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APPLICATION NUMBER:

204958Orig1s000

OTHER ACTION LETTERS



NDA 204958

COMPLETE RESPONSE

The Medicines Company
ATTENTION: Stephen Sherman, JD, M.B.A.
Senior Director, Global Regulatory Affairs
8 Sylvan Way
Parsippany, NJ 07054

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated April 30, 2013, received April 30, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Kangreal (cangrelor) for injection.

We acknowledge receipt of your amendments dated May 2, 6, 15, and 24, June 17, 24, and 26, July 12 and 26, August 2, 9, 15, 19, and 30 (two), September 6, 10, 12, and 20, October 7, 9 (two), 11, 15, and 25, November 6, 8, 15 (three), and 29, December 5, 11, 19, 23, 26, and 30, 2013, and January 10 (two), 14, and 16, February 6, 14, 21, 24, 27, and 28 (two), March 5, 18 (two), 19, 26, and 28, April 2, 10, 14 (two), and 15, 2014

We have completed our review of this application, as amended, and have determined that we cannot approve the application at the present time. We describe our reasons for this action below and, where possible, provide suggestions for addressing these issues (organized by proposed indication; we refer to the first indication you are seeking as the "PCI Indication" and the second as the "BRIDGE Indication"):

PCI Indication

The following issues prevent approval at the current time.

1. Some subcomponents of the primary endpoint in CHAMPION-PHOENIX may not represent clinical benefit.
 - a. Intra-procedural stent thrombosis (IPST) has not been considered evidence of effectiveness in the past and the Cardio-Renal Advisory Committee was plainly skeptical about its meaningfulness. It represented a substantial fraction of the stent thromboses observed in the CHAMPION-PHOENIX study. Whether IPST should have been included in the composite primary endpoint appears debatable. We note your argument that observational studies suggest that patients who have IPST have worse outcomes, but such studies cannot distinguish whether IPST is itself a cause of such outcomes or merely

identifies patients at higher risk for worse outcomes. It could be argued that the results of PHOENIX, with no survival effect, make it unlikely that prevention of IPST had an important effect on later mortality.

- b. The clinical importance of peri-procedural MIs identified solely by increases in serum biomarkers of myocardial necrosis is unclear and has been debated. Although increases in post-procedural cardiac muscle biomarkers are associated with increased risk for subsequent cardiovascular events, it is again unclear whether they increase the risk of subsequent events or are simply a marker for subsequent events. We note that post-procedure measurement of serum biomarkers after uncomplicated PCI is not recommended in guidelines and apparently is not routine. It thus appears that interventional cardiologists are not persuaded that post-procedural measurement of serum biomarkers in the absence of symptoms and/or ECG changes provides clearly useful prognostic information.

On the other hand, we note that we have accepted such biomarker MIs occurring early after a finding of acute coronary syndrome, often with angioplasty, as valid endpoints in studies of prasugrel and ticagrelor, where they were especially prominent early in the study and considerably decreased by the test treatment. We also found, after consulting the literature on this matter, that a consensus document endorsed by the Society for Cardiovascular Angiography and Interventions (JACC 2013; 62:1563–70) concludes that in patients without biomarker elevation prior to PCI the “preponderance of the best scientific evidence support(s) post-PCI elevation of CK-MB to > 10x ULN as being clinically relevant.”

We recognize that your primary composite endpoint included both IPST and other stent thrombosis, and biomarker MIs with varying levels of CK-MB elevation and that the overall result reflected effects on all of these outcomes. We suggest that you perform a series of sensitivity analyses in which you modify the primary analysis of PHOENIX by

- First removing IPST from the endpoint,
- then removing both IPST and MIs identified solely on the basis of CK-MB > 3x ULN but < 10x ULN (i.e., without any accompanying symptoms or ECG changes), and
- finally removing IPST and all MIs identified solely on the basis of an increase in CK-MB (i.e., leaving death, ischemia driven revascularization, and ARC-defined stent thrombosis)

We recognize that you have provided some of these analyses in your clinical study report, but we are expecting a more detailed and formal analysis reflecting the issues raised at the Advisory Committee meeting.

We also suggest you perform a sensitivity analysis analogous to the primary analysis but in which the events included consist solely of site-reported events, defined as death, MIs noted on the checkbox on the MI CRF, and unplanned revascularization or stent thrombosis noted on the checkboxes on the revascularization CRF. We are sure you will want to discuss the implications of these results, as well as the implications of the omitted events.

2. You state in the CHAMPION-PHOENIX clinical study report that the database was initially locked and unblinded on January 4, 2013 and then later unlocked between February 1, 2013 and February 18, 2013 so as to include missing data regarding anticoagulant therapy prior to or during PCI for 5% (553) subjects at 84 investigational sites. We understand that unlocking of a database after unblinding is not unusual and may not be problematic so long as procedures to maintain integrity are documented and followed.
 - a. Please provide the documents that stipulate the procedures followed during this process and that verify the procedures were followed.
 - b. Please provide datasets from before unlocking and after unlocking for any datasets that were changed during the unlocking. Please also provide the AE, BLDH, BLDEVT, DISP, DTH, ENDPOINT, IDRH, MIH, and SAECASE datasets before and after regardless of whether there were any changes.
 - c. Please provide a list of any other changes made to the database between February 1, 2013 and February 18, 2013, other than the anticoagulant changes.
 - d. Please provide a dataset identifying the 553 patients, by site, who were missing anticoagulant data when the database was unlocked and whether or not the site provided updated anticoagulant use data via the paper CRF query that you utilized.
 - e. Please provide a summary table identifying the percentage of sites that responded to the data query, and percent of subjects for which this data was obtained by treatment arm.
 - f. Please provide responses to the following questions:
 - i. Whether a subject was administered heparin or bivalirudin does not appear to be critical for interpreting the efficacy or safety outcomes of PHOENIX, especially as the data was missing for only about 5% of subjects. Why was the missing information thought to be important enough to require unlocking the database? Please provide the reason(s) (i.e., root cause) that some sites did not record information about anticoagulant therapy administered prior to or during the PCI procedure for only some subjects, and why this was not identified during on-site, remote, or central monitoring during the conduct of the study?
 - ii. The clinical study report states that it is “believed that there may have been some confusion on how to collect these data within the eCRF.” If the CRF was confusing, then why was the information missing for only about 5% of subjects?
 - iii. The reason(s) you elected to return paper CRF pages to sites on which the site was to make corrections as opposed to issuing data queries to sites and requesting that they update and resign eCRFs.
 - iv. The reason(s) you elected to unlock the database, and leave it unlocked while you were obtaining corrected data from sites, as opposed to first collecting this information from sites and then unlocking database to make corrections.
 - v. What process did you use to ensure that for those sites that responded, the data provided were accurate?

- vi. A more detailed summary of how it was initially determined that a systemic issue was present that some sites had not recorded anticoagulant therapy prior to or during the PCI procedure for some subjects.
3. Lack of documentation on bioequivalence of the overencapsulated clopidogrel clinical supplies to the US approved clopidogrel product. You failed to perform and submit acceptable studies documenting that the overencapsulated clopidogrel clinical supplies used in the CHAMPION trials are bioequivalent to the US approved clopidogrel product. While we had requested appropriate bioequivalence studies on the actual clinical supplies in an Advice Letter (under IND 56812) dated September 9, 2010, we understand now that actual clinical supplies are no longer available. However, we may be able to judge bioequivalence based on appropriate dissolution studies on clopidogrel tablets overencapsulated to the same specifications used in the CHAMPION trials.
- a. Provide documentation on the clopidogrel products, capsules, and production runs for the overencapsulated clopidogrel clinical supplies for all CHAMPION trials. Based on that documentation we will advise you regarding what studies you should perform to document bioequivalence of overencapsulated clopidogrel formulations to the US approved clopidogrel product.

BRIDGE Indication

We have concluded that a study in which the endpoint is some measure of platelet activity is incapable of providing the substantial evidence of efficacy and safety required for approval under current regulatory standards. Only a prospective adequate and well-controlled study in which outcomes are assessed can result in the data necessary to quantify the relevant clinical safety and efficacy outcomes required to assess the benefit-risk relationship for the use of cangrelor in this indication. We recognize that the rate of stent thrombosis during the brief period in which clopidogrel is stopped would make a study of this endpoint difficult or impossible, but believe effects on bleeding could be assessed.

ADDITIONAL COMMENTS

We have the following comments that should be addressed. They are not currently approvability issues, but could affect labeling:

- 1. You presented the following analysis of outcomes by subject presentation on slide CE-80 titled “Consistent Effect across All Subgroups” to the advisory committee at which this application was discussed:

		Cangrelor	Clopidogrel	OR (95% CI)	P [Int]
Overall		257/5470 (4.7)	322/5469 (5.9)	0.79 (0.67,0.93)	
Stable Angina		181/3120 (5.8)	222/3018 (7.4)	0.78 (0.63,0.95)	
NSTE-ACS		49/1389 (3.5)	62/1421 (4.4)	0.80 (0.55,1.17)	0.98
STEMI		27/961 (2.8)	38/1030 (3.7)	0.75 (0.46,1.25)	

We have performed a similar analysis using the clinical presentation entered into the IVRS during randomization and get somewhat different results; in particular the odds ratio for subjects with STEMI is 1.01 with 95% CI (0.56, 1.83). Your analysis is different because

you classified clinical presentation based on “derived type” using a process we do not fully understand. Please provide an exact and detailed description of this process, including when and why you decided it was necessary, the calendar dates during which it was performed, and the name of the group or groups responsible for performing it. In addition, please provide a tabular data set that lists all subjects for whom the clinical presentation entered into the IVRS is different the derived-type algorithm and includes the following:

- a. Subject ID
 - b. Clinical presentation entered in the IVRS
 - c. Date/time entered in the IVRS
 - d. “Derived” clinical presentation
 - e. Date/time of “derived” clinical presentation
 - f. Reason for reclassification
 - g. Data used to reclassify
 - h. Investigator queried about reclassification (yes or no)?
 - i. If yes to (8), did the investigator agree with the change in diagnosis (yes or no)?
Hyperlink to supporting documentation (i.e. query, response, data correction form), investigator’s signature.
2. We are uncertain whether the data from PHOENIX, although they show an effect in these patients, are sufficient to establish the utility of cangrelor for the treatment of patients with stable angina undergoing PCI. Patients with stable angina can be preloaded with a platelet P2Y₁₂ receptor inhibitor before their angiography and if CABG is needed, it can be delayed for the week or so until the anti-platelet effects have diminished. Giving the P2Y₁₂ receptor inhibitor prior to PCI may be preferable because it avoids the approximately two-hour post-PCI decrease in platelet inhibition that occurs after administration of cangrelor followed by clopidogrel. We believe that if cangrelor were to be approved, it is not clear which patients with stable angina could be given clopidogrel only when PCI is initiated, the population in which an effect has been shown.

Please explain why you believe the data from PHOENIX support use of cangrelor as an adjunct to PCI in patients with stable angina.

3. We are not certain if the data from PHOENIX are relevant to current American practice. The protocol
- Restricted use of glycoprotein 2b/3a inhibitors to treatment for thrombotic complications of PCI, which is not consistent with either current guidelines or practice, although it is clear many patients are not given these drugs.
 - Initiated clopidogrel only at the start of PCI, although as you noted in May 7 2007 Presentation to the CHAMPION-PCI and PLATFORM Executive Committee, clopidogrel must be loaded at least 2 hours before PCI to have adequate effect. It will be important to show that such late initiation (i.e., at the start of PCI) remains reasonably frequent practice.

Please explain why you believe the data from PHOENIX are relevant to current American practice.

4. We remind you of the major labeling issues identified at the late cycle meeting regarding the in-use period of the drug product after dilution. Per your diluted product hold time study, the product label should be (b) (4) the storage period for the reconstituted drug product, diluted in 5% Dextrose to 12 hours at room temperature.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, “Formal Meetings Between the FDA and Sponsors or Applicants,” May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V (‘the Program’). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call:

Alison Blaus, RAC
Senior Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
04/30/2014