Erratum to the FDA Briefing Document
Arthritis Advisory Committee
May 6, 2021

Page numbers refer to PDF page number. Paragraph numbering begins with the first new paragraph on the page unless otherwise noted.

Where these data appear in the Division's pre-recorded presentations, these errata should be applied as well.

Division Memorandum

1. The Agency acknowledges the differences in the analyses of non-multiplicity controlled secondary endpoints and presentation of the same data in the FDA and Applicant AAC backgrounders. The existing footnote 7 on page 12 explains the rationale for the Agency's presented analysis and notes the differences between this analysis and the Applicant's pre-specified analysis. The FDA AAC backgrounder also presents two-sided p-values for all analysis results in order to align with two-sided 95% CIs presented throughout the text.

2. On page 12, the statement should read as follows:

   However, these are general quality of life instruments, not specific to vasculitis.

3. On pages 22 through 26, Table 2 should be replaced by the following text:

   A Pre-IND meeting (April 21, 2014) was held to discuss ongoing Study CL002_168 in Europe. The Agency expressed concerns about timing of endpoint (12 weeks) and clinical meaningfulness of BVAS response. The Agency recommended broadening of patient population to generalized AAV. On May 19, 2014, avacopan received orphan drug designation for the treatment of AAV. On July 2014, ChemoCentryx opened an IND with Study CL003_168, a randomized, double blind, placebo-controlled, dose assessment phase 2 study in AAV.

   On July 14, 2016 (End of Phase 2) meeting, the Agency expressed concerns regarding clinical relevance of CL002_168 and CL003_168 including early time point of assessment and determination of avacopan effect from GCs and background therapy. The sufficiency of the proposed pivotal study, CL010_168, was also discussed. The Agency advised that the non-inferiority study design would not be sufficient to show that avacopan can replace steroids. The Agency suggested alternative designs including: a superiority study to show benefit of avacopan vs. glucocorticoids (GCs), change in the timing of efficacy assessment from Week 26 to Week 52 after patients have been off GCs for a more extended amount of time, and in some of the proposed options, the addition of a third treatment arm such that there is only one change in variable in each arm to determine the benefit of avacopan and the contribution of GCs. ChemoCentryx suggested alternative study designs. The Agency indicated that an assessment of remission based on BVAS 0 at Week 26, and sustained remission based on BVAS 0 at Week 52 in a superiority design would be acceptable.

Further discussions occurred at a subsequent Type C meeting on November 1, 2016 and ChemoCentryx proposed a 52-week study with two treatment groups, avacopan and prednisone, on top of rituximab or cyclophosphamide, and that the superiority analysis would be based on sustained remission at Week 52 utilizing the number of initially randomized patients as the denominator. FDA agreed with the approach and explained that the superiority analysis is critical to demonstrate efficacy and that a demonstration of non-inferiority would not be sufficient, given previously expressed concerns with the non-inferiority margin and interpretation of results from such an evaluation. ChemoCentryx agreed to the superiority analysis. The Agency raised concerns about the proposed secondary endpoints, including relapses which conditions on a post-randomization variable and in addition, the Agency did not agree that "relapse" or "minor flare" should only occur in patients after achieving remission. The Agency also raised concerns about the use and interpretation of the Glucocorticoid Toxicity Index, and health-related quality of life measurements.

On March 19, 2020, at the Pre-NDA meeting, the Agency reiterated concerns on the complexity of CL010_168 study design and determining clinical meaningfulness. The study was not designed to assess whether replacing potential toxicity of treatment with GC with potential toxicities with avacopan represents a clinical benefit to patients. Further, the Agency noted that there was limited long-term safety data of avacopan treatment. The Agency noted external input may be required in the interpretation of the clinical benefits of the avacopan program.

4. On page 33, under the section on "Concomitant therapy," should read as follows:

   Strong inducers of CYP3A4 were prohibited. Strong inhibitors of CYP3A4 were to be avoided during the study but were not absolutely contraindicated.

5. On page 33, under the section on "Concomitant therapy," the following statement should be modified as follows:

   Patients needed to receive prophylactic therapy (e.g., *Pneumocystis jirovecii* prophylaxis with sulfamethoxazole 400 mg-trimethoprim 80 mg daily) and could also receive other precautions/therapies given with RTX, CYC, or AZA.

6. On page 47, under the discussion of the Glucocorticoid Toxicity Index, the 3rd sentence of the paragraph under Table 12 should read as follows:

   Additionally, the bone domain was not included in the GTI assessment, consistent with modifications allowed for trials of less than 12 months duration. Although Study CL010_168 was a 52-week study, the Applicant only assessed the GTI at Weeks 13 and 26.

7. On page 48, the second sentence should read as follows:

   From Week 27 to 52, patients in both treatment arms received glucocorticoids; the mean cumulative dose was 276.0 mg in the avacopan arm and 462.0 mg in the prednisone arm.

8. On page 57, under the discussion of "baseline renal disease," the following 2 modifications should be made:

The bullet for “Hematuria” should read as follows:

- Hematuria: Hematuria is ≥ 10 RBCs/high power field (hpf) on microscopy

In the following paragraph, the 5th sentence should read as follows:

Concerns include only using DBP in the assessment of HTN, inability to differentiate acute versus chronic kidney disease in the elevated SCr criterion, and a lack of guidance on time course for change to determine an increase in creatinine or fall in creatinine clearance.

9. On page 57, under the discussion on “eGFR”, the statement should read as follows:

   The Applicant also performed an exploratory subgroup analysis in patients with stages of kidney disease based on GFR (i.e., eGFR < 30 mL/min/1.73 m2, 30 to 59 mL/min/1.73 m2, and > 59 mL/min/1.73 m2) and noted that the greatest change from baseline occurred in patients with < 30 mL/min/1.73 m2 at baseline.

10. On page 58, Figure 10 should include the following footnote:

    Study medication (avacopan or placebo) was discontinued at Week 52.

11. On page 66, under the discussion on “Infections,” the statement should read as follows:

    Serious opportunistic infections were observed in a lower number of avacopan-treated patients, although differences between groups are due to a small number of patients.