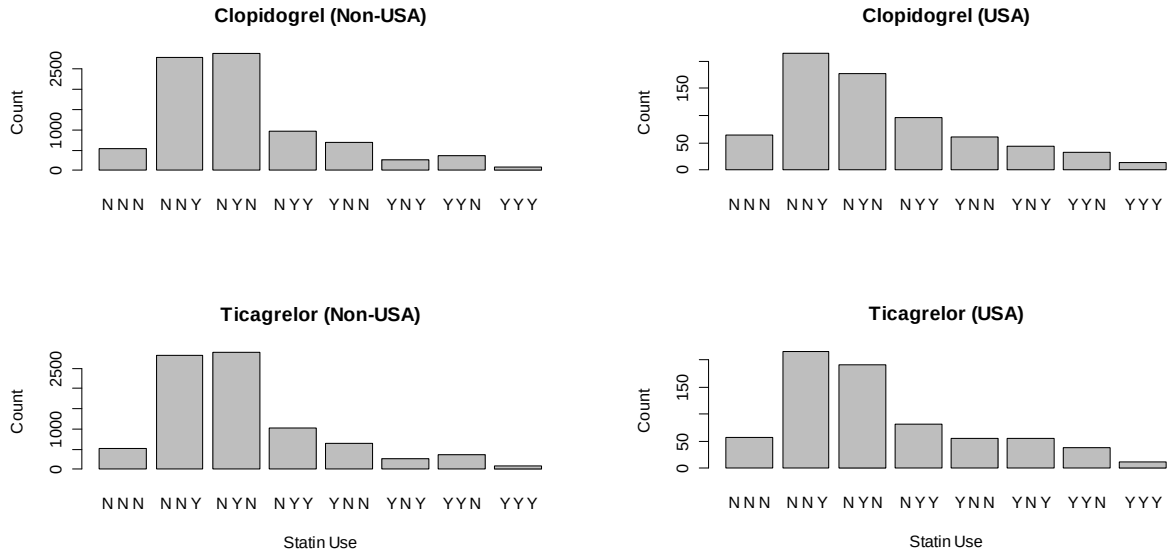



### 4.2.4 Statin Use
Lower statin exposure in patients in the USA receiving ticagrelor was also explored as a possible explanation for the finding in the USA for the following reasons:

- The survival curves for ticagrelor and clopidogrel in the USA begin to diverge at about 100 days whereas more events occur early after the index event. Efficacy events due to low statin exposure would be expected to occur at later times.
- Ticagrelor is a weak inhibitor of CYP3A4 and has been shown to increase levels of simvastatin.
- Choice of statin medication in the USA may differ from the rest of the world.

The distribution of statin use by route of metabolism in PLATO is illustrated in Figure 12. The results show the distribution of statin use for ticagrelor patients was similar to clopidogrel patients, regardless of geographical location. Most patients received a statin at least moderately metabolized by CYP3A4. Non-USA patients were relatively more likely to receive a moderately CYP3A4-metabolized statin whereas USA patients were more likely to receive a predominantly CYP3A4-metabolized. This would suggest, if anything, patients in the USA randomized to ticagrelor had higher exposure to statins than non-USA patients (assuming similar doses of statin medicines).

**Figure 12. Distribution of statin use for ticagrelor and clopidogrel in the USA and non-USA.** The x-axis labels are yes/no (Y/N) answers to whether the patient received: (1) non-CYP-3A4 metabolized statin, (2) other CYP3A4-metabolized statin and (3) predominantly CYP3A4-metabolized statin

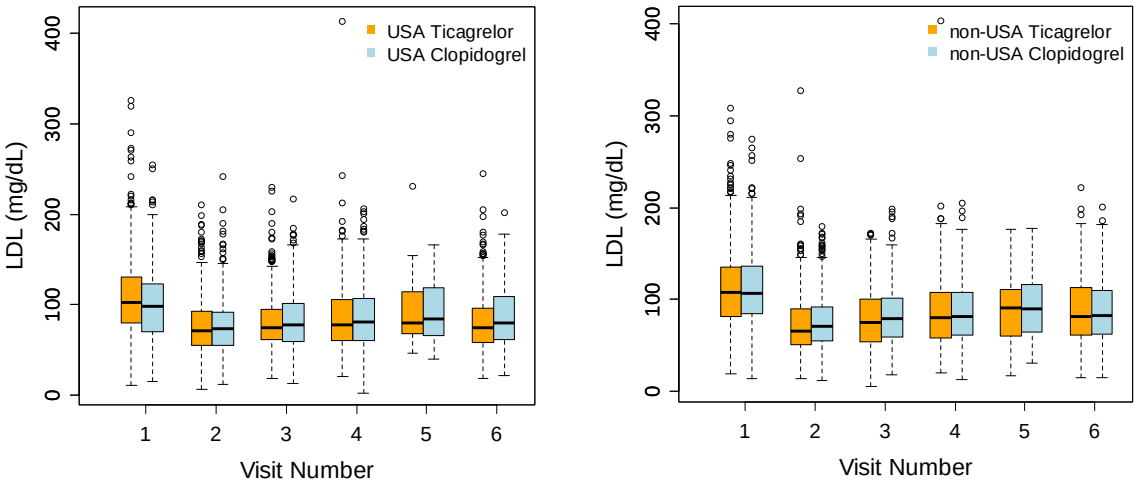



The incidence of myalgia was also explored as a surrogate of statin use. In the USA, clopidogrel patients were more likely to report myalgia (2.7%) than ticagrelor patients (2.0%). If anything, this suggests higher statin exposure in clopidogrel patients, although the numbers are very small. In non-USA patients, a similar proportion of clopidogrel patients reported myalgia (1.6%) compared to ticagrelor patients (1.6%).

Finally, the time course of LDL concentrations did not show any notable differences between USA and non-USA or ticagrelor and clopidogrel treated patients (Figure 13).

Together, these results do not indicate a role of statin exposure in the efficacy findings in the USA population.

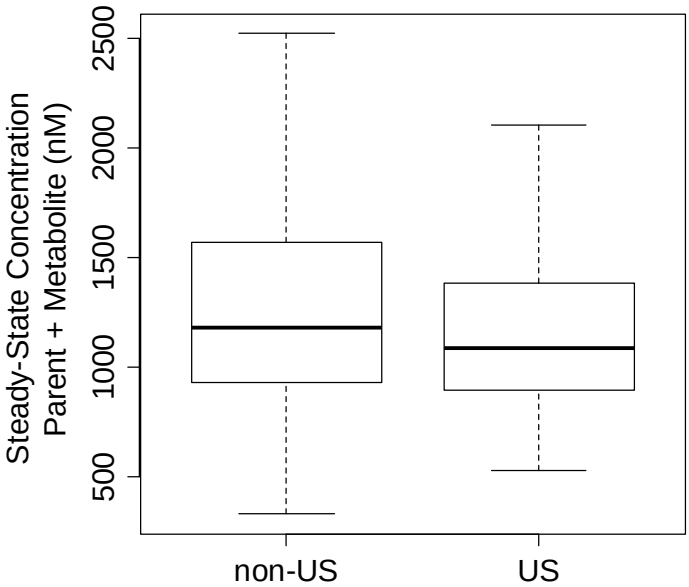
**Figure 13. Time course of LDL concentrations in PLATO**




### 4.2.5 Differences in Ticagrelor Exposure

Differences in ticagrelor exposure between USA and non-USA patients were explored. The results (Figure 14) do not suggest that differences in ticagrelor pharmacokinetics contribute to the differential efficacy findings in the USA. This is also supported by the fact that a positive exposure-response relationship for efficacy could not be established.

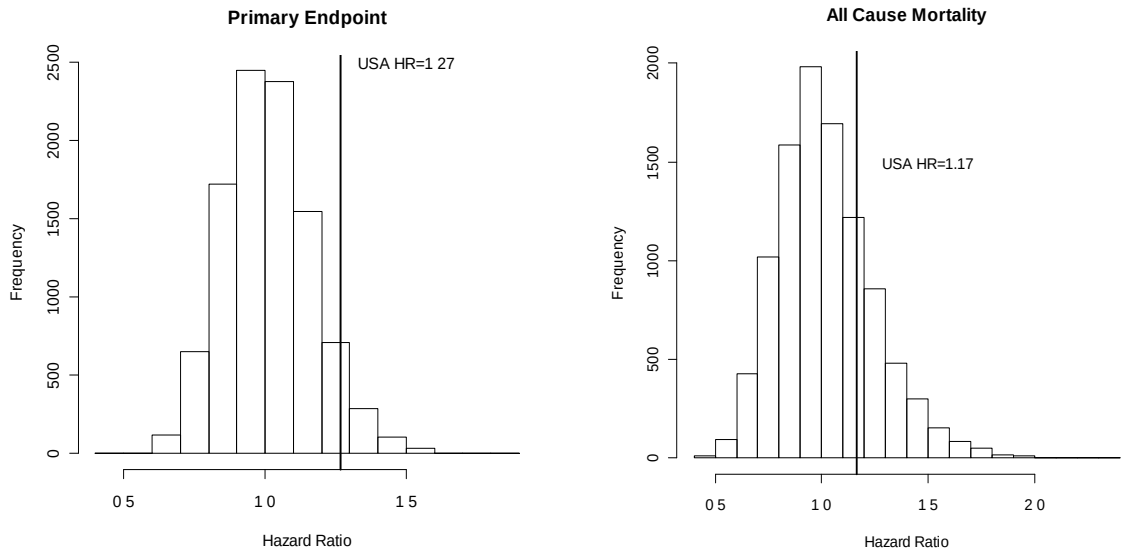
**Figure 14. Steady State Concentration of Ticagrelor + AR-C124910XX in USA and non-USA patients in PLATO**



### 4.2.6 Chance

The differential efficacy findings in the USA could have been the result of chance. To explore the likelihood of a chance finding, the probability of observing the USA finding (HR=1.17 for all-causemortality or HR=1.27 for primary efficacy outcome) was calculated assuming no difference (HR=1) between clopidogrel and ticagrelor treatment arms. A bootstrap analysis was conducted where non-USA clopidogrel patients (n=8585) were sampled into two groups (n=707) representing USA ticagrelor and clopidogrel treatment arms. The hazard ratio under this scenario was calculated for 10,000 bootstrap samples and compared to the observed hazard ratio in the USA (Figure 15). Assuming a HR=1 for primary efficacy outcome, the probability of finding a HR of 1.27 or greater in the USA is calculated to be 5.8%. Assuming a HR=1 for all-cause mortality, the probability of finding a HR of 1.17 or greater is calculated to be 23%.

**Figure 15. Predicted distribution of HR for primary efficacy endpoint (left) and mortality (right) in the USA assuming no difference between clopidogrel and ticagrelor.** The vertical line represents the USA observation in the PLATO trial.




### 4.2.7 Uric Acid, Fructose and Cardiovascular Risk

Epidemiological data have suggested a link between fructose intake, hyperuricemia and increases in blood pressure (Feig DI et al., N Engl J Med 2008;359:1811-21). In PLATO, the mean change from baseline of serum uric acid in patients treated with ticagrelor was 15% compared to 7.5% in patients treated with clopidogrel. To explain the efficacy findings in the USA population, the following hypothesis was explored:

- A high fructose diet in the USA exacerbated the increase in serum uric acid induced by ticagrelor.
- Higher serum acid levels in the USA gave rise to higher blood pressure and thus more cardiovascular events.

Baseline serum uric acid levels were similar in USA and non-USA patients treated with ticagrelor (Figure 16). Patients in the USA treated with ticagrelor had slightly higher serum uric

acid by Visit 6 than non-USA patients, but the time course was generally consistent. In addition, there were no discernible differences in systolic or diastolic blood pressure between ticagrelor and clopidogrel treated patients in the USA (Figure 17).

**Figure 16. Time course of serum uric acid in PLATO in patients treated with ticagrelor**

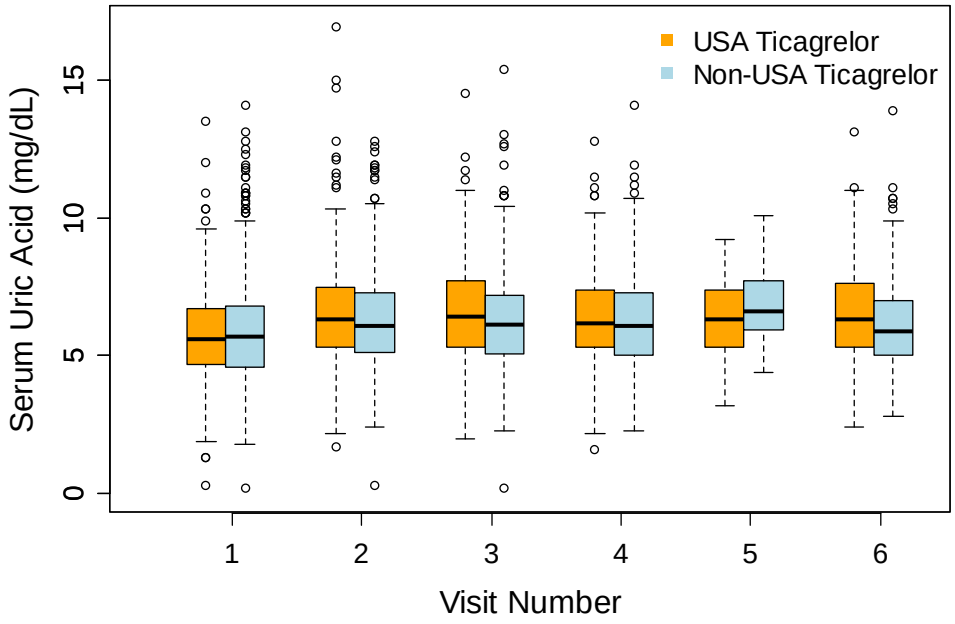
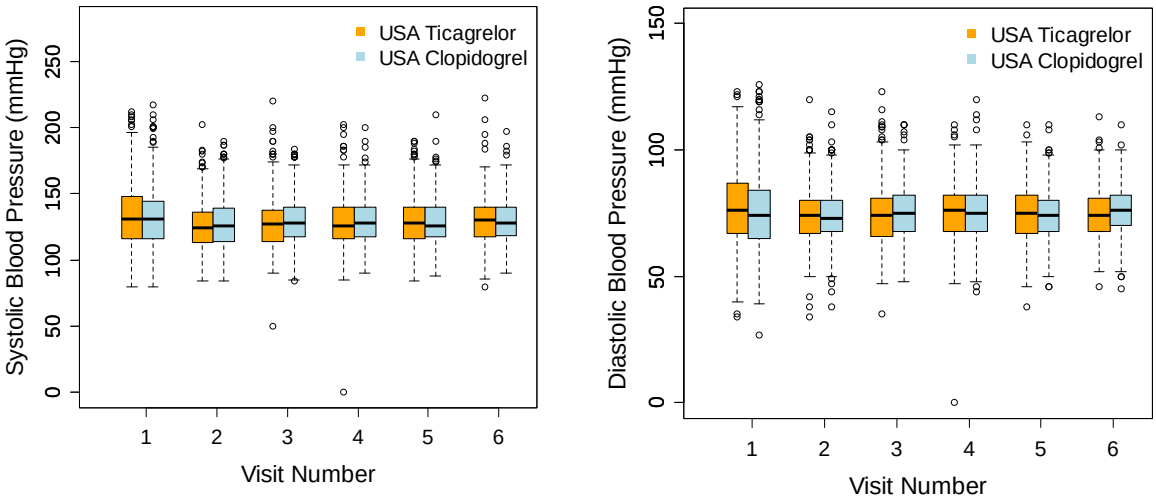



**Figure 17. Time course of systolic (left) and diastolic (right) blood pressure in USA patients treated with ticagrelor or clopidogrel**



# 5 LISTING OF ANALYSIS CODES AND OUTPUT FILES

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| make.bpanalysis.R | Fructose-uricemia analysis | Reviews\Ongoing PM Reviews\Ticagrelor_NDA224333_KMK\ER Analyses\US |
| make.compliance.R | Compliance analysis | Reviews\Ongoing PM Reviews\Ticagrelor_NDA224333_KMK\ER Analyses\US |
| make.event.R | Time to event analysis | Reviews\Ongoing PM Reviews\Ticagrelor_NDA224333_KMK\ER Analyses\US |
| make.ldl.R | Ldl analysis | Reviews\Ongoing PM Reviews\Ticagrelor_NDA224333_KMK\ER Analyses\US |
| make.statins.R | Statin analysis | Reviews\Ongoing PM Reviews\Ticagrelor_NDA224333_KMK\ER Analyses\US |
| make.bootHRclopclop.R | Bootstrap analysis (primary endpoint) | Reviews\Ongoing PM Reviews\Ticagrelor_NDA224333_KMK\ER Analyses\US |
| make.bootHRclopclopmortality.R | Bootstrap analysis (all-cause mortality) | Reviews\Ongoing PM Reviews\Ticagrelor_NDA224333_KMK\ER Analyses\US |

# PHARMACOGENOMICS

## EXECUTIVE SUMMARY

Ticagrelor is a reversible P2YR12 receptor antagonist evaluated for the reduction of thrombotic events in patients with acute coronary syndrome (ACS). The applicant submitted a series of exploratory candidate gene association studies at the Agency's request for 1) pharmacokinetic/ pharmacodynamic (PK/PD) endpoints, 2) dyspnea, and 3) clinical outcomes in the PLATO trial. This review evaluated the pharmacogenetic (PG) studies conducted by the applicant, whether relevant safety PG findings should be communicated in the drug product label, and the need for additional post-action PG investigations.

The main findings of the applicant's PG investigations are as follows:

- Single nucleotide polymorphisms (SNPs) in ticagrelor's target (*P2RY12*), principal mediators of ticagrelor exposure (*ABCB1*, *CYP3A5*), and other candidate genes (*P2RY1*, *ITGA2*, *ITGB3*), did not appear to significantly influence antiplatelet responses to ticagrelor.
- SNPs in adenosine receptors and transporters (97 SNPs in 11 genes) or PK/PD candidate genes did not reveal any robust associations with dyspnea. Gene variants in *PLA2G7* and *PON1*, mediators of lipid oxidation and inflammation, demonstrated nominal associations with dyspnea (odds ratios for variant homozygotes were 0.27 [P=0.004] and 3.23 [P=0.04], respectively); these findings would need to be replicated or supported by additional experimental evidence.
- The applicant genotyped *CYP2C19* and *ABCB1* variants in 55% of the PLATO population (n=10,285). Numerically higher event rates for the primary efficacy endpoint and some components were observed in clopidogrel-treated patients with one or more loss-of-function alleles. Early separation in event rates between treatments was observed among those with at least one *CYP2C19* loss-of-function allele. Bleeding rates were comparable between ticagrelor and clopidogrel irrespective of *CYP2C19* genotype. The impact of CYP2C19 gain-of-function alleles on either ticagrelor- or clopidogrel-associated bleeding could not be concluded due to inconsistent trends with increasing numbers of *17 variants. *CYP2C19* genotype distribution did not differ in the U.S. vs. non-U.S. regions and did not appear to account for the geographic differences in outcomes, although the analysis was limited to a very small subset. *ABCB1* genotype was not robustly associated with outcomes in either treatment arm.

Recommendations from the perspective of the Genomics Group:

- Post-marketing commitments/requirements: None
- Label: The ticagrelor label should reflect treatment effects in *CYP2C19* genotype-defined subgroups.
- Additional comment: PG studies to understand the mechanism of dyspnea and other adverse events (e.g., ventricular pauses) should be conducted with a more agnostic

strategy, such as a genome-wide association study.

# 1 BACKGROUND

The current submission is a NDA for ticagrelor, a reversible P2YR12 receptor antagonist of the cyclopentyltriazolopyrimidine chemical class. The proposed indication is to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or invasively with percutaneous coronary intervention (PCI; with or without stent) and/or CABG.

Following a discussion at the pre-NDA meeting held on 4/20/2009, the applicant included the results of exploratory PG studies in the original NDA submission. Additionally, following revision of the clopidogrel label to include a *Boxed Warning* concerning diminished responses in CYP2C19 poor metabolizers in the ACS/PCI settings (March 2010), the Agency requested *CYP2C19* genotype data for the pivotal Phase 3 trial in which clopidogrel was the comparator (PLATO; request sent 3/18/2010); these data were received on 5/3/2010.

The purpose of this review is to evaluate the PG studies conducted by the applicant, determine whether relevant safety PG findings should be communicated in the drug product label, and assess the need for additional post-action PG investigations.

# 2 SUBMISSION CONTENT RELATED TO GENOMICS

The clinical development program for ticagrelor consisted of 34 clinical pharmacology studies, including the Phase 2 trials OFFSET and RESPOND, two additional Phase 2 trials (DISPERSE, and DISPERSE 2), and one Phase 3 trial (PLATO). Subjects participating in the key Phase 2 and 3 studies consented to DNA sample collection for genetic studies on a voluntary basis.

The results of PG analyses were submitted to the Agency for RESPOND, DISPERSE, DISPERSE2, and PLATO in the following reports: *Ticagrelor Exploratory Genetic Analysis* and the *PLATO Genetics Substudy Report*. General design attributes of the key trials discussed in this review, DNA substudy enrollment rates, and tested PG hypotheses are provided in the following table.

**Pharmacogenomic substudies of ticagrelor Phase 2 and 3 trials**

| Study, population | DNA N / total N* (%) | Treatment† | Objectives | Endpoint (genotyped sample size) and genetic marker sets |
|---|---|---|---|---|
| OFFSET, Stable CAD | 116 / 123 (94%) | T: 180 mg → 90 mg BID<br>C: 600 mg → 75 mg QD | PD‡, PK | Not reported |
| RESPOND, Stable CAD | 71 / 98 (72%) | T: 180 mg → 90 mg BID<br>C: 600 mg → 75 mg QD | PD‡, PK | PD (n=71): *CYP2C19* |
| DISPERSE, Documented ASCVD | 181 / 201 (90%) | T: 50, 100, 200, 400 mg BID<br>C: 75 mg QD | PD‡, PK | Set 1 – PD (n=176): *CYP3A5*, *ABCB1*, *P2RY12*, *PLA2G7*<br>Set 2 – dyspnea (n=20+63): *PLA2G7*, *ABCB1*, *CYP3A5* |

| Study, population | DNA N / total N* (%) | Treatment† | Objectives | Endpoint (genotyped sample size) and genetic marker sets |
|---|---|---|---|---|
| DISPERSE2, NSTE ACS | 777 / 990 (78%) | T: 270 mg → 90 mg BID or 180 mg BID<br>C: 300 mg → 75 mg QD | Safety/ tolerability, PD‡, popPK | Set 1 – PD (n=770, wk4 n=23): *ABCB1*, *P2RY12*, *PLA2G7*<br>Set 2 – dyspnea (n=87+644): *PLA2G7*, *ABCB1* |
| DISPERSE + DISPERSE2 combined | -- | -- | -- | Set 1 – PD (n=197): *ITGA2*, *ITGB3*, *P2RY1*, *P2RY12*‡<br>Set 2 – dyspnea (n=89+531): *ADORA1*, *2A*, *2B*, 3, *ENT1*, *2*, *3*, *4*, *CNT1*, *2*, *3*‡<br>Set 3 – dyspnea (n=107+804): *PON1*‡ |
| PLATO, ACS | 10,429 / 18,624 (56%) | T: 180 mg → 90 mg BID<br>C: ≤600 mg → 75 mg QD | Efficacy, safety, popPK | CV death+MI+stroke, CV death+MI, bleeding [total, non-CABG, CABG], net clinical benefit. stent thrombosis (n=10,393): *CYP2C19*, *ABCB1* |

T=ticagrelor, C=clopidogrel, LTA=light transmittance aggregometry, PK=pharmacokinetics, PD=pharmacodynamics, CV=cardiovascular, MI=myocardial infarction, ASCVD=atherosclerotic CV disease, CAD=coronary artery disease
* DNA N=consented and sample collected, including clopidogrel-treated subjects total N=randomized
† ASA to be coadministered in all patient studies
‡ PD markers were as follows: OFFSET and RESPOND – LTA, VerifyNow, flow cytometry, vasodilator associated phosphoprotein; DISPERSE – LTA and bleeding time; DISPERSE2 – LTA

# 3 KEY QUESTIONS AND SUMMARY OF FINDINGS

## 3.1 What genetic factors influence ticagrelor PK/PD?

*SNPs in ticagrelor's target, P2RY12, or principal mediators of ticagrelor disposition, ABCB1 and CYP3A5, did not appear to significantly influence antiplatelet responses (platelet aggregation) or ticagrelor exposure after 4 weeks of treatment in DISPERSE and DISPERSE2. Other polymorphisms that broadly characterize the genetic diversity of P2RY1, ITGA2, and ITGB3, which encode platelet receptors and glycoproteins, also did not influence antiplatelet responses. None of these polymorphisms have consistently been shown to modulate responses to other P2RY12 antagonists such as clopidogrel.*

Based on published literature, variants in the genes encoding ticagrelor's target (*P2RY12*) or other mediators of platelet function (e.g., integrins) could modulate antiplatelet responses. Additionally, ticagrelor is a substrate for P-glycoprotein (*ABCB1*), which is known to have common genetic polymorphisms that may alter expression. Ticagrelor is metabolized by CYP3A4/5, but is otherwise not known to be a substrate for polymorphic enzymes.

### 3.1.1 Sponsor's analysis

To evaluate the association between PD- and PK-related gene variants and platelet inhibition or ticagrelor exposure, the applicant conducted PG analyses of DISPERSE and DISPERSE2.

#### 3.1.1.1 Pharmacogenetics of antiplatelet response

***DISPERSE***

***Methods*:** All subjects with samples available were genotyped for established markers in *P2RY12* (4 SNPs), *CYP3A5* (1 SNP), and *ABCB1* (1 SNP). Additionally, 21 *PLA2G7*

SNPs (identified through resequencing) were genotyped in a subset of subjects who were selected based on dyspnea status for the purpose of another analysis (see section 3.2.1). Genotype status was analyzed in relation to ADP- and collagen-stimulated aggregation in the per protocol population (n=148), combining all ticagrelor dose groups; clopidogrel was analyzed separately. Genotypic differences in absolute and relative changes in final and maximal platelet aggregation levels on Days 1, Day 14, and Day 28 (pre-dose and at 4, 12, and 24 hours post-dose) were analyzed using ANOVA.

***Results*:** *P2RY12* haplotype did not have a substantial effect on platelet aggregation (ADP or collagen) at baseline (pre-dose) or any time point following ticagrelor (combined or within doses) or clopidogrel treatment. Representative data from Day 14 and Day 28 are shown in the tables below.

**Percent change from pre-dose final aggregation by P2RY12 haplotype for ticagrelor (top) and clopidogrel (bottom)**

| Genotype | n | Day 14 – 4 hours | Day 14 – 12 hours | Day 28 – 4 hours | Day 28 – 12 hours |
|---|---|---|---|---|---|
| H1/H1 | 70 | 87.4 (13.5) | 78.8 (21.9) | 89.5 (12.1) | 87.7 (21.1) |
| H1/H2 | 48 | 85.4 (18.0) | 80.5 (22.3) | 86.1 (18.7) | 78.6 (24.5) |
| H2/H2 | 2 | 91.7 (11.8) | 91.7 (11.8) | 86.7 (18.9) | 89.6 (14.7) |

| Genotype | n | Day 14 – 4 hours | Day 14 – 12 hours | Day 28 – 4 hours | Day 28 – 12 hours |
|---|---|---|---|---|---|
| H1/H1 | 20 | 60.0 (26.7) | 55.7 (23.8) | 63.0 (20.8) | 56.5 (22.8) |
| H1/H2 | 8 | 62.9 (12.9) | 62.9 (23.0) | 62.4 (14.8) | 60.7 (20.0) |

H1 and H2 denote P2RY12 haplotypes determined by genotyping 4 SNPs
*Source Ticagrelor Exploratory Genetic Analysis Report, page 10*

*CYP3A5*, *ABCB1* and *PLA2G7* SNPs reportedly had no association with antiplatelet responses, but detailed results were not presented.

### *DISPERSE2*

***Methods*:** Subjects (n=770) were genotyped for SNPs in *ABCB1* (1 SNP), *P2RY12* (4 SNPs), and *PLA2G7* (17 SNPs). Genotype status was assessed in relation to ADP-stimulated aggregation for platelet function substudy participants at baseline (n=72; 46% clopidogrel naïve) and at week 4 (n=29; 72% randomly assigned to ticagrelor, all doses combined). Data from Day 1 and Day 28 were analyzed pre-dose and at 2, 4, 8 and 12 hours post-dose. The final and maximum aggregation levels at baseline and the percent change from baseline pre-dose levels were analyzed at each day and at each time point.

***Results*:** Approximately one-third of the subjects had the minor *P2RY12* H2 haplotype, which is expected to result in diminished responses (PMID 12912815). The H3 and H4 haplotypes were rare, being observed in 16 of 770 subjects in the overall population. At baseline, pre-dose platelet aggregation was lower for clopidogrel-treated subjects as compared to clopidogrel naïve subjects, but did not differ according to *P2RY12* haplotype (results not shown).

Following the initial dose of ticagrelor, 4-hour ADP-aggregation did not differ according to *P2RY12* haplotype in either clopidogrel pre-treated or clopidogrel-naïve subjects, as shown in the table below.

**Day 1 (4 hours) mean of final ADP aggregation (%)**

| | Clopidogrel pre-treated | | | Clopidogrel naïve | | |
|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD |
| H1/H2 | 26 | 12.4 | 17.4 | 20 | 19.9 | 18.3 |
| H1/H2 | 13 | 15.7 | 20.4 | 13 | 24.9 | 23.8 |

SD Standard deviation

*Source Ticagrelor Exploratory Genetic Analysis Report, page 11*

Following ticagrelor maintenance dosing, week 4 pre-dose, 4-hour post-dose, and 12-hour post-dose inhibition of platelet aggregation did not differ by *P2RY12* haplotype, as shown in the tables below. Changes from baseline to week 4 also did not differ (results not shown). Clopidogrel responses did not differ at any time point according to *P2RY12* haplotype.

**Week 4 final ADP induced platelet aggregation (%) at 4 hours (top) and 12 hours (bottom)**

| | AZD6140 | | | Clopidogrel | | |
|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD |
| H1/H1 | 15 | 86.0 | 21.3 | 3 | 57.5 | 32.2 |
| H1/H2 | 7 | 86.5 | 16.2 | 4 | 61.4 | 17.6 |

SD Standard deviation

| | AZD6140 | | | Clopidogrel | | |
|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD |
| H1/H1 | 15 | 86.1 | 16.8 | 3 | 64.8 | 24.2 |
| H1/H2 | 7 | 75.2 | 21.0 | 4 | 55.8 | 8.2 |

SD Standard deviation

*Source Ticagrelor Exploratory Genetic Analysis Report, page 13*

Analysis results for *PLA2G7* and *ABCB1* were not reported. *CYP3A5* was not genotyped.

### *DISPERSE+DISPERSE2 combined analysis*

***Methods*:** Combined week 4 platelet aggregation results from DISPERSE (ticagrelor n=134, clopidogrel n=33) and DISPERSE2 (ticagrelor n=23, clopidogrel n=7) were analyzed in relation to haplotype-tagging SNPs in the following 4 candidate genes: *ITGA2*, *ITGB3*, *P2RY1*, and *P2RY12*. Genotyping was planned for 167 putatively functional and HapMap-based haplotype-tagging SNPs (MAF>1%) within 10 kilobases of each gene. Associations with ADP- and collagen-induced platelet aggregation at baseline (maximal and final) and at week 4 (4 hours and 12 hours post-dose) were tested using ANOVA under an additive model, followed by a genotypic model where nominally significant associations were identified. Allelic models were tested where genotype counts were <5. Multiplicity was addressed through permutation testing (n=1000). Analyses were performed for each SNP and study, alone and combined. Statistical analyses adjusted for study, prior clopidogrel use, treatment, and baseline final platelet aggregation as appropriate (as appropriate for the dependent variable of interest).

***Results*:** Genotype data were available for a total of 254 patients, of which 197 had ADP aggregation data at week 4. Genotyping was successful for 157 SNPs as follows: *ITGA2* (81/89 SNPs), *ITGB3* (45/46 SNPs), *P2RY1* (7/7 SNPs) and *P2RY12* (24/25 SNPs). The most significant SNP associations are shown in the following table. The only association that was robust to sponsor's adjustment for multiple comparisons was the *ITGA2* rs1445937 (C__8958700_1) SNP, which was associated with baseline ADP-aggregation in DISPERSE2 and not specifically reflective of a ticagrelor PD response.

**Summary of analysis results for ADP aggregation in combined analysis of DISPERSE and DISPERSE2**

| Outcome | Study | Most significant p-value | SNP<br>Gene<br>End-point | Adjusted p-value |
|---|---|---|---|---|
| Baseline pre-dose ADP-induced platelet aggregation inhibition | DISPERSE | 0.0182 | rs17451266<br>*P2RY1*<br>Baseline Final | 0.881 |
| Baseline pre-dose ADP-induced platelet aggregation inhibition | DISPERSE2 | 0.0002 | C___8958700_1<br>*ITGA2*<br>Baseline Final | 0.030 |
| Week 4, ADP-induced maximum platelet aggregation inhibition (4 hours and 12 hours) | DISPERSE and DISPERSE2 | 0.0079 | C__29661528_10<br>*ITGA2*<br>12hrs maximum | 0.811 |

*Source Ticagrelor Exploratory Genetic Analysis Report, page 8*

### 3.1.1.2 Pharmacogenetics of ticagrelor exposure

#### *DISPERSE*

PG analyses of ticagrelor PK in DISPERSE were not presented by the sponsor (the results of the DISPERSE PK analyses conducted by the reviewer are presented in section 3.1.2).

#### *DISPERSE2*

***Methods:*** See section 3.1.1.1 for genotyping and analysis strategy.

***Results*:** AUC and $C_{max}$ data were available for 628 subjects based on the Bayesian post-hoc estimates of the population PK analysis (MetrumRG). Matched AUC/$C_{max}$ and *ABCB1* 3435 C/T genotyping data were available for 505 subjects. Ticagrelor exposures did not differ substantially between *ABCB1* genotype groups, as shown in the table below. Exposures to AR-C124670XX (metabolite) also did not differ (not shown).

**Ticagrelor exposure distribution from population PK analysis by ABCB1 (MDR1) 3435 C/T genotype**

| AZD6140 | | | | | | |
|---|---|---|---|---|---|---|
| Dose | MDR1_C3435T | N | AUC (mg/L) | | $C_{max}$ (ng/ml) | |
| | | | Gmean | CV% | Gmean | CV% |
| 90 | TT | 68 | 5.72 | 40 | 623.91 | 43 |
| 90 | CT | 137 | 5.44 | 53 | 607.27 | 54 |
| 90 | CC | 55 | 5.04 | 54 | 539.16 | 58 |
| 180 | TT | 88 | 12.04 | 48 | 1285.07 | 48 |
| 180 | CT | 104 | 13.29 | 47 | 1445.28 | 48 |
| 180 | CC | 53 | 11.88 | 48 | 1280.76 | 46 |

*Source Ticagrelor Exploratory Genetic Analysis Report, page 16*

*CYP3A5* genotype data were not submitted for DISPERSE2.

### 3.1.2 Reviewer's analysis

SNP associations with pharmacodynamic responses to ticagrelor were reanalyzed for the following priority candidates: *P2YR12*, *ABCB1*, and *CYP3A5*. This analysis focused on 4-week maximal ADP aggregation and ticagrelor PK (dose-normalized, subjects with dense sampling) data from the per-protocol, ticagrelor-treated populations of DISPERSE and DISPERSE2. Analyses were carried out for the individual studies and dose groups, as well as combined studies and dose groups. In addition to the priority candidates, all available markers with HWE P>0.0001, including those SNPs in the adenosine pathway selected for dyspnea studies (described in subsequent sections), were analyzed. Testing was performed under a genotypic model using the F-test. No formal multiplicity correction was performed in this exploratory analysis; P-values <0.01 were regarded nominally significant for reporting purposes. Pooled analysis of DISPERSE and DISPERSE2 was performed for the priority candidates using a general linear model adjusting for study and dose.

Reanalysis of the *P2RY12*, *ABCB1*, and *CYP3A5* data confirmed the lack of significant PG effects on post-ticagrelor ADP-mediated aggregation in both trials, with and without stratification by dose (results for combined dose group in each study are shown below).

**Maximal ADP aggregation 4-hours post-dose at week 4 in ticagrelor-treated subjects**

| Gene | Haplotype/ Genotype | DISPERSE N | DISPERSE Mean | DISPERSE SD | DISPERSE2 N | DISPERSE2 Mean | DISPERSE2 SD |
|---|---|---|---|---|---|---|---|
| *P2RY12* | H1/H1 | 77 | 23.8 | 9.4 | 14 | 24.4 | 8.6 |
| | H1/H2 | 51 | 24.6 | 12.9 | 7 | 25.4 | 11.4 |
| | H2/H2 | 2 | 21.8 | 10.3 | 0 | … | … |
| *ABCB1* | C/C | 29 | 25.2 | 12.6 | 5 | 18.4 | 4.3 |
| | C/T | 62 | 22.7 | 9.6 | 13 | 25.5 | 10.2 |
| | T/T | 39 | 25.4 | 11.3 | 3 | 32.0 | 5.6 |
| *CYP3A5* | Expresser | 18 | 24.9 | 9.6 | | N/A | |
| | Non-expresser | 112 | 23.9 | 11 | | | |
| N/A=not available | | | | | | | |

In the pooled analysis of DISPERSE and DISPERSE2, genotype associations with 4-hour post-dose platelet aggregation at 4 weeks were not significant for any alleles of *ABCB1* (P=0.26), *CYP3A5* (P=0.80), or *P2YR12* (P=0.74).

Additional combined analysis of DISPERSE and DISPERSE2 was performed for all available genetic markers. This analysis included a total of 143 samples that had >90% genotype data for the 312 assayed loci that met the HWE threshold. Only one marker in *ADORA3* (rs9025, 3'UTR) had a P<0.01 for the association with ADP aggregation at 4 weeks (A/A 22.6%, A/T 28.1%, T/T 38.5%, P=0.008); the biologically plausibility of this relationship is not readily apparent.

Steady-state ticagrelor PK and genotype data were available from 128 subjects in DISPERSE and 19 subjects in DISPERSE2. As shown in the following table, ticagrelor PK did not vary substantially according *ABCB1* or *CYP3A5* genotype, consistent with the findings of the population PK analysis of *ABCB1*. Analysis within each dose stratum and for the pooled population produced similar results (not shown).

**Ticagrelor pharmacokinetics by ABCB1 and CYP3A5 genotype**

| | Gene | Genotype | DISPERSE | | | DISPERSE2 | | |
|---|---|---|---|---|---|---|---|---|
| | | | N | Mean | SD | N | Mean | SD |
| *Dose-normalized AUC (mg/L)* | *ABCB1* | C/C | 29 | 71.9 | 43.9 | 4 | 46.7 | 11.5 |
| | | C/T | 61 | 61.7 | 30.0 | 12 | 70.3 | 29.4 |
| | | T/T | 38 | 62.5 | 31.0 | 3 | 51.6 | 22.1 |
| | *CYP3A5* | Expresser | 18 | 52.1 | 21.9 | N/A | | |
| | | Non-expresser | 110 | 66.2 | 34.9 | | | |
| *Dose-normalized Cmax (ng/ml)* | *ABCB1* | C/C | 29 | 9.4 | 4.4 | 4 | 8.1 | 3.7 |
| | | C/T | 61 | 8.7 | 4.2 | 12 | 10.3 | 4.7 |
| | | T/T | 38 | 8.8 | 5.3 | 3 | 7.4 | 1.5 |
| | *CYP3A5* | Expresser | 18 | 7.9 | 5.3 | N/A | | |
| | | Non-expresser | 110 | 9.1 | 4.4 | | | |
| N/A=not available | | | | | | | | |

### 3.1.3 Reviewer's comments

*Previous studies of PY2R12, P2RY1, ITGA2, and ITGB3 gene variants have not demonstrated significant, reproducible effects on antiplatelet responses to P2YR12 antagonists such as clopidogrel (PMID 16181985, 15933261, 18485500, 17157856, 16214444, 16458133, 16411409).*

*CYP3A5 genotype data were not available for DISPERSE2, limiting conclusions related to effects of CYP3A5 on ticagrelor PK and PD. The 19% lower exposure in blacks could be consistent with CYP3A5 genetic variability, given the higher prevalence of functional CYP3A5 in African populations.*

*The applicant's sample testing and analysis strategy is acceptable, as are the gene and SNP selection strategies. The functional and clinical consequences of the ABCB1 3435 T allele have been inconsistent (PMID 11434506, 12142082, 15280437, 16141795, 16370938, 15752383), therefore broader coverage of this gene might be prudent. Additionally, CYP3A5 alleles other than *3 decrease enzyme function, such as the *6 and *7 alleles, although these are more prevalent in populations of African ancestry.*

## 3.2 Are variants in the adenosine pathway, *PLA2G7*, *PON1*, or PK/PD candidate genes associated with ticagrelor-related dyspnea?

*Case-control analysis of dyspnea (89 cases, 544 controls) in DISPERSE and DISPERSE2 did not reveal any robust associations with SNPs in adenosine receptors and transporters (97 SNPs in 11 genes), or PK/ PD candidate genes. Gene variants in PLA2G7 and PON1, mediators of lipid oxidation and inflammation, demonstrated nominal associations with dyspnea (odds ratios for variant homozygotes were 0.27 [P=0.004] and 3.23 [P=0.04], respectively). These findings would need to be replicated or supported by additional experimental evidence.*

Dyspnea occurs commonly (12%) following treatment with ticagrelor. The mechanism for dyspnea is unclear. Nonclinical studies suggest that dyspnea may be related to adenosine because ticagrelor inhibits adenosine uptake and interacts with adenosine receptors (Nonclinical Overview). Other candidates have been proposed owing to their role in lipid oxidation and inflammation (e.g., paraoxonase 1 [*PON1*], platelet activating factor acetylhydrolase [*PLA2G7*]) or ticagrelor disposition or pharmacology (e.g., *ABCB1*, *P2RY12*)

### 3.2.1 Sponsor's analysis

***Methods:*** To identify genetic associations with dyspnea, the sponsor performed case-control analyses of DISPERSE, DISPERSE2, and the two trials combined. The following preferred terms were used to define case status: dyspnea, dyspnea at rest, dyspnea exertional, dyspnea paroxysmal nocturnal, and nocturnal dyspnea. Age-, sex-, and BMI-matched control subjects were sampled for the DISPERSE analysis, while the control population for other analyses seemed to utilize any subjects with available data. Putatively functional or haplotype-tagging SNPs were assayed in *PLA2G7*, *PON1*, 11 adenosine pathway candidate genes, and additional candidates genotyped for analysis of ticagrelor PK/PD.

For the *PLA2G7* analysis, Fisher's exact test for allelic association with case status was performed. For the adenosine pathway analysis, hypothesis testing followed a staged approach wherein the highest priority candidates were tested first so that multiplicity adjustments were greater for lower priority candidates. Genotypic and allelic models were tested where the multiplicative model was nominally significant. Statistical analyses adjusted for age and broad geographic region. For the *PON1* analysis allelic or genotypic logistic regression was performed. Where genotype frequencies were low, Fisher's exact test was used. Multiplicity was addressed by way of permutation testing (n=1000) for the adenosine pathway and *PON1* analyses. Secondary analyses of *PLA2G7* and *PON1* considered case severity and duration. Clopidogrel-treated subjects were analyzed separately to characterize treatment specificity only for the adenosine pathway analysis.

***Results:*** The genes, SNP selection strategy, and major findings are summarized below.

**Case-control genetic association studies for dyspnea**

| Pathway/ Gene, No. SNPs | SNP Selection | Case N / Control N* | Major Findings |
|---|---|---|---|
| *PLA2G7*, n=22 | Sequencing | DISPERSE: 20 / 63<br>DISPERSE2: 87 / 644 | – Arg92His: OR 5.74, 95% CI 1.65-30.6, P=0.002. Several SNPs in the promoter region were present only in controls (P=0.000054; data not shown)<br>– Arg92His association not replicated in DISPERSE2, although Ala379Val was weakly associated (P=0.03) with "severe" dyspnea; no associations with dyspnea duration<br>– Combined analysis not conducted |
| *ABCB1*, n=1 | pfSNP | DISPERSE: 20 / 63<br>DISPERSE2: 87 / 644 | – T/T genotype ("low-expression") OR 3.44, 95% CI 1.53-8.48, P=0.0012 in DISPERSE<br>– Not replicated in DISPERSE2<br>– Combined analysis allelic OR =0.81, P=0.15 |
| *CYP3A5*, n=1 | pfSNP | DISPERSE: 20 / 63 | – No association in DISPERSE<br>– Not assayed in DISPERSE2<br>– Combined analysis not applicable |
| *P2RY12*, n=4 | pfSNP | DISPERSE: 20 / 63 | – No association in DISPERSE<br>– Data not presented for DISPERSE2<br>– Combined analysis not presented |
| Adenosine Pathway/<br>*ADORA1*, n=6<br>*ADORA2A*, n=7<br>*ADORA2B* , n=2<br>*ADORA3*, n=21<br>*ENT1*, n=5<br>*ENT2*, n=4<br>*ENT3*, n=13<br>*ENT4*, n=1<br>*CNT1*, n=13<br>*CNT2*, n=11<br>*CNT3*, n=14 | Common (MAF>5%) pfSNPs (5´ UTR, 3´ UTR, splice sites, 5' and 3' flanking regions within 2 kb) | Combined: 107 / 804 | – Priority 1 genes: *ENT1* and *ADORA2A* were not associated with dyspnea. The strongest trend was rs571335 in ENT1 (P=0.087, 1 df, minor allele overrepresented in cases)<br>– Priority 2 genes: *ADORA1*, *ADORA2B* or *ADORA3* were not associated with dyspnea. The strongest trend was *ADORA1* rs11315020 (3´UTR insertion/deletion, P=0.23, 1df, major allele over-represented in cases)<br>– Priority 3 genes: Two SNPs in *CNT1* exceeded a nominal P-value threshold of 0.05 (rs3825875 [C__25958997_10], OR Aa vs. AA 0.61, 95 %CI 0.36-1.02, OR aa vs. AA 1.50, 95% CI 0.80-2.81, P=0.016 and rs2290272, allelic OR 1.47, 95% CI 1.03-2.10, P=0.032) |
| *PON1*, n=47 | pfSNPs + htSNPs (HapMap, MAF>1%, within 10 kb of gene) | Combined: 107 (77 mild, 27 moderate, 3 severe) / 804 | – 5 SNPs had P<0.05, the smallest adjusted P-value after permutation testing was 0.12<br>– L55M had the smallest unadjusted P-value with OR 1.61, 95% CI 1.16-2.21, unadjusted P=0.003; L55M was more strongly associated with moderate/ severe dyspnea with OR 2.7, 95% CI 1.3-5.3<br>– The promoter SNP -162G/A tended to be associated with higher risk (P=0.019); -108C/T, which has been associated with *PON1* expression not significantly associated with dyspnea (P=0.50)<br>– Compound genotype analysis did not show interaction between the coding and promoter SNPs (data not shown); a trend toward higher risk was noted for subjects with both *PON1* 55L/L and *ABCB1* 3435T/T genotypes (P-interaction=0.07) |

pfSNP=putative functional SNP, htSNP=haplotype-tagging SNP, MAF=minor allele frequency, UTR=untranslated region, kb=kilobases,
* includes both clopidogrel and ticagrelor-treated subjects; only Caucasians were included

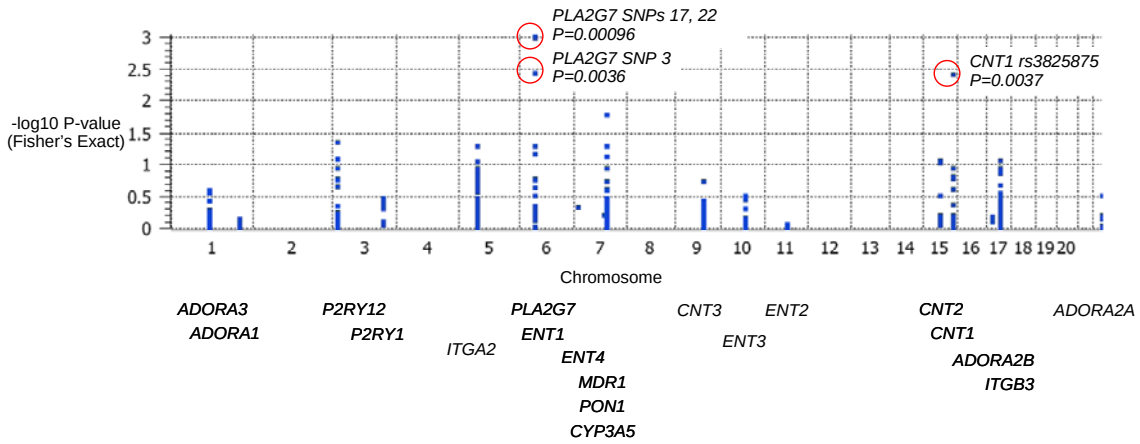
### 3.2.2 Reviewer's analysis

The sponsor's findings were confirmed using a similar analysis strategy. SNP associations with dyspnea were further tested for all genotyped SNPs in all ticagrelor-treated cases and controls with available genotype data from DISPERSE and DISPERSE2. SNP associations were tested under a genotypic model using Fisher's exact test. Haplotype-based logistic regression was performed for SNPs residing in the same gene/chromosome region based on 1) a 3-SNP moving window approach and 2) haplotype blocks inferred using an expectation-maximization algorithm (Gabriel). Haplotype analysis was not performed for *PLA2G7* since SNP location information was not available. P-values <0.01 were regarded as nominally significant. Logistic

regression was performed for top-ranking SNPs, adjusting for age, sex, race, study, BMI, and smoking status and ticagrelor dose.

A total of 89 cases and 544 controls, 96% of which were white, were included in this analysis. A total of 324 loci had genotype data available; loci with Hardy-Weinberg P-values <0.0001 in controls were eliminated, leaving 312 SNPs for analysis. Haplotype-tagging SNP data for *ITGA2*, *ITGB3*, *P2RY1*, and *P2RY12* were available for approximately one-third of the sample set because these SNPs were assayed for the purpose of association testing with platelet aggregation responses, but all other SNP data were available for >75% of the subjects. SNPs with unadjusted P<0.01 are highlighted in the following figure.

**Candidate pathway SNP associations with dyspnea**




Using the moving-window haplotype analysis approach, variants of *PON1*, *ENT1*, and *ITGA2* were also associated with dyspnea (results not shown). However, *ENT1* was not significant in single SNP analysis and *ITGA2* was missing for 60 cases and 374 controls.

Logistic regression results for the most significant SNPs and *PON1* (the most robust of the sponsor's findings) are shown in the following table. The SNP association for *CNT1* did not display the expected gene-dose relationship and was not significant under the additive model (unadjusted P=0.36). None of the SNPs were associated with dyspnea status in the clopidogrel-treated subjects. However, the sample size was very small with less than 20 clopidogrel cases.

**Odds ratios for dyspnea for SNPs with the lowest P-values**

| Gene | SNP | Function? | Treatment | Frequency (AA/Aa/aa) | Dyspnea Odds Ratio (95% confidence interval) Aa vs AA | aa vs. AA | Wald P-value |
|---|---|---|---|---|---|---|---|
| *PLA2G7* | 'SNP_17' (C/T)* | Promoter | Ticagrelor | 291/192/78 | 0.86 (0.50-1.49) | 0.27 (0.12-0.59) | 0.004 |
| | | | Clopidogrel | 147/85/9 | 1.13 (0.39-3.23) | 0.82 (0.09-7.35) | 0.95 |
| *CNT1* | rs3825875 (A/G) | Unknown | Ticagrelor | 246/290/87 | 1.61 (0.95-2.71) | 0.52 (0.28-0.98) | 0.003 |
| | | | Clopidogrel | 101/149/29 | 1.72 (0.62-4.79) | 1.61 (0.29-9.10) | 0.56 |
| *PON1* | rs854560 (A/T) | L55M | Ticagrelor | 255/263/82 | 1.40 (0.86-2.29) | 3.23 (1.23-8.52) | 0.043 |
| | | | Clopidogrel | 96/127/37 | 1.69 (0.54-5.36) | 1.21 (0.23-6.35) | 0.67 |

* 'SNP_27' in strong linkage disequilibrium with 'SNP_22' and 'SNP3' and therefore not shown

### 3.2.3 Reviewer's comments

*The CNT1 association did not follow an expected model of inheritance. Data for ITGA2 were incomplete, limiting any conclusions related to the observed haplotype association with dyspnea for this gene.*

*The results for PLA2G7 and PON1 need confirmation because 1) the biological plausibility of the observed associations as related to the pharmacology of ticagrelor remains unclear, 2) the associations did not replicate in the independent DISPERSE and DISPERSE2 datasets, and 3) the findings were not significant after adjustment for multiple comparisons.*

*Methodologically, the sponsor's analysis strategy was not systematic in that the SNP selection strategies, statistical methods, and case-control test sets varied for each analysis. This complicates interpretation of results across candidate genes.*

*The sponsor's case definition may capture patients with dyspnea consequent to structural heart disease and not specific to ticagrelor's effect.*

## 3.3 What is the impact of *CYP2C19* and *ABCB1* gene variants on the effects of ticagrelor vs. clopidogrel?

*The applicant genotyped CYP2C19 and ABCB1 variants in 55% of the PLATO population. Numerically higher event rates were observed in clopidogrel-treated patients with one or more loss-of-function alleles, particularly for death and stent thrombosis. Treatment differences tended to be greater in this population. Bleeding rates were comparable between ticagrelor and clopidogrel, irrespective of CYP2C19 genotype. No relative excess of bleeding was noted for ticagrelor in intermediate/poor metabolizers, or for clopidogrel in ultrarapid CYP2C19 metabolizers. Factors such as timing of sample collection, proton pump inhibitor use, and stent implantation did not alter the magnitude of CYP2C19 genetic effects on clopidogrel. CYP2C19 genotype distribution did not differ in the U.S. vs. non-U.S. regions and did not appear to account for the geographic differences in outcomes, although the analysis was limited to a very small subset. ABCB1 genotype was not robustly associated with outcomes in either treatment arm,*

*consistent with previously published findings for ABCB1 genetic effects on clopidogrel response and the lack of supportive evidence from PK/PD endpoints.*

*CYP2C19* genotype is a major determinant of clopidogrel response. Individuals with genetically-reduced CYP2C19 activity have lower active metabolite exposure, diminished antiplatelet responses, and poorer clinical outcomes as compared to extensive or ultrarapid metabolizers (PMID 20351750). *CYP2C19* genotype data were requested to assess the primary outcome and bleeding rates among those patients who are genotypically expected to be more (i.e., ultrarapid metabolizers) or less (i.e. poor metabolizers) responsive to clopidogrel. Additionally, clopidogrel and ticagrelor are both CYP3A4/5 and P-glycoprotein (ABCB1) substrates, thus variants in *CYP3A5* and *ABCB1* may influence the outcomes of both treatments. Data for the *ABCB1* 3435 C/T SNP were also provided in the clinical outcomes trial; *CYP3A5* genotyping was not performed.

### 3.3.1 Sponsor's analysis

The applicant assessed *CYP2C19* genotype status in two clinical trials where clopidogrel was the comparator drug, RESPOND (pharmacodynamics) and PLATO (outcomes).

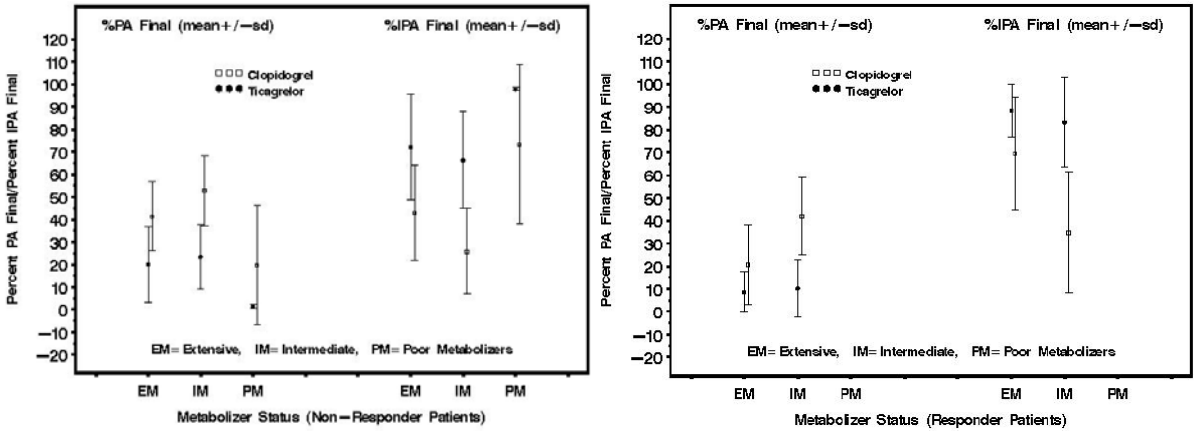
#### 3.3.1.1 Pharmacodynamics

***RESPOND***

***Methods*:** All DNA samples available from RESPOND (n=71; responder n=28) were genotyped for the CYP2C19 *2, *3, *4, *5, *6, *7 and *8 alleles (not *17 which is associated with ultrarapid metabolism). Phenotypes were assigned as follows: extensive metabolizer (EM), *CYP2C19**1/*1; intermediate metabolizer (IM), *CYP2C19**1/*2-*8; poor metabolizer (PM), any combination of two *CYP2C19* alleles *2 through *8. Non-responders were defined as those with absolute change in maximal inhibition of platelet aggregation of <10%. Analyses were descriptive due to the small sample size.

***Results*:** Ticagrelor tended to result in greater inhibition of platelet aggregation than clopidogrel. There was no over-representation of IMs among non-responders to ticagrelor (32.1% of non-responders were IMs and 32.6% of responders were IMs). Both PMs were clopidogrel non-responders. In ticagrelor-treated subjects, mean platelet aggregation and inhibition of platelet aggregation were similar across CYP2C19 metabolic groups, whereas clopidogrel responses tended to be lower in IMs.

**Platelet aggregation responses by CYP2C19 metabolizer status in clopidogrel non-responders (left) and responders (right)**




*ABCB1* and *CYP3A5* genotyping was not performed in this trial.

### 3.3.1.2 Outcomes

#### *PLATO*

PLATO was a prospective, randomized, double-blind, double-dummy, parallel group, international, multicentre Phase 3 study in 18,624 patients with ACS, which compared the efficacy and safety of ticagrelor 90 mg BID (180 mg loading dose) with clopidogrel 75 mg QD (300 to 600 mg loading dose) in the prevention of CV death, MI, and stroke. For the overall trial population, the mean duration of treatment was 10 months. As per the sponsor's analysis, compared to clopidogrel the composite efficacy endpoint of CV death, MI, or stroke after ACS events was reduced 1.9% (absolute) with a hazard ratio (HR) of 0.84 (95% CI 0.77-0.92, P=0.0003) and number needed to treat of 54. Neither PLATO "total major" nor "major fatal/life-threatening" bleeding differed between the ticagrelor and clopidogrel arms (11.6% in ticagrelor vs. 11.2% in clopidogrel).

***Methods*:** According to the protocol, a single blood sample was to be obtained on a voluntary basis for PG research at Visit 1 (as close to randomization as possible). Patients were excluded from the genetic substudy if not eligible for the main trial or if they had undergone bone marrow transplant. *CYP2C19* loss-of-function (LOF) alleles *2, *3, *4, *5, *6, *7 and *8, the gain-of-function (GOF) allele *17, and *ABCB1* 3435 C/T were genotyped using TaqMan. CYP3A5 variants were not genotyped.

The following endpoints were evaluated: 1) composite of CV death or MI or stroke (primary efficacy outcome), 2) composite endpoint of CV death and MI, 3) PLATO "total major" bleeding, 4) PLATO non-CABG total "major bleeding", 5) PLATO CABG total "major bleeding", and 6) a combined efficacy-safety composite endpoint (CV death, MI, stroke, PLATO non-CABG "major" or PLATO CABG-related "major fatal/life threatening" bleeding). Stent thrombosis was also evaluated. Treatment by genotype subgroup interactions were evaluated by Cox proportional hazards regression for each outcome, accounting for the following covariates: ethnicity (e.g., Hispanic, African-

Caribbean, Chinese), sex, concomitant proton pump inhibitor (PPI) use, aspirin dose, smoking, and diabetes. Within- and between-treatment arm analyses were performed.

CYP2C19 metabolic groupings were based on inspection of risk estimates obtained from within-treatment analyses and by predicted phenotype as "extensive metabolizers" (consisting of the EM/EM, UM/UM, and UM/EM groups) versus "LOF" carriers (consisting of the IM/IM, PM/PM, and UM/PM groups). For *ABCB1*, genotypes were referred to as high expression (C/C), intermediate expression (C/T), or low expression (T/T).

***Results*:** The substudy was comprised of 10,285 PLATO subjects. Baseline demographics were comparable between the substudy and the overall PLATO population except the substudy had more Caucasians (98% vs. 92%), fewer patients intended for invasive management (66% vs. 72%), and fewer patients receiving 600 to 675 mg of clopidogrel within 24 hours of randomization (absolute 4% fewer patients in each treatment arm).

Results for key endpoints in the substudy population are shown in the following table. Treatment effects for the primary endpoint were comparable between the genetics substudy cohort and the overall population. However, the treatment effect on CV death was less pronounced in the substudy as compared to the overall population (HR 0.79, 95% CI 0.69-0.91). Also, the all-cause mortality rate was also slightly lower in the substudy (compared with 4.3% and 5.4% for ticagrelor and clopidogrel, respectively, in the overall population).

**ICAC-adjudicated clinical endpoints in full substudy**

| | Ticagrelor N=5137 Events N (%) | Clopidogrel N=5148 Events N (%) | Hazard ratio (95% CI) | P-value |
|---|---|---|---|---|
| CV death/MI (excl. silent MI)/stroke | 432 (8.4%) | 510 (9.9%) | 0.85 (0.74, 0.96) | 0.0104 |
| MI (excl. silent MI) | 271 (5.3%) | 333 (6.5%) | 0.81 (0.69, 0.95) | 0.0109 |
| CV death | 163 (3.2%) | 182 (3.5%) | 0.90 (0.73, 1.11) | 0.3263 |
| Stroke | 61 (1.2%) | 54 (1.0%) | 1.14 (0.79, 1.64) | 0.4977 |
| All cause mortality | 180 (3.5%) | 209 (4.1%) | 0.87 (0.71, 1.06) | 0.1544 |

Outcomes for each of the endpoints stratified by a binary CYP2C19 phenotype grouping are shown in the following table. Primary efficacy endpoint event rates did not differ according to CYP2C19 metabolic status in the ticagrelor arm, but were numerically higher for patients with one or more LOF alleles compared with patients with no LOF alleles in the clopidogrel arm. The absolute risk reduction in the primary endpoint for ticagrelor vs. clopidogrel was more marked for patients with one or more LOF alleles. For non-CABG "total major" bleeding, LOF carriers treated with ticagrelor had the highest bleeding rates, resulting in a greater relative difference between treatments in this group; no trend across genotype groups was apparent in the clopidogrel arm.

**Clinical outcomes of ticagrelor vs. clopidogrel by genotype-predicted CYP2C19 phenotype**

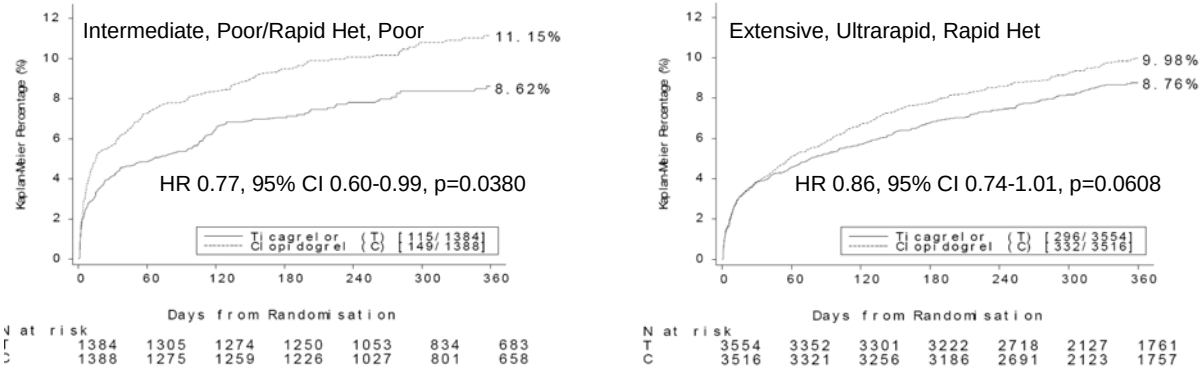
| Outcome | Genotype group† | Ticagrelor Events N (%) | Ticagrelor K-M (%) | Clopidogrel Events N (%) | Clopidogrel K-M (%) | HR (95% CI) | P-value |
|---|---|---|---|---|---|---|---|
| CV death, MI (excl silent MI), stroke | IM+PM | 115 (8.3) | 8.6 | 149 (10.7) | 11.2 | 0.77 (0.60, 0.99) | 0.0380 |
| | EM+UM | 296 (8.3) | 8.8 | 332 (9.4) | 10.0 | 0.86 (0.74, 1.01) | 0.0608 |
| CV death, MI (excl silent MI) | IM+PM | 102 (7.4) | 7.7 | 138 (9.9) | 10.4 | 0.73 (0.57, 0.95) | 0.0184 |
| | EM+UM | 273 (7.7) | 8.0 | 306 (8.7) | 9.2 | 0.86 (0.73, 1.01) | 0.0734 |
| "Total major" bleed | IM+PM | 149 (10.8) | 11.8 | 143 (10.4) | 11.3 | 1.04 (0.82, 1.30) | 0.7687 |
| | EM+UM | 331 (9.3) | 10.3 | 340 (9.7) | 10.6 | 0 96 (0.83, 1.12) | 0.6144 |
| Non-CABG "total major" bleed | IM+PM | 56 (4.1) | 4.6 | 41 (3.0) | 3.2 | 1.39 (0.93, 2.08) | 0.1121 |
| | EM+UM | 121 (3.4) | 3.9 | 110 (3.1) | 3.6 | 1.08 (0.84, 1.40) | 0.5492 |
| CABG "total major" bleed | IM+PM | 96 (7.0) | 7.6 | 107 (7.8) | 8.6 | 0.87 (0.66, 1.14) | 0.3095 |
| | EM+UM | 218 (6.1) | 6.8 | 246 (7.0) | 7.7 | 0.88 (0.73, 1.05) | 0.1636 |
| Net clinical benefit* | IM+PM | 204 (14.7) | 15.2 | 231 (16.6) | 17.1 | 0.88 (0.72, 1.06) | 0.1687 |
| | EM+UM | 476 (13.4) | 14.0 | 533 (15.2) | 15.8 | 0.86 (0.76, 0.97) | 0.0172 |
| Definite stent thrombosis | IM+PM | 15 (1.6) | 1.6 | 21 (2.2) | 2.3 | 0.71 (0.36, 1.37) | 0.3049 |
| | EM+UM | 22 (0.9) | 1.0 | 35 (1.5) | 1.5 | 0.62 (0.36, 1.05) | 0.0772 |

† IM, PM = *1/*X, *17/*X, *X/*X; EM, UM = *1/*1, *1/*17, *17/*17
*CV Death, MI, Stroke, Non-CABG "major" or CABG "major/Life-Threatening" Bleed

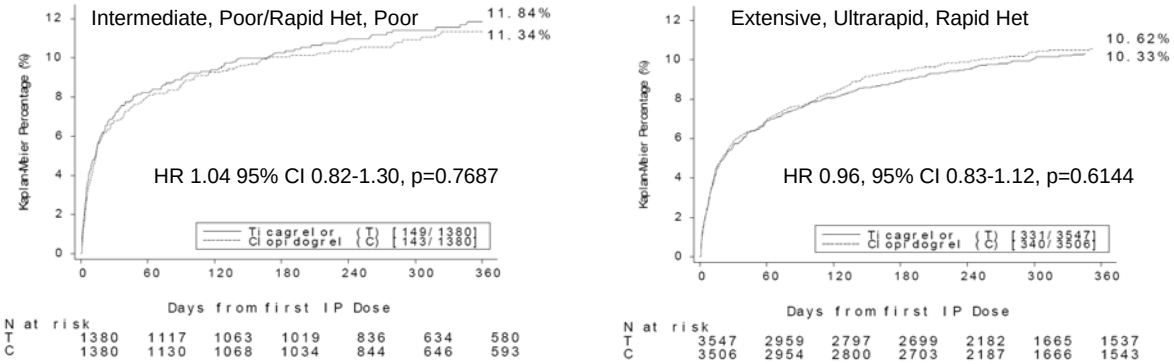
*Source PLATO Genetics Substudy Report, pages 24, 28, 32, 37, 41, 44, 68*

Kaplan-Meier curves for two endpoints of interest, the primary efficacy endpoint and "total major" bleeding, are shown in the following figures. For the primary efficacy endpoint, Kaplan-Meier curves showed early separation of event rates between treatment arms for patients with one or more LOF alleles, whereas for patients with no LOF allele, separation in event rates did not appear until more than 30 days after randomization. PLATO "total major" bleeding rates were comparable between the arms in both extensive/ultrarapid and intermediate/poor metabolizer subgroups,

**Primary efficacy endpoint by CYP2C19 phenotype (full population)**



**PLATO 'total major' bleeding by CYP2C19 genotype (safety population)**




*Source PLATO Genetics Substudy Report, pages 25, 26, 35*

No consistent, strong effect of *ABCB1* genotypes was observed on the efficacy outcomes (primary or CV death/MI composite), bleeding, or the combined efficacy/safety endpoint within either of the treatment arms, and no significant genotype-treatment interaction was observed in the between-arms comparison, as shown in the table below. Stent thrombosis rates did not vary significantly across *ABCB1* genotype groups. For nearly all of the outcomes, heterozygotes had the most extreme event rate.

| Outcome | Genotype Group | Ticagrelor Events N (%) | Ticagrelor K-M (%) | Clopidogrel Events N (%) | Clopidogrel K-M (%) | HR (95% CI) | P-value |
|---|---|---|---|---|---|---|---|
| CV death, MI (excl silent MI), stroke | T/T (lo) | 122 (9.0) | 9.5 | 137 (9.9) | 10.5 | 0.90 (0.70, 1.15) | 0.3954 |
| | C/T (int) | 208 (8.1) | 8.5 | 233 (9.3) | 9.8 | 0.86 (0.71, 1.03) | 0.1079 |
| | C/C (hi) | 98 (8.4) | 8.8 | 138 (11.5) | 11.9 | 0.71 (0.55, 0.92) | 0.0104 |
| CV death, MI (excl silent MI) | T/T (lo) | 110 (8.2) | 8.5 | 124 (8.9) | 9.5 | 0.89 (0.69, 1.16) | 0.3982 |
| | C/T (int) | 188 (7.3) | 7.7 | 218 (8.7) | 9.2 | 0.83 (0.68, 1.01) | 0.0571 |
| | C/C (hi) | 91 (7.8) | 8.2 | 128 (10.7) | 11.1 | 0.71 (0.54, 0.93) | 0.0128 |
| "total major" bleed | T/T (lo) | 132 (9.8) | 10.9 | 137 (9.9) | 10.9 | 0.97 (0.76, 1.23) | 0.7746 |
| | C/T (int) | 240 (9.3) | 10.3 | 245 (9.8) | 10.6 | 0.96 (0.80, 1.15) | 0.6596 |
| | C/C (hi) | 121 (10.4) | 11.5 | 116 (9.8) | 10.8 | 1.06 (0.83, 1.37) | 0.6312 |
| Non-CABG "total major" bleed | T/T (lo) | 47 (3.5) | 4.0 | 35 (2.5) | 3.0 | 1.39 (0.90, 2.15) | 0.1423 |
| | C/T (int) | 91 (3.5) | 4.0 | 80 (3.2) | 3.5 | 1.10 (0.81, 1.49) | 0.5306 |
| | C/C (hi) | 39 (3.4) | 3.7 | 37 (3.1) | 3.5 | 1.07 (0.68, 1.68) | 0.7696 |
| CABG "total major" bleed | T/T (lo) | 88 (6.5) | 7.2 | 105 (7.6) | 8.2 | 0.83 (0.63, 1.10) | 0.1984 |
| | C/T (int) | 155 (6.0) | 6.6 | 178 (7.1) | 7.8 | 0.85 (0.69, 1.06) | 0.1489 |
| | C/C (hi) | 83 (7.1) | 7.9 | 83 (7.0) | 7.8 | 1.02 (0.75, 1.38) | 0.8939 |
| Net clinical benefit* | T/T (lo) | 192 (14.2) | 14.8 | 219 (15.8) | 16.6 | 0.87 (0.72, 1.06) | 0.1644 |
| | C/T (int) | 357 (13.9) | 14.4 | 370 (14.7) | 15.3 | 0.93 (0.81, 1.08) | 0.3507 |
| | C/C (hi) | 157 (13.5) | 14.0 | 210 (17.6) | 18.1 | 0.74 (0.60, 0.91) | 0.0041 |
| Definite stent thrombosis | T/T (lo) | 9 (1.0) | 1.1 | 14 (1.5) | 1.5 | 0.65 (0.28, 1.50) | 0.3097 |
| | C/T (int) | 23 (1.3) | 1.4 | 28 (1.7) | 1.6 | 0.80 (0.46, 1.38) | 0.4218 |
| | C/C (hi) | 6 (0.8) | 0.8 | 17 (2.1) | 2.2 | 0.37 (0.14, 0.93) | 0.0351 |
| *CV death, MI, stroke, non-CABG "major" or CABG "major/life-threatening" bleed | | | | | | | |

*Source PLATO Genetics Substudy Report, pages 47, 51, 55, 58, 61, 64, 68*

### 3.3.2 Reviewer's analysis

The sponsor's analyses presented above were confirmed. Additional analyses were conducted to assess 1) the PG relationships for the individual components of the primary efficacy endpoint, all-cause death, non-CABG "total major" bleeding, "total major" bleeding and stent thrombosis (definite *and* probable) in each of the phenotypic subgroups (i.e., no collapsing of various subgroups) and 2) whether the following factors

influenced the magnitude of the PG interaction: timing of sample collection (potential survivorship bias), geographic region, PPI use (CYP2C19 inhibitor), stent implantation for the index event (consistent with published CYP2C19-clopidogrel PG literature), baseline clopidogrel use, and the safety subset.

Event rates for the primary outcome components and all-cause death according to CYP2C19 genetic subgroup are shown in the following table. For mortality endpoints, clopidogrel-treated individuals carrying LOF alleles tended to have higher death rates compared with ticagrelor-treated patients. CV and all-cause death rates were comparable between clopidogrel and ticagrelor in the EM and UM subgroups. The incidence of stroke was low, although no trends for a PG effect were apparent.

To assess whether bleeding rates differed in those most likely to be responsive to clopidogrel, PLATO ”total major” bleeding rates were compared in subjects who carried the *17 allele, specifically in the subgroups of *1/*17 and *17/*17, who are expected to be ultrarapid metabolizers. *17 homozygotes treated with ticagrelor had the highest “total major” bleeding rate, resulting in a larger between-treatment difference vs. clopidogrel, which had the lowest bleeding rate in this group. In the *1/*17 subgroup, opposite trends were observed, complicating interpretation. Similar findings were apparent for non-CABG “total major” bleeding.

Definite/probable stent thrombosis occurred in 4 of 84 (4.8%) of clopidogrel-treated PMs, which is higher than the overall substudy population rate of 2.5% in the clopidogrel arm and 1.8% in the ticagrelor arm.

**Event rates for CV death, MI, stroke, and all-cause death by CYP2C19 genotype**

| Outcome | Genotype | Predicted Phenotype | Ticagrelor N | Ticagrelor N | Ticagrelor % | Clopidogrel n | Clopidogrel N | Clopidogrel % | Hazard Ratio | (95% CI) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CV death | | | | | | | | | | | |
| | All | … | 163 | 5137 | 3.2 | 182 | 5148 | 3.5 | 0.91 | (0.74, | 1.12) |
| | *1/*1 | EM | 59 | 1849 | 3.2 | 67 | 1862 | 3.6 | 0.90 | (0.63, | 1.28) |
| | *1/*X | IM | 31 | 894 | 3.5 | 37 | 935 | 4.0 | 0.91 | (0.56, | 1.47) |
| | *X/*X | PM | 2 | 121 | 1.7 | 6 | 125 | 4.8 | 0.06 | (0.00, | 0.90) |
| | *17/*X | UK | 10 | 369 | 2.7 | 7 | 328 | 2.1 | 1.26 | (0.47, | 3.38) |
| | *1/*17 | UM | 43 | 1437 | 3.0 | 44 | 1368 | 3.2 | 0.92 | (0.60, | 1.40) |
| | *17/*17 | UM | 8 | 268 | 3.0 | 11 | 268 | 4.1 | 0.72 | (0.28, | 1.84) |
| MI | | | | | | | | | | | |
| | All | … | 271 | 5137 | 5.3 | 333 | 5148 | 6.5 | 0.81 | (0.69, | 0.95) |
| | *1/*1 | EM | 105 | 1849 | 5.7 | 119 | 1862 | 6.4 | 0.89 | (0.68, | 1.16) |
| | *1/*X | IM | 47 | 894 | 5.3 | 64 | 935 | 6.8 | 0.77 | (0.52, | 1.12) |
| | *X/*X | PM | 8 | 121 | 6.6 | 8 | 125 | 6.4 | 0.90 | (0.33, | 2.44) |
| | *17/*X | UK | 17 | 369 | 4.6 | 27 | 328 | 8.2 | 0.49 | (0.26, | 0.92) |
| | *1/*17 | UM | 65 | 1437 | 4.5 | 81 | 1368 | 5.9 | 0.78 | (0.56, | 1.08) |
| | *17/*17 | UM | 18 | 268 | 6.7 | 15 | 268 | 5.6 | 1.27 | (0.63, | 2.56) |
| Stroke | | | | | | | | | | | |
| | All | … | 61 | 5137 | 1.2 | 54 | 5148 | 1.0 | 1.15 | (0.79, | 1.66) |
| | *1/*1 | EM | 22 | 1849 | 1.2 | 19 | 1862 | 1.0 | 1.15 | (0.62, | 2.13) |
| | *1/*X | IM | 16 | 894 | 1.8 | 16 | 935 | 1.7 | 1.16 | (0.57, | 2.36) |
| | *X/*X | PM | 1 | 121 | 0.8 | 0 | 125 | 0.0 | … | … | … |
| | *17/*X | UK | 2 | 369 | 0.5 | 2 | 328 | 0.6 | 1.53 | (0.18, | 12.4) |
| | *1/*17 | UM | 11 | 1437 | 0.8 | 14 | 1368 | 1.0 | 0.73 | (0.33, | 1.61) |
| | *17/*17 | UM | 5 | 268 | 1.9 | 1 | 268 | 0.4 | 4.87 | (0.54, | 43.6) |
| All-cause death | | | | | | | | | | | |
| | All | … | 180 | 5137 | 3.5 | 209 | 5148 | 4.1 | 0.89 | (0.73, | 1.08) |
| | *1/*1 | EM | 63 | 1849 | 3.4 | 74 | 1862 | 4.0 | 0.87 | (0.62, | 1.22) |
| | *1/*X | IM | 35 | 894 | 3.9 | 43 | 935 | 4.6 | 0.89 | (0.56, | 1.39) |
| | *X/*X | PM | 2 | 121 | 1.7 | 6 | 125 | 4.8 | 0.06 | (0.00, | 0.90) |

| Outcome | Genotype | Predicted Phenotype | Ticagrelor N | Ticagrelor N | Ticagrelor % | Clopidogrel n | Clopidogrel N | Clopidogrel % | Hazard Ratio | (95% CI) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *17/*X | UK | 11 | 369 | 3.0 | 10 | 328 | 3.0 | 1.09 | (0.44, | 2.68) |
| | *1/*17 | UM | 51 | 1437 | 3.5 | 51 | 1368 | 3.7 | 0.94 | (0.64, | 1.39) |
| | *17/*17 | UM | 8 | 268 | 3.0 | 12 | 268 | 4.5 | 0.66 | (0.26, | 1.65) |
| Non-CABG "total major" bleeding* | | | | | | | | | | | |
| | All | … | 179 | 5126 | 3.5 | 155 | 5127 | 3.0 | 1.17 | (0.95, | 1.46) |
| | *1/*1 | EM | 61 | 1846 | 3.3 | 52 | 1856 | 2.8 | 1.19 | (0.82, | 1.72) |
| | *1/*X | IM | 36 | 891 | 4.0 | 26 | 929 | 2.8 | 1.55 | (0.93, | 2.60) |
| | *X/*X | PM | 4 | 120 | 3.3 | 6 | 124 | 4.8 | 0.64 | (0.17, | 2.34) |
| | *17/*X | UK | 16 | 369 | 4.3 | 9 | 327 | 2.8 | 1.64 | (0.71, | 3.77) |
| | *1/*17 | UM | 47 | 1434 | 3.3 | 53 | 1383 | 3.8 | 0.87 | (0.59, | 1.30) |
| | *17/*17 | UM | 13 | 267 | 4.9 | 5 | 267 | 1.9 | 2.50 | (0.88, | 7.05) |
| *"Total major" bleeding* | | | | | | | | | | | |
| | All | … | 497 | 5126 | 9.7 | 503 | 5127 | 9.8 | 0.99 | (0.87, | 1.12) |
| | *1/*1 | EM | 176 | 1846 | 9.5 | 161 | 1856 | 8.7 | 1.11 | (0.90, | 1.38) |
| | *1/*X | IM | 94 | 891 | 10.5 | 84 | 929 | 9.0 | 1.04 | (0.78, | 1.39) |
| | *X/*X | PM | 14 | 120 | 11.7 | 14 | 124 | 11.3 | 1.02 | (0.47, | 2.19) |
| | *17/*X | UK | 41 | 369 | 11.1 | 35 | 327 | 10.7 | 1.02 | (0.65, | 1.61) |
| | *1/*17 | UM | 121 | 1434 | 8.4 | 159 | 1383 | 11.5 | 0.72 | (0.57, | 0.91) |
| | *17/*17 | UM | 34 | 267 | 12.7 | 20 | 267 | 7.5 | 1.75 | (1.00, | 3.05) |
| Definite/probable stent thrombosis† | | | | | | | | | | | |
| | All | … | 56 | 3130 | 1.8 | 78 | 3118 | 2.5 | 0.71 | (0.50, | 1.01) |
| | *1/*1 | EM | 20 | 1118 | 1.8 | 21 | 1083 | 1.9 | 0.93 | (0.50, | 1.72) |
| | *1/*X | IM | 13 | 560 | 2.3 | 21 | 562 | 3.7 | 0.62 | (0.30, | 1.25) |
| | *X/*X | PM | 1 | 72 | 1.4 | 4 | 84 | 4.8 | 0.24 | (0.02, | 2.94) |
| | *17/*X | UK | 3 | 230 | 1.3 | 2 | 207 | 1.0 | 0.91 | (0.12, | 6.55) |
| | *1/*17 | UM | 14 | 865 | 1.6 | 22 | 857 | 2.6 | 0.59 | (0.30, | 1.16) |
| | *17/*17 | UM | 4 | 172 | 2.3 | 3 | 176 | 1.7 | 1.33 | (0.27, | 6.62) |

Hazard ratios adjusted for age, sex, race, region, median aspirin dose, diabetes, BMI, and PPI use
*X=null function allele *2 to *8, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer, UK=unknown, UM=ultrarapid metabolizer
* Based on safety subset of patients
† Based on safety subset of patients who received a bare-metal or drug-eluting stent

Primary outcome event rates and relative risks for specific subgroups are shown in the following table. The results in each subgroup were consistent with that of the full substudy population. Analysis of the individual endpoints was also performed for each subgroup and the results were similar to the overall substudy population in all cases (results not shown).

**Primary endpoint event rates by CYP2C19 genotype in selected subgroups**

| Subset | Genotype | Predicted Phenotype | Ticagrelor n | Ticagrelor N | Ticagrelor % | Clopidogrel n | Clopidogrel N | Clopidogrel % | Hazard Ratio | (95% CI) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Full substudy | | | | | | | | | | | |
| | All | … | 432 | 5137 | 8.4 | 510 | 5148 | 9.9 | 0.85 | (0.75, | 0.97) |
| | *1/*1 | EM | 163 | 1849 | 8.8 | 184 | 1862 | 9.9 | 0.90 | (0.73, | 1.11) |
| | *1/*X | IM | 82 | 894 | 9.2 | 102 | 935 | 10.9 | 0.85 | (0.63, | 1.14) |
| | *X/*X | PM | 10 | 121 | 8.3 | 12 | 125 | 9.6 | 0.70 | (0.29, | 1.68) |
| | *17/*X | UK | 23 | 369 | 6.2 | 35 | 328 | 10.7 | 0.51 | (0.30, | 0.88) |
| | *1/*17 | UM | 106 | 1437 | 7.4 | 124 | 1368 | 9.1 | 0.82 | (0.63, | 1.06) |
| | *17/*17 | UM | 27 | 268 | 10.1 | 24 | 268 | 9.0 | 1.18 | (0.67, | 2.07) |
| DNA at baseline | | | | | | | | | | | |
| | All | … | 332 | 3825 | 8.7 | 393 | 3837 | 10.2 | 0.85 | (0.74, | 0.99) |
| | *1/*1 | EM | 120 | 1361 | 8.8 | 138 | 1380 | 10.0 | 0.87 | (0.68, | 1.12) |
| | *1/*X | IM | 66 | 664 | 9.9 | 82 | 689 | 11.9 | 0.87 | (0.62, | 1.20) |
| | *X/*X | PM | 9 | 95 | 9.5 | 9 | 86 | 10.5 | 0.77 | (0.29, | 2.07) |
| | *17/*X | UK | 17 | 285 | 6.0 | 24 | 238 | 10.1 | 0.53 | (0.28, | 1.01) |
| | *1/*17 | UM | 83 | 1072 | 7.7 | 96 | 1043 | 9.2 | 0.81 | (0.60, | 1.09) |
| | *17/*17 | UM | 19 | 201 | 9.5 | 20 | 210 | 9.5 | 1.00 | (0.52, | 1.89) |
| United States | | | | | | | | | | | |
| | All | … | 35 | 282 | 12.4 | 23 | 286 | 8.0 | 1.50 | (0.89, | 2.54) |
| | *1/*1 | EM | 15 | 111 | 13.5 | 9 | 100 | 9.0 | 1.60 | (0.68, | 3.71) |
| | *1/*X | IM | 7 | 53 | 13.2 | 3 | 68 | 4.4 | 4.25 | (0.94, | 19.2) |
| | *X/*X | PM | 0 | 3 | 0.0 | 0 | 7 | 0.0 | … | … | … |
| | *17/*X | UK | 4 | 25 | 16.0 | 1 | 17 | 5.9 | 3.49 | (0.22, | 54.8) |

| Subset | Genotype | Predicted Phenotype | Ticagrelor n | Ticagrelor N | Ticagrelor % | Clopidogrel n | Clopidogrel N | Clopidogrel % | Hazard Ratio (95% CI) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *1/*17 | UM | 6 | 67 | 9.0 | 6 | 65 | 9.2 | 0.83 | (0.23, | 2.97) |
| | *17/*17 | UM | 0 | 10 | 0.0 | 1 | 14 | 7.1 | … | … | … |
| Rest of the world | | | | | | | | | | | |
| | All | … | 397 | 4855 | 8.2 | 487 | 4862 | 10.0 | 0.82 | (0.72, | 0.94) |
| | *1/*1 | EM | 148 | 1738 | 8.5 | 175 | 1762 | 9.9 | 0.87 | (0.70, | 1.08) |
| | *1/*X | IM | 75 | 841 | 8.9 | 99 | 867 | 11.4 | 0.79 | (0.58, | 1.07) |
| | *X/*X | PM | 10 | 118 | 8.5 | 12 | 118 | 10.2 | 0.70 | (0.29, | 1.68) |
| | *17/*X | UK | 19 | 344 | 5.5 | 34 | 311 | 10.9 | 0.46 | (0.25, | 0.82) |
| | *1/*17 | UM | 100 | 1370 | 7.3 | 118 | 1321 | 8.9 | 0.80 | (0.61, | 1.05) |
| | *17/*17 | UM | 27 | 258 | 10.5 | 23 | 254 | 9.1 | 1.08 | (0.61, | 1.92) |
| PPI nonusers | | | | | | | | | | | |
| | All | … | 286 | 3531 | 8.1 | 326 | 3583 | 9.1 | 0.89 | (0.76, | 1.05) |
| | *1/*1 | EM | 114 | 1305 | 8.7 | 114 | 1291 | 8.8 | 1.01 | (0.77, | 1.31) |
| | *1/*X | IM | 51 | 606 | 8.4 | 63 | 652 | 9.7 | 0.89 | (0.61, | 1.29) |
| | *X/*X | PM | 6 | 79 | 7.6 | 7 | 79 | 8.9 | 0.64 | (0.19, | 2.09) |
| | *17/*X | UK | 14 | 237 | 5.9 | 25 | 234 | 10.7 | 0.51 | (0.26, | 1.01) |
| | *1/*17 | UM | 74 | 967 | 7.7 | 80 | 954 | 8.4 | 0.90 | (0.65, | 1.24) |
| | *17/*17 | UM | 16 | 194 | 8.2 | 17 | 192 | 8.9 | 0.91 | (0.45, | 1.83) |
| Clopidogrel naïve | | | | | | | | | | | |
| | All | … | 382 | 4808 | 7.9 | 462 | 4810 | 9.6 | 0.83 | (0.73, | 0.95) |
| | *1/*1 | EM | 140 | 1735 | 8.1 | 165 | 1738 | 9.5 | 0.86 | (0.69, | 1.09) |
| | *1/*X | IM | 73 | 823 | 8.9 | 93 | 857 | 10.9 | 0.82 | (0.60, | 1.12) |
| | *X/*X | PM | 9 | 113 | 8.0 | 11 | 110 | 10.0 | 0.73 | (0.28, | 1.88) |
| | *17/*X | UK | 20 | 348 | 5.7 | 34 | 310 | 11.0 | 0.46 | (0.26, | 0.82) |
| | *1/*17 | UM | 101 | 1360 | 7.4 | 110 | 1313 | 8.4 | 0.87 | (0.67, | 1.15) |
| | *17/*17 | UM | 23 | 252 | 9.1 | 21 | 250 | 8.4 | 1.10 | (0.60, | 2.02) |
| Stent | | | | | | | | | | | |
| | All | … | 261 | 3133 | 8.3 | 301 | 3122 | 9.6 | 0.88 | (0.74, | 1.04) |
| | *1/*1 | EM | 102 | 1119 | 9.1 | 99 | 1083 | 9.1 | 1.00 | (0.76, | 1.33) |
| | *1/*X | IM | 51 | 560 | 9.1 | 63 | 565 | 11.2 | 0.80 | (0.55, | 1.16) |
| | *X/*X | PM | 4 | 72 | 5.6 | 7 | 84 | 8.3 | 0.43 | (0.12, | 1.59) |
| | *17/*X | UK | 14 | 230 | 6.1 | 23 | 207 | 11.1 | 0.47 | (0.23, | 0.94) |
| | *1/*17 | UM | 59 | 866 | 6.8 | 77 | 858 | 9.0 | 0.75 | (0.53, | 1.06) |
| | *17/*17 | UM | 19 | 173 | 11.0 | 15 | 176 | 8.5 | 1.60 | (0.78, | 3.28) |
| Safety population | | | | | | | | | | | |
| | All | … | 430 | 5126 | 8.4 | 507 | 5127 | 9.9 | 0.85 | (0.75, | 0.97) |
| | *1/*1 | EM | 162 | 1846 | 8.8 | 183 | 1856 | 9.9 | 0.90 | (0.72, | 1.11) |
| | *1/*X | IM | 82 | 891 | 9.2 | 101 | 929 | 10.9 | 0.86 | (0.64, | 1.15) |
| | *X/*X | PM | 10 | 120 | 8.3 | 12 | 124 | 9.7 | 0.70 | (0.29, | 1.69) |
| | *17/*X | UK | 23 | 369 | 6.2 | 35 | 327 | 10.7 | 0.51 | (0.30, | 0.88) |
| | *1/*17 | UM | 105 | 1434 | 7.3 | 124 | 1383 | 9.0 | 0.80 | (0.62, | 1.04) |
| | *17/*17 | UM | 27 | 267 | 10.1 | 24 | 267 | 9.0 | 1.17 | (0.66, | 2.05) |

Hazard ratios adjusted for age, sex, race, region, median aspirin dose, diabetes, BMI, and PPI use
*X=null function allele *2 to *8, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer, UK=unknown, UM=ultrarapid metabolizer

The distribution of CYP2C19 genotype by geographic region was as follows for U.S. vs. ROW, respectively: *1/*1 (EM) 39% vs. 38%, *1/*X (IM) 22% vs. 18%, *X/*X (PM) 1.9% vs. 2.5%, (UK) *17/*X 7.8% vs. 7.0%, *1/*17 (UM) 24% vs. 29%, *17/*17 (UM) 4.4% vs. 5.5%.

### 3.3.3 Reviewer's comments

*CYP2C19 genotype effects on clopidogrel treatment outcomes were generally consistent with the known effects on active metabolite pharmacokinetics, antiplatelet responsiveness, and clinical outcomes.*

*The impact of CYP2C19 GOFs on either ticagrelor- or clopidogrel-associated bleeding could not be concluded due to inconsistent trends with increasing numbers of *17 variants.*

*Previous studies have shown that the low-expression ABCB1 3435T/T genotype is associated with lower clopidogrel active metabolite exposures and, consequently, higher event rates in clopidogrel-treated patients (PMID 19106083). Similar effects of ABCB1 genotype would be expected for both clopidogrel and ticagrelor but were not observed, and a linear, gene-dose relationship between genotype and treatment outcome was not apparent in either arm.*

# 4 SUMMARY AND CONCLUSIONS

## 4.1 Ticagrelor pharmacokinetics and pharmacodynamics

- The applicant conducted PG association studies for PK and PD (e.g., aggregometry) endpoints in DISPERSE and DISPERSE2.
- Candidate genes related to platelet function and ticagrelor pharmacology and disposition were selected for analysis, including *P2RY12*, *P2RY1*, *ITGA2*, *ITGB3*, and *PLA2G7*.
- SNPs that broadly cover genetic variation in the aforementioned genes did not significantly influence antiplatelet responses to ticagrelor.
- Gene variants in *ABCB1* or *CYP3A5* similarly did not appear to significantly influence ticagrelor exposure or antiplatelet responses.

## 4.2 Dyspnea

- The applicant conducted case-control candidate gene association studies for dyspnea in DISPERSE and DISPERSE2.
- Candidate genes were selected based on the proposed mechanism of dyspnea (adenosine pathway); SNPs were selected by way of putative functionality and haplotype-tagging to broadly cover gene variation.
- Adenosine is a proposed mediator of dyspnea. Gene variants in adenosine receptors and transporters did not significantly increase the risk for dyspnea. .
- Gene variants in *PLA2G7* and *PON1*, mediators of lipid oxidation and inflammation, demonstrated associations with dyspnea. However, these findings would need to be confirmed because limited information is available to support the biological plausibility.
- The mechanism of dyspnea remains poorly understood. A more agnostic PG strategy, such as a genome-wide association study, would be of value in unraveling the biological mechanism of this event. Additional cases may be drawn from PLATO for such an analysis.

## 4.3 Pharmacogenetics of clinical outcomes

- The applicant genotyped *CYP2C19* and *ABCB1* variants in 55% of the PLATO population.
- Numerically higher event rates for some components of the primary efficacy endpoint

were observed in clopidogrel-treated patients with one or more LOF alleles. Early separation in event rates between treatments was observed among those with at least 1 *CYP2C19* LOF allele.

- *The impact of CYP2C19 GOFs on either ticagrelor- or clopidogrel-associated bleeding could not be concluded due to inconsistent trends with increasing numbers of *17 variants.*
- Robust associations between *ABCB1* genotype and treatment outcomes for either ticagrelor or clopidogrel were not demonstrated, insofar as the trends did not follow a gene-dose relationship, were not consistent across treatment arms, and lacked supportive evidence from PK or PD endpoints.
- Factors such as timing of sample collection, PPI use, and stent implantation did not appear to influence the magnitude of *CYP2C19* genetic effects on clopidogrel.
- Geographic differences in treatment outcomes were observed in the substudy population. *CYP2C19* genotype effects on clopidogrel treatment outcomes did not follow the expected trends in the U.S, but interpretation is complicated by the overall study results in the U.S.

### 4.4 General

- PEGASUS is a planned clinical trial that will enroll 13,500 patients one to three years after an ACS and randomly assign to ticagrelor + aspirin or placebo + aspirin for at least one year. DNA collection is specified in the protocol.
- To the extent that ventricular pauses are clinically relevant, the sponsor should also conduct exploratory genetic studies (e.g., genome-wide association) for this adverse event.

## 5 RECOMMENDATIONS

The Genomics Group has reviewed the PG studies included in the NDA submission and recommends post-marketing studies and label modifications described below.

### 5.1 Post-marketing commitments/requirements

None.

### 5.2 Label

The ticagrelor label should reflect treatment effects in *CYP2C19* genotype-defined subgroups.

### 5.3 Additional comments

To better understand the mechanism of ticagrelor adverse events, specifically dyspnea and ventricular pauses, conduct genome-wide associations studies on subsets of DISPERSE, DISPERSE2, and PLATO participants using case-control strategy.

# EDR Links

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| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
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| NDA-22433 | ORIG-1 | ASTRAZENECA LP | AZD6140 |

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MICHAEL A PACANOWSKI
08/27/2010

MICHAEL A PACANOWSKI on behalf of ISSAM ZINEH
08/27/2010

RAJANIKANTH MADABUSHI
08/29/2010
Concur

# ONDQA BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA#:** | **22-433/S-000** |
| **Submission Date:** | 11/13/2009, 6/4/2010 |
| **Drug Name:** | Ticagrelor (AZD6140) |
| **Formulation:** | Tablets |
| **Strength:** | 90 mg |
| **Sponsor:** | AstraZeneca |
| **Reviewer:** | John Duan, Ph.D. |
| **Submission Type:** | Original NDA |

Ticagrelor (AZD6140) is a selective adenosine diphosphate (ADP) receptor antagonist that can block platelet activation and aggregation, by reversibly binding to the P2Y12-receptor. It is developed for the prevention of thrombotic events in patients with acute coronary syndromes (ACS).

## RECOMMENDATION

1. From the biopharmaceutics perspective, the dissolution results over-discriminate the in vivo performance of the tablets.

2. Through the communications, the Agency and the firm reached an agreement on an interim dissolution acceptance criterion as follows.

| | |
|---|---|
| Apparatus | (b) (4) |
| Dissolution medium | |
| Medium volume | |
| Rotation speed | |
| Temperature | |
| Sampling time | |
| Detection | |
| Acceptance criterion | |

Within one year, the firm will review available data from batch release testing, evaluate the continued need for a (b) (4) dissolution specification, and submit a supplement to set the final acceptance criteria for dissolution testing.

3. The dissolution testing can be performed (b) (4) (b) (4)

John Duan, Ph.D.
**Reviewer**
**ONDQA Biopharmaceutics**

Date

_____ _____

Patrick Marroum, Ph.D. Date
**ONDQA Biopharmaceutics**

cc: NDA 22-433
Patrick Marroum, Angelica Dorantes, John Duan

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| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
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| NDA-22433 | ORIG-1 | ASTRAZENECA LP | AZD6140 |

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JOHN Z DUAN
07/23/2010

PATRICK J MARROUM
07/23/2010

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| **NDA Number:** | 022433 |
| **Submission Type; Code:** | S |
| **Applicant Name:** | AstraZeneca |
| **Submission Dates:** | November 16th, 2009 |
| **Brand Name:** | Brilinta™ (proposed) |
| **Generic Name** | Ticagrelor |
| **Dosage Form:** | Immediate Release Tablets |
| **Dosage Strengths:** | 90 mg |
| **Proposed Indication:** | Reduction of thrombotic events in acute coronary syndrome patients. |
| **OCP Division:** | DCP1 |
| **Primary Reviewer:** | Islam R. Younis, Ph.D. |
| **Team Leader:** | Rajanikanth Madabushi, Ph.D. |
| **Pharmacometrics Reviewer** | Kevin M. Krudys, Ph.D. |
| **Pharmacometrics Team Leader** | Pravin R. Jadhav, Ph.D. |
| **Pharmacogenomics Reviewer** | Michael A. Pacanaowski, Pharm.D., M.P.H |
| **Pharmacogenomics Team Leader** | Issam Zineh, Pharm D., M.P.H |

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# 1 EXECUTIVE SUMMARY

Ticagrelor is a selective and reversible $P2Y_{12}$ ADP-receptor antagonist that is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with acute coronary syndrome (ACS), unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction, who are to be managed medically or invasively. The proposed loading dose for ticagrelor is 180 mg and the proposed maintenance dose is 90 mg twice daily. Ticagrelor will be marketed as 90 mg immediate release tablets.

The application was first submitted to the FDA under IND 065,808 on April 28th, 2003. NDA 022433 was submitted on November 16th, 2009 and was granted a standard review status on January 15th, 2010.

A single Phase III study (PLATO) in patients with Non-ST or ST segment elevation ACS formed the basis for the submission. The primary efficacy endpoint was the time to first occurrence of any event from the composite of death from vascular causes, myocardial infarction (MI), and stroke. The primary objective of this study was to test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events.

The clinical pharmacology program of ticagrelor consisted of 43 studies that investigated the safety, tolerability, pharmacokinetics, pharmacodynamics, bioavailability, bioequivalence, food effect, drug-drug interactions, and pharmacokinetics in specific population. The population pharmacokinetics analysis was conducted in subset of patients from PLATO and the Phase II study (DISPERSEII). Pharmacogenomics analysis was performed using data from the pharmacodynamic study (RESPOND), phase II studies (DISPERSE and DISPERSE2), and PLATO.

## 1.1 Recommendations

- The Office of Clinical Pharmacology has reviewed the submission and cannot resolve the differential effectiveness of ticagrelor in US and Non-US sites. Several factors, such as aspirin usage, statin usage, compliance, and differences in ticagrelor exposure between US and non-US sites were investigated. These factors did not satisfactorily explain the differential effectiveness. Given the overall results, the Office recommends approval of ticagrelor with a study post-approval aimed to reconcile the findings from US region.
- The Office finds the clinical pharmacology information acceptable pending on agreement of labeling changes (which will be conveyed in a separate document) and proposed post-marketing requirements and commitments.

## 1.2 Post Marketing Requirements

- Pharmacokinetic study in subjects with moderate and severe hepatic impairment.

## 1.3 Post Marketing Commitment

- Clinical trial in patients with Non-ST or ST segment elevation ACS with at least 50% of the population from the US region. The proposed trial need not be a repetition of the PLATO study.

## 1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

**Exposure-Response**

- An exposure-response relationship could not be established for the composite efficacy endpoint of cardiovascular death, MI, and stroke in PLATO.
- A shallow relationship between ticagrelor exposure and major bleeding was established.
- A shallow relationship between ticagrelor exposure and dyspnea was established.
- An exposure-response relationship could not be established between ticagrelor exposure and occurrence of ventricular pauses ≥ 3 or ≥ 5 seconds in the Holter sub-study in PLATO.

**Pharmacogenomics**

- A series of exploratory genetic association studies assessing the influence of approximately 325 single nucleotide polymorphisms (SNPs) across 20 candidate genes (including $P2RY_{12}$ [target], *ABCB1*, and *CYP3A5*) on ticagrelor PD responses, exposure, and dyspnea revealed no compelling pharmacogenetic interactions. *CYP2C19* and *ABCB1* were genotyped in PLATO.
- Treatment differences for ticagrelor versus clopidogrel tended to be greater, in favor of ticagrelor, in patients with CYP2C19 loss-of-function alleles; bleeding rates did not differ substantially across genotype groups. CYP2C19 genotype did not appear to account for the geographic differences in ticagrelor treatment outcomes.

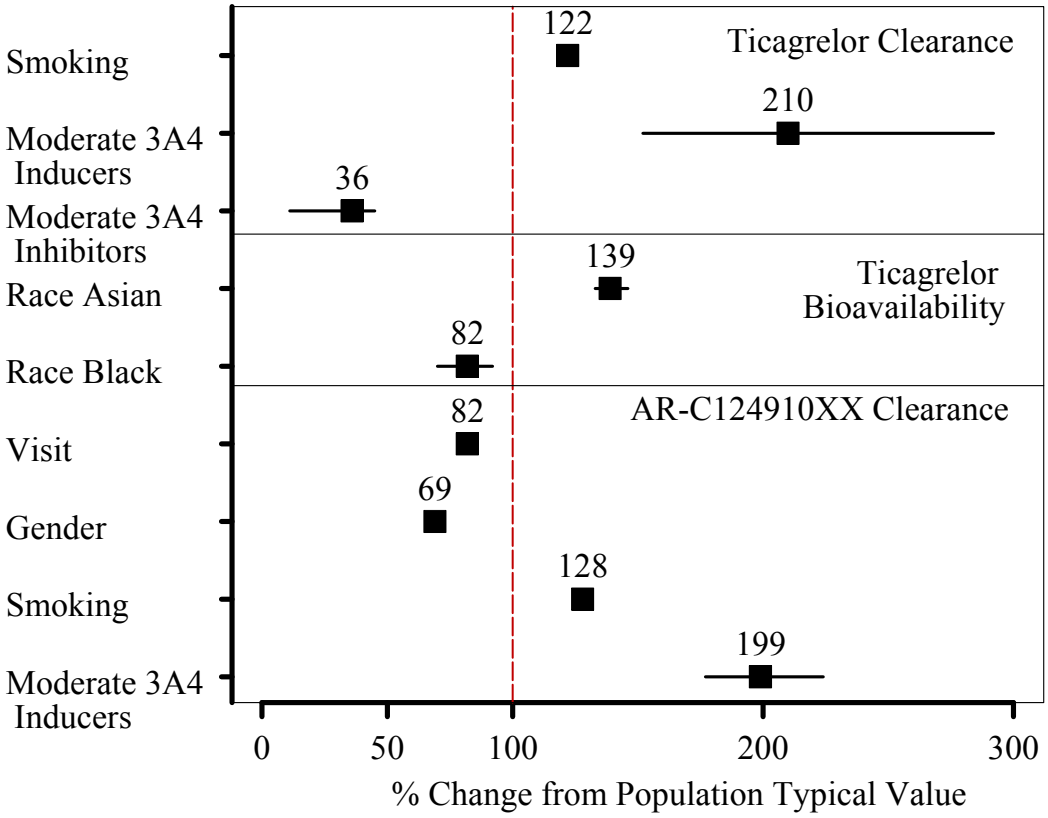
**Pharmacodynamics**

- The rate of onset of pharmacodynamic effect of ticagrelor measured by % inhibition of platelet aggregation (%IPA) is faster than that of clopidogrel in stable coronary artery disease (CAD) patients on aspirin.
- The rate of offset of pharmacodynamic effect (%IPA) of ticagrelor is faster than that in clopidogrel in CAD patients on aspirin. However, given the higher antiplatelet activity and longer half-life of ticagrelor and its active metabolite, the time to conduct surgery following stopping of ticagrelor and clopidogrel may not be much different (5 days).
- Switching from clopidogrel results in a statistically significant increase in %IPA of at least 16.8 units in CAD patients on aspirin and vice versa. The effect is more pronounced in CAD patients on aspirin who are less responsive to clopidogrel.
- Ticagrelor increases serum uric acid by 10% in healthy male volunteers and patients with acute coronary artery disease.
- Ticagrelor does not induce bronchospasm and does not cause any changes in respiratory parameters in healthy elderly, patients with mild asthma, and patients with COPD.

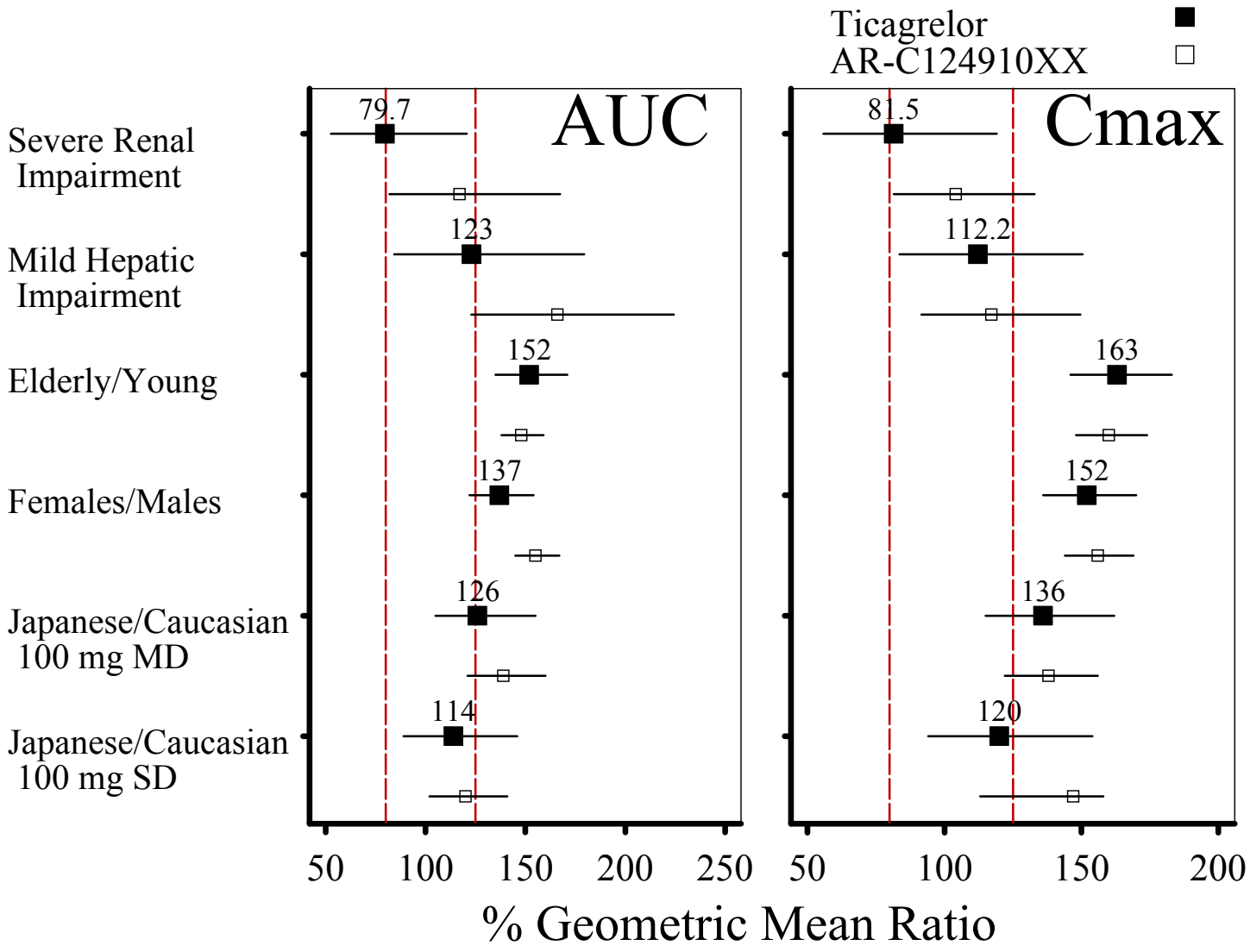
**Pharmcokinetics**

- The plasma concentration of ticagrelor decline mono-exponentially
- Ticagrelor $t_{1/2}$ is 8 h.
- Ticagrelor is rapidly absorbed with median $T_{max}$ of 2.65 h.
- Ticagrelor is > 99% bound to plasma protein
- Ticagrelor is metabolized mainly by CY3A4/5 to produce AR-C124910XX and AR-C133913XX.
- The major metabolite AR-C124910XX is rapidly formed with median $T_{max}$ 3.12 h. It is also equipotent as $P2Y_{12}$ inhibitor as ticagrelor, >99% bound to plasma protein, and metabolized by CYP3A4/5. AR-C124910XX to ticagrelor ratio is 36% – 52%. AR-C133913XX (inactive metabolite) to ticagrelor ratio is 12%.
- Less than 1% of ticagrelor is excreted unchanged in the urine.
- The PK of ticagrelor is slightly more than dose proportional over the dose range 50 – 400 mg in healthy volunteers and in patients with stable atherosclerotic disease.

**Population Pharmcokinetics**

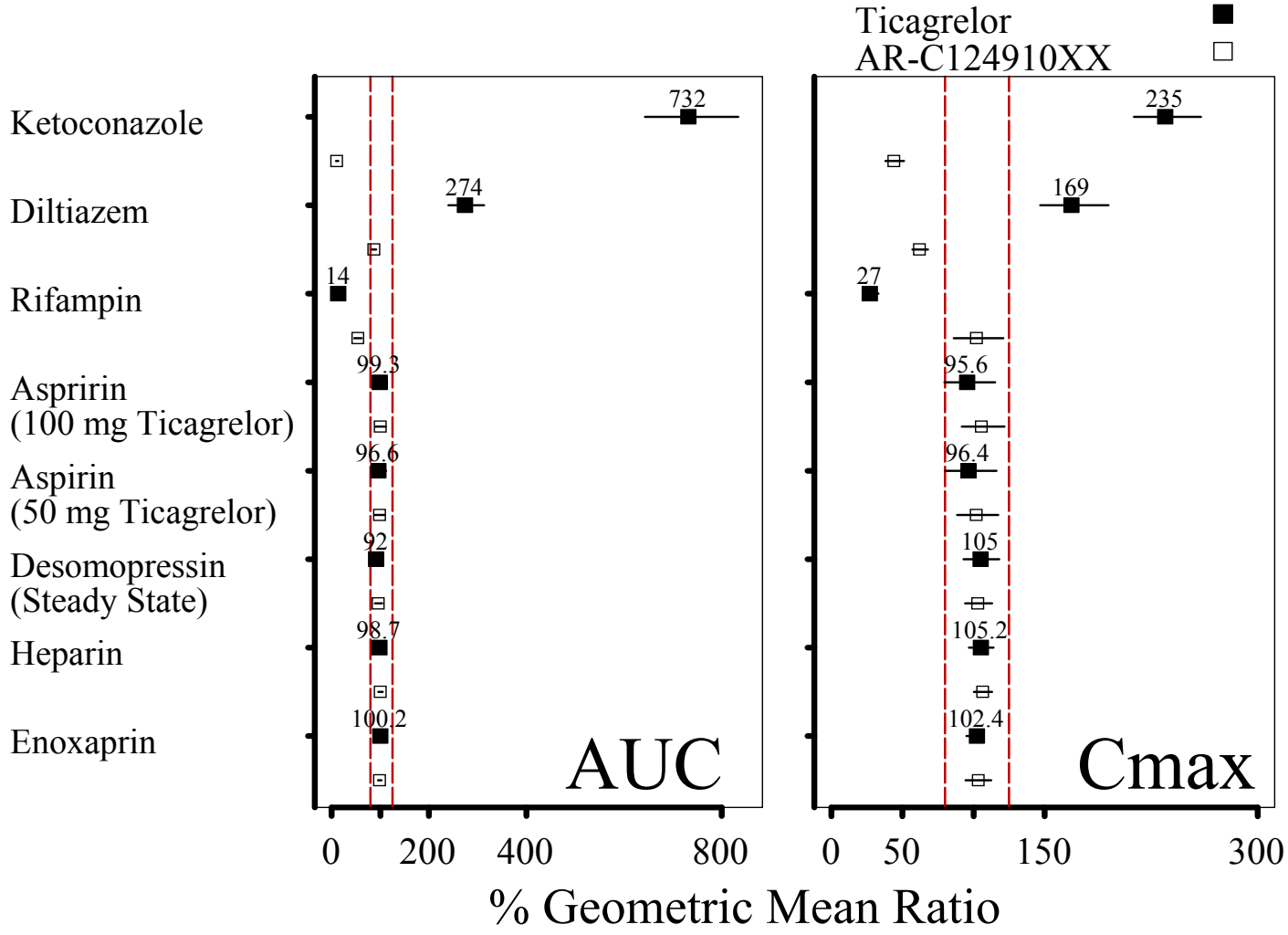


**Specific population**

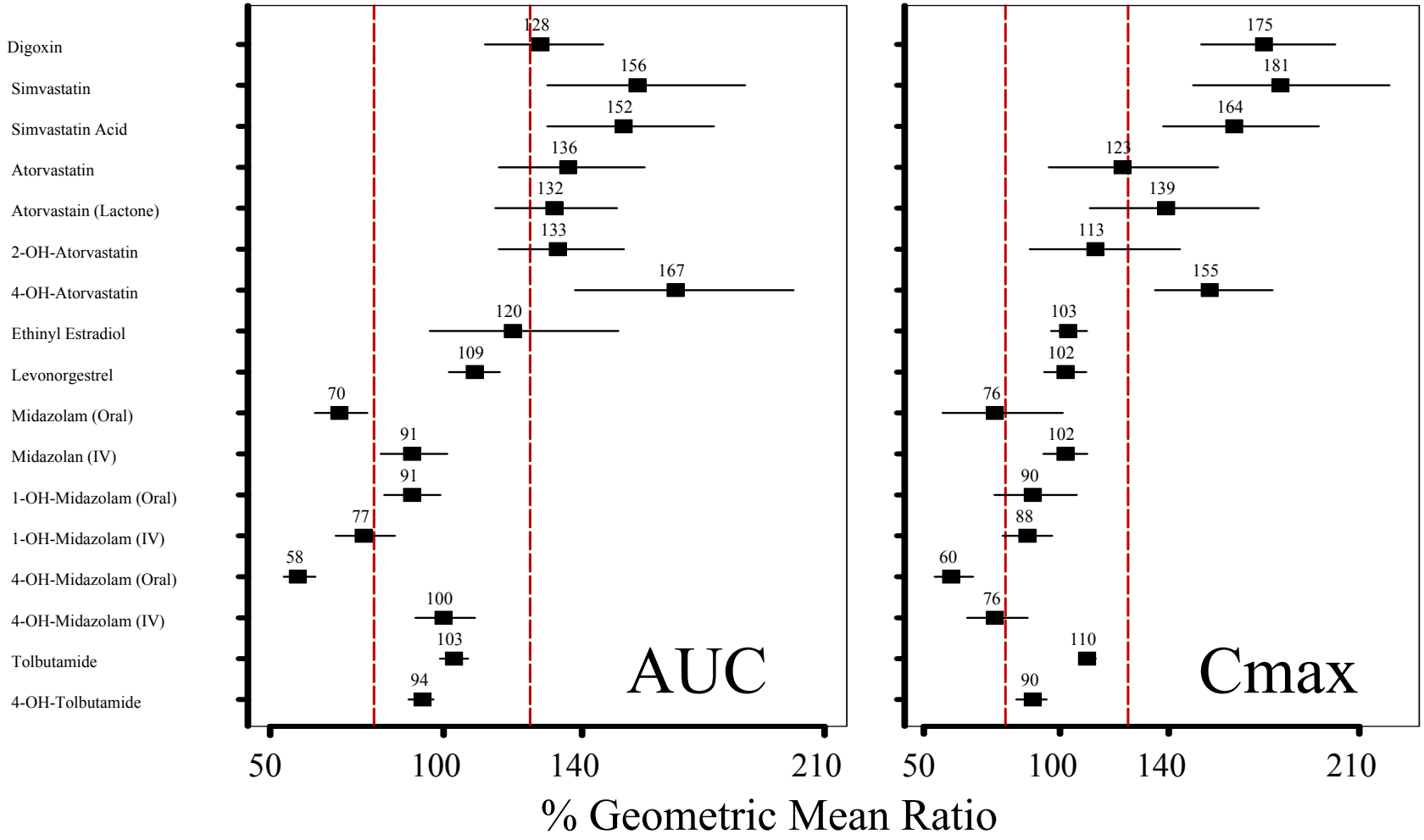


**Drug-Drug interactions**

1. Effect of other medication on ticagrelor systemic exposure



2. <u>Effect of ticagrelor on the systemic exposure of other medications</u>



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Clinical Pharmacology Briefing: 06/09/2010

Attendant: Lawrence Lesko, Norman Stockbridge, Stephen Grant, Shie Mei Huang, Mehul Mehta, Ramana Uppoor, Edward Bashaw, Atiqur Nam Rahman, , Chandrahas Sahajwalla, Elena Mishina, Padmaja Mummaneni , Ping Zhao, Nancy Hu, Divya Menon-Andersen, Darell Abernethy, Lin Zhou, Huixia Zhang, Sayed Al Habet, Jiang Liu, Xinning Yang, Bei Yu, Peter Hinderling, Ju-Ping Lai, Manoj Khurana, Michael Monteleone, Ritesh Jain, Immo Zdrojewski, Zhihong Li, Chinmay Shukla, Christian Grimstein, Suresh Naraharisetti, Arun Agrawal, Partha Roy, Liang Zhao, Sheetal Agarwal, Yoriko Harigaya, Frederico Goodsaid, Lokesh Jain, Sudharshan Hariharan, Rajnikanth Madabushi, Kevin Krudys, Michael Pacanowski, Robert Fiorentino, and Islam Younis.

# 2 QUESTION BASED REVIEW

## 2.1 General Attributes of the Drug

### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

**Drug Substance:** Ticagrelor is a small molecule with 6 chiral centers which are all in S-configuration except those marked by * in the structure depicted in Figure 1.

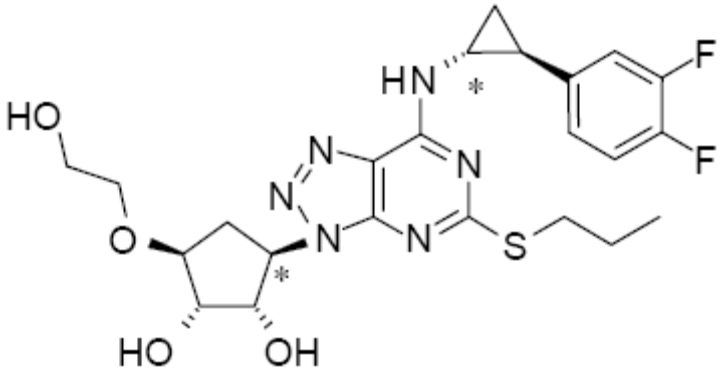


**Figure 1.** Ticagrelor Structure

Ticagrelor physical-chemical properties are displayed in the table 1.

**Table 1.** Ticagrelor physical-chemical properties

| | |
|---|---|
| Molecular Formula | $C_{23}H_{28}F_2N_6O_4S$ |
| Molecular Weight | 522.57 Dalton |
| Physical State | Powder |
| Solid State Form | (b) (4) |
| Solubility | - Water: 0.016 mg/mL<br>- Low and No pH dependant solubility (<0.009 mg/L)<br>- Human Intestinal Fluid: 0.5 mg/L<br>- Highly soluble in organic solvents |
| Partition Coefficient | (b) (4) |
| Stability | (b) (4) |
| Hygroscopicity | (b) (4) |
| Melting Point | (b) |

**Drug Product:** Ticagrelor immediate release tablets are presented as round, biconvex, yellow film-coated containing 90 mg of ticagrelor. The tablets are marked with '90' above 'T' on 1 side, and plain on the other. The proposed initial shelf life is 24 months without any special storage conditions. Table 2 displays the composition of ticagrelor tablets.

**Table 2.** Composition of ticagrelor tablets.

| Component | Quantity | Function | Standard |
|---|---|---|---|
| **Tablet core:** | | | |
| Ticagrelor | 90 | Active | AstraZeneca |
| Mannitol | (b) (4) | (b) (4) | USP |
| Dibasic calcium | (b) (4) | (b) (4) | USP |
| Sodium starch | (b) | (b) (4) | NF |
| Hydroxypropyl | (b) | (b) (4) | NF |
| Magnesium stearate | (b) | (b) (4) | NF |
| Purified water | (4 qs | (b) (4) | USP |
| Core tablet weight | (b) (4) | | |
| **Tablet coating** | | | |
| Hypromellosee | (b) (4) | (b) (4) | USP |
| Titanium dioxide | (b) (4) | (b) (4) | USP |
| Talc | (b) (4) | (b) (4) | USP |
| Polyethylene glycol | (b) (4) | (b) (4) | NF |
| Ferric oxide yellow | (b) (4) | (b) (4) | NF |
| Purified water | qs | (b) (4) | USP |

### 2.1.2 What are the proposed mechanism of action and therapeutic indications?

**Mechanism of Action:** reversible $P2Y_{12}$ ADP-receptor antagonist

**Proposed Indication:** Reduce the rate of thrombotic events (including stent thrombosis) for patients with acute coronary syndrome (ACS), unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction, who are to be:

1. Managed medically
2. Managed invasively with percutaneous coronary intervention (with or without stent) and/or coronary artery bypass graft (CABG).

### 2.1.3 What are the proposed dosages and routes of administration?

Ticagrelor drug product is immediate release tablet (90 mg ticagrelor) for oral administration. The proposed loading dose is 180 mg and the proposed maintenance dose is 90 mg BID.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

Ticagrelor clinical pharmacology and clinical development program consisted of the following studies (number in parentheses represents the number of studies):

I. Phase I (31) (Healthy Volunteers):

1. Pharmacokinetics (5): Single Dose, Multiple Dose, and Mass Balance.
2. Specific population (5): Renal Impairment, Mild Hepatic Impairment, Age/Gender, Race Chinese, and Race Japanese
3. Biopharmaceutics (9): Bioavailability, Bioequivalence, and Food Effect.
4. Drug-Drug Interactions (13): Desmopressin, Ketoconazole, Diltiazem, Rifampin, ASA, Heparin, Enoxaparin, Simvastatin, Digoxin, Atorvastatin, Oral Contraceptive, Tolbutamide, Midazolam

II. Phase II (2)

1. DISPERSE: Dose finding study in patients with documented atherosclerotic disease.
2. DISPERSEII: Dose confirming study in patients with non-ST segment elevation ACS.

III. Phase III (1): PLATO [A Study of PLATelet inhibition and Patient Outcomes]: A randomized, double-blind, parallel group, multi-center, efficacy and safety study to evaluate the superiority of ticagrelor (90 mg BID) to clopidogrel (75 mg QD) for prevention of vascular events in patients with Non-ST or ST elevation ACS. The duration of the study was 6, 9, or 12 month depending on the entry date. The primary efficacy endpoint was time from randomization to first occurrence of death from vascular causes (CV death), MI excluding silent MIs, and stroke. The primary safety endpoint was time from first dose of study drug to first occurrence of any total major bleeding event.

IV. Pharmacodynamics (8):

1. Study to compare the onset and offset of ticagrelor to that of clopidogrel in patients with stable coronary artery disease.
2. RESPOND: Study in patients with stable coronary artery disease to compare platelet aggregation after switching from clopidogrel to ticagrelor and vice versa in clopidogrel responders and non-responders.
3. Study in healthy volunteers to compare platelet aggregation following loading doses of ticagrelor and clopidogrel.
4. Study in healthy male volunteers to evaluate the effect of ticagrelor on uric acid.
5. Thorough QT
6. Two studies to evaluate the effect of ticagrelor on respiratory parameters, one in elderly healthy subjects and the other in subjects with mild asthma or COPD.

7. Study in healthy volunteers to evaluate platelet aggregation of ticagrelor relative to clopidogrel.

Population pharmacokinetic analysis was performed using data from DISPERSEII and PLATO. Exposure-response (safety and efficacy) analysis was performed using data from PLATO.

Pharmacogenomics analysis was performed using data from DISPERSE, DISPERSE2, RESPOND, and PLATO.

### 2.2.2 What are the evidences of efficacy provided by the sponsor in support of the application?

The results of PLATO, the pivotal clinical trial, are presented in Table 3.

**Table 3.** PLATO primary efficacy analysis.

| **Event** | **Ticagrelor 90 mg BID N = 9333** | **Clopidogrel 75 mg QD N = 9291** | **Hazard Ratio (95% CI)** | **p-value** |
|---|---|---|---|---|
| | **Patients with Events** | **Patients with Events** | | |
| Primary Endpoint | 864 (9.3%) | 1014 (10.9%) | 0.84 (0.77, 0.92) | 0.0003 |
| MI | 504 (5.4%) | 593 (6.4%) | 0.84 (0.75, 0.95) | 0.0045 |
| CV Death | 353 (3.8%) | 442 (4.8%) | 0.79 (0.69, 0.91) | 0.0013 |
| Stroke | 125 (1.3%) | 106 (1.1%) | 1.17 (0.91, 1.52) | 0.2249 |

### 2.2.3 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The primary pharmacodynamic endpoint is ADP (20 μM) induced percent inhibition of platelet aggregation (%IPA) (Final Extent). %IPA is calculated as follows:

$$\%\,\mathrm{IPA} = \frac{\mathrm{PA}_{\mathrm{pre-dose}} - \mathrm{PA}_{\mathrm{post-dose}}}{\mathrm{PA}_{\mathrm{pre-dose}}}$$

Where PA is platelet aggregation measured by light transmittance aggregometry. Throughout the clinical pharmacology program PA was measured following induction using 5 μM ADP, 20 μM ADP, and 2 μg/mL collagen at final and maximum extent. PA induced by 20 μM ADP was used as the primary source for pharmacodynamic comparisons.

% IPA is widely used and accepted pharmacodynamic endpoint to evaluate platelet aggregation.

### 2.2.4 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

- Both ticagrelor and the active metabolite (AR-C124910XX) were appropriately identified using liquid chromatography and tandem mass spectrometry (LC-MS/MS).
- AR-C133913XX: (the other metabolite) which is 100 fold less active than ticagrelor) was quantified using an LC-MS/MS in one single dose PK study in healthy volunteers.

### 2.2.5 Exposure-Response

#### 2.2.5.1 What are the characteristics of the exposure-response relationships for efficacy?

An exposure-response relationship could not be established for the composite efficacy endpoint of cardiovascular death, MI, and stroke in PLATO. This is most likely due to the fact that only one dose (90 mg BID) was studied and the number of events was relatively small.

Following the administration of ticagrelor, maximum %IPA is observed 2 – 4 h post-dose and tapers off as ticagrelor and AR-124910XX plasma concentration declines, as shown in Figure 2. This observation depicts the reversibility of action of ticagrelor as $P2Y_{12}$ inhibitor.

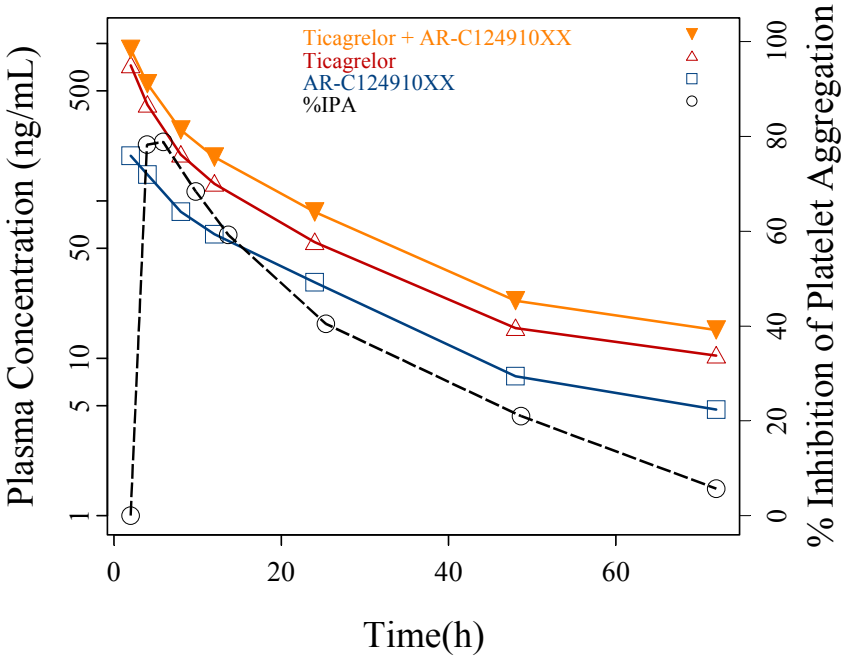


**Figure 2.** Ticagrelor mean pharmacokinetics and pharmacodynamics time profile following the administration of a single 90 mg dose in healthy volunteers.

#### 2.2.5.2 Is there evidence of efficacy in the US population?

The evidence of efficacy in the US population is equivocal. It should be noted that PLATO study was not designed specifically to show evidence of efficacy compared to clopidogrel in the US only.

- The hazard ratio for the primary efficacy endpoint within the USA was 1.27 (95% CI 0.92, 1.75) compared to 0.81 (95% CI 0.74, 0.90) for the non-USA region, suggesting a benefit of clopidogrel over ticagrelor in the USA.
- Several potential explanatory factors were explored, including: compliance, statin exposure, low ticagrelor exposure, chance finding, and a fructose-hyperuricemia relationship. None of these factors satisfactorily explained the observed benefit of clopidogrel over ticagrelor in the USA.
- In the sponsor's multivariate analysis, aspirin dose explained the largest treatment-by region effect, although aspirin dose was highly unbalanced, with most high-dose aspirin use (>300 mg) occurring in the USA. Furthermore, there are no pharmacokinetic or pharmacodynamic interactions that would predict an undesired effect at high aspirin doses.

#### 2.2.5.3 What are the characteristics of the exposure-response relationships for safety?

**Major Bleeding:** A shallow relationship between ticagrelor exposure and major bleeding was established. Given the 10-90th percentiles of total exposure in PLATO at Visit 1 in a patient 62 years of age, the probability of major bleeding was 2.8-3.2% (without coronary artery by-pass grafting (CABG) or percutaneous coronary intervention (PCI)), 58-63% (with CABG) and 0.6% (with PCI).

**Dyspnea:** A shallow relationship between ticagrelor exposure and dyspnea was established. The predicted probability of having a dyspnea event (mild, moderate or severe) given the 10-90th percentile of ticagrelor exposure at Visit 1 was 2.2-2.8% in a patient with no risk factors.

**Ventricular Pauses:** A positive exposure-response relationship could not be established between ticagrelor exposure and occurrence of ventricular pauses ≥ 3 or ≥ 5 seconds in the Holter sub-study in PLATO.

#### 2.2.5.4 What is the onset and offset of ticagrelor compared to clopidogrel?

**Onset:** In patients with stable coronary artery disease, onset of action (measured by 20 µM ADP induced %IPA) is faster following the administration of 180 mg loading dose of ticagrelor compared to a 600 mg loading dose of clopidogrel (Figure 2)

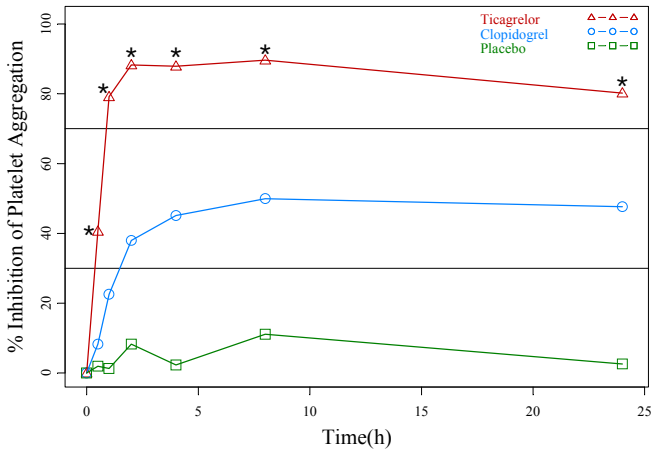


**Figure 3.** %IPA (Final Extent) induced by 20 µM ADP following the administration of ticagrelor, clopidogrel, and placebo on ASA background. Values represent mean. * indicates significant difference ($p < 0.0001$) using Wilcoxon sum rank test.

**Offset:** The rate of offset of effect (measured by 20 µM ADP induced %IPA) in patients with stable coronary artery disease, after six weeks of ticagrelor twice daily administration of 90 mg is faster compared to the once daily administration of 75 mg clopidogrel (Figure 3).

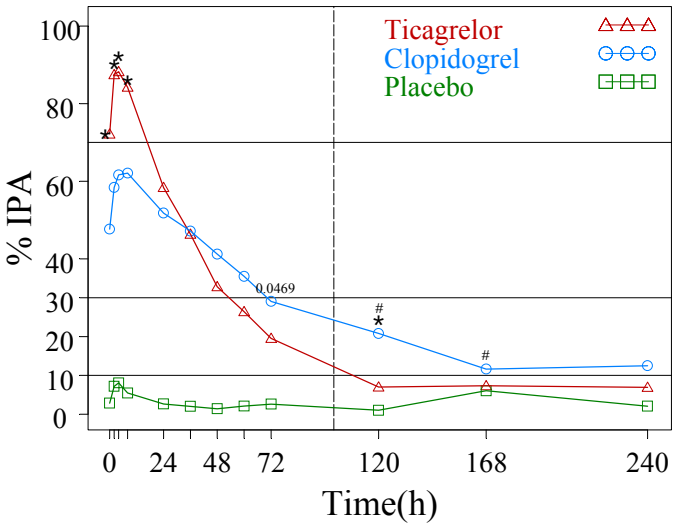


**Figure 4.** %IPA induced by 20 µM ADP following the administration of the last dose of ticagrelor, clopidogrel, and placebo on ASA background. Values represent mean. * indicates significant difference ($p < 0.05$) comparing ticagrelor to clopidogrel. Points in the ticagrelor and clopidogrel groups left to the dashed lines are significantly different from placebo ($p < 0.05$). Points to the right of the dashed lines are not significantly different from placebo unless designated by #.

### 2.2.5.5 What is the effect of switching between clopidogrel and ticagrelor?

In patients with stable coronary artery disease with ≤ 10% absolute change in platelet aggregation in response to a single 300 mg oral dose of clopidogrel (arbitrarily defined non-responders by the sponsor), switching from clopidogrel 75 mg QD to ticagrelor 90 mg BID or vice versa resulted in 34.5 units absolute change in %IPA (4 h post-dose) at steady state.

In responders switching from clopidogrel to ticagrelor resulted in 16.8 units absolute increase in %IPA at steady state (4 h post-dose), while switching from ticagrelor to clopidogrel results in 29.4 units absolute decrease.

### 2.2.5.6 What is the effect of ticagrelor on uric acid?

In a cross-over study in male healthy volunteers and following the administration of twice daily 90 mg ticagrelor for 5 days, ticagrelor produced a statically significant 10% increase serum uric acid concentrations relative to placebo

Similar mild increases were observed in patients with acute coronary artery disease (DISPERSEII and PLATO). Ticagrelor produced a dose dependant increase in serum uric acid (Figure 4).

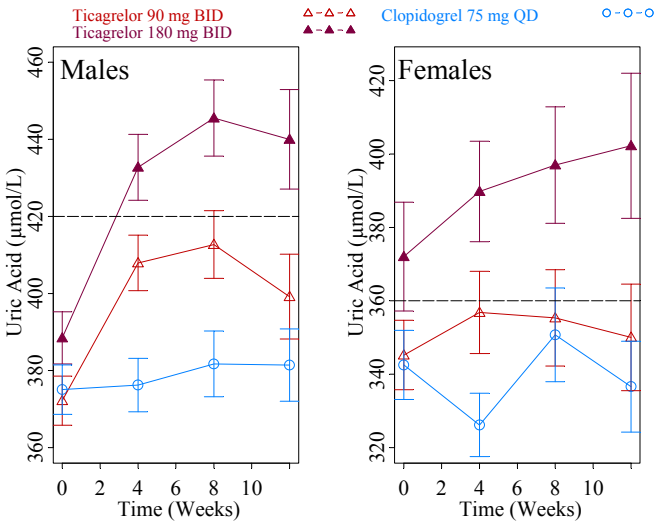


**Figure 5.** Serum uric acid concentration following the administration of ticagrelor (180 mg and 90 mg BID) and clopidogrel (75 mg QD) in DISPERSEII. Values represent mean and error bars represent standard error of the mean. Dashed lines represents the threshold for hyperurecemia, 420 µmol/L for males and 360 µmol/L for females.

### 2.2.5.7 What is the effect of ticagrelor on respiratory parameters?

Dyspnea caused by ticagrelor is not attributed to changes in respiratory parameters. The administration of ticagrelor, 450 mg loading dose + 180 mg BID for 4 days, in healthy elderly, patients with mild asthma, and patients with mild COPD:

- did not affect respiratory rate, minute ventilation, or tidal volume.
- did not cause bronchospasm as assessed by spirometry.
- had no effect on exercise performance, caused no worsening in sensation of breathing or change in perception of breathlessness as measured by the Modified Borg Scale and Bidirectional Dyspnea Index, and had no effect on pulse oximetry.

## 2.2.6 What are the PK characteristics of the drug?

### 2.2.6.1 What are the single and multiple dose PK parameters?

**Single Dose (Healthy Volunteers):** Ticagrelor pharmacokinetics was evaluated in the dose range 3.0 to 1260 mg is 3 single ascending dose studies in healthy volunteers. The plasma concentrations of ticagrelor and AR-C124910XX decline mono-exponentially (Figure 5) with a half-life of ~ 8 and 9 h, respectively. Pharmacokinetic parameters following single dose (30 – 400 mg) are displayed in Table 4. The average between subject variability is ~ 34%.

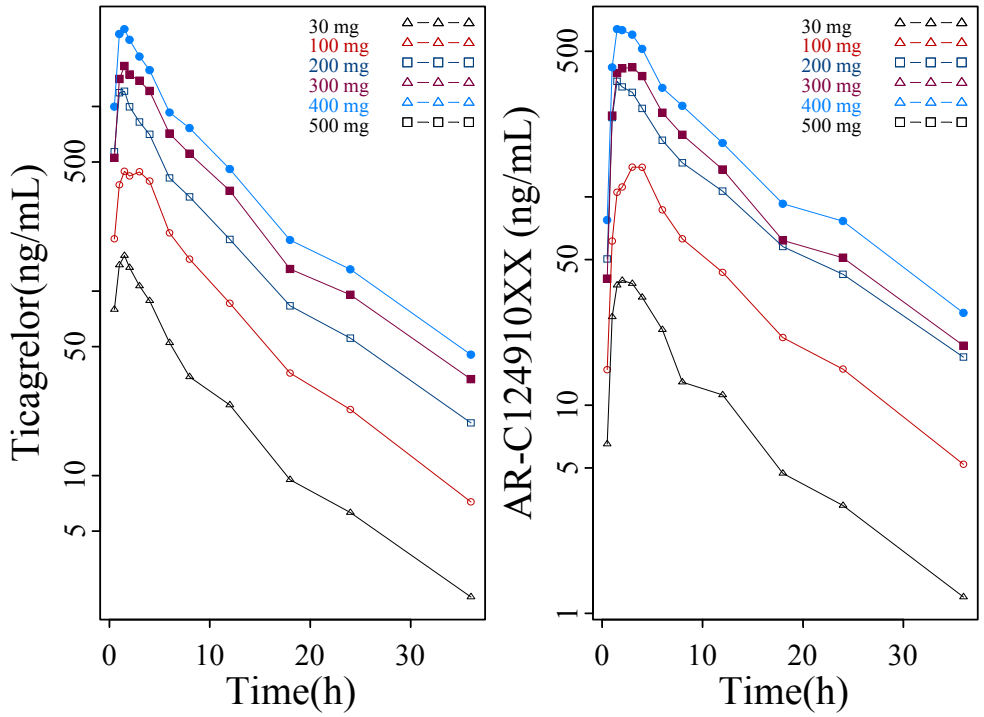


**Figure 5.** Ticagrelor and AR-C124910XX mean plasma concentration vs. time profile following the administration of a single dose of ticagrelor in healthy volunteers.

**Table 4.** Ticagrelor PK and AR-C124910XX PK parameters following a 30 – 400 mg single oral dose

| **Ticagrelor Pharmacokinetic Parameters , Mean (%CV)** | | | | | | |
|---|---|---|---|---|---|---|
| **Dose (mg)** | **N** | **$C_{max}$ (ng/mL)** | **$T_{max}$(h)** Median (range) | **AUC (ng h/mL)** | **$t_{1/2}$ (h)** | **CL/F (mL/min/kg)** |
| **30** | 7 | 161 (20.5) | 1.5 (1-2) | 1005 (14.3) | 7.77 (13.0) | 6.72 (17.7) |
| **100** | 9 | 586 ( 28.8) | 1.5 (1-4.1) | 3683 (20.4) | 7.30 (18.9) | 6.52 (22.4) |
| **200** | 8 | 1295 (32.2) | 1.49 (1-3) | 8213 (25.7) | 8.09 (14.1) | 5.71 (24.0) |
| **300** | 8 | 1746 (18.2) | 1.5(1-3.05) | 13170 (22.6) | 7.57 (14.0) | 5.31 (23.5) |
| **400** | 7 | 2711 (21.0) | 1.5 (1-2) | 18547 (23.8) | 7.88 (13.2) | 5.03 (25.8) |
| **AR-C124910XX Pharmacokinetic Parameters , Mean (%CV)** | | | | | | |
| **Dose (mg)** | **N** | **$C_{max}$ (ng/mL)** | **$T_{max}$(h)** Median (range) | **AUC (ng h/mL)** | **$t_{1/2}$ (h)** | **CL/F (mL/min/kg)** |
| **30** | 7 | 42.1 (31.7) | 2.0 (1.03-3) | 376 (26.1) | 9.39 (22.5) | 18.25 (15.5) |
| **100** | 9 | 166 (27.2) | 3.0(1.5-4.1) | 1460 (27.9) | 8.63 (19.9) | 16.71 (21.8) |
| **200** | 8 | 367 (34.9) | 1.5(1.5-3) | 3722 (44.8) | 10.05 (17.7) | 13.10 (23.9) |
| **300** | 8 | 462 (32.2) | 2.49 (1.5-4) | 4611 (25.4) | 8.54 (17.3) | 14.99 (16.7) |
| **400** | 7 | 713 (21.8) | 1.97 (1.47-3) | 6577 (32.3) | 8.77 (15.1) | 14.13 (18.2) |

**Multiple Doses (Healthy Volunteers):** Ticagrelor steady state was achieved within 2-3 days following multiple once daily (QD) and twice daily (BID) doses. Table 5 displays ticagrelor and AR-C124910XX PK parameters following multiple doses. On average, the between subject variability was ~ 35%.**Table 5.** Ticagrelor and AR-C124910XX PK parameters following multiple doses.

| | Treatment | N | AUCτ (ng h/mL) | | $C_{max}$ (ng/mL) | | $T_{max}$ (h) | | CL/F (L/h) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean | %CV | Mean | %CV | Median | Range | Mean | %CV |
| Ticagrelor | | | | | | | | | | |
| **QD** | 50mg | 7 | 1961 | 30.7 | 233 | 34.9 | 3 | 2-4 | 43.59 | 34.8 |
| | 100mg | 7 | 4585 | 36.3 | 609 | 43.3 | 2.71 | 1.5-4 | 41.9 | 46.0 |
| | 200mg | 14 | 8648 | 43.3 | 1109 | 39.1 | 2.43 | 1.5-4 | 46.58 | 46.6 |
| | 300mg | 7 | 11066 | 32.1 | 1384 | 22.6 | 1.71 | 1.5-2 | 49.02 | 29.5 |
| | 400mg | 6 | 15342 | 23.4 | 1873 | 12.0 | 1.58 | 1-2 | 45.81 | 27.2 |
| | 600mg | 6 | 25111 | 30.4 | 3072 | 27.3 | 2 | 1-3 | 43.42 | 34.2 |
| **BID** | 50mg | 14 | 1771 | 33.2 | 264 | 34.5 | 2.82 | 1-4 | 54.03 | 35.1 |
| | 100mg | 13 | 4455 | 44.9 | 687 | 48.7 | 2.69 | 1-6 | 44.14 | 43.3 |
| | 200mg | 13 | 9781 | 25.3 | 1487 | 26.1 | 2.62 | 1.5-4 | 37.97 | 35.6 |
| | 300mg | 7 | 15754 | 46.7 | 2263 | 56.9 | 3.14 | 2-4 | 41.97 | 47.9 |
| AR-C124910XX | | | | | | | | | | |
| **QD** | 50mg | 7 | 799 | 46.6 | 77 | 48.1 | 4 | 3-6 | | |
| | 100mg | 7 | 2026 | 44.5 | 189 | 54.8 | 3.43 | 2-4 | | |
| | 200mg | 14 | 3371 | 50.1 | 319 | 45.7 | 3.01 | 2-4.12 | | |
| | 300mg | 7 | 4061 | 27.6 | 377 | 31.5 | 1.93 | 1.5-3 | | |
| | 400mg | 6 | 5792 | 30.6 | 513 | 14.7 | 2.33 | 2-3 | | |
| | 600mg | 6 | 9376 | 32.7 | 819 | 27.9 | 2.42 | 1.5-3 | | |
| **BID** | 50mg | NA | NA | NA | NA | NA | NA | NA | | |
| | 100mg | 14 | 666 | 34.8 | 84 | 30.1 | 3.25 | 1.5-6 | | |
| | 200mg | 13 | 1894 | 59.5 | 247 | 61.7 | 3.12 | 1.5-6 | | |
| | 300mg | 13 | 4152 | 61.9 | 514 | 55.7 | 3.19 | 1.5-6 | | |
| τ = 24 h for QD and 12 h for BID, NA: not available | | | | | | | | | | |

#### 2.2.6.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

.

At a 100 mg BID dose (which is bioequivalent to the 90 mg IR tablet) AUC and $C_{max}$ are ~ 17% lower on average in patients with documented atherosclerotic disease compared to healthy volunteers. The between subject variability in patients with documented atherosclerotic disease was ~ 50%.

#### 2.2.6.3 What are the characteristics of drug absorption?

Ticagrelor is rapidly absorbed with a median $T_{max}$ of 2.65 h. *In vitro*, ticagrelor and AR-C124910XX are substrates for P-glycoprotein and a moderate inhibitors of P-gp mediated digoxin transport.

#### 2.2.6.4 What are the characteristics of drug distribution?

Ticagrelor and AR-C124910XX are more than 99% bound to plasma proteins.

#### 2.2.6.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

- Ticagrelor is extensively metabolized and less than 1% of the ticagrelor dose is excreted unchanged in the urine.
- AR-C124910XX appears to be the major metabolite of ticagrelor and together with the parent accounted for ~ 90% of the plasma radioactivity.

#### 2.2.6.6 What are the characteristics of drug metabolism?

- Ticagrelor is rapidly and extensively metabolized by CYP3A4/5.
- The majority of ticagrelor metabolism is oxidative and the main metabolites are AR-C124910XX (loss of the hydroxy-ethyl side chain) and AR-C133913XX (loss of the difluorophenyl-cyclopropyl group).
- The major metabolite AR-C124910XX is rapidly formed with median $T_{max}$ 3.12 h. It is also equipotent as $P_2Y_{12}$ inhibitor as ticagrelor and metabolized by CYP3A4/5. AR-C124910XX to ticagrelor ratio is 36% – 52%.
- AR-C133913XX (inactive metabolite) to ticagrelor ratio is 12%.

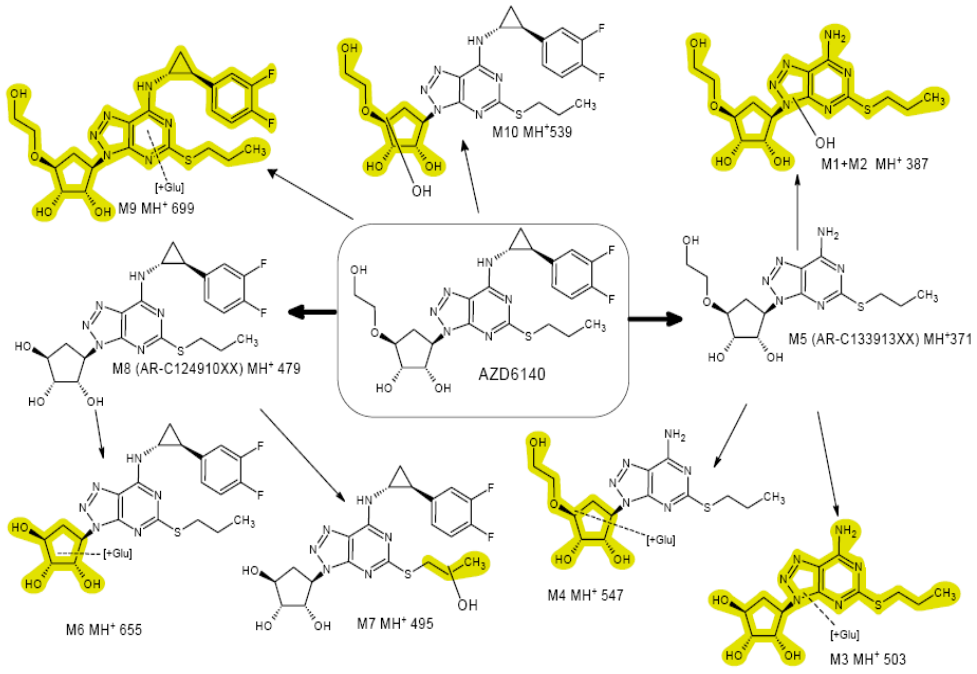


**Figure 6.** Ticagrelor proposed metabolic route.

### 2.2.6.7 What are the characteristics of drug elimination?

Ticagrelor is converted into two major metabolites that are in turn either undergoes glucorinidation or further oxidation prior to excretion. Glucorinides of ticagrelor were also identified.

### 2.2.6.8 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

In the dose range 30 mg – 400 mg in healthy volunteers, ticagrelor and AR-C124910XX pharmacokinetics is slightly more than dose proportional (Table 6).

**Table 6.** Ticagrelor and AR-C124910XX pharmacokinetics dose proportionality.

| | Parameter | Dose Proportionality(95% CI) |
|---|---|---|
| Ticagrelor | AUC (ng.h/mL) | 1.11 (1.07, 1.15) |
| | $C_{max}$ (ng/mL) | 1.07 (0.99, 1.14) |
| AR-C124910XX | AUC (ng.h/mL) | 1.10 (1.06, 1.15) |
| | $C_{max}$ (ng/mL) | 1.07 (1.0, 1.14) |

In patients with atherosclerosis (DISPERSE) ticagrelor and AR-C124910XX $C_{max}$ and AUC increased dose proportionally at doses 50, 100, 200 mg BID and 400 mg QD following the first dose of ticagrelor. At steady state, both $C_{max}$ and AUC increased dose proportional between the 50 and 100 mg BID dose and approximately 50% more than dose proportional for the 200 BID and 400 mg QD.

## 2.3 Intrinsic Factors

### 2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Race, age, gender, severe renal impairment, and mild hepatic impairment alter ticagrelor systemic exposure as described below.

### 2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments are recommended for each group?

#### 2.3.2.1 Elderly

Ticagrelor AUC and $C_{max}$ were 52% and 63% significantly higher in elderly (≥ 65 years old) males and females subjects compared to young subjects following a single 200 mg oral dose. However, this does not require ticagrelor dose adjustment.

#### 2.3.2.2 Pediatric Patients

Ticagrelor was not evaluated in pediatric patients.

#### 2.3.2.3 Race

**Japanese:**

- Ticagrelor systemic exposure is significantly 20% higher (by median ~ 20%) in healthy Japanese compared to healthy Caucasian following the administration of a single oral dose (50 - 600 mg).
- Ticagrelor systemic exposure is 20% higher in healthy Japanese males compared to healthy Caucasian males following multiple oral twice daily 100 mg doses for 7 day.

**Asian:** In population PK analysis of DIPSERSEII and PLATO, Asian patients had 39% (95% CI 33% - 46%) higher ticagrelor bioavailability compared to Caucasian.

**African American:** In population PK analysis of DIPSERSEII and PLATO, patients self identified as black in had a 19% lower (95% CI 6%-28%) bioavailability compared to Caucasians.

There is no need to adjust ticagrelor dose based on race.

#### 2.3.2.4 Renal Impairment

- In subjects with sever renal impairment, relative to subjects with normal renal function, following a 180 mg single oral dose of ticagrelor:

1. Ticagrelor AUC and $C_{max}$ were significantly lower by 20% and 18.5%, respectively.
2. AR-C124910XX AUC and $C_{max}$ were significantly higher by 17.1% and 4.1%, respectively.

- There was no relationship between creatinine clearance and ticagrelor or AR-C124910XX systemic exposure.
- Ticagrelor unbound fraction was < 1% in subjects with normal renal function and subjects with severe renal impairment.
- There is no need to adjust ticagrelor dose in patients with severe renal impairment.

#### 2.3.2.5 Hepatic Impairment

- In subjects with mild hepatic impairment, relative to subjects with normal liver function, following a 90 mg single oral dose:

1. Ticagrelor AUC and $C_{max}$ were significantly higher by 23% and 12%, respectively.
2. AR-C124910XX AUC and $C_{max}$ were significantly higher by 66% and 17%, respectively.

- Ticagrelor and AR-C124910XX unbound fraction to plasma protein is <1% in subjects with mild hepatic impairment and subjects with normal renal function.
- There is no need to adjust ticagrelor dose in patients with mild hepatic impairment.

#### 2.3.2.6 Gender

Ticagrelor AUC and $C_{max}$ were 37% and 52% significantly higher in female subjects compared to male subjects following a single 200 mg oral dose. However, this does not require ticagrelor dose adjustment.

#### 2.3.2.7 Genetics

The applicant submitted a series of exploratory candidate gene association studies for 1) ticagrelor antiplatelet responses and pharmacokinetics, 2) dyspnea, and 3) clinical outcomes in

the PLATO trial. DNA was collected on a voluntary basis from subjects participating in DISPERSE (90%), DISPERSE2 (78%), RESPOND (72%), and PLATO (56%). Subjects were genotyped for approximately 325 single nucleotide polymorphisms (SNPs) across 20 candidate genes. SNPs were selected on the basis of putative functionality or haplotype-tagging properties. The main findings of the applicant's pharmacogenetic (PG) investigations are summarized below. Please see the appended Genomics Group review for additional details.

**PK/PD:**

- SNPs in ticagrelor's target, *P2RY12*, or the principal mediators of ticagrelor disposition, *ABCB1* and *CYP3A5*, did not appear to significantly influence antiplatelet responses (maximal or final ADP-mediated platelet aggregation) or ticagrelor exposure after 4 weeks of treatment in DISPERSE and DISPERSE2.
- Other polymorphisms that broadly characterize the genetic diversity of *P2RY1*, *ITGA2*, *ITGB3*, which encode platelet receptors and glycoproteins, also did not influence antiplatelet responses.
- None of these polymorphisms have consistently been shown to modulate responses to other P2RY12 antagonists such as clopidogrel.

**Dyspnea:**

- Case-control analysis of dyspnea (89 ticagrelor-treated cases, 544 controls) in DISPERSE and DISPERSE2 focused primarily on SNPs in adenosine receptors and transporters (97 SNPs in 11 genes), but did not reveal any robust PG associations with dyspnea status. These findings do not necessarily refute the adenosine hypothesis.
- SNPs in *PLA2G7* and *PON1*, mediators of lipid oxidation and inflammation, demonstrated nominal associations with dyspnea (odds ratios for variant homozygotes were 0.27 [P=0.004] and 3.23 [P=0.04], respectively). These findings are exploratory in nature and would need to be replicated or supported by additional experimental evidence.
- SNPs in the PK or PD candidate genes, *ABCB1*, *CYP3A5*, *P2RY12*, *P2RY1*, *ITGA2*, and *ITGB3*, were also not associated with dyspnea.

**Outcomes:**

- Numerically higher event rates were observed in clopidogrel-treated patients with one or more *CYP2C19* loss-of-function alleles, particularly for death and stent thrombosis. Treatment differences tended to be greater, in favor of ticagrelor, in this population.

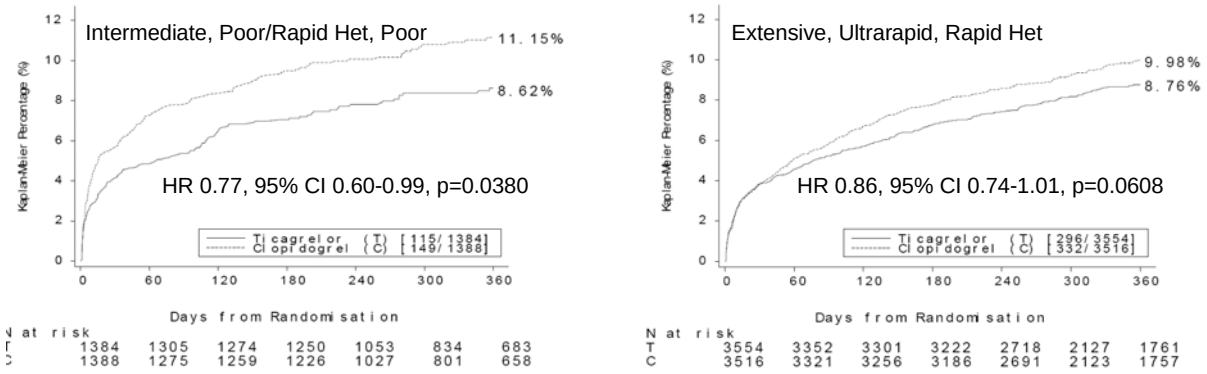


**Figure 7**. Primary efficacy endpoint (death, myocardial infarction, stroke composite) by CYP2C19 genotype-predicted phenotype (full sub-study population; source: PLATO Genetics Sub-study Report, pages 25, 26)

- Bleeding rates were comparable between ticagrelor and clopidogrel, irrespective of *CYP2C19* genotype. No relative excess of bleeding was noted for ticagrelor in intermediate/poor metabolizers, or for clopidogrel in ultrarapid CYP2C19 metabolizers.

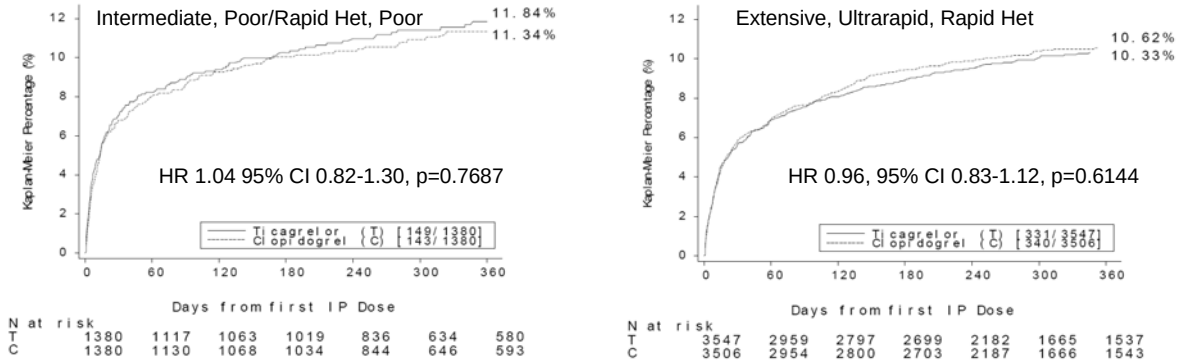


**Figure 8**. PLATO 'total major' bleeding by CYP2C19 genotype-predicted phenotype (safety population; source: PLATO Genetics Substudy Report, page 35)

- Factors such as timing of sample collection, proton pump inhibitor use, and stent implantation did not alter the magnitude of *CYP2C19* genetic effects on clopidogrel.
- *CYP2C19* genotype distribution did not differ in the U.S. vs. non-U.S. regions and did not account for the geographic differences in outcomes, although the analysis was limited to a very small subset.
- *ABCB1* genotype was not robustly associated with outcomes in either treatment arm, considering previously published findings for *ABCB1* genetic effects on clopidogrel response and the lack of supportive evidence from PK/PD endpoints.

### 2.3.3 What pregnancy and lactation use information is there in the label?

Not Available.

## 2.4 Extrinsic Factors

### 2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

CYP3A4/5 inducers and inhibitors will alter the systemic exposure of ticagrelor.

### 2.4.2 What are the drug-drug interactions?

#### 2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Ticagrelor is a substrate for CYP450 and has the potential to induce and inhibit some of CYP450 enzymes.

#### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

In human liver microsomes, ticagrelor metabolism was inhibited approximately 98% by 1 μM ketoconazole (CYP3A inhibitor) and 30-40% by 50 μM omeparzole (CYP2C9 inhibitor) and 10-18% by 10 μM furafylline (CYP 1A2 inhibitor).
Ticagrelor metabolism is not expected to be influenced by genetic variations.

#### 2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

- In human liver microsomes, ticagrelor was found to be a moderate inhibitor for CYP 2C9 ($IC_{50}$ 2.1 μM), 2D6 ($IC_{50}$ 5.3 μM), a weak inhibitor of CY3A4, and strong inhibitor of CYP 3A5 ($IC_{50}$ 1.8 μM).
- Ticagrelor and AR-C124910XX appeared to induce CYP 2C9.

#### 2.4.2.4 Is the drug an inhibitor and/or an inducer of P-gp transport processes?

Ticagrelor and AR-C124910XX are substrates and inhibitor of P-gp. *In vitro*, both compounds inhibited digoxin transport in dose dependant manner with $IC_{50}$ of 7.8 ± 2.6 μM and 9.9 ± 5.1. μM for ticagrelor and AR-C124910XX, respectively.

#### 2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Information is not available

#### 2.4.2.6 Does the label specify co-administration of another drug?

Ticagrelor label states that it should be administered with low dose (75 – 100 mg) of aspirin.

#### 2.4.2.7 What other co-medications are likely to be administered to the target population?

Aspirin, anti-platelet, β-blockers, glycoprotein IIb/IIIa inhibitor for patients undergoing PCI, heparin, nitroglycerin, and ACE inhibitors.

#### 2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

**Effect of other Medications on Ticagrelor exposure:**

**Ketoconazole:**

The co-administration of ketoconazole (200 mg BID for 10 days) with a single oral 90 mg dose of ticagrelor on Day 4:

- Significantly increases ticagrelor AUC by 7.32 fold and $C_{max}$ by 2.35.
- Significantly decreases AR-C124910XX AUC by 56% and $C_{max}$ by 89%.
- Ticagerlor should be contraindicated with ketoconazole and strong CYP3A inhibitors

**Diltiazem:**

The co-administration of diltiazem (240 mg QD for 14 days) with a single oral 90 mg dose of ticagrelor on Day 8:

- Significantly increases ticagrelor AUC by 2.74 fold and $C_{max}$ by 1.69.
- Decreases AR-C124910XX AUC by 13% and significantly decreases its $C_{max}$ by 38%.
- Simulation of the plasma concentration-time course suggest a QD regimen of ticagrelor with moderate CYP3A inhibitors such as diltiazem which will result in steady-state trough and $AUC_{0-24}$ similar to that obtained with ticagrelor 90 mg BID in the absence of diltiazem.

**Rifampin:**

The co-administration of rifampin (600 mg QD for 14 days) with a single oral 180 mg dose of ticagrelor on Day 12:

- Significantly decreases ticagrelor AUC by 86% and $C_{max}$ by 73%
- Significantly reduces AR-C124910XX AUC by 46% and does not affect $C_{max}$.
- Strong CYP3A inducers should not be used with ticagrelor as this may result in lower concentrations and may lead to potential loss of efficacy.

**Aspirin:**

The co-administration of aspirin (300 mg QD for 10 days) with multiple oral doses of ticagrelor 50 mg BID for 5 days followed by 200 mg BID for another 5 days did not alter the systemic exposure of ticagrelor.

**Desmopressin:**

The co-administration of desmopression (0.3 µg/Kg IV infusion for 2 h) following 5 days of the administration of ticagrelor loading dose (270 mg) and maintenance (90 mg BID) did not alter the systemic exposure of ticagrelor.

**Heparin:**

The co-administration of unfractionated heparin (100 IU/Kg IV bolus) with a single oral 180 mg dose of ticagrelor did not alter the systemic exposure of ticagrelor.

**Enoxaprin:**

The co-administration of enoxaprin (1 mg/kg SC injection) with a single oral 180 mg dose of ticagrelor did not alter the systemic exposure of ticagrelor.

**Effect of ticagrelor on the systemic exposure of other medications:**

**Digoxin:**

The co-administration of ticagrelor (400 mg QD for 16 days) with digoxin (0.25 mg QD for 9 days) significantly increases digoxin acid $AUC_{0-72}$, $C_{ss,max}$, and $C_{ss,\ min}$ by 28%, 75%, and 31%, respectively. Hence, digoxin concentrations should be monitored if co-administered with ticagrelor.

**Simvastatin:**

The co-administration of ticagrelor (Loading dose 270 mg, maintenance dose 180 mg for 7 days) with simvastatin 80 mg QD on Day 5:

- Significantly increases simvastatin AUC by 56% and $C_{max}$ by 81%.
- Significantly increases simvastatin acid AUC by 52% and $C_{max}$ by 64%.
- Does not require dose adjustment as the increases are no deemed to be clinically significant.

**Atorvastatin:**

The co-administration of ticagrelor (Loading dose 270 mg, maintenance dose 180 mg for 7 days) with atorvastatin 80 mg QD on Day 5:

- Significantly increases atorvastatin acid AUC by 36% and $C_{max}$ by 23%.
- Significantly increases atorvastatin lactone AUC by 32% and $C_{max}$ by 39%.
- Significantly increases 2-OH atorvastatin AUC by 33% and $C_{max}$ by 13%.
- Significantly increases 4-OH atorvastatin AUC by 67% and $C_{max}$ by 55%.
- Does not require dose adjustment as the increases are no deemed to be clinically significant.

**Oral Contraceptive:**

The co-administration of ticagrelor (90 mg for QD 21 days) with oral contraceptive containing ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg QD for 21 days:

- Significantly increases ethinyl estradiol AUC, $C_{max}$, and $C_{min}$ by 20%, 30.6%, and 20.2%, respectively.
- Does not alter the systemic exposure of levonorgestrel.

**Midazolam:**

The co-administration of ticagrelor (Loading dose 270 mg, maintenance dose 180 mg for 7 days) with oral (7.5 mg) and IV (2.5 mg) midazolam on Day 1 and Day 7:

- Significantly reduces oral midazolam AUC by 10%, and 4'-OH-midazolam by 42%, but does not alter 1'-OH- midazolam AUC.
- does not alter the systemic exposure of IV midazolam and 1'-OH-midazolam, and significantly reduces 4'-OH- midazolam systemic exposure by ~ 23%.

**Tolbutamide:**

The co-administration of ticagrelor (180 mg BID for 9 days) with tolbutamide (500 mg QD on Day 5) does not alter the systemic exposure of tolbutamide or 4-OH-tolbutamide.

## 2.5 General Biopharmaceutics

### 2.5.1 What is the absolute bioavailability of the proposed to-be-marketed formulation?

The absolute bioavailability of ticagrelor immediate release tablets is 36% (95% CI 30% – 42%)

### 2.5.2 What is the effect of food on the bioavailability of the drug from the dosage form?

When administered with food:

1. Ticagrelor AUC significantly increased by 23% and 21% for the micronized and non-micronized formulations, respectively.
2. Ticagrelor $C_{max}$ significantly decreased by 7% and 8% for the micronized and non-micronized formulations, respectively.

AR-C124910XX AUC was not affected; however, $C_{max}$ was significantly reduced by 27% and 22% for the micronized and non-micronized formulations, respectively.

3. Ticagrelor can be taken with or without food.

## 2.6 Analytical Section

### 2.6.1 How are the active moieties identified and measured in the plasma?

Table 7 displays a list of the analytical methods type, calibration curve, matrix and analyte quantified, that were used in ticagrelor clinical pharmacology development program. Both the bioanalytical methods i.e., validation and performance during study sample's analysis are acceptable and consistent with the recommendations of the FDA Guidance on Bioanalytical Method Validation.

### 2.6.2 Which metabolites have been selected for analysis and why?

AR-C124910XX concentrations were quantified in all clinical pharmacology studies since it is the major metabolite and is equipotent to ticagrelor. The inactive metabolite AR-C133913XX concentrations were quantified in two clinical pharmacology studies.

### 2.6.3 For all moieties measured, is free, bound, or total measured?

Total concentration was measured except when protein binding was evaluated.

**Table 7.** Analytical methods used throughout ticagrelor clinical pharmacology clinical development program**.** CIA: Chemiluminescent Immunometric Assay

| Analyte | Method | Calibration Range | Matrix |
|---|---|---|---|
| Ticagrelor | LC-MS/MS | 1.0 – 500 ng/mL<br>5- 5000 ng/mL | Plasma |
| AR-C124910XX | LC-MS/MS | 2.5 – 500 ng/mL<br>2.5 – 2500 ng/mL | Plasma |
| AR-C133913XX | LC-MS/MS | 2 – 1000 ng/mL | Plasma |
| Unbound Ticagrelor<br>Unbound AR-C124910XX | LC-MS/MS | 0.25-100 ng/mL | Dialysate |
| Ticagrelor<br>AR-C124910XX | LC-MS/MS | 2.5-2500 ng/mL | Urine |
| Acid Metabolite of Clopidogrel | LC-MS/MS | 5 – 5000 ng/mL | Plasma |
| Ketoconazole | LC-MS/MS | 10 – 5000 ng/mL | Plasma |
| Diltiazem | LC-MS/MS | 1 – 250 ng/mL | Plasma |
| Rifampin | LC-MS/MS | 2.5-2500 ng/mL | Plasma |
| Simvastatin/ Simvastatin Acid | LC-MS/MS | 0.25 - 250 ng/mL | Plasma |
| Atorvastatin/Atorvastatin Lactone<br>2-OH Atorvastatin/4-OH Atorvastatin | LC-MS/MS | 0.25 - 250 ng/mL | Plasma |
| Digoxin | LC-MS/MS | 2.5 – 500 ng/mL | Plasma |
| Ethinyl Estradiol | LC-MS/MS | 2 – 1000 pg/mL | Plasma |
| Levonorgestrel | LC-MS/MS | 0.1- 50 ng/mL | Plasma |
| 17-β-Estradiol | LC-MS/MS | 2 – 2000 ng/mL | Plasma |
| Follicle Stimulating Hormone | cELISA | 0.05 – 40 mIU/mL | Plasma |
| Luteinizing Hormone | cELISA | 0.1- 50 mIU/mL | Plasma |
| Progesterone | LC-MS/MS | 20 – 2000 pg/mL | Plasma |
| Sex Hormone Binding Globulin | CIA | 4.0 & 77.0 nM | Plasma |
| Midazolam 1'-Hydroxymidazolam<br>Midazolam 4'-Hydroxymidazolam | LC-MS/MS | 0.1 – 100 ng/mL | Plasma |
| Tolbutamide/ 4-OH-tolbutamide | LC-MS/MS | 10 – 5000 ng/mL | Plasma |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22433 | ORIG-1 | ASTRAZENECA LP | AZD6140 |

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ISLAM R YOUNIS
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06/27/2010
Concur with the reviewer's findings and conclusions

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

# Office of Clinical Pharmacology

## *New Drug Application Filing and Review Form*

***General Information About the Submission***

| | Information | | Information |
|---|---|---|---|
| **NDA/BLA Number** | **022433** | **Brand Name** | **Brilinta®** |
| **OCP Division (I, II, III, IV, V)** | **I** | **Generic Name** | **Ticagrelor** |
| **Medical Division** | **Division of Cardiovascular and Renal Products** | **Drug Class** | **Anti-Platelet** |
| **OCP Reviewer** | **Islam R. Younis** | **Indication(s)** | **To reduce the rate of thrombotic events** |
| **OCP Team Leader** | **Raj Madabushi** | **Dosage Form** | **Tablet** |
| **Pharmacometrics Reviewer** | **Kevin Krudys** | **Dosing Regimen** | **90 mg b.i.d.** |
| **Date of Submission** | **11/16/2009** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCP Review** | **06/27/2010** | **Sponsor** | **Astra Zeneca** |
| **Medical Division Due Date** | **06/27/2010** | **Priority Classification** | **No** |
| **PDUFA Due Date** | **09/16/2010** | | |

## *Clin. Pharm. and Biopharm. Information*

| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **x** | | | |
| **Tabular Listing of All Human Studies** | **x** | | | |
| **HPK Summary** | **x** | | | |
| **Labeling** | **x** | | | |
| **Reference Bioanalytical and Analytical Methods** | **x** | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | **x** | **1** | | |
| **Isozyme characterization:** | **x** | **1** | | |
| **Blood/plasma ratio:** | **x** | **1** | | |
| **Plasma protein binding:** | **x** | **2** | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | **x** | **3** | | |
| multiple dose: | **x** | **1** | | |
| **Patients-** | | | | |
| single dose: | **x** | | | |
| multiple dose: | **x** | **2** | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | **x** | **3** | | **Part of the PK studies** |
| fasting / non-fasting multiple dose: | **x** | **1** | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | **x** | **10** | | |
| In-vivo effects of primary drug: | **x** | **5** | | |
| In-vitro: | | **4** | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | **x** | **3** | | |
| gender: | **x** | **1** | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | |
|---|---|---|---|---|
| pediatrics: | | | | |
| geriatrics: | **x** | **1** | | **Same as Gender Study** |
| renal impairment: | **x** | **1** | | |
| hepatic impairment: | **x** | **1** | | |
| **PD -** | | | | |
| Phase 2: | **x** | **4** | | |
| Phase 3: | **x** | **1** | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | **x** | **4** | | |
| Phase 3 clinical trial: | **x** | **1** | | |
| **Population Analyses -** | | | | |
| Data rich: | **x** | **1** | | |
| Data sparse: | **x** | **1** | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | **x** | **1** | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | **x** | **1** | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | **4** | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | **x** | **1** | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **55** | | |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | | x | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | x | | | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | x | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | x | | | |
| 5 | Has a rationale for dose selection been submitted? | x | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | x | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | x | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | x | | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) | | | | | |
|---|---|---|---|---|---|
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | | | x | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | x | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | x | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | x | | | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | x | | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | x | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | x | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | x | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | x | | | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | x | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | x | | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| | |
|---|---|
| Islam R. Younis | 01/12/2010 |
| Reviewing Clinical Pharmacologist | Date |
| Raj Madabushi | 01/12/2010 |
| Team Leader/Supervisor | Date |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22433 | ORIG-1 | ASTRAZENECA LP | AZD6140 |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ISLAM R YOUNIS
01/25/2010

RAJANIKANTH MADABUSHI
01/26/2010
concur