FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE (AAC) MEETING

Virtual Meeting

Thursday, May 6, 2021

10:00 a.m. to 5:11 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. BECKER: I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Dr. Mara Becker, and I'll be chairing this committee. I will now call the May 6, 2021 Arthritis Advisory Committee meeting to order. Dr. Moon Hee Choi is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. CHOI: Good morning. My name is Moon Hee Choi, and I am the acting designated federal officer for this meeting. All voting members have confirmed via email that they have viewed the prerecorded presentations for today's meeting in their entirety. When I call your name, please introduce yourself by stating your name, and

affiliation, and I confirm.

Dr. Becker?

DR. BECKER: Hi. I'm Mara Becker. I'm a pediatric rheumatologist with additional training in clinical pharmacology. I'm an associate professor of pediatrics and vice chair for faculty in the Department of Pediatrics at Duke University School of Medicine. I confirm that I viewed the FDA and ChemoCentryx's prerecorded presentations in their entirety.

DR. CHOI: Dr. Curtis?

DR. CURTIS: Hi. Good morning. My name is Sean Curtis. I'm a senior vice president in charge of regulatory affairs at Merck Research Labs. I am acting as the industry representative today. Thank you.

DR. CHOI: Dr. Dellaripa?

DR. DELLARIPA: Yes. My name is Paul Dellaripa. I'm an adult rheumatologist at the Brigham and Women's Hospital in Boston, and I have reviewed all of the appropriate slides from the FDA and Centryx. Thank you.

DR. CHOI: Ms. Johnson?

MS. JOHNSON: My name is Hetlena Johnson. I'm a consumer representative, and I am in South Carolina.

DR. CHOI: Ms. Johnson, can you please let us know if you have reviewed the prerecorded presentations that were sent to you by stating I confirm?

MS. JOHNSON: I confirm.

DR. CHOI: Thank you.

Dr. Nason?

DR. NASON: Good morning. This is Martha Nason. I'm a mathematical statistician at the National Institute of Allergy and Infectious Diseases, and I confirm that I have viewed all the presentations that were sent.

DR. CHOI: Dr. Oliver?

DR. OLIVER: Good morning. I'm Alyce Oliver. I'm an adult rheumatologist at Augusta University. I confirm that I have reviewed the presentations in their entirety.

DR. CHOI: Dr. Pisetsky?

DR. PISETSKY: Hi. I'm Dr. David Pisetsky, professor of medicine and immunology at Duke University. I am an adult rheumatologist, and I confirm that I have read the material and viewed the presentations.

DR. CHOI: Dr. Richards?

DR. RICHARDS: Good morning. My name is John Steuart Richards. I'm an adult rheumatologist at the VA Healthcare System in Pittsburgh, and I confirm that I have viewed all of the material from the FDA and ChemoCentryx and watched the presentation.

DR. CHOI: Dr. Singh?

DR. SINGH: Good morning. I'm Jasvinder Singh from the University of Alabama Birmingham and a staff physician of the Birmingham VA Medical Center. I confirm that I've reviewed all the prerecorded materials from both the FDA and the pharmaceutical company, as well as all the materials. Thank you.

DR. CHOI: Dr. Wiesendanger?

DR. WIESENDANGER: Yes. Good morning. This

is Margrit Wiesendanger from the Icahn School of Medicine at Mount Sinai in New York City, and I confirm that I have viewed all of the recorded materials from the FDA and ChemoCentryx. Thank you.

DR. CHOI: Dr. Brant?

DR. BRANT: Elizabeth Brant, assistant professor of medicine and nephrology at Dartmouth-Hitchcock Medical Center and Geisel School of Medicine. I'm acting as the patient representative today, and I confirm that I've viewed both of the prerecorded presentations in their entirety.

DR. CHOI: Dr. Chung?

DR. CHUNG: Hello. This is Sharon Chung. I'm an adult rheumatologist at the University of California, San Francisco. I'm an associate professor of clinical medicine and I also direct the Vasculitis Clinic. I also serve as the associate director of Clinical and Translational Medicine at the Immune Tolerance Network. I have reviewed both prerecorded presentations in their

entirety. Thank you.

DR. CHOI: Dr. Kim?

DR. S. KIM: Good morning. I'm Seoyoung Kim, adult rheumatologist and pharmacoepidemiologist at Brigham and Women's Hospital in Boston. I'm also associate professor of medicine at Harvard Medical School. I also confirm that I have viewed all the prerecorded presentations for the meeting.

DR. CHOI: Dr. Kraft?

DR. KRAFT: I'm Walter Kraft. I'm an internist and clinical pharmacologist at Thomas Jefferson University in Philadelphia. I have reviewed in entirety all of the materials from the sponsor and the FDA.

DR. CHOI: Dr. Lewis?

DR. LEWIS: I'm Dr. Julia Lewis. I'm a nephrologist from Vanderbilt University. I confirm I reviewed the FDA and ChemoCentryx's presentations in their entirety.

DR. CHOI: Dr. May?

DR. MAY: Susanne May. I'm a professor of

biostatistics at the University of Washington in Seattle and the director of the University of Washington Clinical Trials Center, and I confirm that I have reviewed all of the prerecorded meeting materials.

DR. CHOI: Dr. Shaw?

DR. SHAW: Hello. My name is Pamela Shaw, and I'm associate professor of biostatistics at the University of Pennsylvania's Perelman School of Medicine. I confirm that I have viewed the prerecorded presentations from both the FDA and ChemoCentryx, and reviewed the meeting materials.

DR. CHOI: Dr. Sperati?

DR. SPERATI: Good morning. I'm John Sperati. I'm an adult nephrologist at Johns Hopkins University, and I confirm that I have reviewed all of the prerecorded material.

DR. CHOI: Dr. Thadhani?

DR. THADHANI: Good morning. My name is Ravi Thadhani. I'm the chief academic officer at Mass General Brigham and professor of medicine at Harvard Medical School, and I confirm I've reviewed

the materials. Thank you.

DR. CHOI: Thank you.

Dr. Beitz?

DR. BEITZ: Good morning. I'm Julie Beitz, the director of the Office of Immunology and Inflammation at CDER FDA.

DR. CHOI: Dr. Nikolov?

DR. NIKOLOV: Good morning. My name is Nikolay Nikolov. I'm the director of the Division of Rheumatology and Transplant Medicine, the same office and same center at the FDA.

DR. CHOI: Dr. Glaser?

(No response.)

DR. CHOI: Dr. Glaser?

DR. GLASER: This is Rachel Glaser. I'm a clinical team leader in the Division of Rheumatology and Transplant Medicine at the FDA.

DR. CHOI: Dr. Peng?

DR. PENG: Hi. I'm Suzette Peng. I'm the clinical reviewer in the same Division of Rheumatology and Transplant Medicine.

DR. CHOI: Dr. Kim?

DR. Y. KIM: Hi. This is Yura Kim, statistician from Office of Biostatistics, CDER, FDA.

DR. CHOI: Thank you.

DR. BECKER: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are

anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Arthritis Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not

limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of

their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of new drug application, NDA, 214487, for avacopan oral capsules, submitted by ChemoCentryx, Inc., for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis.

This is a particulate matters meeting during which specific matters related to ChemoCentryx's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Christopher John Sperati. Dr. Sperati's waiver includes his investment holdings in a healthcare sector mutual fund.

The waiver allows individuals to participate

fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at https://www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees.

Copy of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Sean P. Curtis is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Curtis' role at this meeting is to represent industry in general and not any particular company. Dr. Curtis is

employed by Merck & Co., Inc.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BECKER: We will proceed with FDA introductory remarks from Dr. Rachel Glaser.

FDA Opening Remarks – Rachel Glaser

DR. GLASER: Good morning, Dr. Becker, esteemed advisory committee members, ChemoCentryx team, my FDA colleagues, and members of the audience. My name is Rachel Glaser. I'm a clinical team leader in the Division of Rheumatology and Transplant Medicine, and I'm also a practicing adult rheumatologist.

On behalf of the agency, I'd like to welcome you all to this virtual Arthritis Advisory Committee meeting, where we will be discussing the new drug application, or NDA, 214487, avacopan for treatment of adult patients with anti-neutrophil cytoplasmic autoantibody, or ANCA-associated vasculitis, including granulomatosis with polyangiitis, or GPA, and microscopic polyangiitis, or MPA.

While we would prefer to be sitting in a room with all of you today, we are thankful that we can utilize this virtual setting to proceed with this very important discussion. Before I begin, I would like to thank the members of the panel for your participation in this Arthritis Advisory Committee meeting. We consider your expert scientific advice and recommendations very important to our regulatory decision-making processes.

In an effort to focus the meeting and accommodate different time zones, we have adopted a unique format for today's meeting. Rather than

take the time to give our comprehensive presentations this morning, we have provided prerecorded presentations from both the applicant and the agency ahead of the meeting in addition to the written briefing documents. These prerecorded presentations from the applicant and FDA, as well as their transcriptions, have also been posted on our website.

We thank you for taking the time to review these materials prior to today's meeting. The agenda for today's meeting will be as follows. After my brief introductory and welcome remarks, I will turn the meeting over to Dr. Becker and then ChemoCentryx to give a summary presentation, after which you will have the opportunity to ask clarifying questions of the applicant.

I will then return to similarly give a summary presentation from the agency, followed by clarifying questions to FDA. The scope of the clarifying questions to either the applicant or FDA can cover the entirety of their prerecorded and live presentations.

The advisory committee panel members may refer to any of the slides that have either been shown in the applicant and FDA's summary presentations or those that have been provided to you from the comprehensive prerecorded presentations. We will be able to pull up these slides to facilitate the discussion. We ask that you provide the name of the presenter, title of the presentation, and the slide number to further facilitate the process.

After clarifying questions to the agency, we will take a break for lunch and return for the open public hearing. This will be followed by the charge to the committee; then we will turn to the discussion points and voting questions.

As we navigate the virtual meeting format together, we thank you for your patience should we experience any technological issues. Thank you again for your participation today. We look forward to a robust discussion. I will now turn the meeting back to Dr. Becker.

DR. BECKER: Both the Food and Drug

Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the ChemoCentryx

presentation.

Applicant Presentation – Pirow Bekker

DR. BEKKER: Good morning. I'm Dr. Pirow Bekker, the clinical lead for the avacopan program. I've been doing clinical development for 31 years and have been involved from the start in the development of avacopan for ANCA-associated vasculitis. For the record, I am a shareholder of ChemoCentryx and also a consultant to the company.

The briefing document and prerecorded presentation provide a comprehensive picture of the efficacy and safety profile of avacopan in ANCA-associated vasculitis, the serious, potentially life-threatening autoimmune disease for which avacopan has orphan disease status.

Today's presentation focuses on the phase 3 study design and the results as they pertain to the two prespecified primary endpoints and secondary endpoints of relapse, renal function and glucocorticoid toxicity, safety, and finally the indication for use of avacopan.

First, I will remind the audience that C5a

receptor inhibition represents a novel, targeted mechanism of action for therapy of ANCA-associated vasculitis. Avacopan was developed based on years of in vivo pharmacology that causally connected C5a receptors to severe ANCA-associated vasculitis in the animal models. Human observation supported the link of C5a and C5a receptor to the disease.

This targeted mechanism of action is thought to directly affect an aspect of inflammation that is central to small blood vessel necrosis and resultant tissue destruction in ANCA-associated vasculitis.

By blocking ANCA-associated C5a receptor, our hypothesis was that the need for a substantial part of the glucocorticoid use in ANCA-associated vasculitis might be bypassed and that avacopan's targeted mode of action might provide direct benefit in arresting acute vasculitis symptoms and slowing damaging organs, such as the kidney. This is what we set out to test in clinical trials, culminating in ADVOCATE.

Let's review the design of ADVOCATE. This

phase 3 randomized, double-blind, double-dummy active and placebo-controlled trial included a 52-week treatment period. This was the design we agreed upon with regulators in 2016. Patients were randomized 1 to 1 into two groups, avacopan or prednisone. 166 patients were randomized to receive avacopan 30 milligram orally twice a day plus a matching prednisone placebo. 164 patients were randomized to receive prednisone and avacopan matching placebo twice a day.

Note that the double-dummy design insured blinding for a full 52 weeks. The prednisone scheduling included the starting dose of 60 milligram per day, which was steadily tapered off to zero over 20 weeks. This schedule is within the range of those tested previously. Additionally, both groups received background standard-of-care therapy of cyclophosphamide followed by azathioprine or rituximab.

I would now like to ask Dr. Peter Merkel to present the key efficacy results. Dr. Merkel, along with Dr. David Jayne, who you will also hear

from today, were the lead investigators of our avacopan program in ANCA-associated vasculitis.

Applicant Presentation – Peter Merkel

DR. MERKEL: Thank you, Dr. Becker.

Good morning. I'm Dr. Peter Merkel. I'm at the University of Pennsylvania in Philadelphia. The ADVOCATE study had two primary endpoints, remission at week 26 and sustained remission at week 52. Both endpoints were based on the Birmingham Vasculitis Activity Score, or BVAS, a validated instrument that is the standard tool used in clinical trials to capture disease activity in patients with vasculitis.

Remission was defined as having a BVAS of zero and not taking glucocorticoids within the previous 4 weeks. Both primary endpoints were analyzed for non-inferiority and superiority when all patients had completed the 52-week treatment period. The type 1 error was controlled by testing the two primary endpoints sequentially using a gatekeeping procedure.

All investigators were trained on the use of

the BVAS, however, even though routinely used in clinical trials, BVAS is not necessarily used in clinical practice. Therefore, the prespecified analysis plan stated that all investigator-assessed BVAS assessments would be adjudicated in a blinded manner by an adjudication committee according to a predefined charter. This would ensure accuracy and consistency with scoring across all study centers.

Adjudication was done in accordance with FDA guidance on endpoint assessment and other vasculitis trials. Adjudicated results were prespecified to be used in the primary analyses. Results showed that there was 95 percent consistency between the investigator and adjudication committee BVAS assessments at week 52.

In the small number of discrepant results at week 52 -- 17 patients, 8 in avacopan and 9 in the prednisone group -- the investigators in error scored items that were not due to vasculitis disease activity.

Let's review the primary efficacy results. Let's first look at the results at week 26. The

primary endpoint was met for remission at week 26 with the avacopan group statistically non-inferior to the prednisone group. Specifically, 72 percent of avacopan-treated patients achieved clinical remission compared to 70 percent in the prednisone group.

This graph shows that the lower limit of the 95 percent confidence interval for the treatment difference between the avacopan and prednisone groups was minus 6 percentage points, far to the right of the prespecified non-inferiority boundary of minus 20 percentage points; thus meeting the prespecified primary endpoint at week 26.

The 70 percent remission rate in the prednisone standard-of-care control group is in line with the approximately 74 percent remission rate from the meta-analysis of 20 clinical trials conducted prior to the start of the ADVOCATE study, lending credence to avacopan's efficacy.

As anticipated, superiority was not met at week 26 due to the expected high remission rate in the prednisone group, which was in line with

previous trials. This result shows that a similar remission rate can be achieved by replacing the oral glucocorticoid taper with avacopan, and with fewer toxicities, as will be discussed later.

Now let's look at the results at week 52. For sustained remission at week 52, the avacopan group achieved both non-inferiority and superiority compared to the prednisone group. Sixty-six percent of patients in the avacopan group achieved sustained remission compared to 55 percent in the prednisone group, a difference that is both statistically significant and clinically meaningful.

The 12.5 percent treatment difference and the 95 percent confidence interval are to the right of both the non-inferiority and superiority boundaries, thus demonstrating that the superiority endpoint was achieved.

Per protocol population analyses and several sensitivity analyses, including tipping-point analyses presented in the briefing book, indicated that the primary endpoint results are valid.

Retreatment with rituximab was not given to patients in the rituximab stratum. This is consistent with the treatment practice and the label for rituximab when the study design was finalized in 2016. At that time, rituximab was only approved as initial 4-week treatment for induction of remission. Retreatment with rituximab was not approved by the FDA until late 2018, at which time the ADVOCATE trial was fully enrolled.

This is also consistent with design of the RAVE study, where no treatment was given after the initial treatment with rituximab. In RAVE, the rituximab group was shown to be non-inferior to the cyclophosphamide group, which did receive azathioprine after the initial cyclophosphamide treatment.

Even today, rituximab retreatment is not standard practice in all patients. Importantly, not giving any additional rituximab to patients in the rituximab stratum allowed for an assessment of the efficacy of avacopan at week 52 as monotherapy against the blinded placebo control group.

The primary endpoints in the trial, the data you have just seen, were based on all patients, whether on cyclophosphamide or rituximab background therapy. Importantly, a central benefit to patients in the avacopan group, whether on cyclophosphamide or rituximab background therapy, was that such benefits came while not on the daily oral prednisone regimen.

In the rituximab stratum, which comprised 65 percent of study patients and where avacopan was compared to matching placebo, avacopan showed a superior outcome regarding sustained remission at week 52. Note that rituximab is currently the only approved immunosuppressive drug for ANCA-associated vasculitis.

Within the rituximab stratum, 71 percent of patients in the avacopan group achieved sustained remission compared to 56 percent in the prednisone group, a difference that is both statistically significant and clinically meaningful.

This placebo-controlled comparison of avacopan provides clear evidence of avacopan's

efficacy and indicates that after remission has been achieved, remission can be sustained with avacopan without any other maintenance treatment.

Relapse was also assessed in 95 percent of patients balanced between treatment groups who achieved a BVAS of zero at any point baseline. A Kaplan-Meier graph of time to relapse in the two treatment groups is shown here.

There were 16 adjudicated relapses in the avacopan group compared to 33 in the prednisone group, with an estimated 54 percent lower risk of relapse in the avacopan group compared to the prednisone group over the 52-week treatment period.

I'd like to now ask my colleague, Dr. David Jayne, to review results informing changes in kidney function and quality of life.

Applicant Presentation – David Jayne

DR. JAYNE: Thank you, Dr. Merkel.

This is David Jayne from the University of Cambridge in the United Kingdom. We evaluated kidney function in ADVOCATE because patients with ANCA-associated vasculitis often have renal

vasculitis. In fact, approximately 81 percent of patients in our study had evidence of renal disease at baseline, and impaired renal function dominates long-term outcomes for our patients.

Historically, it has been difficult to improve kidney function in any disease with medications. The recent large meta-analysis showed that a difference as small as 0.75 mL per minute per year in eGFR between treatment groups is clinically relevant in patients with chronic kidney disease.

Let's look at renal results from the ADVOCATE study. The mean estimated glomerular filtration rate, or eGFR, at baseline was approximately 45 mL per minute in both treatment groups, indicating stage 3 kidney disease on average.

At both week 26 on the left and week 52 on the right, there was a greater improvement in eGFR in the avacopan group compared to the prednisone group. The difference in eGFR between treatment groups was approximately 3 mL a minute. This

exceeds the clinically relevant difference of 0.75 mL per minute.

This graph shows results from a prespecified subgroup analysis in the 100 patients with stage 4 kidney disease at baseline, defined as having an eGFR of 15 to 30 mL per minute. These are the patients within this trial most at risk of developing end-stage kidney disease.

The avacopan treatment effect on renal function over 52 weeks was particularly notable among this subset of patients. There was a continued trend in improvement in eGFR between week 26 and week 52, a period when tapering in the prednisone group was completed and avacopan was thus being compared directly to placebo. At week 52, the mean difference of 5.5 mL a minute between groups is clinically important in these patients with stage 4 kidney disease.

Based on a request from the FDA, ChemoCentryx conducted an analysis of changes in eGFR in patients with overt renal disease, i.e., eGFR less than 60 mL a minute; albuminuria of at

least 300 milligrams per gram; and hematuria of at least 10 red cells per high-powered field.

Results are shown here. The mean increase in eGFR in the avacopan group was 13 mL a minute at week 52 compared to 7 mL a minute in the prednisone group. Consistent with the differences in eGFR recovery, we observed more rapid reduction in albuminuria in the avacopan group.

Let's next look at health-related quality-of-life findings. This graph shows the mean change from baseline to week 26 and week 52 in the Physical Component Score of the Short Form 36 and the 4 domains that make up this summary score. You can see that the changes were greater in the avacopan group compared to the prednisone group in the Physical Component Score and all 4 domains at both time points.

Notably, general health perception worsened in the prednisone group at week 26 following the prednisone taper compared to an improvement in the avacopan group.

As shown in the briefing document, with

avacopan treatment, there was also significantly more improvement in the Vitality and Role Emotional domains with the Mental Component Score of the SF-36, as well as the EuroQual 5D-5L Visual Analog Scale and Index.

I will now turn the presentation back over to Dr. Bekker to discuss glucocorticoid use and safety.

Applicant Presentation – Pirow Bekker

DR. BEKKER: Thank you, Dr. Jayne.

This is Dr. Pirow Bekker. It is important to clearly understand the nature of glucocorticoid use by patients in the trial. There were 4 sources of glucocorticoids in our trial. The first source of glucocorticoids was scheduled daily oral prednisone, and this constitutes the biggest glucocorticoid load when treating patients with newly diagnosed or relapsing ANCA-associated vasculitis.

It is this source of glucocorticoids that we attempted to eliminate in this trial. This was absent in the avacopan group but present in the

prednisone group. It is important to note that it is impossible to do a completely glucocorticoid-free trial in patients with ANCA-associated vasculitis, and this could be a source of some confusion, which I will try to clarify here.

There were three sources of glucocorticoids in our trial in addition to the first source of scheduled daily oral prednisone. The second source was intravenous glucocorticoids given to prevent allergic reactions to rituximab. Note that 65 percent of all patients in ADVOCATE received rituximab as background therapy.

Thirdly, in addition to daily prednisone, glucocorticoids given during the pre-randomization screening period had to be tapered for safety reasons. This taper to zero occurred by the end of 4 weeks in our study.

The fourth category of other glucocorticoids was protocol-defined glucocorticoid use for controlled short bursts to manage non-major flares or to treat relapses, and glucocorticoid use for

reasons other than vasculitis, such as adrenal insufficiency.

When all sources of glucocorticoid use are taken into account, it is clear that most of the glucocorticoid use would be within the first 4 weeks of the trial, as will be shown next. We will also present the patient incidence of glucocorticoid use by study period. But note that the overall incidence of any glucocorticoid use may be misleading when one ultimately considers the total glucocorticoid exposure in the two treatment groups.

This figure shows the average daily oral prednisone equivalent dose in milligram by study week for the two treatment groups. It includes both protocol-stipulated prednisone as well as oral glucocorticoid use other than protocol-stipulated prednisone. This slide shows that there was an almost complete elimination of oral glucocorticoid use in the avacopan compared to the prednisone group.

This graph shows the average daily total

prednisone equivalent dose in milligram by study week. This total dose includes the protocol-stipulated prednisone in the prednisone group and any glucocorticoids other than the protocol-stipulated prednisone, including intravenous doses.

During the 52-week treatment period, the total average glucocorticoid dose decreased from more than 3,600 milligram in the prednisone group to approximately 1,300 milligram in the avacopan group. The median total glucocorticoid dose in the avacopan group was reduced 86 percent. That is more than 2,500 milligram compared to the prednisone group.

Most of the glucocorticoid use in the avacopan group occurred within the first 4 weeks of the study. Note that the glucocorticoid use in the avacopan group was rapidly tapered and discontinued almost entirely by the end of 4 weeks.

The proportion of patients who used additional glucocorticoids other than protocol-stipulated prednisone is summarized here.

As mentioned, most of the extra glucocorticoid use was within the first 4 weeks of trial. This occurred in both treatment groups and was mostly from carryover of glucocorticoids used during the screening period, as well as glucocorticoids given as premedication for rituximab.

After 4 weeks, the use of glucocorticoids dropped considerably for the week 4 to week 26 period, and also in the second part of the treatment period week 26 to week 52, where there was somewhat more extra glucocorticoid use in the prednisone group compared to the avacopan group.

As was shown previously, the overall amount of glucocorticoids, based on the area under the curve, was substantially less in the avacopan group and almost none after week 26.

Let's next look at the potential impact of avacopan on prednisone exposure. Avacopan is a weak cytochrome P450 3A4 inhibitor, but it does not alter prednisone exposure area under the curve or AUC. The strong CYP3A4 inhibitor ketoconazole increases the plasma exposure of the sensitive

CYP3A4 probe substrate, midazolam, more than 10-fold. This is in contrast to a drug-drug interaction study where avacopan had a small effect on midazolam with only a 1.8-fold increase in AUC.

It is known that even strong CYP3A4 inhibitors, namely ketoconazole, itraconazole and grapefruit juice, have no material effect on prednisone plasma exposure. This is consistent with an avacopan phase 2 study in patients with ANCA-associated vasculitis, where avacopan when co-administered with prednisone had no material effect on prednisone plasma concentrations, as will be shown on the next slide.

This slide shows the prednisone plasma concentrations after a dose of 60-milligram prednisone in patients with ANCA-associated vasculitis when given without avacopan, the gray line, with 10 milligram twice daily avacopan, the pink line, and with 30 milligram twice daily avacopan, the dark red line.

In this study, all three groups received standard of care, or SOC, which was full-dose

prednisone plus either cyclophosphamide or rituximab. As is clear from these data, there are no notable differences in plasma prednisone levels among the three treatment groups. In summary, avacopan does not alter prednisone exposure.

Now, let's review the glucocorticoid toxicity data. One of the secondary endpoints was the Glucocorticoid Toxicity Index, or GTI, which quantifies the glucocorticoid toxicities listed on this slide. The Cumulative Worsening Score, or CWS, of the GTI reflects cumulative toxicity over time, glucocorticoid toxicity over time.

In the Aggregate Improvement Score, or AIS, toxicities are removed if they improve and can be added if they are new or worsened. With both the CWS and AIS, if a study medication is effective at decreasing glucocorticoid toxicity over time, the scores will be lower in the study medication arm.

Both GTI scores demonstrated that glucocorticoid toxicity was reduced in the avacopan group compared to the prednisone group. Of note, the difference in mean CWS and AIS between the

prednisone and avacopan groups was greater than 10 points, the minimum clinically important difference, including for patients with ANCA-associated vasculitis, at both weeks 13 and 26. GTI was not measured after week 26 because the prednisone taper stopped at 20 weeks, and the goal of using this instrument was to quantify the glucocorticoid toxicity mainly related to study prednisone.

Let's next look at safety. A detailed analysis of the safety results is provided in the briefing book. In this presentation, we will focus on hepatic function test abnormalities and infections. In the phase 3 study, a similar proportion of patients reported at least one adverse event in both treatment groups, however, the number of adverse events was lower in the avacopan group compared to the prednisone group.

Approximately a quarter of patients in each group experienced a severe adverse event, with 71 events in the avacopan group compared to 94 in the prednisone group. The number of serious

adverse events was 116 in the avacopan group compared to 166 in the prednisone group. Life-threatening adverse events occurred in 5 percent of patients in the avacopan group and 9 percent of patients in the prednisone group.

There were 2 deaths in the avacopan group, both occurring at least 79 days after avacopan has been stopped. There were 4 deaths in the prednisone group. The percentage of patients who discontinued study medication due to an adverse event was similar between treatment arms.

Overall, 22 patients in the avacopan and 19 patients in the prednisone group had hepatic test adverse events. Regarding serious events, grade 4 elevations in ALT or AST occurred in one patient in the avacopan and 2 patients in the prednisone groups. The rest of the cases were grade 2 or 3. One patient in the avacopan group had a positive rechallenge with study medication.

Bilirubin increases in the same time frame as liver enzyme elevations occurred in 2 patients in the avacopan group and one patient in the

prednisone group. Note that all patients were required to have prophylaxis for pneumocystis. Co-trimoxazole was used in over 90 percent of patients in the trial, balanced between groups. Co-trimoxazole has well-documented hepatic toxicity.

Alcohol was causative in at least one patient, azathioprine in another, and patients also receive cyclophosphamide, acetominophen, statins, or repaglinide, which could have caused or contributed to the events. Importantly, all patients recovered with the withdrawal of study medication and other potentially hepatotoxic drugs.

Let's next look at infections. There were a lower number of infections and serious infections in the avacopan group compared to the prednisone group. The incidence of serious opportunistic infections was lower in the avacopan group, 4 percent compared to 7 percent in the prednisone group.

Notably, there were no cases of Neisseria meningitidis, an infection of concern

with broad complement C5 inhibitors. The specificity of avacopan for the C5a receptor means it does not affect assembly of the C5b through 9 membrane attack complex. Other safety aspects are covered in depth in the briefing book. Overall, the safety profile of avacopan was favorable compared to prednisone.

The current unmet needs in the treatment of ANCA-associated vasculitis include reducing the high level of toxicity with current therapies, including glucocorticoids; improving upon the low rate of sustained remission and high rate of relapses; addressing the limited effect on renal function of current therapies; and providing treatment that helps improve health-related quality of life.

In summary, the selective C-5a receptor inhibitor, avacopan, represents the first potential alternative to daily oral prednisone for ANCA-associated vasculitis. The data from the ADVOCATE trial demonstrate avacopan's ability to address several unmet needs in treating patients with ANCA-

associated vasculitis. Patients in the avacopan group not only achieved remission without the need for daily glucocorticoid treatment, but also had a higher sustained remission rate compared to the prednisone group.

We saw a significantly lower risk of relapse with avacopan compared to the prednisone group. Avacopan may also be given to sustain remission without the need for additional immunosuppressant drugs such as rituximab. This is especially relevant in the COVID-19 era.

The avacopan group without daily glucocorticoids had significantly greater improvement in kidney function compared to the prednisone group, which was particularly evident in patients with stage 4 kidney disease at baseline, and patients treated with avacopan reported greater improvements in health-related quality of life compared to the prednisone group. We saw this particularly in the physical domains, but also in important mental domains such as vitality; that means fatigue, one of the most devastating aspects

of ANCA-associated vasculitis. Treatment with avacopan was associated with a significant reduction in glucocorticoid toxicities as measured by the GTI and adverse event assessments, as well as a favorable safety profile.

These results demonstrate that avacopan with each targeted mechanism of action could be a valuable treatment for patients with ANCA-associated vasculitis and, importantly, an additional option for patients with ANCA-associated vasculitis.

Finally, how do we recommend that avacopan be used in medical practice if approved? We suggest the following. Avacopan should be used as it was studied in ADVOCATE. Avacopan should be given instead of the daily oral glucocorticoid taper to patients with newly diagnosed or relapsing GPA or MPA.

Avacopan use should be continued in order to sustain remission to protect renal function and to help improve health-related quality of life in these patients. Avacopan could be continued

throughout relapses, consistent with what was done in ADVOCATE. Thank you. We are happy to take your questions.

Clarifying Questions for Applicant

DR. BECKER: We will now take clarifying questions for ChemoCentryx. Please use your raised-hand icon to indicate that you have a question and remember to lower your hand by clicking the raised-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge at the end of your question with a thank you and end of your follow-up question with, "That is all for my questions" so we can move on to the next panel member.

Okay. We will start with Dr. Chung.

DR. CHUNG: Thank you. This is Sharon Chung

from the University of California, San Francisco. I would like to get a better understanding of the glucocorticoid use outside of the study-mandated, or the protocol-mandated, glucocorticoid use. I think the slide that would be useful to present would be the graph -- I believe it was slide 23 -- that showed the mean daily glucocorticoid use outside of study protocol. Thank you.

So I'm going to focus primarily on week 20 and after since that is when all glucocorticoids should have been tapered off or stopped, according to the study protocol or the study design. I'd like to get a better sense of how this mean daily oral prednisone dose was calculated. For example, in the avacopan group, I will randomly pick a number. Let's say at week 32, the mean daily oral dose was 2 milligrams a day.

Was that calculated across all study participants in the avacopan group or was that only calculated among participants who were taking glucocorticoids at that time?

DR. BEKKER: That was calculated across all patients in the avacopan group.

DR. CHUNG: Okay. Let's say if it was 2 milligrams a day; that means at week 32, for example, 2 times 160, that was 320 milligrams across all participants. I guess it would be treated the same if it was one participant getting 320 milligrams a day, for example, in an IV infusion versus 32 participants taking 10 milligrams a day. There was no kind of differentiation between that; is that correct?

DR. BEKKER: For the purposes of this analysis, that was correct. We have to calculate based on the potency of each individual glucocorticoid. We have to calculate a prednisone equivalent milligram dose, and then we did a sum total of that across the whole population and calculated, obviously, an average total dose and an average daily dose.

DR. CHUNG: Okay. And then --

DR. BECKER: Could the sponsor please -- Dr. Chung, I'm sorry to interrupt.

Would you mind, also please for the sponsor, to identify yourself before you speak, so we can keep track?

DR. BEKKER: Yes. I'm sorry.

DR. CHUNG: And then if I am understanding correctly as well, outside glucocorticoid use did not preclude a participant from being considered a responder or achieving the primary endpoint at week 26 or week 52.

DR. BEKKER: This is Pirow Bekker. If a patient was treated for a relapse with glucocorticoids between week 26 and week 52, that patient was considered a non-responder. For other, a lower dose glucocorticoid use, no. The patient was not penalized for that.

DR. CHUNG: So in reviewing the study protocol, to be considered a relapse, if you had one or two minor events on the BVAS, you had to have those events for at least two study visits in order to be considered a relapse; is that correct?

DR. BEKKER: This is Dr. Pirow Bekker. Yes, that is correct.

DR. CHUNG: Okay. Just for my final question, in the FDA-prepared written document, in one of their tables, they presented examples of participants who received glucocorticoids outside of the study protocol. I will confess that I was surprised by some of them.

One of them included a participant who received 250 milligrams of methylprednisolone for 3 days just before -- it looks like 4 days – the week 52 endpoint. And yet, the FDA briefing document indicates that this participant was considered a responder because they had not received glucocorticoids 4 weeks before the 52 endpoint.

Can you confirm that that is the case, or --

DR. BEKKER: This is Dr. -- I'm sorry. Go ahead.

DR. CHUNG: -- the participants that are example participants presented in the FDA briefing document were considered responders?

DR. BEKKER: This is Dr. Pirow Bekker from

ChemoCentryx. So there were a handful of cases where there was very high glucocorticoid use, and still the patients were considered to be responders, as you indicated there.

We did a sensitivity analysis to essentially impute patients with high glucocorticoid use as non-remitters, either at week 26 or at week 52, depending on when it occurred; and those sensitivity analyses were in line with the ITT analyses.

DR. CHUNG: Okay. I guess I would just --

DR. BECKER: Are you --

DR. CHUNG: -- finish with one question.

So just looking at the material that's been provided, even in the avacopan arm, a reasonable percentage, approximately 30 percent, of the study participants received outside glucocorticoids. Even with this, do you feel that it is appropriate for avacopan to be used instead of prednisone, so instead of prednisone completely for this indication, for ANCA-associated vasculitis?

DR. BEKKER: This is Dr. Pirow Bekker again.

I will ask Dr. Peter Merkel to comment from a clinical perspective.

DR. MERKEL: Yes. Hi. This is Dr. Peter Merkel. I would say that, yes, I do think it would be appropriate for avacopan to be used for this indication. I like to think of it, overall -- as you pointed out, Dr. Chung, the data is complex but, overall, it is clear that this strategy of giving avacopan would allow many patients to be on substantively less glucocorticoids.

If you look at the area under the curve from that slide 23, there's really a substantive difference between the exposure of glucocorticoids, even with the allowed extra glucocorticoids that happened.

I also think that the publication of these results, and if the drug is approved, there actually will be more confidence in using the drug without glucocorticoids, although patients will be followed very closely. So I do think it will provide that option for patients and physicians to be able to go on a much lower glucocorticoid

regimen overall. Thank you.

DR. CHUNG: Thank you. I have no further questions.

DR. BECKER: Thank you.

DR. BEKKER: Thank you, Dr. Chung.

DR. BECKER: Thank you.

Let's move forward to Dr. Julia Lewis.

DR. LEWIS: Thank you. This is Julie Lewis, nephrologist. I have two questions. I was interested in your emphasis, both in the presentation briefing document and your hypothesis-generating data, on renal effects. I want first to just -- you can correct anything if I got it wrong, and then I'll end with my particular question.

It is a subset of the randomized population of about 80 percent, and your CKD4 analyses are in a subset of that subset. Delta GFR and change in urine albumin and creatinine ratio, with 10 as the lower limit, are not acceptable, approvable outcomes for renal disease, and arguably not clinically meaningful for patients. Even if you

believed in either of them, your sample sizes were inadequate for both, and some of the benefits reverse after 8 weeks of withdrawal of therapy. And in your briefing document, you suggest avacopan may need to be continued indefinitely.

And you can correct me if I got any of those things wrong. But my question is, when you look at the eGFR graph and the albumin results, there is no separation between chronic kidney disease, non-progressive chronic kidney disease, or people who are having AKI episodes related to relapse. Those are all averaged in.

Is that correct?

DR. BEKKER: This is Dr. Pirow Bekker from ChemoCentryx. So yes, we included all patients with having renal disease at baseline, so it's 81 percent of patients in this analysis.

I'm going to ask Dr. David Jayne, nephrologist, who was obviously leading this study, to comment on the specifics of your question.

Dr. Jayne?

DR. JAYNE: Thank you. This is David Jayne

from Cambridge in the United Kingdom. You're correct. There were greater falls in albuminuria in the avacopan group compared to the prednisone group, and this was also consistently shown in the phase 2 trial. We also saw greater falls, or rather more rapid falls, in red cell counts with avacopan compared to the prednisone groups.

In terms of what happens after week 52, I think this stage is difficult to interpret because there are a number -- there was freedom for physicians to treat with drugs beyond week 52, so I think the data from week 52 to week 60 cannot be necessarily interpreted as showing a falling off of avacopan or a change in the placebo group.

I think the important data is the shape of the GFR recovery curve over the course of the trial out to week 52. Now, we do see this pattern of GFR recovery in patients presenting with renal vasculitis with depressed GFR, but the notable result here was the difference between treatment groups which we have not ever seen before. For example, comparing rituximab to cyclophosphamide,

we saw no difference in rate of GFR recovery.

From what we know of the long-term outcome of these patients, the degree of GFR recovery is related to the long term and stage of renal disease risk, and indeed the long-term patient survival. So from a clinical perspective, we feel this improvement in GFR recovery is important.

DR. BEKKER: Thank you, Dr. Jayne.

DR. LEWIS: Dr. Jayne, may I follow up that question? And I have another.

So again, I think if there was a meaningful difference in GFR that was demonstrated, that would be very intriguing. I think it's hypothesis-generating data at this point. But could you just, again, specifically tell me, those eGFRs represent the average GFR of everybody, including people who are having AKI relapses, including people who have stable non-progressive CKD; is that correct? You didn't in any way distinguish those.

DR. JAYNE: No. This is David Jayne again. We did not distinguish those. But I would add the number of AKI episodes due to renal relapse during

the trial was small.

DR. LEWIS: I'm sorry. I didn't see that data in your briefing document, and I might have missed it.

My second question is a question related to adjudication. In page 145 of your briefing document, you indicate that the adjudicators, in their rules of adjudication, only considered disease worsening if there was evidence by an increase in therapy.

I wondered how that got communicated to the PIs; how did you know that the PIs would increase. Were they told to increase therapy if there was a worsening? I mean, it seems like there could have been clinically significant worsening episodes and that, for whatever reason, perhaps in their understanding of the protocol, the PIs did not treat, and then the adjudication committee would not have marked those as a clinically relevant event to the patient.

DR. BEKKER: This is Dr. Pirow Bekker.

Dr. Merkel, based on your experience in

using the BVAS in clinical trials, would you please respond to this question?

DR. MERKEL: Yes. This is Dr. Peter Merkel. I'm not sure I completely got your question; if you might want to focus it or repeat it.

DR. LEWIS: Sure. I'll repeat it.

It says on page 145 that the adjudication committee was charged with only considering a disease being worse -- even if the BVAS score was worse and the patient was actually potentially worse, I assume -- if it was evidenced by an increase in therapy.

I wondered how you would be assured that you were detecting all the patients who were actually having a clinically meaningful event, but the PI just chose not to increase therapy.

DR. MERKEL: Okay. That's a good, detailed question. The adjudication committee communicated back to the sites -- separate and not directly of course -- to clarify any of those situations, so that we'd like to know was therapy increased or not, and if so, why not; so that we could clarify

truly whether the investigators felt, based on the data in front of them, this was due to active disease.

Really, almost all of the time, a patient who's having significant, as you put, active disease would have a treatment intervention; some change, either additional glucocorticoid, or had another drug, or dropped out of the treatment protocol. So it would be rare for that scenario that you put together to necessarily occur in the setting of the trial.

DR. LEWIS: Okay. Thank you. Those are the end of my questions.

DR. BECKER: Excellent.

I just want to remind everyone, we have about 15 more minutes to ask questions, so if you could keep them brief, that would be terrific.

Next on our list is Dr. Kim.

DR. S. KIM: Hi. This is Seoyoung Kim. My question is, again, related to the outcome of adjudication. According to the presentation and the briefing document, there were fewer remission

cases defined by the investigator than the adjudication committee, and I think the majority of the discrepancies were related to renal assessment.

So I was wondering if the sponsor can explain a bit more what was actually going on, and what made the investigator think that they are having not remission, but then the adjudication committee thought there was remission.

I have an additional question, but I will probably wait for the response to the first question. Thank you.

DR. BEKKER: Yes. I think to illustrate this, could I have slide BE-45, please? Then I will ask Dr. David Jayne to comment on the specifics here. Let me just bring this slide up. So these are cases where they were discrepancies between investigator assessment and adjudicated assessment.

Dr. Jayne, maybe you can just briefly comment on some of these.

DR. JAYNE: Thank you. This is David Jayne from Cambridge. You highlighted the issue with

BVAS assessment of renal items. The BVAS scores hematuria, proteinuria, and marked changes in serum creatinine or GFR, and a common issue with renal vasculitis patients is that you have persistence of hematuria and proteinuria. Indeed, 50 percent of patients have persistence out to 6 months.

For the purposes of adjudicating trials of renal vasculitis, we would only permit hematuria or proteinuria to be scored as an active item if there was clear evidence that either that parameter is deteriorating -- in other words, worse than the previous evaluation -- or that there is clear evidence that the serum creatinine is rising, or GFR is falling, or there has been a repeat renal biopsy offering objective evidence of renal vasculitis activity.

In the majority of cases in this trial, serum creatinine, if it was high entering, would be falling. And in that situation, if hematuria and proteinuria was consistently scored as a BVAS item, that was then removed. And if there were no other BVAS items, that patient was regarded as having a

BVAS item of zero. This was clearly defined in the charter and in the rules that we followed during the adjudication.

DR. S. KIM: Thank you. My second question is related to the slide that was just presented, related to quality of life. There was improvement in SF-36 in the components that you showed, but I don't think the difference between the treatment group and the placebo group is beyond the minimum clinically important difference.

Can you comment on the actual magnitude of difference rather than the numeric difference?

DR. BEKKER: Yes. This is Dr. Pirow Bekker from ChemoCentryx. I will ask Dr. Peter Merkel to comment on this. Peter, Dr. Merkel, has extensive experience using quality-of-life instruments in ANCA-associated vasculitis.

DR. MERKEL: Yes. Hi. This is Dr. Peter Merkel. I agree that some of the differences are small and may not all reach the MCID. I think what I found important is that the direction of change is incredibly consistent, favoring the avacopan

group versus the prednisone group at each of the ways that we looked at it, for each of these different measures.

I think some of them really do reach clinical significance, both statistical significance, as you said, and clinically meaningful differences; and the consistency across each, not just the physical component but the individual subsets, I think was notable. I hope that addresses it. Thank you.

DR. S. KIM: Thank you.

DR. MERKEL: Also, it was consistent with the EQD as well. Each of the measures are always pointing in the same direction. Thank you.

DR. S. KIM: Thank you. I'm through with my questions and responses.

DR. BECKER: Great.

Let's move on to Dr. Sperati next, please.

DR. SPERATI: Thank you. This is John Sperati, adult nephrologist from Johns Hopkins. My question is to Dr. Peter Merkel.

Could you speak in more detail on the

efficacy results in the cyclophosphamide arm at week 52, as compared to the results you presented in the rituximab arm at week 52? Thank you.

DR. MERKEL: Yes. Thank you. This is Dr. Peter Merkel. That's a good question, and I understand where it came from. We presented the data.

I think it's important to realize, from my perspective, not just with the study but as a clinician, that at week 52, in the subset stratum of patients who received cyclophosphamide, in that subset, which is a secondary analysis, there was not superiority compared to the prednisone group; however, there was non-inferiority, and they did as well, not better. But they did so without having been exposed to as much prednisone.

So from my clinical perspective, having a patient who's going to be on cyclophosphamide and not having to give anywhere near as much glucocorticoids is a win and a benefit to the patients, and I'm not surprised that there wasn't necessarily a difference.

The other issue, of course, is sample size. The study was designed for the rituximab and cyclophosphamide groups to be combined, which was our primary analysis. So it gets to be pretty small when you do the subset because only 35 percent of patients were on cyclophosphamide. So I think it's still a clear benefit. I hope that answers your question. Thank you.

DR. BEKKER: Thanks, Dr. Merkel.

This is Pirow Bekker from ChemoCentryx. I just want to also add the avacopan group also showed a benefit with regard to other endpoints. So relapse rate, for example, was lower in the avacopan compared to the prednisone group in the cyclophosphamide stratum. The GTI was lower than in the prednisone group, and the eGFR also was higher in the prednisone group. Thank you.

DR. SPERATI: So I will interpret your response to say that the use of avacopan essentially helped maintain that remission from week 26 to week 52 with the use of lower dose steroids.

The other interpretation, of course, would be that you don't need as much steroids, and avacopan is not helpful with cyclophosphamide. And simply the similar outcomes in the two arms just reflect that this is what happens when you give cyclophosphamide and a lower dose of steroids, but there was a notable difference with your results with the use of avacopan with rituximab.

So I don't know, per the FDA, if we have time for this or if you need to move on to other questions. But it, in my mind, leaves a very unanswered question here as to why there's a differential effect per the results that you've shown.

DR. BEKKER: This is Dr. Pirow Bekker.

Thank you, Dr. Sperati. We think the total dose of glucocorticoids used in the cyclophosphamide stratum was far less than the total dose that was used in the prednisone group.

I think the other thing to note also is during the last 26 weeks of the study, there was a higher percentage of patients who used

glucocorticoid in the prednisone arm compared to the avacopan arm, and the total dose was also about 50 percent higher in the prednisone group. So it appeared as if the prednisone group in the cyclophosphamide stratum required more steroids.

DR. SPERATI: Thank you.

DR. BECKER: Okay. Let's move forward to Dr. Nason, please.

DR. NASON: Thank you. This is Martha Nason, biostatistician at NIAID. I was wondering, you show Kaplan-Meier with the time to relapse starting at the BVAS of zero. And as the FDA has commented, that's hard to interpret since the start for each person is dependent on when they hit BVAS, and that could be different between people and between groups.

I was wondering if you had done the analysis or had the Kaplan-Meier to show a time to BVAS of zero just to give some clarity on whether the two groups, whether that starting point for a BVAS of zero was the same or [indiscernible – audio distorted].

DR. BEKKER: Yes. We in fact have a slide of time to BVAS equals zero; so TR-29. This slide shows the time to achieving a BVAS of zero, and it shows that it's similar between the avacopan and the prednisone groups for the ITT population with no significant difference.

DR. NASON: Okay. Thank you. That's all.

DR. BECKER: Okay. Let's move forward to Dr. Thadhani.

DR. THADHANI: Thank you. This is Ravi Thadhani. I thank the sponsor for a great presentation. I have two questions, very quickly. The first one is in the entry criteria among disease patients. Some had new disease; some had relapsing disease.

I am curious to know if there were further analyses to see if there was a differential effect of achieving the primary endpoint between those two; namely a statistically different effect, is the first question.

DR. BEKKER: Dr. Thadhani, thank you for the question. This is Dr. Pirow Bekker. We looked

across subgroups, I think as you've seen in the briefing book, and we did see that patients with relapsing disease appeared to have numerically a higher sustained remission rate in the avacopan group compared to the prednisone group when we compare that to the patients with newly diagnosed disease. But again, I think it's very important to keep in mind that with all of this, there was the reduction, the substantial reduction, in the glucocorticoid load across all of these patient populations.

DR. THADHANI: Okay. So just to clarify, there was no statistical difference between those two groups, albeit the sample sizes were small?

DR. BEKKER: Exactly.

DR. THADHANI: Okay. The next question is, given the primary endpoint being a non-inferiority trial -- obviously the spotlight goes to side effects -- can you just remind us about the patients that had evidence of liver function abnormalities; whether there were any risk factors to identify beforehand who might have had liver

function abnormalities; were they anticipated; and also specifically patients who might have recovered while still taking avacopan? Thank you.

DR. BEKKER: This is Dr. Pirow Bekker again from ChemoCentryx. We looked at the patients who had the serious adverse events. There were 9 patients who had the serious adverse events in the avacopan group; 6 of the 9 patients actually received cyclophosphamide, and the events occurred actually during the period that cyclophosphamide was given. Cyclophosphamide, as you know, is a known hepatotoxic drug.

The other thing that was notable was that these patients tended to be more on the older side of the spectrum, which again I think that was also seen in the prednisone group when we compared it there. So it does appear that patients who are more elderly are more susceptible, potentially.

I want to emphasize, though, that all these patients had significant confounding factors, so it was difficult to attribute the effect to avacopan specifically.

DR. THADHANI: Great. I'm sorry. Just to push that one step further, I believe we saw some patients continuing on avacopan and still finding their liver function tests improved; is that correct?

DR. BEKKER: That is correct. There were some patients that actually continued treatment. The one patient had an early elevation in transaminases. The transaminases came back down to normal while avacopan was continued, so that patient completed the study successfully.

DR. THADHANI: Thank you. That is all my questions.

DR. BEKKER: Thank you, Dr. Thadhani.

DR. BECKER: Thank you.

Okay. We are going to push this a little bit longer and allow just a few more questions for the people that have been very patiently waiting.

Dr. Pisetsky, you're up next.

DR. PISETSKY: Thank you. David Pisetsky, from Duke. Could you comment more about the use of rituximab? In the trial, only a single period or a

single time of administration was used, whereas now it would be used repeatedly over time.

How would we interpret the response to avacopan given the way standard care has evolved, particularly with the use of rituximab?

DR. BEKKER: Yes. Thank you, Dr. Pisetsky. It's an important question. We do not consider the rituximab arm to be undertreated. I think that's an important point. ChemoCentryx followed the approved indication in treatment practice for rituximab at the time of our study finalization, which was obviously much earlier than 2016, and rituximab was only approved for retreatment in 2018. We discussed the trial at the time with the agency. The agency agreed with the trial design.

I will also ask Dr. Merkel to comment on his perspective briefly.

DR. MERKEL: Yes. Hi. This is Dr. Peter Merkel from the University of Pennsylvania. This is a good question. I think a couple of things I would point out is that in the first phase, from enrollment to week 26, avacopan was given in

addition to rituximab and was able to show the benefit of not having been on the glucocorticoids, which I think is a substantive benefit during the induction of remission phase. So that would be consistent with the care we give now.

Not all patients receive rituximab retreatment. Many do, but not all do. Some patients with new onset microscopic polyangiitis, for example, might not. There may be contraindications with rituximab. So we feel that there's really a need for another option beyond rituximab.

We have concerns about hyperimmunoglobulinemia, infections, especially in this past year with the vaccination and other issues, and I think that the data does show an additive benefit, and it shows efficacy of avacopan separate from rituximab, which gives us another option that we could add to.

So if this drug was approved, I would have that conversation with patients, if they're doing well on avacopan, about perhaps you would stay on

avacopan instead of being retreated with rituximab, and have that option. Thank you.

DR. PISETSKY: Just to follow up, would your sense be that, if approved, this would be used concurrently with rituximab and avacopan? Would both be used over time, or how would you determine that?

DR. MERKEL: This is Dr. Peter Merkel again. I would say it would certainly be used in the induction phase, after a patient with new or relapsing disease. It would be used with rituximab as is done in the phase 3 trial. So I think that would surely be used in combination with rituximab or cyclophosphamide.

Then the question is, what about in the so-called maintenance phase at week 26, where you might retreat with rituximab? Again, I think the data show that patients did quite well if they stayed on avacopan, so I think that would be an option that I would discuss with the patient. It may depend on their history of use of rituximab, contraindications, comorbidities, et cetera. It

could be used in combination with both.

I think we'll have to see how that comes about with practice. But again, there's only one drug approved for ANCA-associated vasculitis, so having another one available gives us those options. Thank you.

DR. PISETSKY: Thank you.

DR. BECKER: Dr. Kraft, you're next.

DR. KRAFT: Walter Kraft from Thomas Jefferson University. This is a question for Dr. Pirow Bekker, slide SP-26.

For drug-drug interaction Study 008, for exposures in the healthy volunteers of avacopan, systemic exposure, could you comment on the relative size of AUC or exposure compared to patients who will have reached steady state at approximately 13 weeks of dosing with food as opposed to fasted dosing? Thank you.

DR. BEKKER: Yes. Dr. Kraft, this is Dr. Pirow Bekker from ChemoCentryx. We do not have that data. As you've seen from the package, the data that we have are the data that we've included

in the package. I think the key thing here for us to consider, though, is the potent CYP3A4 inhibitors -- itraconazole, ketoconazole, grapefruit juice -- barely have an effect on the exposure.

Avacopan is a weak CYP3A4 inhibitor, based on the exposure increase that we're seeing. At best, you can maybe argue its modest/moderate when you take food in steady state into account. But I think it's hard to imagine that that would actually come close to what a potent CYP3A4 inhibitor would do. I think prednisone's metabolism CYP3A4 is somewhat involved, but there's clearly other CYP enzymes that are involved in the metabolism.

DR. KRAFT: Thank you. And then just very quickly, can you confirm, if the material didn't state, that avacopan is not an inhibitor of commonly implicated drug interactions for drug transporters?

DR. BEKKER: No. No, it is not. We did look at that, and it's not.

DR. KRAFT: That answers my question. Thank

you.

DR. BEKKER: This is Pirow Bekker again. I'm sorry.

DR. BECKER: Okay. We're going to take two last questions. Next on the list is Dr. Shaw.

DR. SHAW: Hi. Yes. Thank you. This is Pam Shaw. I just had a quick technical question for perhaps one of the statisticians in the group. I just wanted a little more clarity on the analysis of the primary endpoint.

You presented, I think today it was slide 10, that it's a comparison of the risk difference, say, for the sustained remission at 52 weeks. And you're doing some kind of inverse variance weight. You're not doing an unweighted analysis. You're doing a weighted analysis, and you're using a randomized strata.

So my question is I just wanted to double-check what was the number of strata. I was trying to tell by the tables. I just wanted to confirm my understanding.

Then I was wondering if the tests you were

using had a specific name. You just call it some kind of summary score estimate, and you referenced a book that is a couple 100 pages. So I was just kind of curious as to what statistical test that was. Thank you.

DR. BEKKER: Dr. Shaw, thank you for the question. This is Dr. Pirow Bekker again. I'm not a time statistician. I just have to qualify that.

So we did stratify patients based on three aspects. One is being either newly diagnosed or relapsing disease; the second is having either PR3 or MPO-positive disease; and the third is receiving either cyclophosphamide or rituximab.

Those were the three stratification factors. I cannot give you more specifics on the exact methodology. I apologize. So we could --

DR. SHAW: That's fine. So is that a total -- no. Sorry to interrupt you. And that's fine. I just wanted to ask.

So then that sixth strata, those were all binary factors?

DR. BEKKER: Yes, all binary factors.

DR. SHAW: Okay. Thank you.

DR. BECKER: Excellent.

The final question will be from Dr. Wiesendanger.

DR. WIESENDANGER: Oh, thank you. This is Margrit Wiesendanger from Mount Sinai Hospital in New York. I have a clarification question for Dr. Peter Merkel, slide 8.

Dr. Merkel, I was just wondering, in terms of the discrepancies between the expert committee, centralized adjudication, and the individual investigators at the sites, on the BVAS, were only new and worsening items scored, or also persistent items?

DR. MERKEL: Yes. Hi. This is Dr. Peter Merkel. Thank you. Yes, you know the BVAS. So both persistent and new and worse were scored for that, and they were both considered to be active disease.

If something was persistent for three months, the usual practice is it is considered damaged and scored on the Vasculitis Damage Index.

We checked to see if that was the case, and the adjudication committee would clarify with sites is that the case so that we were very clear what was considered active disease versus what was considered inactive disease and/or damaged. I hope that addresses your question. Thank you.

DR. WIESENDANGER: Yes, that's very helpful. Thank you so much, Dr. Merkel.

DR. MERKEL: I will add that this is standard approach now in our trials. Thank you.

DR. BECKER: Okay. If there are no other clarifying questions for ChemoCentryx, we will now proceed with the FDA summary presentation from Dr. Rachel Glaser.

FDA Summary Presentation – Rachel Glaser

DR. GLASER: Good morning once again. This is Rachel Glaser, and I will now provide FDA summary remarks. The comprehensive prerecorded presentations have been provided to the panel members to view prior to today's meeting and also have been posted to our website.

In this summary, I plan to review the

highlights of the agency's presentation. These slides will be familiar to the panel, as they've been taken from the prerecorded slide deck. Therefore, my presentation of these slides will be abbreviated and focus on the salient points we would like the committee to consider in your discussion of the data submitted to support the application for avacopan, for the treatment of adult patients with ANCA-associated vasculitis.

To support this new drug application, ChemoCentryx submitted the results from a single pivotal trial, CL010-168. In the agency's presentation, we will refer to the study as CL010.

As you have heard, the pivotal trial was a randomized, double-blind, active-controlled study to evaluate the safety and efficacy of avacopan compared to standard of care that is a protocol-specified, 20-week prednisone taper in 331 patients with newly diagnosed or relapsed ANCA-associated vasculitis. ChemoCentryx also submitted data from two smaller phase 2 studies, CL002-168 and CL003-168, which will be referred to

as CL002 and CL003, respectively.

As mentioned, due to differences in the study designs, including different treatment arms with different doses of avacopan and varying concomitant prednisone tapers; shorter treatment duration; small patient populations; and different primary efficacy assessments, the focus of the advisory committee discussion will be data from Study CL010.

For additional context, in general, evidence from at least two adequate and well-controlled studies is required to establish effectiveness. However, under certain circumstances, such as for life-threatening and severely debilitating diseases with an unmet medical need and for certain rare diseases, FDA can consider results from a single adequate and well-designed study. In that case, the evidence needs to be statistically persuasive and clinically meaningful.

We note that in the case of avacopan, the FDA has exercised this regulatory flexibility to consider a single trial, Study CL010, intended to

provide the substantial evidence of effectiveness.

This is the schematic of the pivotal study. The applicant has reviewed some of the design features. I would like to highlight two key design features here. First, patients in both treatment arms received background rituximab or cyclophosphamide standard induction therapy. Patients who received cyclophosphamide received azathioprine for maintenance therapy, while patients who received rituximab induction treatment did not receive maintenance therapy.

As you have heard in the prerecorded presentation by Dr. Peng, 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.

Second, patients with ANCA-associated vasculitis were randomized to two treatment arms, one receiving avacopan 30 milligrams twice daily for 52 weeks, and the other receiving a prednisone taper over 20 weeks. The avacopan arm did not

include prespecified glucocorticoids, however, patients on both arms were allowed to receive non-study supply of glucocorticoids.

As a result, 86 percent of the patients in the avacopan arm received glucocorticoids at some point between week zero and week 26, and 87 percent of the patients in the avacopan arm received glucocorticoids over the study.

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.

Disease remission at week 26 was defined as achieving a BVAS of zero as determined by the adjudication committee and no glucocorticoids received for treatment of ANCA-associated vasculitis within 4 weeks prior to assessment. 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 three non-major items at a single visit, or one or two non-major items for at least two consecutive visits after remission had been achieved.

I will now summarize the statistical review of efficacy. According to the applicant's sequential multiple testing procedure, non-inferiority 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.

Also of note, secondary endpoints were not controlled for multiplicity, and thus are considered exploratory. You may note minor differences in the estimates for these secondary endpoints in the FDA and applicant presentations and background documents as a result of different analyses. The agency has presented the results from analyses considered to be statistically

appropriate, which can be implemented with minimal assumptions.

This slide summarizes the analysis results for the primary endpoints, including the two-sided p-values for the significant test in the multiple testing hierarchy. This may differ from the applicant's presentation, which included one-sided p-values. Based on the prespecified sequential multiple testing procedure, type 1 error rate was to be controlled at 0.05 two-sided significance level.

The first three tests, that is non-inferiority for remission at week 26, non-inferiority for sustained remission at week 52, and superiority for sustained remission at week 52, were statistically significant, while the test of superiority at week 26 was not statistically significant.

While superiority was demonstrated at week 52, we have additional points for your consideration in interpreting the data. Looking further at the results at week 52 where superiority

was demonstrated, this slide shows the primary endpoint results stratified by background induction therapy.

At week 52, there was a noticeable difference in observed treatment effects between the subgroups that received rituximab and cyclophosphamide induction treatment. The estimated treatment effect in the proportion of subjects achieving disease remission at week 52 was 15 percent in the subgroup receiving induction with rituximab and 3.3 percent in the cyclophosphamide plus maintenance azathioprine subgroup.

The agency acknowledges that the primary analyses that demonstrated superiority at week 52 were based on adjudicated assessment of the BVAS remission. However, if sustained remission is defined using the investigator assessment of BVAS remission, the same analyses resulted in a smaller magnitude of treatment effect and would not support the statistical superiority of avacopan, as summarized on this slide. 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.

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 CL010 to support the use of avacopan in ANCA-associated vasculitis. We ask you to carefully consider whether the efficacy results are robust.

As you have heard, 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 when added to rituximab or cyclophosphamide induction to inform the margin of the non-inferiority comparison in this study. FDA does not find the non-inferiority 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 zero to 26. The non-inferiority assessment is not the intended comparison of avacopan versus prednisone, but instead a comparison of avacopan plus lower dose glucocorticoids versus 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 to a treatment effect of avacopan and not due to the specifications of the protocol. In total, the treatment effect of avacopan and the magnitude

of effect at week 26 are unclear.

At week 52, a statistically significantly greater proportion of patients in the avacopan treatment arm achieved sustained remission, demonstrating both non-inferiority 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 treatment 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 CL010 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.

Study CL010 was designed to compare avacopan to a prespecified prednisone taper, however, non-study supplied glucocorticoids were used by patients in both arms. 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's a large difference in the mean daily dose between

the two arms. After completion of the 20-week prednisone taper, the mean daily dose is comparable between arms during the second half of the study.

Patients in the avacopan group received glucocorticoids for treatment of ANCA-associated vasculitis throughout the study. As presented in the FDA background document, table 16, approximately 62 percent of avacopan-treated patients received non-study supplied glucocorticoids for treatment of ANCA-associated vasculitis from week zero to 26. This does not include the use of glucocorticoids as premedication for rituximab infusions. From week 27 to 52, approximately 20 percent of avacopan-treated patients received glucocorticoids for treatment of ANCA-associated vasculitis.

In addition to assessment of cumulative glucocorticoid doses used, the applicant assessed the Glucocorticoid Toxicity Index to evaluate the toxicities of glucocorticoids. Greater improvement from baseline was observed in the avacopan arm on the GTI Cumulative Worsening Score and GTI

Aggregate Improvement Score at weeks 13 and 26. GTI was not assessed at later time points.

The agency recognizes that reducing glucocorticoid use is an important goal in treatment of patients with ANCA-associated vasculitis if it occurs in the context of a treatment that effectively controls disease activity. However, the differences in GTI between the treatment groups are most likely to reflect the study design, which specified the prednisone doses to be used in the control group, rather than dosing glucocorticoids guided by investigator assessment of active disease.

To provide further context to the differences in nominal doses of glucocorticoids, I will highlight some important pharmacology features.

Avacopan capsules were orally administered twice daily with food in the phase 2 and phase 3 studies. Avacopan is a CYP3A4 inhibitor. 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 conditions, midazolam systemic exposure increased by up to 81 percent.

The impact of avacopan on CYP3A4 substrate under fed conditions could be higher than fasted conditions, but has not been studied. In addition, the impact may be higher at steady state.

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 measurements. 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 conditions could not be ruled out.

Therefore, while there were differences in nominal doses of glucocorticoids in the pivotal study with lower doses received in the avacopan study arm, based on the potential drug-drug interaction, these differences in nominal doses may

not accurately reflect the differences in glucocorticoid exposure.

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 CL010 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 week zero to 26, which was also reflected by the data from the Glucocorticoid Toxicity Index.

Based on the study design, there's 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, avacopan is 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 rule 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.

This slide presents the multiple secondary efficacy endpoints prespecified by ChemoCentryx, however, there are limitations to the analysis of these secondary endpoints. When there is more than one study endpoint, care must be taken to ensure that the evaluation of multiple hypotheses does not lead to inflation of the study's overall type 1 error probability. The inflation of the type 1 error rate can be quite substantial if there are

many comparisons.

As you have heard in the prerecorded presentations, no secondary endpoints were adjusted for multiplicity, therefore the secondary endpoints are considered exploratory.

There were fewer relapses observed in the avacopan group, however, other assessments of increased disease activity, including persistent vasculitis, maintenance of remission, and worsening vasculitis, were similar between treatment groups.

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.

For example, patients on the prednisone arm appear to achieve remission faster than those on avacopan, and therefore are at risk for relapse for a longer duration of time, raising questions about the interpretability of the relapse exploratory endpoint.

There were no clinically meaningful

differences in the Vasculitis Damage Index.

With regard to renal endpoints, differences in changes in GFR were small and were not sustained after treatment discontinuation. The applicant has noted that GFR difference observed in the pivotal study exceeds the clinically relevant difference of 0.75 milliliters per minute. However, the cited GFR difference of 0.75 milliliters per minute is referencing a difference in rate of eGFR change or slope for slowly progressive kidney diseases that's used frequently in trials of diabetic nephropathy.

Thus, the cited GFR difference may not be relevant to the assessments of this renal endpoint in the avacopan program, as ANCA-associated vasculitis is a disease that leads to acute kidney injury where the goal of treatment is relatively large improvements in kidney function over a relatively short period of time.

Urine albumin to 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 in Dr. Peng's presentation, 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, but these measures are not specific to vasculitis. Overall, the secondary endpoints provide limited support of efficacy of avacopan.

As you have heard, the applicant also conducted two phase 2 studies. These studies included different study designs compared to the pivotal trial, with 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-milligrams 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 patients received a prednisone taper, avacopan 10 milligrams was better than avacopan 30 milligrams or placebo. Therefore, the phase 2 studies do not provide additional support for the treatment benefit of avacopan when administered without glucocorticoids.

With regard to safety considerations, the FDA notes the avacopan clinical program was relatively small. 239 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, and adverse events related to liver enzyme elevations. There were 5 patients who discontinued study treatment due to hepatic adverse events in the avacopan arm compared to none in the prednisone arm.

As discussed in Dr. Peng's presentation, there were 9 liver-related SAEs, including 7 avacopan-treated patients compared to 2 prednisone-treated patients. Four of the cases were considered probable or highly likely drug-induced liver injury due to avacopan. One patient met Hy's law laboratory criteria. This is considered possible drug-induced liver injury due to the use of an additional medication associated with liver abnormalities. 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. Differences were generally due to small numbers of

patients. 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 pertains 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.

ANCA-associated vasculitis 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 non-inferiority but not superiority. Study CL010 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 non-inferiority margin. In addition, glucocorticoids were used by 86 percent of patients in the avacopan arm through week 26, and therefore the non-inferiority assessment is not the intended comparison of avacopan versus prednisone, but instead a comparison of avacopan plus lower dose glucocorticoids versus higher dose glucocorticoids.

Further, based on the study design, which specified the use of glucocorticoids in the

prednisone arm, there's an outstanding question of whether the differences in doses of glucocorticoids used were due to a treatment effect of avacopan as opposed to the design of the study.

We ask you to consider the interpretation of the superiority of avacopan based on sustained remission at week 52, given that 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, thus 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, angioedema, and CPK elevations observed, despite the relatively small safety

database. And finally, we are interested in the committee's discussion on how avacopan, if approved, would be used in the current treatment approach to ANCA-associated vasculitis, based on the data from a phase 3 clinical study, CL010.

Thank you for your attention, and I'll turn the podium back to you, Dr. Becker.

Clarifying Questions for FDA

DR. BECKER: Thank you.

We will now take clarifying questions for the FDA. Please use the raised-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raised-hand icon after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That

is all for my questions" so we can move on to the next panel member. If you happen to still have your hand up from the first session and you do not have a new question, please remember to lower your hand.

Moon will tell me who was first.

Dr. Richards, would you like to begin with your questions for the FDA?

DR. RICHARDS: Hi. Thank you. This is John Richards.

Dr. Glaser, I think it was slide 16. You mentioned that 20 percent of the patients in the avacopan group received prednisone after week 26. Do you know how many patients in the prednisone group got additional prednisone? Because they should have finished all their study prednisone by week 20. Thank you.

DR. GLASER: This is Rachel Glaser. I'll ask Dr. Yura Kim to respond.

DR. Y. KIM: This is Dr. Yura Kim, statistician from FDA. May I have backup slide 86?

This slide shows the proportion of patients

who are using non-study supplied steroids. You can see the higher proportion of patients used non-study supplied steroids in the first month, and there are these three peaks which corresponds to week 1, 2, and 3 visits, where there was premedication for rituximab.

After the first month, the proportion of patients who used steroids on the avacopan arm was similar across days until the end of treatment. It was around 16 to 20 percent. For the prednisone, the proportion of patients who used steroids was greater after the steroid taper, and at the end of the treatment, it was around 23 percent. Thank you.

DR. RICHARDS: Thank you. That's all.

DR. BECKER: Excellent.

We'll move on to Dr. Thadhani.

DR. THADHANI: Thank you. I just want to first congratulate the agency for a very thorough and clear presentation, and if they can just keep this slide up, slide 86, because that pertains to my question.

I am curious, Dr. Glaser, if the period from 27 to 52 weeks gets closer to what otherwise might be considered a true placebo-controlled trial, given the background rates of steroid use are similar -- obviously, you alluded to the first 26 weeks as perhaps confounded by significant steroid use, especially in the rituximab arm, where there's no maintenance therapy -- to perhaps isolate the effect of, obviously, the study agent. Thank you.

DR. GLASER: This is Rachel Glaser. There are limitations of these subgroup analyses because the selection of the background induction therapy -- that is whether the patient would receive cyclophosphamide or rituximab -- was not randomized and was at the discretion of the investigator. So therefore, there may be differences between these groups, so comparisons between the subgroups need to be interpreted with caution.

DR. THADHANI: Great. Thank you.

DR. BECKER: Okay. If that answers your

question, Dr. Thadhani, we'll move on to Dr. Kraft.

DR. KRAFT: Walter Kraft from Thomas Jefferson University. Getting back to the potential drug interaction, as itraconazole and grapefruit, strong inhibitors, and erythromycin, a moderate inhibitor, have not been shown to increase prednisone concentrations in phase 1 trials, and ketoconazole maybe, at high doses, I guess the question is, does the agency have other evidence to support the suggestion of an increased prednisone exposure?

Regardless of the answer to that, would you characterize this as, in general, a mild, moderate, or of high concern for the drug development program? Thank you.

DR. GLASER: This is Rachel Glaser. I'll ask Dr. Lei He to respond.

DR. HE: Hi. This Lei He, the clinical pharmacology reviewer, FDA. As we presented, avacopan capsules were orally administered twice daily with food in phase 2 and phase 3 studies as they proposed. Remember that food may increase

avacopan AUC by 72 percent, and following the proposed dosing regimen, avacopan steady state could be reached by week 13 with four-fold exposure accumulation.

In general, the dosage administration in the DDI study should reflect a clinically relevant condition, while in DDI Study CL008, avacopan was administered under fasted condition for 10 days, and such co-administration increased the systemic exposure of midazolam by up to 81 percent.

So the impact of avacopan on CYP3A4 substrate under fed condition at steady state could be higher, but has not been studied yet.

DR. KRAFT: Okay. Thank you.

DR. HE: Thank you

DR. BECKER: Okay. Next on the list is Dr. May.

DR. MAY: Susanne May, University of Washington. I understand that the agency has a perspective that the non-inferiority margin was not adequately justified. The actually observed lower limit of the confidence interval was minus 6 rather

than minus 20 percent.

I'm wondering whether the agency has any other perspective or comments regarding the observed lower limit of the confidence interval.

DR. GLASER: This is Rachel Glaser. I'll ask Dr. Kim to respond. Thank you.

DR. Y. KIM: This is Dr. Yura Kim. Before we look at the lower confidence interval of minus 6 percent, I think we should actually focus on what is the question of interest. And here, given that both arms were allowed to get the non-study supplied steroid, as Dr. Glaser mentioned in her presentation, the non-inferiority comparison at week 26 is more appropriately described as non-inferiority between avacopan plus lower dose steroids versus higher dose steroids. And the question to the committee is, is it enough to show the non-inferiority between those two arms.

DR. MAY: Thank you. That answers my question.

DR. BECKER: Excellent.

The next question is for Dr. Kim.

DR. S. KIM: Hi. Seoyoung Kim here. My question is two questions. One is, in my review of some of the safety details about patients, I noticed at least one or two patients had a change in their background therapy; so whether there was any further data on the rate or the proportion of backgrounds that are being changed in either treated or placebo group.

The second question is, given the concern that FDA has on the DDI between avacopan and prednisone, I was wondering, due to the DDI, if the potency or actual concentration of prednisone is higher but then it's not shown as a respective GTI score -- so I just want to hear what other things could potentially be done to further distinguish, further explain,

DR. GLASER: This is Rachel Glaser. I think I'm going to start with the second part of your question with respect to the GTI and potential differences in exposure.

The GTI is an instrument that was developed to assess toxicities associated with glucocorticoid

use and consists of multiple weighted domains that include biomarkers and clinician-reported measures. As presented by the applicant and the FDA in Study CL010, the GTI scores did seem to track well with the differences in cumulative glucocorticoid doses used, which was expected given the design.

With regard to the impact of the potential drug-drug interaction, given the uncertainties with the actual exposures of glucocorticoids in the avacopan group, the magnitude of the actual prednisone exposure differences is unknown.

Did that answer the second portion of your question?

DR. S. KIM: I know the GTI was not calculated at the end of the trial. So hypothetically, if the GTI was calculated for the second part of this follow-up time and if there was no difference, would you still be concerned about potential issues with the DDI?

DR. GLASER: I'll ask Dr. He to respond.

DR. CHEN: Hi. This is Jianmeng Chen from FDA. I think the potential impact of the DDI is

that, as Dr. Glaser mentioned, the magnitude of difference between glucocorticoid exposure could be smaller than what the dose reflected; and by how much, we don't have the data to assess that.

DR. S. KIM: Okay. Thank you.

DR. BECKER: Dr. Pisetsky?

DR. GLASER: Then, Dr. Kim, I think --

DR. BECKER: Oh, forgive me. Go on, please.

DR. GLASER: I was just going to address the first part of Dr. Kim's question. I believe it was about the number of patients that may have had a change in background therapy.

Did I understand that correctly?

DR. S. KIM: Correct.

DR. GLASER: I think the FDA will defer to the applicant to respond to that question.

DR. BEKKER: Yes. This is Dr. Pirow Bekker from ChemoCentryx. In terms of immunosuppressant use, cyclophosphamide or rituximab, the patients obviously were stratified to receive either one of those three options. Very few of the patients actually changed their immunosuppressive regimen

during the study.

There were a number of patients who required additional immunosuppressant use, and that percentage was actually higher in the prednisone group compared to the avacopan group, with most commonly rituximab being used in 18 percent of patients in the prednisone group compared to 11 percent of patients in the avacopan group.

DR. S. KIM: Thank you.

DR. BECKER: Thank you.

Okay. Let's move on to Dr. Pisetsky.

(No response.)

DR. BECKER: Dr. Pisetsky, you may still be on mute.

(No response.)

DR. BECKER: Okay. Let's move on to Dr. Singh, and then we'll come back to you, Dr. Pisetsky.

DR. SINGH: Hi. Jasvinder Singh from University of Alabama at Birmingham. Thank you for a great presentation. I have a clarifying question about where there is the maximum separation of the

compound from the comparator group for the 52-week outcome for sustained remission.

It's very helpful to see the differences between rituximab and Cytoxan, and it seems that the next four are just duplicative of two factors, which is basically the MPA versus GPA, and then the most impressive being relapsing disease, where this actually really separates from the newly diagnosed.

Are there any other insights from either the FDA or the sponsor with regards to what is underlying this separation between avacopan and the comparator arm that is seen in the last group?

Could there be some organ system involvement that's more in the relapsing disease? Is it the severity of the disease that may be captured by some measure or not? Are there some other characteristics like age or sex, which I don't recall or maybe I missed in the briefing document, that's stratified now?

It's very helpful to see that there's not much affecting the Cytoxan background and most of the effect is in the rituximab. It's very

impressive to see the difference between the two arms in relapsing disease versus new disease. But I'm just wondering if there are further insights or analyses, either already performed or could be performed, in future studies that can really tell us about what kind of disease do you see a 25 percent separation in response rate at sustained remission, because that's what you see in relapsing disease versus new disease. Thank you.

DR. GLASER: This is Rachel Glaser.

Dr. Singh, you bring up a good point, and I will refer you to figure 12 and 13 in the FDA background document, which includes the forest plots by different demographic subgroups, and it doesn't appear that there were differences based on age, sex, or other demographic variables.

With regard to the differences observed for disease-related variables, we can say that these are subgroup analyses, and some of these subgroups are very small. But I don't think we can draw any more definite conclusions than that.

DR. SINGH: Thank you. I have no further

questions.

DR. BECKER: Okay. It looks like we have Dr. Pisetsky back online.

Would you like to ask your question?

DR. PISETSKY: Yes. David Pisetsky from Duke. I want to get back to the issue of study design, particularly with respect to rituximab. We've heard that in that arm, maintenance was not possible because rituximab had not been approved yet for maintenance. It had only been approved I guess for initiation of therapy. On the other hand, in the other arm, to the best of my knowledge, neither agent had been approved either for remission or induction.

So the fact that rituximab had not been approved, did that preclude a design where another agent was used to see if remission could be maintained?

DR. GLASER: This is Rachel Glaser. I'll defer to the applicant for this response.

DR. BEKKER: This is Dr. Pirow Bekker from ChemoCentryx.. I will ask Dr. Peter Merkel to

comment on what the status of the field was at the time of the design for this study.

Dr. Merkel?

DR. MERKEL: Yes. This is Dr. Peter Merkel from the University of Pennsylvania in Philadelphia.

Dr. Pisetsky, the standard of care that we had tested, for example in the RAVE trial, was a single course of rituximab versus 18 months of cyclophosphamide and azathioprine. So that was out there with data that supported those two strategies, and they were equivalent.

So it was reasonable to continue that strategy into this trial if rituximab was not going to be retreated because, again, it wasn't approved at that time for that approach. I could argue you could have done it I suppose in a trial. It would have been a different study.

I think the trial that was done, that we've reported on, I would point out really test two strategies, and the strategy of protocolizing and attempting to have significantly less

glucocorticoids was successful. And as a clinician, I'd feel comfortable using this agent with that strategy in mind, where I know many patients would be able to use less glucocorticoids.

So I answered a question and a half, and I apologize, but that's the approach of the rituximab.

You're right that you could retreat them with rituximab. That's a different question. I think it's an option, and I think it's good to have a few options for patients. I hope I answered your question. Thank you.

DR. PISETSKY: If I may follow up, how do we view this; as an agent that helps induction or remission? And this is -- [indiscernible].

(Crosstalk.)

DR. MERKEL: Again, this is Dr. Peter Merkel.

DR. PISETSKY: -- the sponsor.

DR. MERKEL: Okay. Should I answer?

DR. GLASER: I'm sorry, Dr. Pisetsky. This is Rachel Glaser. I didn't hear the end of your

question and who your question was directed to.

DR. PISETSKY: How do we view the agent? Is this something for induction or for remission, or does that distinction matter?

DR. GLASER: This is Rachel Glaser. I think that this is one of the questions that we've brought for the committee to discuss today, is where avacopan, if it's approved, would fit in the treatment approach for ANCA-associated vasculitis.

DR. PISETSKY: Okay. I have no further question.

DR. BECKER: Next in line is Dr. Curtis, please.

DR. CURTIS: Hi. This is Sean Curtis, the acting industry representative. I have a question for the FDA, please.

If you could, I just want to make sure I understand what was agreed to with the sponsor upfront about the success criteria for the trial. Was it non-inferiority, or remission, at 26 weeks, and sustained remission? Was that considered the primary success criteria, or was there an

expectation that superiority also be met for the purpose of an approval?

If you could just clarify that, please.

DR. GLASER: This is Rachel Glaser. The expectation was that the study would demonstrate that avacopan was superior to the comparator arm and that non-inferiority would not be sufficient.

DR. CURTIS: Okay. And that was agreed to between the FDA and the sponsor upfront you're saying.

DR. GLASER: This is Rachel Glaser. Yes, that was agreed to during the presubmission discussions about the study design.

DR. CURTIS: Okay. Thank you.

DR. BECKER: Okay. Thank you.

Next in line is Dr. Dellaripa.

DR. DELLARIPA: Yes. This might have been addressed already and, again, I apologize if this is repetitive; just a little bit more granularity about the prednisone dosing in the two groups, so the avacopan group versus the prednisone group. The reason I'm asking is because many of us have

used in clinical practice low doses of steroids to keep people in remission, or theoretically to keep them in remission, whether it's 2.5 or 5 milligrams.

Can we get a sense for the number of patients in the avacopan group who were on some degree of steroids? What kind of dose were we really talking about on average? Was there a subgroup that was on 2.5 or more?

If that's already been clarified, I apologize for missing that granularity, but that's my question.

DR. GLASER: This is Rachel Glaser. I'll ask Dr. Kim to respond to this question.

DR. Y. KIM: This is Yura Kim. May I have backup slide 78 first? This shows the non-study supplied steroid use adjusted for a time in study up to week 52. Here I calculated the total steroid use across the patients; and then also calculated the time the patients were on study; and then divided that number to get a sense of how much was used per day.

So from week zero to 26, on the avacopan arm, 6.1 milligrams per patient-day was used in comparison to 4.5 milligrams per patient-day in the prednisone group. And for week 27 to 52, 1.6 milligrams per patient-day was used in avacopan versus 2.7 milligrams per patient-day in the prednisone group.

Then regarding the distribution of use of steroids, can I have slide 81? This is the distribution of the use of steroids. You can see that this is for month 1, so there is slightly more used in the RTX arm because of premedication.

Can I have the next slide, please? This is week 5 to week 26, and then the next slide shows week 27 to 52, and these were the cumulative glucocorticoid use. And beginning on the next slide, we can also see the non-study supplied steroid use. This is from day 1 to week 4; then on the next slide we have week 5 to week 26.

DR. DELLARIPA: So on that slide there, are you showing the non-study supplied glucocorticoid use -- I mean, these bars are so small I can't tell

the difference. Are the daily milligrams per day similar comparing the prednisone group to the avacopan group? That's the question I'm asking.

DR. Y. KIM: This is to show how much of the patients were using -- this is to show the distribution, and to see how much is used, I think, slide 78 is better.

DR. DELLARIPA: Okay.

DR. Y. KIM: Thank you.

DR. DELLARIPA: Thank you.

DR. BECKER: Okay. Next is up, Dr. Lewis.

DR. LEWIS: Julie Lewis, nephrologist, Vanderbilt. My question is to the FDA.

In reviewing the briefing documents and your presentation, approximately 134 patients were exposed for greater than 6 months, and I wonder if the FDA can comment on two things; if they had communicated this is not a drug that's been approved; this is our entire safety database about this compound, so it's not actually comparable to rituximab studies.

Did you communicate to the sponsor your

feelings about the adequacy of exposure to be able to adequately assess the safety of this drug, and also on your feeling about, with even such a small safety set, breaking Hy's law and the liver signals that we're seeing?

DR. GLASER: This is Rachel Glaser. I'll start with the first part of your question, which was about the size of the safety database and how that was discussed.

For every application, the FDA needs to weigh the potential benefit with the observed risk and potential risk of a product. So the size of the needed safety database is dependent on the feasibility of the size of the study. And for rare diseases, there may be smaller safety databases that need to be evaluated in terms of the efficacy that's demonstrated. So overall, it comes down to the benefit-risk.

There were discussions with the applicant that the safety database was small for the assessment of rare and latent toxicities, but again, that needs to be interpreted in light of the

efficacy.

Then if you could repeat the second part of your question about Hy's law?

DR. LEWIS: So I wondered what the FDA's view was, potentially, detecting a signal like this, even though the exposure is a very small group. Does that heighten your concern?

DR. GLASER: This is Rachel Glaser. I will ask Dr. Hayashi of the Division of Hepatology and Nutrition to comment.

DR. HAYASHI: Yes. Hi. This is Dr. Hayashi. I'm the team lead for the DILI team and DHN, the FDA.

Your point's well taken. Yes, it did, and it does weigh on my mind. You have an exposure here that's about 160 some odd patients. That is small. For DILI risk of significance, like a Hy's law case, it's really one or two in a large trial of, like, a thousand, is enough for us to be concerned that that drug will have problems postmarketing.

So to answer your question, yes, it is a

small set. And for the realm of DILI, it is a concern. So that's what I can say about -- and I don't know if I answered your specific question.

Did I?

DR. LEWIS: You did, and thank you, and I have no more questions.

DR. BECKER: Okay. I see a hand raised by Dr. Pirow Bekker. Is that accurate?

DR. BEKKER: Yes. I'm sorry. I was on mute. With regard to the liver cases, I think it's really important to point out that none of the cases actually satisfied Hy's law, as Hy's law is stated.

In terms of laboratory criteria, certainly there was one case that had both ALT/AST and bilirubin elevations, and I think the FDA agreed with us that that case actually was not Hy's law. There were too many confounding factors.

This is a really complicated patient population with several other drugs and several other comorbidities. We have not seen any evidence of liver enzyme elevations in other settings where

we studied avacopan, both in hidradenitis suppurativa and also in C3 glomerulonephritis.

So we just wanted to point out two things. One is certainly the safety database and exposure with avacopan now is much larger. At this point in time, we haven't really seen any of these cases in other settings. And secondly, I think it's important to point out that this is a really, really sick patient population. Thank you.

DR. BECKER: Okay. Thank you.

I'd like to, I think, take the last question in our last couple of minutes before we stop for lunch. I was hoping the FDA would be willing to give a little bit of detail on how they calculated the BVAS from the site investigators in light of the fact that there were differences between the adjudication committee and the site investigators' scores.

Did you happen to count those patients that were marked as persistently active? And if you can provide a little bit of detail on that, that'd be great. Thank you.

DR. GLASER: Dr. Becker, I believe that we'd like to just go back and comment further about the Hy's law, and then perhaps I could address the question about the BVAS analysis after that.

DR. BECKER: Absolutely.

DR. GLASER: I'll ask Dr. Hayashi to respond.

DR. HAYASHI: Sure. Yes. First of all, I want to go ahead and agree with sponsor. These are difficult cases, but it's not quite correct that there were no cases that met Hy's law criteria. There was one, but it's the matter of which drug is it.

I would ask, if you want to bring up a slide, we can take a look at that real quick. It's slide 101. This is this slide in question. It does meet Hy's law. There's not a lot of doubt about that. I didn't find any other etiology for this other than a drug, because they did a fairly good workup here.

The problem is, is there were two drugs on board, and simvastatin does compete reasonably

well, but I didn't dismiss avacopan completely. I left it as possible, because of the time course and because, as you say, this whole sample size is small and I'm erring on the side of caution here.

There was also a little something that was a little inconsistent with simvastatin, which was this patient had a bout of neutropenia that was enough to warrant her a bone marrow biopsy. That's unusual for simvastatin. Otherwise, the case was pretty good for simvastatin.

So this is the problem with these patients. But I just did want to point out that there was a Hy's law case. It's just a matter of which drug. Thank you for the comment there.

DR. BECKER: Dr. Pirow Bekker, I see your hand raised.

DR. GLASER: This is --

DR. BECKER: Apologies.

DR. GLASER: Hi. This is Rachel Glaser. I just also wanted to note that, again, as we've discussed avacopan is a CYP3A4 inhibitor, that could increase the concentration of CYP3A4

substrates. And in this case, simvastatin is a CYP3A4 substrate, so a potential role for avacopan in this patient's course can't be excluded.

DR. BECKER: Okay.

DR. GLASER: Dr. Becker, I don't know if you want go on to the question about BVAS or whether there's more to discuss about the Hy's law.

DR. BECKER: I see Dr. Pirow Bekker's hand up. Is this regarding the Hy's law discussion? Do you have anything else you'd like to add?

DR. BEKKER: Just two points quickly for the committee. There were some other drugs here, too, involved. Repaglinide, for example, the dose was increased before the start of the elevation in the transaminases, and only upon discontinuation of repaglinide did the enzymes start to decrease.

The other point is that when avacopan was stopped, there was continued increase in elevations in transaminases and bilirubin, and only upon stopping simvastatin and stopping repaglinide did the levels go back to normal.

I don't want to belabor this further, but

this is an extremely complex case, and I think we do have some disagreements, obviously, on this. Thank you.

DR. BECKER: Thank you.

Dr. Glaser, if it's a long answer to my question about the BVAS, we can put it off. But if you can provide any clarity before lunch, happy to hear it.

DR. GLASER: Can you repeat your question one more time?

DR. BECKER: Sure. I was --

DR. GLASER: Is it about the investigator discrepancies?

DR. BECKER: Indeed. Indeed. I'm curious to know were you counting the site investigators' marking of persistent disease activity as activity, or how did we have such different opinions about the adjudication committee versus the site investigator disease activity on the BVAS?

DR. GLASER: I'll ask Dr. Yura Kim to respond.

DR. Y. KIM: This is Yura Kim. We don't

have the BVAS form the investigators used. We've used scores reported for each item, and there were no details on whether it was scored as persistent, new, or worse.

This presentation shows the discrepancy between two arms, and the discrepancy was most frequently related to the treatment of persistent vasculitis, which was not captured in the version administered in the study.

Can I have slide 70 also? This was actually a specification in the documents. In the protocol, it was specified to use BVAS version 3, and this paper was cited. The next three points are actually cited sentences from this paper.

For BVAS version 3, this paper says, "The persistent boxes for each item were replaced by a single persistent box for the whole form." But in the adjudication form that was provided in the adjudication charter, the single persistent block was omitted.

DR. BECKER: Okay. Well, thank you very much for that clarification.

We will now break for lunch. We'll convene --

DR. CURTIS: Dr. --

DR. BECKER: Excuse me?

DR. CURTIS: I'm sorry, Dr. Becker. This is Sean Curtis. Can I just ask a very quick follow-up question on this, very briefly?

DR. BECKER: And you're going to be between us and lunch. Absolutely. Please.

DR. CURTIS: So I'll be very quick.

This is Sean Curtis, the industry rep. I just wanted to clarify, again, from the FDA, for the purposes of what the sponsor and the FDA agreed upon, vis a vis superiority criteria that was required.

Was it based off of the adjudicated result or investigator assessment?

DR. GLASER: This is Rachel Glaser. The prespecified analysis was on the adjudicated results of the BVAS.

DR. CURTIS: Okay. Great. Thank you.

DR. BECKER: Great point, Dr. Curtis. Thank

you for the clarification.

Okay. Now we will really break for lunch. We will reconvene in 45 minutes at 1:15 -- actually closer to 40 minutes -- Eastern time.

Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin at around 1 o'clock to ensure you're connected before we reconvene at 1:15. Thank you.

(Whereupon, at 12:35 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:17 p.m.)

Open Public Hearing

DR. BECKER: Good afternoon. We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its products, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA

encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any

organization you are representing for the record.

MS. OLEVSKY: My name is Kathy Olevsky. I have no financial relationship or interest. I'm 63 years old and was diagnosed with ANCA-associated vasculitis when I was 50 years old. At the time, my daughter was 16, my son was 24, and I'd been married for 30 years.

Prior to my diagnosis of ANCA-associated vasculitis, I was the CEO of a family business. My husband and I had a chain of five martial arts schools. I was also in the best shape of my life. I was an 8th degree black belt in karate with 30 years of martial arts background. I taught martial arts every day and normally worked 10-hour days, 5 to 6 days a week. I swam a mile a day in the mornings before going to work, and I walked 10 to 20 miles per week.

I was well respected for my organizational skills, my ability to multitask, and my mentorship of all the instructors and managers who worked in the five business locations we owned.

I was first diagnosed with ANCA-associated

vasculitis MPA in 2009. I was being treated by a rheumatologist for pain with unknown etiology, and I had been to 13 different specialists over a one-and-a-half-year period because my primary care doctor knew me really well, and knew that if I said something was wrong, it was a big deal.

Lab work indicated that I did not have rheumatoid arthritis, but I had pain all over my body that was very intermittent. Sometimes it was in my joints, sometimes it was in my upper back, and sometimes in another joint. When a joint hurt, it often felt like a broken bone. I was not able to walk on an ankle for a day, but the next day would be fine. I could not use my wrist for a day, but the next day it would be fine.

My rheumatologist decide to put me on methotrexate to see if it would alleviate my pain. I was sent to get lab work prior to starting this medication. My creatinine came back extremely high, and I got a call to say that they thought I might be in kidney failure. So a kidney biopsy confirmed ANCA MPA.

The next day, I was admitted to the University of North Carolina Hospital, where I remained for 21 days. My treatment began with doses of 500 milligrams of Solu-Medrol for 3 days in a row while I was taking Cytoxan and having plasmapheresis.

The immediate IV dose of Solu-Medrol puffed up my face, gave me acne all over my body. I was hot, then I was cold. I went from being a strong confident leader into someone who cried most of the day, couldn't sleep, and was extremely agitated.

I spent the next six years going through the roller coaster of flares and remissions. Each time I would get a mega dose of steroids with either Cytoxan, CellCept, Imuran, or Rituxan. After a few months, each time I would begin to taper from 60 milligrams a day down to 5 milligrams. When I got that low, my whole body felt like I had the flu that lasted for weeks. I remember telling my doctor that I thought I was going through a drug withdrawal like an addict.

It often took more than three months to get

from 5 milligrams to zero. This process was repeated for six years until I was considered in long-term remission, off treatment in 2015. And during the six-year journey, I developed a fat pad on the back of my neck that resembled a hunchback. I also have large fat pads just below my knees. I was told these were most likely permanent side effects of the steroids.

In my personal life during that six-year treatment journey, my son at age 24 had to take over my role in our business. My daughter had to get herself into college. She stood behind me as I filled out our financial applications, and she watched me cry because I just couldn't do it. My husband worked from 7 a.m. to 9 p.m. to try to keep our businesses intact. We lost two of our five business locations during that period.

Once in remission, I tried really hard to get back to my old self. I am just now at age 63 finally coming to terms that I will never quite be the same person. I'm ready to go back on Rituxan if my vasculitis flares. I'm not ready to take

steroids. I'll do just about anything to avoid the swings of depression and anxiety that come along with them. Thank you for letting me share my story today.

DR. BECKER: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. CALABRESE: Hi. This is Dr. Len Calabrese, vice chair of the Center for Vasculitis Care and Research at the Cleveland Clinic. I've nothing to disclose. I'd like to thank the committee for the opportunity to talk today. And looking over the program, I'm going to go out on a limb and say that I am the most senior person who still does vasculitis care and research who is speaking today.

I say this because I can go back to the early days of my training when it was only a matter of a year or so when Drs. Fauci and Wolff first reported the use of cyclophosphamide in ANCA

diseases that we now know, and this was important.

It was a breakthrough, and a decade later, Dr. Fauci published his work in The ANNALS, outlining the success of this therapy. And by 1992, I was joined by Gary Hoffman, an icon of vasculitis work, and he at that time published the 24-year experience of the NIH using cyclophosphamide therapy. It was impressive, it was effective, but it was toxic, and there were relapses associated with this treatment.

Over the next 20 years, we made improvements by fits and starts: step-down therapy, a major advance in the treatment of ANCA-associated vasculitis; methotrexate for mild disease; prophylaxis for infections; then a decade or so ago, the major advance of rituximab after many starts and failures of other biologics. And that has been great for our patients and their quality of life; yet the name that can't be named, the elephant in the room, has been the use of glucocorticoids. And I heard this last patient talk, and it moved my heart to hear it.

When we talk about all the success in all of our other therapies, what we have never been able to talk about, nor dream about, is to treat this disease with a reduced, or minimal, or even the unthinkable, a non-glucocorticoid based regimen. It is the greatest single need, in my estimation, of the treatment of this disease. It is something we have come to accept.

I will point out -- and the rheumatologists on this committee know -- that over the past 5 to 10 years, glucocorticoids have fallen out of favor in virtually all of our diseases. We now recognize, based upon robust study, that even low-dose prednisone, less than 5 milligrams a day, is attendant with comorbidities.

The most recent ACR guidelines for RA expunged them from use, and people like Michelle Petri has coined the phrase, P is P; "Prednisone is poison in lupus," yet in vasculitis they have been life-saving.

If this drug is approved, this represents an extraordinary opportunity to treat people with

dramatically reduced doses of glucocorticoids and even beyond. And if I had this disease, after 40 years of experience with this, I would insist upon taking this drug.

That is my perspective on this. This is a sea change. This is a tectonic moment in vasculitis care, more than rituximab. Thank you for your time.

DR. BECKER: Thank you for your comments.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. STADLER: Hello. My name is John Stadler. I don't represent any organization, and I have no financial disclosure.

I was diagnosed with granulomatosis polyangiitis vasculitis in February 2017. My illness progressed rapidly from diagnosis, and within six months, I was very fragile and not responding to high doses of prednisone and rituximab, and was able to achieve chemical

remission with the introduction of cyclophosphamide.

Prior to the onset of granulomatosis polyangiitis vasculitis, GPA, I was actively working full-time continually and very active in my daily routines. The effects of GPA and the treatment limited my lifestyle. I'm extremely fortunate to be married and have the support of my wife for the first two years of my diagnosis.

My GPA progressed quickly from onset. I had acute joint pain, pneumonia in both lungs, and over six months, necrosis of both of my upper femurs, which was determined to be from prednisone. Further complications from prednisone included weight gain of 30 pounds; irritability; disruption in sleep; a colorectal fissure; and infection from the long-term use of prednisone to cataracts in both eyes.

Prednisone was extremely hard to eliminate. I was able after nine months to reduce prednisone to 10 milligrams with recurring of symptoms. I had limited success in tapering prednisone. The taper

to zero was extremely difficult and took another nine months.

I retired to focus on my health while being administered prednisone and multiple infusions of rituximab and cyclophosphamide. The consequences of early retirement were the loss of income and social interaction with limited exposure to people because of risk of infections.

I'm enthused that there's an emergent drug, avacopan, that can provide patients like me with therapeutic results without the complications and risks of prednisone. As you consider your decision today, I ask that you remember my story, that these complications and risks are real in the lives of many patients out there. They're challenging, they're expensive, and they're lasting. Thank you very much.

DR. BECKER: Thank you for your comments.

Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. SHAW: Hello. My name is Dianne Shaw. I live in Chapel Hill, North Carolina, where I worked at the University of North Carolina Cancer Center for 30 years as a director of communications, before retiring in 2013. I was diagnosed with vasculitis in 1995. I have no financial disclosures to make.

Vasculitis is a life-changing diagnosis. My life went from somewhat predictable to completely unpredictable because I never know when I might have a flare. Despite the very best medical care, over these 26 years I've had 39 surgeries on my ears, eyes, nose, nasopharynx, and airway. My airway shrinks down, once to the size of a drinking straw.

I am a positive person, so when people ask me how vasculitis has affected me, I don't often mention my loss of sense of smell, hearing, and singing voice, my twice reconstructed nose, and my permanent facial nerve paralysis. That's just some of what this disease has physically taken from me. But I know I'm lucky. It could be far worse.

You can see in the photo that I'm holding a chain of hospital bracelets that represents approximately three-quarters of my surgeries, hospitalizations, and infusions from 1996 to 2016. Flares that erupt with little notice disrupt your work, family, every aspect of your life. You can't plan. I had to give up being a hospice volunteer because I never knew if a flare would make me unable to work with the family.

Over my 26 years, I've taken every drug available for vasculitis, some on a compassionate-use basis, but I'm here to talk about one that I've taken throughout my illness; steroids. Steroid is a drug that patients like me love and hate. We love it because it works quickly. We hate it because it disrupts our already disrupted life. And because we have to take it so often, the life-altering side effects take their toll. Unfortunately, for now, there is no other drug option.

Being diagnosed with a rare disease is a frightening, isolating experience. You feel out of

control, and then must take a drug that further robs you of control. And prednisone is a drug that you have to take repeatedly. Every time steroids are prescribed, I wonder how much closer I am to getting glaucoma, high blood pressure, kidney issues, or other long-term side effects.

The daily effects of steroids are taxing. I must write down everything because otherwise I'm likely to forget. Being even more immunosuppressed means that I have to be even more cautious about being around people, so much so that one year I had to miss Christmas with my family because someone had a cold.

Steroids cause emotional volatility. I yelled at my center director during a senior staff meeting, realized what I had done, and fled the room in tears. Thankfully, I did not lose my job. And because I couldn't sleep, one year I finished my holiday baking in three nights, a task that usually took at least a week.

A treatment shouldn't be worse than the disease or cause patients to suffer such serious

side effects. The drug you're considering today is an answer. It represents the part of a drug we love. It works quickly and addresses the part we hate, the life-altering and life-disrupting side effects.

If approved, avacopan will be a game changer for patients. It will have an enormous positive impact on patients' lives and quality of life, and will offer an additional therapy option for patients and their doctors to consider. I urge you to approve it. Thank you for your time.

DR. BECKER: Thank you for your comments.

(Reverberation.)

DR. BECKER: I want to make sure everyone is muted if possible. Thank you.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. GEETHA: My name is Duvuru Geetha. I'm a nephrologist at the Johns Hopkins Vasculitis Center. I was also the site PI for the ADVOCATE

trial, and a member of the BVAS adjudication committee for the trial. I have received consulting fees from ChemoCentryx.

First, I would like to thank the committee for the opportunity to talk. I began my role as a nephrologist at the Vasculitis Center back in 2005 when the RAVE trial actually started.

Patients with renal involvement represent a unique cohort in ANCA vasculitis for a number of reasons. Number one, kidney involvement is common, affecting up to 90 percent of patients with vasculitis. Renal involvement has prognostic significance and is associated with lower patient survival. Fast-acting therapies to quell the inflammation and therapies to prevent the relapse are what is essentially needed to prevent progression to end-stage kidney disease.

Over the last two decades, since I've joined the Vasculitis Center, several landmark trials have been conducted in ANCA vasculitis that have revolutionized the treatment. The current standard-of-care treatment still involves giving

high doses of prednisone, typically for a period of several months, alongside cyclophosphamide or rituximab to induce remission.

In patients with renal involvement, high doses of glucocorticoids are universally given, beginning with a thousand milligrams of IV methylprednisolone daily for three days.

Although the current standard of care is effective in reducing inflammation, I do see a significant proportion of patients still progressing to end-stage kidney disease, and there is a substantial proportion of patients that experience disease relapse. Additionally, both the short- and long-term adverse events of glucocorticoids, which include infection risk; diabetes; hypertension; weight gain; and decreased health-related quality of life are really relevant and of significance in patients with kidney disease, as they're associated with higher morbidity and mortality.

Therefore, one of the biggest unmet needs is not to have a reduced-dose prednisone regimen, but

actually a glucocorticoid avoidance regimen. The ADVOCATE trial results are terrific, and the benefits of avacopan in patients with renal involvement are remarkable, and it was well tolerated. Avacopan is fast-acting and effective, thereby avoiding high doses of glucocorticoids. There was more sustained remission with avacopan, which is also very impressive.

The biggest impact of avacopan, I think, is going to be marked reduction in the use of glucocorticoids, therefore avacopan is a major advance and a game changer in ANCA vasculitis. It has a different mechanism of action. It is complementary to other approaches that we use in treating ANCA vasculitis patients. I believe this is an extraordinary moment for both patients with vasculitis and physicians caring for them. Thank you.

DR. BECKER: Thank you for your comments.

Speaker number 6, your audio is connected now. Will speaker number 6 begin and introduce yourself? Please state your name and any

organization you are representing for the record.

MR. WADLER: Hi. My name is Jason Wadler. Thank you for giving me the opportunity to share my story and perspective. I do not have any financial disclosures. I live in Glencoe, Illinois, a suburb outside of Chicago. I'm an entrepreneur and a business advisor and investor, married with a teenage daughter and a teenage son.

I was diagnosed with a form of vasculitis called GPA, Wegener's granulomatosis, 11 years ago. Before my diagnosis, I was very active with my business, my family, and I love to work out. GPA affected my lungs to the point where I had a very high level of difficulty breathing, my skin and sinuses to the point where it's difficult to work, be involved with my family, and even walk, let alone go to the gym.

When I looked up GPA online, I learned there was an 80 percent mortality rate within 5 months, so I know I needed to move fast. I went to Cleveland Clinic, where they confirmed GPA. And once I was diagnosed, I was placed on extremely

high doses of steroids. My symptoms began to fade, but other issues began. I gained 40 pounds in a few months, had difficulty sleeping and concentrating, and also had very bad mood swings. Needless to say, I was not an easy person to live with.

Once my GPA stopped flaring and I could get off the steroids and other drugs that you heard mentioned before, it took a while for my life to return to a new normal. It was a struggle to lose weight, get back into a routine, and deal with lingering physical issues that limited by movement.

Though it has taken a few years, I'm happy to share I've been able to return to the physical, mental, and emotional state I was in pre-diagnosis, but I'm not the same as I was before. And I know this disease can come back at any moment, which is why this new treatment is so important.

GPA is a lifelong, life-threatening illness. It can dramatically change, if not end, your life, and the current treatments can sometimes be as bad as the disease. The side effects of long-term

damage of prednisone on your life, on my life, physically, emotionally, financially affect not only the quality of life of the person that has GPA, but also their family.

We need an option like the one you're reviewing to give us another choice. I ask you to remember my story as you make your decision today. It would be life-changing if there was another option, with medication like the one you're reviewing, that we could take to treat our illness that would not cause additional pain and more health complications, as you've heard from me and others. This new treatment can be a true game changer to help get life back to normal. Thank you again for your time and consideration.

DR. BECKER: Thank you for your comments.

Speaker number 7, your audio is connected now. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. ANDERSON: Good afternoon. My name is Trena Anderson, and I have no financial

disclosures. In 2014, things were going very well, and I live in the Phoenix, Arizona area. I was a very happy 41-year-old single mother. My daughter was 11 and my son was 7. I worked full-time as a paralegal at an estate planning law firm, and I really enjoyed the work and the fast-paced schedule in our office. Outside of my work, my children and I were able to have a very active social life with our family and friends.

In 2015, my health rapidly declined. After three months of struggling, I was hospitalized for a couple weeks, and then diagnosed with a form of vasculitis called granulomatosis with polyangiitis. I started heavy steroids and chemotherapy immediately in the hospital, and my life drastically changed at that moment.

I was not able to continue the work that I did, and I had to resign immediately. At the time, I was living in a spacious two-story home, and my parents, who were retired, living in a different city, temporarily needed to move in with me and help for several months.

My parents also helped move me to a one-story home that would be more manageable for me physically. I ended up back in ICU a couple times with pneumonia complications and being on oxygen at home for quite a while.

The combination of chemotherapy and steroids is a very tough treatment to go through, not only for myself, but also for my family. I ended up not recognizing the person that I had changed into, and my biggest struggle was feeling like I couldn't be the mother that I previously was to my children. With taking high doses of steroids, I was experiencing heavy mood swings, and I started treatment for depression, which I had never experienced before. I also had high blood pressure for the first time and had to start on even more medication to treat that.

I had an extremely difficult time getting quality sleep. I gained a lot of weight. I had the moon face and a hump on the back of my neck. I had never been able to get completely off steroids, and I'm going on six years.

Being on steroids long term has been very difficult, and I've had years of pain management, physical struggles, and now osteoporosis. I went from regular cortisone injections; Orthovisc injections; macular nerve ablation; using a walker regularly; ending up in a wheelchair full-time for six months; and I ended up having a total knee replacement in both of my knees at the age of 45, all while caring for my children.

It's hard enough living with a lifelong illness, but having to deal with more health complications because of the medicine we need to take for our primary illness is a real struggle. Dealing with all the side effects of years of steroid use and long-term damage has not only affected the quality of my life for myself, but also affected the quality of life for my children and the struggles we have all had to learn with my limitations.

I ask that you remember my story as you make your decision today. It would be a game changer if there was another option that wouldn't cause some

of the complications that steroids cause. And I do understand it's a necessary evil, the medication we need to take to treat our illness. Thank you again for your time. Thank you so much.

DR. BECKER: Thank you so much for your comments.

Speaker number 8, your audio is connected now. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. KULLMAN: Good afternoon. My name is Joyce Kullman. I'm the executive director of The Vasculitis Foundation, the international non-profit organization dedicated to advocating for people with all forms of vasculitis.

Today I am speaking on behalf of the VF board of directors and our patients about the new drug application for avacopan oral capsules, submitted by ChemoCentryx for the treatment of ANCA-associated vasculitis. The VF has received grants from ChemoCentryx and other industry partners.

The VF Works to advance critical research aimed at broadening understanding of vasculitis and optimizing clinical care of patients through earlier diagnosis, better treatments, and perhaps one-day cures. I come to this meeting both as a long-time VF staff person and as a family member. My father was diagnosed with GPA in 1994 and lived for 23 years with the disease and side effects from daily steroid use.

In my roles with the VF over the past 26 years, I have communicated with thousands of patients about their vasculitis and concerns over steroids. Our patients want a cure for vasculitis, and they want and need more FDA-approved medications to choose from when deciding a treatment plan.

AAV is classified as a rare chronic disease with prevalence estimated at 3 cases per 100,000 in the United States. Because AAV mimics more common diseases, our patients are often misdiagnosed and undergo ineffective treatments prior to receiving a correct diagnosis.

Delays in diagnosis negatively impact clinical outcomes, including increased morbidity and mortality. Even after AAV is diagnosed, treatment options are limited, and effectiveness varies from patient to patient.

Let me repeat this because this is very important. Even after AAV is diagnosed, treatment options are limited. More than 75 percent of our patients have renal involvement. Kidney disease is an important predictor of mortality, and current AAV therapies have limited efficacy on renal function.

Currently AAV treatment consists of courses of nonspecific immunosuppressants such as cyclophosphamide or rituximab, combined with daily steroids for prolonged periods of time; in many cases, years or decades, which can carry significant clinical risks, including death from infection. Use of steroids is associated with serious side effects, including diabetes, weight gain, and other problems such as negative patient-reported outcomes and reduced quality of

life.

AAV symptoms and current treatment options can be emotionally and physically devastating due to persistent pain, fatigue, and loss of physical ability. Patients may not be able to work or participate in social events, and they often talk about the isolation they experience and their frustration with the lack of effective treatments. In our discussion groups, patients share their struggles when trying to reduce or eliminate prednisone because of their concerns over experiencing ongoing damage from the disease versus potential permanent damage from the steroids.

We urge the FDA to consider the impact AAV has on our patients. We ask that you consider the significant clinical risks associated with daily steroid use for prolonged periods of time. As the speakers before me have stated, if avacopan is approved for the treatment of patients with AAV, it will be a game changer for our patients and will represent the potential for symptom relief and additional positive health outcomes for our

patients. We thank you for the consideration of our comments.

DR. BECKER: Thanks very much for your comments.

Speaker number 9, your audio is connected now. Please, speaker number 9, will you begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. DOWNES: Hello. My name is Sean Downes. I represent no organization and I have no financial disclosures. I am 61 years of age. I'm an attorney with a solo law practice. I live in Bayside Queens, New York with my wife, Marianne [ph], of 33 years. I have two grown daughters, Molly, 29, and Katie 26.

In 2016, I was getting sicker and sicker without knowing what was wrong with me. Visits to numerous specialists didn't give me the answers. Finally on January 4, 2017, my internist did another blood and urine test, and phoned me the next day while I was in court, and instructed me to go to the emergency room, as my kidneys were

shutting down.

I was hospitalized immediately at NYU, and I can say that the stay was frightening. It required intensive investigation. While searching for the cause of my conditions, I underwent a multitude of tests, including ultrasound; sonograms; CAT scans; MRIs; x-rays; kidney biopsies; bladder cystoscopes; and constant blood and urine testing.

All of these tests led to being diagnosed with an autoimmune disease, vasculitis, also known as Wegener's granulomatosis polyangiitis, with renal and pulmonary compromise. I received oxygen and plasma, and was treated with high doses of IV prednisone, up to a thousand milligrams at a time. I had a port inserted in my chest cavity and receive plasmapheresis treatments on an emergency basis to assist my kidneys in functioning, as there was concern of complete renal failure and a need for potential permanent dialysis. My arms were black and blue from blood work, and I received painful abdominal injections.

Over the next seven months, I experienced

extreme abnormal fatigue, coldness, reddish bumps on my skin, mouth ulcers, runny nose with bloody discharge, and coughing up blood.

In November of 2017, I participated in a trial at the Hospital for Special Surgery with the drug being reviewed today, avacopan. This was a time-consuming but worthwhile process. During this time period, I had less swelling in my feet, and my entire body experienced less agitation. I was able to sleep somewhat better and did not experience the same degree of difficulty with word finding and overall thought processing. In general, I was less tired and overall felt better.

Although I am thankful for the excellent medical treatment I received and continue to receive, my life has been adversely affected by vasculitis. I am advised it will remain so.

Vasculitis has forced me to slow down and become old before my time, both professional and in my personal life. I was extremely active before my diagnosis. I coached the girls CYO swim team for over 15 years and was involved in numerous

professional and political organizations, and spoke regularly at events, traveled, and socialized frequently.

Most of these activities have ceased or become extremely limited. The high doses of prednisone, Cytoxan, methotrexate, and others have caused me to become confused and forgetful. I sometimes have a hard time finding words and expressing thoughts. My hearing has suffered, and the prolonged prednisone, especially the high doses, make me agitated and irascible and cause problems with my sleep. My body has swollen up and my weight fluctuates.

My law practice has suffered, and I can no longer plan with certainty on future court appearances, trials, depositions, et cetera. My wife had to take early retirement from the New York City Department of Health to assist me.

As you consider your decision today, I ask that you remember my story. It is my own experience, but it tells you the true impact of this condition and the impact of current

treatments. Alternative therapies like this one are needed. Thank you.

DR. BECKER: Thank you very much for your comments.

Speaker number 10, your audio is connected now. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. GERMAIN: Yes. Thank you. This is Michael Germain. I'm a nephrologist from Springfield, Massachusetts and clinical practice in treating patients with glomerular disease and kidney transplant, and I've been in practice treating patients for 43 years. I do have a conflict of interest. I am on the advisory board for ChemoCentryx.

I just want to endorse everything I heard from the prior speakers, both the physicians and the patients, but especially the patients, because this rings true to everything I've seen with my patients that I've treated over many years, and I can tell you that it is a devastating disease.

When I started treating people over 40 years ago, there was no treatment, and patients with this disease had a very high mortality. High-dose prednisone was used, but you heard the complications of that and the fact that they would get frequent relapses if you tried to taper them off it. Cytoxan had many toxic effects, including in young women who could be left infertile after the treatment. And more recently with rituximab, treatments have continued to improve.

I would emphasize two things here, precision medicine and individualization. This is the era we're moving into. Every patient is different. Every patient has a different pathophysiology and predisposition for how their immune system is activated, so one way of treating the immune disease cannot be the same for every patient.

Prednisone is a very nonspecific anti-inflammatory. Cytoxan is a pan-cell cycle inhibitor. Rituximab is a B-cell acting drug. Now we're moving into a drug which is more precise in the disease state with inhibiting complement

activation that we're seeing a lot of other glomerular diseases.

So for a nephrologist, this is fantastic. We're seeing our ability to individualize for the patients. What one person responds to, the other person might not, or have side effects from, so we can individualize treatment. And precision medicine, we're narrowing down on how to treat the exact pathophysiology in a very narrow way, avoiding unintended consequences outside the narrow path that we want to treat.

Finally I'll say, since I've been treating patients from age 6 to 90 with this condition since the 1970s, that I have seen what this does to a patient's life, throughout their life: going on to dialysis; getting a kidney transplant; and in other glomerular diseases seeing recurrence of those. immune diseases in the transplant. I see their children who then have the genetic predisposition for these diseases.

So this is a major advance in our treatment, and it's patient-centered and precision, so I

support approving this drug.

DR. BECKER: Thank you so much for your comments.

Speaker number 11, your audio is connected now. Will speak a number 11 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. CORTAZAR: Good afternoon. This is Dr. Frank Cortazar from the New York Nephrology Vasculitis Center. I'd like to commence by disclosing that I was an investigator for the ADVOCATE trial and previously participated in a scientific advisory board for ChemoCentryx.

I'm a clinical nephrologist with an interest in vasculitis and glomerular disease. I was previously on staff at the vasculitis center at Mass General Hospital and now direct a vasculitis center in Albany, New York. In these settings, I've had the privilege of overseeing the care of hundreds of patients with ANCA-associated vasculitis.

When considering the current induction of

remission regimens for newly diagnosed or relapsing patients, two major areas for improvement immediately come to mind. The first is the need to reduce treatment-related side effects, particularly those driven by steroids. The second is the need for more rapid-acting therapies to mitigate the development of irreversible organ damage. This is of particular importance in patients with renal involvement.

The available data suggest that avacopan has the potential to address both of these unmet needs. Overwhelmingly, the most common complaint received from patients receiving induction therapy is side effects from steroids. I've seen the full spectrum of known side effects in my practice, including diabetes, significant weight gain, mood disturbances, osteonecrosis of the hip, and devastating infections, among others.

More difficult to capture, patients on steroids often report a general feeling of unwellness and difficulty functioning in their daily lives. After interacting with these patients

intermittently on a daily basis, I'm convinced that steroid minimization is key to improving both patient outcomes, as well as the patient experience during treatment.

Even if there is no improvement in efficacy as it pertains to achieving remission and is only equivalent, a drug that offers the ability to replace or significantly reduce steroid exposure would be a major advancement for this patient population. In specific patient subgroups, such as patients with difficult-to-control diabetes or significant underlying psychiatric disease, the ability to use steroid-free protocols would be invaluable.

Another overarching concern in the patients I treat is the potential for the development of chronic kidney disease, and in severe cases, dialysis dependence. Chronic kidney disease has associated itself with adverse cardiovascular outcomes, and the need for renal replacement therapy in ANCA-associated vasculitis dramatically increases patient morbidity and mortality.

It has been observed that patients receiving avacopan have more rapid reductions in albuminuria in patients receiving standard induction therapies. Furthermore, in the ADVOCATE trial, patients in the avacopan arm had significantly greater improvements in kidney function at both 26 and 52 weeks.

In aggregate, this can best be explained by more rapid control of renal vasculitis with avacopan, which ultimately translates into less irreversible kidney damage. For patients with the most severe disease, this improved renal recovery can translate into delaying or avoiding the need for renal replacement therapy.

In summary, I believe avacopan would be of great benefit to patients suffering from ANCA-associated vasculitis by addressing the two major unmet needs with induction therapy: the need to reduce treatment-related side effects and the need for early and effective disease control.

With that, I will conclude my remarks, and thank you for the opportunity to address the committee.

DR. BECKER: Thank you very much for your comments.

Speaker number 12, your audio is connected now. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. SHARRETTS: My name is Tom Sharretts. I'm 56 years old. I have no financial disclosures. I live with my wife Mary Jo in Enola, Pennsylvania. I have two children, Steven 41, and Melinda 39 years of age, respectively.

[Indiscernible – audio distorted] -- industrial equity and pressuring company. I have no financial disclosures, and prior to becoming ill and being diagnosed, I was very active, did lots of cardio exercises, and was able to walk 18 holes of golf. After my diagnosis and treatment, I continued to have difficulty walking very long distances, and while I have recovered most of my recall or memory, I continue to have memory lapses, specifically with short-term memory.

I continue to work, but I'm not as

articulate as I was before my illness. My physical activity is limited, and I ride my bicycle for exercise and no longer walk on the golf course; I ride a cart.

Prednisone definitely has negatively impacted my health. I bruise very easily, have acne, experience weight gain, and have trouble sleeping due to my prednisone treatments. My personality and thought process has been negatively impacted to the point that it has strained my marriage, limited by community involvement, and affected my ability to multitask at home, as well as professionally.

The beginning of May 2017, I began losing weight, and within 4 weeks, I lost 30 pounds. At that point, I was very dizzy, extremely weak, and began losing my voice. My hearing and eyesight were impaired. Then I lost feeling in my feet and hands and could barely get out of bed.

I was sleeping all day and all night. Getting up to go to the bathroom was almost impossible. I was severely anemic and could barely

walk, and had no energy or strength. I had difficulty concentrating and would forget what I was saying in the middle of a sentence.

My neighbor, a doctor, contacted the foremost expert in GPA, a form of vasculitis, at Johns Hopkins University Hospital in Bayview, Maryland. An appointment was set up for a consultation. It was determined that in order to be absolutely sure that I had GPA, I needed to have a kidney biopsy. The biopsy confirmed that I had GPA. The doctors at Johns Hopkins then prescribed a heavy treatment of prednisone. This was administered as an inpatient for three days.

I then was scheduled to meet with a team of doctors at Johns Hopkins to discuss my treatment. They offered me a clinical trial that had just become available. The trial was a double-blind clinical trial, and the trial drug was avacopan. I just had to become a participant in this clinical trial on July 6, 2017.

I began infusions of rituximab the middle of July 2017. The infusions were once per week for

4 weeks. Immediately before the infusions, I was confused whether it was prednisone or avacopan. I began getting strength and feeling better. Doctors prescribed many tests to include chest x-rays; CT brain scans; chest MRIs; bone density tests; lung capacity tests; nerve damage testing; and types of blood work. Clinical therapy was prescribed to begin building up muscle tone, balance, and cardiovascular exercise. Blood work continued to be prescribed every 2 months, monitoring my vitals.

In conclusion, I do not currently know whether I was given avacopan or prednisone during my treatment. I do know that prednisone has many side effects and can even be fatal. I feel very strongly that avacopan must be approved as the drug of choice to eliminate the use of prednisone.

Avacopan has been proven through the clinical trial that it is a safe alternative for prednisone. This FDA approval hearing is extremely important to those of us that require this treatment. So for me and for those requiring treatments with prednisone or avacopan, I truly

hope that the FDA approves the use of avacopan as the alternative and best treatment for all patients.

Thank you for providing me with this opportunity to tell you my story, and I sincerely hope that the FDA approves avacopan.

DR. BECKER: Thank you very much for your comments.

Speaker number 13, your audio is connected now. Will speaker number 13 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Meg Seymour, a senior fellow at the center. We analyze scientific data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

Today you are asked to assess data from a

single phase 3 clinical trial, comparing avacopan to prednisone at 26 and 52 weeks, and discuss the clinical meaningfulness of avacopan for patients. First, let's talk about the effectiveness of the drug and the limitations of this information due to study design.

We know that there is no significant effect of superiority for avacopan at 26 weeks. The applicant would like to claim that there is a difference at week 52 favoring avacopan. However, as stated by FDA in their briefing document, there are issues with the study design that limit whether or not we can interpret a meaningful clinical benefit for avacopan.

For example, 87 percent of patients in the avacopan treatment group also received glucocorticoids during the study period. Although it's prespecified that glucocorticoids above the protocol specified taper must be discontinued by week 4, that did not happen. Instead, 86 percent of patients in the avacopan group received glucocorticoids between week zero and 26.

FDA scientists state that this effectively creates a different comparison, avacopan plus low-dose glucocorticoids versus higher dose glucocorticoids to patients in the prednisone arm. This causes problems for the interpretability and meaningfulness of the comparison.

FDA's briefing document also notes the observed superiority of avacopan at week 52 may be due to differences in the subgroup receiving rituximab instead of cyclophosphamide plus azathioprine. Subgroup analyses suggest that avacopan was only effective when compared to patients who do not receive standard-of-care maintenance with immunosuppression therapy and may be considered undertreated. This obviously raises questions about the adequacy of the comparisons and clinical meaningfulness of data for avacopan at week 52.

Moreover, differences in assessments from the investigator and the adjudication committee occurred in 17 patients measured at week 52. Although the applicant states there are more

adjudicated relapses after remission in the prednisone group compared to the avacopan group, the study was not designed to assess time to relapse or proportion of relapses. Because remission may be achieved in different types of patients in the two treatment arms, differences in relapse cannot clearly be attributed to the treatment, but instead to differences in the characteristics of the subset of patients included in the analysis.

FDA scientists note that this eliminates the advantages of randomization since the treatment arms are no longer balanced with respect to possible confounders, which leads to biased comparisons between treatment arms and limits the interpretability of results.

Finally, let's talk about the safety profile of avacopan. Although safety events such as infections were generally similar between groups, FDA scientists point out that the safety database is limited when it comes to reliable assessment of rare or latent events. However, the data show that

more patients in the avacopan treatment group had adverse events and serious adverse events associated with hepatic abnormalities, such as liver enzyme abnormalities.

Although AAV is a serious disease with an unmet need for new treatments, the FDA must only approve products that have a favorable risk-benefit profile for patients. Due to issues with study design, avacopan has not clearly demonstrated that it is more effective than the existing treatments, and it apparently carries more risk for certain adverse events. We respectfully urge you to consider the shortcomings of the scientific evidence when voting today. Thank you.

DR. BECKER: Thank you for your comments.

Speaker number 14, your audio is connected now. Will speaker number 14 begin and introduce yourself? Please state your name and any organization you are representing for the record.

(No response.)

DR. BECKER: Speaker number 14, your audio is connected now. Will speaker number 14 begin and

introduce yourself? Please state your name and any organization you're representing for the record.

(No response.)

DR. BECKER: Okay. We'll move to speaker number 15. Your audio will hopefully be connected now. Will speaker number 15 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. MASSIE: Good afternoon. My name is Glen Massie. I'm from Springfield, Ohio. I do have a patient consulting relationship with ChemoCentryx, however, I have not been asked to provide any statement on their behalf today, nor am I being compensated to do so. I want to thank you for your time today. I want to thank you for the work that you're doing. It's super important to patients.

I was diagnosed with granulomatosis with polyangiitis in 2012, following several months of failing health. My walk, my journey, started with pleural effusions and lasted over a number of months, and led from the pleural effusions into

extreme joint pain. One of the patients mentioned earlier about joint pain so bad it felt like broken bones, and that's exactly the way it felt.

From the extreme joint pains, it went into petechiae rash, which they were able to biopsy to determine the vasculitis. From there, I went into alveolar hemorrhage, and I just went into respiratory failure, and begin to go into kidney failure as well.

After a couple weeks in ICU here in Springfield, I was flown to Cleveland Clinic where I was treated up there for a couple of months. I spent two weeks on the ventilator at Cleveland Clinic. I spent a month in ICU.

Once I was released from ICU, I spent about a week, almost two weeks, in step-down. When I was able to come out of step-down, I was transferred back to Springfield, where I spent a month and a half in acute rehab, where I learned to walk again. I learned to talk again. I had to learn to feed myself again. Everything about the disease had totally taken everything away from me.

The biggest thing that I would say it took away from me, though, is when I left Cleveland Clinic, I felt like I left a part of me behind. I left there a totally different person than I went up, and that still kind of works on me today.

The other things that I had were plasmapheresis treatments, cyclophosphamide, and once I was discharged, I was on cyclophosphamide for about nine months. I also received high-dose prednisone. I went from cyclophosphamide to Imuran treatment along with prednisone, and then ultimately to rituximab. The one consistent thing about my treatment has always been prednisone.

Currently, I receive 10 milligrams maintenance per day, however, that ranges from 10 to 15 milligrams per day. I have had a number of relapses. I've only had one six-month period that was considered remission for me.

I would like to also say that through this I've experienced weight gain; diabetes; neuropathy; osteoporosis; vision changes; hearing loss; and then most of all, memory loss, short-term memory,

and mood swings. And I've had mood swings that range from agitation to euphoria.

I'm a fairly new grandfather. I have three grandchildren. I would love nothing more than to be able to get on the floor and play with my grandkids. But what I hope for most of all, for myself and the other patients you've heard from -- these folks are like family to me. We've gone through something most people would never understand. I hope for an improved quality of life for each and every one of us that deal with vasculitis and also deal with the side effects of prednisone. And I want to thank you again for your time and your dedication to this process.

DR. BECKER: Thank you very much for your comments.

We'll go back to speaker number 14. Your audio is connected now.

MR. TAYLOR: Hi. My name is Erwin Taylor, and I live here in Burlington, North Carolina. I've been married for 27 years now to my lovely wife Darlene. We are blessed to have three grown

kids married, Justin and Skylar [ph]. I have no financial disclosures.

In 2017, I started a new business as an entrepreneur of a start-up marketing company. It was during that transitional period that I first noticed that my urine was foamy. I remember reading a post on the internet about foamy urine and the possible connections to protein in the urine. After a diagnosis at UNC that confirmed my symptom as ANCA vasculitis, I started on the road that has changed my life.

I went from relatively a healthy man who ate any and everything, to someone who needed to cut back on my intake of spicy, salty, and certain foods known to make me retain more water or even irritate my gout symptoms. I was prescribed more medications than I had ever taken. I used to mock my parents and my in-laws for the number of medications that they took, only to find out that I was now in their company.

I was hospitalized for a few days in April of 2017 due to respiratory problems, and I was told

about a clinical trial for avacopan. My wife Darlene was consistently writing notes and researching the internet for each new piece of information after each of the test results. The doctors treating me during my hospital stay did an excellent job of describing my disease and my current health. I was told UNC was a premier research hub for ANCA vasculitis. Together, this gave me the confidence that my well-being was being considered, so I decided to enroll.

During the trial, I was able to keep living with reasonably good health, which was a good relief for how I felt before all of the medication I'd been taking and the way that it made me feel, which was exhausted. I remember a trip to China with my wife, and I was unable to do a lot of the walking. I was exhausted, and I preferred just to sit at the bottom of the Buddhist temples where we were touring, rather than climb those stairs. I definitely didn't play basketball with the kids anymore. They were too competitive, and I was too tired out.

If I hadn't started the trial, I am sure my life would have been like I would have been unable to go on with those medications. The drugs you are reviewing today made a difference in my life. It helped the average working person like myself, and I pray that you guys make a decision that helps others. Thank you so much.

DR. BECKER: Thank you for your comments.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the charge to the committee from Dr. Rachel Glaser.

Charge to the Committee – Rachel Glaser

DR. GLASER: Good afternoon. This is Rachel Glaser. Thank you all for the fruitful discussion both this morning and afternoon. As we prepare for the committee discussion and voting, I want to provide a brief reminder of the regulatory

framework upon which our decision making is based and the questions to be discussed and voted upon.

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.

The regulations governing determinations of effectiveness are further described in guidance documents from the agency. The gold standard is evidence from at least two adequate and well-controlled studies. However, in some specific 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.

The guidance indicates the 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.

With respect to safety, an application can be refused to be approved in one of several circumstances as listed on the slide. These include information that the drug is unsafe or that there's 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.

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.

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 the adjudication committee versus the investigators.

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 glucocorticoid exposures due to CYP3A4 inhibition by avacopan.

This will be followed by discussion point 4, where we ask you to discuss how avacopan, if approved, should be used in the treatment approach to ANCA-associated vasculitis based on the data from the clinical program; that is, discuss how the data from the clinical program presented today 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 treatment, or more broadly.

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

voted no, we ask that you discuss what additional data, if any, will be needed. If you voted yes, please provide comments.

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 voted no, we ask that you discuss what additional data, if any, will be needed, and if you voted yes, you can also provide comments.

The last voting question is whether the benefit-risk profile is adequate to support approval of avacopan 30 milligrams twice daily for the treatment of adult patients with ANCA-associated vasculitis, GPA and MPA. If you voted no, we ask that you discuss what additional data, if any, will be needed, and if you voted yes, please also provide comments.

Thank you, and I will now turn the meeting back to you, Dr. Becker.

Questions to the Committee and Discussion

DR. BECKER: Thank you, Dr. Glaser.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording, then we will open the question to discussion.

Question 1. Discuss whether the results at week 26 support a clinically meaningful benefit of avacopan. Include discussion of the following: 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.

Does anyone on the committee have any issues

or questions about the wording of the question?

(No response.)

DR. BECKER: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Okay. I'll start with Dr. Singh.

(No response.)

DR. BECKER: Dr. Singh, would you like to comment? If so, you're still on mute.

DR. SINGH: This is Dr. Jasvinder Singh from the University of Alabama at Birmingham. I think, based on the presentation by the FDA scientists and the sponsor, it's apparent that the 26-week data do not show superiority at that time point, and the use of glucocorticoids with non-study in the avacopan group really makes the interpretation of data very difficult at the 26-week time point.

So I think that in terms of the lack of superiority, it actually does not give as much confidence for this time point favoring avacopan over the comparator group.

The other issues were the glucocorticoid use

has been highlighted by the FDA scientific team. One question that I have perhaps that I'm not clear on is, is there perhaps a way forward as to what might be a non-inferiority comparison margin for a later time point or if there is only a superiority design that is appropriate for this time point.

I'd appreciate comments from anyone who has some insights into this and whether there was any proposal by the company or by the FDA as to what might be an acceptable margin if 20 percent is not, in case that design is still a rival [indiscernible] design. That's the end of my comment.

DR. BECKER: Thank you, Dr. Singh.

Since you asked the FDA first, would anyone from the FDA like to comment on the question at hand, as far as what would be a more appropriate non-inferiority range?

DR. GLASER: This is Rachel Glaser. I'm going to ask Dr. Kim to respond.

(Pause.)

DR. ROTHWELL: This is Dr. Rothwell from

statistics. I think Dr. Kim's having some challenges with audio, so maybe I can speak to this a little bit.

I think we had a lot of discussions about non-inferiority early on, and there's really not any existing data to help us isolate the effect of prednisone when used with the background therapies that were used in this trial. That is the main reasoning that we requested that a superiority analysis be used.

DR. BECKER: Excellent. Thank you.

I saw Dr. Pirow Bekker had also raised his hand. Would you like to address that comment, specifically the non-inferiority comment?

DR. BEKKER: Yes. Thank you, Dr. Becker. This is Dr. Pirow Bekker.

As stated, the ADVOCATE trial design was agreed to by the FDA in November of 2016 after extensive discussions. While it's true that superiority at week 52 was a key assessment, superiority at week 26 was never an expectation, at least as expressed by the FDA at the time.

It was deemed to be virtually impossible to reach at 26 weeks in an ANCA-vasculitis trial of this nature simply due to the fact that the remission rate with the standard-of-care background treatment is quite high.

I also want to just refer the committee, again, to the RAVE study for which the primary endpoint was non-inferiority of remission at week 26, and obviously rituximab was approved on that basis. That was the single precedent for registration in ANCA-associated vasculitis, and that was the template that we were originally modeling.

Again, ADVOCATE achieved its two stated primary endpoints; first, the statistical non-inferiority at week 26, and then achieving statistical superiority at week 52.

Thank you, Dr. Becker.

DR. BECKER: Thank you.

Can I follow up with the FDA on that point, then? So just so I can understand, was the expectation to meet superiority at week 26 or no?

DR. NIKOLOV: This is Nikolay Nikolov. I think the study as it was designed -- this was designed as an active control, at least in the first 26 weeks, which is testing or comparing avacopan versus prespecified steroid taper -- in that context, a non-inferiority would be easier to interpret.

I think the question that we're bringing for discussion is in the place of non-protocol specified use of glucocorticoids, how to interpret this non-inferiority.

DR. BECKER: Okay. Thank you.

Next on my hand-raised list is Dr. Lewis.

DR. LEWIS: I have a comment on the discussion that's at hand, and then I have a separate comment.

I just think I feel that I need to remember that our charge is not to make it a fair world for what the FDA and the company decided. Our charge is to decide whether there's enough evidence to allow a drug to be used safely and effectively, and replace another drug.

So it may be unfortunate that Rituxan therapy changed in the time frame after the study started, and the discussions between the FDA and the company may have been somewhat ambiguous at times. But none of that is our concern today. Our concern today is, is the available evidence enough?

I also think that repeated comparisons to RAVE, again, I can't emphasize enough, RAVE was done with a drug that had been widely used and approved for other indications, and there was a large safety database. That is not the case for this drug.

So my question under discussion is, this 26-week non-inferiority, is it a clinically meaningful benefit? And I would say yes. I think it is a clinically meaningful benefit, however, it is qualified by the non-study glucocorticoids. But were there to be another study, this would certainly be a supportive study and maybe qualify as two studies. And that's my comment.

DR. BECKER: Thank you.

Could you expand a little bit on your point

about two studies? I'm trying to make sure I'm able to capture for summarizing our discussion after each question.

DR. LEWIS: Okay. I don't want to jump ahead of the game here, but as we heard from the FDA, for any compound, but particularly for new compounds, two studies are typically expected, and then there are exceptions to that.

I think all of us, most of us, on this committee could list probably close to a dozen studies done in this disease. And even though it's an orphan disease, much kudos to Dr. Jayne, and the EULAR group, and people who have been able to conduct many studies in this disease; and hence, the field is where it is today, which is much better than where it started.

So I don't think it's impossible to do a second disease in this orphan disease, and this could count potentially, in my opinion, as one of two studies that would support, potentially, the safety and efficacy if we had a more expanded safety database and other clinical evidence of

efficacy.

DR. BECKER: Thank you.

Okay. Next on the list is Dr. Wiesendanger.

DR. WIESENDANGER: Yes. Hi. This is Margrit Wiesendanger. With regard to points A and C, which are sort of linked to each other, I'm not too troubled by the fact that superiority was not met at week 26. I feel that this is a relatively short time period, and since prednisone is one of our most effective drugs, albeit with all the side effects that have been described already, I think it's okay that avacopan was not superior at this time point. I still would consider this drug for the stated purpose.

With regard to point B, I guess I would like to know more about the prednisone group, how much extra glucocorticoids they needed. Both groups were liberal, and they were allowing individual investigators to rescue patients or treat them with glucocorticoids outside of a prescription by the study. And I think that's the only humane and ethical way to conduct this kind of trial,

honestly. I would be very worried if we were too strict in allowing these vulnerable patients to not be treated if they had a flare.

So I guess my question is, how do these two groups compare in terms of not the follow-up glucocorticoids outside of the prescribed tapers, et cetera? Thank you.

DR. BECKER: Thank you.

Can someone from the FDA or ChemoCentryx comment on that? I know that that data had been provided in some of the materials that we were able to review pre-meeting but buried in a lot.

Could you summarize how much additional glucocorticoids were provided in both the prednisone group, as well as the avacopan group, for the first 26 weeks?

Hand-raising looks like Dr. Pirow Bekker.

DR. BEKKER: Yes. This is Pirow Bekker from ChemoCentryx. So the so-called non-study supplied glucocorticoid use was actually very similar between the two treatment groups overall in the study, and I think the FDA agreed with our analysis

on that. During the second part of the study, there was actually a somewhat lower mean dose of extra glucocorticoid use in the avacopan group compared to the prednisone group.

If you want a specific number, let me give you a number. So the mean glucocorticoid dose in the avacopan group was 1,349 milligrams, and in the prednisone group, 1,265 milligrams overall in terms of the non-study supplied glucocorticoid use, so very similar numbers.

DR. WIESENDANGER: Thank you.

DR. BECKER: Thank you.

Dr. Oliver?

(No response.)

DR. BECKER: Okay. It looks like Dr. Oliver may have dropped off.

Dr. Brant, please?

DR. BRANT: Hi. Elizabeth Brant. I'm speaking as the patient representative, but I also treat patients with vasculitis and trained for that purpose; so just to have that in mind.

Not to belabor the issue of the

glucocorticoids, but one thing that struck me is -- and it's been stated by the sponsor and by one of the committee members -- that it really wouldn't be ethical to withhold steroids from patients in the avacopan group who were having a flare. And I'm wondering, would the comparison have been more easy to interpret had there been a specified protocol for a lower dose glucocorticoid regimen in the avacopan group, rather than as patients needed it? I think that makes it a little challenging to compare those two.

DR. BECKER: Thank you.

Would anyone from FDA like to comment?

DR. GLASER: This is Rachel Glaser. Can you repeat the question once more?

DR. BRANT: So I go back to a couple of people's comments about it not being ethical to withhold steroids from patients in the avacopan group who were flaring, which makes perfect sense. But rather than just waiting for a flare and treating with glucocorticoids, thereby having sort of not really arbitrary but for an unexpected use

of glucocorticoids, might it have been easier to interpret the glucocorticoid data comparisons if the avacopan group had had a protocolized regimen of lower dose steroids at the outset?

DR. GLASER: Thank you. Yes. This is Rachel Glaser. So I think that is one of the concerns that FDA described in our background document, is that the inclusion of two variables here in this study make the interpretation more challenging. And if there was only one variable in the comparison, it would be easier to attribute an effect to avacopan.

DR. BECKER: Excellent. Thank you.

DR. NIKOLOV: This is Nikolay Nikolov. Can I add --

DR. BECKER: Sure. Please.

DR. NIKOLOV: -- to Dr. Glaser's comment?

We had similar considerations during the development stages, and we had multiple discussions with the applicant on alternative trial designs of how to more reliably assess for treatment effect and avoid any potential unethical trial designs.

Some of these are also included in the FDA background document, but there have been quite extensive discussions on the best approach to showing efficacy.

DR. BEKKER: So on that point, Dr. Becker, if you don't mind, I would like to ask Dr. Peter Merkel just to briefly comment on that concept because he was there at the FDA meetings when those were discussed.

Dr. Merkel, could you please just make a few comments?

(No response.)

DR. BEKKER: You might be on mute.

(No response.)

DR. BEKKER: Dr. David Jayne, I think you were at the meeting as well. Could you please comment?

(No response.)

DR. BEKKER: You might be on mute as well.

(Laughter.)

DR. BEKKER: The challenges of virtual meetings.

I think just suffice it to say we did obviously discuss with the agency, as Dr. Nikolov pointed out, several designs. The one design that included a no or very low-dose prednisone group was considered to be not feasible because these patients do require serious intervention, as you've heard from many of the patients today. And if you do not give them any steroids, and only an immunosuppressant, especially when there's nothing like avacopan on board, that would just simply not be practical in the clinical trial.

So we decided after discussion with people like Dr. Merkel, Dr. Jayne, experts in the field, with that kind of study, it would just not be feasible.

DR. BECKER: Okay. Thank you for those responses.

Doctor Thadhani?

DR. THADHANI? Great. Thank you. I'll just pick up on some comments from my colleagues. The first one is this is a very difficult patient population, as was alluded to --

DR. MERKEL: Hello?

DR. THADHANI: -- by the patients themselves, as well as for those of us who care for these patients. I could not imagine doing a study in this context without steroids. It's ingrained in the way we treat these patients, and I would imagine it would be incredibly difficult to enroll, if not impossible.

In fact, I would argue that one of the reasons why the agency had a difficult time finding previous studies to estimate a non-inferiority margin isolated to glucocorticoid is because it's difficult to do those studies. We just haven't been able to do them. So it's not surprising to me that it's difficult looking at the literature to find isolated effects of glucocorticoids in a randomized trial.

So that said, like some of my colleagues before me, I find the actual evidence persuasive at 26 weeks with what I would have hoped for, not expecting more than that, with a pretty significant p-value. And if the requirement then is, is this

robust, well one interpretation of that is that the ancillary data, albeit subgroup analysis, exploratory, whether you look at GFR, relapse, opportunistic infections, and so forth, all point, if you will, in the right direction. Thank you.

DR. MERKEL: Am I audible now, by the way? This is Dr. Merkel.

DR. BECKER: Yes. Hi, Dr. Merkel. Do you have additional comments?

DR. MERKEL: Yes, I do. I apologize. I've been on the whole time. Thank you.

Yes, I do. Let me gather my thoughts. Regarding glucocorticoids, I think we are understandably focusing on the non-protocol glucocorticoid, and I would agree with Dr. Thadhani's comments. Really, we just can't treat that way until we have strong data that says you can go with a lower or no-dose approach.

So I think this was why the design was as it was, and I think that we could also refocus on the fact that the protocol said the patients in the prednisone group got a substantive amount of

glucocorticoid, quite a lot per protocol, and the group in the avacopan did not. And although there was some non-protocol, it wasn't anywhere near as much as the protocol defined if you look at the curves and the area under the curve, and it was less in the patients who got avacopan.

So it made sense clinically, and I still go back to the idea that, from a strategy standpoint, if you start someone on avacopan, these data support either giving no additional after the first week or so before you get them on, or much lower and coming off faster. So I think from a treatment strategy, it makes sense, and I think if you put it all together, the efficacy speaks to the clinical question in the first 26 weeks, and then carries over to the 52 weeks.

DR. BECKER: Okay. Thank you for your comments.

DR. MERKEL: Thank you.

DR. BECKER: Dr Chung?

DR. GLASER: Dr. Becker --

DR. BECKER: Yes? I'm sorry. Did I miss

your --

DR. GLASER: Sorry. This is Rachel Glaser. We're attempting to bring up a slide that includes the alternative study design that was discussed in the FDA background package.

DR. BECKER: Oh, terrific.

DR. CHUNG: This is Sharon Chung, University of California, San Francisco. Just to somewhat reiterate the previous commentators, I am also less troubled, if not untroubled, by the goal of non-inferiority for week 26. I agree, in order to achieve a superiority by week 26, I think that is just likely impossible, just given the results that we see with our current treatment regimens.

I think what troubles me more about the out-of-study glucocorticoid use is that participants who received a significant amount of outside glucocorticoid use still could be counted as a responder. And this was both true in the avacopan arm, as well as the prednisone arm. So I think just the true efficacy and the true effect of avacopan compared to prednisone is just not well

verified by this study.

I think my other concern is also that it appears from the sponsor, or the applicant, that the goal for avacopan would be for it to be used in the absence of glucocorticoids from initial remission induction therapy. And I am hesitant with that because there was a significant amount of glucocorticoid use in the avacopan arm after weeks 4 or 5 when the prednisone was tapered off.

My last comment is that -- or two comments -- I find the mean prednisone dose very difficult to interpret because it wasn't the mean prednisone dose of participants taking prednisone, but of everyone in the study. So I think it's an underestimation, in some respects, of how much prednisone or the potential impact of prednisone for particular participants.

I forgot my second comment, so I'll just leave my comments there. Thank you.

DR. BECKER: Thank you, Dr. Chung.

Dr. Glaser, would you like to make a comment, when you've found the slides, of the

alternative study design?

DR. GLASER: Yes. Can you see this slide?

DR. BECKER: We can now, yes.

DR. GLASER: I'm going to ask Dr. Rothwell to talk though this study design, and then after that, we have the data that Dr. Chung just referenced before, which is the mean steroid dose in the patients who received steroids. So we can review that after we review this slide.

DR. BECKER: Excellent.

DR. ROTHWELL: Hi. This is Dr. Rothwell from the Office of Biostatistics. I can speak to this a little bit. This was a possible study design that we'd offered in the backgrounder and we'd also like to hear the thoughts from the advisory committee.

So in this design, we proposed three treatment arms. The first would be placebo plus a 20-week prednisone taper. The second would be avacopan plus a 20-week prednisone taper. And those would be the two arms that would be compared. So in doing so, we would be able to isolate the

effect of avacopan on top of a prednisone taper over 20 weeks.

We would also recommend including a third arm, avacopan plus no- or low-dose prednisone, and then additional analysis of treatment arms A and C would provide more insight into the need for that additional prednisone taper when avacopan is used. Thank you.

DR. BECKER: Thank you.

Are there any comments on this from the committee? First, I'm not sure I'm going to pick you out because there are lots of hands rising; or any other comments from maybe ChemoCentryx?

DR. LEWIS: I have a comment.

DR. BECKER: Go ahead.

DR. LEWIS: This is Julie Lewis from Vanderbilt. Did the FDA consider, or the sponsor, using additional off-study drug glucocorticoids and identifying them as a rescue therapy, and only perhaps allowing them for identified rescue therapy, and then sort of like in an anemia study, it would be a failure of one of the arms if they

required rescue therapy or at least would be counted as that?

DR. BEKKER: Yes. Dr. Lewis, I'm sorry. So we did. Indeed, in this study, if a patient had a relapse, which is what would be akin to what you just referred to, those patients would be considered non-remitters. So the protocol made it clear, so I can say categorically that that was the case.

I wanted to also comment on Dr. Chung's comments, because I think there are few important points there to make. The first is that we are not advocating that absolutely no glucocorticoids be used, and obviously there needs to be glucocorticoids used as premedication for rituximab, for example. What we are saying is that the standard all glucocorticoid taper can be replaced with avacopan. That is what we tested in the study, and that is what we've shown with outcome at week 26.

The second point I want to make is we did do a sensitivity analysis where we actually looked at

the patients with a very high glucocorticoid use, and we considered those patients as non-remitters. And maybe I can just show the slides quickly if you would allow me. There are two slides.

May I have --

DR. BECKER: Very quickly, please; very quickly.

DR. BEKKER: Yes.

DR. BECKER: Thank you.

DR. BEKKER: -- slide PE-33? This slide shows where we actually imputed high glucocorticoid users as non-remitters at week 26 for the week 26 analysis, and you can see that the non-inferiority margin was, again, met for this. Then we also looked -- and I want to show actually that week 52 sustained a remitter analysis where it wasn't just non-inferior, but it was also superior.

So we did an analysis, and this was one of the prespecified sensitivity analyses that we conducted, to show that high glucocorticoid users did not impact the ultimate outcome of the study.

Thank you so much, Dr. Becker.

DR. BECKER: Thank you.

Dr. Glaser, I think you had another comment you wanted to make after you reviewed the alternative study designs, if I recall correctly.

DR. GLASER: Yes. I think a slide to address Dr. Chung's comment about the use of glucocorticoids in only the subjects who received glucocorticoids. But I will need a minute for me to select the right slides.

(Pause.)

DR. GLASER: Okay. So this is a slide that presents the non-study supplied glucocorticoid use based only on the subjects who received steroids, and I'll ask Dr. Kim to walk us through this.

DR. Y. KIM: This is Yura Kim. This slide shows the mean steroid use based only on patients who used non-study supplied glucocorticoids. For example, for weeks zero to 26, there were 143 patients in the avacopan arm who used non-study supplied glucocorticoids, and the mean use was 1245.5 milligrams among those patients.

There were 149 patients in the prednisone

group who received non-study supplied glucocorticoids, and the mean use among them was 884 milligrams. And from week 27 to 52, there were 44 patients in the avacopan arm who received non-study supplied glucocorticoids, and the mean use among them was 1,041.2 milligrams. There were 63 patients in the prednisone who got non-study supplied glucocorticoids during that time, and the mean use was 1202.7 milligrams.

DR. BECKER: Excellent. Thank you.

I think, Dr. May, you may be next on the list of people who would like to comment.

DR. MAY: Yes. Susanne May, University of Washington. I feel the same way as some of my other colleagues on the advisory committee, that part C of the question regarding the week 26 superiority is not as much of a concern to not have statistical significance there.

The question A with regard to the non-inferiority margin and interpretability, I think it's intricately linked to part B with regard to the glucocorticoid use. For that one, it seems

as if the answers to the questions and the hypothesis testing were designed for a different study than actually happened because of the change in care and because of the use of glucocorticoids.

One of the questions that I would have is, besides the alternative design on the use and tapering off of prednisone, how much different would a study be with regard to glucocorticoid use if it were started and planned now? That would answer potentially the question, or help answer the question, whether the results that we're seeing right now are interpretable in this context. And that was my question.

DR. BECKER: Okay, Moon. Who do we have to answer that question? Does anyone want to make a comment on that question?

DR. BEKKER: This is Dr. Bekker from ChemoCentryx. I would like to ask Dr. Merkel to comment on that question because they're doing these studies all the time.

Dr. Merkel, could you comment?

DR. MERKEL: Yes. Thank you. This is --

DR. BECKER: Dr. Bekker, before we get to -- excuse me just one moment. Before we move farther along, I will need to call on you before you speak, just to kind of keep track --

DR. BEKKER: Oh, okay. I'm sorry.

DR. BECKER: -- of all this.

No, no, it's quite alright. Just give me a moment to keep track of everyone.

Alright, Dr. Merkel. You're up.

DR. MERKEL: Thank you. This is Peter Merkel from the University of Pennsylvania, where it's noisy outside. I apologize.

So that's a very good question, and I think that the short answer is it would be a very similar study today. People on the committee are aware that Dr. Jayne and I ran another study where we looked at high-dose glucocorticoids versus reduced dose, and found that the reduced dose regimen was equivalent. But that is not that low. It still was high doses for the first 10 days or more, and then it was 30 milligrams a day for quite a while, and tapering off.

So while there is a trend towards using less glucocorticoids, this regimen was right in line with the regimens that we use in the trials. So I think it would not be designed particularly differently if it was today, and I think the message of being able to reduce by that much is still significant. It's a good question. I still personally think it still applies to the practice of vasculitis care today.

DR. BECKER: Okay. Thank you.

Dr. Kim, you're next on the list to speak.

DR. NIKOLOV: Dr. Becker, this is Nikolay Nikolov. I have a quick request.

DR. BECKER: Yes?

DR. NIKOLOV: I think the intent of these questions were more directed towards the advisory committee members, and we would like to have the discussion by the advisory committee, if that's possible.

DR. BECKER: Absolutely.

DR. BEKKER: Oh, absolutely.

DR. NIKOLOV: Thank you.

DR. BECKER: Apologies. Yes.

Dr. Kim, would you like to comment on question 1?

(No response.)

DR. BECKER: Okay. Dr. Pisetsky, you're up next.

DR. PISETSKY: Thank you. I think my question goes back to the issue of, essentially, the two different therapies, rituximab versus Cytoxan plus Imuran. There is really a significant difference between those two arms. While they both have an induction therapy, one has a remission, a period of remission.

So we're really comparing avacopan, to some extent, with a drug that maintains remission, and in that case it would be Imuran. So I have ambiguity as to how this drug is really being viewed. Is it an anti-inflammatory like prednisone, although prednisone has immunosuppressives, or is it an immunosuppressive that could maintain remission?

With respect to the comment about how we

would design the trial now, I think it would be different because I don't think we would just have people with a single cycle of rituximab. The use of just a single cycle I think then creates this uncertainty in how to interpret those data.

That's all. Thank you.

DR. BECKER: Thank you, Dr. Pisetsky.

Dr. Nason?

DR. NASON: Hi. Martha Nason from NIAID. That's absolutely perfect timing because I was going to ask much of the same question and was hoping one of my clinical colleagues on the panel could comment on exactly that, about how the rituximab standard of care has changed.

I've heard repeatedly that it wouldn't be a single cycle, but I guess for those of us who are not clinicians, it would be helpful to understand a little bit more from the clinical people about how different that might be now, again, to put this non-inferiority comparison into context.

And I will say, just before I pass the mic back, that I may be a little bit in the minority

here, but I personally don't find the non-inferiority at week 26 particularly compelling. It seems to me there are too many uncertainties in the comparison and in the glucocorticoid use. I don't see it as a negative, but I don't necessarily see it as a positive piece of evidence either, that those two arms look fairly similar.

So that's my take on that question. But then I was hoping someone, again, could sort of give a little bit of context on how the standard of care in the rituximab arm might have earned -- rituximab use might have changed now, and how that might influence this. Thank you.

DR. BECKER: Thank you for your comment. I can at least answer you from a pediatric perspective. We do not tend to use rituximab as a single dose. But I thought maybe Dr. Pisetsky, who I know certainly treats adults in my own institution, would also want to comment and be a clinical opinion on that.

DR. PISETSKY: Yes. I do not think -- I mean, well, Dr. Merkel mentioned that not everybody

needs a repeat dose; I think a significant number of people. I mean, this is a long-term disease. It's not just actually within a year. It's well beyond that. So I think there would be interest in assuring, first of all, induction, and then assuring remission.

So I think there would be additional therapy given after that first cycle. And I think that's true with Cytoxan, that therapy thereafter would be prolonged, whether it is rituximab, Imuran, methotrexate, or something. I don't think we would have many patients after six months not be on another agent.

DR. NASON: And just to make sure I understand, if rituximab, for instance, was repeated, would you expect that there would be less steroid use in those people then, because perhaps that would avoid --

DR. PISETSKY: Yes.

DR. NASON: -- sort of counterfactual, but that the people historically who might have gone to an additional dose of steroids might instead get

that additional dose of rituximab.

DR. PISETSKY: Right. They would get additional therapy, and there are differences among the vasculitis subtypes as to what the likelihood of relapse would be as well. So I think that would be conservative with respect to GPA as opposed to MPO, because they all have differences on the relapse rate. But I think, to me, there would be therapy beyond that initial cycle.

DR. NASON: Alright. I appreciate your helping me understand the clinical context here, and I think it only reiterates for me that I feel like this non-inferiority comparison is really a little too uncertain to give too much weight to, given all the factors. Thank you.

DR. BECKER: Thank you so much for your comments.

Dr. Singh?

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. I think that as I'm hearing all my other colleagues talk about this, some of this dovetails into question 2. But there's like

two or three big things that come to mind.

One is that with all the good intentions, this is more like an active comparator trial, where one would have to know that both comparators are effective, and one would have to know the estimates of some effect sizes. And I think the other aspect is the change in glucocorticoids, which makes it complicated.

The third point is what Dr. Pisetsky has brought up a few times very clearly. This is sort of a combination of induction and maintenance, so one might have to think of additional evidence in which not only do you establish the control or establish the efficacy as one component by including multiple arms, but also try to re-randomize between the induction phase separately and the maintenance phase separately, and pick the most appropriate comparator that is being used clinically today.

That's the sort of design that's been practiced in a lot of COVID trials with new medication and discovery. I think it's perhaps

needed with this complicated illness for which we do need new drugs, and it seems like this might have the potential.

But I think we need to control for three things: A, do we have effect size estimates for the two comparators, prednisone versus avacopan? If not, would one of the designs the FDA scientist team proposed, can that be addressed at the beginning?

B, how do we control for the non-study use of glucocorticoids to the best of our ability?

C, can we have separate randomizations with induction versus maintenance in a very efficient design for the next study or for additional evidence that can then provide persuasive evidence for this compound, that I'm not sure I'm able to see with a single trial, which then would help with convincing efficacy and safety evidence for one trial's evidence to qualify for approval and making the therapy available?

That's the end of my comment.

DR. BECKER: Thank you very much.

Dr. Kraft, you're next.

DR. KRAFT: Walter Kraft, Thomas Jefferson University. So the question reads, "support of clinically meaningful benefit," which would be the summation of both efficacy and safety.

If I could just turn our attention to safety, given a non-inferiority design -- which is by definition a lower level of evidence and the issues about that design, which I won't revisit -- when we think about the safety, I think our challenges are the safety appeared comparable, but clearly there were larger events over the duration of the study in the glucocorticoid arm. And we have a large knowledge base of side effects for glucocorticoids, oftentimes which are delayed, as we know.

I think the challenge is for the avacopan, while the short-term safety profile appears favorable, we still don't have a large database for long-term efficacy. So I'm a little agnostic on, in general, the virtues of the non-inferiority. But I think if we bring in the uncertainties around

the safety, I think it makes the use of the non-inferiority at 26 weeks a little bit less compelling. Those are the end of my comments.

DR. BECKER: Thank you very much.

Dr. Chung?

DR. CHUNG: Actually, I just took myself off. Sorry. This is Sharon Chung. I just wanted to get back to I believe it was Dr. Nason's comment about treatment practices and how they've changed.

Presentations referenced RAVE, which did not include remission induction therapy for the rituximab arm. But I will say that the need for remission maintenance, or the use of remission maintenance during the time, was truly standard of care, and was actually standard of care, in part, established by Dr. Jayne in some of his previous studies.

So when RAVE was approved, I don't think many of us thought that we could just treat with one dose of rituximab. I think the question that was raised at that point was, "Okay. Now what do we do with remission maintenance, and when do we

start it?"

I think the sponsor has also indicated that rituximab was not approved for remission maintenance until after the trial commenced. But I would say that the studies that showed efficacy for rituximab for remission maintenance were published before this trial protocol was finalized. So I will say that I was quite surprised that there wasn't a remission maintenance aspect to the rituximab arm for this study. Thank you.

DR. BECKER: Thank you, Dr. Chung.

Dr. Curtis?

DR. CURTIS: Hi. I'm Sean Curtis, industry rep. Yes. I just wanted to provide maybe a little bit of industry perspective on the question at hand about evolving standard of practice, so just building on the last comment.

Obviously, it's wonderful that clinical practice advances; that's what we all want. But again, just to remind the committee, it's a challenge to settle on a study design, and it sounds like there were very earnest appropriate

discussions between the sponsor and the FDA on trying to establish a study design. I think it's just we have to be a little careful about redesigning a study after it's been agreed upon and the results are made clearer.

Understanding clinical practice evolves, and it's very challenging, and it's a continued challenge to try to interpret a study as practice changes, but the fact is there is an agreed-upon proposal, generally. So I just want to remind the committee about that because it's important to the industry to understand what the goal posts are for a study as we, in general, sign up, and agree to a design, and execute on it. Thank you.

DR. BECKER: Thank you very much.

Dr. Lewis?

(No response.)

DR. BECKER: Okay. Dr. Kim?

DR. S. KIM: Seoyoung Kim from Brigham and Women's Hospital in Boston. I just want to make a comment -- or a question, actually -- to the group and FDA. Is it the non-inferiority margin that's

causing some uneasiness or a problem, or is having this non-inferiority analysis the problem?

I'm thinking, looking at the primary outcome figure from the earlier presentation this morning, even if the margin was set at minus 20, the lower bound of the confidence interval is minus 6. So it's a little bit far from the bound. So I wasn't sure whether it was the non-inferiority design shouldn't be used in this context or if the margin was set appropriately.

That was one question. Then the second comment is, even looking at the alternative design that was the slide the FDA showed earlier, I anticipate the use of non-study steroids will be still a problem, even in that setup. I don't know if we would have very different discussions even if the study designs were using -- as suggested by the slide earlier. That's just my comment.

DR. BECKER: Would anyone from the FDA like to comment on that?

DR. NIKOLOV: Yes, Dr. Becker. This is Nikolay Nikolov. I think the issue that we wanted

the committee mostly to discuss was, what is the scientific justification for the non-inferiority margin selection, which deviates from the way we usually define non-inferiority in order to interpret the data in a reliable way.

Whether the margin was selected and the difference shown is clinically important and meaningful, that's a separate question, but we'll be happy to hear both of these points discussed by the committee.

DR. BECKER: Dr. Kim, would you like to respond to that before I --

DR. S. KIM: I think not knowing a lot of literature in this area, and I don't think we'll have good evidence to appropriately set the margin any time in future, I think based on the data that's given, at least I feel the two drugs are quite similar at week 26. Maybe clinically, maybe that's important and maybe that's meaningful if we can actually achieve about the same clinical outcome with a lower use of steroids. So that's how I view it. Thank you.

DR. BECKER: Thank you for your comment. I also think, from my perspective, it seemed difficult to have a thorough evidence base from which to gather that non-inferiority margin from trials other than the trials that they used. So I think that would continue to be challenging.

Okay. Dr. Lewis?

DR. LEWIS: Yes. I have two comments. One is, with going into the study, knowing that you didn't have adequate information to set up appropriate margins, that's an argument for not having the non-inferiority as your primary design. Although I have often struggled to make studies happen, and I really super appreciate Dr. Curtis' comments, again, if the study doesn't support the safety and efficacy for our population of patients here in the United States, even if it's the agreed-upon study, it's our duty to comment on that; not on, yes, you did what you said you did.

DR. BECKER: Thank you for your comments.

Dr. Curtis?

DR. CURTIS: Dr. Becker, I'm sorry. I

forgot to lower my hand. I don't have a question. I apologize.

DR. BECKER: Oh, that's terrific. Don't worry. It's hard for me to keep track of all your little hands.

Okay. So we are done with question 1. I think I have to summarize, which is going to be hard.

It sounds to me that from the discussion, which was very robust -- and I'm grateful for all of the comments and apologize for letting it get a little out of hand for a while there. But there was at least a number of people on the committee that felt the statistical significance or superiority at week 26 was not too concerning, or may be necessary, or even surprising in light of the fact that the patients in both groups received induction type therapy.

However, the concept of the appropriateness of the non-inferiority comparison was discussed quite a bit, especially in light of the association or the need in the non-inferiority design to

exhibit significant safety, which was somewhat in question; that without a large enough database and enough patients, and with new safety signals that were notable, were these data supporting enough safety to justify a non-inferiority design, on top of the fact that perhaps the margins of non-inferiority were based on lack of adequate data to determine an adequate non-inferiority margin.

The use of additional non-study supplied glucocorticoids, I think everyone acknowledged being a challenge in the sense that it made it somewhat hard to interpret the data, not only because patients were on glucocorticoids, but they were quite varied in their presentation and their clinical treatment courses, and their baseline clinical statuses.

So I don't think we had an overwhelming agreement, although I think people acknowledged that the non-study supplied glucocorticoids and the non-inferiority comparison both had challenges in our interpretation for this question and this discussion.

Alright. If there is no further discussion for this question, we'll now move on to question number 2.

Question 2 is to discuss whether the results at week 52 support a clinically meaningful benefit of avacopan. Include discussion of the following. And I'm going to go one by one just to keep it a little bit more organized.

The first will be the impact of the lack of maintenance therapy in the rituximab subgroup, and the second will be discrepancies in the Birmingham Vasculitis Activity Score remission responses as determined by the adjudication committee versus the investigators.

So let's talk first about the impact of the lack of maintenance therapy in the rituximab subgroup. For the first question, we talked a little bit about that. Thank you, Dr. Pisetsky and I think it may have been Dr. Nason who also brought that, as far as is this really an issue. And I think certainly we can acknowledge that nowadays we are using more maintenance therapy in the rituximab

subgroup.

It looks like Dr. Lewis has her hand up first.

(No response.)

DR. BECKER: Okay. I apologize.

Does anyone have questions --

DR. LEWIS: My fault.

DR. BECKER: -- about the wording?

DR. LEWIS: Sorry. My fault. I'm sorry. I didn't unmute quickly enough. I will comment quickly or try to.

I agree with Dr. Singh that these could be separated into an induction and a maintenance trial. I think that would be much cleaner data since the group who went in from induction, doing it as a continuous trial, you don't have the randomized group when you're trying to look at the benefits of maintenance.

Basically, although the company only showed us the rituximab data, clearly the cyclophosphamide group did not show a benefit; so avacopan won over, essentially, nothing. And I don't think many of us

practice with no maintenance therapy in this disease, nor is that the guidelines for many of our societies. And I'm done with my comment.

DR. BECKER: Thank you for your input.

I skipped over whether people had questions about the wording of the question. I apologize for that.

(No response.)

DR. BECKER: Any other comments on the impact of the lack of maintenance therapy in the rituximab subgroup?

DR. PISETSKY: Yes. This is David Pisetsky. I do.

DR. BECKER: Oh, wait.

DR. PISETSKY: Oh, sorry.

DR. BECKER: Dr. Pisetsky, hold on. I'm sorry. I'm waiting for Moon to tell me who's next. She gives me the order. I'm trying to stay on task.

(Pause.)

DR. BECKER: Okay. Dr. Shaw, you're next.

DR. SHAW: Hi. Thanks. This is Dr. Shaw.

I had two comments about this question. It's helpful if someone could bring it up, or you could bring up your own copy of the FDA briefing materials. It's figure 7, and it shows the subgroups and the sustained remissions, a risk difference at week 52. Including the risk difference I think comes into question here, which is when you look at the two different background therapies, that there seems to be a different risk difference in those two groups.

But I have two really strong cautions statistically. That's my background, is statistics. The first is this trial was not designed to answer that question. These subgroups, these background therapies, as was pointed out, were not randomized, and they're not a robust size. So that means two things.

The first is, the denominators, they're quite small, particularly for the non-rituximab group, so we can't look at that null result and accept it as proof that there is no effect. We can't tell the difference between noise, because

our sample size is too small and no effect. And I feel like a few times today, people have been sort of accepting that the null has been proven, and it has not. We just didn't design the trial for that question.

Perhaps even more importantly, we like to look at these as hypothesis generating, but what's really interesting about this figure of five different subgroups that had to do with ANCA positivity subgroups; AAV status; whether or not you were the AAV type of GPA or MPA; and duration and whether it was less than a year or more than a year, all of those subgroups had the same kind of difference between the two levels of the subgroups with the risk difference; sometimes even stronger differences. And because it was not randomized by background therapy, what that means is there's a lot of overlap, potentially, between these subgroups, a lot of confounding.

So what we can't tell is if the difference in the risk between the treatment effect in the two background therapy subgroups is related to the

background therapy or the fact that those background therapy subgroups were also imbalanced with respect to other factors related to disease status, which may in fact be driving differences.

So all of that is just to summarize, in 60 seconds, to say that this trial is really not designed to assess the impact of the lack of maintenance therapy on the one background subgroup versus the other, so we're in a difficult spot to comment on that. I don't think the data in this trial can help us. It's very confusing. And I think perhaps a deep dive into whether or not there was overlap in these different subgroups and how there was confounding or not would be helpful maybe in digging in a little deeper, but it is very difficult to use the data in this trial to answer that particular question.

So I think we have to go back to the best estimate of whether or not there was sustained remission at week 52, and it's kind of this overall estimate of the two arms and not the subgroups because of that potential for overlap and

confounding in the small subgroups.

So right now there is this significant effect. I think the weighted estimates were something like 12.5 percent difference. From hearing the comments today, that sounds like a meaningful difference to the patients. This background of the fact that standard of care has changed over time, to me, that's one of the more difficult things to answer.

When you simply look at the treatment arm comparisons, there seems to be evidence that there is a difference between the two arms in the trial. So the question to the committee here is, really, is that still relevant given the standard of care has moved a bit? That's the end of my comments.

DR. BECKER: Thank you for your comments.

Dr. Richards, you're next.

DR. RICHARDS: Thank you. John Richards, VA Pittsburgh in Pennsylvania. Just to comment on the lack of maintenance therapy with rituximab, not having to use repeat doses of rituximab certainly would be beneficial if there was another therapy

where we didn't have to repeatedly immunosuppress somebody with rituximab or prednisone I think is useful information.

But as the prior speaker said, I don't know that this trial was designed to give us that answer. And while I think it is interesting information and certainly something we should look into more going forward, I don't know that the trial was actually designed to answer that specific question for us. Thank you.

DR. BECKER: Thank you very much.

Dr. Sperati?

DR. SPERATI: My comments are very similar to Dr. Richards. To meet the outcome at week 52, you had to be in remission at week 26 and essentially maintain that to week 52. And all the arms, except the avacopan plus rituximab, essentially had relapse.

So one is, is there something different about the use of avacopan with rituximab as compared to its use in cyclophosphamide? Then in regard to maintenance therapy, as Dr. Richards was

pointing out, perhaps this suggests that avacopan is an alternative to more traditional maintenance therapy in the rituximab arm. But now we're deriving this from a single subgroup, and that from a single trial may not be sufficient evidence to support this being an effective therapy, as the trial really was not designed to answer that question. Thank you.

DR. BECKER: Thank you very much.

Dr. Singh is next.

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. I think because the clinical practice has changed, the impact of lack of maintenance therapy in ritux makes it difficult to interpret where this would fit in terms of the clinically meaningful benefit of avacopan.

I think as shared by the previous two speakers, committee members, to have a conditional remission at 26 for you to be at 52 also brings in another challenge. I think that also factors into this issue. But I think it's unfortunate that the clinical practice, or the new evidence that's

emerged since the design of the previous trial, now offers ritux as a maintenance therapy.

I think if the question is whether avacopan would be a good maintenance vis a vis rituximab, then this trial cannot answer that question. You really need a new trial where induction and maintenance are separated for you to be able to answer that, and I think it is a relevant question at this time.

I think I'd also quickly go back to Dr. Shaw's comment that figure 7 -- and I commented briefly before -- except for the first subgroup, the other four subgroups are just duplicative of two characteristics. One is do you have MPA with MPO antibody. The other one is do you have a new disease or previous disease because the duration, less than one year, corresponds.

It's not the exact same construct, but they're very similar constructs. And that's why you see exactly those bars and those squares can overlap with each other because those constructs likely have very high overlap. So figure 7 is

basically three subgroups broken down into five subgroups, and those are all hypothesis generating, I fully agree. That's the end of my comment.

DR. BECKER: Thank you.

Dr. Brant?

DR. BRANT: So as to point A, sustained remission in the rituximab group at week 52 was attributed by the sponsor to the avacopan. But one of the accepted and proven ways of re-dosing rituximab for maintenance is based on B-cell repopulation. So what I did not see -- maybe it exists -- is whether or not we know, of those patients in this subgroup of rituximab who had this sustained remission, do we know their B-cell status; because maybe the reason they were so successful in maintaining remission was actually because they were still B-cell depleted, not simply because they got avacopan.

DR. BECKER: That's a great point. I don't know if the FDA had any of that data released to them, if that was in any of the information that was provided by the sponsor.

DR. GLASER: This is Rachel Glaser. We don't have that data today. You can ask the applicant whether they have that to provide for you.

DR. BECKER: Dr. Bekker, do you have that information to provide?

DR. BEKKER: No. No, we do not have data on B cells in this study.

DR. BECKER: Okay. Thank you.

Thank you for your question.

Dr. Pisetsky?

DR. PISETSKY: Yes. I think the lack of a maintenance allows you to see a biological effect, but the problem is it doesn't tell you what the effect is and what the comparator is. Even though this is being positive and it is something that could save use of steroids, on the other hand, you could also say it's equivalent to rituximab or its equivalent to Imuran in terms of maintaining remission.

So I don't think we have enough information yet to see actually where this agent fits in,

although this approach allows you to see that it does have some activity.

DR. BECKER: Thank you for your comment.

To summarize point A, it sounds like we did have a bit of consensus that although interesting and potentially useful as the potential for not needing to repeat rituximab doses, which has some certain benefits, there was definitely concern by the committee that the subgroups were small. And it might be difficult to tell a difference between effect and noise, and that the treatment effect related to background confounders might be quite challenging, and that this data from the single subgroup is difficult to interpret and have answers to that question specifically.

For discrepancies in the BVAS remission responses as determined by the adjudication committee versus investigators, does the committee have comments or can we discuss a little bit about what the thoughts are on those discrepancies noted as they relate to the results at week 52?

Dr. Shaw?

DR. SHAW: Hi. Yes. I think my comment is more of a question. I really need to understand why this discrepancy exists. We've heard that BVAS is a validated score, and yet there seems like a persistent difference in how the adjudication committee was using the score and scoring these patients in the trial versus how the investigators were doing that.

So I guess a two-part question is, why does this discrepancy exist? Were there instructions that were different? Then the second is do we feel confident that the way it was done by the adjudication committee is clinically important or meaningful? Because that's the one that is the primary endpoint. So yes, two questions there.

DR. BECKER: Okay. Anyone from the FDA want to expand a little bit? I know I asked you that question in the first session regarding the differences in adjudication committee scores as compared to the site investigator scores.

DR. SHAW: And to make sure my question's clear, I would like to understand just clinically,

how do we view this clinical difference in the two scores, some counting some events, some not.

DR. GLASER: This is Rachel Glaser. I think we'll defer to the applicant to discuss why there are these discrepancies, and the instructions that were provided to the investigators that may have led to some of these discrepancies.

DR. BEKKER: Yes.

DR. BECKER: Excuse me. Just one moment.

We'll start with Dr. Pirow Bekker.

Dr. Pirow Bekker?

DR. BEKKER: Hi. This is Pirow Bekker. I'm going to ask Dr. David Jayne to comment on this.

Dr. Jayne, I think you're on mute.

(No response.)

DR. BEKKER: Dr. Merkel, are you still on the line?

DR. MERKEL: I am.

DR. BEKKER: Well, can you please comment on --

DR. JAYNE: This is Dr. Jayne. Can you hear me now?

DR. MERKEL: Oh, there he is.

DR. BEKKER: Dr. Jayne?

DR. JAYNE: All PIs attended a face-to-face training in scoring the Birmingham Vasculitis Activity Score, and all had to undergo some degree of certification in terms of the independent training exercise.

The reason why we adjudicate these responses is to have consistency, particularly in the assessment of the renal response, because we have objective data from the urinary abnormalities and the adjudicators to be able to assess whether or not the persistent BVAS reporting is appropriate or not. And that's what we did to ensure there was consistent reporting across all of the investigators for when renal remission had occurred. Thank you.

DR. BECKER: Would anyone on the committee like to comment, those of us who are clinicians like to comment on the clinical meaningfulness of those differences in the BVAS scores?

I think the one obvious, clearly,

significant issue is that when taking into account the site investigators and their scoring, it changed the statistical significance of it. But in looking at the data that the FDA showed earlier today, it looked like those differences might be attributed to certain scores and different clinical domains.

Would anyone else like to comment? I will give you a moment to do so before I move on to the next hand-raised person to comment.

DR. SHAW: Yes. Chairman, this is Pam. That's exactly my question. Persistent vasculitis I think the difference was between it wasn't be counted by the adjudicated score and it was being counted by the investigators.

So is this clinically meaningful that we have a score that didn't count that? As a non-clinician, I find it quite confusing because it is a difference between our main efficacy primary endpoint being significant or not. And it seemed like it was persistent vasculitis, if I were to understand the briefing material.

DR. BECKER: It appeared that way as well. And as you probably read, if that persistent vasculitis continued for more than three months, it was considered more chronic damage, which moved on to the VDI scale. So I do think it's confusing even for those of us who see patients, so don't worry.

DR. SHAW: Thank you.

DR. CHUNG: This is Dr. Chung. I apologize for interrupting, but I believe there was a slide that summarized the adjudication committee rated things differently than the investigator.

Is it possible to see that slide again?

DR. BECKER: Would the FDA be able to find that slide for us?

DR. GLASER: Yes, we will pull it up. We'll need the slide set loaded.

(Pause.)

DR. GLASER: Dr. Chung, this is Rachel Glaser. Which slide were you -- I'm not sure which slide you were referring to. We do have several backup slides related to the differences. This

slide reviews the differences that were seen at week 26 and the BVAS organ systems in which those differences were observed, and we have a similar slide for week 52.

DR. CHUNG: I believe there was a slide for week 52 for the participants in the avacopan arm whose BVAS score was different between the adjudicated committee and the investigator. I believe it was for items such as hypertension and proteinuria and such. I may be remembering incorrectly.

DR. BEKKER: If I may, this is Dr. Pirow Bekker. It's one of the slides that we showed.

DR. BECKER: Or the slide that the FDA had, at least giving numerically the differences between the adjudicated groups, as well as the non-adjudicated groups, correct?

If ChemoCentryx can pull up that associated slide.

DR. BEKKER: Sorry. This is not the slide. Could I have slide PE-45, please? I think this was the slide that you were referring to, and maybe I

can ask Dr. David Jayne to just comment on this.

DR. JAYNE: The hypertension in the absence of urinary abnormalities we don't regard as an active feature of ANCA vasculitis. Hypertension was scored. We adjudicated it. It should not have been scored.

Again, if headache was scored in the absence of any other features of vasculitis activity, it was not scored. I can go on, but these are sort of examples of where BVAS can be checked, which is against the overall pattern that the patient is following. But they're a small number of these adjudications compared to the size of the trial.

DR. CHUNG: Thank you.

Okay. Dr. Singh, you're next.

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. So it's unfortunate that for a primary outcome, due to the discrepancy between the adjudicator and the investigator, that the one thing that one can interpret with confidence is the non-inferiority that still retains the statistical significance and possibly

clinical significance.

I think that the loss of significance based on investigator assessment at the 52 weeks makes that not a hard outcome that one can put weight on for superiority. So it's unfortunate that for the primary outcome, that there is a measurement error between two groups of people measuring it. To me, non-inferiority is not a question at all. Superiority becomes a question and a debate. That's the end of my comments.

DR. BECKER: Thank you.

Dr. Richards?

DR. RICHARDS: Thank you. John Richards, VA Pittsburgh in Pennsylvania. There was a comment I believe earlier by the FDA that the investigators, when completing the BVAS form, they didn't have the option for persistent vasculitis, and that seems to be something that the adjudicators may have taken into consideration. So I don't know if the FDA could just clarify that if that was an issue that may have led to the difference.

Also, I think if we're getting back to the

persistent vasculitis, did that lead to increased use of prednisone in that group, which could have had a theory on some of the outcomes here?

DR. GLASER: This is Rachel Glaser. Can we have the slide set available? And I will ask Dr. Kim to speak about the analysis of the persistent vasculitis while we bring up the slide.

DR. Y. KIM: This is Yura Kim. I have shown the slide on the specifications of the document on slide 70.

DR. RICHARDS Okay. Thank you, Dr. Kim. Was there a comment when you showed this slide about -- when you brought up, I think it was the BVAS form, that there wasn't the option for persistent disease as opposed to new or worsening for the investigator?

DR. Y. KIM: So we didn't receive the form the investigator used. We only reviewed the adjudication form that was attached to the adjudication charter. In the BVAS adjudication form, the persistent aspect of BVAS was not used.

DR. RICHARDS: Thank you. That was my

question. Thank you. That's all.

DR. GLASER: This is Rachel Glaser. I think that you also asked a second part about the use of glucocorticoids based on persistent vasculitis.

DR. BECKER: Yes. He hypothesized that, potentially, if there was a rating of persistent vasculitis, maybe that resulted in increased prednisone use.

DR. GLASER: This slide shows the non-study supplied glucocorticoid use based on reasons for the initiation of glucocorticoids. There is the third row of each of these subtables for the treatment of persistent vasculitis. This is the proportion of patients in each treatment group that received additional non-study supplied glucocorticoids used for the treatment of persistent vasculitis; so from week zero to 26.

DR. RICHARDS: Thank you.

DR. GLASER: Okay. Thank you.

DR. BECKER: Thank you both.

Dr. Thadhani?

DR. THADHANI: Thank you. I think my

questions have been answered. I've been listening intently here. I think the last point by the agency regarding the clarification of what the adjudication committee saw in the charter was sufficient.

I guess the only comment I'll make was it was prespecified that the adjudication committee's designation was the primary endpoint or the key endpoint. While probably meaningful for another discussion, I'm curious even why the investigator adjudication was examined, but I'm comfortable with the pre-negotiated adjudication committee endpoint. Thank you.

DR. BECKER: Would the FDA like to comment on that last point about the rationale for looking at the investigator BVAS's?

(No response.)

DR. BECKER: Okay. We'll move on to Dr. Wiesendanger.

DR. WIESENDANGER: Yes. Thank you. This is Margrit Wiesendanger. With regard to the question of comparing adjudication committee versus

investigator scoring for the BVAS, it comes down to what do we believe is more valid and meaningful.

I can speak to the fact that even though investigators and the different sites undergo extensive training, as Dr. Jayne has mentioned, it's still very difficult to score these instruments. I don't have personal experience with the BVAS doing studies, but I do with SLEDAI, die which is a simpler, much simpler, instrument. And even then, there can be mistakes by someone who is not fully an expert on this.

So I guess my question to the group is, do we believe that the adjudication committee, which was blinded, are they providing a fair judgment on how these patients were doing? Are they missing some persistent vasculitis patients, which should not be considered in remission by applying their standards? That's my question.

DR. BECKER: Thank you for that comment and question.

I'm going to move on to Dr. Kim and see whether there are any additional comments to your

question.

DR. S. KIM: Seoyoung Kim, Brigham and Women's Hospital in Boston. I have a question of whether the adjudication only led to a higher number of outcomes or whether the investigator classified remission, but adjudication found no remission, like the other way around, whether that happened at all; and whether other previous trials that FDA has reviewed used adjudicated BVAS in the outcome. Maybe if that's been kind of the standard, then maybe that's what it is. I just was curious.

The last comment is, I think the BVAS was also used as one of the eligibility or inclusion criteria, and whether that score was also adjudicated.

DR. BECKER: Can anyone --

DR. GLASER: We're going to bring up -- I'm sorry.

DR. BECKER: Great. Thank you. No. Please, go ahead.

DR. GLASER: This is Rachel Glaser. We're

going to request slide set from Dr. Kim's prerecorded presentation, please. And I'll ask Dr. Kim to respond as we bring her slides up.

DR. Y. KIM: This information on the analysis based on the investigator assessment is presented on my presentation slide 39. In summary, the analysis based on the investigator assessment resulted in a smaller magnitude of treatment effect and smaller magnitude of responder rates. It's slide 39.

DR. S. KIM: Yes. I've seen this slide, and my question was actually specific to more individual cases of adjudication, whether the adjudication led to no remission when investigator classified as remission.

DR. GLASER: This is Rachel Glaser. Perhaps we can defer to the applicant.

DR. JAYNE: This is David Jayne, Cambridge, the United Kingdom. The purpose of the adjudication was to both review the BVAS scores but also to review whether or not the patient was in remission at week 26 and week 52. In addition to

the BVAS being zero, the patient had to be free of all glucocorticoids as a treatment for vasculitis in the 4 weeks prior to either the week 26 or the week 52 endpoints.

There were certainly patients in whom we changed the definition of remission -- sorry; not the definition. We changed the state of remission to one of no remission because the steroids had been continued, because steroids had been given during that 4-week interval. So there were patients who moved in both directions. Thank you.

DR. BECKER: Thank you.

Does that adequately answer your question, Dr. Kim?

DR. S. KIM: Yes. Thank you.

DR. BECKER: Okay.

Dr. Chung, you're next.

DR. CHUNG: Sharon Chung, University of California, San Francisco. Just responding to an earlier comment about persistent disease activity as an indication of damage, I think the rheumatologists in this group know that sometimes

gauging disease activity can be challenging for symptoms that can't be chronic. And what comes to mind is the sinusitis that can be persistent for patients with this disease.

So according to their algorithm, for example, participants who have had chronic sinusitis for three months, that [indiscernible] adjudication could have been rated as damaged as opposed to active disease, and I think that line to draw can be very difficult.

The same goes with the arthralgias that were shown on the previous screen. It can be very hard to assess whether or not something is due to active disease or if it's due to damage, even considering this persistence of three months.

DR. BECKER: That's a really great point. Thank you.

I think, Dr. Curtis, you're going to be last, and then we're going to move on to the next two questions. Thank you.

DR. CURTIS: Sure. Thank you. Hi. Sean Curtis, industry rep. I was going a little where

Dr. Wiesendanger was going, where I think when you have -- and this is true in other therapeutic areas, or imaging studies in oncology where there's central reading of tumor specimens versus investigator or local readings. Typically, one of those is assessed as primary, and then it's important to show consistency for the non-centrally read or non-adjudicated.

But at the end of the day, I'm just wondering is there something about the unadjudicated results here that call into question the primary endpoint, which is the adjudicated reading here. And that's just not clear to me if the FDA has fundamental concerns about the adjudicated result, which I think is, to me, the most important question.

I didn't quite hear that. I've heard concern that there may be lack of complete consistency, but I didn't hear there was a concern about the integrity of the adjudicated result. But perhaps I didn't understand exactly what the FDA said. Thank you.

DR. GLASER: This is Rachel Glaser. As we discussed in the charge slide, there are specific conditions when the FDA can consider a single study to provide substantial evidence of effectiveness, and one of those considerations is when the data is statistically very persuasive and clinically meaningful. The question with regard to the discrepancies in the BVAS remission responses is whether that impacts the assessment of the robustness of the results in order to accept a single study to support an application.

DR. CURTIS: Okay. Thank you.

DR. BECKER: Okay. To briefly summarize, another robust discussion regarding the discrepancies in the BVAS score. I think it was mentioned throughout, with clarification, about the differences in investigator versus the adjudicator, the adjudication committee, prespecified to utilize the adjudication committee scores for the BVAS.

However, there were differences in how those site investigators may have scored the BVAS, and at least in some of the data that was provided by the

sponsor explaining why some of those scores were changed by the adjudication committee.

However, the loss of significance, based on the investigator assessment for some members of the committee, made that less potentially an important significant outcome, and that it may have impacted the weight of the significance noted at 52 weeks.

That's probably the summary that I'll leave. So if there are no further discussions on the question at hand, we will now move on to question 3.

May the committee discuss whether the data support the use of avacopan as a steroid-sparing agent in anti-neutrophil cytoplasmic autoantibody associated vasculitis. Include discussion on the following: number one, the use of additional non-study supplied glucocorticoids in the avacopan group; number two, the impact of a potential increase in glucocorticoid exposure due to the CYP3A4 inhibition by avacopan.

The question is now open for discussion. Are there any questions, first of all, or issues

with the wording of the question?

(No response.)

DR. BECKER: Dr. Curtis, do you still have your hand up?

DR. CURTIS: By mistake. Sorry. I'll put it down right now.

DR. BECKER: Dr. Dellaripa?

DR. DELLARIPA: Yes. This is Paul Dellaripa. I think this follows up with what has been said already about steroids. I'll stick with point A here, which is that the data in my mind does support the use of this medication as a steroid-sparing agent, but if we looked at the non-protocol use of steroids, as Dr. Kim mentioned, both groups used them.

If you looked at some of the slides that were provided by Dr. Glaser, the amount of steroids used was the percentage of people in the study group that did get steroids was less percentage-wise, maybe 25 percent, and the group who are just on prednisone was up to 36 percent.

So there was a difference it seems, but it's

not as if this drug is going to eliminate the use of steroids, or the potential use of steroids, which goes back to the point that at least for the foreseeable future, there's no magic bullet for the treatment of ANCA-associated vasculitis, and steroids are always going to be part of our armamentarium. And lessening the use of them is our short-term goals, and I think that this does support that. But I think there is a bottom level under which getting below certain dose of steroids or no use of steroids is maybe not within our capability at this time because of the heterogeneity of disease that exists as we know it. And I'll leave it at that. Thank you.

DR. BECKER: Thank you very much.

We will, just for the sake of time, lump both A and B into our discussion today.

I think, Dr. Kraft, you are next on my list.

DR. KRAFT: Walter Kraft, Thomas Jefferson. For B specifically, even if the dosing of avacopan in the phase 1 trial had generated exposures similar to that, which we would see at steady

state, I think that the potential increase due to inhibition by avacopan is probably insignificant for the purposes of this discussion.

I think having precedent from other strong and medium inhibitors demonstrates nominal, if any, effects on prednisone. So I would say that probably could be taken off the table for the purposes of our discussion.

DR. BECKER: Excellent. So to summarize, from your opinion, the inhibitory effect on 3A4 by avacopan, based on the data that you have been presented, does not look to be a significant drug-drug interaction and put at risk for increased glucocorticoid exposures.

DR. KRAFT: Yes, based upon known studies with other known inhibitors of a stronger magnitude.

DR. BECKER: Okay. Thank you.

Dr. Pisetsky?

DR. PISETSKY: I actually think there are data since the toxicity index was calculated, and I would presume if it was a significant effect of

avacopan on metabolism with glucocorticoids, it would have been reflected in the toxicity index; so I would agree.

But the other is that I think it's probably useful to distinguish two phases in the use of glucocorticoids, where one is induction and the other is maintaining remission. And I think the data we have really says that in maintaining remission, there may not be that great a steroid-sparing effect because of the similarity in the use of non-study supplied glucocorticoids. But upfront there questionably was a difference, but that was the nature of the design.

DR. BECKER: Okay. Thank you.

Dr. Thadhani?

DR. THADHANI: Thank you. Just to comment and agree with my previous colleagues, in looking at the safety results, I would have expected if there was a significant effect of avacopan on glucocorticoid metabolism, then side effects such as opportunistic infections, psychological, metabolic, and so forth, perhaps would have been

more similar between the two arms, albeit depending on what at time point do you look at.

It doesn't take away from the fact that there may be an effect on CYP3 for other medications, but at least for steroids, I agree with my colleagues, it does not appear significant.

DR. BECKER: Thank you.

Dr. Singh?

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. By dose, there is a difference between the two groups. By proportion of people, I think, as we've seen, the percentages look kind of similar.

I think that one unknown, which I think all of us would like to know as adult rheumatologists, is, if this were tested as a drug for maintenance, what would be the cumulative reduction in the total prednisone dose of a duration of exposure to prednisone?

But even more importantly, what proportion of people will have infections or osteoporotic fractures in the two arms on a person-year basis,

not having that as a primary outcome, but looking at that as data were one or two years?

I think there's a potential for us to go for that dose data that did not exist at present. The total milligrams, there's a difference. The question is what is the clinically meaningful impact of that 2-and-a-half gram difference between the two arms? What does it translate into? How about that experience extended over a 2, 5, 10-period?

Now, we're not going to have a 10-year trial, but does it translate into clinical events, infections or osteoporotic fractures, and some of the other patient-reported outcomes as well?

I think GTI does open up an avenue of a physician-based assessment as a validated tool. I think some patient-based assessment or clinical outcomes, at least on a person-year incident, even if not of statistical significance, for a period of more than one year perhaps could shed some light into what is the long-term clinically meaningful impact of the steroid dose-reduction effect of this

medication.

That is certainly a potential for us to look at additional studies of this medication. That's the end of my comment.

DR. BECKER: Thank you very much.

Dr. Chung, you'll be last.

DR. CHUNG: I actually have a very difficult time with this question -- sorry; Sharon Chung, University of California, San Francisco -- because I do feel that avacopan is likely steroid sparing based on the data that has been presented. But I am not necessarily sure if avacopan can replace prednisone or the oral prednisone that we use outside of, for example, what's given for rituximab therapy or such.

Just given the additional non-study supplied glucocorticoids in the study, I'm not sure I can say comfortably that one can use avacopan instead of oral prednisone, for example, at week 14, or week 16, or something along those lines for all patients. That's my last [inaudible - audio distorted]. Thank you.

DR. BECKER: Okay. Thank you all very much for all of your comments.

To summarize, it sounds -- I'll start with B, which is a little easier -- that there was less concern by the committee that there is potential increase, or at least significant enough increase, in glucocorticoid exposure, due to CYP3A4 inhibition by avacopan, to cause toxicity or problems, especially based on some of the stronger CYP3A4 inhibitor data that was presented, as well as no increased toxicity scores presented in the clinical data.

The use of additional non-study supplied glucocorticoids continues to be sometimes, it sounds like, hard to interpret as far as the additional steroid-sparing effect, or whether this would be completely steroid sparing or partially steroid sparing of an agent. Certainly, people agree that there may be less steroid usage, but the proportion of patients supported that glucocorticoids continue to be needed, even in patients who used or were randomized to the

avacopan group.

Just to make note, we are coming upon 4:15, and we will be running past time. We'll try to finish up question 4 and move along as expeditiously as possible. I just wanted to let the committee know that, clearly, we are running a little bit behind.

So if there are no further discussions on this question, we will now move on to question 4, which is, based on the data from the clinical program, please discuss how avacopan, if approved, should be used in the treatment of ANCA-associated vasculitis.

Are there any questions or issues related to the wording of this question?

(No response.)

DR. BECKER: Okay. It's open for discussion.

Dr. Oliver?

(No response.)

DR. BECKER: Dr. Oliver, you may still be on mute.

DR. OLIVER: Alright. Can you hear me now?

DR. BECKER: I sure can.

DR. OLIVER: Thank you.

What I was going to say is, frankly, I think this is a very difficult question to answer. From all of the discussion that we've been having, we can't get a clear understanding of background steroids and the influence on remission with the non-study steroids. So I think the appropriate question would be what studies we would design so that we could answer the question of how to best use avacopan in the future. That's all I have to say.

DR. BECKER: Excellent. Thank you for your comment.

DR. BECKER: Dr. Sperati?

DR. SPERATI: John Sperati from Johns Hopkins. I agree with that comment, and I think this trial, as designed and then ultimately executed, doesn't directly address its role for induction, nor its role in maintenance, and certainly not maintenance therapy.

So to the point of the question itself, I think if approved, one would have to go with the manner in which it was utilized in this study, which was part of induction therapy. But where its true efficacy lies within the different treatment regimens available to us, I think still remains unclear from these data.

DR. BECKER: Thank you so much for your comment.

Dr. Pisetsky?

DR. PISETSKY: I think like many new drugs, it would likely be used, if approved, in people who had persistent activity or had frequent relapses despite being on other agents like rituximab or Cytoxan and Imuran, who still required high doses of steroids. I think any new agent would probably be first used in that patient setting.

DR. BECKER: Okay.

Dr. Richards?

If I could remind folks to lower their hands once they're done speaking, that would be great, so I don't call on you twice. Thank you

Dr. Richards?

DR. RICHARDS: Hi. John Richards, VA Pittsburgh. Yes, I agree with the comments that were previously made. The study was designed to use this drug, avacopan, to substitute for prednisone at the time of induction. But I think the question is which patients would use that?

Would you use it in patients with extremely active vasculitis with increasing creatinine? It's probably [indiscernible] patients, but I don't know that the study really answers that question with it being non-inferior. And using the rituximab and Cytoxan at the time of induction, I think the gist is that you think it may be beneficial as maintenance therapy, yet the trial really wasn't designed to show that. But that seems to be the gist of where its place may be, so we need studies to show that. Thank you.

DR. BECKER: Thank you.

Dr. Wiesendanger?

DR. WIESENDANGER: This is Margrit Wiesendanger. Thank you for calling on me. The

way I see the data -- because I'm trying to sort of formulate in my mind where is the best evidence or the most robust evidence for benefit to patients, and it seems to me that induction therapy in patients who are treated with rituximab, that's really where the value of this drug is. I'm thinking of patients who are at highest risk of harm from high-dose steroids and protecting those patients.

The best example is a patient with giant cell arteritis who is elderly and could have the most severe side effects from high-dose prednisone. So bringing that to AAV, that would be the population I would be looking at to protect. That's my comment. Thank you.

DR. BECKER: Thank you very much.

Dr. Thadhani?

DR. THADHANI: Thank you. I was actually going to make the same comment as the colleague just before me, those patients at highest risk of complications from steroids: diabetics, pre-existing infection. And albeit a subgroup

analysis, certainly the relapse data -- meaning those individuals that came into the study with a history of relapse and clinicians looking for opportunities to try something different in the context of that -- those data seemed compelling, again. But that was the subgroup analysis, as people know. Thank you.

DR. BECKER: Thank you very much.

Dr. Richards, do you have another comment or is it just a leftover hand raised?

DR. RICHARDS: Sorry. I apologize. I forgot to lower my hand.

DR. BECKER: No worries.

Alright. Dr. Chung?

DR. CHUNG: I think I agree that given a new medication, that it would ideally be used in those patients who are relapsing or not responding well to therapy. I just am concerned that given the aura surrounding glucocorticoid use and the well-known side effects of glucocorticoid use, that if approved, it would just rapidly become first line instead of being a rescue therapy. That's all

I have. Thank you.

DR. BECKER: Okay. To summarize, this was a difficult question for the committee to answer, particularly because the study doesn't necessarily directly address induction versus maintenance therapy, and as such, may force any use to essentially follow the trial design.

However, there were some great points brought up about the concept of utilizing this for induction therapy as design, but also in patients with the highest risk for harm, a risk for complications from high-dose steroids, as well as patients who are at risk for relapse

So in the conversations that the committee had, difficult to answer but were able to think through some specific patient populations where this may be of benefit. But some additional concerns are that it may be used more widespread than just in patients who had -- or are at excessively high risk for high-dose steroids and their harmful effect.

Okay. If there are no further discussions

on this question, on this discussion question, we will now move on to the next question, which is a voting question.

Dr. Moon Hee Choi will provide the instructions for voting.

DR. CHOI: Questions 5, 6, and 7 are voting questions. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting questions into the record and all questions and discussion regarding the wording of the vote questions are complete, the chairperson will announce that voting will begin.

If you're a voting member, you'll be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit

or send your vote. Again, you need only to select the radio button that corresponds to your vote. You have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their votes, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want. However, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. BECKER: Okay. Question number 5. Do the efficacy data support approval of avacopan for the treatment of adult patients with ANCA-associated vasculitis, including granulomatosis

with polyangiitis, GPA, and microscopic polyangiitis, MPA? If you vote no, what data are needed?

Are there any concerns about the wording of this question?

(No response.)

DR. BECKER: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 5.

DR. CHOI: We will now move voting numbers to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. CHOI: The voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. CHOI: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list and each voting member will state their name and their vote into the record. You can also state the reason why you

voted as you did, if you want to. However, you should also address any subparts of the voting question, if any.

For the record, we have 9 yes, 9 no, zero abstentions.

DR. BECKER: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish to.

I'd like to please ask that you stay brief in your explanation, and if your answer is in repetition from thoughts that were already expressed, feel free to pass on re-explaining.

We will start with Dr. Sperati.

DR. SPERATI: This is John Sperati, and I confirm that I voted no. I do feel the data suggest avacopan may mildly reduce steroid exposure, but there are still concerns with the study design and the non-study supplied glucocorticoid use to render it rather unclear the extent to which avacopan is providing the benefit

versus just benefit from lower dose steroids and maintain disease remission in general. There are unresolved questions in regard to its use with cyclophosphamide versus rituximab as well as the maintenance.

In the end, given the charge to us from the FDA for a single study submitted for approval, I do not believe that the data were sufficiently very persuasive from a statistical perspective. Thank you.

DR. BECKER: Thank you.

Dr. Oliver?

DR. OLIVER: Alyce Oliver, Augusta University. I voted no. Although there is an unmet need for improved therapeutics for treatment of ANCA-associated vasculitis, I didn't think that we could determine the magnitude of treatment effect of avacopan, in that I didn't find the statistical analysis persuasive. That is all.

DR. BECKER: My name is Mara Becker. I voted no for largely the same reasons, based on the FDA's guidance that a single study should be

limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect. There were just too many factors to consider in this study to make me feel confident in having it be the single study to result in approval.

Susanne May? Dr. May?

DR. MAY: Susanne May. I voted yes. Even though there were a number of caveats and challenges with regard to the interpretation, I did think that it maybe just barely met the criteria of substantial evidence for efficacy. That's it.

DR. BECKER: Dr. Singh?

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. I voted no. At the cost of not repeating the previous argument, I would say that I did not see persuasive evidence of clinically meaningful, statistically significant persuasive evidence from the single trial.

I do think that additional data can certainly make this a potential treatment, and we really do need new treatments in vasculitis, which

is a life-threatening condition for which very few treatments are available.

DR. BECKER: Dr. Wiesendanger?

DR. WIESENDANGER: This is Margrit Wiesendanger. Even though the results did not show that you could completely remove steroids from the equation, I felt that the steroid-sparing effect was still sufficient to warrant approval of this drug. Thank you.

DR. BECKER: Dr. Thadhani?

DR. THADHANI: Thank you. I think the combination of orphan indication and a very difficult-to-do study in a population where we're not going to get rid of steroids, this study chipped away at that possibility and met its primary endpoint in a robust fashion. So that's why I voted yes. Thank you.

DR. BECKER: Dr. Chung?

DR. CHUNG: Sharon Chung, University of California, San Francisco. I voted no along the lines [indiscernible] -- was robust enough to justify a single study for approval, as indicated

by the FDA.

DR. BECKER: Dr. Kim?

DR. S. KIM: Seoyoung Kim, Brigham and Women's Hospital, Boston. I voted yes despite some limitations in the trial. I think with a newer trial, I don't think it would be easy to make a decision even then.

DR. BECKER: Dr. Lewis?

(No response.)

DR. BECKER: Dr. Lewis, are you on mute?

(No response.)

DR. BECKER: I think she got disconnected.

Dr. Dellaripa?

DR. DELLARIPA: Yes. This is Paul Dellaripa from the Brigham and Women's Hospital, and I do vote yes. I think it does meet a threshold for efficacy despite the limitations. I also think future trials, looking at some of the details we talked about, will run into some similar limitations, but I think for those reasons I voted yes. Thank you.

DR. BECKER: Dr. Nason?

DR. NASON: This is Martha Nason from NIH. I voted no. Similar to what my colleagues have expressed, I felt it was certainly promising but not pervasive or robust statistically enough to be a single study.

To quickly answer the question of what data do I think are still needed, I would expect a confirmatory study would help clarify the best use as far as maintenance or the initial dose, and also give some insight if it could be compared to a current standard of care that includes the maintenance dose.

DR. LEWIS: Dr. Becker, I apologize. I got booted out of the meeting. I'd be glad to read my vote in now, or later if you would prefer.

DR. BECKER: Thank you, Dr. Lewis. That sounds like you. Feel free. You can go.

DR. LEWIS: Okay. I voted no. I agree with all the previous comments. My additional comment would be that I don't think the weight of the efficacy outweighs the limitations of the safety database, and the suggestions within the safety

database that there were safety issues that needed further exploration.

On what other data are needed, I think a more limited trial looking at a standard-of-care induction, followed by using the study of avacopan to be in a maintenance study only, rather than kind of an overreach of induction and maintenance, which I think introduced a lot of technical and interpretation questions. Thank you. I'm done.

DR. BECKER: Excellent. Thank you.

Ms. Johnson?

MS. JOHNSON: Hetlena Johnson, and I did vote yes. Although there needs to be even more of a beneficial change shown with some of the therapies that were provided with how it did the GCs, I still feel there was an achievable response in the data to show that it should be sufficient and beneficial in terms of the efficacy data. Hetlena Johnson.

DR. BECKER: Thank you.

Just to remind folks, if you could also comment on what additional data might be needed,

which I think a number of us forgot in the earlier stages, that would be terrific.

Dr. Pisetsky?

DR. PISETSKY: I voted yes. I think the study met its endpoints. For the novel mode of action for a heterogeneous disease, I think that was sufficient evidence to show benefit.

DR. BECKER: Thank you.

Dr. Richards?

DR. RICHARDS: John Richards. I voted no, somewhat reluctantly. I'm aware of the complications of steroids in this group of patients, and how rare this disease is, and how difficult it is to perform trials. But I think with the FDA mandate, I think the data just weren't robust enough for a single trial; so I think certainly a second trial to show confirmation of efficacy or more robustly showing efficacy.

Again, I think the drug seems to be more positioned for maintenance therapy, and I thought that the trial was [indiscernible] maintenance therapy, and longer term data as well, longer term

follow-up, open-label extension [indiscernible] with this agent.

DR. BECKER: Thank you for your comment.

Dr. Shaw?

DR. SHAW: Hi. Yes. This is Pamela Shaw. I voted no, I think also somewhat reluctantly. But for the reasons that were stated, the interpretability of this result is difficult because of the maintenance issue not being equal across the arms.

In terms of the additional data, just because this was a single trial and there are these questions that persist, I did also think the phase 2 data was somewhat underwhelming, and that we do need additional evidence that's a limited-scope trial.

I actually think, given the difficulties with steroids, especially expressed by the patients today, that a non-inferiority would even be acceptable in this additional trial, I think, if there was a robust data collected that showed and confirmed that the steroid use can be lowered and

that you can maintain a reasonable remission rate, given more equal arms with respect to standard of care and maintenance. Thank you.

DR. BECKER: Thank you.

Dr. Brant?

DR. BRANT: Hi. Elizabeth Brant. I did vote yes, a little bit reluctantly because I do think there are some issues with the trial design that have been discussed at length. However, there are a number of patients, and we heard from some of them today, who cannot get off maintenance immunosuppression, particularly glucocorticoids, who have other more comorbidities that put them at high risk of complications if they're put on glucocorticoids; and this may offer an option for those patients in particular.

DR. BECKER: Thank you.

Dr. Kraft?

DR. KRAFT: Walter Kraft. I voted yes. Regulatory decisions are not made in a vacuum; they're made in the context of existing therapeutics and societal needs. On that basis, I

felt the evidence, though limited, met the societal and therapeutic goals. I was also concerned about the requirement for a subsequent trial in terms of timeline and delay, ultimately, of approval that may put this several years down the road.

DR. BECKER: Okay. Thank you everyone.

To summarize, as may be expected, we as a committee were split in our vote, half voting yes and half voting no to this answer, with a number of suggestions, including the longer term, larger data, maybe in a maintenance phase, to better characterize the effect, with an acceptability for a non-inferiority trial to be considered as well, especially in light of the fact that there's real benefit in steroid-sparing effects. At least it appears to be with this drug thus far.

Okay. We will now move on to question 6, which is another voting question.

Is the safety profile of avacopan adequate to support approval of avacopan for the treatment of adult patients with ANCA-associated vasculitis, including GPA and MPA? If you vote no, what data

are needed?

Are there any questions about the wording of this question?

(No response.)

DR. BECKER: If there are no questions or comments concerning the wording of this question, we will now begin the voting on question 6.

DR. CHOI: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. CHOI: The voting is closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. CHOI: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. However, you should also address any subparts of the voting

question, if any.

For the record, we have 10 yes, 8 no, and zero abstentions.

DR. BECKER: Thank you. We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish to.

We'll start with Dr. Sperati.

DR. SPERATI: John Sperati. I voted yes. The safety database is admittedly small, and I would have concerns, as I would with any new drug entering the market. But I don't believe the current safety data should preclude approving avacopan. I would support a postmarketing surveillance, though, from a safety perspective.

DR. BECKER: Thank you.

Dr. Oliver?

DR. OLIVER: Alyce Oliver, Augusta University. I voted no. Just as Dr. Sperati said, actually it's a small database. I believe there are only 166 patients who were exposed for 52 weeks. So it would be nice, since this is a

novel therapeutic, to have a greater number of patients exposed to the drug to really determine if there is hepatobiliary toxicities, risk of elevated CPKs, and a risk of angioedema. Thanks.

DR. BECKER: Thank you.

My name is Mara Becker. I voted yes. In agreement with Dr. Sperati's comments, I felt that the sponsor also adequately explained some of the signals that were seen, and I think in the complexity of the patient population, they will continue to have signals that will need to be really thought through carefully. More data and more patients to follow over time will be helpful, but I still voted yes.

DR. BECKER: Dr. Lewis?

DR. LEWIS: I voted no, and I agree that data that needs to be added is more patient data; and certainly looking at adverse events with special interest to include rhabdo and angioedema, in addition to elevated liver function tests.

DR. BECKER: Thank you.

Dr. May?

DR. MAY: Susanne May. I voted yes, and I don't really have much to add to the comments that the previous reviewers who voted yes had. That's it.

DR. BECKER: Thank you.

Dr. Singh?

DR. SINGH: Jasvinder Singh, University of Alabama at Birmingham. I voted have no due to concerns about the hepatotoxicity and angioedema. I suggest we have data on more patients, longer term data than 52 weeks, and also data on minorities such as Hispanics and African-Americans, who are very poorly represented in the current trial.

DR. BECKER: Thank you.

Dr. Wiesendanger?

DR. WIESENDANGER: This is Margrit Wiesendanger, and I voted yes. Even though it was a small database, the trend was favoring avacopan compared to the prednisone arm in terms of safety. There was this mention about Hy's law, potentially one case that the FDA highlighted, but there was

some disagreement about whether that truly was a Hy's law case. So since there were no fatalities due to DILI, I still felt that this was safe to proceed. Thank you.

DR. BECKER: Thank you.

Dr. Thadhani?

DR. THADHANI: Thank you. I agree with my colleagues who voted no, albeit for the same reasons that some of the others voted yes. I don't think anyone disagrees that additional data are needed, and monitoring. I think the diversity part was an important point that Dr. Singh brought up. Thank you.

DR. BECKER: Dr. Nason?

This is Martha Mason. I voted no, and I don't really have much to add beyond what's been brought up. It was mostly just the small sample size and the lingering questions.

DR. BECKER: Dr. Kim?

DR. S. KIM: Seoyoung Kim. I voted yes, but I think long-term postmarketing surveillance is needed.

DR. BECKER: Dr. Dellaripa?

DR. DELLARIPA: Yes. It's Paul Dellaripa from The Brigham, and I voted yes. And I don't have anything else to add on top of the comments that have already been added. Thank you.

DR. BECKER: Thank you.

Dr. Chung?

DR. CHUNG: This is Sharon Chung, University of California, San Francisco. I voted yes without additional comments. Thank you.

DR. BECKER: Thank you.

Ms. Johnson?

MS. JOHNSON: Hetlena Johnson. I voted no, as same as the colleagues before me stating that a little bit more data could be sufficient, and I do believe that more subgroups should be studied.

DR. BECKER: Thank you.

Dr. Richards?

DR. RICHARDS: John Richards. I voted no for the reasons already stated by Dr. Singh. Thank you.

DR. BECKER: Dr. Pisetsky?

DR. PISETSKY: I voted no. We have some small sample size concerns about certain side effects and interest in more long-term data, given the way the agent may be used.

DR. BECKER: Dr. Shaw?

DR. SHAW: Pamela Shaw. I voted yes for the reasons already stated; no additional comments.

DR. BECKER: Thank you.

Dr. Brant?

DR. BRANT: I voted yes. Even though there are some risks associated with the avacopan, I think those risks could be mitigated with really good patient education and very close monitoring, compared with the risk of glucocorticoids, which are nearly universal, cause severe morbidity, and are often irreversible.

DR. BECKER: Thank you.

Dr. Kraft?

DR. KRAFT: Walter Kraft. I voted yes, largely for reasons that parallel mine for the efficacy. Thank you.

DR. BECKER: Thank you.

In summary, we have 10 yeses and 8 noes. Interestingly, the rationale tend to be the same on both sides as far as people agreeing that more data would be helpful, more long-term data would be helpful, and that in many folks' eyes it was safe to proceed, and in others, that additional data would be quite helpful in determining its long-term safety in this patient population that are complicated.

Okay. We will now move on to question 7, which is a voting question. Question 7 is, is the benefit-risk profile adequate to support approval for avacopan at the proposed dose of 30 milligrams twice daily for the treatment of adult patients with ANCA-associated vasculitis, including GPA and MPA? If you vote no, what further data are needed?

Are there any questions or issues around the wording of this question?

(No response.)

DR. BECKER: If there are no questions or comments concerning the wording of this question, we will now begin the voting on question 7.

DR. CHOI: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

The voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. CHOI: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. However, you should also address any subparts of the voting question, if any.

For the record, we have 10 yes, 8 no, zero abstentions.

DR. BECKER: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for

your vote, if you wish to. Please remember to state your name after I call on you.

We'll start with Dr. Sperati.

DR. SPERATI: John Sperati. I voted no. I don't believe the phase 2 data, as well as the preclinical data, that was submitted in the briefing documents, clearly establish the optimal dose. We do now, however, have data on 30-milligram twice-daily dosing from ADVOCATE. And since I voted no overall for approval of avacopan based on a single study, my feeling is if additional studies are done, then we ought to have adequate data at that point as to whether 30 milligrams twice daily would be appropriate. Thank you.

DR. BECKER: Thank you.

Dr. Pisetsky?

DR. PISETSKY: I voted no. Given the issues concerning efficacy, I think the amount of data on risks, which is not sufficient to give a yes vote at this time, I think there are too many unknowns.

DR. BECKER: Thank you.

I'm Mara Becker. I voted no, in part because I voted no due to the efficacy on the first voting question. And although it pains me, because I really want more steroid-sparing agents, I think a little bit more data with another confirmatory trial to show steroid-sparing effect and a more clearly designed efficacy trial would be supportive and helpful in this regard.

Dr. Lewis?

DR. LEWIS: I voted --

DR. BECKER: Please remember to state your name.

DR. LEWIS: -- no.

DR. BECKER: Please remember to state your name. Thank you.

DR. LEWIS: This is Julia Lewis. I voted no. Even if I had voted yes for the previous two questions, which obviously I didn't -- I voted no for both -- this is a way too broad written indication far exceeding -- I think even if you had believed yes for the other two -- the data presented to us.

DR. BECKER: Thank you.

Dr. May?

DR. MAY: Susanne May. I voted yes, primarily for the same reasons as I stated in the other questions, but also [inaudible – audio lost].

DR. BECKER: Dr. May?

(No response.)

DR. BECKER: Alright. We may come back to her.

Dr. Singh?

DR. SINGH: Jasvinder Singh. I voted no due to the previously stated concerns about efficacy trial design issues, as well as some concerns of safety data.

DR. BECKER: Thank you.

Dr. Wiesendanger?

DR. WIESENDANGER: This is Margrit Wiesendanger. I voted yes, and I'm going to say that judicious use of this new medication will be warranted, and perhaps additional guidance could be given to rheumatologists to help them decide for whom this medication is best reserved. Thank you.

DR. BECKER: Okay. Thank you.

I'm going to go back to Dr. May since I think she's back and connected.

DR. MAY: Yes. Thank you. My phone call got dropped.

So considering the three aspects of substantial evidence, well-controlled studies and robustness of the confirmatory evidence, I think all of them have some concern, but they did not reach the level for me in relationship to the risk-benefit profile. That was it. Thanks.

DR. BECKER: Thank you.

Dr. Thadhani?

DR. THADHANI: Thank you. Ravi Thadhani. I voted yes. I believe the evidence suggests that the benefits outweigh the risks, given this population is desperately in need of therapy and obviously careful monitoring, and judicious issues would be warranted. Thank you.

DR. BECKER: Thank you.

Dr. Nason?

DR. NASON: This is Martha Mason. I voted

yes. I want to preface that with saying I voted no on the first two, so I do very strongly feel that we need more data on the benefit and the risk in order to really assess this.

I guess I interpreted this question slightly differently since I had already expressed that I thought of this as sort of, if the benefit and risk hold up in a confirmatory study, as they are here, does that seem that the trade-off will be worth moving forward? And in that sort of hypothetical way, I voted yes, but I do not believe we have the data we need yet; so just to clarify that.

DR. BECKER: Okay. Thank you for clarifying that.

Dr. Kim?

DR. S. KIM: Seoyoung Kim from Brigham and Women's Hospital, Boston. I voted yes. However, I think, like some of the others mentioned, maybe if it's approved, labeling can specify appropriate indication or clinical [indiscernible]. Not everybody with the disease are considered with this, so maybe some more directions are needed.

DR. BECKER: Thank you. Dr. Dellaripa?

DR. DELLARIPA: This is Paul Dellaripa from Brigham and Women's Hospital, and I voted yes, primarily for what appears to be a role, especially in induction, and I think that the risks and benefits weigh in the direction of approval at this time. Thank you.

DR. BECKER: Thank you.

Dr. Chung?

DR. CHUNG: Sharon Chung, University of California, San Francisco. I also actually voted no in the first question, but I voted yes for this question because I feel while the efficacy data is confounded by all the factors we have discussed above, there does suggest a steroid-sparing effect. And given the toxicity of steroids in this population, potentially decreasing the use of steroids would be greatly beneficial. Thank you.

DR. BECKER: Thank you.

Dr. Oliver?

DR. OLIVER: Alyce Oliver, Augusta University. I voted no. In terms of what further

data is needed, since there were uncertainties about the effect size of the glucocorticoids, I would recommend specified steroid tapers in the arms, comparator arm and study arm; and then also a study looking solely at induction versus maintenance. Thank you.

DR. BECKER: Thank you.

Ms. Johnson?

MS. JOHNSON: This is Hetlena Johnson, and I voted yes. Although I do feel that more research and data and analysis of the infections should be made, I did vote yes.

DR. BECKER: Thank you.

Dr. Richards?

DR. RICHARDS: John Richards. I voted no. I previously voted no on the other questions; and again, I think just a more clearly defined study showing the specific indication and some more long-term, open-label data on the safety.

DR. BECKER: Thank you.

Dr. Shaw?

DR. SHAW: Hi. Pamela Shaw. I also voted

no. No additional comment.

DR. BECKER: Thank you.

Dr. Brant?

DR. BRANT: I voted yes. I agree with one of the other committee members that this may not be the ideal dose, but it was the dose that was studied, and it's probably a reasonable starting point, again, in very carefully selected patients.

DR. BECKER: And last but not least, Dr. Kraft?

DR. KRAFT: Walter Kraft. I voted yes. Also, I think there may have been some money left on the table in terms of optimizing the dose. But as has been mentioned, the label is driven by the dose that was tested. The dose that was tested, for the reasons I enumerated, is the appropriate one. That's all.

DR. BECKER: Thank you.

Okay. To summarize, for question 7, there were 10 yeses and 8 noes. Interestingly, I think people mentioned frequently the need for therapeutics for this indication and the need for

steroid sparing being a large reason for their vote for yes.

But a number of caveats were mentioned, including additional safety data to assess over time and potentially some additional studies to continue to fine-tune dosing over time as well. But this, again, I think further illustrates the complexity of the questions at hand.

So before we adjourn, does the FDA have any last comments that they would like to provide to the committee?

DR. GLASER: This is Rachel Glaser. On behalf of the entire FDA review team, I just want to extend my gratitude to the committee members for their participation in this meeting today, for staying till the very end.

We acknowledge the preparation that was required for this meeting, and not only reading the briefing documents but watching the prerecorded presentations. Your diligence and preparation was apparent, and we're greatly appreciative of your discussion, which is really helpful to us in our

decision making of this very important topic.

We also understand that all of you took away time from your busy schedules in this very challenging time. And again, a very special thanks to our chair, Dr. Becker, for running a very organized meeting in this virtual format, and thank you again on behalf of all of us here at FDA.

Adjournment

DR. BECKER: Thank you, Dr. Glaser.

I'd like to thank the FDA staff, and of course ChemoCentryx, both of whom provided a lot of detailed, wonderful information to the committee before this, including both written and recorded data, which is terrific.

I'd also like to thank all of the members of the public who presented their stories today. I think it really puts a face on the importance of the topic at hand; and particularly thank our outstanding panel of experts that were assembled to come and debate this today. The robust discussion was really outstanding and it really helped, I think, contribute towards a very deep and

thoughtful discussion, and hopefully that can be helpful for the FDA.

So thanks very much everyone and have a wonderful week, and right now we can adjourn the meeting. Thank you very much.

(Whereupon, at 5:11 p.m., the meeting was adjourned.)