Author's response to reviews

Title: An Open-label, Sequential, Dose-finding Study of Peginesatide for the Maintenance Treatment of Anemia in Chronic Hemodialysis Patients

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Response to Reviewers

Referee 1

Comment 1: The majority of the study population was black patients. Do the authors believe that this fact could have any impact on study outcome?
Response: We agree the high proportion of Black patients may have had an effect on study results because ESA dose requirements tend to be higher in Black than in White patients. This is now discussed in the limitations section of the Discussion on page 19.

Comment 2: Baseline and Demographic characteristics (Table 2, page 26): Are there any significant differences between the analyzed cohorts?
Response: This was a phase 2, open-label, non-randomized, sequential dose-finding study. Per the statistical analysis plan for this study, baseline and demographic characteristics were summarized descriptively and, therefore, no statistical comparisons were planned between the cohorts. An explanation of this was added to the Statistical Analysis section of the manuscript.

Comment 3: Adverse events/Safety (page 9), A high rate of adverse events was reported. “Adverse events were reported in 137 of 164 patients (84%), of which, 93 patients (68%) had AEs considered mild to moderate in severity….Serious adverse events were reported in 27 of 139 patients (20%)”:
- The exact number of patients with AE (139 vs. 137) could be unclear for the reader.
- Of particular interest, these percentages in dialysis patients are similar to that seen in nondialysis patients, reported by MacDougall and colleagues (Clin J Am Soc Nephrol. 2011 Nov;6(11):2579-86). This is important, as the authors state in the discussion: “The observed SAEs were consistent with events that have been described in dialysis populations with multiple comorbidities.” The authors should clarify this potential ambiguity.
Response: It is not unexpected that a high rate of adverse events was reported in a dialysis cohort of patients (because any new symptom or change in parameter from baseline is considered a potential adverse event) and this has been observed in other trials with other ESAs and in the original phase 3 study of epoetin alfa (Eschbach et al, Ann Int Med. 1989;111:992-1000). The high rate of adverse events reported should not be confused with adverse events that were considered to be related to the investigational product which were low overall in this study (reported by 9.1% of patients). Page 13, the number of patients experiencing an SAE has been corrected: “Serious adverse events were reported in 47 of 164 patients (29%).” In addition, the Macdougall paper is now cited in the Discussion section on page 18. Further, all data have been re-checked against original source tables to verify no additional discrepancies were missed.

Comment 4: A potential discrepancy in trends of median peginesatide doses is obvious between the sections Result (page 7) and Discussion (page 12): …both groups trend towards… vs. …this general trend was not observed in cohorts that used tiered conversion tables…. The authors should clarify this.
Response: The description of the trend on page 16 in the Discussion has been clarified to be aligned with that in the Results.

Comment 5: A Dose-finding study of peginesatide for anemia correction in nondialysis chronic kidney disease patients was recently presented by MacDougall and coworkers MacDougall IC et al. Clin J Am Soc Nephrol. 2011 Nov;6(11):2579-86. The authors should include this study in the Discussion section.
Response: The Macdougall paper is now cited on page 18 in the Discussion section.

Comment 6: page 5, last sentence: conversion from instead of to
Response: This text on page 6 has been revised as suggested.

Comment 7: Some words regarding potential harms of peginesatide in the Introduction section could be of interest for those readers who are not so familiar with investigational ESA.
Response: The following has been added to the Background on page 5: “Standard therapies for CKD-associated anemia are erythropoiesis-stimulating agents (ESAs), which have been shown to increase and maintain hemoglobin (Hb) levels leading to a decreased need for red blood cell transfusions [3]. These agents have also been associated with an increased risk of death and cardiovascular events in clinical trials targeting normalized hemoglobin levels [4-7].”

Referee 2

Comment 1: In the results section, the authors refer to combining 3 pairs (sic) of cohorts, D, G and H, but these cohorts look very different in Table 1. This therefore needs to be made much clearer.
Response: The text on page 10 has been revised to clarify that a pair of the original 11 cohorts was collapsed into one cohort for cohort D, and similarly pairs were collapsed into cohort G and into cohort H. This explains why there are only 8 cohorts described and why each these 3 cohorts (D, G, and H) contain 30 patients instead of 15 patients.

Comment 2: The authors do not state in the methods how and how often they screened for antibodies against peginesatide.
Response: This information has been added to the text on page 7.

Referee 3

Comment 1: However, data presentation is suboptimal. In particular: Abstract section, results: some numeric data should also be given, no information is given about study follow-up, number of enrolled patients and administration route. Conversely the background is too long, methods are vague.
Response: The abstract as been revised to include the number of patients, route of administration, and follow-up period and the methods have been clarified.
Comment 2: Key-words: epoetin alfa should be added  
Response: Revised as suggested.

Comment 3: Conflict of interest: the authors should give all their interests in the field of anemia  
Response: Complete disclosure statements from all authors are now provided.

Comment 4: Introduction: the authors should better explain the molecular structure of peginasitide and give information about its pharmacodynamic and pharmacokinetic.  
Response: Additional information about the peginesatide molecule and its pharmacokinetics have been added to the Background on page 5.

Comment 5: Results: please specify the administration route of the two drugs.  
Response: It is now indicated on page 6 that peginesatide was administered intravenously and on page 11 the routes of administration of epoetin alfa are detailed.

Comment 6: Results; efficacy: main numeric data should be given also in the text  
Response: Some additional efficacy data were added to the text on page 12 in the Results section. The rationale for expanding the upper target range by 0.5 mg/dL to 13.0 g/dL from the upper bound of the enrollment range of 12.5 g/dL is provided in the Assessments section of the Methods on pages 8 and 9. We have also indicated the timeframe of the study at the beginning of the Results (page 10) to provide some context for the decision to use a hemoglobin target range of 11.0 to 13.0 g/dL which was consistent with practice guidelines at the time the study was conducted. This is now also discussed in the limitations paragraph on page 20 of the Discussion.

Comment 7: Discussion: mean serum ferritin and TSAT appears quite high. Please discuss this point.  
Response: Text on this topic has been added to the limitations paragraph on pages 19 and 20 of the Discussion section.

Comment 8: Discussion: neutralizing antibodies. This information should be reported in the result section.  
Response: As noted on page 16, “no patient developed antibodies specific to peginesatide;” this includes neutralizing antibodies.