1. Introduction

This variation application was submitted to request the extension of the acute coronary syndrome (ACS) indication as follows:

- *"Patients with ST segment elevation acute myocardial infarction. In this population, clopidogrel reduces the risk of all cause mortality."*

Clopidogrel efficacy in ACS patients with STEMI was evaluated in two double-blind studies [EFC5133 (CLARITY- TIMI 28) and EFC7018 (COMMIT/ CCS-2)], in which patients were treated with ASA and other concomitant medications including fibrinolytics and anticoagulants.

2. Clinical aspects

Rationale for the proposed change

ACS is defined as any clinical syndrome of acute and prolonged myocardial ischaemia related to coronary artery disease (CAD) and comprises unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation acute myocardial infarction (STEMI). ACS is a significant public health concern; in the US alone, the estimated incidence of ACS is 942,000 cases per year. The estimated incidence of MI is 565,000 new attacks and 300,000 recurrent attacks per year, and in 2003 the estimated hospitalisation for acute MI was 767,000 patients. The average age of patients having a first heart attack is 65.8 years for men and 70.4 years for women. International data are available from the GRACE registry [(Global Registry of Acute Coronary Events) from 14 Western countries], which suggests a 34% rate of STEMI among patients who present with ACS, with a hospital death rate of 7.8%. According to the NRMI registry (US National Registry of Myocardial Infarction), the mortality rate for patients with STEMI has declined between 1990 and 2002, but remains substantial: 4.3% and 4.4% in patients receiving fibrinolytics or primary percutaneous coronary intervention (PCI), respectively.

In more recent years, with an aging worldwide population and an increase of co-morbid factors (obesity, smoking), little headway has been made in terms of reducing morbidity and mortality in patients diagnosed with STEMI. Furthermore, despite the existence of effective therapies for STEMI, such as pharmacological therapy with ASA and fibrinolytics associated with a reduction of risk factors, new therapies capable of preventing such events are needed.

Analysis of data submitted

This extension of indication is based on two new studies:

- EFC5133 [CLARITY-TIMI 28, Clopidogrel as Adjunctive Reperfusion TherapY-Thrombolysis in Myocardial Infarction – 28]
- EFC7018 [COMMIT/CCS- 2, Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study]

The Clinical Study Reports state that both trials were conducted according to GCP.

The individual study design and efficacy results are presented followed by a common safety section covering the safety findings for both trials.

EFC5133 (CLARITY-TIMI 28)

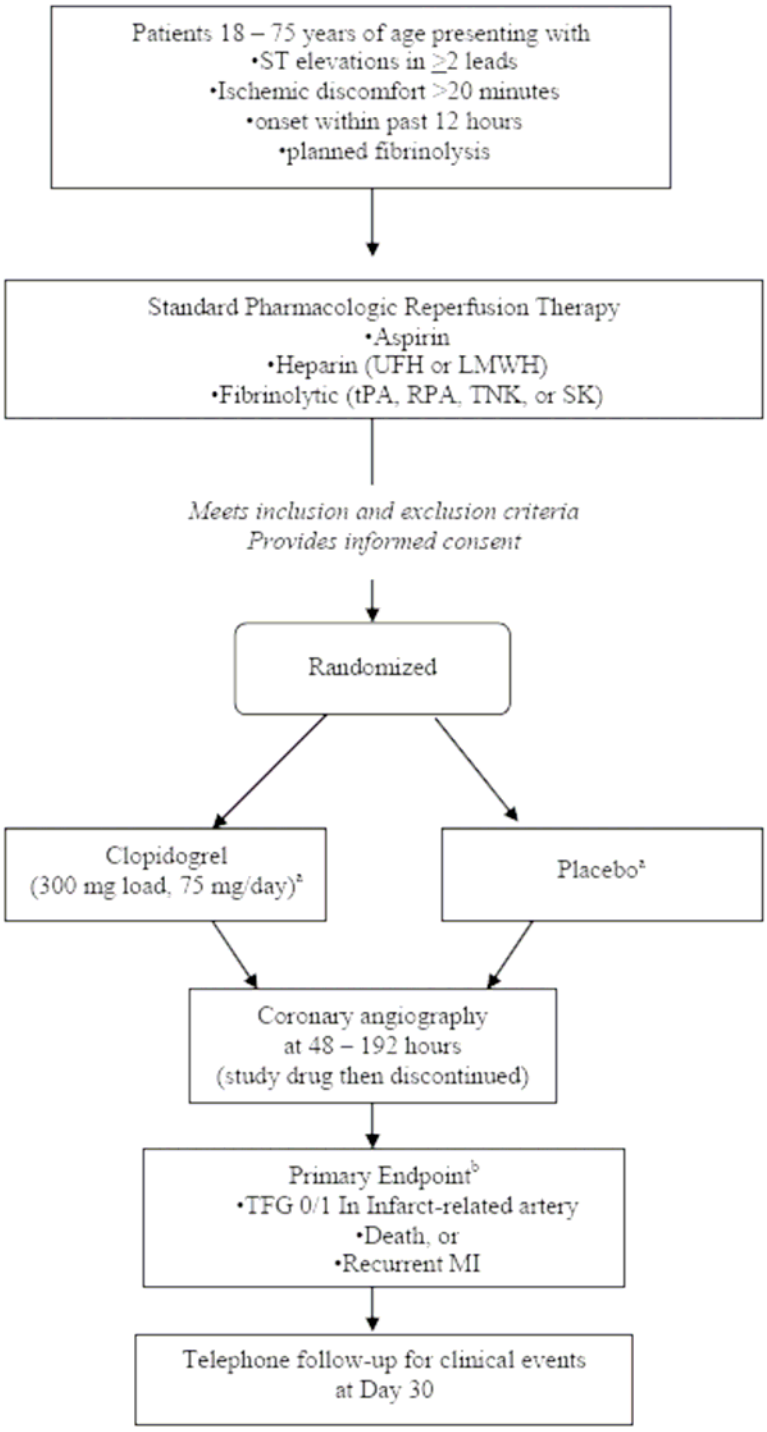
This was a Phase III, multinational, randomised, double-blind, placebo-controlled, 2 parallel group study of clopidogrel (300 mg loading dose followed by 75 mg/day) versus placebo in patients with STEMI treated with ASA and fibrinolytic therapy. The study was conducted at 319 active sites in 23 countries, including Europe, US, Canada, Argentina, Australia, Brazil, Israel, Mexico, South Africa, and Turkey.

The primary objective was to demonstrate that, in patients with STEMI treated with background ASA and initial fibrinolytic therapy, clopidogrel (300 mg loading dose followed by 75 mg/day) reduced the proportion of patients who had an occluded infarct-related artery (IRA) [defined as Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1] on the predischarge angiogram or who died or had a recurrent MI by the time of start of coronary angiography (between 48 and 192 hours after the start of blinded study drug), compared with placebo. For patients who did not undergo angiography, death or recurrent MI by Day 8 or by hospital discharge, whichever came first, was used.

The following *inclusion criteria* were applied: i) patients aged 18 - 75 years, ii) planned fibrinolytic therapy, ASA (150 to 325 mg on the first day and 75 to 162 mg daily thereafter) and, when clinically appropriate, heparin [unfractionated heparin (UFH) and/or low molecular weight heparin (LMWH)], iii) onset of ischaemic discomfort or equivalent at rest occurring from 6 - 12 hours prior to randomisation, iv) symptoms of prolonged (>20 minutes) ischaemic discomfort at rest associated with ECG evidence of new ST segment elevation ≥0.10 mV (80 msec after the J point) in at least 2 contiguous limb leads or ≥0.20 mV in at least 2 contiguous precordial (chest) leads, or left bundle branch block (LBBB) not known to be old.

Regarding use of *concomitant therapy*, use of GP IIb/IIIa inhibitors (eg, abciximab, eptifibatide, and tirofiban) was permitted only after the initial coronary angiogram was performed. Use of open-label ***ADP antagonists*** (clopidogrel or ticlopidine) was prohibited except following coronary stenting. Patients who underwent coronary stenting at the time of their diagnostic angiogram were recommended to receive open-label clopidogrel after the diagnostic angiogram (loading dose of 300 mg followed by 75 mg daily). All patients receiving a fibrin-specific fibrinolytic (i.e., alteplase, RPA, or TNK) were to be treated with a body weight-based heparin regimen.

Patients were to be randomised within 12 hours of the onset of STEMI symptoms to receive either clopidogrel or placebo up to and including the day of angiography or Day 8 or hospital discharge, whichever came first. Patients were scheduled to undergo angiography 48 - 192 hours (2-8 days) after the start of study drug treatment. Patients were also to receive fibrinolytic therapy.
The figure below depicts the general study design



[a] With background ASA and initial fibrinolytic therapy.
[b] By the time of start of pre-discharge angiography, or Day 8 or hospital discharge, whichever came first, for patients who did not undergo angiography.

Figure (9.1) 1 - Study design

Regarding *endpoints*, the primary efficacy assessment was based on the composite endpoint of an occluded IRA (TIMI flow grade 0 or 1) on the pre-discharge angiogram, or death or recurrent MI by the time of start of angiography or Day 8 or hospital discharge, whichever came first.

Secondary efficacy assessments were based on the following endpoints analysed in a hierarchical order: an early electrocardiographic endpoint (degree of ST segment resolution at 180 minutes after first dose of study drug); a late angiographic endpoint (occluded IRA on pre-discharge angiogram);

and a clinical endpoint [composite outcome of death, recurrent MI, or recurrent myocardial ischemia (severe or leading to revascularisation) by the time of start of angiography or Day 8 or hospital discharge, whichever came first].

Other efficacy endpoints involved comparisons between treatment groups in the occurrence of the following clinical efficacy endpoints by the time of the start of coronary angiography (or Day 8 or hospital discharge, whichever came first) and by Day 30: death; cardiovascular death; recurrent MI; recurrent myocardial ischemia; severe recurrent myocardial ischemia; recurrent myocardial ischemia leading to revascularisation; composite endpoint of death or recurrent MI; composite endpoint of death, recurrent MI, or severe recurrent myocardial ischemia; composite endpoint of death, recurrent MI, or recurrent myocardial ischemia leading to revascularisation; severe congestive heart failure; and cardiogenic shock. The other efficacy assessments in angiographic endpoints (eg, epicardial flow) are presented in the clinical study report.

Coronary angiography was to be performed during the index hospitalisation between 48 and 192 hours (2-8 days) after the start of blinded study drug to determine late patency of the IRA. Angiography before 48 hours was permissible only if medically indicated [eg, cardiogenic shock or persistent haemodynamic instability; clear evidence of failed reperfusion (persistent severe chest pain and <50% resolution of ST segment elevation); or recurrent ischaemia documented by recurrent ischaemic chest pain and ECG changes]. Patients could have been transferred to a tertiary care hospital for the procedure if necessary. Angiographic data were sent to the TIMI Angiographic Core Laboratory for analysis. The TIMI Flow Grade (TFG) was defined as follows:

- Grade 0: No perfusion. No antegrade flow beyond the point of occlusion;
- Grade 1: Penetration without perfusion. Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence;
- Grade 2: Partial perfusion. Contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its flow into or clearance from comparable areas not perfused by the previously occluded vessel (eg, opposite coronary artery or the coronary bed proximal to the obstruction). This category is subdivided into:
  - Grade 2.0: TIMI 2 slow flow, dye markedly delayed in opacifying distal vasculature;
  - Grade 2.5: TIMI 2 fast flow, dye minimally delayed in opacifying distal vasculature.
- Grade 3: Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

Three 12-lead ECGs were to be performed: at baseline (pre-randomisation) and at 90 and 180 minutes after administration of the first dose of blinded study drug. These study ECGs were sent to the TIMI ECG Core Laboratory for analysis. Blood samples for analysis of CK-MB and/or troponin were collected 5 times over the 48 hours after initiation of fibrinolysis (ie, approximately every 8 hours). Additional samples for analysis of CK-MB and/or troponin were obtained at approximate 8-hour intervals for 24 hours post-revascularisation in patients who underwent revascularisation (ie, PCI or CABG), or at approximate 8-hour intervals for 24 hours following onset of symptoms for patients in whom recurrent ischaemia or reinfarction was suspected.

The following outcome events were recorded at scheduled times during the study:

Death

Death was defined as all-cause mortality, and was classified as either cardiovascular or non-cardiovascular. All deaths were assumed to be cardiovascular in nature unless a non-cardiovascular cause was clearly provided.

• *Cardiovascular*: cardiac deaths (eg, cardiogenic shock, arrhythmia/sudden death, cardiac rupture) and other cardiovascular deaths (stroke, pulmonary embolism, ruptured aortic aneurysm or dissection);

• *Non-cardiovascular*: all deaths due to a clearly documented non-cardiovascular cause, such as respiratory failure (excluding cardiogenic pulmonary oedema), haemorrhage (other than intracranial), infections/sepsis, neoplasm, and trauma (including suicide and homicide).

Recurrent myocardial infarction
Recurrent MI was defined using an adaptation of the standard ACC definition. In order to meet criteria as an endpoint in this trial, an MI must have been distinct from the qualifying event (ie, must represent reinfarction).
As per the ESC/ACC guidelines:
• ST depression in leads V1-V3 was considered equivalent to ST elevation if the recurrent MI was suspected to be true posterior in location;
• Abnormal Q waves were defined as Q waves in ≥2 contiguous leads that were ≥1 mm in depth and of any duration in leads V1-V3, and ≥30 msec in duration in leads I, II, aVL, aVF, and V4-V6;
• R wave ≥40 msec in lead V1 or ≥50 msec in lead V2 was considered equivalent to abnormal Q waves if MI was suspected to be true posterior in location.

Safety assessments included all reported bleeding-related events (classified into Major, Minor and Minimal), intracraneal bleeding (ICH), stroke, thrombocytopenia, AEs, serious adverse events (SAEs), and discontinuations due to AEs.

Regarding the efficacy analyses, the primary endpoint was analysed using a logistic regression analysis with terms included for treatment group, type of fibrinolytic (fibrin-specific, nonfibrin-specific, or none), type of anticoagulant used up to 2 hours post-randomisation (UFH, LMWH, both, or none), and infarct location (anterior, non-anterior). Odds ratios (OR) with 95% confidence intervals (CIs) were presented. Three sensitivity analyses were performed and consisted of excluding all covariates other than treatment group from the logistic regression model, including Investigator-assessed MIs in the composite endpoint rather than Clinical Events Committee (CEC)-adjudicated MIs, and excluding patients who did not receive initial fibrinolytic therapy. Hypothesis tests were performed using 2-sided tests at the 5% significance level, unless otherwise stated.

The secondary ECG endpoint was analysed using an ANCOVA model that included baseline ST-segment deviation as the covariate and factors for treatment, type of fibrinolytic used, type of anticoagulant first used, and index infarct location. The other 2 secondary endpoints and the other efficacy endpoints were analysed using a model similar to the one used for the primary efficacy analysis.

The rates of the primary efficacy endpoint were calculated for different subgroups, and ORs with 95% CIs were computed for the treatment effect (overall and by subgroup). Treatment-by-subgroup interactions were investigated by fitting a logistic regression model with factors for treatment group, subgroup, type of fibrinolytic, type of anticoagulant used up to 2 hours post-randomization, infarct location, and treatment-by subgroup interaction. To avoid confounding, for the subgroup analysis of primary anticoagulant used, the factor for anticoagulant used up to 2 hours post-randomisation was dropped from the model.

As regards *sample size*, the study was powered to detect a 5% absolute reduction (24% relative reduction, from 21% to 16%) in the rate of the combined endpoint. Due to a concern, at the beginning of enrolment, that the projected event rate might be lower than originally predicted, the sample size for the trial was increased from 2,200 to 3,000 patients. Then as the trial continued, the observed blinded event rate was still lower than planned and the sample size was increased from 3,000 to 3,500 patients. This increased sample size provided 95% power to detect a 4.6% absolute reduction (24% relative reduction, from 19% to 14.4%) in the rate of the primary endpoint between clopidogrel and placebo using a 2-sided significance level of 0.05.

Results

Participant flow and data sets analysed

The participant flow is shown in figure 10.1, under the safety section.

Table (10.5) 1 - Data sets analyzed

	Clopidogrel 300/75 mg[a]	Placebo[a]	Overall
Efficacy datasets (as randomized)[b]			
ITT population	1752	1739	3491
Efficacy-related PP population	1591	1586	3177
Safety datasets (as treated)[b]			
Treated population	1733	1719	3452
Safety-related PP population	1671	1669	3340

[a] With background ASA and initial fibrinolytic therapy.

[b] 4 patients randomized to the clopidogrel group and 8 patients randomized to the placebo group received incorrect study drug. For the efficacy analyses, these patients were included in the randomized group, and for the safety analyses, these patients were included in the group according to the study drug received.

Ref.: Figure (10.1) 1; Tables (10.2) 1 and (10.2) 2

Baseline demographics

Table 1 Summary of baseline demographic data (ITT population) – CLARITY, COMMIT, ASSENT-3 and GRACE

Parameter	EFC5133(CLARITY-TIMI 28)		EFC7018 (COMMIT/CCS-2)		ASSENT-3	GRACE[h]
	Clopidogrel 300/75 mg[a] (N = 1752)	Placebo[a] (N = 1739)	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)	Overall N = 6095	Overall N=6625
Sex - n (%)						
Female	352 (20.1%)	336 (19.3%)	6366 (27.7%)	6393 (27.9%)	1435 (23.5%)	1921 (29%)
Male	1400 (79.9%)	1403 (80.7%)	16595 (72.3%)	16498 (72.1%)	4660 (76.5%)	4704 (71%)
Age (years)[b]						
< 60	986 (56.3%)	987 (56.8%)	9624 (41.9%)	9463 (41.3%)	NA	NA
60-69	493 (28.1%)	526 (30.2%)	7361 (32.1%)	7470 (32.6%)	NA	NA
70 +	273 (15.6%)	226 (13.0%)	5976 (26.0%)	5958 (26.0%)	767[f] (12.6%)	NA
Mean age (SD)	57.7 (10.3)	57.2 (10.3)	61.3 (11.9)	61.4 (11.8)	61 (13)	64
Range	28-78	18-79	15-100	15-99	NA	54-74
Race[c]			NA	NA	NA	NA
Caucasian	1569 (89.6%)	1556 (89.5%)				
Asian/oriental	43 (2.5%)	30 (1.7%)				
Black	28 (1.6%)	35 (2.0%)				
Other	112 (6.4%)	118 (6.8%)				
SBP (mmHg)						NA
Mean (SD)[d]	133.9 (23.0)	135.1 (22.4)	128.2 (22.6)	128.2 (22.5)	133-134 (22)	
Range	60.0-210.0	65.0-215.0	60.0-250.0	60.0-250.0	NA	
HR (bpm)					NA	NA
Mean (SD)[e]	75.0 (17.6)	75.0 (17.0)	82.2 (17.2)	82.1 (17.2)		
Range	30-160	30-161	40-228	40-225		
Killip class	1747	1735				NA
I	1612 (92.3%)	1590 (91.6%)	17320 (75.4%)	17283 (75.5%)	5347 (87.7%)	
II	131 (7.5%)	143 (8.2%)	4601 (20.0%)	4504 (19.7%)	674 (11.1%)[g]	
III	3 (0.2%)	2 (0.1%)	1040 (4.5%)	1104 (4.8%)	NA	
IV	1 (0.1%)	0 (0.0%)	NA	NA	23 (0.4%)	
TIMI score for STEMI			NA	NA	NA	NA
n with data	1636	1621				
0	193 (11.8%)	213 (13.1%)				
1	384 (23.5%)	390 (24.1%)				
2	352 (21.5%)	350 (21.6%)				
3	261 (16.0%)	270 (16.7%)				
4	210 (12.8%)	198 (12.2%)				
5	120 (7.3%)	94 (5.8%)				
6	59 (3.6%)	48 (3.0%)				
7	39 (2.4%)	31 (1.9%)				
8	13 (0.8%)	15 (0.9%)				
>8	5 (0.3%)	12 (0.7%)				

* All treated patients received daily ASA (162 mg).

[a] With background ASA and initial fibrinolytic therapy.

[b] For EFC5133 (CLARITY-TIMI-28), age categories of < 65 years [clopidogrel 1219 (69.6%), placebo 1252 (72.0%)] and 65-75 years [clopidogrel 532 (30.4%), placebo 485 (27.9%)] are reported in the CSR. One clopidogrel patient was 78 years and 2 placebo patients were 78 and 79 years.

[c] Race was not collected in EFC7018 (COMMIT/CCS-2), the study was conducted in the People's Republic of China.

[d] In EFC5133 (CLARITY-TIMI 28), n with data was 1752 for clopidogrel, 1738 for placebo.

[e] In EFC5133 (CLARITY-TIMI 28), n with data was 1746 for clopidogrel, 1733 for placebo.

[f] Number (%) of patients >75 years.

[g] Data for pooled II/III classes.

[h] Data from (70).

HR = heart rate; NA = not available/not applicable; SBP = systolic blood pressure; SD = standard deviation.

The study populations in the placebo and treatment groups were comparable. The overall study populations in CLARITY and COMMIT were not too dissimilar, although in CLARITY there were more men, the patients were younger and the Killip class was lower, representing a generally lower risk patient population.

The placebo and clopidogrel-treated populations were also comparable in terms of cardiovascular medical history prior to the qualifying event.

Primary Efficacy analysis

The results for the primary endpoint are presented below.

Table 2 Primary efficacy analysis: occurrence of an occluded IRA on the predischarge angiogram, or death or recurrent MI by the time of start of predischarge angiography, or Day 8 or hospital discharge, whichever came first (ITT population) – CLARITY

Primary Efficacy Endpoint	Clopidogrel 300/75 mg[a] N = 1752	Placebo[a] N = 1739	p value	Odds Ratio	95% CI
Number (%) of patients reporting the endpoint	262 (15.0%)	377 (21.7%)	0.00000036	0.64	0.53,0.76

[a] With background ASA and initial fibrinolytic therapy.

Clopidogrel produced a statistically significant reduction of 36% in the odds of occurrence of the primary endpoint, compared with placebo, [262 (15.0%) with clopidogrel vs. 377 (21.7%) with placebo; p = 0.00000036]. As seen from the table below, the statistical significance is driven by the effect on occluded Infarct Related Arteries, which is a surrogate endpoint.

Table 3 Components of the primary endpoint

	Clopidogrel 300/75 mg[a]	Placebo[a]	Odds Ratio (95% CI)
Occluded IRA			
N	1640	1634	0.59
n (%) of patients reporting endpoint	192 (11.7%)	301 (18.4%)	(0.48, 0.72)
Death			
N	1752	1739	1.17
n (%) of patients reporting endpoint	45 (2.6%)	38 (2.2%)	(0.75, 1.82)
Recurrent MI			
N	1752	1739	0.70
n (%) of patients reporting endpoint	44 (2.5%)	62 (3.6%)	(0.47, 1.04)

[a] With background ASA and initial fibrinolytic therapy.

Clopidogrel treatment also resulted in significantly lower odds ratio of an occluded IRA on the pre-discharge angiogram compared with placebo treatment [192 (11.7%) vs 301 (18.4%), respectively], supporting the favourable primary efficacy endpoint results. The occurrence of recurrent MI was numerically lower in the clopidogrel arm but the number of deaths was numerically higher with clopidogrel.

Table 4 Secondary efficacy endpoint analyses (ITT population) – CLARITY

Secondary Efficacy Endpoint	Clopidogrel 300/75 mg[a]	Placebo[a]	p value	Mean Difference	95% CI
Adjusted mean ST segment resolution of an ECG at 180 minutes after the first dose of study drug	N = 1068 53.0	N = 1021 55.1	0.223[b]	-2.11	-5.50,1.28
Secondary Efficacy Endpoint	**Clopidogrel 300/75 mg**	**Placebo**	**p value**	**Odds Ratio**	**95% CI**
Number (%) of patients with occluded IRA on predischarge angiogram	N = 1640 192 (11.7%)	N = 1634 301 (18.4%)	<0.001[b]	0.59	0.48,0.72
Number (%) of patients with death, recurrent MI, or recurrent myocardial ischemia (severe or leading to revascularization) by the time of the start of predischarge angiography[c]	N = 1752 145 (8.3%)	N = 1739 162 (9.3%)	0.274[b]	0.88	0.69,1.11

[a] With background ASA and initial fibrinolytic therapy.

[b] p-value to be interpreted following the hierarchical procedure described in Section 9.7.1.9 of EFC5133 (CLARITY-TIMI 28) report.

[c] For patients who did not undergo angiography, Day 8 or hospital discharge, whichever came first, was used.

No statistically significant difference was observed between clopidogrel and placebo in the composite of "death, recurrent MI or recurrent myocardial ischaemia by the time of the start of predischarge angiography" or in ST-segment resolution, which is known to be an important prognostic parameter. Further to a request from CHMP, the Applicant clarified that 180 min ECGs were available for only 60% of the population; 684/1752 (39.0%) clopidogrel patients and 718/1739 (41.3%) placebo patients were not included in this analysis because their ECGs were either not assessed, not collected within the protocol allowed timeframe, or not interpretable because of poor quality. Moreover, the Applicant argues that clopidogrel produced a statistically significant benefit on the composite primary endpoint ($p < 0.001$) even in patients with no apparent ST segment resolution at 180 minutes – see table below

Table 5 - Primary efficacy analysis according to the ST segment resolution at 180 minutes - ITT population (only patients with ECG evaluable at 180 minutes) - (CLARITY-TIMI 28).

	Number of events/number of patients in the analysis (%)		Odds Ratio (95% CI)
	Clopidogrel 300/75 mg[a]	Placebo	
Patients with complete ST segment resolution at 180 minutes	37/572 (6.5%)	64/534 (12.0%)	0.50 (0.32,0.76) p=0.001
Patients with partial ST segment resolution resolution at 180 minutes	51/292(17.5%)	77/312 (24.7%)	0.67 (0.45,1.00) p=0.050
Patients with no ST segment resolution resolution at 180 minutes	37/203 (18.2%)	62/174 (35.6%)	0.38 (0.23,0.62) p<0.001

[a] With background ASA and initial fibrinolytic therapy.

Among all other efficacy endpoints evaluated, the reduction in recurrent MI (4.1% with clopidogrel vs. 5.9% with placebo; p = 0.018) and the composite endpoint of "death, recurrent MI, or myocardial ischaemia leading to revascularisation (11.8% vs 14.1%, p = 0.034) up to Day 30" were statistically significant in favour of clopidogrel.

Clopidogrel treatment (+ background ASA and initial fibrinolytic therapy) improved all angiographic measurements compared with placebo treatment (+ background ASA and initial fibrinolytic therapy).

A number of points were raised by the CHMP in respect of the CLARITY trial. The major point relates to the *low level of risk of the studied population*, possibly rendering this population unrepresentative of the general STEMI population. The Applicant argues that when comparing the

TIMI risk score, which measures the mortality risk for an individual STEMI patient, between CLARITY and other studies in STEMI patients such as the recently performed GUSTO V and In TIME-II studies the distribution of risk is almost identical among these 3 studies. Furthermore, the mortality in CLARITY at Day 30 was 4.6% in the clopidogrel group vs 4.5 % in the placebo group, which is not much lower than that recently reported in a meta-analysis of 11 clinical trials (conducted between January 1990 and December 2004) in STEMI patients treated with abciximab versus control, where 30-day mortality was 5.2% and 5.5%, respectively. Another meta-analysis of randomised STEMI trials evaluated LMWH vs UFH and demonstrated again that the 30-day mortality rate [5.6% in LMWH patients vs 6.0% in UFH patients] was within the same range as observed in CLARITY. Comparable 30-day mortality results were observed in GUSTO V, where the level of baseline risk was similar to the observed risk in CLARITY. Finally, when looking at general clinical practice across Europe, the Euro Heart Survey Programme of the European Society of Cardiology (ESC) reported on 7769 consecutive patients with established coronary artery disease between 2001 and 2002 in 130 hospitals across 31 countries. The results were stratified by treatment option and type of diagnosis. The STEMI cohort in this group showed a similar risk of 30-day mortality (5%) as seen in CLARITY.

The CHMP agrees that the additional data suggest that the risk of the population included is low but not too dissimilar to what has been recorded in other recent studies.

The second point raised related to the exclusion of certain patient populations from the CLARITY trial, notably the elderly and low body-weight patients, and whether these patients should receive clopidogrel in combination with full-dose fibrinolytic therapy and ASA, given their higher risk of bleeding. The Applicant states that 11% of patients in the COMMIT trial were 75 years of age or older and that in view of the much higher absolute risk of reaching the composite endpoint of "death, reinfarction or stroke" in patients >75 years (19.3%) than in younger patients (5.4% for <60 years), the similar proportional risk reduction with clopidogrel across different age groups translated into substantially larger absolute benefits in older patients (30 fewer events per 1000 treated vs 4 per 1000). Regarding body-weight, this exclusion criterion is linked to the labelling of a concomitant medication (heparin). Nonetheless, although no information on body mass index (BMI) was collected in COMMIT, other studies in China show that the mean BMI in Chinese patients is generally lower than that in the Western population, suggesting that COMMIT has provided evidence of benefit in lower body-weight patients.

The CHMP agrees with the Applicant's argumentation that there is no reason to exclude the elderly (>75) or low body-weight patients from the population likely to benefit from clopidogrel treatment.

EFC7018 (COMMIT/CCS- 2)

This was a Phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with suspected acute MI (AMI) conducted at 1,250 active sites in China. The objectives of this study were to determine whether the addition of clopidogrel to ASA for up to 4 weeks in hospital after suspected AMI can reduce mortality and the risk of major vascular events compared with ASA alone.

All patients received daily ASA (162 mg). Each patient was randomised in a 2x2 factorial design (see Figure 9.1) to receive 75 mg clopidogrel once daily or placebo, and metoprolol or placebo, up to 4 weeks in hospital or death or hospital discharge, whichever came first. Patients were to be enrolled within 24 hours of onset of the symptoms of suspected MI with documented electrocardiogram (ECG) abnormalities [ie, ST elevation/depression or bundle branch block (BBB)]. The clopidogrel 75 mg once daily regimen was selected because it was the effective dose that had demonstrated superior efficacy to ASA in atherosclerotic patients at risk. Although the CURE trial, conducted in NSTEMI ACS patients, demonstrated a sustained incremental benefit of clopidogrel 75 mg/day preceded by a 300 mg loading dose on top of standard therapy including ASA, at the time of publication of the CURE results, around 15,000 patients had been included in the COMMIT trial. Thus, the study continued without an initial loading dose of clopidogrel.

Regarding *inclusion criteria*, patients, both high and low risk, were eligible if, in the view of the responsible physician: i) there were signs or symptoms of suspected AMI [with definite ECG

abnormalities: ST elevation/depression or BBB], and ii) the onset of these symptoms was within 24 hours; and iii) there were no clear contraindications to any one of the trial treatments: ASA, clopidogrel or metoprolol (and there were no clear indications for either clopidogrel or metoprolol).

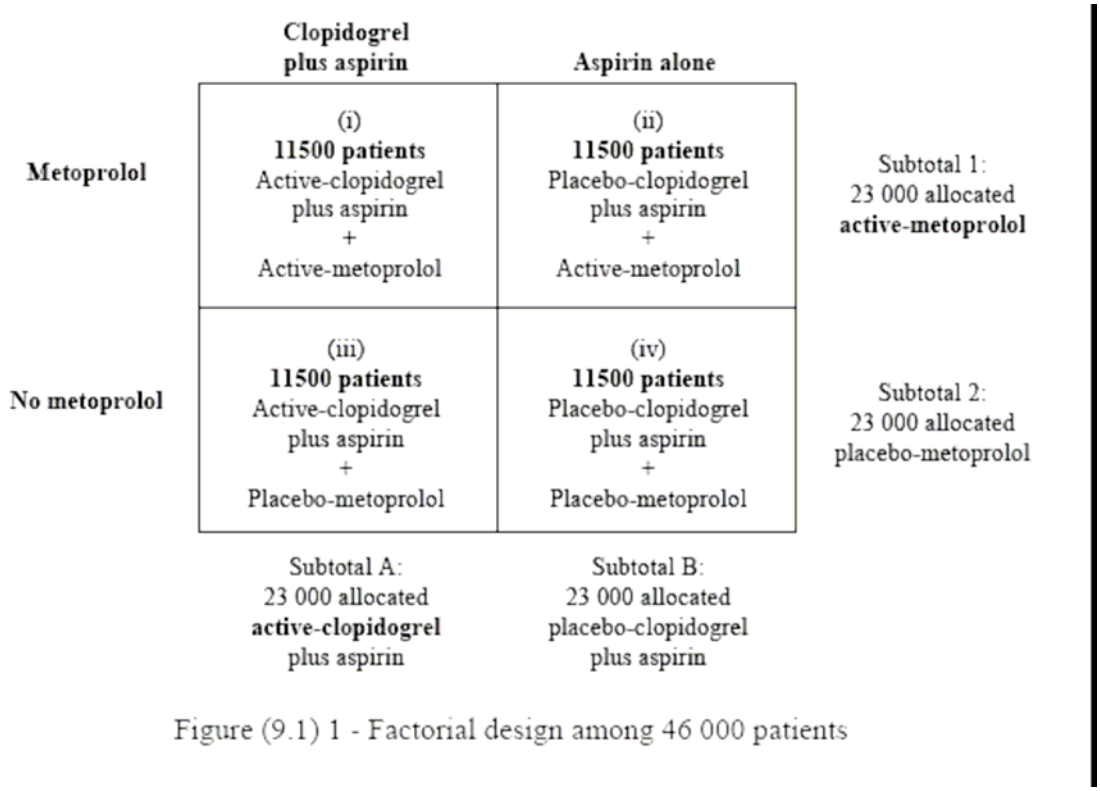


Figure (9.1) 1 - Factorial design among 46 000 patients

The *primary efficacy assessment* was based on two co-primary endpoints occurring by Day 28 or hospital discharge, whichever came first:

(i) the combined endpoint of "death, reinfarction or stroke"
(ii) death from any cause.

Other pre-specified efficacy endpoints included: i) any re-infarction (classified as fatal and nonfatal); ii) any stroke [classified as ischaemic or not; with and without computed tomography (CT)/magnetic resonance imaging (MRI) confirmation; with and without residual handicap]; iii) other major clinical events in hospital during the scheduled treatment period that were explicitly recorded (ie, cardiogenic shock, heart failure requiring persistent treatment, presumed cardiac rupture, ventricular fibrillation/other cardiac arrest).

As regards the *efficacy analyses*, although patients were randomised among 4 treatment groups, the analyses for clopidogrel involved 2-way comparisons of clopidogrel (+ ASA) versus placebo (+ ASA). Outcomes among all patients allocated active clopidogrel were compared with those among all patients allocated placebo clopidogrel, even though half patients of both groups received metoprolol and half did not. This design was used for efficiency in testing the two hypotheses of interest, one involving clopidogrel and the other involving metoprolol. The design is most powerful if the treatment effect is the same regardless of the presence of the other drug (ie, no interaction). A test for interaction was performed for the coprimary combined endpoint. All analyses were based on the allocated study treatment, irrespective of adherence, and thus included all randomised patients (ITT analysis).

The relative efficacy of clopidogrel versus placebo was assessed for each primary endpoint by comparing the survival curves for the 2 treatments using a log-rank test (primary test of treatment effect). These analyses were based on the time to the first event during the scheduled treatment period in hospital. The treatment effect (95% CI) was presented as both the OR (clopidogrel vs placebo) and the absolute benefit/1000 (placebo minus clopidogrel). For other endpoints where the timing of an event was not collected/used, the analyses were based on ordinary OR calculations. Events occurring from randomisation to death in hospital, first discharge from hospital, or Day 28 (ie, during the

scheduled trial treatment period), whichever came first, were included in the analyses. When the timing of an event was unknown for a patient, then it was assumed to have occurred as early as possible, given other known dates for the patient including date of randomisation.

No adjustment for multiple comparisons was made to the p-value calculation for the combined primary outcome. However, if the overall p-value was more extreme for death than for the composite outcome, then only the p-value for the composite endpoint would be used in assessing the statistical significance of the effects on mortality. Hypothesis tests were performed using 2-sided tests ($p < 0.05$ significance). The principal subsidiary comparisons were of the efficacy of clopidogrel on the coprimary outcomes during the following post-randomisation periods: Days 0, 1, 2-3, 4-7, and 8-28.

The following drug-demographics and drug-baseline characteristics *interaction analyses* were conducted to estimate the effect on the combined coprimary endpoint within selected subgroups defined by individual baseline characteristics and to test for possible heterogeneity/trend:

- Protocol-specified: Sex (male, female); age at entry (<60, 60-69, 70+); hours since symptom onset (<6, 6 to <13, 13 to 24); SBP (<120, 120-139, 140-159, 160+ mm Hg); HR (<70, 70-89, 90-109, 110+ bpm); fibrinolytic agent given before randomisation (yes, no); prognostic index (good, average, poor); metoprolol allocation (yes, no).
- Non-prespecified: Killip class (I, II/III); previous MI (yes, no); history of hypertension (yes, no); baseline ECG change [BBB, ST elevation, ST depression]; infarct location (anterior, other); prior ASA (yes, no); prior beta-blocker (yes, no).

The *sample size* determination was based on the rates of death, non-fatal MI, and non-fatal stroke observed in the first Chinese Cardiac Study (CCS-1). It was assumed for COMMIT/CCS-2 that with 20,000 to 40,000 patients there would be a 98% chance of achieving a conventionally significant result for the combined efficacy endpoint. To reduce the risk of a false negative mortality result, an upper limit of 40,000 patients for the study was initially recommended by the co-chairman of the Steering Committee and the Principal Investigator. During the course of the study, however, tracking of the blinded event rates revealed a lower in-hospital mortality rate than was originally assumed (8% as opposed to 10%). This resulted in a revised recommendation to recruit as many as 48,000 patients, given that in order to have at least 95% statistical power to detect a 10% relative risk reduction with a two sided p-value <0.05, it was considered necessary to recruit at least 45 000 patients.

Results

Participant flow and data sets analysed

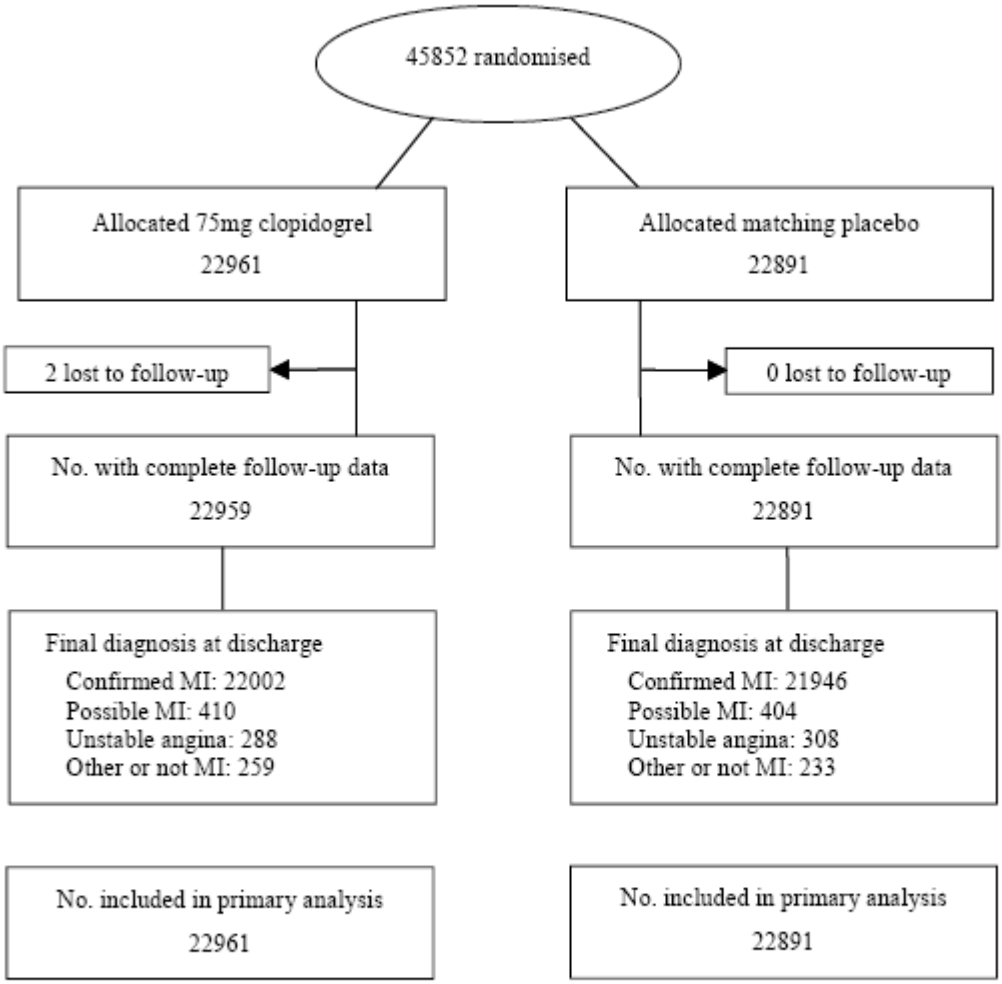


Figure (10.1) 1 - Summary of patient accountability during the treatment and follow-up period

Both treatment groups were balanced with respect to demographic and other baseline data (see Table 1), including relevant prior disease history, qualifying events and medication use prior to randomisation.

Primary Efficacy analysis

The results for the primary endpoint are presented below.

Table 6 Summary of frequency of co-primary endpoints (ITT population) – COMMIT

Event	No. (%) With Event		Odds Ratio (95% CI)	Absolute Benefit /1000 (SE)	Two-sided p-value[a]
	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)			
Composite endpoint: Death, re-MI, or Stroke[b]	2121 (9.2%)	2310 (10.1%)	0.91 (0.86, 0.97)	8.5 (2.8)	0.002
Death	1726 (7.5%)	1845 (8.1%)	0.93 (0.87, 0.99)	5.4 (2.5)	0.029
Nonfatal re-MI[c]	270 (1.2%)	330 (1.4%)	0.81 (0.69, 0.95)	2.7 (1.1)	0.011
Nonfatal stroke[c]	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.7 (0.7)	0.333

* All treated patients received daily ASA (162 mg).

[a] Based on log-rank test.

[b] The difference between the composite endpoint and the sum of death + nonfatal re-MI + nonfatal stroke indicates that 9 patients (2 clopidogrel and 7 placebo) suffered both a nonfatal stroke and a nonfatal re-MI.

[c] Nonfatal re-MI and nonfatal stroke exclude patients who died (of any cause).
SE = standard error; re-MI = reinfarction.

Clopidogrel in combination with ASA significantly reduced by 9% the relative risk of the combination of "death, re-infarction or stroke" [2,121 (9.2%) in the clopidogrel group vs 2,310 (10.1%) in the placebo group; p = 0.002] and by 7% the relative risk of death from any cause [1,726 (7.5%) vs 1,845 (8.1%); p = 0.03]. In absolute terms, clopidogrel + ASA was associated with 9 fewer patients with death, reinfarction or stroke and with 5 fewer patients dying per 1000 allocated treatment.

This clinical benefit of clopidogrel in combination with ASA on both co-primary endpoints appeared to emerge rapidly from Day 0 (an average of 12 hours), despite the lack of a loading dose. Furthermore, the benefit was independent of the patients' characteristics at baseline and prior and concomitant treatments the patients received.

The results for the other two subcomponents of the primary endpoint are shown below.

Table (11.1.2) 1 - Summary of reinfarction and stroke

Endpoint	No. (%) With Event		Odds Ratio (95% CI)	Absolute Benefit[a] /1000 (SE)	Two-sided p-value[b]
	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)			
Reinfarction:					
Died[c]	209 (0.9%)	223 (1.0%)	0.93 (0.77, 1.13)	0.6 (0.9)	0.46
Survived	270 (1.2%)	330 (1.4%)	0.81 (0.69, 0.95)	2.7 (1.1)	0.011
Any reinfarction	479 (2.1%)	553 (2.4%)	0.86 (0.76, 0.97)	3.3 (1.4)	0.016
Stroke:					
Died[c]	90 (0.4%)	108 (0.5%)	0.83 (0.63, 1.10)	0.8 (0.6)	0.19
Survived	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.7 (0.7)	0.33
With residual handicap	79 (0.3%)	95 (0.4%)	0.83 (0.61, 1.11)	0.7 (0.6)	0.21
Without residual handicap	48 (0.2%)	47 (0.2%)	1.02 (0.68, 1.52)	0.0 (0.5)	0.94
Ischemic/unknown stroke					
CT/MRI confirmed	114 (0.5%)	110 (0.5%)	1.03 (0.79, 1.34)	-0.2 (0.7)	0.82
Clinical/other diagnosis	50 (0.2%)	84 (0.4%)	0.60 (0.43, 0.84)	1.5 (0.5)	0.003
Any ischemic	164 (0.7%)	194 (0.8%)	0.84 (0.68, 1.03)	1.3 (0.8)	0.10
Hemorrhagic stroke					
CT/MRI confirmed	25 (0.1%)	27 (0.1%)	0.92 (0.53, 1.59)	0.1 (0.3)	0.77
Clinical/other diagnosis	30 (0.1%)	29 (0.1%)	1.03 (0.62, 1.72)	0.0 (0.4)	0.91
Any hemorrhagic	55 (0.2%)	56 (0.2%)	0.98 (0.67, 1.42)	0.1 (0.4)	0.90
Any stroke	217 (0.9%)	250 (1.1%)	0.86 (0.72, 1.03)	1.5 (0.9)	0.11

* All treated patients received daily ASA (162 mg).

[a] Placebo minus clopidogrel.

[b] Based on log-rank test.

[c] Had the event and died in hospital (not necessarily from that event) before Day 28.

Subgroup Analyses

The results of the composite endpoint of "death, reinfarction or stroke" according to the different protocol-specified subgroups are presented below in Figure (1.) 2. Some of these results were queried by CHMP, notably the finding that the positive effect of clopidogrel on the primary endpoint loses its significance when the patient group is restricted to those patients who received metoprolol. The CHMP believes that this raises important questions on the external validity of this Chinese study, given that *beta-blockers* are currently standard treatment in the EU. The Applicant argues that the general principle in assessing the statistical relevance of any subgroup analyses findings is not whether the effect in a particular subgroup is statistically significant, but rather whether it differs significantly from the overall effects observed for the whole study population. Given the lack of statistical heterogeneity of the risk reduction (RR) in different circumstances (p=0.1 for metoprolol), it would be statistically inappropriate to consider results in isolation within any particular subgroup. In particular, the formal statistical test indicated that the RR with clopidogrel among those randomly allocated metoprolol in this 2x2 factorial design did not differ significantly from the RR with clopidogrel among those not allocated metoprolol. Hence, the Applicant concludes that the benefit of clopidogrel is largely independent of whether or not beta-blockers are part of the background therapy.

Another finding is that the relative RR with clopidogrel appeared to be greater when treatment was initiated early (<12h) after symptom onset. A similar trend was noted for mortality, but not for reinfarction. However, given the number of subgroups examined and the lack of significance after correction for multiple comparisons, this apparent trend should be interpreted cautiously. No such time-dependent effect on reinfarction or mortality was found in the large ISIS-2 trial of ASA in acute MI, nor is it consistent with the beneficial effect of long-term antiplatelet therapy following MI. Furthermore, it is recognised in international guidelines for STEMI, and as stated in a recent statement from the ESC, that reperfusion therapy has a greater benefit when started soon after the start of symptoms, and if possible within the first 12 hours. Thus, not surprisingly, the benefit of clopidogrel was greater for patients who are treated early, but no conclusion can be drawn about whether this benefit would be lost in patients with an onset of symptoms >13 hours prior to the initiation of treatment. In order to emphasise that the benefit is greater when clopidogrel is started early from the symptoms, the posology section of the SPC will specify to start as early as possible after symptoms.

Regarding the *use of thrombolytics*, the Applicant maintains that the results were consistent whether or not they were used [8.8% vs 9.9% in the clopidogrel and placebo groups, respectively, in patients who received fibrinolytic agents [Relative risk reduction (RRR)=11%], and 9.7% vs 10.3% in the clopidogrel and placebo groups, respectively, in patients who did not receive fibrinolytic agents [RRR=6%]; p value for interaction =0.4].

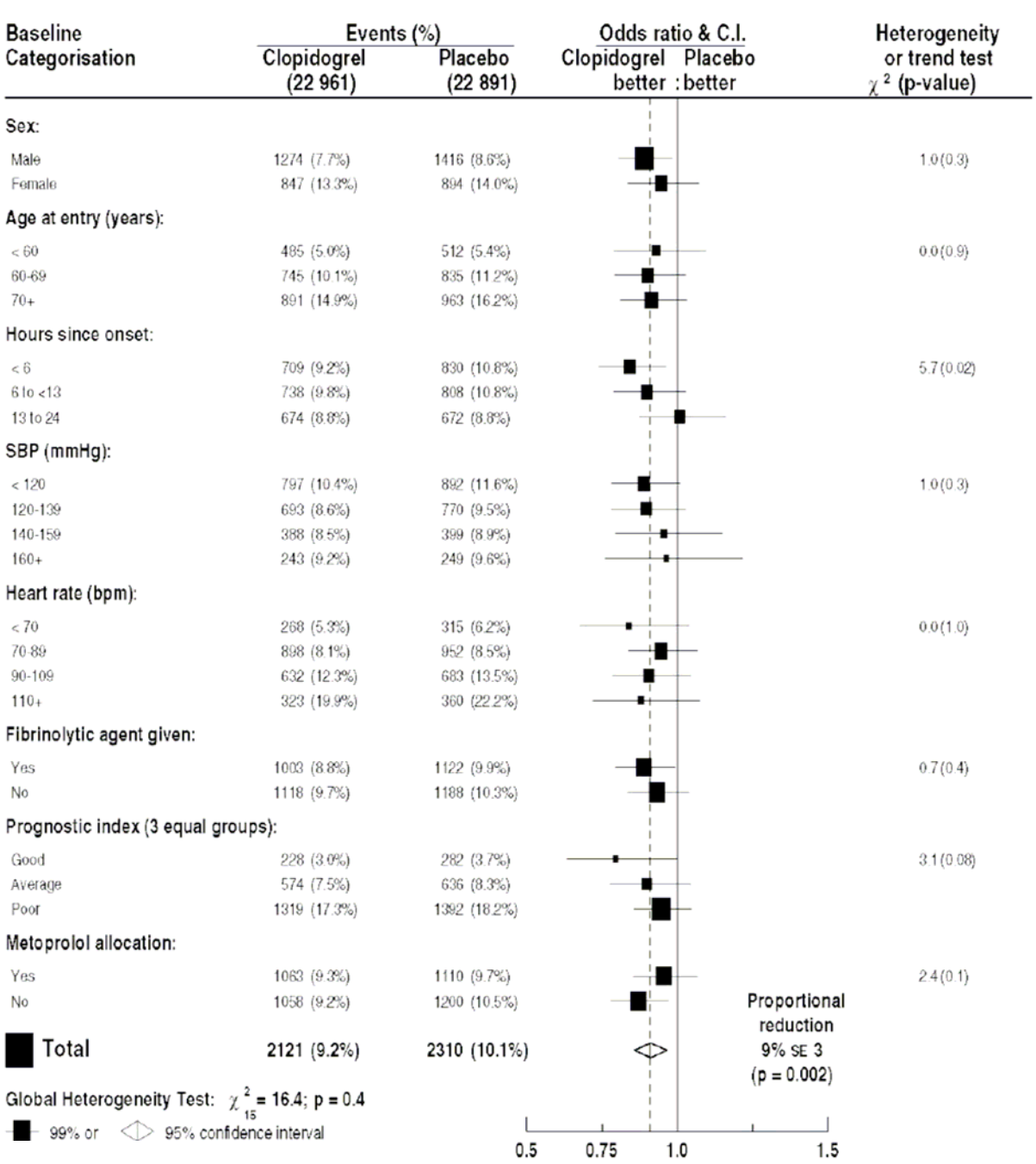


Figure (1.) 2 - Proportionnal effects of adding clopidogrel to aspirin on the combined coprimary endpoint (death,reinfarction, stroke) by the protocol-specified subgroups of baseline characteristics - EFC7018 (COMMIT/CCS-2)

Relevance of the Chinese clinical setting to Western clinical practice

This was one of the main points challenged by the CHMP. In particular, the CHMP queried the use of baseline comedication (e.g. beta-blockers) and access to reperfusion therapy (thrombolytics and PTCA), and hospital facilities for the Chinese population. The Applicant argued that baseline characteristics of patients included in COMMIT did not differ substantially from data reported for Western patients, in international registries (GRACE registry) or in clinical studies (ASSENT-3), with the majority of patients being male and with a mean age of 61-64 years [Table $$]. Moreover, international registries, such as GRACE or CRUSADE in NSTEMI patients, have demonstrated that medical practice variability among major geographic regions (e.g. China and Europe) are smaller than the variability among hospitals within a single geographical region. Regarding *concomitant*

medications recommended in STEMI patients, their use was similar between the 2 treatment groups in both COMMIT and CLARITY, and patients received therapy usually recommended in patients with STEMI for whom pharmacological reperfusion is planned. In both studies, the anticoagulant was mainly heparin and the use of ACE inhibitors, diuretics, and calcium antagonists was similar and quite similar to the reported use in the GRACE registry. Overall, according to the Applicant, the concomitant drugs used in COMMIT reflect the current guidelines and were identical to those used in Western studies such as ASSENT-3 or in a Western registry (GRACE).

The Applicant argues that both COMMIT and CLARITY are complementary, and although CLARITY was not powered to look at clinical endpoints, additional analyses of the clinical endpoints at Day 30 with regard to PCI, lytics and lipid lowering agents were performed (see table 1.4 below). In order to facilitate the comparison with the COMMIT study, the composite endpoint of "cardiovascular death, recurrent MI or stroke" was analysed, as well as the composite endpoint of "death, recurrent MI or stroke" [identical to the one studied in the COMMIT study], by use of PCI, type of thrombolytic used (fibrin specific or non-fibrin specific) and the use or not of statin.

Table (1.) 4 - Summary of clinical endpoints [death, recurrent MI , stroke (excluding TIA)] at Day 30 - EFC5133 (CLARITY-TIMI 28)

Endpoint	Clopidogrel[a] (N=1748)	Placebo[a] (N=1733)	p-value	OR	95% CI	Interaction p-value
CV death, recurrent MI, stroke (excl. TIA)	156 (8.9%)	185 (10.7%)	0.079	0.82	(0.65, 1.02)	NA
PCI						
Yes	69/934 (7.4%)	108/929 (11.6%)	0.003	0.62	(0.45, 0.85)	0.012
No	87/814 (10.7%)	77/804 (9.6%)	0.551	1.10	(0.80,1.53)	
Thrombolytic Use:						
Fibrin	111/1206 (9.2%)	132/1191 (11.1%)	0.135	0.82	(0.63, 1.07)	0.974
Non-fibrin	45/542 (8.3%)	53/542 (9.8%)	0.359	0.82	(0.54, 1.25)	
Statin Use:						
Yes	60/1106 (5.4%)	73/1072 (6.8%)	0.174	0.78	(0.55, 1.11)	0.685
No	96/642 (15.0%)	112/661 (16.9%)	0.327	0.86	(0.64, 1.16)	
Death, recurrent MI, stroke (excl. TIA)	159 (9.1%)	185 (10.7%)	0.115	0.84	(0.67, 1.04)	NA
PCI						
Yes	69/934 (7.4%)	108/929 (11.6%)	0.003	0.62	(0.45, 0.85)	0.007
No	90/814 (11.1%)	77/804 (9.6%)	0.406	1.15	(0.83, 1.58)	
Thrombolytic Use:						
Fibrin	111/1206 (9.2%)	132/1191 (11.1%)	0.135	0.82	(0.62, 1.07)	0.752
Non-fibrin	48/542 (8.9%)	53/542 (9.8%)	0.553	0.88	(0.59, 1.33)	
Statin Use:						
Yes	63/1106 (5.7%)	73/1072 (6.8%)	0.278	0.82	(0.58, 1.17)	0.851
No	96/642 (15.0%)	112/661 (16.9%)	0.327	0.86	(0.64, 1.16)	

a Patients who did not receive fibrinolytics are excluded from these analyses

CV=cardiovascular

These data show a consistent trend towards a clinical benefit for clopidogrel versus placebo independent of the type of fibrinolytic used and whether or not a statin was used. The CHMP did note

that this post-hoc analysis shows a positive benefit of clopidogrel in those patients who underwent subsequent PCI, although post-hoc analysis findings should always be interpreted with caution.

There was no systematic collection of information on the *use of PCI* or lipid lowering agents in COMMIT. According to an epidemiological study conducted in China, 48.9% of STEMI patients received PCI as reperfusion therapy, which does not differ from what is observed in Western countries. A study recently published, evaluating the impact on medical practice of the first guidelines for the management of AMI patients issued in China in 2001, showed that PCI was undertaken in 35.8% of patients compared to 21.7% before publication of the guidelines. Over a period of the 3-years from 1999 to 2001, the Chinese registry showed that stents were implanted in 81% of the PCI procedures performed, which is similar to the rate observed in Western countries. Data from the literature also show that the use of lipid lowering agents in China is 72.5%-93.0%, is not too different to that recorded in CLARITY (63% of patients received statins.)

Although, COMMIT data did not document the specific characteristics of the *population living close to the hospital sites*, the mean duration of time from symptoms to randomisation or initiation of treatment are not different from that observed in Western countries. Of note as shown by the European task force, 19% of the European countries contributing into this evaluation of practice do not have access to primary PCI and about 39 % of patients do not even receive pharmacological or mechanical reperfusion therapy.

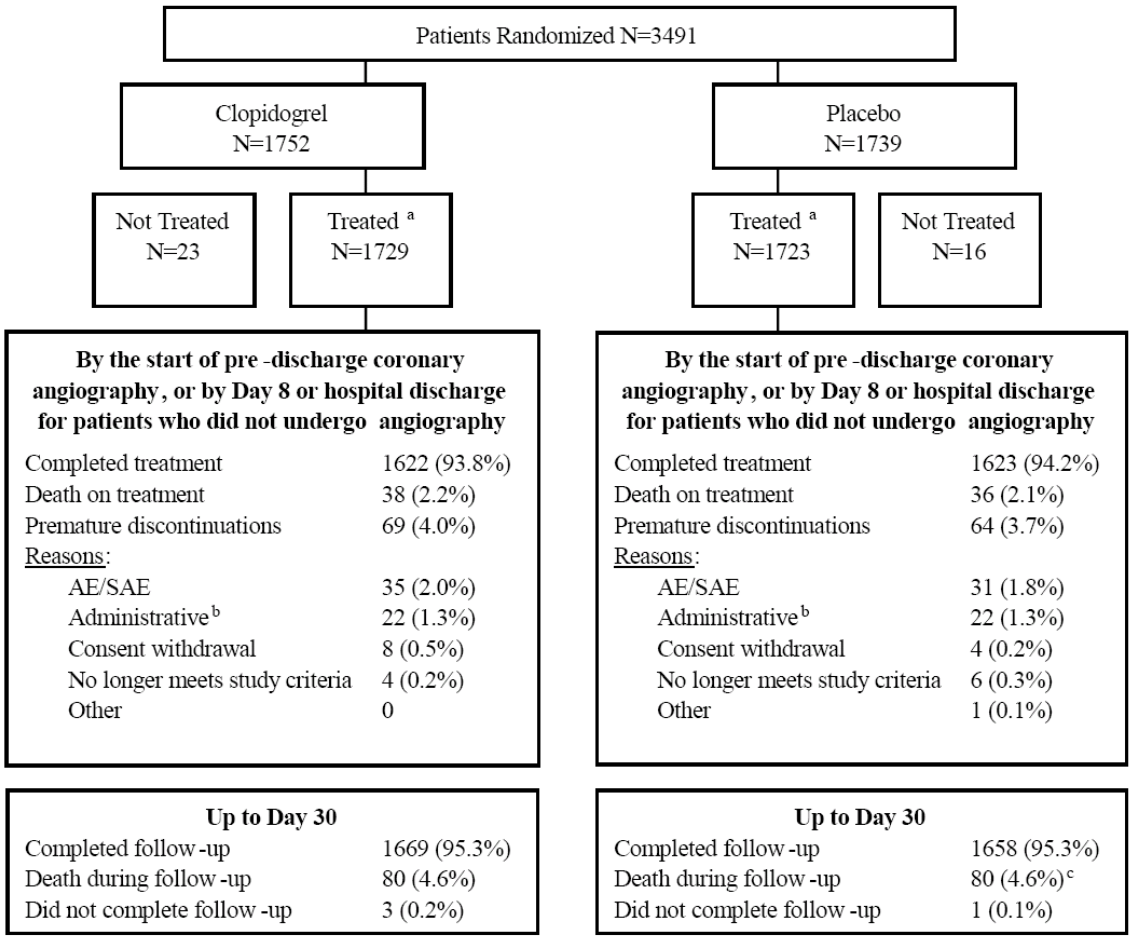
Thus, the Applicant maintains that the population included in COMMIT is a not a selected population and it closely resembles what is observed in Western countries.

The CHMP acknowledges there are disparities in the treatment of STEMI patients across the EU but does not entirely agree with the Applicant. Indeed, the low use of background beta-blockers in the COMMIT population (currently standard treatment in the EU STEMI population) and the much higher mortality rate observed in COMMIT (8.1 % in the placebo group) compared to the rate observed in CLARITY (<5% at Day 30) suggest significant differences in background clinical care justifying great caution in the extrapolation of the COMMIT results to the European STEMI population. For this reason, this trial has been considered as “supportive” in this application to extend the ACS indication.

Clinical Safety [CLARITY & COMMIT]

A total of 49,343 patients were randomised in the 2 studies: 24,713 patients were randomly assigned to receive clopidogrel (of these, 1752 were allocated to receive a 300 mg loading dose) and 24,630 patients were randomly assigned to receive placebo.
Patient disposition in the CLARITY trial is summarised in Figure 1

Figure 1 Summary of patient disposition (CLARITY)



[a] With background ASA and initial fibrinolytic therapy; 4 patients randomized to the clopidogrel group and 8 patients randomized to the placebo group received incorrect study drug. For the efficacy analyses, these patients were included in the randomized group.

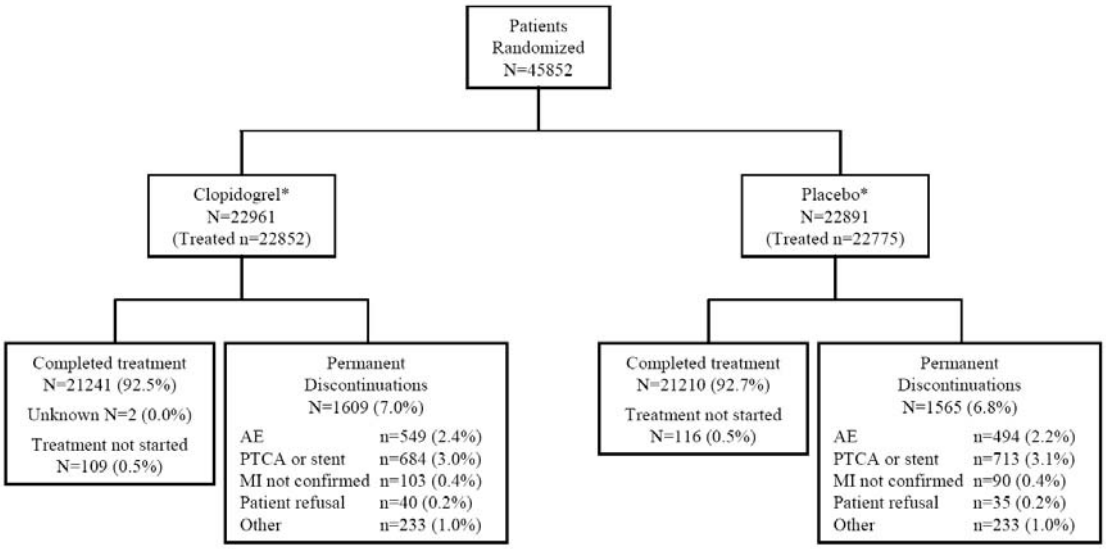
[b] Patients who prematurely discontinued study drug were classified as discontinuing for "administrative" reasons when drug was stopped for reasons other than adverse events or withdrawal of consent. For example, study staff forgot to give the medication or the patient was transferred to another hospital for the angiogram, and the study drug was not given after transfer.

[c] Includes one death reported >30 days after randomization (Day 37).

A total of 3,491 patients were randomly assigned to receive either clopidogrel (1,752) or placebo (1,739). Of these, 3,452 (98.9%) patients received at least one dose of study drug. Most treated patients (94.0%) completed the study drug treatments. Overall, 3.9% of patients prematurely discontinued treatment, with no difference between the 2 treatment groups. The main reason for study drug discontinuation was AEs/SAEs in both treatment groups (2.0% of patients with clopidogrel and 1.8% of patients with placebo).

Patient disposition in the COMMIT trial is summarised in Figure 2

Figure 2 Summary of patient disposition (COMMIT)



*All treated patients received daily ASA (162 mg).

A total of 45,852 patients were randomly assigned to receive either clopidogrel (22,961) or placebo (22,891). Of these, 45,627 (99.5%) received at least one dose of study drug. The vast majority of the randomised patients (92.6%) completed the study drug treatments. Overall, 6.9% of patients prematurely discontinued the study drug treatment, with no difference between the 2 treatment groups. The main reasons for study drug discontinuation were angioplasty (3.0% with clopidogrel and 3.1% with placebo) and AEs (2.4% with clopidogrel and 2.2% with placebo) in both treatment groups.

Duration of exposure

In CLARITY, the mean duration of treatment was similar for both treatment groups (clopidogrel 4.5 days and placebo 4.4 days).

In COMMIT, the vast majority of the patients [92.5% (21,241 patients) in the clopidogrel group and 92.7% (21 210 patients) in the placebo group] completed the study drug treatment as planned. No exposure information is available for approximately 7% of patients who prematurely discontinued treatment. Thus, extent of exposure was estimated by the summary of duration of hospitalisation. For patients discharged or still hospitalised at 28 days (21,235 in the clopidogrel group and 21,046 in the placebo group), the estimated mean duration was 14.9 days in each group.

The CHMP noted that the mean treatment duration was only 15 days and the maximum treatment duration was 1 month. It is regrettable that there are no data for a longer period of time, making it difficult to determine the optimal treatment duration. The Applicant discussed this point, emphasising that the long-term benefit of clopidogrel alone in MI patients has been already assessed in the CAPRIE study. Consequently, it has been decided to add the following sentence under the section 4.2 of the SPC:

"*The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied*".

Bleeding

Table 7 Incidence of adjudicated TIMI major bleeding from the time of first dose of study drug to the end of the calendar day following pre-discharge angiography, or Day 8 or hospital discharge, whichever came first (treated population) – CLARITY

Primary Safety endpoint	Clopidogrel 300/75 mg[a] N = 1733	Placebo[a] N = 1719	p value	OR	95% CI
Number (%) of patients reporting TIMI major bleeding	23 (1.3%)	19 (1.1%)	0.642	1.20	0.62,2.35

[a] With background ASA and initial fibrinolytic therapy.

The incidence of the primary safety endpoint, adjudicated major bleeding (MB), observed during the treatment period in *CLARITY* was low and similar in both treatment groups. Fatal bleeding was experienced by 13/1733 (0.8%) and 10/1719 (0.6%) patients in the clopidogrel and placebo groups, respectively.

The incidence of adjudicated TIMI major bleeding from the time of first dose of study drug up to the end of follow-up was low and similar for the clopidogrel and placebo groups (1.9% and 1.7%, respectively).

Table 8 Number (%) of patients reporting any bleeding (including adjudicated and non-adjudicated bleeding) from the time of first dose of study drug to the end of the calendar day following pre-discharge angiography, or Day 8 or hospital discharge, whichever came first (treated population)- CLARITY

Safety endpoint	Clopidogrel 300/75 mg[a] N = 1733	Placebo[a] N = 1719	p value	OR	95% CI
Number (%) of patients reporting any bleeding	302 (17.4%)	221 (12.9%)	<0.001	1.43	1.19,1.73
Adjudicated bleeding	67 (3.9%)	44 (2.6%)	-	-	-
Major	23 (1.3%)	19 (1.1%)	-	-	-
ICH	8 (0.5%)	12 (0.7%)	0.380	0.66	0.23,1.76
Minor	17 (1.0%)	9 (0.5%)	-	-	-
Minimal	28 (1.6%)	16 (0.9%)	-	-	-
None	1 (0.1%)	1 (0.1%)	-	-	-
Non-adjudicated bleeding	246 (14.2%)	185 (10.8%)	-	-	-

[a] with background ASA and initial fibrinolytic therapy.
ICH=intracranial hemorrhage.

However, the number of patients with any bleeding was clearly increased in the clopidogrel group (17.4% vs 12.9% p<0.001) and has been reflected in the SPC.

The overall rate of non-cerebral MB (transfused or fatal) or cerebral bleeding (main safety endpoint) in *COMMIT* was low and similar in both treatment groups. In particular, no excess in cerebral bleeding, non-cerebral MB, fatal, or non-fatal MB was observed with clopidogrel + ASA during the scheduled treatment period. Clopidogrel + ASA was associated with a small, but statistically significant excess of non-MB and this has been reflected in the SPC.

Table 9 Number (%) of patients with bleeding events (ITT population) – COMMIT

Type of Bleeding	No. % With Event		Odds Ratio (95% CI)	Absolute Benefit[a] /1000 (SE)	Two-sided p-value[b]
	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)			
Major noncerebral[c] or cerebral bleeding	134 (0.6%)	125 (0.5%)	1.07 (0.84, 1.36)	-0.4 (0.7)	0.59
Major noncerebral[c]	82 (0.4%)	73 (0.3%)	1.12 (0.82, 1.54)	-0.4 (0.5)	0.48
Fatal	36 (0.2%)	37 (0.2%)	0.97 (0.61, 1.54)	0.0 (0.4)	0.90
Hemorrhagic stroke	55 (0.2%)	56 (0.2%)	0.98 (0.67, 1.42)	0.1 (0.5)	0.91
Fatal	39 (0.2%)	41 (0.2%)	0.95 (0.61, 1.47)	0.1 (0.4)	0.81
Other noncerebral bleeding (non-major)	831 (3.6%)	721 (3.1%)	1.15 (1.04, 1.28)	-4.7 (1.7)	0.0054
Any noncerebral bleeding	896 (3.9%)	777 (3.4%)	1.16 (1.05, 1.27)	-5.1 (1.8)	0.0037

* All treated patients received daily ASA (162 mg).

[a] Placebo minus clopidogrel

[b] Chi-square test.

[c] Major noncerebral bleeds are those noncerebral bleeds thought to have caused death or that required transfusion.

NOTE: 3 patients in the clopidogrel group and 4 in the placebo group had suffered both cerebral and major noncerebral bleeding during scheduled treatment in the hospital.

Deaths and Serious Adverse Events (SAEs)

- CLARITY

The total number of deaths recorded during the study was 80 (4.6% of 1752 patients) with clopidogrel and 80 (4.6% of 1739 patients) with placebo. The overall incidence of patients with treatment-emergent SAEs with an outcome of death up to the end of follow-up was similar in both treatment groups. Cardiac failure was the most commonly reported treatment-emergent SAE associated with death for both treatment groups. Bleeding events reported as the primary cause of death occurred in 13 (0.8%) clopidogrel patients and 10 (0.6%) placebo patients.

The incidence of SAEs did not differ between the treatment groups during the treatment period. In both groups, the most frequent treatment-emergent SAE was *angina pectoris*.

- COMMIT

The overall rate of deaths recorded during the study is summarised below

Table (2.7.4.2.1.3) 2 - Number (%) of deaths and summary of the cause of death (ITT population) - EFC7018 (COMMIT/CCS-2)

Event	No. (%) With Event	
	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)
All death[a]	1726 (7.5%)	1845 (8.1%)
Arrhythmia	432 (1.9%)	454 (2.0%)
Asystole	642 (2.8%)	697 (3.0%)
Cardiac rupture	188 (0.8%)	210 (0.9%)
Cardiogenic shock	503 (2.2%)	562 (2.5%)
Reinfarction	113 (0.5%)	101 (0.4%)
Stroke	72 (0.3%)	87 (0.4%)
Pulmonary embolus	26 (0.1%)	18 (0.1%)
Severe bleeding	19 (0.1%)	14 (0.1%)
Other cardiac	21 (0.1%)	18 (0.1%)
Other noncardiac	26 (0.1%)	53 (0.2%)

* All treated patients received daily ASA (162 mg).

[a] Some patients had more than one reported cause of death.

No SAEs were reported during the study. As per protocol definition, only SAEs that were both unexpected (unexpected AEs were defined as those that would not be expected among patients given antiplatelet therapy or a beta-blocker for suspected MI) and believed with a reasonable probability to be due to study treatment were to be reported.

Other Adverse Events (AEs)

- CLARITY

There was no difference between groups in the rate of patients experiencing treatment emergent AEs presented by System Organ Class. Treatment-emergent AEs with an incidence >2.5% were mainly related to the underlying cardiovascular conditions. Except for MI, which was more frequent with placebo, the rates of AEs by Preferred Term were similar between the 2 treatment groups.

- COMMIT

There was no difference in the overall incidence of "volunteered" AEs between the treatment groups during the scheduled treatment period. The incidence of AEs leading to permanent discontinuation of study drug was also similar in each treatment group.

Table 10 Number of patients with recorded ("volunteered") AE (ITT population) – COMMIT

Event Class	No. % With Event		Odds Ratio (95% CI)	Absolute Benefit[a] /1000 (SE)	Two-sided p-value[b]
	Clopidogrel 75 mg* (N = 22961)	Placebo* (N = 22891)			
Any	542 (2.4%)	509 (2.2%)	1.06 (0.94, 1.20)	-1.4 (1.4)	0.33
AV Block	372 (1.6%)	355 (1.6%)	1.05 (0.90, 1.21)	-0.7 (1.2)	0.55
Other Vascular	90 (0.4%)	83 (0.4%)	1.08 (0.80, 1.46)	-0.3 (0.6)	0.61
Hematological	3 (0.0%)	5 (0.0%)	0.60 (0.15, 2.42)	0.1 (0.1)	0.48
Respiratory	30 (0.1%)	28 (0.1%)	1.07 (0.64, 1.79)	-0.1 (0.3)	0.80
Gastrointestinal	2 (0.0%)	1 (0.0%)	1.94 (0.20, 18.67)	0.0 (0.1)	0.57
Allergic	13 (0.1%)	11 (0.0%)	1.18 (0.53, 2.62)	-0.1 (0.2)	0.69
Other	32 (0.1%)	26 (0.1%)	1.23 (0.73, 2.05)	-0.3 (0.3)	0.44

NOTE: Patients could be counted in more than one category, but only once in the total.

* All treated patients received daily ASA (162 mg).

[a] Placebo minus clopidogrel.

[b] Chi-square test.

AV = atrioventricular

Safety in special populations

In CLARITY, there was no apparent increase in the risk of adjudicated TIMI major bleeding with clopidogrel in any of the prespecified demographic or other subgroups analysed [infarct location, age, gender, weight, race, and location of patient (ambulance/mobile care unit versus hospital) at the time of randomisation.

In COMMIT, the relative rate of major non-cerebral or cerebral bleeding with clopidogrel compared with placebo was independent of age and gender. In particular, no excess of such bleeding was observed with clopidogrel among the 11,934 patients aged 70 years or older.

Drug interactions

In CLARITY, there was no apparent increase in the risk of adjudicated TIMI MB with clopidogrel in any of the subgroups prespecified according to the type of fibrinolytic agent, the type of anticoagulant used up to 2 hours post-randomisation, or the primary anticoagulant used.

In COMMIT there was no excess of major non-cerebral or cerebral bleeding with clopidogrel, compared with placebo, in patients who received fibrinolytic therapy prior to randomisation compared to those who did not.

Discussion

Efficacy
The two placebo-controlled trials supporting the indication of clopidrogel in STEMI are methodologically sound, are well designed and appear to be well conducted.

The main objective in CLARITY was to evaluate the efficacy of clopidogrel (300 mg loading dose+75 mg daily) in STEMI on the top of a background of standard treatment that include ASA, thrombolysis and heparin. Clopidogrel produced a statistically significant reduction of 36% in the odds of occurrence of the primary endpoint, namely "an occluded Infarct Related Arteries (IRA), or death or recurrent MI". However, it should be highlighted that the the statistical significance was driven by the effect on the IRA, considered a surrogate endpoint, as the trial was not powered to look at hard clinical endpoints. Regarding secondary endpoints, the reduction in recurrent MI and the composite endpoint of "death, recurrent MI, or myocardial ischaemia leading to revascularisation up to Day 30" were also statistically significant in favour of clopidogrel. The two main weaknesses debated by CHMP (see results section) relate to the lack of positive results in the main hard outcomes established as primary endpoints in the study (e.g. death, recurrent MI) and the surprisingly low event rate in the trial population, making it a very low risk population (30-day mortality was <5%, the lowest in all STEMI trials as pointed out in the New England Journal of Medicine).

COMMIT was a megatrial with nearly 50,000 patients carried out in China to determine whether the addition of clopidogrel to ASA for up to 4 weeks in hospital after suspected AMI reduced mortality and the risk of major vascular events (reinfarction or stroke) compared with ASA alone. Clopidogrel + ASA significantly reduced by 9% the relative risk of the combination of "death, re-infarction or stroke" and by 7% the relative risk of death from any cause. In absolute terms, clopidogrel + ASA was associated with 9 fewer patients with "death, reinfarction or stroke" and with 5 fewer patients dying per 1000 allocated treatment. The main issues highlighted by CHMP (see results section) pertain to the differences in background clinical care, mostly in the low use of beta-blockers and thrombolytic perfusion, and the much higher mortality rate (8.1 % in the placebo group) compared to the rate observed in CLARITY, leading to significant concern on the appropriateness of extrapolating the COMMIT results to the European STEMI population.

The CHMP acknowledges the differences in design and outcomes in the two trials and agrees that they could be regarded as complementary. Indeed, while CLARITY showed positive results on a surrogate endpoint (angiographic patency) in a population representative of the EU STEMI clinical setting, albeit at low risk, COMMIT showed positive results on hard, established endpoints but in a population regarded as considerably less pertinent to EU patients. Thus, to a certain extent these 2 trials validate each other since the results in hard outcomes observed in COMMIT reassure the Committee regarding the angiographic patency results in CLARITY, and the population studied in CLARITY, despite its lower than average risk, is more representative of the target population. Overall, the CHMP was reassured by the fact that the results for all major endpoints and subgroup analyses are either favourable to clopidogrel or show a favourable trend, ruling out any heterogeneity.

The main issue discussed by CHMP relates to which of the two trials should be regarded as more representative or "pivotal", in order to define the wording of the indication to be granted. Despite the huge weight of the surrogate endpoint in CLARITY, it was decided to consider this trial as more important given the similarity of the trial population to the EU STEMI clinical setting and the concerns raised in this respect with the COMMIT trial, which was finally considered as "supportive" in this application. Hence, the approved indication reflects the population studied in CLARITY, namely patients eligible for thrombolytic therapy.

The specific claim of "reduction in mortality" in the indication requested by the Applicant is not acceptable. In CLARITY, the absolute difference was only 0.4% in favour of placebo when the primary endpoint was taken into account, whereas the total number of deaths during the study was similar. In COMMIT, a significant effect was seen, but its clinical relevance is questionable, taking into account the small difference in absolute numbers and the loss of significance of the combined endpoint in those patients taking metoprolol, which is current standard treatment. Moreover, the SPC

guideline states that specific clinical outcomes achieved should not be mentioned under the indication section (4.1), but rather in section 5.1.

The dose regimen was different in the CLARITY and COMMIT trials, given that a loading dose was not administered to patients in COMMIT. Consequently, the CHMP discussed whether the loading dose offers any advantage given the results obtained in the two trials. The explanations for the lack of a loading dose in COMMIT offered by the Applicant are reasonable. Considering that the CHMP finally regarded CLARITY as the more representative trial in this patient population, it has been decided to support the treatment protocol followed in CLARITY and thus recommend in section 4.2 of the SPC the use of a loading dose, except in patients >75 yrs, as they are at a higher risk of bleeding and were also excluded from CLARITY. Moreover, there are no safety data on clopidogrel therapy in elderly patients receiving lytic therapy with a loading dose.

The mean treatment duration in COMMIT was only 15 days and the maximum treatment duration was 1 month. It is regrettable that there are no data for a longer period of time as it makes it difficult to determine the optimal treatment duration. Therefore, the CHMP considers that the demonstration of efficacy of the combination of clopidogrel and ASA limited to 4 weeks should be reflected in section 4.2 of the SPC.

Safety

The well-established safety profile of clopidrogel is not challenged by the data provided in these 2 new trials. In CLARITY, the incidences of major bleeding were similar in both treatment groups and consistent across patient subgroups defined by patient characteristics or concomitant therapy. The incidences of fatal bleeding and intracranial haemorrhage were low and similar in both treatment groups. The significant overall increase in bleeding in the clopidrogel group has been reflected in section 4.8 of the SPC.

Limited safety information was gathered in COMMIT due to its massive size of almost 50,000 pts. The overall rate of non-cerebral major bleeding or cerebral bleeding was low and similar in both groups. No untoward safety findings were reported.

Conclusions and Benefit/Risk Assessment

The Applicant has provided two placebo-controlled randomised controlled trials to support a new indication for clopidrogel in STEMI. Despite the weaknesses identified by CHMP, the difference in the design and outcomes between the two trials makes them, to a certain extent, complementary. The results for all major endpoints and subgroup analyses are either favourable to clopidogrel or show a favourable trend, ruling out any heterogeneity, which is reassuring. Given the differences in background clinical care (low use of beta-blockers and thrombolytic perfusion) and the high mortality rate, leading to concerns regarding the relevance of the Chinese population studied in COMMIT to European STEMI population, the CHMP has opted to consider CLARITY as the more relevant trial, despite the fact that the results in the primary endpoint were mainly related to a reduction in a surrogate endpoint. This is counterbalanced by the positive findings on hard endpoints reported in the COMMIT. Therefore, the approved indication reflects the population treated in CLARITY.

The safety profile established for clopidrogel is not challenged by the data provided by the 2 new trials. It is acknowledged that COMMIT is a huge trial with almost 50,000 patients enrolled.