May 6, 2021 Arthritis Advisory Committee Meeting

Script for FDA Presentation 1: Overview of Clinical Program

FDA Presenter: Suzette Peng, MD, Medical Reviewer

Slide 1

Hello, my name is Suzette Peng. I am a practicing adult rheumatologist and a clinical reviewer in the Division of Rheumatology and Transplant Medicine.

I want to thank you for participating in the virtual advisory committee meeting to discuss the data to support the new drug application for avacopan for the treatment of adult patients with ANCA-associated vasculitis.

Slide 2

The FDA presentations will proceed as outlined here.

I will begin with an overview of the clinical program for avacopan, after which Dr.Yura Kim will discuss the statistical review of efficacy. I will then present the clinical review of efficacy, safety, and the overall benefit-risk assessment. Finally, Dr.Rachel Glaser will present the charge to the committee.

Slide 3

At this point, I will start with the first presentation, the Agency's overview of the clinical program.

My presentation will begin with an introduction on avacopan and its proposed indication.

I will review ANCA-associated vasculitis and provide a brief overview of currently available therapy and treatment guidelines.

I will next review the pertinent regulatory history, focusing on the communications regarding the phase 3 study CL-ten_168.

Then, I will present the clinical program supporting avacopan and the treatment of ANCA-associated vasculitis.

And, lastly, in this presentation, I will summarize important clinical pharmacology results from the clinical program.

Slide 4

NDA 214487 was submitted by ChemoCentryx for the new molecular entity, avacopan, an oral small molecule C5a-receptor antagonist, for the treatment of adult patients with ANCA-associated vasculitis (specifically, granulomatosis with polyangiitis and microscopic polyangiitis). The proposed dosing regimen is 30 mg by mouth twice daily, with food.

Slide 5

Vasculitis is an autoimmune disease caused by inflammation and necrosis of blood vessels and can be categorized based on the size of the vessels involved. Antineutrophil cytoplasmic antibody-associated vasculitis (or ANCA vasculitis) is a group of the small vessel vasculitides – as shown on the bottom right of this classic diagram by Jennette and Falk. These include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). As the name implies, these vasculitides are associated with antineutrophil cytoplasmic antibodies that target proteinase 3 (PR3) or myeloperoxidase (MPO). Avacopan is being developed for the treatment of GPA and MPA, as EGPA is often considered separately and will not be further discussed in this presentation.

As defined by the Chapel Hill Consensus, MPA and GPA are types of necrotizing vasculitis predominantly affecting small and medium arteries. GPA is also characterized by necrotizing granulomatous inflammation, predominantly affecting the respiratory tract.

The spectrum of disease manifestations covers a wide range from skin to upper airway to lung and kidney involvement. Based on these clinical symptoms, AAV is described as localized or generalized, which is further categorized as limited or severe. The avacopan development program focuses on severe generalized disease.

Prior to the availability of treatment, ANCA-associated vasculitis was uniformly fatal with a mean survival time of < 1 year.

Slide 6

The availability of treatment has had a profound impact on mortality. Remission rates are now as high as 90%, and mortality has decreased to 20% at 5 years.

A fundamental paradigm in the treatment of ANCA-associated vasculitis is that it is comprised of 2 phases: induction and maintenance treatment. Induction treatment typically lasts 3-6 months with the goal of establishing remission quickly. Once remission is achieved, maintenance therapy is initiated to prevent relapse. The optimal duration of maintenance is unknown.

Choice of therapy for induction and maintenance is determined by the severity of disease manifestations. As already stated, we are focusing on “severe” systemic disease.

Randomized controlled trials in the last 2 decades have led to an evidence-based approach to treatment, and guidelines have been developed by several scientific societies with similar over-arching principles. In the next slides, I will review the current treatment guidelines from the European League Against Rheumatism (EULAR) and European Renal Association-European Dialysis and Transplant Association (EDTA).

Slide 7

Current standard of care for induction treatment includes cyclophosphamide (oral or IV) or rituximab along with glucocorticoids.

Slide 8

After the introduction of glucocorticoids in the treatment regimen for vasculitis in 1948, it has had a large contribution to the improvement in mortality in ANCA-associated vasculitis, and glucocorticoids have become a mainstay in all treatment guidelines. The optimal dose, route, and duration of therapy remains uncertain.

The EULAR guidelines recommend induction with a dose of a prednisone-equivalent of 0.5 to 1 mg/kg/day, tapered to 10-15 mg after 12 weeks. EULAR recommends continuing low dose glucocorticoids as part of maintenance treatment, which will be discussed next.

The toxicities associated with glucocorticoid use, including weight gain, infection, osteoporosis, diabetes, psychosis, depression, and anxiety, are major concerns of patients and providers. Studies are evaluating whether a reduced dose of glucocorticoids may be sufficient in the treatment of ANCA-associated vasculitis. A recently published study, the Plasma Exchange and Glucocorticoids for Treatment of ANCA-associated vasculitis or PEXIVAS, showed that a reduced-dose regimen of glucocorticoids may be non-inferior to a more standard, high dose regimen.

Slide 9

Despite high remission rates and improved mortality, over 50% of patients will relapse, particularly in the 12-18 months after immunosuppression is discontinued. Therefore, after remission is achieved, maintenance therapy is initiated to prevent relapse, as well as disease and treatment-related morbidity and mortality. Generally, maintenance therapy is started within 3-6 months after the initiation of induction therapy.

All current treatment guidelines recommend some type of maintenance therapy. The EULAR guidelines recommend low dose glucocorticoids in combination with azathioprine, rituximab, methotrexate, or mycophenolate *mofetil* (MMF). The recommended duration of maintenance therapy is 24 months. The EULAR guidelines recommend glucocorticoid taper be attempted, but note that, based on a metanalysis of 13 studies, continuation of GC treatment is associated with fewer relapses.

Slide 10

At this point, I want to highlight the role of rituximab in the treatment of AAV. It is the only FDA-approved therapy for AAV.

Rituximab was first approved for treatment of adult patients with GPA and MPA in combination with GCs in April 2011.

Multiple trials have been conducted to evaluate the use of rituximab for both induction and maintenance treatment. In the MAINRITSAN study, published in 2014, patients who received RTX maintenance therapy had fewer relapses than those who received azathioprine. Based on the results of the study, in October 2018, the prescribing information was updated to include the use of follow-up treatment with rituximab in patients with GPA and MPA who have achieved disease control with induction treatment.

Slide 11

Interactions between ChemoCentryx and the Agency began in April 2014 with discussions about their phase 2 studies. Highlighted on this slide are pertinent topics that were discussed between the Agency and ChemoCentryx regarding trial, CL-ten_168 over the course of 3 meetings.

The Agency expressed how the complicated study design will make the results difficult to interpret. We noted that there were multiple variables such as removing SOC glucocorticoids and replacing it with avacopan and then comparison of a prednisone taper over 20 to 26 weeks to avacopan treatment for 52 weeks which would make it difficult to determine the treatment effect of avacopan.

In pre-submission communications, FDA stated that a non-inferiority comparison would not be sufficient to show that avacopan can replace glucocorticoids as it would be difficult to establish whether avacopan is effective or whether RTX or CYC was the primary driver of efficacy in both treatment arms. The Agency expressed concerns about the ability to adequately justify an acceptable non-inferiority margin, which will be presented in detail in Dr. Kim's presentation. Because of these concerns about non-inferiority, The Agency advised that the pivotal trial needs to show superiority of avacopan over the comparator arm.

The Agency advised ChemoCentryx to consider how they intended avacopan to be used in clinical practice in the treatment regimen for AAV to help in designing their pivotal trial. With that, the Agency also offered the Applicant several alternative study designs to consider to address the Agency's concerns. For example, in order to minimize variables and to help interpret the data, the Agency recommended a third treatment arm with no steroids or a rapid steroid taper in order to adequately assess the treatment effect of glucocorticoids compared to the treatment effect of avacopan. The Agency recommended the time point of efficacy assessment should be extended from Week 26 to Week 52 to better evaluate an effect after discontinuation of glucocorticoids.

The Agency's concerns with the secondary endpoints will be presented in more detail as we discuss the results in the next 2 FDA presentations.

Slide 12

To support this New Drug Application, ChemoCentryx submitted the results from a single pivotal trial, CL-ten_168, also referred to as ADVOCATE. In the Agency's presentation, we will refer to this study as "CL-ten." Chemocentryx also submitted the data from two smaller phase 2 studies, CL-two_168 (also referred to as CLEAR) and CL-three_168 (also referred to as CLASSIC). In the Agency's presentation, we will refer to these studies as "CL-two" and "CL-three."

Slide 13

The pivotal trial was a randomized, double-blind, active controlled study to evaluate the safety and efficacy of avacopan in ANCA-associated vasculitis.

Slide 14

331 patients were randomized to 2 treatment arms, one receiving avacopan 30 mg BID for 52 weeks and the other receiving a prednisone taper over 20 weeks. The avacopan arm did not include pre-specified

glucocorticoids. Patients in both treatment arms received background rituximab or cyclophosphamide standard induction therapy. Patients who received CYC received azathioprine for maintenance therapy, or mycophenolate (mofetil) if AZA was not tolerated, while patients who received RTX induction treatment, did not receive maintenance therapy." The primary efficacy endpoints were remission at Week 26 and sustained remission at Week 52.

Slide 15

Two phase 2 trials were conducted. Both were 12-week, R, DB, PC studies. Study CL-two evaluated avacopan 30 mg BID without steroids and avacopan and low dose steroids compared to a control of a standard prednisone taper. Study CL-three evaluated two doses of avacopan (10 mg BID and 30 mg BID) compared to placebo; all treatment arms received a standard prednisone taper.

Slide 16

The phase 1 and phase 2 studies attempted to characterize the pharmacokinetic profile of avacopan. I will highlight some important pharmacology features.

Avacopan capsules were orally administered twice daily with food in phase 2 and 3 studies. A mono-hydroxylated metabolite, M1, is the major metabolite, representing approximately 12% of the drug-related plasma exposure, and has approximately the same pharmacological activity as avacopan. Following a single dose administration of 30 mg of avacopan, a high-fat, high-calorie meal increased avacopan AUC by approximately 72% as compared to fasted condition. Avacopan and M1 may inhibit CYP3A4. A clinical study evaluating the drug-drug interaction between avacopan and a sensitive CYP3A4 substrate, midazolam, indicated that, when co-administered with avacopan under fasted condition, midazolam systemic exposure increased by up to 81%. The impact of avacopan on CYP3A4 substrates under fed condition could be higher than fasted condition but has not been studied. In the phase 2 studies, prednisone taper regimens were administered with or without avacopan, and PK samples were collected throughout the study for prednisone plasma concentration measurement. While due to the limited number of subjects, prednisone exposure could not be adequately compared among the treatment arms, the potential exposure increase of prednisone when co-administered with avacopan under fed condition could not be ruled out.

This ends the Agency's Overview of the Clinical Program. Dr. Kim will now present study CL010 and the statistical review of efficacy.

Slide 17

No Script

May 6, 2021 Arthritis Advisory Committee Meeting

Script for FDA Presentation 2: Statistical Review of Efficacy

FDA Presenter: Yura Kim, PhD, Statistical Reviewer

Slide 1

Good morning. My name is Yura Kim. I'm a statistical reviewer from the Office of Biostatistics at CDER FDA. I'm going to present the phase 3 trial efficacy results for avacopan.

Slide 2

In this presentation, first we will provide a brief overview of the phase 3 trial including trial design, primary endpoints, and analysis methods. Next, we will discuss efficacy results, followed by supplemental analyses and concluding remarks.

After each of these topics, we will discuss considerations raising uncertainties about the interpretability of the data and the clinical meaningfulness of the efficacy results.

Slide 3

No Script

Slide 4

Trial CL010_168 was a multicenter, randomized, double-blind, parallel-group, active-controlled trial. This trial enrolled patients with newly diagnosed or relapsing ANCA-vasculitis, particularly, granulomatosis with polyangiitis or microscopic polyangiitis. This trial included a 52-week double-blind treatment period and an 8-week follow-up period.

This trial is the only pivotal study and is the main source of support for this NDA. This trial will be the focus of this presentation and the phase 2 trials will be discussed in more depth in the Dr. Peng's presentation.

Slide 5

Three hundred and thirty-one patients were randomized in a 1 to 1 ratio to receive a protocol-specified 20-week prednisone taper or 30mg of avacopan twice daily for 52 weeks. The randomization was stratified by background induction therapy, ANCA type, and AAV status.

Both treatment arms received background standard of care consisting of either rituximab or cyclophosphamide.
Patients who received cyclophosphamide induction treatment received azathioprine as maintenance therapy, while patients who received rituximab induction treatment did not receive any maintenance therapy.

The primary endpoints were the proportion of patients achieving disease remission at Week 26 and the proportion of patients achieving sustained remission at Week 52, each evaluated using the Birmingham Vasculitis Activity Score. Each endpoint was tested for non-inferiority and superiority based on a pre-specified hierarchical multiple testing procedure.

FDA identified several concerns regarding the study design.

Slide 6

First, patients who received cyclophosphamide induction treatment received azathioprine as maintenance therapy, while patients who received rituximab induction treatment did not receive any maintenance therapy. At the time the study was designed, repeat dosing with rituximab was not established as maintenance therapy; however, long-term immunosuppression had been demonstrated to reduce disease relapse and was standard-of-care.

Slide 7

Second, patients on both arms were allowed to receive 'non-study supplied' glucocorticoids.
As a result, 86% of the patients in the avacopan arm received glucocorticoids at some point between Week 0 and Week 26.

Slide 8

These two design elements create challenges for interpreting the trial's efficacy results.
Because the lack of maintenance therapy on the rituximab arm may not be representative of standard of care, the treatment comparisons of avacopan at Week 52 in the subgroup of patients receiving rituximab may not be clinically meaningful.

Second, as a result of the widespread steroid use on both arms, the comparison in this trial is more accurately described as a comparison of avacopan plus lower dose glucocorticoids vs. higher dose glucocorticoids. Dr. Peng will further discuss the use of steroids in her presentation.

Slide 9

We will now discuss the primary endpoints in this study.

Slide 10

The primary endpoints in this trial were the proportion of patients achieving disease remission at Week 26 and the proportion of patients achieving sustained remission at Week 52.
Both endpoints were defined using the Birmingham Vasculitis Activity Score, or BVAS.

Slide 11

BVAS is a clinical scoring system of disease activity to identify active vasculitis in nine organ systems and an "other" category. A higher BVAS total score indicates a higher disease activity. In this trial, the 'persistent' disease aspect of the BVAS was not used in the determination of remission, and only

items that were ‘new or worse’ were considered active, representing disease activity. As a result, subjects who had stable but persistent symptoms were not considered as having disease activity.

BVAS was assessed at Week 4,10,16, 26, 39, and 52. For the Week 4 BVAS assessment, the disease activity present within the 7 days prior to the visit was recorded. For all the other study visits, the disease activity present within the 28 days prior to the visit was recorded.

Slide 12

The BVAS assessments performed by the study Investigators were adjudicated by an Adjudication Committee, comprised of independent and external vasculitis experts, who were blinded to individual subject treatment assignment.

Slide 13

Disease remission at Week 26 was defined as achieving a BVAS of 0 as determined by the Adjudication Committee and no glucocorticoids received for treatment of AAV within 4 weeks prior to assessment.
Furthermore, if BVAS was collected at an unscheduled visit during the 4 weeks prior to Week 26, the subject’s BVAS had to be scored as 0 at this visit to be considered in disease remission.

Slide 14

Sustained remission required disease remission at Weeks 26 and 52 along with no relapses between Weeks 26 and 52. Relapse in this trial was defined using the BVAS as the occurrence of at least one major item at a single visit, at least 3 non-major items at a single visit, or 1 or 2 non-major items for at least 2 consecutive visits, after remission (BVAS=0) had been achieved

Slide 15

We will now discuss the analysis methods.

Slide 16

The primary analysis set included all randomized subjects who received at least one dose of study drug, and it was used for evaluation of efficacy endpoints.

Subjects who discontinued treatment were not automatically withdrawn from the study but were supposed to remain in the study for all regularly scheduled visits.

The primary analysis was based on the stratified analyses adjusted for randomization strata. Due to the low number of subjects in the oral cyclophosphamide randomization stratum, IV and oral cyclophosphamide strata were combined for the analyses.

Slide 17

A summary score test adjusted for randomization strata was used for both non-inferiority and superiority tests at Weeks 26 and 52.

For the non-inferiority comparison at both weeks, margin of 20% was used. Details on the non-inferiority test and the margin selection will be discussed in the later slides.

For the primary endpoints, subjects with missing data were imputed as not achieving remission at Week 26 or sustained remission at Week 52.

Sensitivity analyses were conducted to assess the robustness of results to alternative missing data assumptions.

Slide 18

According to the Applicant's sequential multiple testing procedure, noninferiority was first assessed for remission at Week 26 and then for sustained remission at Week 52, followed by superiority tested first for sustained remission at Week 52 and then remission at Week 26.

Secondary endpoints were not controlled for multiplicity and thus are considered purely exploratory. We note that the clinical study report evaluated over 20 exploratory endpoints, including different time points of assessments, which may lead to substantial type I error rate inflation. Hence, efficacy achieved by a secondary endpoint should be interpreted with caution.

Slide 19

The Applicant's justification for the non-inferiority margin of 20% was based on meta-analyses of 20 published studies to assess the historical disease remission rate at Week 26.

Slide 20

Based on the lower bound of the 95% confidence intervals, the Applicant proposed 60.9% as an estimate of disease remission rates for a clinical trial of patients receiving cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids.

Slide 21

The disease remission rate with glucocorticoids alone was estimated to be 45.5% with a 95% CI of (28.7%, 62.3%) based on the meta-analysis of 3 published studies of glucocorticoids alone.

Slide 22

By either taking the half of 60.9% (assuming the contribution of glucocorticoids to the remission rate is at least half) or taking the lower limit of the 95% CI of the remission rate with glucocorticoids only, the Applicant estimated the contribution of glucocorticoids to the remission rate of the control arm as ~30%

Slide 23

By further discounting these treatment effect estimates by one-third to account for remaining uncertainties, a 20% margin was derived as the pre-specified non-inferiority margin.

This algorithm of calculation is not consistent with the standard approach recommended by the FDA NI guidance.

Slide 24

In the design stage of the trial, FDA expressed concerns regarding the NI comparison in this trial.

In a non-inferiority (NI) study, the goal is to demonstrate that the test drug has an effect by showing that its effect is sufficiently close to the effect of an active control. As such, the study must be carefully designed to detect differences between treatments, should such differences exist.

In this case, both treatment arms received background therapy in the form of cyclophosphamide or rituximab. The benefit of glucocorticoids on top of cyclophosphamide or rituximab is not well-understood. As a result, it is difficult to determine if similar remission rates observed on both arms can support a conclusion that avacopan is effective or if similarities can be primarily attributed to both arms receiving rituximab or cyclophosphamide.

Slide 25

In addition to the general concerns with the NI approach, there are several concerns with the Applicant's proposed method to derive the non-inferiority margin. First, there are no historical placebo-controlled trials evaluating the efficacy of glucocorticoids as an add-on therapy to cyclophosphamide or rituximab. Thus, the Applicant relied on single arm results from various different studies.

The relevance of many of the historical studies cited for the setting of the proposed NI study is also questionable because of potential differences in important factors such as the patient population, treatment regimen, and even the definition of 'remission' and the time point of endpoint assessment.

Slide 26

Second, the determination of the extent of the contribution of glucocorticoids to the historical estimated remission rate on glucocorticoids + cyclophosphamide or rituximab relies on implausible and unverifiable assumptions. It is unlikely that the efficacy of glucocorticoids alone is similar to that of glucocorticoids when added on to cyclophosphamide or rituximab.

Non-inferiority designs are credible and appropriate only in situations in which the active control has shown a consistent effect (generally compared with placebo) in prior superiority trials conducted in a patient population similar to the population in the clinical investigation being planned. The utility of a non-inferiority comparison is dependent on knowing that the active control had its expected effect in the non-inferiority study. However, the Applicant has not provided adequate data or information that would isolate the effect of prednisone to inform the margin of the non-inferiority comparison in this study.

Slide 27

As mentioned earlier, there were multiple secondary endpoints explored in the trial without accounting for multiplicity.

To further examine the outcomes evaluated by the primary endpoint, relapse, which was one of the secondary endpoints, will be discussed in this presentation.

Time to relapse was calculated from the time of achieving BVAS score of 0.
The applicant conducted an analysis of time to relapse using Kaplan Meier methodology and log rank testing of the differences between treatment groups.

Slide 28

The Applicant's analysis of relapse, however, is limited, as it depends on post-randomization variables. The subset of subjects included in this analysis and the time those subjects are at risk for relapse can no longer be assumed to be similar across treatment arms. The advantages of randomization are eliminated because the treatment arms are no longer balanced with respect to possible confounders, leading to potentially biased comparisons between treatment arms and limiting the interpretability of these results. For example, remission may be achieved in different types of patients in the two treatment arms. Thus, when the treatment arms are compared with respect to relapse, differences may not be attributed to the treatment, but rather to differences in the characteristics of the subset of patients included in the analysis.

FDA performed an alternative exploratory analysis to assess the proportion of patients who never achieved remission or achieved remission but relapsed. This analysis incorporates all patients and addresses the concerns of conditioning on a post-randomization variable.

Slide 29

We will now discuss the efficacy analysis results.

Slide 30

Of 331 randomized subjects, 330 subjects received at least one dose of study drug. Approximately 94% of subjects completed the study through Week 26. The most common reason for study discontinuation provided by the Applicant was experiencing an adverse event in the prednisone arm, and withdrawal by subject in the avacopan arm.

Slide 31

Approximately 92% of subjects completed the study through Week 52. The proportion of patients who discontinued study were slightly higher in the avacopan arm; 91% of patients in the avacopan arm completed the study through Week 52 while 92.7% of patients in the prednisone arm completed the study through Week 52. The most common reason for discontinuation was experiencing an adverse event in the prednisone arm, and withdrawal by subject in the avacopan arm.

Slide 32

This table summarizes the analysis results for the primary endpoints. The percentage of remission at Week 26 was 72.3% in the avacopan arm and 70.1% in the prednisone arm, with an estimated treatment difference of 3.4%. The percentage of sustained remission at Week 52 was 65.7% in the avacopan arm and 54.9% in the prednisone arm, with an estimated treatment difference of 12.5%.

The first three tests in the sequential multiple testing procedure were statistically significant, while the test of superiority at Week 26 was not statistically significant.

Tipping point analyses showed the efficacy results were robust to missing data assumptions.

Slide 33

The majority of patients achieved BVAS score of 0 during the 52-week double-blind treatment period.

Slide 34

The number of patients in each treatment arm who never achieved BVAS of 0 was similar in each treatment arm; 4.8% in the avacopan arm and 4.3% in the prednisone arm.

Slide 35

The percentage of patients who achieved BVAS of 0, but later experienced a relapse was 20.1% in the prednisone arm and 9.6% in the avacopan arm.

Slide 36

Hence, the proportion of patients who never achieved remission or achieved remission but had a relapse in the avacopan arm was 14.5% versus 24.4% in the prednisone arm, with the estimated difference of -9.9% and 95% CI of [-18.4%, -1.5%].

It should be noted that this post-hoc exploratory analysis does not account for the time of achieving BVAS of 0.

For example, between two otherwise similar patients, the patient achieving BVAS=0 early will have a higher chance of experiencing relapse by Week 52 compared to a patient who achieves BVAS=0 later in the trial.

As designed, the study was not suitable for comparative evaluation of relapse rates.

Slide 37

We will now discuss the supplemental analysis results.

Slide 38

This slide shows the primary endpoint results stratified by background induction therapy.

At Week 52, there was a noticeable disparity in observed treatment effects between the subgroups that received rituximab and cyclophosphamide induction treatment. The estimated difference in the proportion of subjects achieving disease remission at Week 52 was 15.0% with 95% CI of [2.2%, 27.7%] in the subgroup receiving induction with rituximab and 3.3% with 95% CI of [-14.8%, 21.4%] in the cyclophosphamide plus maintenance azathioprine subgroup.

Based on the data, there is no evidence of clinically meaningful treatment effect in the cyclophosphamide induction subgroup. Further, there are concerns that the treatment comparison in the complementary rituximab induction subgroup may not be considered meaningful because these patients did not receive a maintenance therapy.

Slide 39

This table examines the primary endpoint results when using the Investigator's assessments. Statistical analyses of the primary endpoint using the Investigator assessment of BVAS remission resulted in smaller magnitude of treatment effect and would not support superiority of avacopan.

Slide 40

Differences between the assessments performed by the Investigator and the Adjudication Committee were most frequently related to the attribution of persistent vasculitis which was not captured in the modified BVAS.

The investigators considered persistent vasculitis as active vasculitis when scoring the BVAS. The adjudicators only scored items indicative of new or worsening disease activity.

While the pre-specified analysis used the Adjudicator assessments, the assessment based on the Investigators, experienced in management of vasculitis, may better reflect real-world use.

Slide 41

No script

Slide 42

In summary, at Week 26, avacopan did not demonstrate a statistically significant treatment effect versus prednisone on the primary endpoint of Disease remission.
The non-inferiority comparison was successful based on the proposed margin of 20%.

However, throughout development, FDA reiterated that a non-inferiority comparison would not be sufficient to determine whether avacopan is effective given the contribution of glucocorticoids on top of rituximab/ cyclophosphamide is not well understood. At IND stage, FDA indicated that the superiority analysis is critical to demonstrate efficacy.

Furthermore, non-protocol-specified glucocorticoids were used to control disease activity which resulted in glucocorticoid use in both treatment arms. Thus, the interpretation of the non-inferiority assessment is challenging.

Slide 43

In the overall study population, the avacopan arm showed statistical significance when compared to the prednisone arm in achieving sustained remission at Week 52.

However, due to the lack of maintenance therapy in the rituximab subgroup, treatment comparison in this subgroup may not be an informative / clinically meaningful comparison.

At the same time, based on the efficacy analyses in the complementary cyclophosphamide subgroup, there is not enough evidence of presence of clinically meaningful treatment effect.

Furthermore, there was discrepancy between Investigator and Adjudicated BVAS scores, and of note, statistical analyses based on Investigator assessments would not support superiority of avacopan in achieving sustained remission at Week 52.

May 6, 2021 Arthritis Advisory Committee Meeting

Script for FDA Presentation 1: Clinical Overview of Efficacy, Safety, and Benefit-Risk Assessment

FDA Presenter: Suzette Peng, MD, Medical Reviewer

Slide 1

Now that Dr. Kim has reviewed Study CL-10 and the primary efficacy results as well as the relapse data, I will present a clinical review of efficacy, safety, and the benefit-risk assessment.

Slide 2

My presentation will begin with a review of the glucocorticoid use in the pivotal trial as well as the results of the glucocorticoid toxicity index.

I will then review the rest of the secondary endpoints not already presented.

Based on the efficacy assessments presented by Dr. Kim and myself, I will then discuss clinical considerations on the efficacy of avacopan in the treatment of AAV.

I will also present a summary of the safety from the pivotal trial and the clinical considerations of these results.

The phase 2 studies were submitted to support the pivotal trial, and I will present the efficacy and safety data.

Lastly, I will conclude with a discussion of the overall benefit-risk considerations.

Slide 3

"The aim of the pivotal trial was not only to evaluate the safety and effectiveness of avacopan as a treatment for AAV, but also to demonstrate that avacopan can be steroid-sparing."

The control arm included a pre-specified 20-week prednisone taper. The avacopan arm did not include pre-specified glucocorticoids. If patients entered the study on glucocorticoids, it should be tapered off over the initial 4-week period. The protocol recommended that non-study supplied glucocorticoids should be avoided as much as possible.

Slide 4

However, non-study supplied glucocorticoids were utilized in both treatment arms.

Over the 52-week treatment period, 87.3% of patients in the avacopan arm and 90.9% of patients in the prednisone arm received non-study supplied glucocorticoids. GC use was permitted for pre-medication for treatment (including rituximab), for adrenal insufficiency, and for other conditions. Importantly, GC could also be administered for vasculitis. I will review this further in an upcoming slide.

Slide 5

This figure shows the cumulative total glucocorticoid use, including protocol-specified prednisone and non-study supplied glucocorticoids, by mean daily dose in each treatment arm. The avacopan arm is represented in blue, and the prednisone arm is represented in red. In the initial portion of the study, because of the protocol-specified prednisone taper, there is a large difference in the mean daily dose between the 2 arms. After completion of the 20-week prednisone taper, the mean daily dose is comparable during the second half of the study.

Slide 6

This figure shows the cumulative non-study supplied glucocorticoids by mean daily dose in each treatment arm. Like the previous figure, the avacopan arm is in blue, and the prednisone arm is in red. During the induction period, the avacopan arm required more non-study supplied glucocorticoids. Following induction, all glucocorticoid use was non-study supplied, and the mean daily dose was generally comparable in both treatment arms.

Slide 7

This table shows the mean dose of cumulative glucocorticoid use, both the total glucocorticoids (including the pre-specified prednisone taper and non-study supplied GC) shown on the top part of the table as well as just the non-study supplied GC, on the bottom half of the table. The mean cumulative total glucocorticoid use over 52 weeks was greater in the prednisone arm (3654 mg in the prednisone arm and 1349 mg in the avacopan arm). This is expected as it includes the pre-specified prednisone taper. However, the mean cumulative non-study supplied glucocorticoid dose was comparable between treatment arms, 1265 mg in the prednisone arm and 1349 mg in the avacopan arm.

The clinical relevance of the differences in the nominal glucocorticoid doses between the prednisone and the avacopan arm is uncertain, as it may be an artifact of the study design rather than a reflection of avacopan's control of disease activity.

Slide 8

The assessment of glucocorticoid use in both treatment arms is further complicated by the clinical pharmacology findings as previously summarized. Avacopan is a CYP3A4 inhibitor, and the phase 2 program could not rule out the potential exposure increase of prednisone, a CYP3A4 substrate, when co-administered with avacopan.

Slide 9

All non-study supplied glucocorticoids used in the pivotal trial are summarized in this table. They were identified as CYP3A4 substrates. However, the PK concentrations of glucocorticoids were not assessed in this study. Overall, while the impact of avacopan coadministration on prednisone exposure is inconclusive based on available information, the potential exposure increase of glucocorticoids used in the phase 3 study when co-administered with avacopan due to drug-drug interactions could not be reliably ruled out. This potential drug-drug interaction between avacopan and glucocorticoids raises questions whether differences in glucocorticoid use between the avacopan and control arms based on

the nominal doses of glucocorticoids used reflect true differences in glucocorticoid exposures and about the role of avacopan as a steroid-sparing agent.

Slide 10

Investigators could treat patients with non-study supplied glucocorticoids for a variety of reasons. Specifically, for the treatment of AAV, non-study supplied glucocorticoids were used to treat persistent vasculitis, worsening vasculitis, and relapse. Patients had persistent vasculitis if they had one or more major items in the BVAS before study entry and did not show improvement or stabilization of these major items within the first 4 weeks of the study. Relapse was defined as occurrence of at least 1 major item in the BVAS or ≥ 3 minor items in the BVAS or 1 or 2 minor items in the BVAS recorded at 2 consecutive visits after having achieved a BVAS of 0 at any time during the treatment period. Worsening of disease was a worsening in BVAS without meeting relapse criteria.

Over the 52-week study period, 117 patients (71.3%) in the prednisone arm and 106 patients (63.9%) in the avacopan arm received glucocorticoids for vasculitis. This table shows the non-study supplied glucocorticoid use for vasculitis during the first and second halves of the study by treatment arm. More patients required glucocorticoids for vasculitis in the first half of the study in both treatment arms.

Slide 11

The proportion of patients requiring non-study supplied GC was similar for treatment of worsening vasculitis, persistent vasculitis, and remission.

Slide 12

However, a greater number of patients in the prednisone arm required non-study supplied GC for relapse.

Slide 13

The Applicant supported the assessment of the steroid-sparing effect of avacopan with the prespecified secondary endpoint of Glucocorticoid Toxicity Index (or GTI) to quantify toxicity associated with glucocorticoid use. The index is composed of 9 domains such as body mass index, glucose tolerance, and infection. Observed changes in items in these domains are weighted to determine a score.

Slide 14

GTI-Cumulative Worsening Score or GTI-CWS assesses cumulative glucocorticoid toxicity, regardless of whether the toxicity has lasting effects or is transient. GTI-CWS may increase or remain the same over time but does not decrease.

GTI-Aggregate Improvement Score or GTI-AIS is intended to assess both improvement and worsening of toxicities over time. GTI-AIS may increase or decrease.

For both measures, a higher score is associated with greater toxicity.

GTI was assessed while patients in the control arm received protocol-specified prednisone, that is, an assessment at Weeks 13 and 26. A greater improvement from baseline on GTI-CWS and GTI-AIS was seen in the avacopan arm at both time points. Although non-study supplied GC were administered in both arms throughout the treatment duration, there is no assessment of GTI at any later time points.

There are limitations to the interpretation of the GTI. The GTI is not a clinical outcome, that is, it is not a direct measure of how a patient feels, functions or survives, rather it is a measure of clinician-reported outcomes and biomarkers.

Differences in GTI between the treatment groups may reflect the study design of the pivotal trial which specified the prednisone doses to be used in the control group. Therefore, the GTI does not provide information beyond that of the cumulative glucocorticoid doses to further inform the effect of avacopan.

Slide 15

At this point, I will review the secondary endpoints that were assessed in the pivotal trial. The secondary efficacy endpoints prespecified by ChemoCentryx are presented here.

There are limitations to the results of the secondary endpoints. As you have heard from Dr.Kim, no secondary endpoints were adjusted for multiplicity and are, therefore, considered exploratory. A nominal significance achieved by a secondary endpoint that is not adjusted for multiplicity should be interpreted with caution.

Furthermore, secondary endpoints were assessed at multiple time points.

Slide 16

The assessments of GTI and relapse have already been presented.

Early remission (defined as BVAS of 0 at Week 4) and one of the renal assessments (% change in urinary MCP-1 to creatinine ratio) will not be presented.The clinical meaningfulness of these particular efficacy endpoints are unclear.

I will present the other secondary endpoints in the pivotal trial, beginning with vasculitis damage index.

Slide 17

Vasculitis Damage Index or VDI is intended to assess organ damage that have occurred since the onset of vasculitis. It includes 64 items in 11 organ systems. Items are scored if they have been present for at least 3 months. The VDI score can deteriorate or remain stable, but damage is defined as being irreversible and, thus, cannot decrease over time.

This table shows change from baseline in VDI in both treatment arms at Weeks 26 and 52. The change from baseline was similar between treatment arms at both timepoints.

As already noted by Dr. Kim, “persistent” active disease was not scored as part of the BVAS. The Applicant has stated that persistent active disease would instead be captured by the VDI; however, it is

difficult to distinguish how much "persistent" disease is active disease, which would potentially be responsive to treatment and a more important assessment of potential therapeutic benefit of avacopan.

Slide 18

Analyses of the secondary renal endpoints were limited to patients with renal disease at baseline defined as meeting one or more of the BVAS "renal" or "other" criteria based on the investigator's assessment at screening. Presented here are the criteria used to train investigators on how to identify patients with baseline renal disease and the proportion of patients who met each criterion by treatment arm. 134 patients in each arm, approximately 80% of the trial population, met the criteria for renal disease at baseline with proteinuria and hematuria being the most common criteria met.

Of note, it is not clear how well the specified BVAS criteria identified a population with significant kidney involvement or how to characterize the level of kidney involvement such that we can readily interpret the nature and clinical importance of effects on kidney function and albuminuria. For example, data on pre-flare kidney function, proteinuria, or hematuria are not available to differentiate changes related to AAV from pre-existing chronic kidney disease or other comorbidities. It is also not clear how the "other criterion" "RBC casts and/or glomerulonephritis" was defined, as this was not specified in the protocol, investigator training materials, or the statistical analysis plan.

Slide 19

This plot shows the change in eGFR from baseline, which was evaluated for all patients with baseline renal disease. There is a trend toward greater improvement in eGFR over time in the avacopan arm; however, the differences between groups were small and not sustained after discontinuation of treatment, raising questions about the clinical importance of the findings. At Week 52, the change in eGFR was 7.3 mL/min/1.73 m2 in the avacopan arm compared to 4.0 mL/min/1.73 m2 in the prednisone arm. After discontinuation of avacopan, by Week 60, there was no difference.

Slide 20

This graph shows the change in albuminuria from baseline, as measured by urine albumin-to-creatinine ratio or UACR. The endpoint was limited to patients with baseline renal disease who also had a baseline UACR of at least 10 mg/g. A UACR of 10 mg/g is a normal value for young adults and thus would not necessarily limit the analysis to a population with substantial baseline proteinuria. There is a decrease in both treatment arms. Although the improvement appears to be faster in the avacopan arm, particularly in the first 4 weeks, there were no differences at later time points. Although the Applicant did not provide data supporting the use of UACR as a surrogate for clinical outcomes in AAV, it seems unlikely that these findings would predict a meaningful clinical benefit of avacopan over prednisone.

Although the trial was not designed or powered to show an effect on the need for dialysis, we note that the number of patients requiring dialysis was similar between groups (4 patients in the prednisone group vs. 3 patients in the avacopan group).

Overall, we note that the observed differences in eGFR and UACR were small and not sustained.

Slide 21

Quality of life was assessed based on the SF-36 and the EQ-5D-5L (or EuroQuality of Life). Both are general quality of life instruments that are not specific for the assessment of vasculitis.

On the SF-36, the point estimate for the mean change from baseline in the physical component score (PCS) and mental component score (MCS) at Week 52 trended toward greater improvement in the avacopan group across the 8 domains although the confidence intervals did not rule out zero effect in most of the domains. There was large variability around the point estimates.

The EQ-5D-5L is based on a Visual Analogue Scale (VAS) and a population norm-based index. The EQ-5D-5L showed improvement in the avacopan arm compared to the prednisone arm for the VAS and the Index score.

The improvement in these measures and whether the differences between the avacopan and prednisone arm are clinically meaningful are unknown. Importantly, the results of these general health-related quality of life measures should be considered as supportive of the primary evidence of efficacy, that is, the product must show efficacy at its primary endpoint. Improvement in these measures do not alone establish efficacy of the product.

Slide 22

As you have heard, there are a number of issues that raise concerns about the clinical meaningfulness of the results of trial CL-ten to support the use of avacopan in the treatment of ANCA-associated vasculitis.

The trial demonstrated noninferiority of avacopan to a 20-week prednisone taper regimen on top of standard induction therapy on the primary endpoints of remission at Week 26 and sustained remission at Week 52 and demonstrated superiority on sustained remission at Week 52. However, superiority was not demonstrated in disease remission at Week 26.

As discussed by Dr.Kim, the Agency does not agree that the non-inferiority margin has been adequately justified. Interpretation of non-inferiority is further limited by the large number of patients (87%) who received glucocorticoids in the avacopan arm through the study. Because both treatment arms received glucocorticoids, the true non-inferiority comparison is a treatment arm with avacopan plus lower doses of glucocorticoids compared to a control arm with higher doses of glucocorticoids. In addition, the data from the clinical pharmacology program has identified avacopan as a CYP3A4 inhibitor that has the potential to increase exposures to systemic glucocorticoids which are CYP3A4 substrates, raising further questions about the true difference in glucocorticoid exposures. Therefore, the treatment effect of avacopan and the magnitude of the effect are unclear.

At Week 52, a statistically significantly greater proportion of patients in the avacopan treatment arm achieved sustained remission, demonstrating both noninferiority and superiority. The treatment effect was not consistent across background therapy subgroups. Subgroup analyses showed a greater treatment difference in sustained remission in patients who were induced with rituximab and did not receive maintenance therapy, while no meaningful treatment effect was observed in the cyclophosphamide induction subgroup that did receive maintenance treatment with AZA. Additionally, at Week 52, there were discrepancies between the Investigator and Adjudication Committee assessments of BVAS. While superiority was met at Week 52 using the adjudicated BVAS score,

superiority was not supported based on the Investigator assessment of BVAS. These results raise questions about the adequacy of the comparisons and clinical meaningfulness of the avacopan effect at Week 52.

Slide 23

We also have several questions for the committee to consider with regard to the proposed role for avacopan as a steroid sparing agent. As discussed, patients in both treatment arms received non-study supplied glucocorticoids, including glucocorticoids for the management of active vasculitis. In addition, the control arm received pre-specified prednisone. Following the pre-specified taper, the mean cumulative dose of glucocorticoids used was comparable between treatment groups.

The clinical relevance of the differences in the nominal glucocorticoid doses between the prednisone and avacopan arms is uncertain, as it may be an artifact of the study design rather than a reflection of avacopan's control of disease activity. In addition, the potential DDI between avacopan and glucocorticoids raise questions about the true difference in GC exposures and the proposed role of avacopan as a steroid-sparing agent.

Lastly, there is limited support of a treatment benefit of avacopan from the secondary endpoints.

Slide 24

The safety database in the pivotal trial is small. In the avacopan arm, 166 patients were exposed to avacopan, and 134 patients received more than 6 months of therapy with avacopan.

This table presents an overview of safety in the pivotal trial. A similar proportion of patients in both treatment arms experienced adverse events during the entire study. There are small differences, favoring avacopan, but, because of the small database, conclusions on safety are limited.

Slide 25

The phase 3 safety database showed that there were more liver-associated adverse events in the avacopan arm. 22 patients in the avacopan arm compared to 19 patients in the prednisone arm experienced an AE related to hepatic abnormalities. More patients in the avacopan arm also experienced serious adverse events or SAEs of elevated liver tests.

Based on the Agency's review, there are 4 cases of liver-related SAEs that were likely due to avacopan, which will be further described on the next slide.

Additionally, one patient had peak transaminases over 3 times the upper limit of normal with concurrent jaundice and only modest alkaline phosphatase elevation (thus, meeting Hy's law laboratory criteria). The event was felt to be possibly due to avacopan.

Hy's law criteria identify drug induced liver injury (DILI) cases that have a mortality risk of approximately 10%. The criteria have been used in drug development to identify drugs that may have significant or unacceptable risk of severe liver injury.

Slide 26

The components of Hy's law are: Evidence of hepatocellular injury by any elevated aminotransferase of >3xULN, Evidence of liver dysfunction by increase in bilirubin ≥2xULN and without evidence of cholestasis by ALP <2xULN, and that there is no other cause such as viral hepatitis (A, B, or C); preexisting or acute liver disease; or another drug capable of causing the observed injury.

Typically 1 or 2 Hy's Law cases attributed to the study medication in large registry trials (N of 1000 to 2000) is enough to raise concerns that drug may be unsafe for wider market use.

Slide 27

ChemoCentryx provided the analysis to the left, an evaluation of Drug Induced Serious Hepatotoxicity or eDISH plot. This plot includes all ALT and bilirubin data from the phase 3 study, including laboratory results from local and central labs. This plot is incomplete, as it does not include AST or alkaline phosphatase data. However, the Agency was able to confirm the analysis.

Slide 28

Based on this plot, there are 2 patients in the avacopan arm and 1 patient in the prednisone arm who fall in the right upper quadrant (which is representative of potential drug induced liver injury).

On the right is the Agency's analysis of the 9 SAEs in the pivotal trial related to elevated liver enzymes with or without jaundice. Of these cases, 3 were considered unlikely avacopan hepatotoxicity due to other causes being more likely.

Three cases were considered probably DILI due to avacopan and 1 case was considered highly likely DILI due to avacopan. The remaining 2 cases were considered possible due to competing diagnoses. The case meeting Hy's law laboratory criteria was one of the possible DILI cases.

Slide 29

Infections occurred in similar proportions in both treatment arms. For overall treatment emergent infections, a greater proportion of patients in the prednisone arm experienced infections with a difference of 7.5%.

In terms of serious infections, severe infections, and infections leading to study drug discontinuation, life-threatening infection, or death, adverse events were similar across both treatment arms.

The most common serious infection in both arms was pneumonia, occurring in 8 patients in the avacopan arm and 6 patients in the prednisone arm.

More serious opportunistic infections occurred in the prednisone arm with 11 patients compared to 6 patients in the avacopan arm.

No cases of Neisseria meningitides or other infections by encapsulated bacteria occurred in the avacopan arm.

Slide 30

Hypersensitivity was assessed utilizing preferred terms from the SMQ for hypersensitivity. Overall 68 patients in the avacopan arm and 70 patients in the prednisone arm had an adverse event that fell under this SMQ.

However, in evaluating the serious adverse events possibly related to study drug, there were 2 of concern in the avacopan arm. These included a case of angioedema and a case of rash with eospinophilia. In both cases, the symptoms improved with avacopan discontinuation, and the patients were not re-challenged.

There was an additional non-serious case of angioedema in the avacopan arm, and no cases of angioedema (serious or non-serious) in the prednisone arm.

We also note that there were more cases of elevated CPK in the avacopan arm, with 6 patients with this AE compared to 1 patient in the prednisone arm. In the avacopan arm, this led to 1 study drug interruption and 1 study drug discontinuation. There were no major difference, however, in myalgias or myopathies.

Slide 31

The safety database in Study CL-ten was small. The proportions of patients with treatment-emergent adverse events, including deaths, serious adverse events, and adverse events leading to discontinuation, were similar across treatment arms or nominally lower in the avacopan arm.

There did not appear to be a major difference in the number of patients with infections.

More patients in the avacopan arm experienced adverse events related to hepatic abnormalities, hypersensitivity events, and elevated CPK.

With the small safety database, conclusions are limited.

Slide 32

Two phase 2 trials were conducted. As already described, both were 12-week, R, DB, PC studies. These phase 2 studies were submitted to support the results of CL-ten. However, there are challenges in interpreting the data from the phase 2 studies.

First, these were shorter studies with a treatment duration of 12 weeks.

Second, there was a small number of patients in each study. Study CL-two randomized 67 patients, 26 of whom had limited renal vasculitis. Study CL-three enrolled 42 patients.

Doses of avacopan differed in study CL-three, and patients were taking different doses of prednisone at the time of efficacy assessment in both studies.

Lastly, the efficacy assessments were different than those in the pivotal trial and were assessed at an early time point of Week 12.

Slide 33

In study CL-two, the primary efficacy assessment was BVAS 50% response at Week 12. The Agency advised the Applicant that BVAS 50% response was not an acceptable surrogate for disease remission. Additionally, whether a treatment effect at Week 12 is predictive of long-term clinical outcomes in AAV is not known.

Additional efficacy assessments that may be more relevant to the pivotal trial included BVAS remission and BVAS of 0 at Week 12. There are limitations to a remission assessment in these studies as patients with protocol-specified prednisone tapers would still be on prednisone at Week 12, and, thus, it would be difficult to isolate the treatment effect of avacopan.

What I will highlight here is the endpoint of BVAS of 0, which is most similar to the endpoint used in CL-ten, and, with this endpoint, the greatest response was in the avacopan and low dose prednisone taper arm at 46% compared to 40 % in the control arm and 33% in the avacopan and no prednisone arm.

In summary, the results do not provide support for the treatment benefit of avacopan when administered without GCs over standard of care.

Slide 34

In study CL-three, the primary efficacy endpoint was BVAS 50% response at Week 12 or Day 85. Other relevant efficacy assessments included BVAS of 0 at Day 85 and early remission defined as BVAS of 0 on Days 29 and 85. Again, I will highlight the endpoint most similar to the primary endpoint of CL-10. BVAS of 0 was greatest in the lower dose avacopan (10 mg BID) at 67% compared to 54% in the control arm and 47% in the avacopan 30 mg BID arm.

As previously noted, these assessments are limited because patients were still receiving prednisone in all 3 treatment arms.

Slide 35

The safety database from the two phase 2 studies is small. The safety from both studies cannot be pooled due to differences in doses of avacopan utilized as well as different doses of concomitant prednisone.

There were no deaths in the phase 2 program. In study CL-two, serious adverse events occurred in a greater proportion of patients in the avacopan 30 mg BID + no prednisone arm. SAEs related to vasculitis were the only SAEs reported in more than one patient. There was one case of liver toxicity. This case was considered possible DILI due to avacopan, as there was a competing diagnosis of sulfamethoxazole and trimethoprim liver injury.

In Study CL-three, SAEs were similar across treatment arms and did not cluster by type of SAE.

Slide 36

Therefore, the phase 2 studies, which included different treatment arms with different doses of avacopan and varying concomitant prednisone tapers, shorter treatment duration, small patient

populations, and different efficacy assessments do not contribute to the substantial evidence of effectiveness. Determination of the overall benefit-risk of avacopan in ANCA-associated vasculitis relies primarily on the results from the single pivotal study.

The pivotal trial demonstrated non-inferiority of avacopan to a pre-specified prednisone taper at Weeks 26 and 52 with both arms receiving background therapy and non-study supplied glucocorticoids. The avacopan arm demonstrated superiority over the prednisone arm in achieving sustained remission at Week 52. Glucocorticoids were administered in both treatment arms, but the nominal glucocorticoid doses was lower in avacopan arm. The Agency has reviewed our concerns with these results, as summarized in this slide.

Overall, the safety database is limited for the reliable assessment of rare or latent events. Despite the small safety database, some notable differences in the safety profiles between avacopan and the control group were observed, specifically for liver toxicity, hypersensitivity, and CPK elevation. Other safety events were generally similar between treatment arms.

In conclusion, AAV is a rare and serious disease associated with high morbidity and mortality. It also has high unmet need for new therapies. We recognize the importance of wanting to decrease glucocorticoid use and its toxicities, particularly if the steroid-sparing occurs in the context of a treatment that effectively controls disease activity. In principle, a single adequate and well-controlled study may be considered to establish substantial evidence of efficacy. However, because of the uncertainties around the phase 3 study design and results, there are questions about the adequacy of this single trial to inform the benefit-risk assessment. The Agency wants to ensure that new products have a defined context of use, that is, how a product would be used in clinical practice, and a favorable benefit-risk assessment for patients.

May 6, 2021 Arthritis Advisory Committee Meeting

Script for FDA Presentation 4: Charge to the Committee

FDA Presenter: Rachel Glaser, MD, Cross Disciplinary Team Leader

Slide 1

Hello, my name is Rachel Glaser and I am a clinical team leader in the Division of Rheumatology and Transplant Medicine. On behalf of the Division and the Agency, I would like to take this opportunity to thank the Advisory Committee members for their participation in this meeting. We look forward to a fruitful discussion on May 6. Now that you have had the chance to view the presentations by Dr. Peng, Dr. Kim, and the Applicant, I would like to take the next 15 minutes to provide a brief overview of the scientific issues, the regulatory framework upon which our decision-making is based, and the questions to be discussed and voted upon. These questions will be presented to you again on the day of the meeting.

Slide 2

As you have heard in the Agency's presentations, there are a number of issues that raise concerns about the clinical meaningfulness of the results of Study CL10 to support the use of avacopan in AAV. We ask you to carefully consider whether the efficacy results are robust.

As you have heard, according to the Applicant's sequential multiple testing procedure, noninferiority was first assessed for remission at Week 26. The proportion of patients in disease remission in the avacopan group was non-inferior to the prednisone group. However, superiority was not demonstrated. Throughout the development program, FDA advised the Applicant that a non-inferiority comparison would not be sufficient to show that avacopan can replace glucocorticoids as it would be difficult to establish whether avacopan is effective or whether an effect was due to the rituximab or cyclophosphamide administered to both treatment arms. In addition, the Applicant has not provided adequate data or information that would isolate the effect of prednisone to inform the margin of the non-inferiority comparison in this study. FDA does not find the noninferiority margin to be adequately justified.

Interpretation of the non-inferiority at Week 26 is further limited by the large number of patients who received glucocorticoids in the avacopan arm from Week 0 to 26. The noninferiority assessment is not the intended comparison of avacopan vs. prednisone, but instead a comparison of avacopan plus lower dose glucocorticoids vs. higher dose glucocorticoids. Furthermore, based on the study design which specified the glucocorticoid use in the prednisone arm, it cannot be concluded that any differences in cumulative glucocorticoid use was due a treatment effect of avacopan, and not due to the specifications of the protocol. In addition, the treatment effect of avacopan and the magnitude of effect at Week 26 are unclear.

Slide 3

At Week 52, a statistically significantly greater proportion of patients in the avacopan treatment arm achieved sustained remission, demonstrating both noninferiority and superiority. However, the

treatment effect was not consistent across background therapy subgroups. A treatment effect was observed in the rituximab induction subgroup, that did not receive maintenance standard of care during the second half of the study, while no meaningful treatment effect was observed in the cyclophosphamide induction subgroup that did receive maintenance therapy with azathioprine. These data suggest that avacopan may have a treatment effect compared to no treatment in the rituximab induction subgroup but doesn't appear to add to the treatment effect of azathioprine maintenance in the cyclophosphamide induction subgroup. This raises questions about whether a treatment effect would be observed if the rituximab subgroup had received standard of care maintenance treatment. This further raises the question of how the data from Study CL10 can inform the use of avacopan.

In addition, there were differences between the BVAS assessments performed by the Investigators and the Adjudication Committee. When the primary endpoint was analyzed based on the Investigator Assessment, which may be more reflective of real-world use, the superiority of avacopan at Week 52 was no longer supported.

Slide 4

As noted in the FDA background materials, the Applicant has set as one of the objectives of the clinical program, to demonstrate that avacopan can be steroid-sparing. Respectively, Study CL10 was designed to compare avacopan to a standard protocol-specified dosing regimen of high dose prednisone tapered down over 20 weeks. This design resulted in a lower mean cumulative glucocorticoid dose in the avacopan group from Weeks 0-26, which was also reflected by the data from the Glucocorticoid Toxicity Index. Based on this study design, there is inadequate information to isolate the effect of prednisone from that of the induction therapies.

We also note that the mean cumulative glucocorticoid doses were comparable between treatment groups after Week 26. In addition, the data from the clinical pharmacology program has identified avacopan as a CYP3A4 inhibitor that has the potential to increase exposures to systemic glucocorticoids which are CYP3A4 substrates, raising further questions about the true difference in glucocorticoid exposures and the proposed role of avacopan as a steroid-sparing agent.

Given these considerations and that the differences in the cumulative glucocorticoid use was dictated by study design and not by the need to control disease activity, the interpretation of the meaningfulness of the observed differences in glucocorticoid use is challenging, which is one of the points we would like the committee to discuss today.

Slide 5

The study also evaluated multiple secondary endpoints, however, they were not adjusted for multiplicity to control the overall type 1 error rate, and therefore are considered exploratory.

- There were fewer relapses observed in the avacopan group, however, other assessments of increased disease activity were similar between treatments. In addition, this trial was not designed to assess relapse. The analyses were not based on the randomized population in remission at baseline, and, thus, the treatment arms may not be comparable for assessing relapse. Therefore, the interpretability of these results is limited.

- Results of the Glucocorticoid Toxicity Index, an instrument to assess the toxicities of glucocorticoids, reflect the differences in glucocorticoid use based on the study design, but does not define the impact of the treatment on the underlying disease.
- There were no clinically meaningful differences in the Vasculitis Damage Index.
- With regard to renal endpoints, differences in changes in GFR were small, with a mean difference between treatment arms of 3.3 mL/min/1.7 m2 at Week 52, and was not sustained; the mean difference decreased to 0.6 by Week 60, 8 weeks post-treatment. Urine albumin: creatinine ratio improved in both arms, and more quickly in the avacopan arm by Week 4, however improvement was similar between treatment arms after this early time point. There were no differences in need for dialysis observed. In addition, as you have heard, the criteria used to define renal disease at baseline may not have adequately selected for patients with active renal vasculitis.
- There were favorable trends in quality of life measures, based on SF-36 and EQ-5D-5L, however there was large variability around the point estimates, and these measures are not specific to vasculitis.

Overall, the secondary endpoints provide limited support of efficacy of avacopan.

The Applicant has conducted two phase 2 studies. These studies included different treatment arms,with different doses of avacopan and varying concomitant prednisone tapers, shorter treatment duration, small patient populations, and different efficacy assessments. Further, the results did not demonstrate that avacopan 30 mg twice daily without concomitant prednisone (that is, the Applicant's proposed dose) had the greatest treatment response over standard of care. In Study CL002, avacopan with low dose prednisone had a greater response compared to avacopan without prednisone or a standard prednisone taper without avacopan, while in Study CL003, in which 2 doses of avacopan were compared to placebo and all arms received a prednisone taper, avacopan 10 mg was better than avacopan 30 mg or placebo. Therefore, the phase 2 studies do not provide additional support for the treatment benefit of avacopan when administered without glucocorticoids.

Slide 6

With regard to safety considerations, the FDA notes that the avacopan clinical program was relatively small. Two-hundred thirty nine patients were treated with avacopan, including 166 patients exposed for up to 52 weeks in the phase 3 study. Despite the small safety database, some notable differences in the safety profiles between avacopan and the control group were observed.

A greater proportion of avacopan-treated patients had hepatobiliary adverse events and serious adverse events, adverse events related to liver enzyme elevations, and hepatobiliary adverse events leading to discontinuation in the avacopan group. In addition, there were 2 patients with angioedema in the avacopan group, compared to none in the prednisone group. Elevations in CPK were also observed.

Treatment-emergent infections, serious infections, and opportunistic infections were similar or fewer in the avacopan group. No Neisseria meningitidis infections were reported. Other events including treatment-emergent adverse events, serious adverse events, and adverse events leading to discontinuation occurred in similar numbers of patients between the treatment groups.

Given the small safety database, conclusions regarding rare and latent toxicities, which are more relevant for chronic immunosuppressants like avacopan, are limited, however, imbalances in hepatotoxicity, liver enzyme elevations, and angioedema are observed despite the small sample size.

As noted in the FDA background materials, the potential benefits of steroid-sparing pertain to sparing the toxicities associated with the use of exogenous glucocorticoids. However, these potential benefits need to be considered in the context of the potential toxicities of the investigational treatment.

Slide 7

AAV is a rare and serious disease associated with morbidity and mortality. It is also a disease with high unmet need for new therapies. On this slide are listed the benefits and risk considerations discussed in the prerecorded presentations.

We ask you to consider the results at Week 26 demonstrating noninferiority but not superiority. Study CL10 was designed to compare avacopan to a standardized 20-week prednisone taper, with background rituximab or cyclophosphamide induction treatment in both arms. The Agency has determined that the Applicant did not provide adequate justification for the selected noninferiority margin. In addition, glucocorticoid were used by 86% of patients in the avacopan arm through Week 26, and therefore, the noninferiority assessment is not the intended comparison of avacopan vs. prednisone, but instead a comparison of avacopan plus lower dose glucocorticoids vs. higher dose glucocorticoids. Further, based on the study design which specified the use of glucocorticoids in the prednisone arm, it cannot be concluded that differences in doses of glucocorticoids used were due to a treatment effect of avacopan, rather than the design of the study.

We ask you to consider the clinical significance of the superiority of avacopan based on sustained remission at Week 52. The treatment effect was seen in the rituximab subgroup that did not receive maintenance therapy for the second half of the study, but not in the cyclophosphamide subgroup treated with azathioprine maintenance.

In addition, the data from the clinical pharmacology program has identified avacopan as a CYP3A4 inhibitor that has the potential to increase exposures to systemic glucocorticoids which are CYP3A4 substrates, raising further questions about the true difference in glucocorticoid exposures and the proposed role of avacopan as a steroid-sparing agent.

We ask you to consider the potential risks of hepatotoxicity, and angioedema, and CPK elevations observed despite the relatively small safety database.

And finally, we ask you to consider how avacopan, if approved, would be used in the current treatment approach to AAV.

Slide 8

The efficacy standard in the regulations describes the need for substantial evidence from adequate and well-controlled investigations supporting the language in labeling. Avacopan was granted orphan drug designation. Orphan designation does not alter the standard regulatory requirements and process for obtaining marketing approval. Safety and effectiveness of a drug must be established through adequate and well-controlled studies.

Slide 9

The regulations governing determinations of effectiveness are further described in guidance documents from the Agency. The gold standard is evidence from at least 2 adequate and well-controlled studies.

Slide 10

However, in some settings, a finding of substantial evidence of effectiveness to support a claim can be made based on "one adequate and well-controlled clinical investigation plus confirmatory evidence". Key factors to allow for such a determination include the "persuasiveness of evidence from a single study" and the "robustness of confirmatory evidence."

Slide 11

The guidance indicates that reliance on a single study should "be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect…"

There are situations where a single study of a new treatment may be sufficient to support a marketing application, in particular, when there is independent substantiation from related, supportive study data and/or when evidence from the single study is both clinically and statistically very persuasive.

Slide 12

With respect to safety, an application can be refused to be approved in one of several circumstances as listed on this slide. These include, information that the drug is unsafe or that there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

Slide 13

I will now move on to the Discussion Points and Voting Questions.

Question 1 is a discussion question. We ask the Committee to discuss whether the results at Week 26 support a clinically meaningful benefit of avacopan. We ask you to include the following elements in your discussion.

- The appropriateness of a primary non-inferiority comparison
- The use of additional non-study supplied glucocorticoids in the avacopan group, and
- The lack of statistically significant superiority at Week 26

Slide 14

Question 2 is also a discussion question. We ask the Committee to discuss whether the results at Week 52 support a clinically meaningful benefit of avacopan. We ask you to include the following elements in your discussion:

- The impact of the lack of maintenance therapy in the rituximab subgroup, and the
- Discrepancies in BVAS remission responses as determined by Adjudication Committee vs. Investigators

Slide 15

Then, the Committee will be asked to discuss whether the data support the use of avacopan as a steroid sparing agent in ANCA-associated vasculitis. Include discussion of the use of additional non-study supplied glucocorticoids in the avacopan group and the impact of a potential increase in glucocorticoids exposures due to CYP3A4 inhibition by avacopan.

Slide 16

This will be followed by Discussion point 4, where we ask you to discuss based on the data from the clinical program how avacopan, if approved, should be used in the treatment of ANCA-associated vasculitis. That is, discuss how the data from the clinical program presented inform where avacopan would fit in the management of ANCA-associated vasculitis. For example, whether avacopan should be used instead of steroids, instead of other treatments, as part of induction treatment, as part of maintenance treatmen, or more broadly.

Slide 17

The remaining questions are voting questions. The Committee will be asked to vote whether the efficacy data support approval of avacopan for the treatment of adult patients with ANCA-associated vasculitis (GPA and MPA).

If you vote no, we ask that you discuss what additional data, if any, will be needed.

If you vote yes, please provide comments.

Slide 18

Then, the Committee will be asked to vote on whether the safety data are adequate to support approval of avacopan for the treatment of adult patients with ANCA-associated vasculitis (GPA and MPA).

If you vote no, we ask that you discuss what additional data, if any, will be needed.

If you vote yes, you can also provide comments.

Slide 19

The last voting question is whether the benefit-risk profile is adequate to support approval of avacopan 30 mg twice daily for the treatment of adult patients with ANCA-associated vasculitis (GPA and MPA).

If you vote no, we ask that you discuss what additional data, if any, will be needed.

If you vote yes, please also provide comments.

Thank you. We look forward to your discussion on May 6th.

Slide 20

No script