Single Technology Appraisal

Ticagrelor For The Treatment Of Acute Coronary Syndromes

NICE Clarification Letter - AstraZeneca Response

17th December 2010

Section A: General information

Please provide electronic copies of:

A1. The PLATO Study Protocol with any amendments.

A2. The PLATO Study Analysis Plan with any amendments.

A3. The PLATO Clinical Study Report with appendices.

A copy of the PLATO Clinical Study Report (CSR), excluding appendices, has been provided in confidence. Specific tables from the CSR appendices will be provided upon request in response to specific questions. The PLATO CSR contains the key elements of the Clinical Study Protocol (including the amendments) and the final Statistical Analysis Plan so these documents have not been provided separately.

Section B: Clarification on clinical effectiveness

Study conduct

B1. Please clarify how compliance with study treatments was measured (for example pill count returned at each visit or any other method) and please provide the rates of compliance for each arm for each inter-assessment time period of the trial.

At each study visit, the investigator assessed the patient's compliance and recorded it in the electronic case report form (eCRF). If the patient reported taking more than 80% of the expected doses of study medication between each visit the investigator regarded the patient as compliant.

A summary of the investigator-reported assessment of study drug compliance by visit is provided in Table 1. Patients received study drug under supervision during the index hospitalisation. After discharge from hospital, patients were considered compliant at each visit if the investigator assessed that they had taken more than 80% of prescribed study drug, after taking account of temporary interruption and premature permanent discontinuation of study drug. Unused medication was returned to the site. At each visit investigators were asked to assess compliance by assessing all returned unused investigational products and empty packages at each visit. At each visit investigators assessed that at least 90% of patients achieved the aforementioned threshold of compliance (>80%).

Table 1: Investigator assessment of study drug compliance by visit - PLATO full analysis set

Characteristic	Statistic or category	Randomised treatment	
		Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291
Overall[a]	n	9312	9272
	>80% Compliant	7724 (82.9%)	7697 (83.0%)
Visit 2 (1 month +/- 10 days)	n	9305	9267
	>80% Compliant	8524 (91.6%)	8493 (91.6%)
Visit 3 (3 months +/- 10 days)	n	7115	7186
	>80% Compliant	6727 (94.5%)	6804 (94.7%)
Visit 4 (6 months +/- 10 days)	n	6747	6864
	>80% Compliant	6427 (95.3%)	6550 (95.4%)
Visit 5 (9 months +/- 10 days)	n	5169	5311
	>80% Compliant	4959 (95.9%)	5085 (95.7%)
Visit 6 (12 months +/- 10 days)	n	3667	3685
	>80% Compliant	3516 (95.9%)	3563 (96.7%)

[a]Overall compliance defined as at least 80% compliance on all visits.
bd Twice daily dosing; od Once daily dosing

B2. Please provide details of the number and type of protocol violations for each arm of the PLATO trial.

In this large outcomes based study looking at acute coronary syndrome (ACS) patients managed in the hospital, protocol deviations captured via the eCRF included failed inclusion and exclusion criteria. Table 2 summarises the number of patients with important protocol deviations in each treatment group.

Table 2: Number (%) of patients with important protocol deviations – PLATO full analysis set

Category	Ticagrelor 90 mg bd N=9333	Clopidogrel 75 mg od N=9291	Total N=18624
Total number of deviations	287	302	589
Patients with at least 1 deviation	286 (3.1%)	301 (3.2%)	587 (3.2%)
Failed any of the inclusion criteria	219 (2.3%)	228 (2.5%)	447 (2.4%)
Failed inclusion criteria - consent form	1 (0.0%)	1 (0.0%)	2 (0.0%)
Failed any of the exclusion criteria	67 (0.7%)	73 (0.8%)	140 (0.8%)

If a patient failed inclusion criteria, only the first reason was captured in the eCRF. Patients who failed inclusion criteria could also have had 1 or more deviation captured.

bd Twice daily dosing; eCRF Electronic case report form; od Once daily dosing.

There were few patients randomised to the study who were later found to have not met entry criteria (587, 3.2%). Protocol deviations were balanced across the treatment groups. For additional information on protocol deviations, see the PLATO CSR, Section 6.2.

B3. Please provide confirmation of details of the adjudication of outcomes specified on page 40 of the submission. Were all outcome events in the PLATO subject to adjudication? If not, what percentage was adjudicated?

PLATO employed an adjudication process to ensure consistency of reporting events across all sites and regions. An Independent Central Adjudication Committee (ICAC), independent of the sponsor and investigators, adjudicated and evaluated all clinical primary and secondary efficacy events. The investigator collected these events in the eCRF and identified the events using standard questioning of the patient at each visit or from information that the investigator received as part of standard medical practice. All cases adjudicated as cardiovascular (CV) death were evaluated to determine whether a myocardial infarction (MI) was the cause of death.

Clinical MIs and periprocedural MIs detected by biomarkers were included in the primary variable, as adjudicated by the ICAC. Due to absence of symptoms, the date of occurrence of silent MIs detected by electrocardiogram (ECG) usually cannot be determined. For these reasons, the primary efficacy variable time to event analysis does not include silent MIs. However, for completeness, silent MIs are included in a secondary composite endpoint using date of ECG as date of occurrence, and are also presented separately. In addition, sensitivity analysis of the primary efficacy variable includes silent MI.

The ICAC documented all final adjudication decisions, which were entered in the study database. Analyses were based on events confirmed by the adjudication committee; unconfirmed reports of suspected events by investigators were not counted.

The ICAC adjudicated bleeding events according to the PLATO definitions. The analyses show bleeding events categorised using PLATO definitions. Another analysis algorithmically reassigned these events to TIMI-defined bleeding categories (Wiviott *et al.* 2006). Bleeding events were not adjudicated a second time using TIMI bleeding definitions.

The ICAC evaluated the clinical study data of every patient who underwent CABG during the study to adjudicate for a possible bleeding event, whether or not the investigator designated an event. The ICAC also evaluated all bleeding events designated by investigators as ‘Major’ or ‘Minor’. ICAC reviewed the information provided by Investigators and rigorously applied consistent criteria to categorise each event as 1 of the following: ‘Major Fatal/Life-threatening’, ‘Major Other’, ‘Minor’ and ‘Minimal’. Non-CABG bleeding events reported by investigators as ‘Minimal’ were not adjudicated by ICAC, and were combined for analysis with events adjudicated by ICAC to be ‘Minimal’. ICAC determined that some events reported by Investigators did not qualify as bleeding events. On occasion, ICAC identified additional events

and directed the sponsor to query a site to register the events for official adjudication. If the Investigator agreed, the event was registered and processed by ICAC.

The ICAC classified clinical endpoints of MI subtypes according to a modification of the scheme proposed by Thygesen *et al*. 2007 to demonstrate that the PLATO study represented a comprehensive range of MI subtypes. The MI trigger program identified potential MIs by CK MB or troponin that were ICAC-adjudicated, and when confirmed were included in the primary efficacy analysis with other MIs.

B4. Please provide the criteria used to censor patients in each of the presented analyses.

The analyses of the efficacy endpoints, bleeding events, and analyses of events according to node assignments employed censoring rules as follows.

In the time-to-event analysis of death due to vascular causes and composites including death due to vascular causes, deaths not due to vascular causes are treated as a censoring event. For all endpoints not encompassing death (e.g., bleeds, MI, stroke), all deaths are treated as censoring events. Censoring events included end of treatment, withdrawal of consent and last contact with the patient.

The analyses of bleeding events censored patients at death or last dose-of-study-drug plus 7 days, whichever occurred first. This time frame is consistent with all of the safety analyses and is based on the predicted offset of clopidogrel.

Censoring in analyses of events by node is according to node assignments, which were mutually exclusive and applied as described in Section 6.2.4 of the submission document.

B5. Please expand on the method used for multiple testing, in particular the rationale for the order of the secondary endpoints.

The confirmatory analysis of the primary objective of the study involved the statistical analysis of the primary and secondary efficacy endpoints. The hierarchical test procedure included the hypothesis tests for the endpoints. In order to address the issue of multiplicity, a hierarchical test sequence was performed. Once the null hypothesis concerning the primary composite efficacy endpoint was rejected, the secondary composite efficacy endpoints were tested using statistical analysis analogous to that described for the primary composite endpoint separately in the order given in Table 5.6 (Section 5.3.5) of the submission document. Statistical hypothesis testing continued until the first statistically non-significant treatment difference was observed. This procedure was followed in order to control family-wise type I error.

In PLATO a closed hierarchy of tests was applied to address multiple secondary endpoints. In a closed hierarchical testing procedure important secondary endpoints are rank-ordered and tested in sequence until either the list is exhausted or a given test is not ‘statistically significant’. In the later case, the test that is not statistically significant and all tests that would have been performed are then formally classified as not being ‘statistically significant’.

In order for this process to be properly applied, the tests and their exact sequence have to be pre-specified; 'closed' refers to both the pre-specification of the tests and their order within the hierarchy. This was exactly the approach used in PLATO.

The question then arises as to how the exact order for testing of the secondary endpoints was determined. The exact hierarchy of sequence of tests in the PLATO trial is outlined below.

The first test in the hierarchy of the secondary endpoints was of the primary (composite) endpoint (CV mortality, non-fatal MI, non-fatal stroke) in a sub-population for which there was a prior expectation of substantial treatment difference (i.e. the intent to invasively manage subgroup) and which was thought to mirror the majority of current ACS treatment.

The next test in sequence was of the composite of all-cause mortality, non-fatal MI and non-fatal stroke in the whole population. This captures the importance of all-cause mortality (not just CV mortality) in evaluating composite outcomes.

The third test examined all cardiovascular events, including all MI (including silent MI by ECG), stroke, CV death, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack, and other arterial thrombotic events

The fourth, fifth, and sixth tests were of the individual components of the primary endpoint, in decreasing order of the expected number of events (MI, CV death, and then stroke).

The seventh test in the hierarchy was of all-cause mortality, an important individual endpoint beyond the components of the primary composite (recognizing that CV mortality may not necessarily be reflective of total mortality). This, as noted above, was incorporated into the composite second test in the hierarchical sequence, but was here tested individually.

B6. Please confirm if an interim analysis of the clinical efficacy data took place and, if so, how many events had occurred at that time.

One formal interim analysis of the primary composite efficacy endpoint was planned when approximately 1200 adjudicated events (2/3rds of the total target number of 1780 events) were observed. The interim analysis was guided by the Peto-Haybittle group sequential boundary corresponding to a critical p-value of 0.001. To maintain the overall significance level at 5%, the critical p-value at the final analysis was 0.0497. The independent Data and Safety Monitoring Board (DSMB) performed the interim analysis.

The interim analysis occurred on 22 December 2008. Only members of the DSMB were aware of the interim analysis results.

Patient outcomes: Key events

B7. Please provide outcomes, including safety endpoints, for the cohort of patients from Europe.

A post-hoc analysis of the primary and secondary efficacy endpoints and the primary safety endpoint (major bleeding) in the PLATO study (full analysis set) for patients recruited in the European Union (EU) region is provided. The primary and secondary efficacy endpoints results for the European Union region are consistent with the results observed for the primary and secondary efficacy endpoints results of the full analysis set.

Table 3 presents the primary and secondary efficacy endpoints, the primary safety endpoint for the “European Union region”. In this instance, the European Union region includes the 16 Member States that participated in PLATO plus Bulgaria, Romania and the EEA member, Norway. Switzerland, Turkey, Ukraine, Georgia and Russia are not included in this cohort. This is a post-hoc definition of the EU region.

Table 3: Primary and secondary efficacy endpoints and primary safety endpoint for the European Union[a] - PLATO full analysis set

Endpoint	Ticagrelor 90 mg bd N=5733 Patients with events	KM%/ year	Clopidogrel 75 mg od N=5713 Patients with events	KM%/ year	HR (95% CI)	p-value
Primary efficacy						
Composite of CV death/ MI (excl. silent MI)/stroke	470 (8.2%)	8.7%	598 (10.5%)	11.2%	0.78 (0.69, 0.88)	<0.0001
Secondary efficacy						
Composite of CV death/ MI (excl. silent MI)/stroke-intent for invasive management	303 (7.4%)	7.9%	338 (9.6%)	10.2%	0.77 (0.66, 0.89)	0.0005
Composite of all-cause mortality, MI (excl. silent MI)/stroke	488 (8.5%)	9.0%	624 (10.9%)	11.7%	0.77 (0.69, 0.87)	<0.0001
Composite of CV death/total MI/Stroke/SRI/RI/TIA/Other ATE	735 (12.8%)	13.6%	873 (15.3%)	16.2%	0.83 (0.75, 0.92)	0.0002
CV death	165 (2.9%)	3.1%	231 (4.0%)	4.4%	0.71 (0.58, 0.87)	0.0008
MI (excl. silent MI)	289 (5.0%)	5.4%	370 (6.5%)	7.0%	0.77 (0.66, 0.90)	0.0010
Stroke	77 (1.3%)	1.5%	70 (1.2%)	1.3%	1.10 (0.79, 1.52)	0.5776
All-cause mortality	190 (3.3%)	3.5%	264 (4.6%)	5.0%	0.72 (0.59, 0.86)	0.0005
Primary safety						
'Total Major' bleeding	600 (10.6%)	11.9%	585 (10.3%)	11.5%	1.03 (0.92, 1.15)	0.6364

[a]European Union includes: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom. Also includes a member of the EEA: Norway.

Hazard ratio and p-value calculated from Cox proportional hazards model with study treatment as only explanatory variable. Kaplan-Meier percentage calculated at 12 months. For patients with multiple events the analysis uses the time to the earliest event: each patient is counted only once in each row. A single event may be counted in more than 1 row.

Note: The number of first events for the components CV death, MI, and stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

ATE Arterial thrombotic events; bd Twice daily dosing; CI Confidence interval; CV Cardiovascular (CV death is death from vascular causes); excl. Excluding; HR Hazard ratio; KM Kaplan Meier; MI Myocardial infarction; od Once daily dosing; RI Recurrent cardiac ischaemia; SRI Severe recurrent cardiac ischaemia; TIA Transient ischaemic attack.

B8. Please provide the results of any analyses that compare rates of bleeding noted between countries or regions.

AstraZeneca conducted pre-specified analyses of bleeding in the 4 regions defined in the statistical analysis plan. Table 4 presents the data for 'Major' bleeding in these 4 regions. Additional analyses of non-CABG 'Major' bleeding and non-procedural 'Major' bleeding in these 4 regions are shown in Section 8.2.8 of the PLATO CSR. No specific regional subgroups have been identified as having an increased risk of bleeding with ticagrelor.

Table 4: Major bleeding by subgroup – PLATO safety analysis set

			Randomised Treatment				
			Ticagrelor 90 mg bd N=9235	Clopidogrel 75 mg od N=9186			
Characteristic	**Group**	**n**	**KM%**	**KM%**	**Hazard Ratio (95% CI)**	**p-value**	**p-value (Int.)**
Region	Asia and Australia	1692	10.6	10.8	1.03 (0.76, 1.40)	0.8363	0.7545
	Central and South America	1230	15.6	13.2	1.22 (0.89, 1.66)	0.2176	
	Europe, Middle East and Africa	13747	11.1	11.0	1.01 (0.91, 1.13)	0.7862	
	North America	1752	12.9	12.2	1.06 (0.80, 1.40)	0.6884	

bd Twice daily dosing; CI Confidence interval;;KM Kaplan Meier; MI Myocardial infarction; od Once daily dosing.

B9. Please provide Kaplan-Meier survival analysis results for primary and secondary endpoints in the form of numeric tables showing for each event/censored observation:

- the time from randomisation

- the estimated event-free survival (with standard error)

- the number of patients remaining at risk

- the cumulative number of events and

- the cumulative number of censored observations

Table 5 shows the requested Kaplan-Meier survival analysis.

Table 5: Kaplan-Meier survival analysis results by clinical endpoint, treatment and time intervals- PLATO full analysis set

Clinical endpoint	Randomised treatment	Days from randomisation	Patients at risk	Estimated event-free survival	Survival standard error	Cumulative number of events*	Censored observations (cumulative)
Composite of CV Death/MI (excl. silent MI/Stroke)	Ticagrelor 90 mg bd	30	8762	0.9521	0.00222	444	127
		60	8625	0.9433	0.0024	525	183
		90	8539	0.9361	0.00254	591	203
		120	8459	0.9303	0.00265	644	230
		150	8396	0.9247	0.00275	694	243
		180	8195	0.9208	0.00281	730	408
		210	7022	0.9178	0.00287	754	1557
		240	6738	0.9139	0.00295	783	1812
		270	6469	0.9109	0.00301	805	2059
		300	5145	0.9067	0.0031	831	3357
		330	4818	0.9039	0.00318	846	3669
		360	4056	0.9018	0.00323	857	4420
	Clopidogrel 75 mg od	30	8687	0.9456	0.00236	503	101
		60	8519	0.9325	0.00261	623	149
		90	8436	0.9258	0.00273	684	171
		120	8361	0.9189	0.00284	747	183
		150	8285	0.9124	0.00295	806	200
		180	8108	0.9077	0.00302	849	334
		210	6939	0.903	0.0031	887	1465

Table 5: Kaplan-Meier survival analysis results by clinical endpoint, treatment and time intervals- PLATO full analysis set

Clinical endpoint	Randomised treatment	Days from randomisation	Patients at risk	Estimated event-free survival	Survival standard error	Cumulative number of events*	Censored observations (cumulative)
		240	6649	0.898	0.00319	924	1718
		270	6361	0.8947	0.00325	948	1982
		300	5093	0.8904	0.00334	974	3224
		330	4747	0.8863	0.00343	996	3548
		360	1745	0.8828	0.00354	1013	6533
MI (excl. silent MI)	Ticagrelor 90 mg bd	30	8805	0.9728	0.00169	250	278
		60	8675	0.9678	0.00184	295	363
		90	8597	0.9636	0.00196	333	403
		120	8519	0.9599	0.00205	366	448
		150	8455	0.9559	0.00215	401	477
		180	8246	0.9534	0.00221	423	664
		210	7075	0.9509	0.00228	443	1815
		240	6776	0.9488	0.00234	458	2099
		270	6522	0.9473	0.00238	469	2342
		300	5193	0.9442	0.00248	487	3653
		330	4811	0.9429	0.00252	494	4028
		360	4099	0.9417	0.00257	500	4734
	Clopidogrel 75 mg od	30	8718	0.9688	0.00181	286	287
		60	8557	0.9603	0.00204	362	372

Table 5: Kaplan-Meier survival analysis results by clinical endpoint, treatment and time intervals- PLATO full analysis set

Clinical endpoint	Randomised treatment	Days from randomisation	Patients at risk	Estimated event-free survival	Survival standard error	Cumulative number of events*	Censored observations (cumulative)
		90	8477	0.956	0.00215	401	413
		120	8404	0.951	0.00227	445	442
		150	8330	0.9466	0.00236	484	477
		180	8073	0.9437	0.00242	509	709
		210	6988	0.9414	0.00248	527	1776
		240	6697	0.939	0.00254	544	2050
		270	6409	0.9366	0.0026	561	2321
		300	5133	0.934	0.00268	576	3582
		330	4779	0.9319	0.00275	587	3925
CV Death	Ticagrelor 90 mg bd	30	9021	0.9805	0.00144	181	131
		60	8921	0.9763	0.00158	219	193
		90	8877	0.9736	0.00167	244	212
		120	8821	0.9712	0.00174	266	246
		150	8788	0.9692	0.0018	284	261
		180	8602	0.9678	0.00184	297	434
		210	7389	0.9666	0.00188	306	1638
		240	7107	0.9646	0.00195	321	1905
		270	6796	0.9627	0.00201	335	2202
		300	5265	0.9615	0.00205	342	3726
		330	5123	0.9604	0.0021	348	3862

Table 5: Kaplan-Meier survival analysis results by clinical endpoint, treatment and time intervals- PLATO full analysis set

Clinical endpoint	Randomised treatment	Days from randomisation	Patients at risk	Estimated event-free survival	Survival standard error	Cumulative number of events*	Censored observations (cumulative)
		360	3208	0.9595	0.00214	352	5773
	Clopidogrel 75 mg od	30	8970	0.9765	0.00157	217	104
		60	8862	0.9706	0.00176	271	158
		90	8817	0.9681	0.00183	294	180
		120	8775	0.9657	0.0019	316	200
		150	8737	0.9635	0.00196	336	218
		180	8573	0.9614	0.00201	355	363
		210	7362	0.9588	0.00208	376	1553
		240	7077	0.9561	0.00216	396	1818
		270	6620	0.9548	0.0022	405	2266
		300	5438	0.9528	0.00227	417	3436
		330	5084	0.9504	0.00236	430	3777
		360	4303	0.9485	0.00243	440	4548
Stroke	Ticagrelor 90 mg bd	30	8976	0.9938	0.00082	57	300
		60	8868	0.9923	0.00091	70	395
		90	8807	0.9908	0.001	84	442
		120	8736	0.9898	0.00106	93	504
		150	8721	0.9891	0.00109	99	513
		180	8443	0.9884	0.00113	105	785

Table 5: Kaplan-Meier survival analysis results by clinical endpoint, treatment and time intervals- PLATO full analysis set

Clinical endpoint	Randomised treatment	Days from randomisation	Patients at risk	Estimated event-free survival	Survival standard error	Cumulative number of events*	Censored observations (cumulative)
		210	7162	0.988	0.00115	108	2063
		240	7057	0.9876	0.00117	111	2165
		270	6736	0.9871	0.0012	114	2483
		300	5148	0.9866	0.00124	117	4068
		330	5078	0.986	0.00128	120	4135
		360	2784	0.9851	0.00137	124	6425
	Clopidogrel 75 mg od	30	8935	0.9951	0.00073	45	311
		60	8816	0.9936	0.00083	58	417
		90	8757	0.9927	0.00089	66	468
		120	8719	0.9923	0.00092	70	502
		150	8680	0.9915	0.00097	77	534
		180	8456	0.9906	0.00102	85	750
		210	7092	0.99	0.00105	89	2110
		240	6959	0.9889	0.00112	97	2235
		270	5725	0.9884	0.00116	100	3466
		300	5184	0.9879	0.0012	103	4004
		330	5009	0.9877	0.00121	104	4178
		360	1847	0.987	0.00134	106	7338
All Cause Mortality	Ticagrelor 90 mg bd	30	9021	0.9799	0.00146	186	126

Table 5: Kaplan-Meier survival analysis results by clinical endpoint, treatment and time intervals- PLATO full analysis set

Clinical endpoint	Randomised treatment	Days from randomisation	Patients at risk	Estimated event-free survival	Survival standard error	Cumulative number of events*	Censored observations (cumulative)
		60	8921	0.9745	0.00164	236	176
		90	8877	0.9712	0.00174	266	190
		120	8821	0.9683	0.00183	293	219
		150	8788	0.9657	0.00189	316	229
		180	8621	0.9636	0.00195	335	377
		210	7389	0.9624	0.00199	345	1599
		240	7107	0.9601	0.00206	362	1864
		270	6796	0.9578	0.00213	379	2158
		300	5265	0.9565	0.00218	387	3681
		330	5123	0.9552	0.00223	394	3816
		360	3208	0.9543	0.00227	398	5727
	Clopidogrel 75 mg od	30	8970	0.9757	0.0016	225	96
		60	8862	0.9683	0.00182	292	137
		90	8817	0.9654	0.0019	319	155
		120	8775	0.9624	0.00198	346	170
		150	8737	0.9595	0.00206	373	181
		180	8573	0.9569	0.00212	396	322
		210	7362	0.9538	0.0022	421	1508
		240	7077	0.9508	0.00228	444	1770
		270	6620	0.9491	0.00233	456	2215

Table 5: Kaplan-Meier survival analysis results by clinical endpoint, treatment and time intervals- PLATO full analysis set

Clinical endpoint	Randomised treatment	Days from randomisation	Patients at risk	Estimated event-free survival	Survival standard error	Cumulative number of events*	Censored observations (cumulative)
		300	5438	0.9465	0.00241	472	3381
		330	5084	0.9434	0.00252	489	3718
		360	4316	0.9407	0.00261	503	4472

*Cumulative patients with first event at the timepoint of interest.
bd Twice daily dosing; CV Cardiovascular; MI Myocardial infarction; od Once daily dosing.

B10. Please provide more detailed results of primary and secondary endpoints stratified by gender and age, preferably in 10 year bands (for the whole trial population).

Table 6:

[redacted]

Table 6: [redacted]

[redacted]

Table 6: [redacted]

[redacted]

Section C: Clarification on cost-effectiveness data

C1. Priority question: Please clarify the rationale for the chosen model structure and assumptions in light of the following:

The ERG has commented on the simplicity of economic model and raised concerns that this could hinder the exploration of key issues and provision of robust evidence of cost-effectiveness. The ERG has highlighted that, given the small outcome difference between the treatments, the ICER must be considered vulnerable to small alterations in projection methods, modelling assumptions and parameter values. It notes that the final estimated survival gain is 20 times the initial result reported in the PLATO trial. Since nearly 95% of the estimated benefit is generated by the post-trial Markov model, it is important that this model should be robust and reflect current knowledge of the long-term experience of patients with chronic cardiovascular disease. The ERG has commented that the Markov model is designed with a basic structure which assigns patients to health states on the basis of the occurrence of a first non-fatal MI or stroke event which then governs their future care and mortality until death. There are concerns that this may not reflect the natural history of cardiovascular disease and does not allow for exploration of key assumptions, for example whether early survival gain could be attenuated over time as accumulating patient histories converge. The ERG suggests that a more detailed model reflecting the complex sequence of events suffered by cardiovascular patients over their lifetime could be more appropriate.

In particular, the ERG have noted the following as areas of concern:

- long-term non-fatal event risks are fixed for life and do not reflect known alterations due to ageing, previous (and accumulating) event history, patient type (single or multivascular disease) and disability status (following a severe stroke)

- long-term mortality rates are adjusted for age but not for event history or patient type

- only initial non-fatal MI and stroke events are projected, so that subsequent non-fatal events and all fatal events are not explicitly estimated and no NHS costs are explicitly estimated for them

- implicitly the fatality rates of subsequent events are assumed to be immaterial within the model, though the ERG has shown that fatality is influenced by age, gender, previous event history and patient type.

Our response to this query is in line with that emailed on 2nd December 2010 with additional justification provided.

We are, extremely concerned with the Evidence Review Group's (ERG's) comments regarding the simplicity of the model and the ERG's view that if these issues are not addressed the Appraisal Committee will have insufficient evidence to inform decision making. We have provided some clarification in response to these comments which

we hope will provide further reassurance regarding the robustness of the results and the validity of the ticagrelor model.

- Consistency with previous NICE STAs and clinical guidelines

We are particularly concerned that the ERG does not appear to have considered other ACS models reviewed and accepted by NICE for the following clinical guideline and technology appraisals:

  - The early management of unstable angina and non-ST-segment elevation myocardial infarction. Clinical Guideline No. 94. March 2010 (referred to hereafter as CG94)

  - Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. Technology Appraisal No.182. October 2009 (TA182)

  - Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. Technology Appriasal No. 82. July 2004 (TA82)

  - The use of glycoprotein inhibitors in the treatment of acute coronary syndromes. Technology Appraisal No. 47. September 2002 (TA47)

In order to ensure consistency with the NICE methods and assumptions accepted within each of these appraisals / clinical guideline, we have reviewed the modelling approaches used in each and adopted a similar approach for the ticagrelor model, addressing any issued previously raised. The approach adopted in the recent clinical guideline (CG94) was a key determinant of the approach used in the ticagrelor Markov model extrapolation. We are concerned that the ERG now, via their comments, considers the approach taken in the previous models and consequently the ticagrelor model to be inappropriate.

The view of the ERG is also inconsistent with the reference case requirements of NICE. In explaining the concept of the reference case paragraph 5.2.1 of the NICE "*Updated guide to the methods of technology appraisal"* states:

"the Institute has to make decisions across different technologies and disease areas. It is therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be the most appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources."

- Post-trial extrapolation via a Markov model

The ERG comment that '*95% of the estimated benefit is generated by the post-trial Markov model*' 'is highly misleading. Ticagrelor is borderline cost-effective in the one-year trial period (cost per QALY of £36,177) and at five years the ICER estimates for all subgroups are well below current thresholds, ranging from £4,946 for STEMI patients to £10,172 for patients with unstable angina (UA). While the model projects cost effectiveness over a lifetime horizon, ticagrelor becomes highly cost-effective after very short extrapolation periods. Indeed, within two years the ICER for ticagrelor

for the overall population is £13,940 per QALY gained, well below the threshold of £20k. These results provide reassurance that the cost-effectiveness of ticagrelor is not reliant on the lifetime projections and compares favourably with the results of other NICE HTAs and peer-reviewed published papers in ACS as follows:

- *TA182 - Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention, October 2009*

  Results based on lifetime time horizon (40 years): £5,751

  Results based on 10 year time horizon: £57,641

  Results based on one-year time horizon: Clopidogrel dominant

- *TA80 - Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome, July 2004*

  Results based on lifetime time horizon (40 years): £6,078

  Results based on 5-year time horizon: £14,844

- TA47 - *The use of glycoprotein inhibitors in the treatment of acute coronary syndromes* September 2002

  Results based on lifetime time horizon (50 years): £5,738

  Results based on 5-year time horizon: £11,671

- *A cost-utillity analysis of clopidogrel in patients with non-ST-segment-elevation acute coronary syndromes in the UK* (Karnon *et al.* 2006)

  Base case results based on lifetime time horizon (34 years): £7,365

- *A cost-utillity analysis of clopidogrel in patients with ST elevation acute coronary syndromes in the UK* (Karnon *et al.* 2010)

  Base case results based on lifetime time horizon: £3,891

- Robustness of data sources

We would also highlight the robustness of the data sources we have used for the more limited time horizon of five years or less.

The transition probabilities for both the Non-fatal Stroke to Dead and Post Stroke to Dead health states within the Markov model were based on relative risks from Dennis *et al*, 1993. This paper provides the relative risk of death for both the first year and subsequent years post stroke compared with people of a similar age and sex in the general population in Oxfordshire (7.43 and 2.07 respectively). This study was selected as it was based on a UK dataset (the Oxfordshire Community Stroke Project) and had the longest follow-up of all papers reviewed with 6.5 years i.e. well beyond the period of time within which ticagrelor becomes cost-effective.

The transition probabilities for both the No Event to Dead and Non-fatal MI to Dead health states within the Markov model were taken from GG94 published in March 2010. For the purposes of the cost-effectiveness analysis the economic model

developed by the National Collaborating Centre for Chronic Conditions, calculated standardised mortality ratios and estimates of life expectancy for people who were: 1) alive at one year and had had a new MI in the past year; and 2) alive at one year but had not had a new myocardial infarction (MI) in the past year. These standardised mortality ratios, based on an analysis of Myocardial Ischaemia National Audit Project (MINAP) data, were 1.9720 and 5.2103 respectively, and these values have been used in our Markov model. As stated in the guideline, "*These results were plausible and these methods were used to provide estimates of life expectancy for those alive at one year in the cost–effectiveness analysis".*

The transition probabilities for the No Event to Non-fatal MI or Non-fatal Stroke health states have been taken from a Myocardial Ischaemia National Audit Project/General Practice Research Database (MINAP/GPRD) study, titled *Long-term treatment strategies, outcomes and resource use in patients with acute coronary syndrome – an observational study across secondary and primary care in a UK population*, which is due for publication in the first half of 2011. This study, sponsored by AstraZeneca and undertaken by GPRD with a steering committee including Alan Begg, Professor Keith Fox, Professor Harry Hemingway, Professor Kausik Ray and Professor Adam Timmis, follows up patients admitted to hospital with ACS for a period of up to 24 months in both secondary and primary care. Based on data from the study, the probability of having a non-fatal MI in the period 12-24 months post initial event was 3.15% whilst the probability of having a stroke was 1.02%. It was assumed for the purposes of the Markov model that these probabilities remain constant. This assumption is consistent with that made in CG94, "*It is assumed the probability of having these events is constant over time",* the only difference being that in CG94, the annual probability of MI was 4%. This assumption is also consistent with that used in TA80 and TA47 in which the probability of MI in the Markov model was taken from the Nottingham Heart Attack Register, which included a cohort of patients with five year's follow-up, and was found to be constant over this time period.

- Robustness of Results

In addition to the extensive sensitivity analyses already performed and detailed in the submission document, further sensitivity analyses are provided in Table 7 to show the robustness of the results to changes in the time horizon and relative risks associated with the Markov extrapolation.

Table 7: Further sensitivity analyses on the ICER for different time horizons, changes to the relative risks used in the extrapolation and reduction in clopidogrel costs

ICER	Time Horizon						
Relative Risks (RRs)	**1-year**	**2-years**	**3-years**	**5-years**	**10-years**	**20-years**	**40-years**
RRs as per base case*	£36,177	£13,940	£9,215	£6,075	£4,182	£3,705	£3,696
Reduce all RRs by 25%	£36,177	£13,890	£9,136	£5,961	£4,007	£3,438	£3,416
Reduce all RRs by 50%	£36,177	£13,841	£9,059	£5,849	£3,838	£3,170	£3,117
Reduce all RRs by 75%	£36,177	£13,793	£8,982	£5,740	£3,675	£2,905	£2,782
Increase all RRs by 25%	£36,177	£13,990	£9,295	£6,192	£4,364	£3,968	£3,965
Increase all RRs by 50%	£36,177	£14,040	£9,375	£6,311	£4,552	£4,226	£4,225
Increase all RRs by 75%	£36,177	£14,090	£9,457	£6,433	£4,745	£4,479	£4,479
Increase all RRs by 100%	£36,177	£14,141	£9,540	£6,557	£4,943	£4,729	£4,729
Changes in cost of clopidogrel							
Pack cost reduced by 50%**	£38,759	£14,891	£9,891	£6446	£4,410	£3,894	£3,885
Clopidogrel free of charge	£41,341	£15,843	£10,423	£6,818	£4,637	£4,083	£4,073

* Base case relative risks:

Relative risk of death from any cause for patients with no further event in the PLATO study = 2.21

Relative risk of death first year after a Non-fatal MI = 5.84

Relative risk of death second and subsequent years after a Non-fatal MI = 2.21

Relative risk of death first year after a Non-fatal Stroke = 7.43

Relative risk of death second and subsequent years after a Non-fatal Stroke = 2.07

**Base case cost of clopidogrel = £3.40 per pack

As can be seen from Table 7, the ICER remains consistently below £15k at two years and £5k at 40 years despite substantial variations to the size of the relative risks in the Markov model extrapolation. This provides further reassurance that the cost-effectiveness of ticagrelor is not driven by the extrapolation but rather from the mortality benefit that can be seen at one-year, based on the PLATO study. With respect to changes in the price of clopidogrel, reducing the pack price by 50% from £3.40 to £1.70 does not increase the ICER to above £15k within the 2-year time horizon and even if the price of clopidogrel is set to zero, the ICER at two years is still only £15,843. This serves to provide reassurance that as the price of generic clopidogrel continues to fall, ticagrelor will remain cost-effective.

- Requirement for a model of the natural history of cardiovascular patients

While we acknowledge that, as suggested by the ERG, a more detailed model could potentially provide additional precision; such an approach was not deemed necessary for the ticagrelor submission since it is unlikely to make any material difference given the comments made above about the time horizon. In addition, it should be noted that the appraisal of ticagrelor is for the treatment of acute coronary syndromes – this is an acute event currently treated with clopidogrel for a period of up to 12 months. As an acute event it could be questioned whether extrapolation over the lifetime of the patient is actually necessary. This is in contrast to the treatment of other cardiovascular conditions such as the prevention of occlusive vascular events where longer term treatment is required. In the recently published NICE guidance on clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (TA210) the treatments reviewed are used for longer durations and as a consequence extrapolation over a longer periods of time becomes more appropriate.

In summary we do not agree with the concerns of the ERG and believe that the ticagrelor model will provide the Appraisal Committee with a clear and robust evidence base on which to base their decisions on the cost effectiveness of ticagrelor. The approach taken within the ticagrelor submission is entirely consistent with that taken within previous NICE work programmes, including the recently published NICE clinical guideline (CG94), which has already been accepted as valid by NICE. In addition, the health economic model for ticagrelor is highly transparent and, as a result of the modelling approach taken, can be easily modified by the ERG to explore any alternative assumptions - this is actually a major strength of the modelling approach employed.

Baseline Characteristics

C2. Please provide a table showing the following baseline characteristics for each treatment group by each modelled population/sub-population:

- age: mean, standard deviation, minimum, maximum

- proportion with previous history of stroke/TIA

- proportion with previous history of peripheral vascular disease (PAD)

- proportion with substantial/severe disability (Rankin scale 3+ or equivalent) at baseline.

Tables 8 to 10 below show the requested parameters for patients with UA, non ST elevation Myocardial Infarction (NSTEMI) and ST elevation Myocardial Infarction (STEMI). The data for baseline disability (Rankin scale) are not available as this information was not collected on the eCRF.

Table 8: Summary of age and medical history of prior stroke, TIA or PAD at enrolment for UA patients - PLATO full analysis set

Characteristic	Statistic or Category	Randomised Treatment Ticagrelor 90 mg bd N = 1549	Randomised Treatment Clopidogrel 75 mg od N = 1563
Age (years)	Mean	64.0	63.9
	SD	10.55	10.48
	Median	65	64
	Min	28	28
	Max	97	90
Non-haemorrhagic Stroke	No	1465 (94.6%)	1474 (94.3%)
	Yes	84 (5.4%)	88 (5.6%)
Transient Ischaemic Attack (TIA)	No	1497 (96.6%)	1504 (96.2%)
	Yes	52 (3.4%)	59 (3.8%)
Peripheral Arterial Disease	No	1428 (92.2%)	1426 (91.2%)
	Yes	121 (7.8%)	137 (8.8%)

bd Twice daily dosing; od Once daily dosing; PAD Peripheral atererial disease; TIA Transient ischaemic attack; UA Unstable angina.
Note: Unstable angina classification is based on the final diagnosis of the index event.

Table 9: Summary of age and medical history of prior stroke, TIA or PAD at enrolment for NSTEMI patients - PLATO full analysis set

Characteristic	Statistic or Category	Randomised Treatment Ticagrelor 90 mg bd N = 4005	Randomised Treatment Clopidogrel 75 mg od N = 3950
Age (years)	Mean	63.7	64.0
	SD	10.98	11.08
	Median	64	64
	Min	26	25
	Max	95	94
Non-haemorrhagic Stroke	No	3843 (96.0%)	3784 (95.8%)
	Yes	162 (4.0%)	166 (4.2%)
Transient Ischaemic Attack (TIA)	No	3878 (96.8%)	3820 (96.7%)
	Yes	127 (3.2%)	130 (3.3%)
Peripheral Arterial Disease	No	3713 (92.7%)	3651 (92.4%)
	Yes	292 (7.3%)	299 (7.6%)

bd Twice daily dosing; NSTEMI Non-ST elevation myocardial infarction; od Once daily dosing; PAD Peripheral atererial disease; TIA Transient ischaemic attack.
Note: NSTEMI classification is based on the final diagnosis of the index event.

Table 10: Summary of age and medical history of prior stroke, TIA or PAD at enrolment for STEMI patients - PLATO full analysis set

Characteristic	Statistic or Category	Randomised Treatment Ticagrelor 90 mg bd N = 3496	Randomised Treatment Clopidogrel 75 mg od N = 3530
Age (years)	Mean	59.5	59.6
	SD	11.15	11.05
	Median	59	59
	Min	19	21
	Max	91	92
Non-haemorrhagic Stroke	No	3399 (97.2%)	3423 (97.0%)
	Yes	97 (2.8%)	107 (3.0%)
Transient Ischaemic Attack (TIA)	No	3436 (98.3%)	3476 (98.5%)
	Yes	60 (1.7%)	54 (1.5%)
Peripheral Arterial Disease	No	3354 (95.9%)	3399 (96.3%)
	Yes	142 (4.1%)	131 (3.7%)

Bd Twice daily dosing; od Once daily dosing; PAD Peripheral aterial disease; STEMI ST elevation myocardial infarction; TIA Transient ischaemic attack.
Note: STEMI classification is based on the final diagnosis of the index event.

Patient Pathways

C3. Please provide separate analyses in the format of Table 6.4 of the manufacturer's submission for sub-groups defined by:

- each modelled subgroup split between:

(i) those patients with a previous history of stroke/TIA and/or PAD and

(ii) those with no such previous history (i.e. only with history of previous cardiac events/diagnosis).

Table11: [redacted]

Table 11: [redacted]

[redacted]

[redacted]

Risk Regression Analysis

C4. Please carry out for each modelled population/sub-population Cox proportional hazards regression analyses of the following events (censored by the other two events and other withdrawals):

- acute MI (fatal and non-fatal combined)

- acute Stroke/TIA (fatal and non-fatal combined)

- other death (not MI or stroke)

Please include the following factors as covariates in the analyses:

- age (in years) at baseline

- gender

- serious/severe disability (Rankin 3+ or equivalent) at baseline

- randomized treatment

Table 12 below shows the Cox proportional hazards regression analysis for MI and stroke with age, sex, and randomised treatment as covariates. The requested analyses could not be performed exactly as specified because some of the data required to do so are not available as specified in the PLATO database. Specifically:

- TIA was not included in the stroke endpoint.
- Deaths were adjudicated according to the protocol as CV death or non-CV death. The CV death definition included a broader group of events than fatal MIs and fatal strokes, so it is not possible to derive "other death."
- Strokes were not classified according to Rankin scale at baseline because that information was not collected on the eCRF.

In addition, further analyses broken down by modelled subgroups would not be meaningful because of the small number of events.

Table 12: Risk regression analysis - PLATO full analysis set

Clinical Endpoint	Covariate	Regression coefficient	Standard Error	p-value
MI(exc silent)	Age	0.0247	0.00289	<0.0001
	Sex	0.0254	0.06707	0.7048
	Treatment	-0.17	0.06057	0.005
Stroke	Age	0.0451	0.00651	<0.0001
	Sex	0.0985	0.14232	0.4889
	Treatment	0.167	0.13213	0.2063

MI Myocardial infarction

The treatment effect observed in this analysis is consistent with the original analysis of the PLATO primary composite efficacy endpoint and its components.

C5. Please report regression coefficients for each variate with standard errors and significance level (p-value).

See the response to question C4.

References

Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. Stroke 1993 Jun;24(6):796-800.

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Thygesen, K, Alpert JS, and White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28: 2525–38.

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