2. SYNOPSIS

Name of Sponsor Company: Eisai	Individual Study Table	(For National Authority Use Only)
Name of Finished Product: E5555	Referring to Part of the Dossier	
Name of Active Ingredient: E5555	Volume:	
	Page:	

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Tolerability of E5555, and its Effects on Markers of Intravascular Inflammation in Subjects with Coronary Artery Disease (CAD)

Investigators: 136 principal investigators

Study centers: Multicenter in 11 countries (136 sites were initiated, of which 106 enrolled ≥1 subject)

Publication (reference): None at the time of this report

Studied Period: 13 Sep 2007 (first subject signed informed consent) to 14 Aug 2009 (last subject visit)

Clinical Phase: 2

Objectives: The primary objectives of the study were to assess the safety and tolerability of E5555 in subjects with coronary artery disease (CAD).

The secondary objectives were to determine the effect of E5555 on: (a) the incidence of major adverse cardiovascular events (MACE) (cardiovascular death, myocardial infarction, stroke, and refractory ischemia); (b) platelet aggregation inhibition (in selected sites in subjects that were willing to take part in this component of the study); and (c) to determine the effects of E5555 on high sensitivity C-reactive protein (hsCRP) levels.

The exploratory objective was to determine the effect of E5555 on the endovascular inflammatory processes that were believed to be integral to the pathogenesis of CAD.

In addition, the pharmacokinetics (PK) of E5555 and its metabolites were determined; qualified sites conducted comprehensive plasma sample collection for measurement of levels of E5555 and its metabolites to evaluate the relationship between E5555 PK and pharmacodynamics (PD). Results relating to the PK and PD analyses will be reported in a separate supplemental report.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled study in which eligible subjects were randomly assigned to one of four treatment groups (E5555 50 mg, 100 mg, or 200 mg, or placebo) after a baseline assessment. Study drug was taken orally, once daily, from Day 1 through Day 168. Adverse events (AEs) and concomitant medications were monitored from screening through follow-up. Physical examinations, vital signs recordings, and clinical laboratory tests were performed at screening, baseline, at the Week 1, 2, 4, 8, 12, 16, 20, and 24 visits, and at the follow-up (Week 28) or early termination visit. A Week 25 visit was also conducted for subjects who participated in the PK/PD component of the study.

The incidence of MACE during the study was ascertained through interval history at study visits, and ongoing AE reporting.

Electrocardiograms (ECGs) were recorded at screening for local reading to determine study eligibility. ECGs were recorded at baseline and at Weeks 1, 2, 4, 8, 12, 16, 20, and 24 for central reading.

Selected sites conducted additional PK/PD studies, based on their ability, experience, and willingness to conduct more intensive PK sampling and platelet aggregation studies. These studies were conducted on seven study days (one predose sample for all visits): Day 1 (baseline), between Days 14 and 28, Day 84, and Days 168, 170, 171, and 175 (single samples on each of these days). In addition to predose samples, up to

three further samples could have been taken on each of Day 1, between Days 14 and 28, and Day 84. It was anticipated that approximately 80 evaluable subjects would participate in this part of the study.

Measurement of plasma levels of a panel of biomarkers, including but not limited to hsCRP, myeloperoxidase (MPO), soluble CD40 ligand (sCD40L), placental growth factor (PlGF), interleukin-6 (IL-6), interleukin-1β (IL-1β), interleukin-18 (IL-18), and lipoprotein-associated phospholipase A_2 (Lp-PLA_2), believed to indicate the degree of risk for MACE in subjects with CAD, were performed at baseline, and at Weeks 2, 4, 12, 16, 20, 24, and 28. hsCRP was also measured at screening to help determine subject eligibility.

Blood samples for measurement of steady-state plasma levels of E5555 and its metabolites were collected from all subjects predose at the Week 2, 4, and 12 visits.

Data were periodically reviewed by an unblinded independent Data Monitoring Committee (DMC), and a blinded Clinical Endpoint Committee (CEC) adjudicated event outcome.

Number of Subjects: Planned: N=600 (main study), N=80 (substudy)
Randomized: N=720
Completed: N=581
Analyzed: N=718 (Safety population), N=718 (Intent-to-treat [ITT] population), N=649 (Per Protocol [PP] population), N=82 (Substudy)

Diagnosis and Criteria for Inclusion: Males or nonpregnant females; aged 45 to 80 years, inclusive; confirmed CAD and at high risk of MACE; receiving low-dose aspirin (75 mg to 325 mg) and/or clopidogrel 75 mg once daily and both must have been taken at least 1 month prior to screening (ticlopidine 250 mg twice daily with or without low dose aspirin once daily was also allowed); and written informed consent.

Test Product, Dose, Mode of Administration, Batch No(s): E5555 (50 mg or 100 mg tablets) were administered by mouth from Day 1 through Day 168 (Week 24). Subjects randomized to active treatment received one of the following regimens:

- 50 mg E5555 daily (Day 1 – 168)
- 100 mg E5555 daily (Day 1 – 168)
- 200 mg E5555 daily (Day 1 – 168)

Placebo tablets were also administered to provide identical treatment regimens to maintain blinding.
All treatments were taken with food in the morning at approximately the same time. The subject was not to have taken study drug before coming in on visit days because assessments had to have been completed before study drug was taken. After completion of all study-related procedures at the site visit, the subject took the study drug.

Batch numbers for 50 mg active E5555 tablets: P59005ZZA, P73026ZZA
Batch numbers for 100 mg active E5555 tablets: P56008ZZA, P56009ZZA, P59006ZZA, P67016ZZA, P72013ZZA, P73027ZZA, P73028ZZA, P72012ZZA

Duration of Treatment: Total duration of individual study participation was 28 weeks (196 days) consisting of a treatment period of 24 weeks (168 days) and a follow-up period of 4 weeks (28 days).

Reference Therapy, Dose, Mode of Administration, Batch No(s): E5555 matching 50 mg or 100 mg placebo tablets were administered by mouth from Day 1 through Day 168 (Week 24). All treatments were taken with food in the morning at approximately the same time. The subject was not to have taken study drug before coming in on visit days because assessments had to have been completed before drug is taken. After completion of all study related procedures at the site visit, the subject took the study drug.

Batch numbers for matched 50 mg placebo tablets: P53013ZZA, P53014ZZA, P53017ZZA, P53018ZZA, P72001ZZA
Batch numbers for matched 100 mg placebo tablets: P53016ZZA, P56004ZZA, P56005ZZA, P56006ZZA, P56007ZZA, P67011ZZA, P72005ZZA, P72006ZZA, P73021ZZA, P73022ZZA, P73023ZZA, P73025ZZA

Criteria for Evaluation:
Efficacy: Assessments of the efficacy endpoints were based on data derived from subject case report forms (CRFs) regarding the proportions of subjects with CEC-adjudicated MACE, inhibition of platelet aggregation, levels of hsCRP, and levels of sCD40L. Assessments of exploratory endpoints were based on data derived from subject CRFs regarding markers indicative of endovascular inflammation.

Safety: Assessment of the primary safety endpoint was based on data derived from subject CRFs regarding the proportions of subjects with clinical CEC-adjudicated bleeds according to both the Thrombolysis in Myocardial Infarction (TIMI) and Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial criteria. Assessment of the secondary safety endpoints were based on data derived from subject CRFs regarding: the proportions of subjects with CEC-adjudicated bleeding events according to TIMI criteria (includes major, minor, and minimal); the proportions of subjects with CEC-adjudicated bleeding events according to CURE criteria (includes major life-threatening, major non-life-threatening, and minor); the number of subjects withdrawn from treatment due to bleeding; severity of the bleeding AEs using AE severity classification; the outcome of the bleeding AEs (spontaneous or instrumented); the number of AEs and serious adverse events (SAEs); the number of treatment-emergent abnormal values (TEAVs) for laboratory parameters; ECG changes in the three E5555 treatment groups compared with those in the placebo group (QT corrected according to Bazett's and Fridericia's formulae[QTcB and QTcF]).

Statistical Methods:
Study Populations
Safety: Subjects included in the Safety population were those who were randomized and took at least one dose of double-blind study drug. Analyses in the Safety population were based on the actual treatment received.

Intent-to-treat (ITT): The ITT population was defined as all randomized subjects. However, due to practical limitation, subjects without valid consent or subjects receiving no treatment and having no postrandomization follow-up were excluded from the ITT population. Analyses in the ITT population were based on the randomized treatment assignment.

Per protocol (PP): The PP population was defined as all subjects in the ITT population who no major protocol violations. Analyses in the PP population were based on the randomized treatment assignment.

Baseline and demographic data were summarized in the randomized population by treatment group using descriptive statistics.

All efficacy analyses were performed in the ITT population. The treatment groups were compared in terms of overall MACE rates (using both count and person-time denominators), category-specific MACE rates, time to first MACE, inhibition of platelet aggregation, and changes from baseline levels of hsCRP and other selected inflammatory biomarkers. Active and placebo bleeding rates were compared using the relative risk (RR) accompanied by exact 95% confidence intervals (CIs) and p-values based on the Agresti-Min method (for count denominators) and the binomial method (for person-time denominators). Dose-response trends were assessed using the exact Cochran-Armitage test. Time to first MACE was compared between the pooled treatment and placebo groups using the Kaplan-Meier procedure and log rank test. Comparisons of MACE rates (using count denominators) were repeated in the PP population. The analysis of covariance (ANCOVA) models and t-tests based on least-square means were used to compare platelet aggregation mean change from baseline among the treatment groups. Inhibition of platelet aggregation was assessed using descriptive statistics. ANCOVA models and t-tests based on least-square means were also used to compare continuous biomarkers and Fisher's exact test was used to compare the proportions of subject differences in categorical biomarkers.

All bleeding event analyses were performed in the ITT population. The treatment groups were compared in terms of overall TIMI and CURE bleeding rates (using both count and person-time denominators), TIMI and CURE category-specific bleeding rates, proportions of subjects with discontinuations due to bleeding events, and time-to-first bleeding event. Active and placebo bleeding rates were compared using the RR accompanied

by exact 95% CI and p-values based on the Agresti-Min method (for count denominators) and the binomial method (for person-time denominators). Dose-response trends were assessed using the exact Cochran-Armitage test. Time-to-first bleed was compared between the combined active E5555 treatment groups and the placebo group using the Kaplan-Meier procedure and log rank test. Comparisons of TIMI and CURE bleeding rates (using count denominators) were repeated in the Safety and PP populations.

All additional safety analyses were performed in the Safety population. The incidence of AEs, SAEs, treatment-emergent adverse events (TEAEs), TEAVs, changes in ECG parameters, vital signs, physical examination results, as well as changes in clinical laboratory values from pretreatment values, were summarized by descriptive statistics. Mean changes in QTcF and QTcB from baseline were also compared within and between treatment groups using paired and independent t-tests, respectively.

Interim analyses were conducted by an independent DMC. Several unblinded interim analyses for safety monitoring purposes were planned at the time when approximately 120, 240, 360, 480, and 600 subjects were randomized. There were no a priori stopping rules based on differences in the incidence, frequency, severity, or seriousness of general AEs between the different treatment groups. However, the DMC at their discretion could have recommended stopping the trial based on safety concerns. Details of the interim analyses were provided in the DMC charter and the interim analysis plan, which were finalized before the first unblinded interim analysis.

This was an exploratory pilot study evaluating primarily the safety and tolerability of E5555 in subjects with CAD who were at high risk of MACE. The treatment comparisons of interest were individual and combined active E5555 treatment groups versus placebo.

The statistical package SAS® (Version 9.1 or later) was used to produce all summary tables and listings. In general, categorical data were presented using counts and percentages, while continuous variables were presented using the mean, standard deviation, median, minimum, maximum, and number of subjects.

SUMMARY – CONCLUSIONS:
RESULTS:

Disposition and Demographics:
A total of 720 subjects were randomized and the majority completed the 24-week treatment period (581 [80.7%] subjects). Of the 720 subjects randomized, 718 qualified for the Safety population and the ITT population. Two of the 720 randomized subjects were not treated and excluded from the Safety population. These same two subjects did not meet the ITT criteria and were excluded from the ITT population. Of the 720 randomized subjects, 649 (90.1%) had no major protocol violations, which comprised the PP population.

A total of 139 (19.3%) randomized subjects discontinued before Day 168. The primary reasons for discontinuation were AEs (66 [9.2%] subjects) and subjects withdrew consent (51 [7.1%] subjects). The mean (standard deviation [SD]) overall age of subjects was 63.7 (8.05) years (range 45 – 80 years). The majority of subjects were male (546 [75.8%] subjects). A total of 683 (94.9%) subjects were white, and 18 (2.5%) were black.

Efficacy:
The primary endpoint to assess efficacy was CEC-adjudicated MACE at Week 24. In the ITT population subset, lower rates of MACE were observed for all active E5555 treatment groups compared with placebo. However, the difference was not statistically significant.

There was a lower incidence of MACE in the combined active E5555 treatment groups than in the placebo group (14 [2.58%] vs. 8 [4.55%] subjects, respectively). Among the individual active E5555 treatment groups, the incidence was lowest in the 50 mg group (3 [1.65%] subjects) and highest in the 200 mg group (6 [3.23%] subjects), and all active E5555 treatment groups demonstrated a numerically lower incidence of MACE events relative to placebo. The RR for CEC-adjudicated MACE incidence (combined active E5555

treatment groups vs. placebo) was 0.568 (0.247, 1.351). MACE rates in the PP population were similar to those in the ITT population.

In terms of the exploratory efficacy objective (to determine the effect of E5555 on the endovascular inflammatory processes that are believed to be integral to the pathogenesis of CAD), of the 82 enrolled substudy subjects, 63 subjects had predose evaluable PD data on Day 1, which served as a baseline to calculate the change in PD response. Data were available for 55 subjects at the end of Day 1, 39 subjects at the end of Weeks 2 to 4, 36 subjects at the end of Day 84, and 31 subjects on Day 168. In the 200 mg group, >90% mean inhibition of platelet aggregation (IPA) was demonstrated at all time points for the visit between Weeks 2 and 4 and was maintained through Day 168. In the 100 mg group, >85% mean IPA was demonstrated and maintained between Weeks 2 and 4 and Day 168. In the 50 mg group, >90% IPA was demonstrated at 2 to 3 hours postdose on Day 84 but not maintained throughout the 24-hour period. On Day 1, mean maximum IPA was 19% in the placebo group, 45% in the 50 mg group, 91% in the 100 mg group, and 97% in the 200 mg group. Between Weeks 2 and 4, mean maximum IPA was 16% in the placebo group, 93% in the 50 mg group, 98% in the 100 mg group, and 98% in the 200 mg group. On Day 84 mean maximum IPA was 14% in the placebo group, 91% in the 50 mg group, 97% in the 100 mg group, and 98% in the 200 mg group. On Day 168 mean maximum IPA was 8% in the placebo group, 65% in the 50 mg group, 94% in the 100 mg group, and 96% in the 200 mg group.

Although the results showed trends in some of the inflammatory markers, no consistent effects were observed with any of the markers studied.

Overall, the combined active E5555 treatment groups showed evidence of platelet aggregation inhibition and suggested the potential for a reduction in the incidence of MACE as compared with the placebo treatment group.

Safety:

The primary safety endpoint was the proportion of subjects with any CEC-adjudicated bleeds up to Week 24 according to both TIMI and CURE criteria. There was a signal of increased TIMI bleeding rates by dose in the ITT population but the trend was not statistically significant (p=0.0724 using the Cochran-Armitage trend test). A dose-related trend was statistically significant using the CURE criteria (p=0.0103). Using the TIMI criteria, higher incidence rates were found for CEC-adjudicated any bleeds in the combined active E5555 treatment groups (10.33%, 56/542) compared with placebo (6.82%, 12/176), with RR=1.52. Further, using the TIMI criteria, the incidence rate for CEC-adjudicated any bleeds for the combined active E5555 treatment groups compared with placebo was not statistically significant (p=0.1693). The majority of TIMI bleeds were minimal. Of the 68 subjects with bleeding events, 3 had TIMI major (2 at 50 mg and 1 at 200 mg), 3 had TIMI minor (1 at 50 mg and 2 at 200 mg), and 62 had TIMI minimal. Of the 62 subjects with TIMI minimal bleeds, 21 required medical attention: 20 (3.69%) in the combined active E5555 treatment groups compared with 1 (0.57%) in the placebo group. This difference was statistically significant (p=0.0342). The CURE bleeding rates were mainly driven by minor bleeds (17 of 22, of which 16 were in active treatment groups). Bleeding rates in the PP population were similar to those in the ITT population.

In the Safety population, 536 (74.7%) subjects experienced at least one TEAE: 128 (72.7%) in the placebo group, 133 (73.1%) in the 50 mg group, 131 (75.3%) in the 100 mg group, and 144 (77.4%) in the 200 mg group. In the combined active E5555 treatment groups, 408 (75.3%) subjects experienced at least one TEAE. The proportions of subjects with at least one TEAE did not appear to differ among the four treatment groups. The most common TEAEs observed in the combined active E5555 treatment groups were headache and dizziness.

A total of 92 (12.8%) subjects experienced a serious TEAE: 17 (9.7%) in the placebo group, 25 (13.7%) in the 50 mg group, 22 (12.6%) in the 100 mg group, and 28 (15.1%) in the 200 mg group. The proportion of serious TEAEs was higher in the combined active E5555 treatment groups compared with the placebo group (75 [13.8%] vs. 17 [9.7%] subjects).

A total of 68 subjects reported at least one TEAE that led to treatment withdrawal: 57 (10.5%) subjects in the combined active E5555 treatment groups (18 [9.9%] on 50 mg, 18 [10.3%] on 100 mg, and 21 [11.3%] on 200 mg) and 11 (6.3%) subjects in the placebo group. The most commonly reported reasons for discontinuation of treatment were gastrointestinal disorders (11 [2.0%] subjects), nervous system disorders (10 [1.8%] subjects), and cardiac disorders (7 [1.3%] subjects).

The subjects experiencing ECG changes with QTcF >500 msec were rare and appeared to occur randomly across different treatment groups throughout the duration of the study. The proportion of subjects with a QTcF change from baseline >60 msec was 0.4 to 1.4% with treatment and 1.4% at the final visit.

The proportions of subjects with aspartate aminotransferase (AST) elevations ≥3 x upper limit of normal (ULN) were 0, 2 (1.1%), 3 (1.8%), and 7 (3.8%) in the placebo, 50 mg, 100 mg, and 200 mg treatment groups, respectively. The comparable proportions of subjects with alanine aminotransferase (ALT) elevations ≥ 3x ULN were 0, 2 (1.1%), 5 (2.9%), and 11 (6.0%). Overall, the elevations in liver function test (LFT) results were transient and resolved by end of study, and there were no cases of Hy's Law.

Serum creatinine changes were noted to be dose-related. The magnitude of change (i.e., mean change from baseline) was small and ranged from 5.1 to 7.9 µmol/L for the combined active E5555 treatment groups and –0.9 to 0.9 µmol/L for the placebo group.

CONCLUSION: In conclusion, over a 24-week period and a 4-week follow-up period, E5555 was shown to be safe and generally well tolerated. Pharmacodynamic evaluations in this study showed evidence of inhibition of platelet aggregation.

Date of the Report: 30 Nov 2010