1. Introduction

This variation application is submitted to request the addition of a sentence in the approved non-ST segment elevation acute coronary syndrome (NSTEACS) indication in order to make clear that patients undergoing a stent implantation following percutaneous coronary intervention (PCI) are included in the indication. The rewording applied for is as follows:

"Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA)."

Clopidogrel efficacy in NSTEACS patients undergoing a coronary stent placement following PCI has been evaluated in a post-hoc analysis of the CURE study (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events), in the subset of patients who underwent an intra-coronary stent placement following PCI [Stent-CURE population (CURE restricted to stent PCI)]. The MAH also reviewed recently published experience with clopidogrel in patients with coronary stenting. Safety was primarily assessed on the basis of Stent-CURE. Additional safety data from two studies [EFC7086 (CREDO) and EFC3401 (CLASSICS)] in stent-related populations were also taken into account.

2. Clinical aspects

2.1 Rationale for the proposed change

PCI causes trauma to the vessel wall, rendering the endoluminal surface thrombogenic. As a consequence of mechanical plaque rupture by angioplasty, subendothelial components are exposed inducing platelet adhesion to the injured endothelium and platelet aggregation. Stent utilisation amplifies platelet activation compared to angioplasty. With ASA alone, thrombotic complications following PCI remain high. Studies have demonstrated that the adjunctive use of ticlopidine with ASA reduced subacute thrombosis after stent placement and was superior to anticoagulant regimens (ASA with heparin or warfarin). However, ticlopidine has uncommon but potentially lethal side effects (neutropenia ~1%, thrombotic thrombocytopenic purpura and aplastic anemia) that have limited its routine use in PCI.

Clopidogrel is a newer thienopyridine, which produces active metabolite(s) with antiaggregatory effects and displays a better safety profile than ticlopidine (lower risk of neutropenia and thrombocytopenic thrombotic purpura). Efficacy and safety of clopidogrel for the prevention and treatment of atherothrombotic events has been demonstrated by four Phase III randomised controlled trials (CAPRIE, CURE, CLARITY-TIMI 28, and COMMIT/CCS-2).

The use of clopidogrel in the treatment of NSTEACS patients in the context of PCI is widely generalised. A multinational registry of 401, 255 patients of all ages hospitalised with ACS at 100 sites in 14 countries over a 5-year period (1999-2004) revealed that ACS patients from Europe frequently received clopidogrel during hospitalisation (52%). The administration of clopidogrel was strongly associated with the performance of PCI at all sites (range of use from 82% to 90%).

International Guidelines in Europe and America contain a Class I recommendation for the routine use of clopidogrel in addition to ASA in the treatment of NSTEACS patients and recommend 9-12 month administration of clopidogrel for these patients when managed with PCI and stenting.

2.2 Analysis of data submitted

The justification for the applied rewording of the NSTEACS indication is mainly based on a post-hoc analysis of the *CURE* study, specifically in the subgroup of patients who underwent intra-coronary stent placement following PCI i.e the *Stent-CURE* population.

2.2.1 Design of CURE and Stent-CURE.

CURE was a large scale, multicentre and multinational trial which investigated the efficacy and the safety of clopidogrel 75 mg daily after an initial loading dose of 300 mg, in addition to ASA (75 to 325 mg/day, left to the Investigators' decision) and other background therapy, in a population of patients with NSTEACS (UA or NQMI) treated for a minimum of 3 months and a maximum of 12 months.

This double-blind, randomised, parallel-group trial of clopidogrel (+ ASA) versus placebo (ASA), provides information on the clinical benefit of clopidogrel in a broad range of patients in the presence of numerous and representative concomitant therapies. It was the largest ever performed trial to evaluate antiplatelet agents in this indication and also the largest completed study involving ACS patients with stent.

The study has already been assessed in the context of a Type II variation (II/24 of Plavix and II/22 of Iscover). The Scientific Discussion module of the EPAR provides a detailed summary of the study design and the results. Hence, only a brief general summary will be included in this report.

2.2.2. Methods of CURE and Stent-CURE.

Inclusion criteria. Patients were eligible if they presented within 24 hours of onset of ischaemic chest pain or angina-equivalent symptoms suspected to be NSTEACS.

Randomisation had to be performed within 24 hours of onset of the most recent episode of chest pain or angina equivalent symptoms. Study drugs, as well as ASA (continued if patients were already taking ASA prior to entry into the study), were to be started immediately after randomisation. Regular *follow-up* assessments ended, as specified in the protocol, either 90 days after the randomisation of the last patient (study end date) or one year after randomisation, whichever date came first.

Concomitant therapies, including usual therapy for ACS, were unrestricted, except for those that might interfere with the assessment of the clinical benefit. Specifically, concomitant oral anticoagulants, antithrombins (other than heparins), open-label use of thienopyridines (clopidogrel or ticlopidine at the investigator's discretion) and dipyridamole were not allowed. If patients underwent stent placement after entry into CURE, blinded medication could be stopped for up to 2 to 4 weeks to allow substitution with an open-label non-investigational thienopyridine (clopidogrel or ticlopidine) during this short period. The use of GPIIb/IIIa inhibitors was allowed in connection with PCI.

The first *co-primary efficacy outcome* was the first occurrence of any component of the composite cluster of cardiovascular (CV) death, MI or stroke (ischemic, hemorrhagic or of uncertain type). Cardiovascular death in this cluster was defined to exclude only deaths due to a well-documented non-vascular cause. MI was defined as a new acute MI (differentiated from index-MI) which fulfilled at least 2 of the accepted 3 criteria: characteristic symptoms, consistent new ECG changes and (re) elevation of cardiac enzymes or troponin levels [twice the upper limit of the normal reference range, 3 times this limit if the event occurred after a percutaneous intervention or 5 times this limit if the event occurred post coronary artery bypass grafting (CABG)].

The *second co-primary efficacy outcome* was the first occurrence of any component of the first composite or of refractory ischaemia. The refractory ischaemia definition depended on whether the patient was still in his/her initial hospitalisation or if the event occurred after discharge. The refractory ischaemia definition during initial hospitalisation had very stringent criteria: the patient was to have recurrent chest pain or ischaemic symptoms lasting longer than 5 minutes while on optimal medical therapy and leading to additional intervention (thrombolysis for threatened MI, cardiac catheterisation, insertion of intra-aortic balloon pump or revascularisation procedure, ie, percutaneous transluminal coronary angioplasty PTCA/stent or CABG surgery) or transfer for these procedures by midnight of the next day. The post-discharge definition, "rehospitalisation for UA", was less stringent and included any hospital stay for at least 24 hours with clinical symptoms of typical prolonged chest pain unresponsive to the patient's usual medication associated with ECG changes consistent with acute myocardial ischaemia.

Subgroup analyses. The variables of specific clinical interest were prior ASA and thienopyridine (clopidogrel/ticlopidine) use, prior PTCA/CABG surgery, concomitant use of heparins/hirudin, oral anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), intravenous (IV) GPIIb/IIIa receptor antagonists, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and lipid-lowering agents and ASA dose. Other factors examined included elevated cardiac enzymes/troponin levels at randomisation, ST depression ≥1 mm a randomisation, history of diabetes, peripheral arterial disease, MI and stroke, and diagnosis at discharge (non-Q-wave MI, unstable angina, other). The occurrence of PTCA (with or without stent) and PTCA/CABG surgery was also used as a covariate, although these and the concomitant medication subgroups were recognised as improper subgroups since they were defined on the basis of post-randomisation events. In this case, the results could be confounded with treatment effects and are to be interpreted with caution. The occurrence of periprocedural events within 7 days after PTCA/CABG surgery was also analysed. Other factors examined included age, gender, race, and smoking status.

The main efficacy analysis was an ITT analysis including all patients randomised in the study regardless of whether they actually received study drug. All events occurring during the follow-up period, but not beyond 365 days or the study end date were counted, including events occurring after permanent discontinuation of study drug. Data from patients lost to follow-up were considered as censored at the last date the patient was known to be alive for those patients without an event. However, for patients experiencing an event prior to being lost to follow-up, that patient's event was included in the analysis.

The number of patients with outcome events was summarised by treatment group using counts and percentages and in the form of event rate curves. The event rate curves were estimated using the Kaplan-Meier method. The relative risk reduction (RRR) and 95% confidence intervals (CIs) from the Cox proportional hazards model were reported along with Kaplan-Meier estimates of 1-, 2-, 3-, 7-, and 15-day, and 1-, 3-, 6-, 9-, and 12-month event rates.

Safety parameters. The safety analyses included the rate of life-threatening bleeding and serious adverse events (SAEs). Safety data were to be recorded from randomization up to 365 days or the study end date (06 December 2000). The safety population analysed in CURE was based on the ITT analysis of the subset of patients who underwent stent following PCI, so that benefit and risk could be assessed in the same population.

Sample Size. A total of 12,562 patients were enrolled in CURE: 6,259 in the clopidogrel treatment group and 6,303 in the placebo group. Of the 12,562 enrolled patients, 2,172 (1,080 in the clopidogrel treatment group and 1,092 in the placebo group) underwent a stent placement following PCI. These 2,172 patients (17.3% of the entire CURE population) represent the Stent-CURE population and have been subjected to post-hoc subgroup analysis.

2.2.3. Results

2.2.3.1. Extent of Exposure

The extent of exposure is described in Table 1. Of the 2172 patients, 50.8% of patients in the clopidogrel group and 51.9% of patients in the placebo group were followed up for more than 9 months, including, respectively, 32.6% and 35.4% followed up for at least 12 months.

Table 1 Summary of duration of drug treatment (months) – Stent-CURE

Duration of Study Drug Treatment	Clopidogrel 300/75 mg QD	Placebo	Total
Duration (months)			
Number of patients	1080	1092	2172
Mean (SD)	8.5 (3.6)	8.6 (3.7)	8.6 (3.7)
Median	9.1	9.2	9.1
Maximum	18	16	18
Duration (months) - n (%)			
<3	73 (6.8)	90 (8.2)	163 (7.5)
3-6	214 (19.8)	209 (19.1)	423 (19.5)
6-9	244 (22.6)	226 (20.7)	470 (21.6)
9-12	197 (18.2)	180 (16.5)	377 (17.4)
>=12	352 (32.6)	387 (35.4)	739 (34.0)

SD = standard deviation.

Approximately 18.0% (18.6% in the clopidogrel group, and 17.4% in the placebo group) permanently discontinued study drug before 12 months, common study end date, or death (see Table 2). The main reasons for discontinuation of study drug were withdrawal of patient consent and AEs.

Table 2 Summary of patient accountability during the study period

Status	Clopidogrel 300/75 mg QD	Placebo	Total
Randomized	1080	1092	2172
Randomized and treated	1078	1090	2168
Completed treatment	878 (81.3)	902 (82.6)	1780 (82.0)
Completed alive	855 (79.2)	883 (80.9)	1738 (80.0)
Death	23 (2.1)	19 (1.7)	42 (1.9)
Patients who permanently discontinued study drug[a]	201 (18.6)	190 (17.4)	391 (18.0)
Adverse event	59 (5.5)	46 (4.2)	105 (4.8)
Patient withdrawn consent	90 (8.3)	82 (7.5)	172 (7.9)
Qualifying condition not present	1 (0.1)	3 (0.3)	4 (0.2)
Intervention	8 (0.7)	7 (0.6)	15 (0.7)
Oral anticoagulants or other contraindicated meds	24 (2.2)	24 (2.2)	48 (2.2)
Patient refusal or non compliance	6 (0.6)	10 (0.9)	16 (0.7)
Other	13 (1.2)	17 (1.6)	30 (1.4)
Reason for withdrawal missing		1 (0.1)	1 (0.0)

[a] Of the 4 patients who never took study drug, the investigator recorded 3 of them as permanently discontinuing, but the other 1 was not permanently discontinued.

3.2.1.2. Demographics and baseline characteristics

Demographic and baseline medical data were similar and well balanced between groups, as shown in Table 3.

It should be mentioned that in the original CURE trial an association of the treatment with clopidogrel and a significant decrease of refractory ischemia during hospitalisation *(Relative Risk (RR) 0.68, 95%CI 0.52-0.89, p=0.005)*, resulting in fewer early revascularisation procedures *(RR 0.92, p=0.03)*, was identified. However, in the Stent-CURE population no significant differences in the timing of stent placement were observed.

Table 3 Demographic and Baseline data

Characteristic	Clopidogrel 300/75 mg QD (N=1080)	Placebo (N=1092)	Total (N=2172)
Age (yr)			
Mean (SD)	61.6 (11.2)	61.4 (10.9)	61.5 (11.0)
Range	30-92	32-93	30-93
Age (yr) - N (%)			
< 65	617 (57.1)	631 (57.8)	1248 (57.5)
>= 65	463 (42.9)	461 (42.2)	924 (42.5)
Gender - N (%)			
Female	319 (29.5)	327 (29.9)	646 (29.7)
Male	761 (70.5)	765 (70.1)	1526 (70.3)
Race - N (%)			
Black	4 (0.4)	5 (0.5)	9 (0.4)
Caucasian	890 (82.4)	897 (82.2)	1787 (82.3)
Oriental	15 (1.4)	17 (1.6)	32 (1.5)
Other	171 (15.8)	172 (15.8)	343 (15.8)
Weight (kg)			
Mean (SD)	79.3 (15.4)	78.7 (14.7)	79.0 (15.0)
Range	38.0-173.0	38.0-212.0	38.0-212.0
Smoking - N (%)			
Current	345 (31.9)	317 (29.0)	662 (30.5)
Former	420 (38.9)	455 (41.7)	875 (40.3)
Never	315 (29.2)	320 (29.3)	635 (29.2)
Supine systolic blood pressure (mm Hg)			
Mean (SD)	132.3 (22.39)	132.0 (21.16)	132.2 (21.77)
Median	130.0	130.0	130.0
Range	80 - 216	84 - 214	80 - 216
Supine diastolic blood pressure (mm Hg)			
Mean (SD)	75.8 (13.69)	75.7 (13.13)	75.8 (13.41)
Median	75.0	75.0	75.0
Range	40 - 130	33 - 130	33 - 130
Heart rate (beats/min)			
Mean (SD)	70.7 (13.61)	70.1 (13.14)	70.4 (13.37)
Range	32 - 154	38 - 130	32 - 154

Table 4 Medical and surgical history

Previous Event	Clopidogrel 300/75 mg QD	Placebo	Total
None	128 (11.9)	117 (10.7)	245 (11.3)
Previous MI	274 (25.4)	272 (24.9)	546 (25.1)
PTCA/atherectomy without stent	88 (8.1)	102 (9.3)	190 (8.7)
PTCA/atherectomy with stent	66 (6.1)	49 (4.5)	115 (5.3)
CABG surgery	124 (11.5)	142 (13.0)	266 (12.2)
Other evidence of coronary artery disease	368 (34.1)	385 (35.3)	753 (34.7)
Stroke	38 (3.5)	31 (2.8)	69 (3.2)
Peripheral arterial disease	75 (6.9)	81 (7.4)	156 (7.2)
Hypertension	568 (52.6)	538 (49.3)	1106 (50.9)
Heart failure	39 (3.6)	31 (2.8)	70 (3.2)
Diabetes	196 (18.1)	193 (17.7)	389 (17.9)
High cholesterol	537 (49.7)	560 (51.3)	1097 (50.5)
Cancer	46 (4.3)	80 (7.3)	126 (5.8)
Other	399 (36.9)	413 (37.8)	812 (37.4)

2.2.3.2. Efficacy results

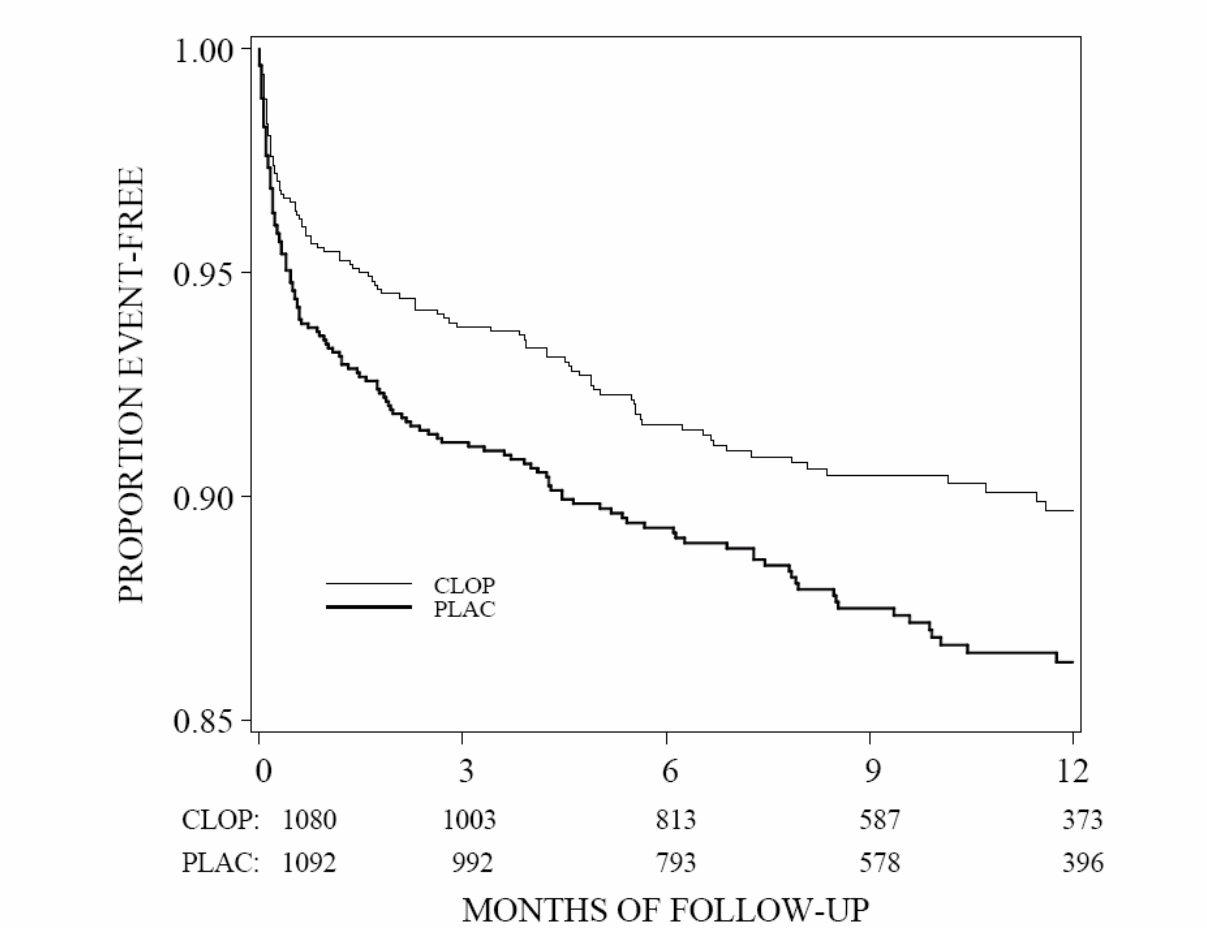
A total of 237 patients (10.9%) experienced a first co-primary outcome confirmed by adjudication. Among these were 192 MIs (81.0%), 19 strokes (8.0%), and 26 other CV deaths (11.0%). The results for the first co-primary endpoint are shown in Table 5: 101 (9.4%) patients in the clopidogrel group versus 136 (12.5%) patients in the placebo group experienced the first co-primary outcome, resulting in a significant relative risk reduction of 26.2% in favour of clopidogrel (95% CI: 4.5%, 42.9%, p = 0.020). The positive result was driven by a reduction in MI.

Table 5 Summary of frequency of first co-primary endpoint outcome

Coprimary Outcome	No. (%) With Event		Relative Risk Reduction (%) (95% CI)	P-Value
	Clopidogrel 300/75 mg QD (N=1080)	Placebo (N=1092)		
MI/stroke/CV death	101 (9.35)	136 (12.45)	26.2 (4.5, 42.9)	0.020
MI (fatal or not)	78 (7.22)	114 (10.44)		
Stroke (fatal or not)	9 (0.83)	10 (0.92)		
Other CV death	14 (1.30)	12 (1.10)		

The Kaplan-Meier curve in Figure 1 displays the first co-primary outcome event rate over time in each treatment group. The clopidogrel and the placebo curves group start to diverge rapidly after study start. The divergence is present until the end of the follow-up, i.e. after 12 month. A Relative Risk Reduction (RRR) of 31.9% was observed for the first co-primary endpoint (95% CI, 2.1%-52.6%, p = 0.038) within the first 30 days after randomisation; and a RRR of 19.8% (95% CI, - 15.6% - 44.4%, p = 0.237) was observed beyond 30 days (up to 1 year).

Figure 1 Proportion of patients remaining event-free over time for first co-primary outcome (adjudicated outcome events) (CLOP, clopidogrel group; PLAC, placebo group)



Second co-primary endpoint. A total of 227 (21.0%) patients in the clopidogrel group versus 290 (26.6%) patients in the placebo group experienced the second co-primary outcome (MI, stroke, CV death, refractory ischaemia), resulting in a significant relative risk reduction of 23.9% in favour of clopidogrel (95% CI: 9.5%, 36.1%, p = 0.002). The results are displayed in Table 6.

Table 6 Summary of frequency of second co-primary endpoint outcome

Coprimary Outcome	No. (%) With Event		Relative Risk Reduction (%) (95% CI)	P-Value
	Clopidogrel 300/75 mg QD (N=1080)	Placebo (N=1092)		
MI/stroke/CV death/refractory ischemia	227 (21.02)	290 (26.56)	23.9 (9.5, 36.1)	0.002
MI (fatal or not)	69 (6.39)	93 (8.52)		
Stroke (fatal or not)	7 (0.65)	8 (0.73)		
Other CV death	12 (1.11)	9 (0.82)		
Refractory ischemia	139 (12.87)	180 (16.48)		

Table 7 Summary of frequency of co-primary outcomes up to 30 days and beyond 30 days in Stent-CURE

	Period <= 30 Days		Period > 30 Days	
Coprimary Outcome	**Clopidogrel 300/75 mg QD (N = 1080)**	**Placebo (N = 1092)**	**Clopidogrel 300/75 mg QD (N = 1080)**	**Placebo (N = 1092)**
MI/stroke/CV death	49 (4.54)	72 (6.59)	52 (4.81)	64 (5.86)
MI (fatal or not)	41 (3.80)	67 (6.14)	37 (3.43)	47 (4.30)
stroke (fatal or not)	2 (0.19)	2 (0.18)	7 (0.65)	8 (0.73)
Other CV death	6 (0.56)	3 (0.27)	8 (0.74)	9 (0.82)
MI/stroke/CV death/refractory ischemia	121 (11.20)	162 (14.84)	106 (9.81)	128 (11.72)
MI (fatal or not)	39 (3.61)	57 (5.22)	30 (2.78)	36 (3.30)
Stroke (fatal or not)	2 (0.19)	2 (0.18)	5 (0.46)	6 (0.55)
Other CV death	5 (0.46)	3 (0.27)	7 (0.65)	6 (0.55)
Refractory ischemia	75 (6.94)	100 (9.16)	64 (5.93)	80 (7.33)

CV = cardiovascular; MI = myocardial infarction.

Comparision of results in subpopulations of the Stent-CURE population. The results obtained in the demographic subgroups analysed were consistent with the results in the overall population. The efficacy observed with clopidogrel was independent of all covariates examined. In all subgroups, the treatment difference was in favour of clopidogrel. The results of the analyses according to prior and concomitant medication/therapy also showed that efficacy observed with clopidogrel was independent of all parameters examined. In particular, the efficacy was independent of other concomitant acute and long-term cardiovascular therapies, such as heparins (LMWH/UFH)/hirudin, IV GPIIb/IIIa receptor antagonists, beta-blockers, ACE inhibitors, ASA and lipid-lowering drugs.

Comparision of the Stent-CURE population with the CURE population without stent. As displayed in Table 8, the 2 subsets of patients (with intracoronary stent and without intracoronary stent) contributed to the positive results in the entire CURE population [RR = 0.80 (95% CI 0.72- 0.90, p< 0.001)], without significant interaction (p = 0.47).

Table 8 Summary of primary outcome in the subset of patients who underwent stent placement following PCI

	No. (%) With Event			
Subgroup	**Clopidogrel 300/75 mg QD**	**Placebo**	**Hazard Ratio (95% CI)**	**p-Value for Interaction**
CURE pts w Stent (N=2172)	101 (9.4)	136 (12.5)	0.74 (0.57,0.96)	0.468
CURE pts w/o Stent (N=10390)	481 (9.29)	583 (11.2)	0.82 (0.73,0.92)	

Optimum Treatment Duration

One of the aspects more thoroughly debated by CHMP was the optimum treatment duration in this clinical setting, considering that patients in CURE were treated for a minimum of 3 months and a maximum of 12 months. This point was also intensely debated at the time of the approval of the NSTEACS indication (see relevant Scientific Discussion in EPAR).
In a recent trial intended to show the superior efficacy of a slow-release, polymer-based, paclitaxel-eluting stent in reducing the risk of clinical and angiographic restenosis compared to a bare-metal stent, clopidogrel was administered during a 6-month period. The authors empirically recommended a 6-month post-procedural clopidogrel treatment, while experimental data have demonstrated equivalent rates of endothelialisation with slow-release paclitaxel-eluting stents and bare-metal stents. The authors reported that no late stent thrombosis was observed after clopidogrel discontinuation at 6 months. In this study, patients with complex coronary lesions, such as thrombus containing lesions,

bifurcations, and calcified stenoses were excluded from the study. In addition, the population with drug-eluting stent was broader than ACS patients only, and therefore did not necessarily integrate the higher risk potentially inherent to ACS.
As newer reports are emerging, indicating a continued risk of late stent thrombosis at 1 year as well as increased mortality when antithrombotic treatment with ASA and clopidogrel is discontinued even at such late stage in patients with drug-eluting stents, international guidelines recommend administering 75 mg/day clopidogrel with ASA for up to 12 months for ACS and for patients undergoing a PCI, irrespective of the type of stent placed. It states that stent patients should initially receive a higher-dose ASA of at least 325 mg/day for less than a month for bare-metal stents, for 3 months for sirolimus-eluting stents, and more than 6 months for paclitaxel-eluting stents, followed by 75 to 162 mg/ day.
The 2005 European Guidelines for Percutaneous Coronary Interventions recommend that clopidogrel should be started and continued up to 12 months after drug-eluting stent implantation (Class 1C evidence).

Further to a Request from CHMP concerning the optimal duration of the treatment with clopidogrel, the MAH presented data comparing the frequency of the first co-primary efficacy outcome up to 30 days and for the time beyond 30 days post-randomisation in the stent-CURE and the overall CURE population, as seen in the table below.

Table 9 Summary of the Frequency of the first Co-Primary Outcome (Adjudicated Outcome Events) up to 30 Days and beyond 30 Days in the Stent-CURE And overall CURE populations

First Co-Primary Outcome (MI/Stroke/CV death)	Period ≤ 30 days post-randomization			Period > 30 days post-randomization		
	Clopidogrel 300/75 mg	Placebo	RRR (95% CI)	Clopidogrel 300/75 mg	Placebo	RRR (95% CI) p-value
Stent-CURE – N=2172 (1080 clopidogrel / 1092 placebo)	49 (4.54%)	72 (6.59%)	31.9 % (2.1, 52.6)	52 (4.81%)	64 (5.86 %)	19.8 % (-15.6, 44.4)
Overall CURE – N=12562 (6259 clopidogrel / 6303 placebo)	272 (4.35%)	349 (5.54%)	22.0 % (8.6, 33.4)	310 (4.95%)	370 (5.87%)	17.4 % (3.9, 28.9)

Although, during the first 30 days post-randomisation, the RRR in the Stent-CURE population was higher than in the overall CURE population, possibly due to the higher placebo event rate in the higher risk Stent-CURE population, the RRR were similar and quite large in both populations beyond 30 days. Actually, the event rates in the Stent-CURE population, both in the placebo group and the clopidogrel group, were similar to those in the overall population at the end of this long-term period, indicating that the long-term risk levels and risk reductions are similar in both populations.

The cumulative event rates for the first co-primary outcome (Table 10) showed that the absolute difference between the group treated with clopidogrel and placebo increased over the whole 12-month treatment and follow-up period.

Table 10 Summary of event rates for first co-primary outcome (adjudicated outcome events, ITT) in the Stent-CURE population

Time (days)	CUMULATIVE EVENT RATE (%)		ABSOLUTE DIFFERENCE (%) (95% C.I.)
	CLOPIDOGREL 300/ 75 MG OD	PLACEBO	
1	0.56	1.10	0.54 (-0.22, 1.30)
2	1.11	1.74	0.63 (-0.37, 1.62)
3	1.67	2.38	0.71 (-0.47, 1.90)
7	2.78	3.94	1.16 (-0.35, 2.67)
15	3.43	5.40	1.98 (0.25, 3.70)
30	4.54	6.59	2.06 (0.13, 3.98)
90	6.20	8.79	2.59 (0.38, 4.80)
180	8.38	10.70	2.32 (-0.18, 4.82)
270	9.53	12.50	2.97 (0.23, 5.71)
365	10.33	13.70	3.37 (0.42, 6.32)

Moreover, the Cox's proportional hazard model used for the calculation of the RRR of the primary endpoint revealed no significant difference in the risk of any event in the treatment group and placebo over the time, suggesting a consistency of the benefit of clopidogrel treatment up to the end of the study duration.

The overall analysis of the first co-primary endpoint in the Stent-CURE population using a Cox's proportional hazards model showed a 26.2 % RRR favouring clopidogrel. This model using time as a variable assumes that, even though rates of events can change over time, the risk of an event in the treated group relative to the placebo group is constant over time. A test of this assumption was non-significant ($p>0.5$), therefore showing the lack of interaction with time, and further demonstrating, as was shown in the overall CURE population, the consistency of the benefit over time. Thus, although we can find different estimates of the RRR with different periods of time, the estimate from the overall model (26.2%) applies across the whole time period.

In order to explore the optimum treatment duration within the 12-month study duration, and help support a medical decision to terminate clopidogrel treatment before 12 months, the effect of discontinuing clopidogrel prematurely was assessed for the first co-primary endpoint using a Cox proportional hazards model, which included a time-dependent covariate for discontinuation of study drug. These post-hoc analyses are very similar to those performed for the entire CURE population to address the CHMP concerns in the context of the variation for the NSTEACS indication, but have been further refined by dividing premature permanent discontinuations into 3 groups:

1. All permanent discontinuations: N= 392
2. All inappropriate permanent discontinuations (for non-AE reason): N= 287
3. Permanent discontinuations for withdrawn consent only: N= 172

As expected, the loss of protection resulting from clopidogrel discontinuation translates into no difference between the clopidogrel and placebo groups in first co-primary endpoint event rates at the end of the study.

2.2.3.3. Safety results

Primary safety data of Stent-CURE.

Safety evaluations in the Stent-CURE population were the same as those performed in the overall CURE population. The safety evaluation was based on the ITT analysis of the Stent-CURE population, so that benefit and risk could be assessed in the same population. The frequency of bleeding events is displayed in Table 11.

Table 11 Summary of number (%) of patients with bleeding events

Type of Bleeding	Clopidogrel 300/75 mg QD (N=1080)	Placebo (N=1092)	Difference Clopidogrel - Placebo (%) (95% CI)	P-Value
Adjudicated major/life-threatening bleeding	36 (3.33)	32 (2.93)	0.40 (-1.15,1.96)	0.590
Life-threatening bleeding	19 (1.76)	19 (1.74)	0.02 (-1.18,1.21)	0.973
Fatal bleeding	1 (0.09)	0 (0.00)	(,)	
Nonfatal bleeding	18 (1.67)	19 (1.74)	-0.07 (-1.25,1.11)	
Major bleeding	18 (1.67)	15 (1.37)	0.29 (-0.83,1.41)	0.577
Minor bleeding	50 (4.63)	34 (3.11)	1.52 (-0.20,3.23)	0.067
Other bleeding	166 (15.37)	119 (10.90)	4.47 (1.54,7.40)	

There was no significant difference in bleeding, adjudicated major/life threatening bleeding, either according to bleeding characteristics or site of bleeding.

The frequency of other adverse events, serious adverse events, deaths, adverse events leading to withdrawal is shown in Table 12.

Table 12 Overall incidence of treatment-emergent adverse events, treatment emergent serious adverse events, deaths, and adverse events leading to permanent discontinuation of study drug (Stent-CURE)

Event	Clopidogrel 300/75 mg QD (N = 1080)	Placebo (N = 1092)
Patients with any AE	467 (43.2)	495 (45.3)
Patients with SAEs	141 (13.1)	135 (12.4)
Patients with nonhemorrhagic SAEs	107 (9.9)	115 (10.5)
SAEs with an outcome of non-CV death	4 (0.4)	4 (0.4)
Patients who permanently discontinued study drug due to AEs	59 (5.5)	46 (4.2)
Hemorrhagic AEs	19 (1.8)	12 (1.1)
Non-hemorrhagic AEs	31 (2.9)	26 (2.4)
Unspecified	9 (0.8)	8 (0.7)

AE = adverse events; CV = cardiovascular; SAE = serious adverse event.

There was no significant difference between the clopidogrel group and the placebo group in any of the AE categories depicted in the table above.

Additional safety data in stent-related populations undergoing long-term treatment with clopidogrel.
The double-blind trial CLASSICS was a safety study of clopidogrel versus ticlopidine on top of ASA 325 mg with the primary endpoint consisting of major peripheral or bleeding complications, neutropenia, thrombocytopenia, or the early discontinuation of the study drug for noncardiac adverse events. The primary endpoint occurred more frequently among patients treated with ticlopidine (9.1%) than in the clopidogrel group (4.6%) (p = 0.005), supporting a superior safety profile of clopidogrel. However, bleeding occurred more frequently in the clopidogrel 75 mg group than in the other study groups. The overall rate of AEs, SAEs, and permanent discontinuations due to an AE was higher in the ticlopidine group than in the clopidogrel groups. Skin disorders, primarily rash, were the most frequent reason for discontinuing therapy, with incidences of 2.6% in ticlopidine users and 0.6% in clopidogrel users. One ticlopidine patient developed neutropenia (neutrophil $<0.1 \times 10^9/l$) 28 days after randomization and four clopidogrel patients had mild and transient thrombocytopenia.

CREDO was a multicentre, randomised, double-blind, parallel group study to evaluate the effects of long-term treatment (12 months) with clopidogrel (75 mg once daily) on top of ASA 325 mg in the prevention of vascular events and all-cause mortality in patients undergoing PCI. In addition, the effects of a preprocedural loading dose of clopidogrel (300 mg) were examined. All randomised patients received clopidogrel 75 mg with or without a 300 mg loading dose plus ASA 325 mg once daily for 28 days. After the short-term therapy of 28 days, patients who had received a loading dose continued treatment with clopidogrel 75 mg plus ASA (81 to 325 mg) once daily for up to 365 days. Those who had not received a loading dose continued treatment with placebo plus ASA (81 to 325 mg once daily) for up to 365 days. In the population that initially received a loading dose, there was a trend toward an increase in major bleeding in patients treated with clopidogrel for 1 year (p = 0.07). On the contrary, there was no difference regarding the incidence of minor bleeding episodes between the two study groups. None of the major bleeding events were intracranial haemorrhages, and none were fatal. Furthermore, most of the major bleeding events were related to a procedure (angiography, PCI, CABG, other surgery).

In GRACE, a large prospective, international clinical registry (94 hospitals in 14 countries), a significant increase in major bleeding with the use of thienopyridines in the overall population (2.8% with thienopyridines versus 2.2% without thienopyridines; p= 0.002) was found. In contrast, no difference was observed when limiting the analysis to patients undergoing PCI, with or without stenting or CABG (3.1% with thienopyridines vs 3.7% without thienopyridines; p= 0.22).

Further to a request from CHMP, the MAH presented the frequency of life-threatening bleeding events in Stent-CURE of the clopidogrel and the placebo group compared over time (Table 13).

Table 13 Number (%) of patients experiencing life-threatening bleeding events by pooled category and time – Randomized patients in Stent-CURE

Time period months	Clopidogrel 300/75 No. with event/ No. for period (%)	Change from previous period (%)	Placebo No. with event/ No. for period (%)	Change from previous period (%)
0-1	10/1080 (0.93)		13/1092 (1.19)	
1-3	1/1071 (0.09)	-0.84	1/1085 (0.09)	-1.1
3-6	5/1063 (0.47)	0.38	2/1077 (0.19)	0.1
6-9	3/880 (0.34)	-0.13	1/889 (0.11)	-0.08
9-12	0/645 (0)	-0.34	2/668 (0.3)	0.19

The rate of life-threatening bleeding events was comparable in both the clopidogrel and the placebo study groups, and also when comparing the Stent-CURE and the overall CURE population. Therefore the application of the current routine safety monitoring was suggested.

3. Discussion

Efficacy

The main data provided to support the rewording of the NSTEACS indication to specifically mention patients undergoing PCI are derived from a post-hoc analysis of the CURE trial in the subset of patients who underwent an intra-coronary stent placement following PCI (Stent-CURE). The CURE trial has previously been assessed in the context of the NSTEACS indication. At the time of the evaluation, the CHMP was of the opinion that CURE was a well designed, well conducted and generally consistent study, performed according to the current standards. The main criticism to this study highlighted by the CHMP was the failure to establish an optimal treatment duration.

The results in Stent-CURE show that treatment with clopidogrel resulted in a significant relative risk reduction of the first and the second co-primary endpoint. The 2 subsets of patients (with intracoronary stent, i.e. the Stent-CURE population, and without intracoronary stent) contributed to the positive results in the entire CURE population without significant interaction

The main issue discussed by the CHMP was the validity of the post-hoc design of the subgroup analysis in Stent-CURE to support the proposed change in the indication. There was no doubt that, in general, subgroup analyses which are not predefined in the study protocol are less valuable from the methodological point of view and also in terms of statistical power, as stated in the CHMP guidline CPMP/EWP/908/99 (The Points to Consider on Multiplicity Issues in Clinical Trials). However, the CHMP was of the opinion that patients undergoing PCI and subsequent stent placement are already included in the current indication. Therefore the CHMP considered the applied rewording to be a clarification of the indication granted rather than an extension of the indication, i.e. a new indication, so that the CHMP guideline does not apply. The CHMP further acknowledged that the conduct of a new clinical trial comparing clopidogrel and ASA in patients undergoing PCI and stenting would be ethically difficult to perform, since clopidogrel is already commonly used and accepted in this indication. Moreover, international guidelines highly recommend the routine use of clopidogrel in the management of patients with NSTEACS receiving a stent. Since the efficacy of clopidogrel has been confirmed in the CURE study also for the subset of patients undergoing PCI (PCI-CURE) and stenting is a widely accepted routine management following PCI, the CHMP stated that the re-analysis of the Stent-CURE population is adequate to support the applied rewording of the NSTEACS indication.

As with the CURE study and the NSTEACS indication, the CHMP questioned the optimal duration of treatment. The MAH presented data indicating an increase in the number of cardiovascular events following premature treatment discontinuation. Since the benefit/risk ratio remained comparable over the entire duration of the study, the CHMP agreed with the MAH that there is no need to change the current wording in section 4.2 of the SPC, which states that

"The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section 5.1)."

The CHMP requested the update of section 5.1 of the SPC to reflect the results of the Stent-CURE post-hoc analysis as follows:

"*In the CURE trial, 17% of the total population underwent stent placement. A post-hoc analysis of the data showed that, in this subgroup of patients, Clopidogrel (300 mg loading dose followed by 75 mg daily) compared to placebo, demonstrated a significant relative risk reduction (RRR) of 26.2% favoring Clopidogrel for the co-primary endpoint (CV death, MI or stroke) and also a significant RRR of 23.9% for the second coprimary endpoint (CV death, MI, stroke, or refractory ischemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset of patients seem to be in line with the overall trial results."*

Safety
The safety of clopidogrel has been already assessed during the initial NSTEACS indication evaluation. The results in Stent-CURE do not differ from those observed in the overall CURE population, which was previously assessed in the context of the NSTEACS indication. Despite the methodical weakness of post-hoc subgroup analysis, the CHMP was of the opinion that the safety data of Stent-CURE are reliable, since they match the overall CURE outcomes such as in case of the efficacy results.
Since the Stent-CURE population, i.e. patients undergoing a stent placement represent a group of high-risk patients, the possibility of a specific safety monitoring programme was discussed by the CHMP. Taking into account the extensive clinical and post-marketing experience in the treatment of NSTEMI with clopidogrel and the well-known safety profile of clopidogrel, it was deemed unnecessary.

4. Conclusions and Benefit / Risk Assessment

The Applicant presented a re-analysis of the CURE trial in the subset of patients who underwent an intra-coronary stent placement following PCI (Stent-CURE) to support a rewording of the NSTEACS indication, i.e. the insertion of a sentence pointing out that patients with stent after PCI are included in the target population. Acknowledging the widely generalised use of clopidogrel and the recommendation of treatment guidelines to use clopidogrel in NSTEMI patients with PCI and

subsequent stenting, the CHMP considered the applied rewording to be a clarification of the existing indication rather than a new indication. Despite the drawbacks due to the post-hoc design, recognised by the CHMP, the CHMP was of the opinion that the presented data are sufficient to support the applied rewording.

Importantly, the Stent-CURE outcomes showed a similar positive benefit / risk ratio for the subset of NSTEACS patients undergoing stent placement after PCI as for the overall NSTEACS population investigated in the CURE trial. It is acknowledged that clopidogrel is already routinely used in patients receiving a stent after PCI. The same recommendations on treatment duration as for the overall NSTEACS population apply to PCI patients.