7. Clinical/Statistical – Phase 3 Clinical Study Essential to Regulatory Decision

Study TAAL: "A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects who are to Undergo Percutaneous Coronary Intervention/TIMI 38."

7.1. Design/Protocol Study TAAL

Study TAAL was a Phase 3, multinational, randomized, double-blind, double-dummy, active-controlled study in subjects with acute coronary syndrome (ACS), who were scheduled to undergo PCI. The primary objective of the study was to test the hypothesis that prasugrel plus aspirin is superior to clopidogrel plus aspirin in the treatment of these subjects, as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke (to be referred to as the "triple endpoint" in this review document), at a median follow-up of ≥ 12 months. The study involved 717 principal investigators at 725 study centers (8 investigators oversaw 2 study sites, each) in 30 countries.

The 1° endpoint (triple endpoint) was to be analyzed first in subjects with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI), followed by the entire group of ACS subjects (UA/NSTEMI and ST-segment elevation myocardial infarction [STEMI]).

7.1.1. Study population

For inclusion, subjects must have presented with ACS (based on the disease diagnostic criteria, below), and have been scheduled to undergo PCI.

Disease Diagnostic Criteria:
ACS was to include: 1) moderate to high risk UA and NSTEMI; and 2) STEMI, as follows:

- Moderate to high risk UA ≡ history of chest discomfort or ischemic symptoms of ≥ 10 minutes duration at rest ≤ 72 hours prior to randomization, with persistent or transient ST-segment deviation ≥ 1 mm in one or more electrocardiogram (ECG) leads without elevation of creatine kinase muscle-brain (CK-MB) or troponin T or I but with a TIMI Study Group (TIMI) risk score ≥ 3

- Moderate to high-risk NSTEMI ≡ history of chest discomfort or ischemic symptoms of ≥ 10 minutes duration at rest ≤ 72 hours prior to randomization with no evidence of persistent ST-segment elevation. Subjects must also have CK-MB or troponin T or I greater than the upper limit of normal (ULN) and a TIMI risk score ≥ 3. If neither CK-MB nor troponin were available, total CK > 2 X ULN was acceptable.

- STEMI ≡ history of chest discomfort or ischemic symptoms of >20 minutes duration at rest ≤ 14 days prior to randomization with one of the following present on at least one ECG prior to randomization: a) ST-segment elevation ≥ 1 mm in two or more contiguous ECG leads; b) new or presumably new left bundle branch block (LBBB); c) ST-segment depression ≥ 1 mm in two anterior precordial leads (V1 through V4) with clinical history and evidence suggestive of true posterior infarction.

Subjects receiving alteplase, reteplase, or tenecteplase could have been randomized ≥24 hours after completion of infusion; subjects receiving streptokinase (no longer marketed in the US) could have been randomized ≥48 hours after completion of infusion.

Key exclusion criteria (subjects must have met none):

- Cardiovascular:
  - cardiogenic shock
  - refractory ventricular arrhythmias
  - New York Heart Association (NYHA) Class IV congestive heart failure (CHF)

- Bleeding:
  - Receipt of alteplase, reteplase, or tenecteplase < 24 hours prior to randomization (study entry ≥ 24 hours after completion of infusion allowed)
  - Receipt of streptokinase (no longer marketed in the US) < 48 hours prior to randomization (study entry ≥ 48 hours after completion of infusion allowed)
  - active internal bleeding or history of bleeding diathesis
  - history of hemorrhagic stroke, ischemic stroke ≤ 3 months prior to screening, intracranial neoplasm, arteriovenous malformation, or aneurysm
  - International Normalized Ratio (INR) > 1.5
  - platelet count < 100,000/mm^3
  - anemia (hemoglobin [Hgb] < 10 gm/dL)

- Prior/Concomitant Therapy
  - Receipt of a thienopyridine (ticlopidine or clopidogrel) ≤ 5 days prior to PCI
  - Receipt of oral anticoagulation or other antiplatelet therapy that cannot be safely discontinued for the duration of the study
  - Receipt of daily nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued, or anticipated to require > 2 weeks of daily treatment during the study.

- General
  - Females known to be pregnant, ≤ 90 days post-partum, or breastfeeding
  - Severe hepatic dysfunction (i.e., cirrhosis or portal hypertension)

7.1.2. Randomization

Subjects were randomized 1:1 to either prasugrel (60-mg load; 10-mg daily maintenance) or clopidogrel (300-mg load; 75 mg daily maintenance) via an interactive voice response system (IVRS). Randomization was carried out at the site level and stratified by clinical presentation: UA/NSTEMI versus STEMI. Subjects who presented with STEMI within 12 hours of symptom onset (in whom 1° PCI was planned) could be randomized at the time of diagnosis, prior to diagnostic arteriography. All other subjects could be randomized only after diagnostic coronary arteriography confirmed anatomy suitable for PCI.

The study employed a double-dummy design, with subjects receiving the active formulation of one drug and placebo formulation of the other. The LD of the study drug was to be administered at any time between randomization and completion of the PCI (defined as no more than 1 hour after the subject left the catheterization laboratory). The LD consisted of 10 tablets: either six prasugrel 10-mg tablets and four clopidogrel placebo tablets, or four clopidogrel 75-mg tablets and six prasugrel placebo tablets. The subject and all site personnel were blinded to identity of the study drug and placebo. Clopidogrel was supplied as Plavix, Sanofi-Synthelabo.

The initial maintenance dose was to be administered within 20 to 28 hours of the LD, with subsequent maintenance doses administered once daily.

7.1.3. Concomitant Therapies

- Aspirin was to be administered (75-325 mg PO or 250-500-mg IV) within 24 hours prior to the index PCI.

- GPIIb/IIIa inhibitors were permitted before randomization, as well as during and after PCI. Decisions regarding use of a GPIIb/IIIa inhibitor, choice of agent, dose, and duration of therapy were left to investigators' discretion, and were to reflect contemporary practice.

- Antithrombin therapy was to be administered to all subjects as part of standard of care, with the choice of specific agent left to the judgment of the investigator. If unfractionated heparin was used without a GPIIb/IIIa inhibitor, the target for maximal activated clotting time (ACT) during PCI was 350 seconds. If unfractionated heparin was given with a GPIIb/IIIa inhibitor, the target ACT was 200-250 seconds.

- Fibrinolytic therapy was permitted for re-infarction or other indications after the index PCI, if deemed necessary by the investigator. Study drug could be temporarily discontinued at the investigator's discretion if thrombolytic therapy was instituted.

- GPIIb/IIIa inhibitors, antithrombin therapy, and fibrinolytic agents could be discontinued for bleeding events. The study drug could be temporarily discontinued for up to 14 days, or longer is necessary.

- Other medications permitted at the discretion of the treating physician included: H2 receptor blockers, PPIs, nitrates, calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins, anti-arrhythmic drugs, vasodilators, and intravenous vasopressors.

7.1.4. Monitoring

Subjects were evaluated at 24 hours post-PCI or hospital discharge, Days 30, 90, 180, 270, 360, and 450 (or last visit). At each visit, subjects were queried for adverse events and concomitant medications. In addition, each visit included assessments of vital signs, a targeted physical examination, ECG, complete blood count, platelet count, and clinical chemistries.

Primary efficacy endpoint: was a composite of CV death, nonfatal MI, or nonfatal stroke ("triple endpoint") at a median of 12 months follow-up.

Secondary endpoints: were to compare prasugrel with clopidogrel with respect to:

- Composite of CV death, nonfatal MI, nonfatal stroke or urgent target vessel revascularization (UTVR) at Day 30 (this endpoint per protocol, section 6.1.2.; however, endpoint in Statistical Plan omits nonfatal stroke [section 8.2])
- Composite triple endpoint at Day 30
- Composite of CV death, nonfatal MI, or UTVR at Day 90
- Composite triple endpoint at Day 90
- Composite triple endpoint or re-hospitalization for cardiac ischemic events at a median of ≥12 months
- Composite of all-cause mortality, nonfatal MI, or nonfatal stroke at a median of ≥12 months

- Definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end

The 2° endpoints were to be analyzed in both the UA/NSTEMI and entire ACS populations.

7.1.5. Definitions

- CV death ≡ death due to documented cardiovascular cause. In addition, death not clearly attributable to non-CV causes was considered to be CV death.

- Nonfatal MI: The definition of MI was adapted from the American College of Cardiology (ACC) definition and dependent on the timing of the event in relation to the presenting syndrome and cardiovascular procedures.

Peri-procedural events must have been temporally distinct from the index event. If cardiac biomarkers were elevated at the onset of a suspected event, there must have been evidence of a falling biomarker level prior to the event, and the subsequent peak must have exceeded 1.5 times the value prior to the event.

The biomarker levels required for the diagnosis of MI were dependent on the temporal relationship to cardiac procedures:

- If the suspected event was within 48 hours of a PCI, the CK-MB value must have been > 3X the ULN on ≥ 2 samples; symptoms were not required. A January 10, 2006 amendment extended the definition of peri-procedural MI to include a CK-MB > 5X ULN on one sample if it was the last available sample and was drawn ≥12 hours after PCI.

- If the suspected event was within 48 hours of a CABG, the CK-MB value (on a single measure) must have been >10X the upper limit of normal; no symptoms were required.

- If the suspected event was not within 48 hours of a PCI or CABG, the diagnostic criteria for MI were met if the subject had CK-MB or cardiac troponin > ULN and the presence of either chest pain ≥ 20 minutes in duration or ST-segment deviation ≥ 1mm.

The appearance of new Q-waves distinct from a prior event (including the presenting event) or pathologic evidence (such as autopsy) showing a new MI thought to be distinct from a prior event was considered evidence for MI, as was ST segment elevation (meeting enrollment criteria) lasting for at least 20 minutes and accompanied by ischemic chest pain or hemodynamic decompensation.

Five major sets of criteria were used for diagnosis of nonfatal MI:

1. ST elevation or re-elevation, and either ischemic chest pain ≥ 20 minutes in duration or hemodynamic decompensation.

2. Spontaneous CK-MB or troponin >ULN, and ischemic chest pain (or anginal equivalent) ≥20 minutes in duration or ST segment deviation ≥ 1 mm in one or more leads

3. CK-MB > 3X ULN on ≥ 2 samples following PCI

4. CK-MB > 10X ULN on one sample following CABG

5. New Q waves ≥ 0.04 seconds, or pathology distinct from prior MI

ECGs and other supporting clinical tests and evaluations were to be centrally adjudicated by a Clinical Endpoints Committee (CEC).

- Nonfatal Stroke ≡ the acute onset of new-persistent neurologic deficit lasting >24 hours. Head computed tomography (CT) or magnetic resonance imaging (MRI) scan imaging was strongly recommended. CT or MRI scans were to be considered by the CEC to support the clinical impression. Nonfatal stroke was to be classified as either ischemic or hemorrhagic based on imaging data, if available, or uncertain cause if imaging data were not available.

- Urgent target vessel revascularization (UTVR) ≡ PCI or CABG for recurrent ischemia that, in the investigator's opinion, is non-elective and cannot be delayed for more than 24 hours. UTVR must include the vessel(s) dilated at initial PCI.

Safety objectives were primarily focused on bleeding, designed to compare prasugrel with clopidogrel with respect to:

- TIMI Study Group (TIMI) major bleeding ≡ any intracranial hemorrhage (ICH) or overt bleeding associated with a hemoglobin (Hgb) decrease ≥ 5 g/dL from baseline
- TIMI life-threatening bleeding (a subset of the above). "Life-threatening" ≡ fatal, causes hypotension that requires IV inotropic agents, surgical intervention, ≥ 4 units blood or packed RBCs within 48 hours, or symptomatic ICH.
- TIMI minor bleeding ≡ clinically overt bleeding associated with a decrease in Hgb of ≥ 3 g/dL but < 5 g/dL from baseline

Bleeding was categorized as related to, or not related to, coronary artery bypass graft (CABG) surgery.

- assessments of clinical findings, laboratory values, and adverse events (AEs)

7.1.6. Safety Endpoints

• Non-CABG related TIMI major bleeding

• Non-CABG-related TIMI life-threatening bleeding (any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension, requires surgical intervention, or necessitates transfusion of ≥4 units blood products over a 48-hour period; or any symptomatic ICH)

• Non-CABG-related fatal bleeding

• Non-CABG-related TIMI minor bleeding (clinically overt bleeding associated with a fall in Hgb of ≥ 3 g/dL but < 5 g/dL)

• CABG related bleeding

Analytic Methodology:
The statistical analysis plan was finalized on September 18, 2007. The analyses of the primary and secondary endpoints are discussed below.

7.1.7. Efficacy Endpoints

An independent CEC performed blinded adjudicated all efficacy events reported by investigators. Per protocol, the 1°, 2°, and other efficacy endpoint analyses were based on the determinations of events as adjudicated by the CEC.

Primary endpoint: Due to a potentially varying hazard ratio, the analysis for the 1° efficacy endpoint was based on the time from randomization to the first primary outcome using the Gehan-Wilcoxon test. Primary analyses were carried out in a hierarchical manner. At the first step, time-to-first primary outcome was carried out at a one-sided significance level of 0.025 (equivalent to a two-sided test at 0.05) in the UA/NSTEMI subject population. If superiority of prasugrel was established in the UA/NSTEMI population, then time-to-first primary outcome was to be carried out at a one-sided significance level of 0.025 in the All ACS population. For the latter analysis, ACS classification (UA/NSTEMI or STEMI) was to be used as a stratification factor. No adjustment for multiplicity was applied, because of the closed nature of hypothesis testing.

Secondary endpoints:

- Plan for evaluating secondary endpoints in UA/NSTEMI subject population

Following the establishment of the superiority of prasugrel over clopidogrel relative to the primary endpoint, additional analyses for secondary efficacy endpoints were performed using the log-rank test. Per agreement with FDA, the secondary endpoints were comprised of two groups: the first (Group 1) are those endpoints that do not require adjustment for multiplicity; the second (Group 2) are those that need to be predefined in a hierarchical manner (see Figure 4).

Group 1 secondary endpoints were each evaluated at a one-sided 0.025 alpha level (i.e., equivalent to a two-sided 0.05 level).

- Triple endpoint at Day 90
- Triple endpoint at Day 30

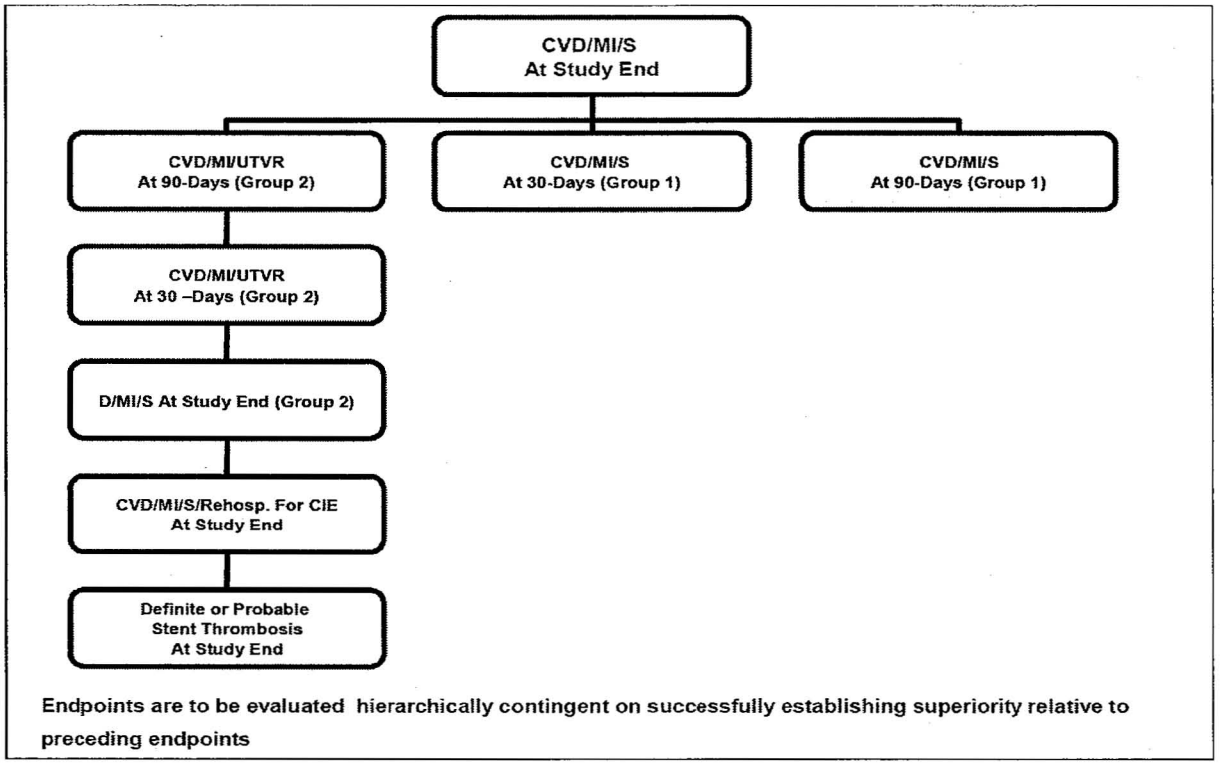
Both 2° endpoints in Group 1 were to be eligible for inclusion in labeling if the results were statistically significant.

The evaluations of Group 2 endpoints were dependent on demonstration of superiority of prasugrel on the 1° endpoint in the UA/NSTEMI population. To protect the overall type 1 error rate at a level of 0.05, the 5 remaining secondary endpoints were evaluated hierarchically, each at a one-sided 0.025 alpha level:

- CVD, nonfatal MI, or UTVR at 90 days post-randomization
- CVD, nonfatal MI, or UTVR at 30 days post-randomization
- All cause mortality, nonfatal MI, or nonfatal stroke at study end
- CVD, nonfatal MI, nonfatal stroke, or rehospitalization for cardiac ischemic event at study end
- Definite or probable stent thrombosis.

Numerous exploratory endpoints included components of the above composite endpoints at various timepoints.

Figure 4: Hierarchical plan for secondary endpoints



(Source: Sponsor's Figure 9.2, page 9169 of H7T-MC-TAAL Study Report. Abbreviations: CVD = cardiovascular death, D = death, Rehosp. = rehospitalization, S = stroke)

- Plan for evaluating secondary endpoints in All ACS subject population

Contingent on a demonstration of superiority of prasugrel for the 1° endpoint in the All ACS population, each of the 7 secondary endpoints was evaluated in the hierarchical method described above in All ACS population. The log-rank test was used for each analysis at a one-sided 0.025 significance level. The clinical presentation (UA/NSTEMI or STEMI) was used as the stratification factor in these analyses.

7.1.8. Power and Sample Size

For UA/NSTEMI subjects, the study was planned to provide 90% power to establish superiority on the triple endpoint based on the following assumptions:

- 10.5% of subjects in the clopidogrel group would reach the triple endpoint within 1 year of PCI, based on event rates of the "Clopidogrel in Unstable Angina to Prevent Recurrent Events" (CURE) trial, for the subset of subjects with a TIMI risk score ≥3
- A mean hazard ratio of 0.80 for prasugrel versus clopidogrel relative to the primary endpoint, and
- The time-to-first event analysis based on a two-sided log-rank test used a two-sided significance level (alpha) of 0.05 to assess superiority relative to the triple endpoint.

The proposed sample size was 13,000 subjects, assuming that ≥95% of subjects would be evaluable for the primary endpoint and that STEMI subjects would comprise 20 to 30% of the total enrollment (with a cap of 3500 subjects).

The study was to continue until 875 UA/NSTEMI subjects experienced a triple endpoint event, a median duration of therapy of 12 months, and a minimum follow-up of 6 months.

The blinded event rate was to be evaluated when 650 UA/NSTEMI subjects had reached the primary endpoint. However, the Study Operations Committee conducted a blinded review of the aggregated event rate when 589 subjects with UA/NSTEMI reached the primary endpoint and determined there was a slightly lower than anticipated aggregated event rate. Thus, the size of the UA/NSTEMI population was expanded to 10,100 subjects to achieve a target of 875 events.

7.2. General Results

7.2.1. Conduct

TAAL was conducted from November 5, 2004 through July 22, 2007. A total of 13,619 subjects were enrolled over a period of approximately 26 months, with entrance of the final subject on January 14, 2007. The study involved 725 centers in 30 countries, for an overall average of approximately 19 subjects enrolled per site. The database was locked on September 20, 2007.

Reviewer's Comments: In light of the rapid enrollment of the study, and the fact that the study was concluded only within the past year, the data are very much representative of contemporary medical practice. Beyond this, the requirement for all subjects to undergo PCI ensured a fair degree of consistency in medical management of ACS, consistency that could be lacking in studies where PCI is only optional.

Protocol violations, identified from both the clinical database and site monitoring, were relatively unimportant, low in number, and similar in frequency between treatment groups. As such, they are deemed unlikely to influence the study results.

7.2.2. Disposition of Subjects

Overall, 18,357 potential subjects were screened, in order to enroll 13,619 subjects (approximately 25% were screening failures). Of the 13,619 subjects enrolled, 11 had an incomplete informed consent document, and were not included in the analyses. Thus, the intent-to-treat population included 13,608 subjects: 6,813 subjects were randomized to prasugrel and 6,795 subjects were randomized to clopidogrel. Approximately 98.8% of randomized subjects received the study agent (13,457), and comprise the safety population. Median length of follow-up was 450 days (mean 380 ± 121 days). Nineteen percent (19%) of subjects had unstable angina, 55% had NSTEMI, and 26% had STEMI (18% treated within 12 hours, 8% beyond 12 hours).