The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

2.0 SYNOPSIS

Title of Study: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of TAK-442 in Subjects With Acute Coronary Syndromes	
Name of Sponsor: Takeda Global Research & Development Center, Inc. (TGRD) One Takeda Parkway, Deerfield, IL 60015, United States Takeda Global Research & Development Centre (Europe) Ltd. (TGRD [EU]) 61 Aldwych, London, WC2B 4AE, United Kingdom	
Name of Active Ingredient: TAK-442	
Name of Finished Product: Not applicable.	
Investigators: PPD Plus investigators at 209 study sites in 18 countries worldwide.	**Study Sites:** CCI
Publication (reference): None.	
Study Period (years): 28 March 2008 to 21 June 2010	**Phase of Development:** Phase 2

OBJECTIVES

Primary:

The primary objective of this study was to evaluate the effect of TAK-442 on the incidence of major bleeding when added to standard treatment for prevention of recurrent ischemic events in subjects with recent acute coronary syndrome (ACS), including non-ST segment elevation myocardial infarction (NSTEMI), ST segment elevation myocardial infarction (STEMI), or unstable angina (UA).

Secondary:

The secondary objectives of the study were to evaluate the following in ACS subjects:

- The effect of TAK-442 on cardiovascular (CV) outcomes.
- The effect of TAK-442 on the incidence of other bleeding event categories.
- The general safety and tolerability of TAK-442.
- The anticoagulant and antithrombotic effects of TAK-442 as determined by monitoring pharmacodynamic variables and markers of coagulation.
- The population pharmacokinetics of TAK-442 and metabolites (M-I and M-II).

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METHODOLOGY

This was a phase 2, randomized, double-blind, adaptive, 24-week, placebo-controlled study. Eligible subjects included those who had been hospitalized for an event of myocardial infarction (MI) (NSTEMI or STEMI) or UA, had at least 1 additional ischemic risk factor, and were able to initiate study drug within 7 days (168 hours) of the index event, but no sooner than 36 hours after the acute treatment of ACS. Subjects who required staged or delayed coronary revascularization beyond 7 days of the index event also were eligible. Each subject also received standard-of-care for the prevention of recurrent ischemic events, including antiplatelet and other CV medications, as determined by the investigator.

The study consisted of a Pretreatment Period (during which subjects were evaluated for study entry criteria), Randomization, a Treatment Period (24 weeks), and a Follow-up Visit (30 days after the last dose of study drug).

This adaptive study was conducted over 3 consecutive stages, during which subjects were ultimately randomized to 1 of 9 treatment groups:

- Stage 1: placebo (n=250) or TAK-442 10 mg twice daily (BID) (n=250), 20 mg BID (n=250), or 40 mg once daily (QD) (n=250).
- Stage 2: placebo (n=250) or TAK-442 40 mg BID (n=250), 80 mg QD (n=250), 80 mg BID (n=250).
- Stage 3: placebo (n=250) or TAK-442 160 mg QD (n=250) or 120 mg BID (n=250).

Each stage was intended to add higher dose groups to the study design. The decision to proceed from one stage to the next was made by the Data and Safety Monitoring Board (DSMB), which met approximately every 6 weeks once Stage 1 enrollment was underway, and was based primarily on an acceptable incidence of major bleeding events in the high-dose groups from the previous stage, although other safety and tolerability findings also were evaluated. Low-dose groups also were considered for discontinuation, if reductions of coagulation marker concentrations (D-dimer and prothrombin activation fragment 1+2 levels) were not observed compared with placebo. The study progressed to its subsequent stages only if the DSMB judged safety to be acceptable at each of the several interim review points.

Randomization continued throughout each stage of the study until a total of approximately 250 placebo subjects per stage were enrolled, and until the final sample size in each active dose group reached approximately 250 subjects. Randomization was stratified by thienopyridine use, based on the investigator's intent to treat with a thienopyridine.

Regardless of when subjects were enrolled into the study (during Stage 1, 2, or 3), treatment continued for a duration of 24 weeks (except for subjects who were prematurely discontinued from the study).

The Adjudication Committee independently reviewed and adjudicated each potential endpoint event, including all deaths, all suspected ischemic events (MI, stroke, myocardial ischemia requiring hospitalization, or hospitalization for heart failure), and all suspected bleeding events as follows:

- Each death was categorized as: CV, hemorrhagic, or other.
- The diagnosis of MI followed the guideline prepared by the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Health Federation Task Force for the Redefinition of Myocardial Infarction. The full definitions for MI and UA were outlined in the protocol. Additional assessments for Academic Research Consortium Definite Stent Thrombosis and Repeat Target Vessel Revascularization were adjudicated by the Committee.
- All bleeding events were categorized as: (a) major, (b) minor, or (c) minimal bleeding events, according to the Thrombolysis in Myocardial Infarction (TIMI) scale. Each bleeding event also was categorized according to the secondary bleeding event scale as: (a) major, (b) clinically significant nonmajor, or (c) minor. All bleeding events also were adjudicated as coronary artery bypass graft (CABG) or non–CABG-related events, which was introduced into the study design as of 20 January 2010, resulting from a DSMB recommendation; Takeda personnel identified events that occurred prior to this date for readjudication by the Committee.

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Additional safety and tolerability reviews, including all bleeding events, were completed by the DSMB on an ongoing basis and via the planned interim analyses.

Number of Subjects:

Planned: 2750 subjects

Analyzed:
Full Analysis Set (FAS)—745 subjects in the placebo group, 2008 subjects in the All TAK-442 group (approximately 250 subjects per individual dose group).
Per-Protocol Set—659 subjects in the placebo group; 1746 subjects in the All TAK-442 group (214-225 subjects per individual dose group).

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects had to have been hospitalized for ACS (UA or MI [NSTEMI or STEMI]). Study drug was initiated if: the index event occurred within the past 7 days (the date of initial hospitalization was used as the date on which the index event occurred), and the final acute medical or cardiac procedural intervention for the treatment of ACS (eg, glycoprotein IIb/IIIa inhibitor, anticoagulant doses of low-molecular weight or unfractionated heparin, fibrinolytics, percutaneous coronary intervention [PCI], etc) was last administered or performed at least 36 hours before administration of the first dose of study drug (ie, initiation of study drug occurred no earlier than 36 hours after discontinuation of the last medical or cardiac procedural intervention). Subjects also were to have had at least 1 of the following additional ischemic risk factors: age ≥65 years; previous MI; the index event was an anterior MI; presence of multivessel coronary disease (stenosis ≥50%); left bundle branch block; left ventricular ejection fraction <40% at any time during hospitalization for the index event; Killip class ≥II at any time during hospitalization for the index event; history of symptomatic congestive heart failure (New York Heart Association functional class II-IV); history of ischemic stroke or transient ischemic attack more than 12 months prior to Randomization; presence of peripheral arterial obstructive disease; diabetes mellitus requiring medical therapy to maintain glycemic control; current smoker (smokes a tobacco product at least 3 times daily); or moderate renal impairment (calculated creatinine clearance ≥30 and <50 mL/min/1.73 m^2). Qualified subjects were willing to sign informed consent and agreed to use adequate contraception, if sexually active.

Subjects were not eligible if they were aged <30 or >80 years and had: body weight <50 kg; severe hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg); a known bleeding/clotting disorder (including hemophilia A or B and Von Willebrand disease); acute pericarditis; a history of intracranial or intraocular bleeding; gastrointestinal bleeding or gastric or duodenal ulceration within 12 months prior to Randomization; ischemic stroke or transient ischemic attack within 12 months prior to Randomization; major surgery, including CABG, within 3 months prior to Randomization; nonmajor laparoscopic surgery or nonmajor minimally invasive surgery within 2 weeks prior to Randomization; cancer that had not been in remission for at least 5 years (exception: basal cell or stage I squamous cell carcinoma of the skin); a condition for which long-term anticoagulation therapy was indicated (ie, atrial fibrillation, mechanical prosthetic heart valve, or left ventricular thrombus) or required ongoing use of other excluded medications; severe renal dysfunction (calculated creatinine clearance <30 mL/min/1.73 m^2); anemia (ie, hemoglobin <10 g/dL) or thrombocytopenia (ie, platelet count $<100\times10^3/\mu L$) unresolved prior to Randomization; alanine aminotransferase (ALT) or total bilirubin levels (except documented Gilbert's disease) >2 times the upper limit of normal (ULN), active liver disease (including hepatitis C), or jaundice unresolved prior to Randomization; a history of illicit drug use or excessive alcohol intake within 2 years prior to Randomization. Subjects also were ineligible if they were pregnant or lactating; had received TAK-442 previously; or had a history of hypersensitivity or allergies to other activated factor X (fXa) inhibitors; or had received any investigational compound within 30 days prior to Screening (for drugs with a long half-life, within a period of less than 5 times the drug's half-life) or was currently participating in another study.

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Test Product, Dose and Mode of Administration/Lot Number:

	Batch/Lot Number
TAK-442 10 mg BID, oral TAK-442 20 mg BID, oral TAK-442 40 mg QD, oral TAK-442 40 mg BID, oral TAK-442 80 mg QD, oral TAK-442 80 mg BID, oral TAK-442 160 mg QD, oral TAK-442 120 mg BID, oral	Batch/lot numbers are provided in the clinical study report appendix.

Duration of Treatment:

The study consisted of a Pretreatment Period (during which subjects were evaluated for study entry criteria), Randomization, a Treatment Period (24 weeks), and a Follow-up Visit (30 days after the last dose of study drug).

Reference Therapy, Dose and Mode of Administration, Batch Number:

	Batch/Lot Number
None (matching placebo only)	N/A

Criteria for Evaluation:

The primary endpoint in this study was the incidence of major bleeding events, as defined by the TIMI scale.

Secondary endpoints included:

- Composite of CV death, nonfatal myocardial infarction (NFMI), nonfatal stroke (NFS), or myocardial ischemia requiring hospitalization.
- The individual components of the CV composite endpoint.
- All-cause death.
- Hemorrhagic death.
- Composite of CV death, NFMI, or myocardial ischemia requiring hospitalization.
- Composite of CV death, NFMI, or NFS.
- Hospitalization for heart failure.

Pharmacokinetic and pharmacodynamic variables also were evaluated for TAK-442 and its metabolites (M-I and M-II).

Safety:

The primary safety endpoint was the incidence of major bleeding events (TIMI scale). Additional safety variables included pretreatment events, adverse events (AEs), safety laboratory tests, vital sign measurements, physical examination findings, and 12-lead electrocardiogram (ECG) tracings. Other bleeding-related measures included: the incidence of minor and minimal bleeding events (TIMI scale); and the incidence of major, clinically significant nonmajor, and minor bleeding events as defined by the secondary bleeding scale.

Statistical Methods:

The FAS was used for the efficacy analysis. The per-protocol set, as well as all randomized subjects with any study drug use, also were used. Subjects were analyzed according to the treatment group randomized. Potential efficacy endpoints were captured as AEs of special interest. Final determination of endpoints was provided by an independent Adjudication Committee.

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The primary efficacy endpoint was the composite of CV death, NFMI, NFS, or myocardial ischemia requiring hospitalization. All events occurring from Randomization through the end of the study were included. Incidence of the composite endpoint was estimated using the observed proportion and the corresponding 95% confidence interval (CI) for each treatment group. Logistic regression and survival analysis including Cox model were used to analyze the primary efficacy endpoint and included terms for categorized dose group, region, and thienopyridine use. The relative risk (odds ratio) and the corresponding 95% CI were provided for each TAK-442 dose group. In addition, logistic regression and Cox model with the total daily dose of TAK-442 (placebo not included) as a continuous explanatory variable were used to assess the dose-response effects. Exploratory efficacy analyses also were performed, such as subgroup analyses on age group (<65 years, ≥65 years), gender, weight (<60 kg, ≥60 kg), body mass index (BMI) (<18.5 kg/m^2, ≥18.5 kg/m^2), region (Western Europe, Eastern Europe, North America, South America, and Africa/Asia), diabetes mellitus (yes, no), creatinine clearance (<60 mL/min, ≥60 mL/min), medical history of MI, revascularization history of PCI, revascularization history of CABG, previous ischemic stroke, diagnosis at index event (UA, NSTEMI, STEMI), PCI performed for index event (yes, no), antiplatelet therapy at time of randomization up to 7 days postrandomization (thienopyridine, acetylsalicylic acid alone, none). Other exploratory efficacy analyses were performed, including comparison of placebo effect across different stages. The assumption of proportionality on Cox model was assessed.

The secondary efficacy endpoints were analyzed using the methods described for the primary efficacy endpoint.

The primary safety endpoint was the incidence of major bleeding events (TIMI scale). Other safety measures included: the incidence of minor and minimal bleeding events (TIMI scale); the incidence of major, clinically significant nonmajor, and minor bleeding events (defined by the secondary bleeding scale); AEs; laboratory tests; vital signs; physical examination findings; and 12-lead ECGs. All potential bleeding events were captured as AEs of special interest. Final determination of events was provided by the Adjudication Committee. Agreement between Adjudication Committee conclusions and local site assessments were explored using kappa statistics, if needed. The CABG and non-CABG–related bleeding also were explored. The frequency of bleeding in each category was estimated using the observed proportion and the corresponding 95% CI for each treatment group. In order to assess treatment differences in each of the bleeding categories, the data were analyzed using the chi-square test or Fisher exact test, as appropriate. Bleeding events that occurred post-ACS but no later than 2 days after the last dose of study drug were used in the above analyses. Additional analyses for bleeding also were done.

SUMMARY OF RESULTS

Subject Disposition:

Investigators at 209 study sites in 18 countries worldwide screened a total of 2966 subjects for participation in this study, 2753 of which were randomized to treatment. Of the 2753 subjects who were randomized, 2718 received at least 1 dose of study medication, while the remaining 35 were randomized but never treated (6 subjects [0.8%] in the placebo group and 29 subjects [1.4%] in the All TAK-442 group). The majority of randomized subjects completed treatment with study drug: 598 subjects (80.3%) in the placebo group and 1558 subjects (77.6%) in the All TAK-442 group. The majority of subjects also completed all of their planned study visits: 633 subjects (85.0%) in the placebo group and 1695 subjects (84.4%) in the All TAK-442 group. “Voluntary withdrawal” and “adverse event” were the most common reasons for discontinuation from study drug and study visits in both the placebo group and the All TAK-442 group. Across each of the 8 individual TAK-442 dose groups, 71.9% (40 mg BID dose group) to 82.4% (10 mg BID dose group) of subjects completed study drug, and 81.4% (40 mg BID dose group) to 87.2% (10 mg BID dose group) of subjects completed all planned study visits. “Voluntary withdrawal” and “adverse event” were also the most common reasons for discontinuation from study drug and visits in each of the individual TAK-442 dose groups. No clear trends were observed across the TAK-442 dose groups in the incidences of subjects who completed or discontinued from the study, for example, the incidence of withdrawal did not always increase with increasing dose.

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The majority of subjects were white, men, younger than 65 years of age (mean age around 58 years), had a mean BMI of approximately 28, were current or former smokers, and were using a thienopyridine (approximately 83%). No meaningful differences were observed across treatment groups for any of the demographic or baseline characteristics.

Efficacy Results:

The incidence of the primary efficacy variable (composite event of CV death, NFMI, NFS, or myocardial ischemia requiring hospitalization) was 4.4% in the placebo group and 4.8% for all TAK-442 doses combined. The individual dose groups of TAK-442 had incidence rates of 2.8% to 6.7%, with no trend across the dose range. Calculated as difference from the placebo rate, individual dose groups of TAK-442 had 1.63% lower to 2.29% higher rates of the composite event. Again, there was no pattern or trend observed in either increase or decrease of the event rate as the dose was increased. None of the differences from placebo was statistically significant. Similar results were seen with the secondary efficacy variables.

Table 1. Composite Event: Summary of Primary Efficacy Endpoint

		TAK-442 Dose								
	Pla-cebo N=745	**10 mg BID N=250**	**20 mg BID N=250**	**40 mg QD N=250**	**40 mg BID N=253**	**80 mg QD N=252**	**80 mg BID N=253**	**160 mg QD N=251**	**120 mg BID N=249**	**All TAK-442 N=2008**
Composite event (a)										
n (%)	33 (4.4)	13 (5.2)	7 (2.8)	10 (4.0)	17 (6.7)	13 (5.2)	15 (5.9)	13 (5.2)	9 (3.6)	97 (4.8)
95% CI for observed proportion	3.07, 6.16	2.80, 8.73	1.13, 5.68	1.93, 7.23	3.96, 10.54	2.78, 8.66	3.36, 9.59	2.79, 8.69	1.67, 6.75	3.93, 5.86
Difference between placebo and treatment (%)		0.77	-1.63	-0.43	2.29	0.73	1.50	0.75	-0.82	0.40
95% CI for difference (%)		-2.35, 3.89	-4.15, 0.89	-3.27, 2.41	-1.13, 5.71	-2.38, 3.83	-1.76, 4.76	-2.36, 3.86	-3.56, 1.93	-1.35, 2.15
P-value for difference		0.6040	0.3515	0.8589	0.1807	0.6059	0.3945	0.6049	0.7165	0.7616
Odds ratio (b)		1.183	0.622	0.899	1.554	1.174	1.360	1.179	0.809	1.095
95% CI		0.613, 2.286	0.271, 1.423	0.437, 1.851	0.850, 2.841	0.608, 2.267	0.726, 2.547	0.610, 2.276	0.382, 1.715	0.731, 1.641
Relative risk (b)		1.174	0.632	0.903	1.517	1.165	1.338	1.169	0.816	1.091
95% CI		0.628, 2.195	0.283, 1.411	0.452, 1.806	0.860, 2.676	0.623, 2.177	0.739, 2.423	0.625, 2.186	0.396, 1.681	0.741, 1.604

Note: Adjudication Committee results for FAS.
(a) Composite of CV death, NFMI, NFS, or myocardial ischemia requiring hospitalization.
(b) Compared to placebo.

Possible differences between subgroups were observed for concomitant thienopyridine use. In both the placebo and all TAK-442 groups, 83% of the subjects used thienopyridines. With thienopyridines, the difference between placebo and treatment ranged from -0.91% to 3.48%, with a difference of 1.07% for all TAK-442 doses. Without thienopyridines, there was a trend of greater treatment effect; the differences ranged from -7.81% to 1.08%, with a difference of -2.84% for all TAK-442 doses. Trends toward greater treatment effects also were apparent in subgroups not treated with PCI for the index event and subgroups whose index event was NSTEMI.

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The primary bleeding endpoint, TIMI-major bleeding, occurred at an incidence of 0.5% in the placebo group and 0.9% in the All TAK-442 group. The differences from placebo ranged from 0.54% lower incidence to 1.08% higher incidence in the various TAK-442 groups (0.32% higher for TAK-442 overall), without a clear pattern across doses, consistent with the low event rates. None of the differences from placebo was statistically significant.

Table 2. Primary Study Objective: Incidence of TIMI Major Bleeding

		TAK-442 Dose								
	Placebo N=737	**10 mg BID N=248**	**20 mg BID N=246**	**40 mg QD N=247**	**40 mg BID N=246**	**80 mg QD N=248**	**80 mg BID N=250**	**160 mg QD N=248**	**120 mg BID N=248**	**All TAK-442 N=1981**
TIMI-major bleeding										
n (%)	4 (0.5)	0	3 (1.2)	1 (0.4)	4 (1.6)	3 (1.2)	2 (0.8)	1 (0.4)	3 (1.2)	17 (0.9)
95% CI for observed proportion	0.15, 1.38	0.00, 1.48	0.25, 3.52	0.01, 2.23	0.44, 4.11	0.25, 3.49	0.10, 2.86	0.01, 2.23	0.25, 3.49	0.50, 1.37
Difference between placebo and treatment (%)		-0.54	0.68	-0.14	1.08	0.67	0.26	-0.14	0.67	0.32
95% CI for difference (%)		-1.07, -0.01	-0.79, 2.15	-1.09, 0.82	-0.58, 2.75	-0.79, 2.13	-0.97, 1.48	-1.09, 0.81	-0.79, 2.13	-0.35, 0.98
P-value for difference		0.5773	0.3758	1.0000	0.1133	0.3771	0.6466	1.0000	0.3771	0.4719

Note: Adjudication Committee results, safety analysis set.

Dose-related bleeding effects were more apparent with secondary bleeding endpoints (TIMI-minor and -minimal bleeding, and major, clinically significant nonmajor, and minor bleeding by the secondary scale), which had higher incidence rates than those for TIMI-major bleeding. In the secondary endpoints, a pattern emerged whereby the increased incidence of bleeding in the TAK-442 groups started to show a dose response at doses of TAK-442 40 mg BID and higher (ie, >40 mg total daily dose); many of the differences between TAK-442 and placebo were statistically significant. The rates of bleeding were generally higher for the subjects taking thienopyridines than those of subjects not taking thienopyridines.

Anticoagulation biomarkers showed dose-related effects that paralleled the dose-related increase in bleeding.

Safety Results:

More than 60% of subjects in each treatment group reported at least 1 treatment-emergent adverse event (TEAE), 60.5% and 65.5% of subjects in the placebo and All TAK-442 groups, respectively. No noteworthy differences were observed in the overall incidence of TEAEs between the placebo group and the All TAK-442 group, and no apparent dose-related pattern was observed in the overall incidence of TEAEs across the increasing TAK-442 treatment groups. Most TEAEs were reported by less than 1% of subjects in any of the treatment groups. The most frequently reported TEAEs in the All TAK-442 group were angina pectoris (6.5%), epistaxis (4.7%), hematuria (4.6%), noncardiac chest pain (3.6%), angina unstable (3.2%), cough (3.1%), and headache (3.0%). In the placebo group, the most frequently reported TEAEs were angina pectoris (6.4%), headache (3.5%), ALT increased (3.5%), noncardiac chest pain (3.3%), epistaxis (3.0%), and dyspnea (3.0%).

Most TEAEs were considered by the investigator to be not related to study medication. A higher percentage of subjects in the All TAK-442 group (26.2%) experienced treatment-related TEAEs compared with placebo (20.1%). Epistaxis and hematuria were the most frequently reported treatment-related TEAEs in both the placebo and All TAK-442 groups. Most other treatment-related TEAEs were also bleeding-related events, such as hemoglobin decreased and ecchymosis, and occurred more frequently in the All TAK-442 group compared with placebo.

Most subjects with TEAEs experienced events considered by the investigator to be mild or moderate in intensity.

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Comparable percentages of subjects experienced severe TEAEs in the placebo group and in the All TAK-442 group (6.8% and 7.3%, respectively). Most treatment-related TEAEs also were mild or moderate in intensity. An equal percentage (1.4%) of subjects in the placebo group and in the All TAK-442 group experienced severe treatment-related TEAEs.

The incidence of deaths during the study was the same in the placebo group (1.6%, 12 subjects) and in the combined TAK-442 group (1.6%, 31 subjects), and no dose-related patterns were observed in the number of deaths across the increasing TAK-442 treatment groups.

The percentages of subjects who experienced treatment-emergent serious adverse events (TESAEs were comparable between the placebo group and the All TAK-442 group (15.5% vs 16.7%, respectively). Most TESAEs were considered by the investigator to be not related to study medication. TESAEs led to temporary or permanent study drug discontinuation for 8.1% and 9.7% of subjects in the placebo and All TAK-442 groups, respectively. No apparent dose-related pattern was observed in the incidence of TESAEs across the increasing TAK-442 treatment groups. The percentage of subjects with drug-related TESAEs also was similar in the placebo and All TAK-442 groups (2.4% and 3.3%, respectively), with no noteworthy differences between treatments. Most drug-related TESAEs were reported by only 1 subject. Drug-related TESAEs occurred most frequently in the system organ classes of cardiac disorders (1.1% and 0.9% of subjects in the placebo and All TAK-442 groups, respectively) followed by gastrointestinal disorders (0.3% and 0.9%, respectively). The percentage of subjects with drug-related TESAEs was slightly higher in the 2 highest TAK-442 dose groups (160 mg QD and 120 mg BID) compared with the other lower dose groups.

TEAEs led to temporary or permanent study drug discontinuation for 12.9% and 17.4% of subjects in the placebo and All TAK-442 group, respectively, and 6.8% and 10.6% of subjects, respectively, withdrew from the study altogether because of TEAEs. The most common TEAEs causing discontinuation in the All TAK-442 group were angina unstable, gingival bleeding, epistaxis, and hemoglobin decreased. A dose-related pattern was observed among the individual TAK-442 dose groups, with a notably higher incidence of TEAEs leading to discontinuation in the 40 mg BID and higher dose groups compared with the lower dose groups.

In general, there were no remarkable findings with respect to physical examinations, vital signs, and ECG results. Among the clinical safety laboratory parameters, there was a small imbalance of mild creatinine abnormalities >30% from Baseline and >ULN in the All TAK-442 group compared with placebo (3.8% vs 2.2%, respectively), while virtually no difference was observed in the percentages of subjects with creatinine levels >50% from Baseline and >ULN (1.4% vs 1.3%, respectively).

Overall, treatment with TAK-442 in doses ranging from 10 to 120 mg BID were well tolerated, with no apparent signals for clinically significant hepatotoxicity or increased QTc. The small imbalance in mild creatinine outliers by itself does not appear clinically significant.

CONCLUSIONS:

- TAK-442 is a biologically active fXa inhibitor, with a dose-related anticoagulation effect on biomarkers and bleeding frequency. Combination of TAK-442 with antiplatelet therapy results in increased bleeding at doses of 40 mg QD and higher.
- There is no clear evidence for TAK-442 reducing CV events in ACS when added to standard of care, particularly thienopyridines.
- There was no signal that TAK-442 caused clinically significant hepatotoxicity or increased QTc.
- There was a small imbalance in mild creatinine outliers, consistent with that observed in the previous phase 2 study of VTE prevention, that will need to be further evaluated in larger studies.

Date of Report:

20 May 2011