FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC) MEETING

Virtual Meeting

Wednesday, October 26, 2022

9:00 a.m. to 5:29 p.m.

Meeting Roster

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Jessica Seo, PharmD, MPH

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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Volunteer and Advocate

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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

(9:00 a.m.)

Call to Order

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

My name is Julia Lewis, and I will be chairing this meeting. I will now call the October 26, 2022 Cardiovascular and Renal Drugs Advisory Committee meeting to order. Dr. Jessica Seo is the acting designated federal officer for this meeting and will begin with introductions.

Dr. Seo?

Introduction of Committee

DR. SEO: Good morning. My name is Jessica Seo, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

We'll begin with the standing CRDAC members. Ms. Alikhaani?

MS. ALIKHAANI: Good morning. I'm Jacqueline Alikhaani. I am a Los Angeles-based heart survivor, heart patient, and citizen scientist. I am a long-time volunteer with the American Heart Association and WomenHeart, and I also serve as an ambassador for PCORI, the Patient-Centered Outcomes Research Institute. I'm very happy to be here today; very honored to serve as a consumer representative.

DR. SEO: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: Good morning. Noel Bairey Merz, clinical and investigative cardiology Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles; delighted to be a member of this board.

DR. SEO: Thank you.

Dr. Butler?

(No response.)

DR. SEO: Dr. Butler --

(Crosstalk.)

DR. LEWIS: Dr. Butler, you're muted.

(No response.)

DR. LEWIS: Dr. Butler, you're muted.

DR. BUTLER: Javed Butler. I am a heart failure cardiologist at the Baylor Scott and White Research Institute in Dallas, Texas. I'm honored to be here today.

DR. SEO: Thank you, Dr. Butler.

Next is Dr. Cook.

DR. COOK: Thomas Cook, biostatistician and clinical trialist from the University of Wisconsin-Madison. Thank you.

DR. SEO: Thank you.

Dr. Kasper?

DR. KASPER: Ed Kasper, cardiologist, Johns Hopkins.

DR. SEO: Thank you.

Dr. Lewis?

DR. LEWIS: Dr. Julia Lewis, nephrologist, Vanderbilt University Medical Center.

DR. SEO: Thank you.

Next is Dr. O'Connor.

DR. O'CONNOR: Good morning. Dr. Christopher O'Connor, president of the Inova Heart and Vascular Institute, heart failure clinician and clinical trialist; privileged to be here. Thank you.

DR. SEO: And we have Dr. Thadhani.

DR. THADHANI: Good morning. Ravi Thadhani, chief academic officer at Mass General Brigham, nephrologist. Thank you.

DR. SEO: Next we have our temporary voting numbers, and we'll begin with Dr. Abbott.

DR. ABBOTT: Hello there. Kevin Abbott, NIDDK, urologist, program official. I also serve as the director of the United States Renal Data System. Thank you for me being able to participate today.

DR. SEO: Thank you.

Dr. Bagiella?

DR. BAGIELLA: Hi. Emilia Bagiella. I'm a professor of biostatistics and a clinical trialist at the Icahn School of Medicine at Mount Sinai in New York.

DR. SEO: Next is Dr. Cho.

DR. CHO: Leslie Cho, Cleveland Clinic, interventional cardiologist.

DR. SEO: Thank you.

Next is Mr. Conway.

MR. CONWAY: Paul Conway of Falls Church, Virginia. I serve as chair of Policy and Global Affairs for the American Association of Kidney Patients. I'm a 42-year kidney and heart patient with experience with anemia, dialysis, and transplant. Thank you.

DR. SEO: Dr. Nachman?

DR. NACHMAN: Good morning. Patrick Nachman. I'm a nephrologist at the University of Minnesota, and I'm director of the Division of Nephrology and Hypertension.

DR. SEO: Thank you.

Dr. Packer?

DR. PACKER: Milton Packer., a cardiologist, heart failure clinical trials, Baylor University Medical Center in Dallas.

DR. SEO: Dr. Parsa?

DR. PARSA: Hi. I'm Afshin Parsa. I'm a nephrologist and a scientific advisor and program director at the NIH.

DR. SEO: And Dr. Wang?

DR. WANG: Hi. Thomas Wang. I'm a cardiologist and chair of medicine at UT Southwestern Medical Center.

DR. SEO: Thank you.

We have our acting industry representative, Dr. Soergel.

DR. SOERGEL: Hello. David Soergel, head of Cardiovascular, Renal, Metabolism and Drug Development at Novartis.

DR. SEO: Thank you.

We'll now go to our FDA participants, and we'll begin with Dr. Joffe.

DR. JOFFE: Hey. Good morning. This is Hylton Joffe. I'm the director of the Office of Cardiology, Hematology, Endocrinology and Nephrology at FDA.

DR. SEO: Thank you.

Dr. Farrell?

DR. FARRELL: My name is Ann Farrell. I'm the division director of the Division of Nonmalignant Hematology.

DR. SEO: Dr. Wroblewski?

DR. WROBLEWSKI: Good morning. I am Tanya Wroblewski. I am the associate director of therapeutics in the Division of Nonmalignant Hematology.

DR. SEO: Dr. Penzenstadler?

DR. PENZENSTADLER: Good morning. Justin Penzenstadler, clinical reviewer.

DR. SEO: Thank you.

And Dr. Tran.

DR. TRAN: Good morning. My name is Van Tran, and I'm a statistical reviewer from the Division of Biometrics VII in the Office of Biostatistics.

DR. SEO: Thank you.

Dr. Lewis?

DR. LEWIS: 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 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. Jessica Seo will read the Conflict of Interest Statement for the meeting.

Dr. Seo?

DR. SEO: Thank you, Dr. Lewis.

Conflict of Interest Statement

DR. SEO: The Food and Drug Administration, or FDA, is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, or FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, or SGEs, 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 the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S. Code 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. Code 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 interest 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. Code 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 the discussion of new drug application, or NDA, 216951, for the hypoxia inducible factor prolyl hydroxylase inhibitor, daprodustat tablets, submitted by GlaxoSmithKline, LLC, for the treatment of anemia due to chronic kidney disease in adult patients not on dialysis and on dialysis. This is a particular matters meeting during which specific matters related to GlaxoSmithKline's NDA will be discussed.

Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. David Soergel is participating in this meeting as a non-voting industry representative, acting on

behalf of regulated industry. Dr. Soergel's role at this meeting is to represent industry in general and not any particular company. Dr. Soergel is employed by Novartis.

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. Lewis?

DR. LEWIS: We will proceed with FDA introductory remarks from Dr. Ann Farrell.

Dr. Farrell?

FDA Opening Remarks - Ann Farrell

DR. FARRELL: Good morning, and welcome, advisory committee members, GlaxoSmithKline, FDA

staff, and members of the public, to the Cardiovascular and Renal Drugs Advisory Committee meeting. My name is Ann Farrell, and I am the division director of the Division of Nonmalignant Hematology. Today we are going to discuss the agency's findings and concerns regarding the daprodustat application.

Daprodustat is proposed to treat the anemia due to chronic kidney disease in adults on dialysis and not on dialysis. The proposed dosing is oral, administered daily or 3 times a week. The mechanism of action is under review and is the hypoxia inducible factor prolyl inhibitor that is believed to lead to increased transcription of HIF-responsive genes, including erythropoietin and transferrin.

Since 1989, erythropoiesis stimulating agents have been approved to treat the anemia due to CKD. They're administered either intravenously or by subcutaneous injection. Over the years, there have been many revisions to the approved ESA labeling as a result of clinical trial information;

so several clinical trials have been conducted with the hypothesis that targeting a higher hemoglobin would result in better clinical outcomes and, unfortunately, all of the trials conducted have suggested the opposite, a worse outcome.

Therefore, the agency and the applicant have worked to improve the labeling to include a boxed warning for increased mortality and serious cardiovascular and thromboembolic events, as well as the revision to the dosing and administration section to include a recommended target hemoglobin level and a recommendation to discontinue if the hemoglobin doesn't respond adequately over a 12-week period.

Because of the safety issues that have arisen with the ESAs, the development of any agent to treat anemia due to CKD is predicated on the ESA. So all trials of new agents for the anemia CKD must achieve a similar target hemoglobin as the comparator and include a prespecified analysis of MACE, which is a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal

stroke. This is a slight departure from the typical MACE that is discussed in the Cardiovascular and Renal Drugs Advisory Committee.

Now the development programs of these agents are separate by the indication, i.e., the non-dialysis and the dialysis indications are usually separately developed, but they are supportive of each other. For daprodustat, we're focusing primarily on the two large clinical trials, the ASCEND-ND for patients not on dialysis, and the ASCEND-D for patients on dialysis.

These were two similar event-driven, international, open-label, randomized, parallel group trials in different CKD populations. Both trials compared daprodustat to ESA, and both trials had two co-primary endpoints, which had a noninferiority hypothesis testing. There was an efficacy endpoint, which was mean change in hemoglobin from baseline to weeks 28 to 52 and a safety endpoint time to first occurrence of adjudicated MACE.

The agency's review team concurred that both

trials established safety as well as efficacy on the predefined endpoint. The agency conducted additional secondary and exploratory analyses, and as a result, a couple of issues arose which we would like you to consider during your deliberations today. The ASCEND-ND trial had elevated estimated hazard ratios for myocardial infarction; stroke; thromboembolism, including vascular access thrombosis; acute kidney injury; hospitalization for heart failure; gastrointestinal erosions; and bleeding. In addition, the U.S. subgroup had higher hazard ratio estimates for the cardiovascular endpoints, except for stroke, than the non-US subgroup. In the ASCEND-D trial, there were elevated estimated hazard ratios for hospitalization for heart failure, as well as gastrointestinal erosions and bleeding.

To recap, the ASCEND-D and ASCEND-ND trials achieved their goals of demonstrating noninferiority to the ESAs on hemoglobin change. There was a similar rate of red blood cell transfusions on the treatment arm. There were no

other meaningful benefits established. Safety was noninferior to MACE by the prespecified analysis, but there was no superiority demonstrated in terms of safety to ESAs, which have a boxed warning for increased mortality and serious cardiovascular and thromboembolic events.

Also, warnings were hypertension, seizures, thrombotic events, including vascular access thromboses, and a recommended target hemoglobin, and a recommendation to discontinue the ESA if an inadequate response. Secondary and exploratory safety analyses suggest the potential for increased risk with daprodustat compared to the ESAs, particularly from the non-dialysis population and the U.S. subgroup.

We think the oral formulation may provide convenience, but its usefulness is less clear for the hemodialysis population, which is treated in clinic. We see the potential for increased harm in the U.S. subgroup and in the non-dialysis population. We think safety monitoring may be more challenging for those patients who are not seen

frequently, those on home dialysis, including peritoneal dialysis and the non-dialysis population.

I'm going to read the discussion and voting questions.

Number 1. Discuss the benefits of daprodustat in adults with non-dialysis-dependent chronic kidney disease.

Number 2. Discuss the benefits of daprodustat in adults with dialysis-dependent CKD.

Number 3. Discuss the risks of daprodustat in adults with non-dialysis-dependent CKD, including cardiovascular harm, gastrointestinal erosions, hemorrhage, and acute kidney injury.

Number 4. Discuss the risks of daprodustat in adults with dialysis-dependent CKD, including the risks of heart failure, gastrointestinal erosions, and hemorrhage.

These are the two voting questions.

Question 5. Do the benefits of daprodustat outweigh its risk for the treatment of anemia due to CKD in adults not on dialysis? Provide the

rationale for your vote. If you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment.

Six. Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults on dialysis? Provide the rationale for your vote. If you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment. Thank you very much.

DR. LEWIS: 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 applicant such as consulting fees, travel expenses, honoraria, and interest in the applicant, 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 any 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 GSK's presentations.

GSK members?

Applicant Presentation - Janet van Adelsberg

DR. VAN ADELSBERG: Good morning, members of the Cardiovascular and Renal Drugs Advisory Committee and the FDA. I'm Janet van Adelsberg, vice president of research and development at GSK, and leader of the daprodustat team. As a former academic nephrologist, I am particularly pleased to be bringing a new treatment for patients with

anemia of chronic kidney disease.

I'd like to thank the advisory committee and the agency for the opportunity to present our clinical development program for daprodustat. Daprodustat is a new treatment for patients with anemia due to chronic kidney disease or CKD. Unlike the current treatment options that are administered parenterally, daprodustat provides patients and their physicians with an oral treatment option to individualize care and meet treatment needs.

Daprodustat is a member of a new class of drugs, the hypoxia inducible factor prolyl hydroxylase inhibitors, which for brevity we'll refer to as HIF-PHI. Daprodustat has a short half-life of 1 to 4 hours and can be administered once daily or 3 times per week. The effective dose range is 1 to 24 milligrams daily or 2 to 48 milligrams 3 times a week, with dose adjustments being made based on hemoglobin levels. There is no need to adjust the dose for dialysis or for concomitant use with phosphate binders and oral

iron.

Let me review our clinical development program. We conducted a robust evaluation of efficacy and safety in five pivotal global phase 3 studies, two studies in patients not on dialysis and three studies in patients on dialysis. The majority of these studies were active controlled against the standard of care, erythrocytosis stimulating agents or ESAs.

ASCEND-NHQ was the only double-blind, placebo-controlled study in our phase 3 program. It assessed the effects of daprodustat on hemoglobin, quality of life, and safety. ASCEND-ND provides the primary evidence of efficacy and safety in patients not on dialysis. This was a large cardiovascular event-driven, open-label study. In this study, patients could have been either previous ESA users or non-users.

ASCEND-ID enrolled incident dialysis patients who had recently started or were about to start dialysis. As patients with CKD receiving hemodialysis are typically treated 3 times a week

at a dialysis center, the ASCEND-TD study assessed daprodustat administered 3 times per week. And finally, the primary study in dialysis patients, ASCEND-D, was a large event-driven study designed similarly to ASCEND-ND. Patients on both hemodialysis and peritoneal dialysis were enrolled in this trial.

We have performed a number of prespecified and post hoc analyses, which are in your briefing books and also in peer-reviewed publications. The primary evaluation of efficacy and safety was an intention-to-treat analysis or ITT. We performed a number of on-treatment analyses of safety using different definitions for the end of the on-treatment period. The rationale for these analyses will be described later in our presentation.

Finally, for some analyses of general safety, modified intention-to-treat, or mITT, analyses were performed. These excluded the few patients who were randomized but who never received a dose of study medication.

In the FDA briefing book, you will have seen that FDA speaks to the adequacy of the design and the conduct of our pivotal study. The primary efficacy and safety objectives of the studies were met. FDA noted that the similarity in hemoglobin response would translate into similarity in the need for red blood cell transfusion, which is an accepted benefit of anemia treatment. Our agenda will therefore be focused on the discussion points raised by FDA.

First, Dr. Kirsten Johansen will discuss the unmet need for treatment of both dialysis and non-dialysis patients with anemia of CKD; then Dr. Alex Cobitz will present the clinical trial results, including a discussion of quality of life established by the SF-36 vitality domain endpoint in the placebo-controlled study.

Next, Dr. Kaivan Khavandi will review the cardiovascular safety, focusing on endpoints used for the assessment of cardiovascular safety subgroup analyses and heart failure; then Dr. Kevin Carroll will discuss the on-treatment analyses that

I mentioned previously, followed by Dr. Heather Stein, who will review the general safety findings from the ASCEND program, focusing on gastric erosions and acute kidney injury. Finally, Dr. Ajay Singh will provide his clinical perspective and conclude our presentation.

The ASCEND clinical studies had extensive scientific and academic oversight with an executive steering committee and steering committee both chaired by Dr. Singh. We also have additional experts with us today to help answer your questions. All external experts have been compensated for their time and expenses involved in today's meeting.

Thank you. I'll now turn the lectern over to Dr. Johansen.

Applicant Presentation - Kirsten Johansen

DR. JOHANSEN: Thank you. I'm Kirsten Johansen. I'm the director of the nephrology division at the Hennepin County Medical Center and professor of medicine at the University of Minnesota. I've been studying quality of life and

physical functioning in patients with CKD for more than 25 years. Clinically, my focus is on patients with advanced CKD and those treated with dialysis. In my discussion today, I'll focus on anemia of CKD and the unmet need, despite current standard of care, for treatment option that's effective and more accessible. Let me start with some background.

CKD afflicts about 1 in 7 adults in the general U.S. population or approximately 37 million people. Anemia is a common complication for patients with CKD, and its prevalence increases with advancing kidney disease. Overall, anemia of CKD affects almost 5 million patients, and almost 90 percent of patients receiving dialysis have anemia, so it's clearly a common occurrence and a challenge we face when treating our patients with kidney disease.

Specifically, the prevalence of anemia among patients with CKD in the U.S. increases from just over 18 percent in patients with stage 3a CKD to almost three-quarters of patients with stage 5 CKD.

Additionally, anemia and increasing severity of anemia are associated with reduced quality of life and with higher rates of cardiovascular comorbidity, hospitalizations, and mortality.

Introduction of ESAs improved health-related quality of life among patients with anemia and end-stage kidney disease. Unfortunately though, despite improvements after the introduction of ESAs, patients with anemia of CKD still report low quality of life, and fatigue is a particularly bothersome symptom.

Here you see the vitality score from the SF-36, which is used in many populations to assess fatigue. The dark blue bar shows the results from an observational study of patients with anemia of CKD and with a hemoglobin of less than 11 from seven clinical sites in the U.S. and Canada. The light blue bar shows the U.S. healthy population, and you can see that the general population has a score of roughly 50 percent higher than CKD patients. To further contextualize this, the red and teal bars show the scores for heart failure and

COPD patients generated from the disease-specific benchmark study.

I think we all recognize that dialysis patients have a low quality of life, but we may not be aware that patients with anemia and non-dialysis-dependent CKD have so much fatigue. Furthermore, their ability to engage in daily activities and their quality of life is affected not only by their fatigue, but also by other symptoms like shortness of breath and cognitive impairment that are related to their anemia.

Part of the reason why quality of life might be low is because patients are being inadequately treated. Currently, available therapies are injectable and often require in-clinic administration and cold chain storage to be burdensome to patients and clinics. Patients also report that they prefer oral treatment to avoid painful injection and for convenience.

But it goes way beyond convenience for many patients. For example, access to in-clinic treatment with ESAs is more difficult for people

who live far away from the clinic, or live in rural areas, or who work or rely on working caregivers for transportation. I work in a safety net hospital, and my patients' safety is challenged regularly. The only option for most of them is to come into the clinic for injections to treat their anemia.

I take care of an older woman with stage 5 CKD with a hemoglobin of 8.3 and felt fatigued at a recent clinic visit. She had missed ESA injections because her daughter couldn't get off work to take her to the clinic, and because of language and financial issues, she couldn't get there on her own. I tell you about this patient because she's not an outlier. Even when we have effective treatment available, if the delivery is inconvenient, many patients will not receive adequate, timely care.

This gap in anemia treatment might not have occurred if this patient had been able to get her treatment at home and her hemoglobin monitoring closer to home, rather than having to come all the

way downtown to our nephrology clinic. This is not only a problem for patients with non-dialysis-dependent CKD, but also affect patients receiving dialysis.

Since 2011, the percentage of patients on home dialysis has been increasing, and new payment models have further incentivized providers to offer home dialysis began in the last two years. In 2019, over 13 percent of prevalent dialysis patients received dialysis at home, and in some areas the percentage is even higher. As shown in dark blue on the map, in some regions as many as one 1 in 4 patients were on home dialysis, and this is particularly apparent in rural areas where access to routine care is burdensome.

These patients face the same barriers related to injectable therapy as non-dialysis patients. Although use of ESAs is much higher in the home dialysis population than in those not on dialysis, percentage is lower than for patients on in-center hemodialysis. And although many patients receive monthly injections that coincide with

clinic visits, there are others who need more than one in-clinic injection per month, which is time-consuming and burdensome, especially for patients living in rural areas.

Let's turn to the data on treatment. Unfortunately, the predominant treatment for anemia of CKD is currently transfusion. This slide shows the frequency of use of ESA, iron, and transfusion over a one-year period among younger commercially insured patients with stage 3 to 5 non-dialysis-dependent CKD on the left and Medicare-covered older patients on the right.

As you can see, in both younger commercially insured and older Medicare patients, red blood cell transfusions were used more than ESAs and iron to treat anemia. Only 11 percent of the commercially insured and 13 percent of Medicare patients who are anemic received ESA treatment, and this is consistent with evidence from other studies. The higher rate of transfusion than of treatment with the currently approved injectable therapy clearly indicates that better medical options are needed.

This slide shows that the more anemic patients with CKD are, the more likely they are to receive transfusions. In this study of stage 3 to 5 CKD patients with Medicare Advantage coverage, there was an overall rate of 14 transfusions per 100 person-years, and there was also a strong association between hemoglobin and rate of transfusion. Of course those with very low hemoglobin were much more likely to receive transfusion and may have been bleeding, but I'd like to focus on those with hemoglobin between 8 and 9 or 9 and 10 because it's not at all uncommon to have patients with hemoglobin in these ranges at routine clinic visits. Those with a hemoglobin of 9 to 10 are almost twice as likely to receive a transfusion as those with a hemoglobin between 10 and 11, and those with a hemoglobin between 8 and 9 were 4 times more likely.

So why is transfusion a problem for patients with CKD or end-stage kidney disease? Initial risks of transfusion such as infections and transfusion reactions are similar as for non-CKD

patients, but in addition there are some risks that are heightened by CKD, including hyperkalemia and volume overload. But perhaps the biggest concern relates to alloimmunization or sensitization.

The risk of sensitization is high even from a single transfusion event. This risk is not trivial, nor is the potential impact on patients' candidacy for a kidney transplant. Sensitized patients are less likely to get a living donor transplant, and thus often wait longer on dialysis, which has a higher mortality. Those who do receive a kidney transplant are at higher risk of rejection, so they often receive higher doses of immunosuppression, which increases their risk of infection and malignancy.

For example, I take care of a patient who's been waiting five years for a kidney transplant who had previously had a transfusion event. She was finally called in to receive a transplant, but ended up being cross-match positive and wasn't able to receive that kidney. That was six months ago, and she's still awaiting a transplant.

Given all the challenges I've outlined, it is apparent that a large subset of the CKD population suffers from anemia, with many patients not receiving injectable therapies. Undertreated patients suffer from low quality of life and are at higher risk of receiving transfusions, especially as anemia becomes more severe. There are significant logistical challenges and barriers to parenteral treatment, and they fall more heavily on our most vulnerable patients.

Although I focused on patients not on dialysis, the same issues apply for patients on home dialysis. Given that there's a major initiative to increase home dialysis in the U.S., this population is expected to increase in the coming years. There remains a significant need for novel, accessible treatment options for this patient population that can be provided with appropriate monitoring and clinical oversight by healthcare providers like me.

I'll now turn over the presentation to Dr. Cobitz.

Applicant Presentation - Alexander Cobitz

DR. COBITZ: Thank you.

Good morning. I'm Dr. Alex Cobitz, senior medical director at GSK, and I am pleased to share the clinical trial results for daprodustat. I'll begin by describing the study endpoints.

The primary efficacy endpoint, change from baseline in hemoglobin to the average of the values in the evaluation period for daprodustat versus the control group, was consistent across all five phase 3 studies. Other secondary efficacy endpoints include transfusion and quality-of-life measurements.

Adjudicated MACE, defined as a composite of first event of either all-cause mortality, myocardial infarction, or stroke, was the co-primary safety endpoint in the ASCEND-D and ND trials. The principal secondary safety endpoints common to both studies were MACE plus thromboembolic events and MACE plus hospitalization for heart failure. We incorporated MACE, including the all-cause mortality component, as the safety

co-primary and as the basis for the relevant principal secondary endpoint to effectively address disease-free survival. The ASCEND-ND also contains the objective principal secondary safety endpoint of time to chronic kidney disease progression.

Now turning to the results, ASCEND-NHQ in patients not on dialysis was the only placebo-controlled trial in the development program. Daprodustat met NHQ's primary endpoint, demonstrating superiority over placebo in the change in hemoglobin from baseline to the evaluation period of weeks 24 to 28, achieving and maintaining a mean hemoglobin within the target range of 11 to 12 grams per deciliter by 16 weeks. Thus, it is not surprising that a 3- to 4-fold greater percentage of placebo-treated patients received a transfusion compared to daprodustat patients.

Turning to quality of life, at week 28, daprodustat was superior to placebo in the mean vitality score change from baseline. The respond analysis of patients achieving a 6-point minimal

clinically important difference reveals that 58 percent of daprodustat patients meaningfully improved fatigue, with a significant difference from placebo of 13 percent.

Let's now turn to the active-controlled studies. The major cardiovascular exclusions are listed here. Across all trials, patients remained in the study even if they discontinued randomized treatment, and for the ND study, patients remained in the study even if they initiated dialysis. With respect to study populations, more than 6,000 patients were treated with daprodustat with nearly 6700 person-years of exposure. Notably, nearly 1500 patients received daprodustat for at least two years along a robust assessment of long-term safety for a therapy that is intended to be used in the chronic disease setting.

Demographics and baseline characteristics were generally similar across treatment groups and representative of the U.S. population with CKD. Renal characteristics were also generally similar between treatment groups. Baseline CV

characteristics were well-balanced and generally comparable between the treatment groups within each study. As expected, patients frequently had a history of hypertension, diabetes, and cardiovascular disease.

Here we see the baseline characteristics of the U.S. patients. Approximately one-third of the patients in the U.S. region were African American, paralleling the ratio of those afflicted in the U.S. Within the U.S. subpopulations in ASCEND-ND, there are some important imbalances. These are heart failure, hospitalization within 6 months of screening, and baseline CKD in both stages 2/3a and 5. These could confer bias against daprodustat.

Turning to disposition, study completion was high across all four studies and vital status was captured in 98 to 100 percent of patients. Within each study, a similar proportion of patients across arms discontinued study medication. This includes patients who died on therapy. These rates in the CV outcomes trials when adjusting for duration are

similar to other CKD outcomes trials with no fixed follow-up. The time to discontinuation of randomized treatment was also similar between groups. Notably, 73 and 77 percent of the on-study follow-up was on treatment for the ASCEND-D and ASCEND-ND, respectively. In the ASCEND-ND study, more than a third of patients transitioned to dialysis and remained in the study.

Now let's look at the results. The FDA briefing document notes that the hemoglobin efficacy is undisputed, thus I will not spend a great deal of time reviewing. However, the overall conclusion is that in each study, daprodustat was noninferior to ESA for change from baseline in hemoglobin.

More specifically, the between group difference of daprodustat minus control for change from baseline to the evaluation period demonstrates noninferiority; that is, the lower bound of the 95 percent confidence interval was above the predefined noninferiority margin of negative 0.75 grams per deciliter. These findings are

consistent with the observation that the proportion of patients with a first occurrence of transfusion during the on-treatment time period was similar across arms within each study.

So in summary, daprodustat met the primary hemoglobin endpoint in all five pivotal studies, showing superiority to placebo and noninferiority to ESA, achieving and maintaining mean hemoglobin within the target range regardless of dialysis status or prior ESA use. Daprodustat was superior to placebo in improving patients' fatigue, as measured by the SF-36 vitality score, looking at both treatment difference from baseline and responders. Patients treated with daprodustat had fewer transfusions compared to placebo, a major goal of treating patients with anemia of CKD.

Now, I'd like to thank you for your attention and will turn the presentation over to Dr. Khavandi.

Applicant Presentation - Kaivan Khavandi

DR. KHAVANDI: Good morning. My name is Kaivan Khavandi, and I'm vice president of clinical

development at GSK. I'm pleased to be here today to review the safety results, and we'll start by discussing the cardiovascular safety. Before presenting the data, I'd like to first take a moment to highlight the areas I will be focusing on.

In ASCEND-ND and ASCEND-D, both studies met the primary safety endpoints for MACE, demonstrating that daprodustat is noninferior to the standard of care ESA comparators based on the prespecified ITT analyses as agreed with FDA. Consistent findings were observed for the principal secondary endpoints which assess atherosclerotic risk and survival through MACE, but also include outcomes for thromboembolic events and heart failure through expanded MACE composites.

However, we are aware that the FDA considers additional elements of cardiovascular safety important for discussion. These include exploratory or post hoc analyses, which we will present today alongside the primary and principal secondary endpoints that the studies were designed

to formally test.

To evaluate cardiovascular safety, we studied major adverse cardiovascular events, or MACE, which was the primary safety endpoint in the two large outcomes trials. This was defined as a composite measure of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke.

The composition of the MACE endpoint was discussed with FDA at study inception, with the recommendation and agreement to include all-cause mortality to assess survival. This is consistent with all landmark outcome trials in anemia of CKD, and is by design different from studies assessing cardiovascular mechanisms for efficacy and CV risk reduction, where CV mortality is often used.

However, in assessing safety of a novel investigative product and in a population where deaths from non-CV causes are collectively greater than CV deaths, as the case here, all-cause mortality is the most appropriate approach and permits an assessment of MACE-free survival.

An external, independent, clinical events

classification group from Duke blinded to treatment allocation adjudicated all events that might have constituted MACE or other CV events using prespecified diagnostic criteria. The studies were designed to assess noninferiority information using the ITT approach, which is interchangeably referenced in the FDA briefing documents as on-study. This preserved the balance afforded by randomization and captures all events from randomization to the date of study completion or withdrawal. Deaths occurring after this point were also included. This approach was therefore able to capture events with longer latency, which is important in a real-world setting.

The statistical model used was a Cox proportional hazards regression model adjusting for treatments and randomization stratification factors to estimate the hazard ratio and two-sided 95 percent confidence intervals Noninferiority was established if the upper limits of the two-sided 95 percent confidence interval for the hazard ratio was less than the prespecified margin

of 1.25. This noninferiority margin was supported by reviewed evidence from relevant historical RCTs with ESAs and agreed with FDA.

Now, let's take a look at the results for MACE, where we will review data for the two outcome studies side by side. In the ASCEND-ND trial on the left and ASCEND-D on the right, daprodustat was noninferior to the respective ESA control for the co-primary endpoint of time to the first MACE. In patients not on dialysis, the hazard ratio was 1.03, and in patients receiving dialysis, the hazard ratio was 0.93.

In both studies, the upper bound of the 95 percent confidence interval was lower than the prespecified margin of 1.25, and you can see visually here that the cumulative incident curves for each arm completely overlapped in both studies.

On the next slide, we will look at these events in the other phase 3 studies. Although the fixed duration studies were not powered for treatment group comparisons to MACE, the absolute rate difference for cardiovascular events per

100 patient-years was similar between daprodustat and the ESA treatment groups in both ASCEND-ID and TD, as shown in the middle of the figure. Additionally, in the placebo-controlled NHQ study, shown at the bottom of the slide, a lower incidence in first occurrence of MACE was observed in participants on daprodustat compared to the placebo control.

As detailed in our briefing book for both ASCEND-ND and D, the risk of MACE was generally consistent across the 20 prespecified subgroups. There was some heterogeneity across geographic regions with significant interaction across the five regions shown on the slide. Hazard ratio point estimates for these regions are distributed either side of 1, and with the exception of Asia-Pacific, include highly overlapping confidence intervals.

Additional to general limitations of subgroup analyses, in the setting of noninferiority and an overall hazard ratio close to 1, relevant here, it would be highly improbable for all

subgroups to be either positive or negative, but instead expected to be distributed either side of 1, as seen here. Instances of greater variability would also be expected surely as a result of chance variability when looking at 20 subgroups.

Nevertheless, acknowledged there can be differences in patient profiles across different regions, we will next look at other prespecified subgroups to determine if there was any corroborating pattern based on relevant clinical characteristics.

So when we look at those with prior history of cardiovascular disease, diabetes, or those in older age groups, we see no evidence of any treatment group difference across these phenotypes, indicating that any variability in the U.S. subgroup is unlikely due to any intrinsic difference in how the U.S. population responds to daprodustat compared to other regions. Similarly, external factors, such as those related to healthcare practice in the U.S., are unlikely, as we do not see the same direction of variability in

similar healthcare settings such as Western Europe.

The greater proportion of heart failure in advanced CKD at baseline may have been relevant in the U.S., as participants randomized to the daprodustat arm would have had greater background risk irrespective of drug. However, overall, the subgroup data we observed are entirely consistent with expected chance variability. Without any plausible explanation for differences, the most precise estimate of a treatment effect for any subgroup is derived from the estimate of the hazard ratio to the overall trial.

Next, we will look closer at individual component events for MACE in each outcome study. These are all-cause mortality, MI, and stroke. We'll start with all-cause mortality, again with ASCEND-ND on the left and ASCEND-D on the right.

Adjudicated all-cause mortality was similar between treatment groups in both studies. With respect to the cause of death, there were more non-CV than CV deaths in both studies. Exploratory post hoc analyses for CV MACE have been presented

extensively in the FDA briefing document, which replace the prespecified MACE components of all-cause mortality with CV mortality. We previously described the importance of all-cause mortality in a comprehensive assessment of risk, and I'd now like to take a moment to describe the significant and real issues that arise when looking at this subgroup of events rather than the prespecified composite.

The first relates to the magnitude and categorization of deaths with an undetermined cause. You can see in the bottom row that this represents a significant number of deaths, which were particularly prominent in the ESA arm for ASCEND-ND, representing almost a quarter of the patients who died, which is more than those from CV causes.

Analyses of CV mortality do attempt to identify patients with presumed CV or presumed sudden deaths from this set, but this represents clear challenges and uncertainty in adjudication, not consequential in the prespecified primary

analysis with all-cause mortality but problematic in these post hoc assessments. Truncating the prespecified composite endpoints in this way therefore results in a modest set of events and with inference that is sensitive to the significant number of undetermined and unknown deaths.

Additionally, censoring non-cardiovascular deaths and deaths of unknown cause makes the implausible assumption that all these deaths are random and entirely unrelated to the patient's disease status. This informative censoring prohibits a patient-centric assessment of risk, as the safety of the drug takes into consideration only a single cause of death, entirely ignoring all others. This is particularly problematic in the ASCEND population where the majority of deaths were non-cardiovascular or unknown.

Given the substantial limitations, GSK strongly disagrees with the suggestion that CV MACE may provide a better estimate of risk, and continue to consider the prespecified primary safety analysis with MACE, using all-cause mortality as

the most objective and precise means to evaluate clinically important risks, including cardiovascular risk and survival.

Now turning to myocardial infarctions, the proportion of patients with an adjudicated fatal or nonfatal MI was generally similar between treatment groups in each of the studies, with absolute treatment rate differences that were small. The hazard ratio was 1.06 in the non-dialysis study and 0.81 in the dialysis study.

Next, we will look at results for the components of stroke. The hazard ratio for stroke was 1.33 in the non-dialysis study and 0.84 in the dialysis trial. You will see that the number of patients who experienced the fatal or nonfatal stroke in each study was small, with event numbers favoring daprodustat in ASCEND-D and ESA in ASCEND-ND.

The hazard ratio of 1.33 in ASCEND-ND is noted but relates to a small number of events, 45 compared to 34 patients, with wide confidence intervals across unity and an absolute rate

difference of 0.31 per 100 patient-years. This observation must also be considered against the results from ASCEND-D, where a similar magnitude of difference is seen in the opposite direction.

In the next slide, we will look at the totality of stroke data from across the program. This figure shows the absolute rate difference per 100 person-years for stroke across all the active-controlled studies. The stroke rate in ASCEND-ID in incident dialysis patients was consistent with the large ND and D outcomes trials, with all three studies showing a minimal variation in point estimates around unity. The small ASCEND-TD study with dialysis patients dosed 3 times per week was the exception.

Of note, in ASCEND-TD there were zero strokes in the ESA arm, which is unexpectedly low based on rates reported in other ESA trials. The unequal randomization schedule in this trial resulted in only 137 participants in the control group, which is grossly underpowered for any risk assessment for stroke. Across the nearly 3,000

participants evaluated in ASCEND-D, which was conducted in a similar population, there was a lower number of stroke events with daprodustat compared with ESA. Nevertheless, an in-depth review of stroke data from ASCEND-TD was performed and showed no obvious pattern in time of onset, no trend in hemoglobin increase prior to events, and no dose-dependent response.

Therefore, considering the totality of data across the ASCEND program, and with fewer stroke events in ASCEND-D, where the burden of stroke is greatest and therefore the setting expected to be most sensitive to the treatment effects, the evidence does not support any increased risk of stroke with daprodustat compared to ESAs.

Next, we will discuss the MACE-related principal secondary endpoints. The cardiovascular outcomes trials included two principal secondary endpoints, which were tested for superiority. These assessments were designed as composites of MACE but expanded to include the risk of other important aspects of safety. The composite

endpoint for time to first MACE, or thromboembolic events, provides an assessment for risk of thromboembolism, which included DVT, pulmonary embolism, and vascular access thrombosis, inclusive of general CV risk and survival. This endpoint was chosen over thromboembolism alone to overcome the competing risk that individual endpoints are otherwise subject to.

To illustrate this, in an assessment of TEE by itself, a fatal thrombotic stroke, for example, would be ignored, whilst an uncomplicated DVT would be captured in the event counts. If these events are spread across two treatment groups, the analysis would conclude that the less severe thrombotic events infers greater risk from drug, as the fatal event will be censored. The MACE-plus composite approach overcomes this and provides a more methodologically correct and patient-centric assessment of risk. The incidence of this composite endpoint was statistically similar between treatment groups, and so the results did not meet its superiority.

We will now proceed to describe events for components of the composite. Consistent with published regulatory guidance, these data are considered descriptive and not intended to alter key interpretation, determined from the adequately powered and multiplicity adjusted composite endpoints. As seen in the bottom row of the table, when looking at thromboembolic events as part of the composites, compared to the ESA comparator, we see a higher number of events in the daprodustat arm in ASCEND-ND and a lower number in ASCEND-D.

Next, when we look at thromboembolic events as a stand-alone endpoint, it becomes evident that the hazard ratio in ASCEND-ND not favoring daprodustat is derived from a very small number of events. In comparison, the rate difference in ASCEND-D, which favored daprodustat, was relatively greater. It's also notable how few thromboembolic events there are in the ND study overall, which we will examine further in the next slide.

Looking at deep vein thrombosis and pulmonary embolism together as venous

thromboembolism, there was a similar incidence between treatment groups in both studies. In the bottom right, we see the remaining components of the composite, vascular access thrombosis, or VAT. The first thing to note here is that there are almost 5 times more VAT events in ASCEND-D compared with ND. This is to be expected, as only a small minority of patients had vascular access at baseline in ASCEND-ND. So the assessment of VAT is not a randomized comparison in the study, but instead relates to those patients with access created during the course of the trial as a result of various individual patient factors.

These events will therefore also include primary excess failures known to be driven by factors entirely unrelated to thrombotic risk or any drug effect. In contrast, in ASCEND-D, nearly all patients were on hemodialysis enrollments, therefore with vascular access permitting a robust assessment of any treatment risk on VAT. With this background, we see 30 more VAT events with daprodustat compared with the comparator in

ASCEND-ND, but 33 fewer events with daprodustat in ASCEND-D.

Data from across the ASCEND program provide evidence to support no increased risk of thromboembolic events with daprodustat compared with standard-of-care controls, with a lower percentage of thromboembolic events observed with daprodustat in all pivotal studies other than the ND trial, and in that study only a minority of participants had vascular access, resulting in very few events and a small rate difference between treatment groups.

MACE or hospitalization for heart failure was the other principal secondary endpoint in the trials, and results for this composite did not meet superiority, with data showing a lower number of events in the daprodustat group in ASCEND-D and a higher number in ASCEND-ND. When reviewing the breakdown of this composite, it becomes evident that the imbalance in ASCEND-ND, in the bottom-left of the table, results from hospitalizations for heart failure.

When assessing recurrent events, which is important in this population, where repeat hospitalization is not uncommon and represents a significant measure of morbidity, we observed that the findings remain consistent with assessment of first events with negative binomial analyses performed post hoc, reporting a relative risk favorable to daprodustat in ASCEND-D, but favoring the ESA comparator in ND

When evaluating hospitalization for heart failure as a stand-alone endpoint, we see a higher number of events with daprodustat compared with control in both studies, 25 more events in ASCEND-ND and 11 more in ASCEND-D. Of note, the mortality components of the composite were similar between treatment groups in both studies.

Assessing recurrent events with a dialysis study on the right, we see no imbalance between treatment groups for repeat hospitalization for heart failure. In the non-dialysis population on the left, we observed that the imbalance in first events for hospitalization are preserved when

assessing recurrent events. Although confidence intervals for all prespecified assessments include unity, observations in the non-dialysis population give plausibility to potential treatment effects and prompted additional post hoc analyses to evaluate any risk specific to heart failure.

We must, again, consider the critical importance of competing risks, as analyses of hospitalization for heart failure censor patients at death, which overlooks the very real possibility that these deaths may in fact relate to underlying heart failure. This is particularly important in the ASCEND population where the underlying risk of death will exceed the risk of decompensation or cardiac pump failure.

So here we present analyses that adopt the approach precedented in outcome studies in CKD, as well as heart failure trials in populations with anemia such as red HF, using the composite endpoint of all-cause mortality or hospitalization for heart failure; and what we see is that in ASCEND-D on the right, time to first occurrence to the composite of

mortality or hospitalization for heart failure was similar for daprodustat and ESA, but in ASCEND-ND on the left, there were more events observed in the daprodustat arm. Of note, in ASCEND-ND, there was no difference in the mortality components of the composite, whilst in ASCEND-D, there were 14 fewer deaths in the daprodustat arm compared to the ESA control.

To further characterize heart failure outcomes, we identified a clinically recognizable subgroup of patients with a medical history of heart failure. This represented approximately 13 percent of the study population in ASCEND-ND and 17 percent in ASCEND-D. These patients would be expected to be most sensitive to any treatment risk for heart failure complications, and therefore post hoc analyses were performed using these subgroups.

Here we will look at data in the overall population and by subgroups with a history of heart failure. The top panel represents data for hospitalization for heart failure when assessed

alone, and in the bottom panel, with part of the composite endpoints with all-cause mortality. In a dialysis study, shown in this slide, we see there is no increased risk of heart failure with daprodustat in the overall population when accounting for survival, illustrated by the black line in the bottom panel, and this remains consistent with recurrent event analyses, shown with gray lines in the second rows of each panel.

When we then look at outcomes based on a history of heart failure, we can see that in those without heart failure, represented in blue, there is no treatment group difference. Next, in those with a history of heart failure, whilst there was a higher number of events with daprodustat when assessing hospitalization data in isolation, the green line in the top panel, there was a higher number of deaths in the ESA comparator arm, which in this subgroup with heart failure could very reasonably represent fatal complications related to heart failure risk. So in the bottom panel, when accounting for this clear competing risk of death,

we again confirm that there is no difference in hospitalization-free survival even in those with a history of heart failure.

Now, moving to the non-dialysis study, again, with data on hospitalization for heart failure alone at the top and for the composite endpoint at the bottom, in the overall population, there was a higher number of the composites of mortality or hospitalization for heart failure with consistent observations when assessing recurrent events.

However, when we look at outcomes based on whether there was heart failure at baseline, this imbalance was not apparent in the population without a history of heart failure, represented in blue, where there was no difference in hospitalization-free survival, and therefore reflecting no increase in incident heart failure.

So it becomes apparent that the imbalance observed in the overall population is derived from those 13 percent of patients in the study, represented in green, who had heart failure at

study enrollments. Here the hazard ratio for the composite endpoint is 1.2 with 28 more events in the daprodustat arm, driven largely by hospitalization for heart failure.

Given these observations, we were interested to look at outcomes for other CV endpoints in ASCEND-ND, evaluating those 87 percent of patients in the study who did not have a history of heart failure. Here we can see that for MACE, its components endpoints and the heart failure assessments already described, or hazard ratio point estimates, are near unity with the exception of stroke, but this relates to 5 events across nearly 3,350 participants, so it's not considered a true treatment group difference.

This analysis also illustrates the interdependence of these components or individual endpoints, where exclusion of a single small subset of the population changes the hazard ratio point estimate across all endpoints. This helps demonstrate the rationale and importance of looking at the prespecified composite endpoints when

interpreting study results, rather than considering that each endpoint represents an independent assessment of risk.

In summary, across both populations, the ASCEND outcomes trials provide significant evidence to support that there is no increased risk for incident heart failure with daprodustat. This is additionally supported by a lack of any nonclinical findings for cardiac toxicity, no adverse changes on echocardiogram in phase 2 studies in both hemodialysis and those not on dialysis, and with no plausible mechanism to direct myocardial injury.

In the dialysis population, even when looking at those with pre-existing heart failure, there is no increased risk for adverse heart failure outcomes when accounting for survival. However, in the non-dialysis population with a history of heart failure, there was an increased risk in hospitalization for worsening heart failure.

Of note, post hoc analyses indicate that this subgroup of participants may have contributed

to the higher hazard ratio point estimates observed for other endpoints in the ND trial overall. Although noninferiority was still established with the ITT population, when we evaluate those without a history of heart failure, we see hazard ratios near and some below unity across all of the CV endpoints in ASCEND-ND.

In a clinical setting, this vulnerable group of patients are at a high underlying risk of decompensation and require close monitoring of their weight and fluid status as part of standard care. Measures to mitigate any risk of daprodustat in this subgroup of patients, who can be readily identified as demonstrated by medical history in the trial, will be discussed later in the presentation.

I will next introduce the topic of on-treatment for MACE outcomes. In the top panel, we have MACE results using the primary intention-to-treat safety analyses and underneath for the supplementary on-treatment analyses. We can see that on the right-hand side of the slide,

the on-treatment analysis for first occurrence of MACE was similar to the primary ITT analysis in ASCEND-D, with hazard ratios of 0.96 and 0.93, respectively. However, in ASCEND-ND, the on-treatment results for time to first MACE was not consistent with the primary ITT analysis, with an on-treatment hazard ratio of 1.4 compared with the primary ITT analysis of 1.03.

I will now hand over to Dr. Kevin Carroll, an expert independent statistician and member of the executive steering committee for the ASCEND program, to discuss the reason for this discrepancy in ASCEND-ND.

Dr. Carroll?

Applicant Presentation - Kevin Carroll

DR. CARROLL: Thank you, Kaivan.

In the next few minutes, I wanted to address the important issue of differential dosing frequency in randomized-controlled trials and discuss how this can seriously bias on-treatment analyses. As has already been said, the prespecified primary analysis of MACE in ASCEND was

intent to treat, which FDA refers to as on-study. The ITT analysis, which was agreed with FDA, fully respects the randomization and provides the best reflection of the effect of a given treatment policy.

Supplemental on-treatment analyses are also conducted in ASCEND, being prespecified to include events occurring on or before the subjects' last dose, plus a 28-day ascertainment window. While on-treatment analyses are commonplace in CV outcomes trials, it is well known that such analyses are problematic, as they carry a common set of well-known issues of functions and biases, including the lack of a valid randomization and subject self-select.

Differential dosing frequency, if not correctly accounted for, serves only to compound these pre-existing biases. As I will show, this occurs because the on-treatment events are undercounted in the arm with the lower dosing frequency, and this is the case in ASCEND, where daprodustat was dosed daily and ESA was dosed less

frequently, most notably in ASCEND-ND where 93 percent of ESA subjects were dosed 2 weekly or 4 weekly.

Now just before I move on to my next slide to describe the nature of this bias, please do note that this is not a matter of ITT versus on treatment and which of these analyses is preferred in a noninferiority trial design; rather, it's a matter of ensuring we minimize the additional artefactual bias introduced by differential dosing frequency so that we can fairly assess and evaluate what the data are really telling us.

So to help appreciate this bias, consider these subjects, they are dosed daily as indicated by the yellow arrows, which in fact span the full length of the blue bar, and they have their final dose, as depicted by the pink arrow, at around 6.7 months. As shown by the blue circle, the subjects had a MACE event at about 6.3 months, and so this event is counted as on treatment.

Now suppose these subjects had been dosed monthly. Their monthly doses are shown by the

yellow arrows, and they have a final monthly dose at 6 months. Note that while the yellow shady area coming immediately after their last dose is included as part of the on-treatment period, if dosed daily, this area is lost when dosing monthly. Because of this, their MACE events fall after their last monthly dose, so there event is now reclassified as off treatment, and note that this phenomenon would occur even if we trialed monthly placebo versus daily placebo.

So it's easy to see how when we dose in intervals as opposed to daily, we lose on-treatment events, and if the time to stop dosing and the time to the event are well correlated, this undercounting of events can introduce serious bias when we compare daily to non-daily dosing.

So what can we do about it? Well, we could redefine on treatment as those events occurring on or before the date of last dose, plus the dosing frequency interval, which in ASCEND would be 1, 2, or 4 weeks for darbe and one day for dapro; or alternatively, the decision to stop dosing was

collected in the case report form, and so could be used as a reasonable substitute for what might had been the date of last dose if darbe had been dosed daily. Arguably, this is more appropriate as an approach as we would effectively be comparing like with like items in terms of on-treatment period with dapro and darbe.

As you will see in my next slide, either one of these approaches will work to dampen the bias introduced by differential dosing frequency. Here you can see the key MACE analyses in ASCEND-ND with and without dosing frequency adjustment. You'll find these analyses presented in more detail in the briefing book.

To the left, we have the primary ITT analysis where we see no difference in MACE between dapro and darbe, with a hazard ratio very close to unity. Alongside this, we see the result of the prespecified on-treatment analysis, which gave a hazard ratio of 1.40, which we now know is heavily biased, as dosing frequency is not accounted for and, hence, events are miscounted on darbe.

The two bottom panels to the left show the results of on-treatment analyses, adjusting first for dosing frequency, and then the dosing frequency plus a further 28-day ascertainment window. In both instances, we see the on-treatment hazard ratio is attenuated, and the difference in the account of events is narrowed, and the two bottom panels to the right show a similar pattern of results when we use the date of the decision to stop dosing in darbe subjects as an approximation, so it might have been their last dose date if they had been dosed daily.

So we see that both approaches to tackle the dosing frequency issue provide results that are less biased, however, it remains the case that it is the ITT analysis that provides the most appropriate and least bias comparison of treatments for MACE.

To summarize, we should first not forget that at the highest statistical level, all on-treatment analyses are problematic and carry a common set of well-known issues and biases. My

goal here today is not to try and fix the issues with on-treatment analyses, that would be impossible, but rather to highlight the dosing frequency issue in ASCEND and to try to arrive at on-treatment assessments that are as free as possible from the additional bias that it introduced.

Note that this bias affects all on-treatment analyses, not just MACE, but all variants of MACE, and on-treatment adverse event analyses, too, including the analysis of cancer incidence that FDA notes in their briefing materials. The magnitude of the bias increases as the dosing frequency lengthens, and the correlation between time to event and time to stop dosing grows in strength, as indeed is the case in ASCEND.

Unfortunately, the pre-planned on-treatment analyses in the ASCEND program did not account for differential dosing frequency. This oversight was unfortunate, however, the on-treatment definition employed was simply that commonly applied in randomized-controlled trials, and as far as I'm

aware, the impact of differential dosing frequency has never been previously addressed in the context of CV outcome studies.

So albeit post hoc, the simple correction for differential dosing frequency, I've described, reduces the associated statistical bias, and in so doing provides results rather more in keeping with the primary ITT analysis. And importantly, this is supported by the date of the decision to stop dosing such that when adopted, the date of last daily dose for darbe subjects, again, attenuates the bias.

With that, I'd like to thank you for your time and attention, and I'll turn the lectern over now to Dr. Stein.

Applicant Presentation - Heather Stein

DR. STEIN: Thank you, Dr. Carroll.

My name is Heather Stein, and I'm a vice president in the global safety department at GSK. Our review of the general safety results conclude that across the ASCEND program, daprodustat has a safety profile comparable to establish ESA

treatments across the spectrum of patients with anemia of CKD. For this presentation, I'm going to take a similar approach as the FDA and focus on key elements of the daprodustat safety profile, starting with gastric erosions, followed by acute kidney injury.

Esophageal and gastric erosions were identified as adverse events of special interest, or AESIs, based on preclinical findings following oral or IV administration of daprodustat, at doses that led to both rapid increases and high absolute levels of hematocrit.

Our method for identifying these erosive events focused on the dosing frequency adjusted data and cast a wide net using a variety of terms reflective of ulceration or perforation, as well as non-specific terms such as GI hemorrhage. The events were not adjudicated and diagnostic confirmation with endoscopy was not required in the ASCEND program. As you can see in the table, terms reflective of GI hemorrhage are among the most frequently reported within the category of

esophageal and gastric erosions, therefore, we'll refer to this AESI as a composite of gastric erosions and GI hemorrhage.

This table shows the data for gastric erosions and GI hemorrhage using both the GSK and FDA list of terms, the latter of which cast an even wider net by including more events associated with gastrointestinal bleeding. There is some variability depending on which definition is used, but overall the results indicate that there is no signal of increased risk in the dialysis study, but a higher rate of gastric erosions and GI hemorrhage in the daprodustat arm in the ND study.

When looking at these events, it's important to recognize that gastric erosions and GI bleeding are a common comorbidity in patients with CKD anemia, increasing in prevalence as their kidney disease worsens. Here we see that across both treatment arms in all three studies, the majority of events were considered unrelated to treatment with study medication, and resolved despite continuing therapy.

Serious AESIs of gastric erosions and GI hemorrhage were reviewed by blinded external gastroenterology experts whose primary aim was to determine the prevalence of confirmed clinically significant erosive events. In the opinion of the experts, in the absence of sufficient medical history and diagnostic evaluation required for adequate assessment, the role of daprodustat remains uncertain, and the results seen in the ND study could be a play of chance or represent a true difference given that there is no imbalance observed in ASCEND-D.

In the two large cardiovascular outcomes trials, the incidence of gastric erosions and GI hemorrhage in the daprodustat arm was similar. It's not clear why the active comparators behaved differently, however, according to their labels, neither rh-EPO nor darbepoetin are causally associated with gastric erosion or GI hemorrhage.

Furthermore, the imbalance seen in ASCEND-ND is not replicated in the double-blind, placebo-controlled NHQ study, also in non-dialysis

patients. And finally, there has been no signal to date for erosions or GI hemorrhage following approval of daprodustat in Japan in June of 2020. Therefore, following our extensive review, we concluded that the totality of data does not support an increased risk of gastric erosions or GI hemorrhage relative to the standard of care ESA.

I will now move on to a discussion of acute kidney injury or AKI. Preclinical data suggested that HIF-PHIs could be protective against both AKI and renal progression. Therefore, one of the study objectives for ASCEND-ND was to evaluate the effects of daprodustat on measures of kidney function and injury, including time to CKD progression, change in eGFR from baseline, and investigator reported adverse events.

A concern was raised by FDA regarding a potential clinically important risk for serious events of AKI. Using FDA's definition of AKI, the overall number of serious events was small, and none were assessed by the investigator as related to study drug. The ITT analysis was consistent

with the on-treatment analysis, with differences between treatment arms of 1 to 2 percent.

AKI is important because it can result in end-stage kidney disease or death, both of which were prespecified endpoints in the ASCEND-ND trial. Earlier in the presentation, we saw that all-cause mortality did not differ between treatment groups in ASCEND-ND. An analysis of time to CKD progression captured the composite of a 40 percent decline in eGFR, chronic dialysis, or transplantation in patients starting the trial with an eGFR greater than or equal to 15. No difference between treatment arms was noted, with a hazard ratio of 0.98.

Patients starting the trial with CKD stage 2 through 4, who later experienced serious AKI resulting in CKD progression, are captured in this analysis. While we agree there is an imbalance in investigator-reported events of serious AKI, this is inconsistent with these robust and objective measures of its important clinical consequences.

In addition, the decline in eGFR over time

did not differ between the two treatment groups. Similarly, the percentage of participants with any post-baseline, on-treatment change of greater than or equal to 40 percent decline in eGFR was identical in both treatment arms of the ASCEND-ND study at 26 percent.

This is an important observation since the 40 percent decline in eGFR represents an approximately 1.5-fold increase in serum creatinine, which is the minimum increase that would constitute stage 1 AKI under the KDIGO definition of AKI. Therefore, this metric of a 40 percent decline in eGFR provides an objective laboratory-based surrogate for changes in creatinine that would identify even stage 1 AKI. These results are consistent with the FDA finding that there was no notable treatment difference in the routine safety laboratory assessment of serum BUN in creatinine in ASCEND-ND.

Further reassurance is provided by data on kidney function from the double-blind, placebo-controlled NHQ study. In this study, the

rate of decline in eGFR was slower in the daprodustat arm compared to placebo. Given the totality of data, including the lack of a preclinical signal for nephrotoxicity, a slower rate of eGFR decline in the placebo-controlled study, and no indication from any of the objective kidney endpoints in the ASCEND-ND trial to indicate a treatment effect on clinically important AKI, we conclude that the difference in investigator-reported serious AKI is an inconsistent observation that is not reflected in any objective measures of renal function in the ASCEND studies.

Taking into account the safety profile of daprodustat discussed here, as well as outlined in our briefing book, we're proposing a proactive program of pharmacovigilance and risk management activities to ensure the safe use of daprodustat in the postmarketing setting. Regarding malignancy, we agree with the FDA's assessment that the risk of tumor progression does not appear to be increased compared to ESA, but the duration of the studies

was not sufficient to refute or substantiate long-term risk.

Therefore, if approved, postmarketing pharmacovigilance activities will include additional data collection for cancer-related events to facilitate further characterization and longer term monitoring. We will also be proactively providing prescriber education materials regarding the risk of heart failure for non-dialysis patients with a history of heart failure to support prescribers in their individual benefit-risk decision-making conversations with their patients.

I would like to end by reviewing the safety conclusions from today's presentation in our briefing document. The ASCEND-NHQ study showed no notable differences between treatment groups in the first occurrence of an adjudicated MACE, and no clinically significant safety concerns were identified. Both large cardiovascular outcome studies met the co-primary safety endpoint, demonstrating that the risk of MACE with

daprodustat is noninferior to ESA in both dialysis and non-dialysis patients.

We did identify that hospitalization for heart failure is considered a risk for daprodustat among non-dialysis patients with a history of heart failure. GSK proposes that this risk can be minimized through appropriate labeling and proactive prescriber education materials.

With respect to general safety across the studies, the most frequently reported AEs were events characteristic of the target population. Considering the identified AESIs, daprodustat did not increase the risk of malignancy, or gastric erosions, or GI hemorrhage. The data also do not support an increased risk of AKI or CKD progression in non-dialysis patients.

Furthermore, safety issues associated with other HIF-PHIs such as drug-induced liver injury were not observed with daprodustat. Overall, the phase 3 studies have encompassed the gamut of safety from stage 3 CKD through chronic dialysis patients. The totality of data show that

daprodustat has a favorable benefit-risk profile for both non-dialysis and dialysis patients that is comparable to ESAs.

I will now hand over the presentation to Dr. Singh, who will provide his clinical perspective.

Applicant Presentation - Ajay Singh

DR. SINGH: Thank you.

My name is Dr. Ajay Singh. I'm the chair of the ASCEND executive steering committee. I'm also senior associate for post-graduate medical education at Harvard Medical School and a nephrologist at Brigham and Women's Hospital. The executive steering committee of the ASCEND trials program consisted of two cardiologists, Scott Solomon and John McMurray, and a nephrologist, Vlado Perkovic, and senior statistician, Kevin Carroll. We have a steering committee with several nephrologists, an independent data monitoring committee chaired by Dr. Karl Swedberg, and including Mark Borer [ph], Ian Ford, Marc Pfeffer, and Amit Garg.

My clinical perspectives reflect my own thoughts and are contextually based on my 35 years as a nephrologist, including 20 years as a clinical trialist. I led the CHOIR trial that we published in the New England Journal of Medicine, and the TREAT and DRIVE trials in which I was on the executive steering committee. I've had the safety of ESAs on my horizon for many years, dating back to testifying to the House Ways and Means Committee twice in the U.S. Congress, as well as providing input to the FDA.

The vast number of CKD patients are those not on dialysis and receive treatment for their anemia via the clinic. Clinic-based therapies have a bottleneck, and this bottleneck in fact is the clinic. Getting to a clinic regularly for subcutaneous ESA therapy takes a lot of effort, energy, and time. All things are in short supply for people with CKD. For patients, their challenges are obvious in terms of transportation, time, and cost. For the provider, ESAs must be refrigerated during shipping and storage, and then

injected by a clinician.

My own research using the representative NHANES data set also reveals that there are disparities with respect to anemia and its treatment. African Americans and people from disadvantaged socioeconomic backgrounds have a higher prevalence of anemia. Studies show that African Americans in particular are not receiving treatment at similar rates to white and/or wealthier patients, and these disparities have persisted and gotten worse over the past 20 years.

Although it is true that many hemodialysis patients can easily access conventional ESAs, the population of patients with kidney disease is heterogeneous. It currently includes about 13 percent of patients on home therapy. Most of these patients are on peritoneal dialysis, but 11 percent of the U.S. dialysis population, with a smaller and growing group on home hemo.

There are also 250,000 patients in the U.S., some of whom have a functioning kidney transplant but have developed anemia. Both home therapy

patients and kidney transplant patients with anemia could benefit from oral treatment options, especially if they live in a disadvantaged or rural setting and are remote from a dialysis center. The other point is that the proportion of home therapy patients is rapidly growing, in part encouraged by national initiatives. An oral treatment option for anemia would be an important tool in facilitating optimal care for these patients.

When we think about the unmet needs in our ND and dialysis patient population, it's important that we consider the real risk of not treating anemia and the risk of existing inappropriate treatment of anemia. As you've heard from Dr. Johansen, patients have the risk of transfusion, which comes with several other important risks, including allosensitization. By raising antibodies from exposure to blood transfusion, a patient's candidacy for a potential kidney can be diminished.

Transfusions, particularly acutely in already volume-expanded patients with kidney

disease, pose a risk of precipitating acute volume overload and hyperkalemia. If one takes a liberal approach to blood transfusion and transfuses patients when the hemoglobin is less than 8 grams per deciliter, there are well documented adverse events, including a high rate of cardiac events, particularly in hospitalized patients. There's also a small but well-defined risk of infection.

Also, patients with CKD who are not treated for anemia have a reduced health-related quality of life as you heard from Dr. Johansen. Indeed, data from the SONG Initiative, which stands for Standardized Outcomes in Nephrology Initiative, points to fatigue being the most important symptom that CKD patients complain about. For these reasons, it's critical that both non-dialysis and dialysis patients with anemia CKD have additional effective treatment options.

The ASCEND phase 3 program was an academically-led robust, well-designed program across the spectrum of CKD. The program had excellent follow-up for the endpoints of interest,

including MACE, and the studies have internal validity, which give us all confidence in the results. The results are generalizable because we enrolled a representative population in terms of demographics, including race and other comorbidities.

The primary efficacy data shared earlier in the presentation showed that daprodustat was noninferior to conventional ESA for the hemoglobin co-primary endpoint. There's no debate about this. The ITT analyses demonstrated that in the dialysis population, daprodustat was well tolerated with no statistically significant findings pertaining to safety, although there were numerical imbalances, heart failure, which appear restricted to those with a history of heart failure. For gastric erosions, the data was somewhat inconsistent. Based on these data, in my view, many well-informed patients would reasonably choose daprodustat as a more convenient and flexible treatment option.

In its briefing book, the FDA focuses on the safety of daprodustat in the ND population, raising

six concerns that have been discussed earlier, but I would like to also comment. First, both the FDA's and the sponsor's analyses explored the prespecified on-treatment data for MACE. Our independent analysis from our team at the Brigham and Women's Hospital, working with academic executive steering committee members, showed that this was clearly because of biased estimates of risk in ASCEND-ND.

Events were undercounted from patients in the darbepoetin alpha arm. Analyses that account for longer darbepoetin alpha dosing intervals or used the date of decision to stop treatment plus analyses, that extend duration of follow-up, showed a neutral and more valid estimate of risk.

Second, the FDA's post hoc analyses of all endpoints by U.S. versus non-US, here it's important to point out: 1) subgroup analyses generally are unreliable and underpowered; 2) when the overall hazard is close to unity, subgroup analyses can only throw up some positive and counterbalancing negative data; 3) to imply, as the

briefing document does, that the U.S. findings are strengthened by the fact that multiple safety endpoints of similar hazard ratios needs to be challenged because these are not independent endpoints.

Third, the FDA post hoc analyses about the CV endpoints, the FDA has looked post hoc at all CV safety endpoints but excluded non-CV and unknown causes of death. In my view, this is a flawed approach. Non-CV death cannot be censored or excluded because these events could be informative; besides, the reasons for excluding them is implausible and most done post hoc by the FDA using untestable assumptions.

Fourth, the FDA and the sponsor's post hoc analysis on adjudicated hospitalization for heart failure showed an imbalance. However, in contrast to the sponsor's approach, the FDA's analysis did not use the composite of all-cause mortality and hospitalization for heart failure. When these analyses are done using this approach, it shows that any potential increase incidence of heart

failure events is confined to those with pre-existing heart failure were not yet on dialysis.

With respect to AKI, both the FDA briefing book and the sponsor's analyses both showed an imbalance in AKI rates, however, the data on AKI is inconsistent and conflicting. It is important to point out the difference between the treatment groups and AKI was derived from adverse event reports, which is subject to bias because this was an open-label study, and there was no difference in the rate of CKD progression and no difference in the 40 percent drop in eGFR endpoint, or the hard endpoints of dialysis initiations between daprodustat and darbepoetin.

Furthermore, an independent blinded review of AKI events by Dr. James Wetmore and Dr. Richard Lafayette was performed. Among those patients with an eGFR greater than 15 and you had not met the CKD progression endpoint, the review concluded that none of the AKI events on the daprodustat arm were related to study drug, and this risk was not

observed in the NHQ trial, a placebo-controlled trial in ND patients.

For erosions, there is a higher rate of erosions in the ND patients randomized to daprodustat both in the FDA and the sponsor's analysis. There doesn't seem to be an explanation for this observation. It is important to note that these events were resolved while patients remained on treatment.

Furthermore, an independent blinded review of these data, led by Dr. McQuaid and by Dr. Loren Laine, reported that these SAE events could reflect a play of chance or a true difference in results between study arms. Furthermore, this risk was inconsistent with results from the D trial, which did not demonstrate an imbalance, and the risk of erosions was not observed in the NHQ trial. As you recall, NHQ is a placebo-controlled trial in ND patients.

The FDA has raised the concern about monitoring patients on oral medication, but from my perspective, I would monitor patients very closely

as I've done with ESAs for years. The ASCEND program showed us that daprodustat provided consistent hemoglobin control without overshoots in hemoglobin fluctuations. Patients would still have close hemoglobin monitoring with daprodustat, but it could be done at a local clinic rather than at a potentially distant facility that administers ESAs. Like many of my colleagues, I'm very comfortable with assessing fluid overload in CKD patients and strongly believe that physicians will maintain the same level of close, careful monitoring that is standard with conventional ESA treatment.

Lastly, I would respectfully submit that the committee should also consider the views of the well-informed patient who may want to have the ability to choose their preferred option to treat their anemia. These patients may select the convenience and flexibility of dosing from an oral treatment.

Daprodustat represents a convenient and flexible treatment option. It would be an important advance for our patients receiving or not

receiving dialysis and provide nephrologists and other clinicians an additional tool to effectively care for anemia in our patients. Overall, in our prespecified ITT analysis, daprodustat demonstrated similar efficacy and a safety profile comparable to ESA. There were concerns with daprodustat in the ND population, but I believe that we have respectfully provided alternative explanations to the ones provided by the FDA in their briefing book.

Thank you, and I'll turn my presentation back to the sponsor.

(Pause.)

DR. VAN ADELSBERG: GSK is finished with their presentation.

(Pause.)

Excuse me FDA, but if you're speaking, we cannot hear you.

DR. LEWIS: Is GSK done with their presentation?

DR. VAN ADELSBERG: Yes, we are finished. Thank you.

Clarifying Questions

DR. LEWIS: Thank you.

We will now take clarifying questions for GSK. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-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 the end of your question with a thank you and the end of your follow-up question with, "That is all for my question," so we can move on to the next panel member.

I will take the liberty of asking two questions. This is Dr. Julia Lewis asking two questions.

In the FDA briefing document, it was stated that during the first year of the study, the

subjects were evaluated every 4 weeks. For the home dialysis and non-dialysis patients, could you clarify, were those in-person visits, and how the HemoCue monitoring was done, by patient or study staff; and how was the drug dispensed, a 4-week supply at a time or 90 days with 3 refills, which would be available, if approved? What were the contingency plans for patients who did not get their monitoring done in terms of access to study drug?

My second question is, your drug is in a new class of agents. Two agents in this class have received a complete response letter from the FDA due to safety concerns, and none have been approved. Could you comment in what you might think is unique about your drug compared to the other drugs in the class that would persuade us not to consider the totality of information with drugs in this class of agents in weighing the safety signals in your study?

Thank you. That's the end of my questions.

DR. VAN ADELSBERG: I'm going to ask

Dr. Alex Cobitz to talk about the drug supply question that you asked. And just to make sure we hit on all the points, it was, were visits in person; how frequently in person; how was HemoCue used; what was the length of the drug supply; and what were the contingency plans for supplying study drug; correct?

DR. LEWIS: That's correct.

DR. VAN ADELSBERG: Thank you.

Here's Dr. Cobitz.

DR. COBITZ: Hello. Dr. Alex Cobitz, clinical. With regard to the first year of follow-up, individuals, whether they were on home hemodialysis, PD, or HD within the unit, actually were seen every month to actually get their study drug and have their HemoCue done. During the second year of the study, individuals could be seen less frequently, up to 3 months from their last visit. During that time, they would get a 90-day supply as opposed to the month supply they would get during the first year.

I'm sorry. What's the --

DR. VAN ADELSBERG: I think it was the contingency plans to --

DR. COBITZ: Oh, yes; yes, yes.

With regard to contingency, yes, there were contingencies in terms of actually having individuals be checked via telephone and having their drugs actually given to them. And point of fact, during some of COVID, we have to utilize that and also -- but again, they have to have the hemoglobin checked. And at times, we actually have to turn them over to receiving regular ESA.

DR. VAN ADELSBERG: So the second question you asked was regarding daprodustat as being the third member of the class to be reviewed, given the lack of approval of the first two candidates.

I think that the first observation is that all of these drugs as small molecules differ on the molecular level with different chemical structures, different pharmacokinetic properties, and actually different dose levels, so direct comparisons really cannot be done since we have no head-to-head studies. Ultimately, I think the review of these

drugs come down to the study results and the assessment of this drug compared to the standard of care, erythropoietin.

DR. LEWIS: Thank you.

Dr. Abbott, you have the first next question.

DR. ABBOTT: Yes. Thank you. I'm going to be asking about gastric ulcerations, but it also has to do with infusions, so it may involve both Dr. Johansen and Dr. Stein.

If I'm reading the documents in the presentation correctly, one of the primary concerns for the gastric ulceration was the risk of transfusion, although there are of course other risks. Is there any way to compare this rate of transfusion from gastric ulceration with the baseline risk of transfusion in the non-dialysis-dependent population?

In other words, despite the development of gastric ulceration, is there still perhaps a net lower transfusion requirement accounting for the other risks of gastric ulceration in this

population?

DR. VAN ADELSBERG: Just to clarify to make sure we're answering the right question, the concern is about the erosions, but the specific question is, are transfusion rates different or similar overall, and to understand the risk of bleeding overall, and then transfusions related to bleeds; correct?

DR. ABBOTT: Yes. Yes. Thank you.

DR. VAN ADELSBERG: I'm going to ask Tara Barker to talk about the rate of GI hemorrhages observed overall in our two cardiovascular outcomes studies. I think Dr. Cobitz showed -- can you call up the transfusion slide? Dr. Cobitz will talk about the transfusion results, and then Tara Barker will provide the hemorrhage results.

DR. ABBOTT: Thank you.

DR. COBITZ: Let me throw this slide up. Alright. Just to remind you, the transfusions amongst, actually, all the studies were comparable between the two arms, and again, you're looking specifically at ND, and you can see that at the far

left.

MS. BARKER: This is Tara Barker from clinical safety -- global safety.

Looking here, there was a concern about the risk for gastrointestinal bleeding, and we actually looked at bleeding alone outside of the risk of ulceration. And using the measure SMQ for GI hemorrhage, what you can see here is that in both the dialysis and non-dialysis populations, the incidence of bleeding was similar across both treatment arms, both for any bleed, as well as the serious bleeds.

Yes. You can see the any events on the top portion of the slide, 3 percent versus 3 for ND, and then the bottom of the slide is where the serious events are provided for you.

DR. ABBOTT: Thank you.

So will I be able to ask one more question or should I get back in line?

DR. LEWIS: You may ask a follow-up question.

DR. ABBOTT: In an unrelated matter, one of

the other outcomes of concern listed was acute kidney injury. I didn't see a whole lot about that. In the general presentation papers we were given, it mentioned that there was a higher risk of AKI, although this was not necessarily presented by stage or severity and whether they were hospitalized or dialysis dependent, from what I could tell; and it appeared to be no increased risk of CKD progression.

Was there any data on the severity of AKI attributed to daprodustat?

DR. VAN ADELSBERG: The AKI data are investigator reports, which did not describe how severe the AKI was or didn't describe the severity. I'm sorry.

DR. ABBOTT: Okay. Thank you

DR. LEWIS: Thank you.

Mr. Conway?

MR. CONWAY: Great. Thank you. Paul Conway. I have two questions that are related, actually.

In your briefing package that you had

submitted, on page 28, paragraph 3, sentence 3, there's a note in there that says that when you were, I guess, submitting the SF-36 to FDA, that you had also provided qualitative and quantitative information to FDA, and my question for you is this, the first one.

Can you characterize what that qualitative data was about the efficacy of the SF-36, and did FDA say to you that they would discount it or they were not going to weigh it heavily?

DR. VAN ADELSBERG: To address this question, I'd like to call on Tom Keely.

DR. KEELY: Thank you. Tom Keely from the patient-centered outcomes team. With regards to the qualitative evidence, that was a 38-person qualitative study that was looking at the content validity of the vitality domain. It shows that the vitality domain was a relevant endpoint and that patients understood. It was an endpoint that patients' valued change in as well. That has been, as you said, submitted to the FDA. We have had initial discussions with them on that, but we

haven't had a conclusive discussion as yet.

MR. CONWAY: So just a quick follow-up to that; at any point, were you told then the data that you were submitting was insufficient or that the SF-36 was insufficient?

DR. KEELY: This is Tom Keely again. No, we haven't been told that.

MR. CONWAY: Okay. The reason why I'm asking, I have the honor to serve as the chair of policy and global affairs for the largest kidney patient organization in the United States. But probably more important than that, I don't know about my fellow committee members, but I've actually lived this life: so 13 years of CKD; 3 years on dialysis; 25 years out on a transplant, with anemia and trying to maintain a job.

When I went on to dialysis, I was the Deputy Secretary of Health in the State of Virginia. I later had the honor to serve as the chief of staff for the U.S. Department of Labor, so I actually view this issue as both a healthcare and a workforce issue, and that's where I'm going on

this.

The second question that I have -- and this is briefer, and I don't know if this will fall in the domain of Dr. Singh or not -- in the opening statement today, FDA said that there is no meaningful -- no other meaningful benefits were established in looking at this data in terms of efficacy; beyond the studies, and the risk, and that type of thing, no other meaningful benefits were established.

Then in the briefing document, FDA on page 59 says that in regard to the SF-36, although it was a statistically higher significance, that quote, "It's not clinically meaningful." And as a clinician, I guess I'd like somebody on your team to comment on whether or not the data they saw in the SF-36 is clinically meaningful, in your opinion. Thank you.

DR. VAN ADELSBERG: To address your question, I'd like to call on Dr. Kirsten Johansen.

DR. JOHANSEN: Thank you. This is Kirsten Johansen.

Yes, I believe that that is meaningful for our patients for a couple of reasons. Fatigue is one of the number one symptoms that people express with anemia in terms of the frequency with which they experience it and in terms of the importance that they give it. For example, the SONG Initiative was mentioned, and that was the study that has qualitative interviews with patients, and they've consistently reported fatigue as an important concern.

In terms of what actual difference in the vitality score means, a change of 6 points on that scale is a difference between saying that you feel worn out most of the time to worn out some of the time, or from some of the time to a little bit of the time. I would imagine that that would be important to people.

In addition to that, there is some additional quality-of-life data and some other fatigue data that was collected, and I'm putting it up on the slide here. The vitality score was a key secondary endpoint, and this one was an exploratory

outcome. But the sponsor developed a questionnaire specifically to address symptoms among patients with CKD by conducting interviews with patients, then putting that together into an instrument, and then talking to patients about whether the instrument was valid, and then this instrument was used in the NHQ study.

So it ended up with three domains: a tired, low-energy weak domain that you can see here on the far right; chest pain and shortness of breath came up as well; as well as cognitive dysfunction. So on this additional measure, all three of those improved significantly in the patients that received daprodustat in NHQ compared to those who received placebo.

MR. CONWAY: Great. Thank you very much.

DR. LEWIS: Dr. Bairey Merz?

DR. BAIREY MERZ: Thank you very much, Dr. Lewis.

Noel Bairey Merz. I have a question also for Dr. Johansen, a practicing nephrologist with good insight into this issue.

One of the early slides that you showed demonstrated a really infrequent use of ESAs in both the non-dialyzed and the dialyzed population. Because most Americans don't live rurally, a majority of U.S. are receiving dialysis in dialysis centers directed by nephrologists. This relatively low use of the ESA to me indicates there's a general reluctance probably regarding safety.

What is your opinion, therefore, about how an oral agent will then affect benefits of U.S. patients given this reluctance of practicing nephrologists to use the existing agents? Thank you.

DR. VAN ADELSBERG: This is Dr. van Adelsberg. Before Dr. Johansen speaks, I do want to correct that slide CO-15 -- I'll put it up -- only refers to non-dialysis patients. Patients who are on dialysis are, more than 90 percent of them, treated with ESAs. But with that, I'm going to turn this over to Dr. Johansen.

DR. JOHANSEN: This is Kirsten Johansen. Thank you. I'd like to clarify one thing as well.

The majority of dialysis patients are treated with the ESAs. It's more the non-dialysis population that I think you were particularly referring to and that I showed were undertreated with this.

In my practice, I use these agents frequently. I don't believe that the undertreatment is related to issues of risk as much as issues of access concern. It is difficult for patients to get in and get these treatments, and they are often reluctant for their own reasons that I talked about, either transportation issues coming in; fear of injections. So for me in my practice and the colleagues that I know, those are the barriers rather than fear of bad outcomes

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Yes. Thank you.

Dr. Chris O'Connor; two quick questions. First, I want to compliment the sponsor team for an outstanding development program. These are directed to Dr. Khavandi.

Obviously, adjudication committees are

necessary as a high standard for these open-label CVOT outcomes trials, but what happens with adjudication committees with nonfatal events is that there's a reduction in those events in contrast to the investigator-determined events; that is, the investigator may call an event an MI, a stroke, or heart failure, and because of the committee's high standards, those events could be thrown out. That can occur up to 20 percent in nonfatal events in CVOT trials, and it results in broadening the confidence intervals and is particularly a challenge in noninferiority trials.

Can you tell us how many events of the nonfatal events of the MACE composite were thrown out? In particular, I'm interested in slide 49, which is the ACM plus heart failure hospitalization. What would that look like if that was the investigator-determined heart failure hospitalizations as opposed to the committee-determined ones?

That's my first question, and then I have a brief second question.

DR. VAN ADELSBERG: To address your first question, which was with concordance with regard to the adjudicated events, I'm going to call on our statistician Allison Blackorby.

MS. BLACKORBY: This is Allison Blackorby from GSK biostatistics. Overall, the concordance for the MACE endpoint was high and consistent across treatment groups in both the non-dialysis and dialysis outcomes studies; 84 percent of reported MACE events were concordant in the non-dialysis study and 83 percent of the reported MACE events were concordant in the dialysis study.

I can show you that data for the non-dialysis study here. On this table, you'll see that the yellow highlighted 790 events were adjudicated to be MACE and matched the investigator-reported event type, and then the 491 events were adjudicated not to be MACE, which matched the investigator-reported event type as well, for an overall concordance of 84 percent.

DR. VAN ADELSBERG: We talked about the concordance in the events. To discuss the heart

failure data in particular, I'd like to call on Dr. Kaivan Khavandi.

DR. KHAVANDI: Kaivan Khavandi, GSK clinical. I'm going to put a slide up, and it's a little bit busy, but I'm going to walk through it. I'm actually going to start off with the bottom-right corner in relation to the question.

There were 140 events for hospitalization for heart failure in the daprodustat arm, which could be fatal or nonfatal, and 115 in the darbepoetin arm. Acutely in relation to those events, four of the events in the daprodustat arm were fatal events and five in the 115 in darbepoetin were fatal.

So as you can see on the slide, if you follow up those participants through the course of the study, the 25 excess hospitalization for heart failure events in the daprodustat arm did not translate to any difference in mortality, so you have of those two cohorts, 47 deaths through the remaining course of the study and 45 with darbepoetin.

Specifically, in terms of concordance between PIs and adjudication committees, I think there's some important data in the top left which relates to the challenge that I'm sure everyone's familiar with in terms of discriminating uremic fluid overload in relation to advancing CKD and fluid overload from heart failure.

You can see that, overall, of those events that were positively adjudicated for hospitalization for heart failure, between a quarter and a third were deemed by the investigator to be related to fluid overload rather than checking the box for heart failure per se, and you can see on the top panel that there was actually more of those events characterized by the PI as fluid overload in the daprodustat arm.

So I think when you consider those in conjunction with the prognostic data, our interpretation is that uremic fluid overload in the context of CKD was very important here.

DR. O'CONNOR: Thank you.

Then briefly, there appears to be higher

rates of cardiovascular events in the non-dialysis versus dialysis, and particularly the CVD stroke thromboembolic and heart failure. If this is a true signal -- and I think you've made an argument whether it's a true signal or not -- is there a plausible physiologic explanation?

DR. VAN ADELSBERG: I think the first statement that you made about more MACE events in the non-dialysis than the dialysis study, I don't think that that's correct. Numerically, there are more MACE events in the dialysis study.

DR. O'CONNOR: I apologize; in comparison to the ESA --

DR. VAN ADELSBERG: I see. You're talking about --

DR. O'CONNOR: -- the rate --

DR. VAN ADELSBERG: -- the rate.

DR. O'CONNOR: -- hazard ratio.

DR. VAN ADELSBERG: In terms of the primary and principal secondary endpoints, the hazard ratios are close to unity, and thus, overall, we do not see a difference in overall CV risk in the

non-dialysis and the dialysis studies. We have discussed -- and Dr. Khavandi showed, and we can show again -- what the CV event rates look like in the patients who do not have a history of heart failure, where, again, were formally noninferior -- the hazard ratio's close to 1 -- but in the patients who have no history of heart failure there seems to be a numerically small but still observable attenuation of risk.

DR. O'CONNOR: Thank you. No further questions.

DR. LEWIS: Dr. Butler?

DR. BUTLER: Thank you.

Javed Butler. My question is for Dr. Carroll, and if he can go to slide CO-58, please.

DR. VAN ADELSBERG: Dr. Carroll is coming in.

DR. BUTLER: Let me know if you want -- so the question here is I'm just trying to understand this analysis a little bit better.

So if you look at the monthly injection

group and take exactly the same example of the last shot being given at 6 months and an event occurred at 6.7 months, as was stated, there are three scenarios here. One is that the study has ended and it occurred afterwards; or for whatever clinical reason, the decision has been made not to give the injection; or it is still scheduled to be given at 7 months, but the last injection was at 6 months. In all of these scenarios, it should still be counted as an event and the DF was 28 analysis that you showed.

Did I get that correct? And if I did, then in the adjustment, which were the events that were not counted?

DR. CARROLL: Thank you. This is Kevin Carroll, consultant statistician. In principle, I think you understand the slide correctly.

Just very briefly, what I was illustrating here is that if you dose daily, then it's relatively straightforward to know if an event occurred on or off treatment. But if you dose monthly, because you have these discrete chunks of

dosing, then when that last monthly dose is given, there's a period of time thereafter that would be counted as on treatment if you dose daily, but is lost when you dose monthly. And it's that loss of that information which can lead to events being in the counted. And this particularly is acute if the correlation between time to event and time to stop is high, which is what exactly is the situation in ASCEND. So that is what I was trying to illustrate here.

Does that answer your question?

DR. BUTLER: But if that is the case, then if you can go down two more slides, then you show your DF 58 analysis and the significant attenuation in the signal, which events are counted for, because in that case, these will be included; correct?

DR. CARROLL: Yes. We have to be a little careful here. What I showed here is in the bottom boxes on the slide -- if we just look at those on the left-hand side for a moment at the bottom -- we have the time up to and including last dose, plus

the dosing frequency interval, which would be, as I said in my presentation, one day afterward, so 1, 2, 4 weeks for darbe. There we are correctly accounting for this issue with differential dosing frequency in the first box on the bottom left.

There is a slight issue with the ascertainment window because what we do is we're adding a fixed amount of time on to each arm, and when we do that, we are essentially not taking account of -- we are kind of being ignorant for the fundamental reality that patients are dosed at intervals for a reason.

There's probably some kinetic or dynamic reason why you dose monthly versus daily, and consequently, the ascertainment window that we have on top, to capture kind of latent events that may be associated with treatment, really probably should reflect the fact that you've got a different dosing frequency interval. In other words, the ascertainment window itself should probably be tailored in relation to daily dosing versus monthly dosing.

DR. BUTLER: Thank you very much.

Dr. Lewis, may I ask one quick other question.

DR. LEWIS: Sure, Dr. Butler.

DR. BUTLER: Thank you. This is for anyone on the sponsor's side.

Was there any difference in the baseline hemoglobin levels or in the baseline cardioprotective medications in U.S. versus non-US patients?

DR. VAN ADELSBERG: I'm going to ask Dr. Cobitz to answer that question.

DR. COBITZ: Yes. This is Dr. Alex Cobitz. You're wondering if there was any difference in baseline characteristics between U.S. patients in terms of their hemoglobin, as well as the baseline medications, and there wasn't.

DR. BUTLER: Thank you very much.

DR. LEWIS: Dr. Packer?

DR. PACKER: Yes. It's Milton Packer. I just wanted to clarify with the sponsor about a plausible mechanism of action that would cause

myocardial injury. The sponsor said that there was no plausible mechanism, but in fact the prolyl hydroxylase inhibitors do potentiate hypoxia-inducible factor 1 alpha -- the sponsor has said that -- and that prolyl sustained activation of HIF-1 alpha does have deleterious effects on cardiac function, which has been shown in a variety of models.

Does the sponsor have any comment on that?

DR. VAN ADELSBERG: I'd like to call on Tim Hart to talk about the preclinical results.

DR. HART: Yes. Good morning. Tim Hart from GSK nonclinical safety. Daprodustat does inhibit the PHD enzymes 1, 2 and 3, and has led to stabilization of both HIF-1 and HIF-2 in cellular assays. And in vivo, we see the induction of hemoglobin through erythropoiesis stimulation, but in nonclinical safety testings out to 2 years duration, we haven't seen any effect on cardiac endpoints in those animal studies there.

I will point out that in certain models of rodent chronic kidney disease, say, with a

nephrectomy model, dosing with the PHI inhibitors has led to cardio and renal protection in those models, so seeing both a decrease in inflammatory responses and a decrease in fibrotic, which are potential mechanisms of HIF stabilizations.

DR. PACKER: I just wanted to clarify, the action of these drugs to potentiate HIF-1 alpha that produces a deleterious cardiac effect is a potentiating effect in the presence of prior or concomitant cardiac injury; in other words, you wouldn't see it in an animal model where the hearts were completely normal. You would have to stress the heart to see the adverse effect of HIF-1 alpha potentiation.

Can I just ask one other follow-up question? When you asked investigators about worst history of heart failure, was that a checkbox or did you ask investigators to give any more elaboration of history of heart failure? Because determining if a patient with chronic kidney disease has a history of heart failure is a difficult proposition under many clinical circumstances.

DR. VAN ADELSBERG: I'd like to answer your question in two parts. I think, first, the answer to your simple question is it was a checkbox, meaning to indicate the clinical syndrome of heart failure. To go beyond that, I'd like to call on Dr. Vlado Perkovic to talk about his clinical interpretation, as a nephrologist and a trialist, of the meanings of the data in our study.

DR. PERKOVIC: Thank you. Vlado Perkovic, nephrologist and clinical trialist from Sydney, Australia, dean of medicine at UNSW in Australia, and thanks, Dr. Packer, for the question.

I think here it was a simple checkbox, and of course, as you rightly point out, the prevalence of heart failure in this patient population is high, and we as clinician nephrologists have to deal with these patients on a daily basis. This isn't an unusual situation, and whilst we didn't collect data on ejection fraction and other things -- that we would love to have now if we'd been able to do that and if we thought that this day would be of interest when we started the

study -- I think there's no reason to doubt the information provided by the nephrology community.

DR. PACKER: Oh, I'm not doubting the information. I'm trying to determine how replicable it would be in the clinical setting. As the sponsor has already said, there were many heart failure events that were, quote, "classified as volume overload." Cardiologists typically consider volume overload to be a manifestation of heart failure, and it would be difficult for us to distinguish volume overload from heart failure.

You can't really use natriuretic peptides here. It's a very difficult proposition because all of these patients teeter on the edge of heart failure. It's a little bit easier to manage in the dialysis patient because you can remove volume, but much more difficult to manage in the non-dialysis patient.

DR. PERKOVIC: Yes, [indiscernible] --

(Crosstalk.)

DR. LEWIS: Thank you, Dr. Packer. Thank you.

DR. PARSA: Hi. This is --

DR. LEWIS: Dr. Parsa, you may need to --

DR. PARSA: -- Afshin Parsa. I have a question pertaining to the signal for potential increase in AKI.

You claim that given no increase in progression as defined by 40 percent decline in function, that there's no evidence of impact of the noted increase in AKI in the non-dialysis subgroup, obviously. However, there's a median study duration of about 17 months and a modest number of AKI events distributed throughout this period, or in other words, AKI did not occur at the beginning of the study, so they would have a shorter follow-up period; and now AKI and the 40 percent decline is likely meaningfully underpowered and, hence, potentially unreliable.

Would you agree or did you do any other analyses that would counter that?

DR. VAN ADELSBERG: I'm sorry, but you're saying that the duration of follow-up -- I'm sorry. I don't totally understand your question.

DR. PARSA: I'll rephrase. All I'm asking, obviously, if they're not adequately powered, have the chance of proving a false negative finding

Here, the number of AKIs is modest. The duration of the study is also relatively short for those number of AKIs to show a meaningful increase in a 40 percent decline in renal function. So my point is --

DR. VAN ADELSBERG: I've got it.

DR. PARSA: -- the lack of association with AKI, and that could just be an underpowered subanalysis as opposed to not providing evidence of no effect of potential increase in AKI.

DR. VAN ADELSBERG: I'm going to call on Vlado Perkovic again to address your question now that I understand it. Thank you.

DR. PERKOVIC: Vlado Perkovic again from Sydney, Australia. This is clearly an area of major interest for me, and one that I've spent most of my career studying. I think there are a few points to make.

You're right. The study duration here was

relatively short, but if anything, that should be more of an issue for demonstrating long-term renal benefit rather than AKI, which tends to occur linearly in most studies rather than the exponential pattern that we see with the harder renal outcomes.

It is important to note that we had over 700 primary renal outcomes in this trial, so we actually had very, very strong power. This is one of the best powered studies ever conducted, frankly, to demonstrate any evidence of benefit or harm for the clinically important hard renal outcomes, and the results for those outcomes were almost exactly neutral, and meaningful differences were effectively ruled out. On top of that, we have even better powered measures of kidney function as a continuous measure, and again, there was absolutely no difference between the two arms.

So the AKI data is interesting. The number of AKI events is much smaller, and of course in an open-label study, there is the risk of potential differential reporting between a novel experimental

treatment and a treatment that nephrologists are using routinely every day in their patients. So I draw great reassurance from both the eGFR data, but especially the very well-powered data on hard renal outcomes.

DR. LEWIS: Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Lewis.

Again, like others, I want to commend the sponsor and the steering committee, and these presentations, they're just excellent. Many of my questions have been addressed, but there are two remaining.

One short question, when we look at the aggregate of data of preclinical models and the human data, if the sponsor can just comment on gastric erosions and what preclinical models have taught us about the incidence of those events, if you will, in animal models and how that perhaps correlates with the human data, going back to the issue of potential or plausible mechanisms of action. That's the first question.

DR. VAN ADELSBERG: I'm going to call on Tim

Hart again to speak to the preclinical data.

DR. HART: Hi. Tim Hart, nonclinical safety at GSK. We did observe gastric erosions and ulcerations in our animal toxicology studies, and it must be remembered that we're using normo-athymic animals in those studies, and dosing them with daprodustat led to marked increases in hematocrit in these animals.

Histologically, we observed the gastric ulcer and erosions in primarily in the rats, but also in nonhuman primates at the end of the one year on a long-term dosing study. Our interpretation of the results and the mechanism here is that there's a compromised microcirculation in the gastrointestinal tract as a result of the markedly increased hematocrit in these animals, resulting in poor perfusion and subsequent local damage to the tissue.

DR. THADHANI: Great. Thank you.

One other follow-up question, Dr. Lewis, if that's ok.

DR. LEWIS: Yes.

DR. THADHANI: Thank you.

The differential that was seen in the USA versus the non-USA group in the non-dialysis populations of course raises the possibility of the heterogeneity in the U.S. population compared to the non-USA population. And while the analysis, at least for heart failure, focused on a predisposition, meaning a history of heart failure, as a driving effect and perhaps adding bias on what we saw, was there further analysis done on other components that differentiate U.S. versus non-US populations? For example, was there an increased risk in different racial or ethnic groups observed by the sponsor?

DR. VAN ADELSBERG: We did many analyses, and to refer to some of them, I'm going to ask Dr. Kaivan Khavandi to address your question.

DR. THADHANI: Thank you.

DR. KHAVANDI: Kaivan Khavandi, GSK, clinical. I'm going to share a slide that we did share in the core presentation, as a reminder of what at first might appear to be small differences

in baseline characteristics, but those that are quantitatively related to outcomes.

For example, we can see that there was 27 percent of patients in the daprodustat arm of the U.S. with CKD stage 5 compared with 21 percent in the darbepoetin arm. Similarly, you can see there was a greater number of these patients who were recently hospitalized, and there was also a significantly greater number who had heart failure at enrollment. So I think it's quite clear that the phenotype, by chance, that was enrolled into this subgroup was a more severe phenotype.

But to build on that, I'd like to share an analysis that we did, just including two covariates additionally, and looking at the primary and the principal secondary endpoints in the U.S. population. What we see in that analysis, which I'll share shortly, is a meaningful movement of the hazard ratio point estimates back towards unity, and that's by including baseline eGFR and baseline history of heart failure as additional covariates; and just bear with me while we share that slide

with you.

So here you can see when those covariates are included, there's really no meaningful treatment group difference for the primary endpoints or the principal secondary endpoints that consider thromboembolic risk or heart failure. So I think it really demonstrates the sensitivity of smaller subgroups to chance imbalances.

DR. THADHANI: I see. But just, again, to make sure I understand this, you did not find a differential with regards to any racial or ethnic predisposition, even though baseline characteristics may have been similar, but no differential effects by race and ethnicity in terms of predisposition to these events.

DR. VAN ADELSBERG: We did 20 subgroup analyses of our primary and key secondary endpoints, and in those analyses, for various baseline histories and for race, we did not see a difference between groups.

DR. THADHANI: Thank you.

DR. LEWIS: Thank you. We do have many

remaining questions, however, time is running short. I hope we will be able to do that either after the FDA questions or after our open public hearing.

We will take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We will reconvene at 11:40 or 11:39 Eastern time.

(Whereupon, at 11:30 a.m., a recess was taken.)

DR. LEWIS: We will now proceed with the FDA presentation, starting with Dr. Justin Penzenstadler.

Dr. Penzenstadler?

FDA Presentation - Justin Penzenstadler

DR. PENZENSTADLER: Thank you.

Good morning. My name is Justin Penzenstadler. I am a clinical reviewer in the Office of Cardiology, Hematology, Endocrinology and Nephrology. I'll be presenting the FDA's major findings from the daprodustat application along

with Dr. Van Tran from the Division of Biometrics VII in the Office of Biostatistics.

Here is the review team assessing the application. This is the outline of our presentation today. We will briefly discuss the product, the regulatory history, and efficacy. The focus for our presentation will be the safety, particularly the mortality and cardiovascular safety.

Daprodustat is a small molecule. It is a hypoxia-inducible factor prolyl hydroxylase inhibitor that's posited to enhance erythropoiesis by increasing endogenous erythropoietin and reducing hepcidin. The proposed indication is for the treatment of anemia due to CKD in adults not on dialysis and on dialysis. Daprodustat is orally administered, and the dose is adjusted on the basis of hemoglobin response. No HIF inhibitor has been approved in the United States. If approved, daprodustat would be the first in class. Daprodustat was approved in Japan in June 2020 for the treatment of patients with anemia due to

chronic kidney disease.

Anemia is associated with an increased cardiovascular morbidity and mortality. Anemia in patients with CKD is multifactorial, including erythropoietin deficiency; impaired ability to absorb and utilize iron; blood loss; and shortened red blood cell survival. The current standard of care includes iron monitoring and supplementation of patients with iron deficiency.

Some patients, particularly those with more severe CKD, require erythropoiesis stimulating agents, or ESAs for short, to correct anemia. One of the objectives of these treatments is to reduce the need of red blood cell transfusions since transfusions themselves carry unique risks such alloreactivity and increased risk of rejection after kidney transplantation.

ESAs are glycoproteins produced by recombinant technology. They have been in the market in the United States since 1989. There are four ESAs approved for this indication listed under the first bullet. All are approved for use in

patients on dialysis and not on dialysis, and all are administered parenterally.

Four large randomized-controlled studies have shaped the labeling of the ESAs: the normal hematocrit, the CHOIR; CREATE; and TREAT. They are all designed to demonstrate that higher hemoglobin targets would result in better clinical outcomes, but instead they showed, or they tended to show, adverse cardiovascular outcomes with higher rather than lower hemoglobin targets.

The optimum hemoglobin target remains unknown despite the first approval of an ESA being over 30 years ago. In light of these prior results, the ESA label for CKD has undergone significant revisions, including the addition of a boxed warning and several warnings and precautions.

Here you see the boxed warning for the ESAs as related to the CKD. This highlights the risk of death; myocardial infarction; stroke; venous thromboembolism; and thrombosis vascular access. It also warns that targeting a hemoglobin greater than 11 grams per deciliter increases the risk of

death, serious adverse cardiovascular events, and stroke. The warnings and precautions section of the ESA labeling also highlights other important risks such as hypertension and seizure.

After the fourth large randomized-controlled trial suggested harm rather than benefit when targeting higher rather than lower hemoglobin levels, the former division discussed the previous study results at the 2010 Cardio-Renal Drug Advisory Committee meeting. We asked whether the indication for treatment of anemia in patients who are not on dialysis should be withdrawn; 15 out of 17 members voted no.

Now that we have covered the regulatory history and background, we'll switch gears to the daprodustat development program. The daprodustat development program was concurrent in non-dialysis-dependent and dialysis-dependent populations. The key clinical efficacy endpoint is change from baseline in hemoglobin. We often abbreviate this as Hb. The key safety endpoint is time to first major cardiovascular event or MACE for short. MACE

in this context included nonfatal stroke, nonfatal myocardial infarction, and all-cause mortality. We also conducted standard safety analyses consistent with our approach to all new molecular entities. We will discuss these endpoints in more detail in the safety and efficacy presentations to follow.

The phase 3 program for daprodustat included five phase 3 studies. ASCEND-ND and ASCEND-D were large, event-driven cardiovascular outcome trials, or CVOTs for short, which were designed to constitute a stand-alone MACE assessment. There were three additional studies, all with unique design elements to meet specific objectives.

ASCEND-NHQ was a randomized, double-blinded, placebo-controlled study in the non-dialysis population. This study collected patient-reported outcomes, or PROs for short, with the objective of comparing daprodustat against placebo. It is notable that the hemoglobin target was higher in the study, 11 to 12 grams per deciliter, whereas all other studies used 10 to 11 grams per deciliter.

ASCEND-TD was a randomized, blinded, and active-controlled study in dialysis patients. Subjects were randomized 2 to 1 to daprodustat or an ESA comparator. In this study, daprodustat was given 3 times a week rather than daily to coincide with hemodialysis frequency. The primary objective was to support 3 times a week dosing in this population.

ASCEND-ID was a randomized, active-controlled, open-label study. The primary objective was to support once daily dosing in patients transitioning to dialysis. These three studies, being both substantially smaller and scenario specific, provide limited additional utility in the global safety assessment for daprodustat.

Since our focus here today is safety, we won't discuss much about these three ancillary studies in our presentation today, but now I'll move on to discuss ASCEND-D and ASCEND-ND in more detail.

ASCEND-D and ASCEND-ND were open-label,

sponsor-blind, active controlled, events-driven CVOTs. ASCEND-D included subjects undergoing stable hemodialysis at least twice weekly or stable peritoneal dialysis at least 5 times weekly and receiving ESA. ASCEND-ND included subjects with stage 3, 4, or 5 CKD who were not expected to start dialysis within 90 days of screening. ASCEND-ND included subjects receiving an ESA and subjects not receiving an ESA.

Screening began 8 weeks off of randomization. We have denoted the relative study time in weeks as the blue arrow at the bottom. Subjects were excluded from the study if they had severe heart failure. Those with a medical history of myocardial infarction, acute coronary syndrome, stroke, TIA, or gastrointestinal bleed within 4 weeks of screening were excluded. Subjects with a medical history of malignancy within 2 years prior to screening were also excluded.

During the 4-week run-in period, patients received placebo tablets. Those who had received prior ESA therapy continued to receive an ESA

during the screening and run-in periods. Subjects were excluded from randomization if deemed non-adherent. Subjects were then randomized 1 to 1 to daprodustat or ESA control. For those not on dialysis or undergoing peritoneal dialysis, darbepoetin, a long-acting ESA, was used as comparator.

For those on hemodialysis, recombinant human epoetin was used. The starting randomized dose was prespecified and depended on the hemoglobin and the dose of the priory ESA, if any, of the subject baseline. Following randomization, subjects were allowed 28 weeks to titrate to steady state, after which the co-primary efficacy endpoint was assessed from weeks 28 to 52 or so called the evaluation period. After completing the evaluation period, subjects remained in the study until the 664th MACE event, the co-primary safety endpoint. The time between week 52 and the administrative cutoff date is called the follow-up period.

Throughout the study, there was a prespecified algorithm for management of

hemoglobin, which was similar for both daprodustat and ESA comparator besides the dosing. The target hemoglobin range was 10 to 11 grams per deciliter. There were also algorithms to maintain iron repletion, initiate red blood cell transfusions, and initiate anemia rescue. We'll see how these algorithms performed in later slides.

The study population demographics were balanced between the two treatment groups for each study. Regarding ASCEND-ND, the median age was 67 years old. Males and females were well represented. Approximately one-quarter of subjects enrolled were in the United States and about half were ESA users. Approximately one-half of subjects were white.

Regarding ASCEND-D, the median age was 58 to 59 years old. Males and females were well represented. Approximately 30 percent of subjects enrolled were in the United States and all were ESA users per enrollment criteria. 11.5 percent of subjects were peritoneal dialysis users; the rest were on hemodialysis. About two-thirds of subjects

were white.

The treatment arms were well-balanced regarding disease status. Regarding ASCEND-ND, the median eGFR was near the threshold value for stage 5 CKD, the most severe stage, at 17 to 18 milliliters per minute. Diabetes and cardiovascular disease were present in approximately 58 and 37 percent, respectively. Warfarin and clopidogrel use were infrequent but not unremarkable, at about 4 and 9 percent, respectively; 18 percent of subjects had a history of heart failure, and transferring saturation was approximately 30 percent, above the repletion threshold of 20 percent with about 8 to 9 percent of patients requiring IV iron.

Regarding ASCEND-D, diabetes and cardiovascular disease were well-represented at around 41 to 45 percent, respectively. Warfarin and clopidogrel use was about 5 and 10 percent, respectively. About one-quarter of subjects had heart failure. Transferrin saturation was about 30 percent as well, above the repletion threshold

of 20 percent, with 60 percent of patients requiring IV iron.

There were no significant differences in study discontinuation rates. We've displayed one-number summaries for study completion; completed randomized treatment, or CRT for short; and complete CV follow-up because they are identical between arms when rounding to the first whole percentage point.

The study completion rate counted subjects who completed 52 weeks of treatment and the end-of-study visit, and included subjects who died. CRT was the important factor for efficacy analyses and includes those who completed 52 weeks of treatment and had an observed hemoglobin. The complete CV rate only included subjects who have a known CV endpoint status at the end of study. This excludes subjects who completed the study but did not have their CV endpoint assessed during or after the end-of-study visit.

This slide presents a high-level summary of reasons for treatment discontinuation. We

inspected lower-level groupings of reasons for treatment discontinuations, such as specific adverse events are reasons for subject withdrawal, and we did not find any credible treatment differences. Overall, the study population showed no significant differences in disposition between daprodustat and comparator groups, perhaps remarkably so.

Lastly, let's review the exposure and follow-up from ASCEND-D and ASCEND-ND. Consistent with the disposition findings, it is notable that the overall exposure and overall follow-up are balanced between randomized treatment arms, so I'll briefly describe these data study-wide rather than break the data down by treatment arm.

Subjects in ASCEND-D were exposed to randomized treatment for a median time of 26 months and followed for approximately 4 months longer. The total exposure was approximately 2700 patient-years and the total follow-up was approximately 3500 patient-years.

Subjects in ASCEND-ND were exposed to

randomized treatment for a median time of 18 months and followed for approximately 4 months longer. The total exposure was approximately 3,000 patient-years and the total follow-up was approximately 3600 patient-years. Importantly, the percentage of overall follow-up time, which was spent being exposed to drug, was 77 to 85 percent among studies.

For both ASCEND-D and ASCEND-ND, one of the co-primary endpoints was mean change in hemoglobin from baseline to the evaluation period. The analysis model was ANCOVA with missing data handled by multiple imputation. The test was for noninferiority with a margin of 0.75 grams per deciliter. We corroborated the applicant's efficacy results and believed that the applicant provided substantial evidence of effectiveness.

Let us review the hemoglobin results. Here we have displayed the mean level longitudinal results for ASCEND-D and ASCEND-ND. The Y-axis shows the mean hemoglobin concentration in grams per deciliter and the X-axis shows time in weeks.

Please note the scale of the Y-axis, which ranges from 9.5 to 11.0. We have overlaid horizontal lines to signify the target hemoglobin range of 10 to 11 grams per deciliter. Daprodustat is shown in red and the ESA comparator is shown in blue. Daprodustat shows a slightly higher hemoglobin throughout time in both studies, although both arms are well within the hemoglobin target.

One of the secondary endpoints was time to red blood cell transfusion. These figures show the percentages of subjects received at least one red blood cell transfusion or anemia rescue. ASCEND-D is on the right and ASCEND-ND is on the left. The blue bars represent daprodustat and the red bars represent the ESA comparator.

The use of rescue therapy for anemia and the red blood cell transfusions was similar between arms. Taken together, this reinforces the noninferiority conclusion of the efficacy of daprodustat on hemoglobin. Overall, the hemoglobin and rescue results provide some assurance that the prespecified titration algorithms performed

reasonably similarly and also provide some assurance that hemoglobin is not driving differences in safety findings.

Patient-reported outcomes were collected in ASCEND-ND and ASCEND-NHQ to evaluate clinical benefit, however, the FDA review team focused on ASCEND-NHQ, as the open-label trial design of ASCEND-ND was a limitation in interpreting the PRO data due to the patient's knowledge of the treatment assignment. As a reminder, ASCEND-NHQ was the only double-blinded and placebo-controlled study, and as such, the readout was against placebo, not an ESA comparator.

The key secondary PRO endpoint in ASCEND-NHQ was mean change in the vitality domain of the 36-item, short-form Health Survey version 2.0, or we'll say SF-36 for short, between baseline and week 28. This vitality domain measures different aspects of fatigue.

Daprodustat had statistically significant improvement in the SF-36 vitality domain compared to placebo, however, the magnitude of the observed

changes at the item and domain level using both raw and transformed score scales were minimal. The change observed in the raw domain scores reflect less than one response category change on each item. Given the minimal change demonstrated in the raw and domain scores, and the small between-arm differences in response rates, the observed changes are unlikely to be considered meaningful improvements from the patient perspective.

Importantly, we do not agree that this benefit is relevant to the indication at hand since ASCEND-NHQ used a higher hemoglobin target, 11 to 12 grams per deciliter, while ASCEND-D and ASCEND-ND established safety using a target of 10 to 11 grams per deciliter. If there are any follow-up questions on why we do not view the PRO results to be clinically meaningful, we can provide more specifics in the Q&A session.

In summary, daprodustat is noninferior to ESAs in raising hemoglobin both in those on dialysis and those not on dialysis. The results were robust among subgroups in sensitivity analyses

and extended to statistics beyond the mean, such as within patient visit-to-visit variability. There were similar rates in study disposition and, importantly, similar rates of red blood cell transfusions and anemia rescues for both studies. Finally, we did not identify other meaningful benefits.

This concludes my presentation. Dr. Van Tran will now discuss the FDA's findings of daprodustat's cardiovascular safety. Thank you.

FDA Presentation - Van Tran

DR. TRAN: Thank you, Dr. Penzenstadler.

My name is Van Tran, and I'm a statistical reviewer in the Division of Biometrics VII in the Office of Biostatistics. For the discussion of cardiovascular safety, I will first discuss the CV safety endpoints and their statistical analyses.

The objective of the ASCEND-ND and ASCEND-D primary safety analysis is to demonstrate noninferiority of MACE comparing daprodustat to the active control. Noninferiority to the active control on MACE would be claimed if the upper limit

of the two-sided 95 percent confidence interval was less than the hazard ratio of 1.25 that prospectively defined this margin.

The co-primary safety endpoint was the time to first occurrence of adjudicated MACE, defined as a composite of all-cause mortality, nonfatal MI, and nonfatal stroke. Secondary, prespecified safety time to first event endpoint included all-cause mortality; CV mortality; MI; stroke; hospitalization for heart failure; and thromboembolic event.

Additional but not prespecified, time to event endpoints exceeding MACE, which is a composite of CV mortality, nonfatal MI, and nonfatal stroke, and endpoint of vascular access thrombosis were also considered to be clinically meaningful. MACE and secondary CV endpoints were adjudicated by an external independent clinical events committee.

The statistical analyses were the same for both the ASCEND-ND and ASCEND-D studies. The primary analysis population for the analysis of

MACE and CV endpoints is the intention-to-treat population. The analyses considered multiple event ascertainment windows with on-study as the primary analysis approach and on-treatment as supportive. An on-study analysis approach includes all events, whether exposed to treatment or not, whereas an on-treatment analysis approach includes only events that occur while subject is exposed to treatment less than time window.

The primary analysis of time to first MACE and other time to first event endpoints is a Cox proportional hazards model controlling for treatment and adjusting for baseline variables using stratified randomization. Analyses of secondary and exploratory CV endpoints of subgroups were conducted but not multiplicity controlled. Given the disparate MACE risk estimates of on-treatment and on-study analyses, we felt it was important for us to be transparent and share our perspective on the two approaches to outcomes ascertainment.

For the assessment of MACE and other CV

safety outcomes, the review team focused on the on-study risk estimates. The design and conduct of both the ASCEND-D and ASCEND-ND trials were suitable to evaluate on-study estimates of risk, and comparative analyses using the on-study approach preserves the integrity of randomization and are less subject to bias. For these reasons, the review team focused on the on-study risk estimates in the assessment of CV safety.

Although the on-treatment analysis results were inconsistent with on-study results for MACE, on-treatment analysis is subject to bias. For these reasons, the remainder of my presentation will discuss only on-study estimates of risk.

Next, I'll discuss the analysis results for the non-dialysis-dependent population studied in the ASCEND-ND study. This table presents the primary analysis results for time to first MACE in ASCEND-ND. 1937 subjects in the daprodustat arm and 1935 subjects in the darbepoetin alpha arm were at risk for MACE for approximately 3500 person-years in each arm.

You'll notice that these followed numbers are slightly different from previous slides because of slightly different definitions used. 378 MACE in the daprodustat arm corresponded to an incidence rate of 10.9 events per 100 person-years and 371 MACE in the darbepoetin alpha arm corresponded to an incidence rate of 10.6 events per 100 person-years,

The hazard ratio for time to first MACE was 1.03 with a 95 percent confidence interval of 0.89 to 1.19 comparing daprodustat to control. The upper bound of the confidence interval was lower than the prespecified risk margin of 1.25, therefore the study ruled out the risk margin.

Five components of MACE -- all-cause mortality, nonfatal MI, nonfatal stroke -- are shown with number of events and percentage out of MACE. Note that a subject was counted only once using their first component event in the component summary. MACE comprised mostly of all-cause mortality, followed by nonfatal MI, and nonfatal stroke.

Kaplan-Meier, or KM curves, for MACE are shown in this plot with daprodustat annotated in blue and the control in black. The curves overlap throughout the follow-up period. This figure is consistent with the results shown in the previous slide. In addition to the assessment of MACE, this plot shows KM curves for time to all-cause mortality with daprodustat annotated in blue and control in black. The curves overlap throughout the follow-up period. The hazard ratio was 1.03 with 95 percent confidence interval and 0.87 to 1.20. The curves together with a hazard ratio estimate suggests that all-cause mortality was similar between arms.

This forest plot shows the results for prespecified subgroup analyses in MACE. Estimated hazard ratios for MACE were greater than 1.0, comparing daprodustat to control in several subgroups. Of particular interest was the elevated hazard ratio estimate in the USA subgroup compared to the non-USA subgroup because the USA is under FDA's jurisdiction. The point estimate for the USA

subgroup is to the right side of the vertical line, denoting the null value of 1.0.

These USA subgroup sample sizes were moderate, approximately 500 subjects per treatment arm, and the treatment effect estimates were relatively precise compared to other subgroups. Exploratory analyses across the secondary CV endpoints for USA compared to non-USA subgroup will be discussed later in the slides.

In general, a limitation on looking at many subgroups in an exploratory manner is that the chance of observing a signal that is an overestimation of the truth was non-negligible. Also, low event rates and small sample sizes for some subgroups limit the interpretability of those analyses.

Looking beyond MACE, CV risk in the non-dialysis-dependent population was evaluated further by assessing the adjudicated CV endpoints. The endpoints included CV MACE; CV mortality; MI; stroke; hospitalization for heart failure; thromboembolic event; and vascular access

thrombosis. This plot for ASCEND-ND shows the estimated hazard ratio comparing daprodustat to control is greater than 1.0 for each of the adjudicated CV endpoints. The point estimates lie to the right side of the vertical line, denoting the null. The hazard ratios range from 1.06 to 1.49. These estimates are shown to visually assess the trend in the endpoints, but we emphasize that the error for performing multiple comparisons was not controlled in these analyses.

We provided estimates, but not statistical testing, of the separate endpoints of fatal or nonfatal MI, fatal or nonfatal stroke, which are different from the components of first MACE. These are distinct endpoints that give the number of patients who ever experienced an event, either fatal or nonfatal, of each type. However, we acknowledge the limitations of these analyses to include lower precision compared to MACE because of lower event rates and, hence, wider 95 percent confidence intervals, and no type 1 error control for treatment arm comparisons.

Despite these limitations in ASCEND-ND, the consistently increased risk estimates across different CV endpoints, measuring related aspects of CV risk, and a cardiovascular outcomes trial raises concern as to whether daprodustat is safe relative to darbepoetin alpha, which itself carries an increase of CV risk.

To further explore CV endpoints in the regional subgroups, exploratory analyses were conducted for each adjudicated CV endpoint in the USA, the top plot, and non-USA subgroup, the bottom plot. The estimates for the USA subgroup ranged from 1.2 to 2.0, while the estimate for the non-USA subgroup recoils to the null, with exception of stroke. Comparing the two plots, except for stroke, the hazard ratio estimates for the USA subgroup were greater than the non-USA estimate.

Note that the variability of hazard ratio estimates, demonstrated by the confidence interval width, depended on the number of events and sample sizes, the lower precision for the USA subgroup compared to the non-USA subgroup, and for endpoints

at stroke and thromboembolic event.

While there were differences between USA and non-USA subgroups in terms of baseline demographics and characteristics, we are unclear if these differences contributed to the discrepant results between the USA and non-USA subgroup because of the exploratory nature of these comparisons. Although exploratory analysis could introduce bias and produce unreliable results, the higher risk estimates in the USA subgroup compared to the non-USA subgroup in the ASCEND-ND study were seen across multiple CV endpoints, and were consistent with unfavorable MACE prespecified region subgroup results.

In summary, the analysis of MACE rules out the risk margin of 1.25 in the ASCEND-ND study. The Kaplan-Meier curves overlap. All-cause mortality was similar between daprodustat and control. Hazard ratio estimates were consistently greater than 1.0, ranging from 1.06 to 1.49 for all adjudicated CV endpoints. USA subgroup analysis had greater hazard ratio estimates of CV endpoints,

except stroke for non-USA subgroup.

Because of ESA, like darbepoetin alpha, already carries CV risk, a further increase in these risks beyond that seen with ESAs is concerning. Some limitations of these CV endpoints in subgroup analyses include hazard ratio estimates at lower precision compared to MACE because of smaller sample size and few events. There was no type 1 error control, which means that the chance of observing false safety signals is higher than the nominal 0.05 level.

Next, I'll discuss the analysis results for the dialysis-dependent populations studied in the ASCEND-D trial. This table presents the primary analysis results for time to first MACE in the ASCEND-D study. 1487 subjects in the daprodustat arm were at risk for MACE for approximately 3400 person-years; 1477 subjects in the ESA arm were at risk for MACE for approximately 3300 person-years. 374 MACE in the daprodustat arm corresponded to the incidence rate of 11.1 events per 100 person-years; 394 MACE in the ESA arm

corresponded to the incidence rate of 11.9 events per 100 person-years.

The hazard ratio estimate for time to first MACE was 0.93 with 95 percent confidence interval from 0.81 to 1.07, comparing daprodustat to ESA. The upper bound of the confidence interval was lower than the prespecified risk margin of 1.25, and therefore the study ruled out the risk margin. Five components of MACE -- all-cause mortality, nonfatal MI, nonfatal stroke -- are shown with number of events and percentage out of MACE. MACE comprised mostly of all-cause mortality followed by nonfatal MI and nonfatal stroke. KM curves for MACE overlapped throughout the follow-up period, with daprodustat annotated in blue and ESA in black. This figure is consistent with the results shown in the previous slide.

Shown in this plot are KM curves for time to all-cause mortality, with daprodustat annotated in blue and ESA in black. The curves overlap throughout the follow-up period. The hazard ratio estimate was 0.96 with 95 percent confidence

interval spanning from 0.82 to 1.13. The curves together with the hazard ratio estimate suggests that all-cause mortality was similar between arms.

This forest plot shows the results for prespecified subgroup analyses of MACE. Subgroup hazard ratio estimates were less than or equal to 1.03 and generally consistent with the overall study population MACE estimate.

Similar to the CV analyses conducted in the ASCEND-ND study, I present here analyses of adjudicated CV endpoints only. A higher incidence of hospitalization for heart failure was observed in the daprodustat arm compared to the ESA arm, corresponding to a hazard ratio estimate of 1.10, a 95 percent confidence interval from 0.84 to 1.45. It is the only endpoint in this plot that is to the right of the vertical lines, noting the null.

If you recall, a higher incidence of hospitalization for heart failure was also observed in the daprodustat arm in the ASCEND-ND study, corresponding to a hazard ratio estimate of 1.22. A higher incidence was not observed for other

adjudicated CV endpoints in the daprodustat arm in this ASCEND-D study. It's unclear why there is a pattern of increased risk estimates in all the CV endpoints in the ASCEND-ND study and not in this study. Again, these estimates are shown to visually assess the trend in the endpoints, so we emphasize that the error for performing multiple comparisons was not controlled in these analyses.

The applicant presented the composite endpoint of all-cause mortality or hospitalization for heart failure. If interest lies in understanding the risk of hospitalization for heart failure, using a composite endpoint with all-cause mortality appears to answer a different question; that is the risk of hospitalization for heart failure and other causes of mortality, but does not directly address hospitalization for heart failure.

In addition, it's important to note that the risk estimate of such a composite would be dominated by all-cause mortality, which is neutral, and potentially obscure any safety signal in the hospitalization for heart failure, which included

both fatal and nonfatal events.

This plot shows exploratory subgroup analysis of hospitalization for heart failure by history of heart failure, yes or no. Although we are discussing the ASCEND-D study, I've included here the results for the ASCEND-ND study because of consistent findings across trials. The subgroup analysis of hospitalization for heart failure, we've provided here, use predefined, as specified in the SAP, subgroups with history of heart failure, which included four terms from the medical history; that is, heart failure; left ventricular systolic dysfunction; left ventricular diastolic dysfunction, and pulmonary arterial hypertension. This is in contrast with sponsor's presentation of subgroup results using post hoc subgroup definitions that included only the medical term "heart failure," which is a narrower definition than the prespecified subgroup definition.

In both ASCEND-ND and ASCEND-D, a higher incidence of hospitalization for heart failure was observed in the daprodustat arm compared to the

control arm in the subgroup with a history of heart failure. The hazard ratios from subgroups with history of heart failure were greater than the hazard ratios for the subgroups without a history of heart failure, which had hazard ratio point estimates less than the null value of 1.0.

In summary, the analysis of MACE ruled out the risk margin of 1.25 in the ASCEND-D study. The Kaplan-Meier curves overlapped. The subgroup analysis results were consistent with overall study population. All-cause mortality was similar between daprodustat and control. The hazard ratio estimate was greater than 1.0 for HHF, or hospitalization for heart failure, comparing daprodustat to control. The subgroup with a history of heart failure had greater hazard ratio estimates in the subgroup without a history of heart failure.

Similar to the study, the ASCEND-ND study also had elevated hazard ratio estimates for hospitalization for heart failure. Other CV endpoints had hazard ratio estimates less than 1.0

unlike hospitalization for heart failure. Some limitations of the CV endpoints in subgroup analyses include the hazard ratio estimates have a lower precision compared to MACE because of smaller sample size and fewer events. There was no type 1 error control. These limitations are similar to those discussed in the ASCEND-ND study.

That concludes my presentation on clinical CV safety. I will now turn the presentation over to my colleague, Dr. Justin Penzenstadler.

FDA Presentation - Justin Penzenstadler

DR. PENZENSTADLER: Thank you, Dr. Tran.

Yes. This is Justin Penzenstadler again, and I'll be closing the FDA presentation with a brief summary of general safety findings, as well as summarizing the benefits and risks observed.

The FDA conducted a standard battery of ad hoc and adverse event analyses consistent with our approach for other new molecular entities. We identified some notable treatment differences in daprodustat that seemed to have additional risks beyond the ESA comparators. We already covered

heart failure and other CV risks, but I'll now focus on GI erosions and acute kidney injury in the slides to follow.

I will not present unremarkable findings from a boilerplate analyses, but first I want to establish that unremarkable findings observed in ASCEND-D and ASCEND-ND noninferiority studies imply that daprodustat carries the same risks. This includes, but is not limited to, hypertension, seizure, sepsis, and malignancy. Finally, we did not identify risks that are present in ESAs but lower or absent to a convincing extent in daprodustat.

Now before I start with clinical gastrointestinal erosions, I want to acknowledge the applicant's nonclinical data, which demonstrated gastric erosions and ulcerations in mice, rats, dogs and monkeys with a possible basis for erosions and ulcers being compromised vascular perfusion associated with marked increases in hematocrit.

The FDA nonclinical team notes that the

cardiovascular stomach and other adverse effects in animals did coincide with high hematocrit or red blood cell mass, and thus it's reasonable to conclude that those effects are a consequence of the high red blood cell mass. Discerning another potential mechanism is confounded by the robust exaggerated effect on hematocrit, especially considering the studies uses healthy, for example, non-anemic animals.

So regarding the clinical endpoint, we did identify a treatment difference in serious esophageal and gastric erosions disfavoring daprodustat in both ASCEND-D and ASCEND-ND. Most identified clinical events were over gastrointestinal bleeding with over half requiring transfusion. The events were ascertained as an adverse event of special interest, but they weren't adjudicated. Not all of the patients who had an event underwent an EGD or h. pylori testing.

Now, these treatment arms were balanced for antiplatelets, anticoagulants, and prophylactic agents such as antiacids. These are the cumulative

incidence plots for the time to first serious gastrointestinal erosion. The Y-axis is cumulative incidence and the X-axis is time since treatment start in months. The red curve represents the ESA comparator and the black curve represents daprodustat. We've overlaid incidence rates for each arm to help interpret these data.

The cumulative incidence plot for ASCEND-D on the left shows a small treatment difference not favoring daprodustat. The cumulative incidence plot for ASCEND-ND is on the right. This plot shows the more pronounced treatment difference, not favoring daprodustat, and there does not seem to be a time dependence of this risk. The resulting rate difference was about seven additional events per 1000 patient-years for ASCEND-ND and two additional events per 1000 patient-years for ASCEND-D. It is notable that the estimates for harm have poor precision as evidenced by the wide 95 percent confidence intervals.

Importantly, we use an intention-to-treat analysis in contrast to the applicant who presented

events occurring within the last dose given plus dosing frequency window or similar. The last dose given plus dosing frequency window may bias in favor of daprodustat in cases where treatment discontinuation is not related to the adverse event itself since patients with less frequent dosing intervals would be followed for longer, on average.

There was a treatment difference in investigator-reported serious acute kidney injury not favoring daprodustat. However, we acknowledge that time to progression of CKD, a principal secondary endpoint, did not suggest harm, nor did routine clinical laboratory assessments such as serum creatinine or BUN when looking at aggregate level plots or laboratory shift tables.

This is a cumulative incidence plot for the time to first serious acute kidney injury. The Y-axis is cumulative incidence and the X-axis is time since treatment start in months. We've also provided tables underneath showing the number of subjects at risk and cumulative number of events. The red curve represents the ESA comparator and the

black curve represents daprodustat.

Here we see a pronounced treatment difference not favoring daprodustat, which begins to occur after approximately 16 months of treatment. At 3 years, a point which I've chosen arbitrarily, the cumulative incidence difference between treatment arms was approximately 2.7 percent.

We will conclude this FDA presentation with a brief discussion of overall benefits and risks for daprodustat in patients on dialysis and patients not on dialysis. Regarding the benefits, daprodustat is not inferior to approved ESAs in improving hemoglobin level with similar continued need for red blood cell transfusions or rescue therapy.

Daprodustat is administered orally in contrast to the ESAs, which are administered by injection. This may provide some convenience over parenteral ESAs. However, there is a less clear benefit in patients who receive hemodialysis since they typically receive ESAs during an in-center

hemodialysis session, and this benefit may be a double-edged sword. There's a risk of inadequate hemoglobin monitoring, which may lead to worse outcomes than demonstrated in the clinical trial setting.

Here we have summarized the issues discussed today in terms of absolute risk. This plot shows the incidence rate difference per 1000 patient-years and 95 percent confidence intervals for the adverse events in the non-dialysis population. Estimates on the right side of the vertical dotted line, which corresponds to zero, corresponds to a higher incidence in the daprodustat arm.

For example, an incidence rate difference of 20 would represent 20 additional patients experiencing at least one event compared to an ESA if a thousand patients were treated for one year. Also, the incidence rates of the adverse events in the comparator arm are shown in the box to the right for reference.

The plot shows that all the incidence rate

difference estimates are to the right of the vertical line, meaning that incidence rate for each adverse event is higher in the daprodustat arm compared to control, however, there remains uncertainty for the estimate of effects for these outcomes as shown by the variable confidence interval width.

Estimates for stroke; thromboembolic event; hospitalization for heart failure; GI bleed and erosion; and AKI are larger, as seen by the point estimates being further to the right compared to MACE and all-cause mortality, which are the two reported at the top of the plot, however, all point estimates are below 10 events per 1000 patient-years.

This plot shows the USA specific incidence rate difference estimates in red, with the overall study population estimates, which were presented in the previous slide, presented in transparent gray. Please take note of the scale of the X-axis. This has been expanded from the previous slide. The USA subpopulation estimates are all to the right of the

vertical line, meaning that the incidence rate for each endpoint is higher in the daprodustat arm compared to control. Except for stroke and GI bleeds, the USA subpopulation had higher rate difference estimates compared to the overall population. Note that the precision of the USA subgroup is lower than the overall population.

This plot shows the incidence rate difference estimates for adverse events in the dialysis population. Only estimates for hospitalization for heart failure and GI bleed or erosions are elevated, lying to the right of the vertical line.

Thank you very much for your attention, and we would appreciate you considering these issues as you deliberate, and this concludes my presentation.

Clarifying Questions

DR. LEWIS: Thank you.

We will now take clarifying questions for the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-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 the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I will once again start the questioning.

As is stated in the briefing document from the sponsor, all-cause mortality was used for CV safety evaluation in the previous ESA trials that were done, and I supported that. However, in CHOIR, TREAT, PEARL, EMERALD, virtually all of the previous ESA CV safety studies, CHF was also included, and in the CHOIR study, it was demonstrated as a strong safety signal.

Could you explain why it was not included in the co-primary outcome of this study?

DR. WROBLEWSKI: Hi. This is [indiscernible - audio distorted].

DR. LEWIS: I'm sorry. I couldn't hear your response.

Was it broken up for anyone else?

MALE VOICE: Yes.

DR. WROBLEWSKI: Hi. This is [indiscernible]. Is this better now?

DR. LEWIS: I'm sorry. It's still broken up, so I actually can't understand what you're saying.

DR. PENZENSTADLER: Hi. This is Justin Penzenstadler from FDA. We're working on this technical issue from our side; one moment.

DR. LEWIS: While you're working on it, I'll make another question/comment.

I would just say that when you're averaging GFRs or events of 40 percent decline in GFR over time, a few AKI events are unlikely, given the overwhelming majority of people who didn't have AKIs, GFRs being averaged in, and their loss of 40 percent being averaged in, to be noted. I'm

also surprised that you didn't discount that.

DR. WROBLEWSKI: Hi. This is Tanya Wroblewski. Can you hear me better? I was having some technical issues.

DR. LEWIS: Yes.

DR. WROBLEWSKI: Okay. Great.

So your first question to us was regarding the use of CHF. I'm going to have Dr. Farrell address that first question about the heart failure, and then we'll proceed to the subsequent question. Thank you.

(No response.)

DR. LEWIS: Dr. Farrell, if you're speaking, you may be muted.

DR. FARRELL: This is Dr. Farrell. Can you hear me now?

DR. LEWIS: Yes, ma'am.

DR. FARRELL: Oh, great.

It had to do with discussions a number of years ago about the reliability of adjudicating heart failure and hospitalization for heart failure. So the decision was made that it was more

complex, and therefore to stay with the MACE definition that we used for the clinical trials.

DR. LEWIS: Thank you.

I don't know if you're going to comment on my second question, but while you're thinking about it, I will move on to Mr. Conway.

MR. CONWAY: Thank you, Dr. Lewis. This is Paul Conway; first a clarifying question, and then a specific question on one of the slides.

To FDA, I'm curious. In this study, or the series of studies, what did the FDA put to GSK in terms of what you wanted for patient preference information, PROs, patient insights, or patient risk tolerance levels? Was the SF-36 the only thing that was used, and did you request that?

DR. WROBLEWSKI: Hi. Thank you for your question. I'm going to have --

DR. LEWIS: I'm sorry. Is this Dr. Farrell speaking?

DR. WROBLEWSKI: No. This is Tanya Wroblewski again with the FDA.

I'm going to have our clinical outcomes

assessment team comment a little bit about that question regarding the selection of the instruments for the NHQ trial, as well as the other instruments used in the ND and D studies.

DR. DANIELS: Thank you. This is Selena Daniels from the Division of Clinical Outcome Assessment. With regard to instrument selection, I believe the applicant proposed to use the SF-36 vitality domain.

MR. CONWAY: Okay. So here's my follow-up question. We had an opening statement today from FDA that there were no other meaningful benefits established. On page 59 of the FDA briefing, it says that there's a statistical -- that it's noteworthy in terms of statistics, the differences that were shown on the SF-36, but it says also not clinically meaningful. Then on slide 36 of the presentation here by Mr. Penzenstadler, it said "not considered meaningful improvement from a patient perspective."

So there are a lot of terms I believe that have been turned around, and for patients that are

listening and for policy makers that are listening, I think this is vitally important because I'd like to know whose judgment is it that said not considered meaningful improvement from a patient perspective because on the slide it's very definitive, but in the language that was used in presenting that side it says not likely.

So --

DR. WROBLEWSKI: Hi. This is --

MR. CONWAY: Sorry.

DR. WROBLEWSKI: This is Tanya Wroblewski with the Division of Nonmalignant Hematology. I am going to have Dr. Penzenstadler address that question first, and then have our clinical outcome team, as well as our statistical colleagues with the clinical outcomes address those questions.

Dr. Penzenstadler?

DR. PENZENSTADLER: Thank you.

This is Dr. Penzenstadler. First, I think we can step up a little higher level when we're talking about the clinical meaningfulness of this. The scenario studied in ASCEND-D and ASCEND-ND are

consistent with our current ESA labeling, where the target was 10 to 11 grams per deciliter of hemoglobin.

Now, NHQ was a bit different, so efficacy results under this clinical scenario are hard to extrapolate to ASCEND-D and vice versa. ASCEND-NHQ looked at hemoglobin levels between 11 and 12. So even suppose a benefit that was not arguable was established, the clinical meaningful benefit, it would be hard to attribute that to the scenario where safety was confirmed. Well, sorry. I shouldn't say confirmed, but where safety was studied and established.

Does that help answer your question?

MR. CONWAY: Not exactly. So let me go back to this one second.

On your slide 36 that you presented there's a bullet on there that says it's not considered meaningful improvement from a patient perspective. What patients did you talk to, to get to that conclusion?

DR. WROBLEWSKI: This is Tanya Wroblewski

again. I'm going to have our COA team delve into this a little bit more to get into some more of the details regarding the actual anchor scales and the instruments regarding your questions.

DR. DANIELS: Thank you. This is Selena Daniels from the Division of Clinical Outcome of Assessment. FDA agrees that fatigue is an important and relevant concept for the target population in ASCEND-NHQ, and while the SF-36 vitality domain is not a comprehensive fatigue assessment, it does measure some important aspects of fatigue based on the submitted qualitative data from the applicant.

FDA acknowledges that the applicant conducted anchor-based analyses to help interpret the clinical meaningfulness of the PRO results in ASCEND-NHQ, however, the external anchors used to derive the 6-point threshold, which are the Patient Global Impression of Severity, or PGIS scale, and Patient Global Impression of Change, or PGIC scale, have limitations that limit the interpretability of the results of the anchor-based analyses.

Specifically, the concepts measured in the PGIS and the PGIC anchor scales, which are the overall CKD symptoms which goes beyond fatigue, are not fully aligned with the concepts measured in the SF-36 vitality domain, which measures concepts of tiredness, weakness, fullness of life, and energy. FDA generally recommends that an anchor scale measures the same concept as the target instrument to provide the most direct evidence.

Due to the limitations of the PGIS and PGIC anchor scales, FDA used items 1 and 2 from the Chronic Kidney Disease Anemia Questionnaire, or CKD-AQ, as the primary anchors, which measures tiredness and energy, as these concepts were better aligned with the SF-36 vitality domain. The use of these anchors generated a different range of thresholds than what was proposed by the applicant, and I will turn it over to my colleague, Xin Yuan, from the patient-focused statistical support team to elaborate further.

DR. YUAN: Thank you, Dr. Daniels. This is [inaudible].

DR. LEWIS: You are also hard to hear. It's very soft.

DR. YUAN: Okay. Can you hear me ok?

MR. CONWAY: Yes. Thank you.

DR. LEWIS: I can now.

DR. YUAN: Thank you, Dr. Daniels. This is Xin Yuan, statistical reviewer from CDER biostatistics. Can we please have backup slide 105?

We would like to point out that the applicant conducted anchor-based analysis and proposed a clinically meaningful within patient change threshold range between 6 and 21 points in the 0 to 100 scale SF-36 vitality domain total score using data from studies ASCEND-ND and ASCEND-ID.

The applicant derived the range of 6 to 21 based on four patient self-reported anchor scales. As Dr. Daniels pointed out earlier, FDA considers CKD-AQ items 1 and 2 as more appropriate anchor scale to support the evaluation of clinically meaningful improvement. Using the information provided by the applicant, as you see on this

slide, FDA considers the range of 18 to 21 appropriate based on the applicant's anchor-based analysis results.

Regarding the question about why FDA does not consider the observed treatment effect as clinically meaningful, can we please have backup slide 103?

The empirical cumulative distribution function, the ecdf plot on the left, displays a continuous view of the cumulative proportion of patients reporting any amount of change from baseline to week 28 in the 0-to-100 scaled SF-36 vitality domain score between treatment arms. Note that a positive change larger than zero, to the left, represents an improvement in the score, and a negative change smaller than zero, to the right, represents a worsening in the score.

This figure has lines at changes of 12 and 21 points. The 12-point threshold uses an anchor that does not directly measure fatigue. There is not a clear and consistent separation between daprodustat and placebo arms within the range of

18 to 21, which as we showed previously on slide 105, are the thresholds from the anchors that do directly measure fatigue and the change on those anchors that the applicant proposed, and we agree with.

The applicant additionally provided the response rate of patients achieving different levels of improvement for each arm and the difference in response rates between arms. The corresponding table on the right shows the applicant's post-hoc responder analysis results using different cutoffs, at the thresholds of 18 and 21. The treatment difference is 8 percent and 6 percent, respectively. We do not consider these small treatment differences as a clinically meaningful improvement to patients.

I'd like to ask our DCOA colleagues do you have additional comments on this issue of the small treatment differences?

DR. DANIELS: This is Selena Daniels from the Division of Clinical Outcome Assessment. I have nothing further to add. Thank you.

MR. CONWAY: Okay. Just to make a final point here -- and I appreciate your indulgence -- slide 36, can you put that back up, please, on the presentation that Dr. Penzenstadler put up?

The final bullet point right there, "Vitality domain scores are not considered meaningful improvements from the patient perspective." So my question was, were patients talked to? And you gave me a very good and definitive statistical analysis, but my conclusion is patients weren't talk to.

I just want to make that point because when this was presented, the narrative was that it was unlikely, but here FDA is saying in the bullet point, quite definitively, they are not considered meaningful improvements. And I just respectfully disagree with that, but I wanted some clarity on the background. Thank you very much. That concludes my question.

DR. LEWIS: Dr. Abbott?

DR. ABBOTT: I'd just like to follow up.

This is Kevin Abbott, NIDDK.

If I could follow up on Dr. Conway's point, the presenters make a good case that they're making a comparison between daprodustat and ESAs. But given that 80 to 90 percent of the non-dialysis-dependent population doesn't receive ESAs -- which as Dr. Johansen pointed out, there are many barriers to this, and it hasn't changed recently -- and probably over 60 percent of this population stage 4 to 5 has anemia, we don't know exactly what percent, but over half probably would have untreated anemia; is it still fair to say that this group would not experience any benefit from the oral delivery of this medication? Thank you. That concludes my questions.

DR. WROBLEWSKI: Hi. This is Tanya Wroblewski with the Division of Nonmalignant Hematology. I'm going to have just a couple of points, and then I'm going to have Dr. Penzenstadler state a couple of comments as well.

I do want to point out something that

Dr. Penzenstadler said earlier. In the NHQ study, the target hemoglobin was 11 to 12, which is higher than the target hemoglobin in the ND and the D studies. So it calls into question whether or not targeting a higher hemoglobin, whether that change seen in the SF-36 would be seen when a hemoglobin at a lower target would be observed. So what is the relevance of the findings if NHQ applies to the other populations is something to be considered.

Dr. Penzenstadler, and then as well as Dr. Daniels, do you want to add anything else regarding the patient-reported outcomes, in terms of clinical benefit?

DR. PENZENSTADLER: Hi. This is Dr. Penzenstadler. I have nothing to add. Thank you.

DR. DANIELS: This is Selena Daniels from the Division of Clinical Outcome Assessment, and just going back to the previous question, patient input was included in the anchor scales that were used, so the Patient Global Impression of Severity and Patient Global Impression of Change from the

participants that were in ASCEND-NHQ, as well as the items 1 and 2 from the CKD-AQ instrument. Typically how the agency interprets clinical meaningfulness of a PRO or COA endpoint is to use anchor-based methods, so you'll use the patient global ratings to anchor what amount of change on that anchor translates onto the target instrument.

Generally, we also recommend that sometimes sponsors use qualitative data; so talking to patients to see what's actually a meaningful change on the anchor scale, as well as another target instrument. In this case, there were no interviews that were done with patients to determine what meaningful change on the anchor scale or the target instrument. So all we had were the anchor scales to anchor to the target instrument, and those were the results that were presented. Thank you.

DR. LEWIS: I would like to ask GSK to please put their hand down. This is the FDA question period.

(No response.)

DR. LEWIS: Dr. Cho, you may still be muted.

In fact, you are still muted. You're muted on the computer on the top bar.

DR. CHO: Ahh, thank you.

I have a comment and a question. My one question is there was such discrepancy between the dialysis patient and the non-dialysis patient, and it seems to me, as a cardiologist, that the dialysis patients are much higher risk, and yet the event rates are higher in the non-dialysis trials.

Can the FDA comment on why that might be? That's my one question.

Then my comment is, is I am very disappointed by the low enrollment of U.S. patient population in the ASCEND trial, and actually my question, that was a question to GSK, but we didn't have time to answer that question. But that is something that I find concerning about these trials. Thank you.

DR. LEWIS: Thank you, Dr. Cho.

Thank you, Dr. Cho.

DR. WROBLEWSKI: Hi. This is Tanya Wroblewski with the Division of Nonmalignant

Hematology. Regarding the question in the event rates between the non-dialysis as well as the dialysis, I'll have Dr. Penzenstadler and possibly Dr. Tran address that question. Thank you.

DR. PENZENSTADLER: Thanks.

This is Dr. Penzenstadler. I think it's a good point to raise, showing that the incidence rates of composite MACE are similar between ASCEND-ND and ASCEND-D.

Now, I can give sort of an unsatisfying answer to this, which is we were careful in not conducting cross-study analyses. I think it's of general interest, when you look up and down the forest plots, you see ASCEND-D might point more favorably among the list, and then when you look at ASCEND-ND, it tends to go on the other side. But to that end, we did do a little hypothesizing over on this side, but I'm not prepared to speak authoritatively on why these event rates or differences on hazard ratios might be different.

DR. WROBLEWSKI: This is Tanya Wroblewski.

Dr Tran, do you want to add any additional

follow-up?

DR. TRAN: This is Dr. Tran, statistical reviewer with FDA; nothing substantially to add to Dr. Penzenstadler's comments, but we do want to note that the comparators are different between ASCEND-D and ASCEND-ND studies. Thank you.

DR. LEWIS: Thank you.

Dr. Wang? Please identify yourself and unmute; unmute and identify yourself.

DR. WANG: Yes. Thanks a lot. This is Thomas Wang. First off, I appreciate the FDA's careful review of the issues. I'm just personally wrestling with this issue of whether to place any weight at all on the on-treatment MACE analyses. I get the message from the FDA's presentation that they really are discouraging us from focusing on it. That being said, it occupied a lot of the briefing document, and I think that's appropriate given that the hazards ratio 1.4 of possible harm was as high as any other signal observed in the secondary analyses.

I guess my comment and question is, if the

rationale is not paying attention to the on-treatment analyses as partly because the results are inconsistent with the primary analyses and these were not prespecified analyses, why should we pay any more attention to these than to all of the subgroup analyses and secondary analyses, which the FDA did encourage us to consider?

Second, what led these analyses to be conducted in the first place? Again, if results were consistent with the primary analyses, then they wouldn't have added any more information. That's my question.

DR. WROBLEWSKI: Hi. This is Tanya Wroblewski with the FDA. Thank you for your question. I'm going to have Dr. Tran start off, and then Dr. Penzenstadler as well to follow up. Thank you.

DR. TRAN: Hi. This is Dr. Tran, statistical reviewer with FDA. Regarding your question, first I just want to make the correction that both on-treatment and on-study analyses were prespecified, and specifically for on-treatment, it

was the OT plus 28. So I think it's fair that we presented both analyses. However, as you have pointed out, we wanted to focus the results on the on-study analyses because we do think that it provided for cleaner and more interpretable analysis results. I think you've seen in our presentation the reasons why, as well as the applicant's presentation.

Now, you also brought up why should we consider those analyses as opposed to the other exploratory analyses that we have presented, and to answer that question, I think when we were looking at this, we were very aware of the dominance of all-cause mortality and MACE, and given that CV safety is a very relevant concern, we wanted to take a look at a non-MACE endpoint, and we saw that there was this pattern of consistent elevated risk in the other CV endpoints.

For the ASCEND-ND study, I didn't pick out particular endpoints, but showed instead the list of CV endpoints and to look at that trend. And we're not claiming that there's statistical

significance or it rules anything out, but we wanted to bring that up on for your consideration.

I'm going to turn this over to Dr. Penzenstadler to see if he has anything additional to add or I've missed anything.

DR. PENZENSTADLER: Thank you. This is Justin Penzenstadler. Dr. Tran did an excellent summary of our position. I just want to point out a couple of additional things here.

Look, we're sympathetic to the idea of an on-treatment estimate as a supportive analysis. Due to concerns there's a high background rate of all-cause mortality in this population, there's the suggestion of the idea that due to such a high background rate of all-cause mortality, you might have a reversion to the null, which might hide important safety findings.

We were, and still continue to be, sympathetic to that idea of an on-treatment estimand, however, in this case, for ASCEND-ND in particular, it was quickly apparent that this on-treatment definition, anchored on the last dose

given, was fundamentally flawed. And not only was it fundamentally flawed, but it was fundamentally flawed in a way that is beyond what we typically hear from statisticians, et cetera, on there's a bias in an unknown direction because of discontinuation that can be related to treatment. This is actually a unique mechanism of it being flawed.

To the point -- neither the applicant nor FDA caught this issue about the prespecified last dose given plus 28 days. We didn't catch this until we saw the data. Then you might ask, did we try to fix it? And yes, I think it's clear, based on the applicant's presentation, that they looked to more unbiased ways of defining this window, but from the FDA perspective, the choice of definition in a post hoc fashion was very sensitive to the choice of window itself. So the best way we handled this was to go with the ITT and leave it at that.

So with that, did that answer your question? Thank you.

DR. WANG: It did. That's very helpful. I appreciate it.

DR. WROBLEWSKI: This is Tanya Wroblewski again. Dr. Tran has one additional comment regarding this question.

DR. TRAN: This is Dr. Tran, statistical reviewer with FDA. We just want to note that, again, the on-treatment analysis is biased. What we presented for this subgroup analysis was on-study, which would not be as biased, but the issue with subgroup analysis is that it's not multiplicity controlled, but that would be the issue with that, and lesser with OT versus OS for subgroup analysis. Thank you.

DR. LEWIS: Thank you.

Dr. Butler?

DR. BUTLER: Thank you. Javed Butler here. My question is for Dr. Penzenstadler.

Assuming that all therapies have a spectrum of response, were there any analyses done on individuals that had a higher degree or a more robust response than that correlated with adverse

outcomes seen in especially the non-dialysis study, or perhaps some other measure like time outside the desired range after the therapy was initiated? Thank you.

DR. PENZENSTADLER: Thank you for your question, Dr. Butler. I can provide analyses and thoughts that we have that are sort of tangential to your question, and I can answer it then directly.

We did have the thought that hemoglobin behavior, trajectory versus time, might influence safety outcomes. So -- I said this earlier in my talk -- what we looked at was not only mean level, but actually visit-to-visit variability, and also the sponsor conducted a battery of supplemental analyses that showed time in range, and so on. And what we found is almost in everywhere we looked regarding the population of individual level and population level behavior of the hemoglobin trajectory, they were very balanced between arms. So what that did is then that provided assurance that based on randomized comparisons -- so a

statistically rigorous comparison -- that the hemoglobin trajectories are balanced, and thus they most likely don't influence safety.

Now then, if we did see something -- and this is where I answer your question directly -- one might go to a non-randomized comparison, and we might do a case control analysis, where individual patients at the time of the event, what was occurring, what was their hemoglobin level, and so on. The issue with those is it's confounded for many reasons and a bit less rigorous.

So what we determined in the course of our review is that we didn't need to go that route. We were able to look on randomized level comparisons and see that the behavior of hemoglobin was very similar between arms.

Now does that answer your question?

DR. BUTLER: Great. Thank you very much.

DR. PENZENSTADLER: Thank you.

DR. LEWIS: Dr. Nachman?

DR. NACHMAN: Yes. Thank you, Dr. Lewis.

Patrick Nachman. I had a high-level question that comes back a little bit to the question that Dr. Cho asked earlier.

So my understanding is that with respect to cardiovascular events, the frequency of events was not necessarily higher in the non-dialysis study versus the dialysis study, but that the difference, between group difference, was greater in the non-dialysis study than the dialysis study. The hazard ratios were attenuated or were not as large in the dialysis study than the non-dialysis study.

The high-level question that is in my mind is the following. We have a signal -- maybe -- that we are worried about, and the question is, is this a direct effect of the study drug itself? Is the study drug somewhat causing a toxic effect or deleterious effect on heart function or on risk of thrombosis? Or is this an indirect effect of the study drug on increased hemoglobin, for example, or is this signal that we're seeing related to the underlying disease, and the underlying disease population and their morbidities?

If I can start with the last scenario, in my mind, if a drug is directly injurious and you study a very high-risk population, the effects of that drug should be augmented by the pretreatment risk, right?

So if you study a very high-risk population, in this case the dialysis population compared to the non-dialysis population, you should see more events, whereas when studying a very high-risk population, the effect of the treatment is attenuated or not as visible. In my mind it argues that it is not a direct injurious effect of the drug on the target organ or pathogenic mechanism, but that it's we're measuring the effect of the underlying disease.

My question I guess is to Dr. Penzenstadler. Is this a way that we can think about this analysis or -- I'm not trying to compare the two studies, but I'm trying to understand how can we compare these effects of the drug in between treatment groups with respect to the potential pathogenic mechanism of events. And that's my long question.

Sorry.

DR. WROBLEWSKI: Hi. This is Tanya Wroblewski with the FDA. Just for clarification on this question, you're asking can we parse out whether it's a direct drug effect or due to the increase in hemoglobin, which is a potential effect of the drug as well as the baseline risk of these patients in terms of the safety findings, and the differences in the event rates between the dialysis study and the non-dialysis study?

Is that correct in understanding?

DR. NACHMAN: I think that there was an answer that we don't think that it's an effect of the hemoglobin. This was answered just a few minutes ago. But again, in my mind the big discussion here today is, is this class of medication or is daprodustat itself particularly risky with respect to cardiovascular events, whether it's through thrombus formation or a direct deleterious effect on heart function, or on blood pressure? And in my mind, if we're worried that there is a direct toxic effect of this drug, then

we should see an augmented toxic effect when we study a very high-risk population, which is the dialysis population compared to the non-dialysis population.

I'm wondering whether the fact that we're seeing a difference in the effect, the hazard ratio between treated and controlled, in the non-dialysis patient population, that at least in theory has a lesser risk of cardiovascular event than the very high risk event, argues in my mind that what we're seeing is not a direct toxic effect of the drug but that it's really all of the comorbidities that go with having severe kidney failure and being on dialysis.

DR. WROBLEWSKI: Hi. This is Tanya Wroblewski with the FDA. I think, based upon the data that we've reviewed from the applicant, establishing or knowing the direct drug effect or drug toxic event on the cardiac issues versus whether it's due to the differences in the baseline CV risk to the population is difficult.

DR. LEWIS: Can I interrupt for a second? I

think what Dr. Nachman is asking -- and Dr. Nachman, correct me -- is if the dialysis population has a higher baseline CV risk, there's a higher risk population for CV events, so they're enriched for people who are at higher risk for CV events. Shouldn't you be seeing the differential signal in that group preferentially to a lower risk group, which would be the non-dialysis?

DR. WROBLEWSKI: Yes. No, thank you. That is something that we have internally discussed and wondered why the risk is seen in the non-dialysis and not the dialysis population, and we just have hypotheses at this point and whether or not the dialysis patients may be more uremic, maybe their platelets don't work as well, and perhaps that's a protective effect, and could that be a reason. But these are all just hypotheses, and we don't really have a conclusive answer as to why the risk is seen in the non-dialysis, and more so than in the dialysis.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Hi. Thank you. Chris O'Connor. This is a question directed to Dr. Tran. On slide 49 regarding the CV endpoints, 7 out of 7 of those endpoints had a hazard ratio greater than 1, and then in slide 50, which is the ND study, and then in slide 58, 6 out of 7 in the dialysis group had a hazard ratio less than 1.

Do you think that's due to chance?

DR. WROBLEWSKI: Dr. Tran, do you want to take that question, please?

DR. TRAN: Hi. This is Dr. Tran, statistical reviewer with FDA. Thank you for your question. As we stated in our limitations of these analyses, there could be a multiplicity issue in these comparisons because they're not controlled for.

A couple of things. In the ASCEND-ND study, I think what was notable was the consistency among the events, where the estimates were elevated in the dapro arm. For the ASCEND-D study, yes, we cited hospitalization for heart failure, and that could very well be by chance, but when we saw that

hospitalization for heart failure was elevated in the subgroup of patients with history for her failure, that raised a concern, and we saw it in both studies.

So to answer your question, yes, there is that possibility, but I think seeing it either across multiple CV endpoints in both studies was concerning to us, and therefore we're bringing it to the AC for consideration.

DR. O'CONNOR: Thank you.

DR. LEWIS: Thank you.

Dr. Soergel?

DR. SOERGEL: Thank you, Dr. Lewis.

David Soergel, industry representative, a question for Dr. Tran. Actually, it follows exactly on the question from Dr. O'Connor and Dr. Nachman.

I'm curious about what you thought about the analysis of the sponsor in individuals with pre-existing heart failure looking at MACE. The reason why I'm asking is because the sponsor is suggesting that they would provide educational

materials, et cetera, to inform benefit-risk in those specific patients. So I'm curious about how you view that analysis. Thank you.

DR. WROBLEWSKI: This is Tanya Wroblewski with the FDA.

Dr. Penzenstadler, if you want to take that one first, and then Dr. Tran?

DR. PENZENSTADLER: This is Justin Penzenstadler. Sure, I'll take a first shot at it, and then Dr. Van Tran can touch on the statistical perspectives.

Regarding this subgroup, this post hoc subgroup for heart failure, it does sort of fit in to a predominant or canonical model where we're seeing a little bit of excess AKI and peripheral edema, and reports of fluid overload. It does fit in the idea that this adverse event would be more prevalent in those with pre-existing heart failure rather than incident.

So the idea is that it does make sense, from at least my perspective, that this drug wouldn't cause heart failure, new onset or incident heart

failure, but it might, due to fluid issues, et cetera, act on those with pre-existing heart failure. And that sort of predominant, canonical hypothesis may also fit in with why the effect was, at least based on point estimates, attenuated in the dialysis population who have their fluid shifted 3 times a week or 5 times, depending on what they're using.

So at least from a clinical perspective, not ignoring the post hoc and exploratory nature, which Dr. Tran will touch on, the clinical review team's view is that it does sort of fit in mechanistically. Thank you.

Dr. Tran, do you want to take over?

DR. TRAN: Hi. Yes. Thank you, Dr. Penzenstadler.

This is Dr. Tran, statistical reviewer with FDA. I just want to note a couple things that were different from our presentation of the subgroup analysis for hospitalization for heart failure compared to the sponsor's. We did use different subgroup definitions. FDA used the prespecified

subgroup definition for history of heart failure and sponsor presented a narrower definition, so the results would be different.

In particular, the sponsor showed I guess an attenuation of the treatment effect based on the study for hospitalization for heart failure with their choice of definition for subgroup analysis, that subgroup, but that wasn't the case where we presented the prespecified definition of subgroup of history for heart failure.

I just wanted to circle back. Did that answer your question?

DR. SOERGEL: Yes. Thank you.

DR. LEWIS: Ms. Alikhaani?

(No response.)

DR. LEWIS: You'll want to unmute at the computer level at the bar.

MS. ALIKHAANI: Yes. Jacqueline Alikhaani here. I'm an African American heart patient. My mother was a kidney dialysis patient. She had kidney failure. She had a lot of problems with her dialysis. She had strokes, heart attacks, several,

and the works, and I'm really concerned that since we know that African Americans have the highest risk for cardiovascular problems and disability and death from cardiovascular disease, I'm really concerned about the very small amount of African Americans and other high-risk ethnic groups represented in the trial. And I wanted to know -- it would have been really helpful -- especially, I'm also a little concerned about how the PROs were interpreted.

I think it would have been really helpful if there was a team of patients, and family members, and caregivers helping to design and lead this trial, and it would have been super great if they could have spoken to us today and shed a little more light on the PROs.

So I wanted to know did this trial have an executive team, or patients, family members, and caregivers as part of the leadership team of the trial? Is there any information about that? I didn't hear any.

DR. WROBLEWSKI: Hi. This is Tanya

Wroblewski with the FDA. I think this question would be best for the sponsor, GSK.

DR. LEWIS: GSK, do you want to respond?

DR. VAN ADELSBERG: This is GSK. The answer is we did not have a steering committee of patients and providers in this study.

DR. LEWIS: Thank you.

Dr. Packer?

DR. PACKER: Yes. Thank you.

I have two questions to FDA. One of them is related to the use of the on-treatment analyses vis a vis the ITT analyses. There has always been a concern about using ITT analyses for noninferiority trials because I guess, theoretically, if everyone in a randomized trial stopped treatment, then the treatments would be noninferior by an ITT analysis, yet there could be differences on an on-treatment analysis.

Has the FDA ever given any weight to an on-treatment analysis when you look at noninferiority? This is different than the usual superiority type of trial. I'm wondering if the

FDA ever gives weight to an on-treatment analysis.

DR. WROBLEWSKI: This is Tanya Wroblewski with the FDA. I'm going to turn this to Dr. Soukup with the FDA for a response. Thank you.

DR. SOUKUP: Hello. This is Mat Soukup, deputy director in the Division of Biometrics VII, Office of Biostatistics.

Dr. Packer, it's a great question. It's certainly something we consider when we're looking at -- especially in these large outcome trials designed for safety. Ideally, we design these trials to look at on-study estimates, and we use the on-treatment really as supportive, knowing that there is the potential for bias in the on-treatment assessment.

We're also aware of the potential for bias in the on-study analyses, as you point out, because of the potential for the effect to attenuate towards the null. But I think in the end, at least in this particular program, we're not dealing with super long trials. We're not dealing with situations where we feel like there is too much

attenuation towards the null in our on-study analyses. So that's where we feel like in this particular circumstance, because it was a well-designed program to estimate and on-study estimate of risk, that's been our focus here.

DR. PACKER: I really appreciate that. I think what you're saying is that under the current circumstances, you would emphasize the ITT, but you would look at the on-treatment analyses as being part of the picture, especially given the noninferiority hypothesis being tested. But I wanted to just ask one other question from FDA, and this is also I guess either statistical or clinical.

When you look at the SF-36 vitality score, and you look at the separation of the waterfall plot, what separation would have impressed the FDA? In other words, I understand the FDA is not impressed by statistical significance and thinks that the degree of separation is clinically modest. What degree of separation of the waterfall plot would the FDA have considered to be clinically

important?

DR. WROBLEWSKI: Hi. This is Tanya Wroblewski. This question is pertaining to the NHQ study, then, in terms of the 6-point difference observed?

DR. PACKER: I'm not terribly enamored with looking at specific thresholds. I was really referring to the FDA waterfall analysis where you have -- if you could put up that slide. I'm sorry. I don't even know whether the slide had a number. It's the cumulative incidence response rate in the two treatment arms.

Do you know what I'm referring to?

DR. WROBLEWSKI: Yes.

DR. PACKER: Yes. That's it. That's it. Perfect. I guess what we're seeing here is what we typically see with a PRO type of analyses. The curves converge at the far bottom and at the far top, and there's this separation in the middle, and I think what you're saying is that that degree of separation is clinically unimpressive.

I guess what I wanted to know was, in the

body of the curve, where the curves separate, what degree of separation would have impressed the FDA?

DR. WROBLEWSKI: Dr. Yuan, with the PFSS team, do you want to take an initial response to this question?

DR. GARRARD: Hi. This is Dr. Lili Garrard, statistical team leader from CDER Biostatistics. I will actually take over this question. Thank you for that question.

I think the degree of separation between the curves will depend on the type of disease we're looking at and also the effect of the treatment. So in this case, what we're really looking for is consistent separation, and based on our experience working in many therapeutic areas, when you're looking at symptomatic improvement, a difference less than 10 percent is usually regarded as not very impressive. And again, this is based on our experience looking at different types of patient self-reported data.

On this graph that you see, the cumulative distribution function graph, in the threshold of

18 to 21, where FDA considers to be more appropriate, at the threshold of 18, you're only looking at an 8 percent, and at 21, a 6 percent.

We recognize this as post hoc analysis. The confidence interval actually included zero. So in our opinion, based on our experience, this is not very impressive. And it would have been very helpful to have additional supported qualitative data from patients, but this is the available data that we have.

DR. PACKER: Okay. Thank you.

DR. LEWIS: Thank you.

We will now break for lunch. We will reconvene sharply at 2:10 p.m. Eastern time. Panel members, please remember that 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 1:55 p.m. to ensure you are connected before we reconvene at 2:10 pm.

Thank you, and I apologize for the shortened lunch rate.

(Whereupon, at 1:32 p.m., a lunch recess was taken.)

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

(2:11 p.m.)

Open Public Hearing

DR. LEWIS: 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 applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant'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.

DR. ZELDES: Good afternoon. I am Nina Zeldes, a health researcher at Public Citizen's Health Research Group. I have no financial conflict of interest.

Public Citizen strongly opposes FDA approval of daprodustat for the treatment of anemia due to chronic kidney disease both in adult patients not on dialysis and those on dialysis. As detailed in the FDA review, this drug offers no additional benefits compared to ESAs, the currently available FDA-approved treatment options, while putting patients at substantial additional safety risks.

ESA is already carrying a black boxed warning because of an increased mortality risk for patients, as well as an increased risk for adverse events such as stroke and myocardial infarction. We, thus, agree with the FDA that any further increase in risks, quote, "beyond death seen with the ESAs is concerning," unquote.

In the pivotal trials in patients not on

dialysis and those on dialysis, daprodustat was noninferior to ESAs regarding the change in the hemoglobin level from baseline. The need for red blood cell transfusions or rescue therapy was also similar between the treatment arms, and as stated by the FDA, quote, "There were no other benefits demonstrated on how patients feel, function, or survive," unquote. In contrast to the lack of clear clinical benefit relative to the current treatment with ESAs, both trials demonstrated that this drug has serious additional safety risks for patients.

Patients taking daprodustat in both trials had higher incidence of hospitalizations for heart failure and bleeding gastric erosions. For example, the hazard ratio for hospitalization for heart failure for non-dialysis patients was 1.22 and 1.10 for patients on dialysis, and patients with a history of heart failure were at higher risk. The hazard ratio for serious gastric erosion events, the risk of which seemed to accumulate constantly over time, was 1.96 in non-dialysis

patients and 1.16 for those on dialysis.

In general, the risks of this drug for patients not on dialysis are particularly concerning. The data showed this group, especially in the USA subgroup, had increased risk estimates for several cardiovascular outcomes, including cardiovascular mortality, myocardial infarction, stroke, thromboembolic disease, and vascular access thrombosis. Patients also had elevated hazard ratios for MACE in some analyses and potentially increased risk for acute kidney injury.

The elevated hazard ratios for cardiovascular outcomes are particularly concerning, as the incidence across all cardiovascular outcomes, except for stroke, was higher in the U.S. subgroup, as can be seen here in figure 5. For example, in the daprodustat group, the incidence rate of thromboembolic events was 3.1 per 100 patient-years compared to 1.5 in the ESA group, a hazard ratio of 2.03. The hazard ratio for cardiovascular mortality was similarly increased at 1.86, where the incidence rate was

4.4 per 100 patient-years for daprodustat compared to 2.4 in the ESA arm.

FDA's analysis of treatment-emergent serious adverse events also showed that 4.9 percent of patients not on dialysis taking the new drug had acute kidney injury compared to 3.3 percent in the ESA group, with a relative risk of 1.5. The cumulative incidence at years 2 and 3 are shown here in figure 8.

In conclusion, this drug has serious additional safety risk for patients, particularly those not on dialysis, and offers no additional clinical benefits for patients. The oral route, while offering convenience, also appears to put patients at a higher risk for serious harm. In fact, this pattern of increased safety risk compared to ESA seems to be a concern of drugs of this class. In a similar drug, roxadustat was not recommended for approval over similar concerns earlier this year. We therefore urge the committee to vote no on the two voting questions and recommend that the FDA not approve daprodustat.

Thank you for your time.

DR. LEWIS: 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. SILVA: Good afternoon. I am Dr. Arnold Silva, a nephrologist and director of clinical research at Boise Kidney and Hypertension Institute in Boise Idaho, and I work in conjunction with Frenova Renal Research. I have served as a clinical investigator on studies evaluating the safety and efficacy of the hypoxia-inducible factor prolyl hydroxylase inhibitor, daprodustat. I've participated in studies evaluating daprodustat in patients with anemia of chronic kidney disease not on dialysis, as well as patients with anemia and end-stage kidney disease receiving dialysis treatments. I am not financially compensated for my time today.

As a physician and clinical investigator who has participated in anemia clinical studies with multiple industry sponsors for over 23 years, I am

encouraged by both the efficacy of this new oral therapy to treat anemia chronic kidney disease with an adverse effect profile that is comparable to injectable erythropoietin stimulating agents. Furthermore, I believe daprodustat as an oral agent offers more than a new treatment option to raise hemoglobin in kidney patients with anemia.

In the day-to-day clinical care of patients with renal disease, access to therapy poses difficulties for a patient population with multiple socio-economic challenges. Many rural areas, of which Idaho is an example, pose transportation issues for patients who must travel to medical centers or clinics that provide injectable therapies to treat anemia of chronic kidney disease. This impacts patient compliance with treatment and ultimately can adversely affect both their quality of life and their clinical outcomes.

An oral therapy for anemia reduces transportation needs and the associated financial burden for many of these patients. Moreover, in patients with end-stage kidney disease on renal

replacement therapy, use of oral daprodustat empowers patients to take a more active role in the management of their anemia that can have beneficial effects on both compliance with treatment and overall well-being.

Many of the patients who've participated in the daprodustat clinical trials voice great enthusiasm for a new option to treat their anemia with an oral medication. Oral therapies can also positively impact dialysis workflow in both in-center and home treatment programs and provide a smoother and more efficient clinical operation.

Of additional consideration is the increased prevalence of chronic kidney disease and end-stage kidney disease and the challenges of meeting patient needs for renal replacement therapies. In-center treatment facilities can no longer meet this growing demand, necessitating that more patients pursue home therapies. While it has been shown that home therapies can be very effective for management of end-stage kidney disease, home treatment does pose additional challenges in

meeting the medical needs of patients, particularly anemia management. Access to daprodustat will help alleviate this burden for patients on home therapies in a safe and effective manner.

Finally, study data and operations aside, the positive reports from patients taking daprodustat therapy, including stable hemoglobin values, with improved energy levels and a preference for oral versus injectable therapies, suggest that daprodustat be given consideration for approval as an additional and important tool to treat anemia of chronic kidney disease.

In summary, I enthusiastically recommend the approval of daprodustat. I would like to thank the committee today for the opportunity to speak. Your consideration is most appreciated. Thank you.

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.

MS. ARNTSEN: Kathleen A. Arnstsen. I'm a patient advocate, and president, and CEO of Lupus

and Allied Diseases Association or LADA for short. LADA is an all-volunteer and patient lab national organization that does receive program funding from healthcare related organizations, including biopharmaceutical companies for our programs. However, the viewpoints of LADA representatives are entirely our own unique patient perspective. I had submitted written comments and hope you have them in front of you.

Thank you for the opportunity to provide our unique patient perspective regarding NDA 216951, daprodustat, the proposed treatment for anemia due to chronic kidney disease in adult patients. I submit these comments as an organization leader, advocate, and an individual who knows firsthand we desperately need new treatments for people with debilitating conditions like anemia in CKD, and urge you to vote in favor to approve daprodustat to expand treatment options and address the significant unmet medical needs.

As a person with lupus, I struggle daily to have a productive life while managing multiple

autoimmune disorders and comorbid conditions, including anemia of CKD and interstitial nephritis. I take 48 medications a day and have unique allergies to both active and inactive ingredients and drugs. I have an infusaport for ongoing infusions, and I'm blind in my right eye.

No one-size-fits-all product exists for complex patients like me. Our immune system to treatments is unique, contrary, and at times adverse. Effectively treating patients like me requires thinking outside the box, immediate accessibility, the entire arsenal of treatments, and open and transparent communication between me and my providers. My treating physician knows best what drugs to use for someone as complex as me to balance therapeutic and safety concerns. We have been eagerly awaiting more efficacious and safer innovative treatments, and in a perfect world I would take one pill a day for treatment.

When I was originally treated for anemia of CKD, I received several iron injections. Not only did it turn my skin brown, but I had a

lipodystrophic reaction that left me with a crater in my buttocks and my right hip. I had to walk with a cane for several months until the area filled in enough to hold my weight. After two iron infusions, the local physicians decided that I was too high risk for them to treat, so I was forced to travel an hour and 20 minutes each way to be treated at an academic medical facility.

At that point, I had surgery to place an infusaport. I was infused regularly with both iron and Apigen until my infusaport stopped working. The catheter cracked and was piercing the blood vessels in my chest, so I was rushed into emergency surgery to remove that one and place another one on the opposite side.

The second has lasted and continues to work, however, I'm afraid that there are limited options available to place one in my chest if this one fails. I still receive iron infusions regularly. Traveling to and from the center is a tremendous burden to my husband and I since I am visually impaired and he is my driver and care partner.

Having the option to be treated at home with an oral therapy would be much more preferable to us.

At LADA, we often hear stories about the challenges our community faces in getting their infusible and injectable treatments. Transportation could be a major issue no matter where they reside, as well as the inability to self-inject due to hand strength, arthritis, or tremors. Taking time from school and work has been shared as an impediment. These issues are further intensified by ongoing concerns and having to leave our homes during the COVID-19 pandemic.

These issues impact the patient and their family members and care partners, and can result in non-adherence, poor outcomes, and devalue the treatments. Newer effective therapies such as daprodustat show tremendous promise and therapeutic advantages for people living with anemia CKD just as Apigen had for countless individuals. Access to appropriate medication can approve disease outcome and quality of life, and treatment can reduce the severity of disease activity and slow its

progression, enabling people like me to remain productive.

We desperately need safer, more innovative treatments that address the pathogenesis of diseases, while impacting what matters most to patients, reducing symptoms, and improving daily functioning and quality of life. We believe that daprodustat has the potential to do that as an oral treatment for people with CKD. The data from the ASCEND clinical trials showing that patients receiving daprodustat either improved and/or maintained target hemoglobin levels was a noninferior safety profile versus standard of care.

Thank you for the opportunity to share our unique perspective as you evaluate daprodustat tablets for anemia due to CDK, and we strongly encourage you to support this application based on the positive results of the trial because it would provide an additional treatment for physicians and patients to choose from, promoting shared decision making and treatment adherence, resulting in improved outcomes while also delaying further

damage in ESRD.

We commend the FDA for continuing to recognize the importance of the patient's voice during the drug review process, especially --

DR. LEWIS: Speaker number 3, thank you.

MS. ARNTSEN: -- for all stakeholders.

DR. LEWIS: Speaker number 3, thank you. Your time is up.

MS. ARNTSEN: Thank you.

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

MS. HARRISON: Hi. I'm Carly Harrison. I'm a patient advocate and researcher by academic training, and chief researcher and innovative officer of patient-led healthcare organization, LupusChat. I have no financial conflicts or disclosures.

I'd first like to thank you for the opportunity to provide my patient perspective regarding NDA 216951, daprodustat. I offer these

comments as an advocate, a researcher, and as an individual with personal anecdotal evidence that in-treatments are needed for people with anemia and CKD. I implore you to vote in favor of daprodustat to assist with meeting this crucial medical need.

For two decades I've lived with systemic lupus erythematosus. For just over one decade, I have lived with knowledge that I suffer from nephritis or chronic kidney disease. Along with SLE, I have several other conditions inclusive of anemia, cardiac involvement, and a microadenoma on my pituitary gland, currently suppressing my optic nerve, which has now limited my ability to drive.

I take several medications daily, and I also must travel to medical facilities both near and far to be treated for both my lupus and my anemia. Managing my medical care has been stringent on me mentally, emotionally, and financially. The medical team and I work hard to ensure that we are utilizing the best medical interventions to improve not only my health but also my quality of life.

As you may well know, chronic kidney disease

is an illness characterized by the gradual loss of kidney function. Several years after my diagnosis of kidney involvement, I was notified also of my anemia. I was first treated with iron tablets. This caused GI issues and was at the time very burdensome in conjunction with the many other tablets that I had to consume daily. After some discussion with my healthcare team, I was then switched to iron infusions. This created an issue for me because at the time I was a full-time student doing laboratory research while also maintaining a full-time job to support my family. I had to now add infusions to my daily list of responsibilities.

Unfortunately, the iron infusions lasted a few hours, but the side effects were extensive; the most cumbersome being the fatigue that they caused. I was unable to be productive for the remainder of the day and had to sleep for that entire time. This caused financial strain on me, as I was unable to work. I have been getting infused for several years, and each time that I go, I anticipate that I

am at a risk of losing income.

If there are more options available for the treatment of anemia of CKD, the likelihood of my disease and my quality of life improving would increase. As more of the safer and effective treatment options become available within the United States, they increase the likelihood of positive health outcomes for hundreds of thousands of people. The healthcare arena and the U.S. government as a whole must remain steadfast in ensuring patient safety while boosting access to care and treatments.

As a researcher, I'm very interested in the data regarding daprodustat. Trial results reveal that while there were risks, there were patients receiving the drug that either improved overall and their hemoglobin levels increased. There are millions of Americans who could benefit from innovative drugs now, and many more in the future who aren't even diagnosed.

Patients like me, who have chronic diseases and have a very limited amount or no therapies at

all, we could benefit from having options in what we can access for our medical needs. Thank you so much for the opportunity to share my perspective as you evaluate NDA 216951.

DR. LEWIS: 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.

MR. SPIGLER: Good afternoon. My name is Mike Spigler, and I am the vice president of Patient Support and Education for the American Kidney Fund. I do not have any personal financial relationship with the applicant. The American Kidney Fund fights kidney disease on all fronts as the nation's leading kidney nonprofit. AKF works on behalf of the 37 million Americans living with kidney disease and the millions more at risk, with an unmatched scope of programs that support people wherever they are in their fight against kidney disease. Those 37 million Americans include my mother, who is a chronic kidney disease stage 3b patient with anemia.

So on behalf of the American Kidney Fund, the patients we serve, and myself as a primary caregiver to a kidney disease patient with anemia, I want to thank you for the opportunity to address you this afternoon.

Anemia is very common in people with chronic kidney disease, also known as CKD. CKD patients with anemia often struggle with quality-of-life issues, including fatigue, shortness of breath, headaches, and sensitivity to cold. And as in the case with patients like my mom, the fatigue and shortness of breath can often exacerbate issues with a sedentary lifestyle and other comorbidities such as the number one cause of kidney failure, diabetes, which my mother has struggled with most of her adult life.

Historically, there has been a lack of innovation in nephrology. Many treatments, especially in dialysis, have remained mostly unchanged for several decades. However, over the past 5 to 10 years, we've seen many innovations in rare kidney disease, CKD progression, and the

management of comorbidities, and these innovations have improved the quality and length of life for millions of kidney patients.

The American Kidney Fund supports similar efforts to find innovative treatments in CKD-related anemia. While current anemia treatments have been an important part of effective CKD management, there is room for improvement, as COVID-19 has shown patients need a greater ability to manage their own care. This is especially true for two groups of patients, those in rural areas and those who are doing dialysis at home.

While some patients can be taught to self-administer injections at home or have the means and ability to travel to a medical office, it is not suited for many patients. Many patients with advanced CKD or kidney failure face severe economic hardships. At the American Kidney Fund, transportation is the most common request for financial assistance from our safety net program. Providing anemia treatment options for patients that would allow for less travel to and from a

provider for an injection would be welcomed by many of the patients that we serve.

I want to thank you again for allowing the American Kidney Fund and other patient advocates to speak to you today. We appreciate the committee's careful attention to improving the lives of kidney patients through treatment innovations. Thank you.

DR. LEWIS: 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. STEDTNITZ: My name is Martin Stedtnitz. I'm a kidney patient. I'm not representing any organizations. I was a part of this trial, and I took the drug and had no ill effects from it whatsoever; improved my quality of life tremendously, as I was able to eliminate some of the side effects of the anemia as it boosted my blood count up.

I highly recommend that you approve this drug. It was a major improvement in my life and my lifestyle during that time. I am now currently a

dialysis patient and still going through the process, so I appreciate your time. Thank you for letting me speak.

DR. LEWIS: 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.

DR. HENRY: Thank you very much. I'm on a cell phone, so please tell me if you can hear me ok. I'm in and out of patient rooms.

DR. LEWIS: We can hear you.

DR. HENRY: Thank you.

I'm Dr. David Henry. Thank you for the opportunity to speak. I am a practicing clinical hematologist/oncologist at the University of Pennsylvania, Abramson Cancer Center in Philadelphia, and vice chairman of the Department of Medicine here at Pennsylvania Hospital. I have no financial or otherwise involved with this drug, nor have I had clinical trials with this drug. Full disclosure, I am a clinical investigator with roxadustat in cancer and MDS not in renal failure.

My thoughts, as you've heard already this morning and these testimonies, we see anemia so often in our chronic renal failure and cancer patients. It's a huge burden on patient quality of life and the medical system, and especially on the medical system lately and our precious resource of transfusions, if they're needed.

So many times with our ESAs, as others have said, we give to treat this anemia, and particularly today talking about chronic renal failure, with or without IV iron. Much of my career has been involved with clinical trials of ESAs plus or minus IV iron or IV iron alone. Actually, I was present and had the opportunity to speak at the ODAC in 2007 where the ESAs were up for consideration, and I'm sure the FDA members today recall the mandated trials after that ODAC in metastatic breast and non-small cell lung cancer, ESA versus placebo, to see if there was a change in survival, and those studies did not show a change in survival, which was really reassuring, and responding patients did actually have higher

hemoglobins, lower blood transfusions, and better quality of life.

But however, as others have said, this requires a visit to the cancer center usually; in my case, an ejection, either sub-Q, or IV, or both, depending on what the patient's getting, ESA, whether that's IV iron. It's time away from home, and the expense and time to get here, and of course the expense in getting this at the infusion center.

These HIF-1 alpha stabilizers have this wonderful new mechanism of action -- I'm sure you've heard this morning -- and in your consideration of chronic renal failure, or even in cancer chemotherapy anemia -- probably under study -- it's a pill instead of a shot 3 times a week. What a great benefit if approved.

While I have mentioned I have no involvement with the chronic renal failure studies, I do have with the HIF-1 alpha stabilizers in cancer and mild dysplasia. We've had some of those studies actually presented in our hematology meetings in both those entities, MDS and CIA, with the

roxadustat molecule. The phase 2 CIA study in the U.S. has shown encouraging results soon to be published, and the global phase 3 MDS study with the roxadustat molecule to treat anemia still ongoing.

For these reasons and this background, I've been really impressed by this group of molecules. Hopefully you will be impressed by the data presented to you today. If you agree it demonstrates safety and efficacy, which I know is your mandate, I would encourage your favorable review and recommendation for this novel new mechanism of action, HIF-1 alpha stabilizers to treat chronic renal failure, and hopefully in the future, that other large group of patients, cancer chemotherapy anemia and MDS, and I thank you for the opportunity to speak.

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

DR. HAASE: Hi. My name is Volker Haase.

I'm a nephrologist and physician-scientist, and I serve as the Krick-Brooks professor of medicine at Vanderbilt University. I thank you for the opportunity to speak here today.

I have been working on the oxygen sensing pathway and HIF biology for over 20 years, and a large part of my work is focused on mechanisms and therapy of anemia associated with chronic kidney disease. I've written extensively about HIF prolyl hydroxylase inhibitors and their use in patients with CKD, and I also was involved in the design and the analysis of phase 1 and 2 studies with roxadustat. As a recognized expert in this field, I have consulted for all major companies involved in the clinical development of HIF-PHI, including GSK.

I would like to say that I'm making this public comment solely as an individual and not on behalf of anyone else or of any academic or commercial entity. I do not own stocks in any company that either develops or markets HIF-PHIs for clinical use. I would like to make two short

comments, one as a scientist and one as a practicing nephrologist.

My first comment concerns the issue of class effects with a compound-specific effect. Why are there obvious pharmacokinetic differences between the different PHI compounds such as half-life? I believe that it is also important to recognize the potential pharmacodynamic differences between the different PHIs, which I believe will have significant implications for the safety profile.

So while compounds approved for marketing outside the U.S. target all three HIF-PHDs, PHD-1, 2, and 3, and stimulate erythropoiesis, they are likely to have differential inhibitory effects on other 2-oxobutyrate-dependent deoxygenated such as collagen prolyl 4-hydroxylase, PP4H [ph], and this was recently demonstrated for three HIF-PHis in two publications from Patrick Maxwell's group in Cambridge, and there are two references for this one regarding mannose binding lectin, which is hydroxylated by collagen prolyl 4-hydroxylase and inhibited by some of the PHD inhibitors.

This was a paper in Kidney360 in 2020 by Bhute, et al., B-H-U-T-E, and the second paper regarding complement C1q, which is also hydroxylated by collagen prolyl 4-hydroxylase, and was sensitive to inhibition by roxadustat in Kidney International 2017.

I also would like to refer you to a publications from Chris Schofield's group in Oxford, which compares four different HIF-PHIs side by side and demonstrated differences in their dynamics of HIF alpha stabilization in the degree of HIF target gene expression in cell culture. This is a citation by Yeh [ph], et al. in Chemical Science in 2017. I'm sure you're familiar with it.

The second comment I would like to make is as a practicing nephrologist who treats patients with anemia of CKD, six HIF-PHIs have been approved for the treatment of anemia CKD outside the U.S. In China, over 100,000 patients have been treated with roxadustat, and as suggested by case reports from China, the use of a HIF-PHI, in this case roxadustat, which has not been approved in the U.S.

but is approved in China, the EU, and also the UK, and Chile [indiscernible] as well. It may be beneficial in patients that do not adequately respond to the recombinant epo.

Furthermore, I believe that an oral agent for the treatment of anemia of CKD would facilitate anemia management of patients with CKD not on dialysis and positively impact the quality of life of many patients. These include patients, as you have heard, who need to travel to infusion centers or live in rural areas that have been now -- I echo the comment of the previous speakers with difficult access to health care, patients on home dialysis and patients on peritoneal dialysis.

So I strongly believe that many nephrologists in this country, and most importantly, patients, would agree with me that the availability of an alternative agent to recombinant epo, in particular an oral agent, would positively impact the management of patients with CKD anemia. I thank you for listening to my comments. Thank you.

DR. LEWIS: We will skip speaker number 9.

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

DR. COLEMAN: Hello. My name is Dr. Jessica Coleman, and I'm a private practice nephrologist in the Beaufort, South Carolina, low-country area of the United States. I want to first thank the committee for allowing me a few moments to speak and hopefully bring alive to you what a day in the life of my typical CKD patient looks like, and really what the burden of anemia does to these patients.

I'd like to first off admit that I have had no financial remuneration or incentivization here today, and I have no stocks in any of these companies. I have had some relationships with the variety of companies who have developed these HIF inhibitors for anemia of CKD, both on dialysis and non-dialysis-dependent patients, however, again, I have no financial obligations or incentivizations

to be here today.

My incentivizing factor to be here today is to really try to bring to life the burden that anemia of CKD can bring to my patient population, so I'd like to divide my talk similar to one of my previous peers who spoke so eloquently, and really first talk about the CKD patient not on dialysis, and then transition to our dialysis-dependent population.

What I'd like for the committee to consider is that the necessity of having an oral anemia drug is really profound in our patient population. Our chronic kidney disease patients who are not on dialysis really face numerous challenges in really trying to basically satisfy the complex nature of their chronic kidney disease. But even more so than that, just having to treat anemia with current standards of care with ESAs brings about another doctor's visit, another co-pay, transportation costs, extra lab draws, and even more so, it really inhibits their normal day-to-day activities, not only by virtue of these extra burdens, but also by

the fact that, given the complexities of dosing, our current supplementation strategies, patients often times find themselves in this peak and valley effect of anemia management.

In fact, I am currently in clinic right now. I just saw a gentleman who is 90 years old, but unfortunately has severe anemia CKD. Two months ago, his hemoglobin was 11.7, and today it is 7.7. Now, this is an extreme example, but I hope you can appreciate the clinical symptoms that he is feeling, the fatigue, the tiredness, the overwhelming lack of energy that he feels. Today's hemoglobin is 7.7, and then also think about really how difficult this is as far as the burden of disease on his body.

Now, when we transition to think about our CKD patients who are on dialysis, I also would like to underline the importance of consistency of care and highlight the potential non-responsiveness to current strategies. My goals in being here today is to hope that we can really all agree that improving patients' choices and improving access to

care really allows patients and physicians to move forward to unburden them from the complexities of anemia of CKD.

I really appreciate the opportunity to speak to you today, and I would hope that you would consider approving an oral anemia of CKD drug agent such as daprodustat. Thank you so much for your time today.

DR. LEWIS: We will skip speaker number 11.

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. DITSCHMAN: Thank you, and good afternoon. My name is Erich Ditschman. While I have had some involvement with various organizations with providing educational materials on CKD anemia, for this presentation I have no conflict of interest. Also, for this presentation, I am representing the many members of Home Dialyzors United, which is a nonprofit organization that inspires, informs, and advocates for an

extraordinary quality of life for those of us like me who are doing home dialysis.

Though I was diagnosed with CKD when I was 15 years old, the anemia CKD system didn't hit me until 20 years later when I crashed in dialysis. My wife Andrea was a match and donated one of her kidneys to me, but FSGS shortly shut it down. Some months later I was stabilized on home hemodialysis in 2001. I was back to work, but over time the fluctuations in my blood count made it difficult for me to maintain the quality of work my water resources clients depended on.

The anemia of chronic kidney disease symptoms stood in the way of full-time employment. Andrea went back to work, and I focused what energies I had on being the best dad that I could be to our son Jacob, and later our daughter Antonia. Eventually I added volunteer activities such as scouting 4-H and advocating for kidney patients.

Early on, I spent a lot of time at infusion centers receiving iron injections and at times

blood infusions, and at clinic where I would receive my erythropoiesis stimulating agent, which impacted every aspect of my life. Eventually I switched to doing the ESA injections at home, which helped, but they were administered after my hemoglobin had dropped, and they took time to have my count increase. But each of these episodes of decreasing and increasing blood counts, I was much less active, and this made it difficult to keep up with my responsibilities. It took me many years to learn how to just ride this lull and not beat myself up about it. Even with my in-home portable dialysis, I must make decisions around when I can travel and whether I can make plans.

Because I'm still very active and have family and volunteer obligations, I really need to make sure I am aware of when my hemoglobin levels drop. This is not easy because it is always trending one way or the other, with a short time at an actual decent level, and by decent level, I mean 3 points down from my previous KD level.

When I first got diagnosed and put on

dialysis, I felt like such a burden, especially when I had drops in my hemoglobin and would be stuck on the couch. No matter what I do to manage my kidney disease, I must manage the ups and downs of my anemia. At twice a month hemoglobin testing, at-home ESA administration, and switching to an iron-based phosphorus binder has helped, but I still deal with the seesaw effect. If I had access to a daily dose of a tablet form of ESA such as daprodustat, I'm sure that my stability would greatly improve, and that seesaw of anemia CKD would become much better balanced.

I would like daprodustat to be made available so that my doctor and I can make appropriate anemia CKD management decisions so that I can achieve my best outcome for me, my family, and communities in which I volunteer, and for my fellow home dialyzors as represented here today by Home Dialyzors United. Thank you very much.

Clarifying Questions (continued)

DR. LEWIS: I want to thank all our public speakers.

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 -- well, before we turn our attention to the task at hand, I am going to take the extra time we have to return to our unanswered questions for GSK.

Dr. Cho?

(No response.)

DR. LEWIS: Dr. Cho, can you unmute, and do you still have a question?

DR. CHO: Yes. Thank you.

Here is my question for GSK, and that is, the low enrollment in the U.S. population, I would like to understand a little bit more about that. And then number two; what would be the dosing for a HD patient and PD patient if the drug were to be approved? And then lastly, can they comment about the difference in the non-dialysis versus dialysis discrepancy?

DR. VAN ADELSBERG: Yes. This is Janet van Adelsberg. With regard to U.S. enrollment, we

enrolled 2,160 patients from the U.S., which is a quarter of the total worldwide population.

DR. CHO: I think the discussion with the FDA had been to enroll around 30 percent, so it was definitely below the expected mark; correct?

DR. VAN ADELSBERG: Excuse me. Let me get Alex Cobitz, who was involved in those discussions.

DR. COBITZ: Hello. This is Alex Cobitz here, and I just wanted to say with regard to the targeting, we had anticipated targeting 30 percent in the U.S., but we had in the ND 25 percent and in the D study, actually the 30 percent. And again, sometimes you can't get what you anticipate in terms of targets, but it doesn't mean that the conclusions are in any way invalid.

DR. CHO: I guess my concern is the fact that the U.S. population for non-dialysis -- and obviously there's bias with selection. But the U.S. population seems to be thicker than the non-US population in the ND.

DR. VAN ADELSBERG: So with regard to the results in the subgroup analysis of the U.S.

population, I'd like to call on Janet Wittes to speak to the interpretation of these results, and she's coming to the podium but not quite here yet.

DR. WITTES: Hi. I'm Janet Wittes, so I'm another Janet, and I'm a statistician.

What I would like to comment on is that the FDA in several of its comments -- I think slide number 49, or 59 from the FDA -- commented that the -- no, that's not the one. It's later on. It shows the various --

DR. LEWIS: I'm sorry. May I interrupt?

Are you. Are you addressing the question at hand?

DR. VAN ADELSBERG:

DR. WITTES: Yes. The question at hand I thought was -- I thought had segued --

DR. LEWIS: That the U.S. population was a sicker population. Are you going to show us some evidence that the U.S. population was a sicker population or not?

DR. VAN ADELSBERG: No. We were intending to address the interpretation of the results in the

U.S. subgroup. The U.S. population in our view was not a sicker population compared to the rest of the world.

DR. LEWIS: Thank you.

Dr. Nachman, you have a question?

DR. NACHMAN: I don't know if you can hear me. Patrick Nachman at the University of Minnesota.

I wanted to come back a little bit about the issues to decrease burden on the patient by using an oral agent. A lot of the discussion we've had so far has focused on the SF-36 vitality measure. With the design of the studies the way they were done, if my understanding is correct, there wasn't really a good way of measuring decreased burden on the patient the way we've heard from the speakers and from Mr. Conway this morning.

Is that a fair statement? In other words, there is no data available to us now to see if given the choice between coming to a clinic and getting an injection versus being treated at home, this would be a valuable thing for our patients.

Do you have a --

(Crosstalk.)

DR. NACHMAN: -- on that?

DR. VAN ADELSBERG: Sorry. Please go on. I'm sorry I interrupted.

DR. NACHMAN: I was asking if there was any attempt at measuring decreased burden on the patient other than the SF-36, which doesn't really address the question.

DR. VAN ADELSBERG: So with regard to the design of our pivotal studies, you are correct that they weren't designed to answer that question because I think what we've heard today was that the burden is in terms of getting to the clinic to get the injection or other kinds of ex-study things. However, we do have data, I believe, regarding patient preference that I can have Kirsten Johansen speak to.

DR. JOHANSEN: Hi. Kirsten Johansen here. Yes. I want to just echo what Janet just said. I think the premise to begin with was that this would be reducing patients' burden, and you know that I

agree with the speakers that we just heard from, that my patients suffer a lot from this burden. I do wish that there was a formal measure of that, though, and I haven't seen that.

DR. LEWIS: Thank you.

Dr. Wang?

(No response.)

DR. LEWIS: Dr. Wang, do you want to unmute if you still have a question?

DR. WANG: Yes. Actually, I do have a question, although it's a different question than the one I had earlier this morning, but if I could ask a clarifying question to GSK.

There seems to be a discrepancy in the dialysis population in the analysis of hospitalization for heart failure as an endpoint in specifically those with a prior history of heart failure. If I understood correctly, one source of that discrepancy was a different definition of history of heart failure, but I just wanted to make sure that I understood that correctly.

So I'm referring to slide CO-48 on the GSK

slide deck, where the recurrent heart failure events in the dialysis population, the hazard ratio is 1.03, where in the FDA slide deck, slide 59, the hazard ratio is 1.44. Is that all due to a different definition of what represents a prior history of heart failure, or is there some other source that I'm not detecting?

DR. VAN ADELSBERG: Let me call on Dr. Kaivan Khavandi to clarify the differences between FDA's definition of the subgroup with history of heart failure and the definition that we presented in our presentation. I think that both definitions are actually in our briefing book, but let's clarify that for the record.

DR. WANG: Thank you.

DR. KHAVANDI: Kaivan Khavandi, GSK clinical. I'm going to show a slide that shows the two different definitions, and to clarify, the subgroup that the FDA presented for heart failure is actually a heterogeneous group consisting of four terms by medical history, which were heart failure; those with LV systolic dysfunction;

LV diastolic dysfunction; or pulmonary hypertension.

This was really intended as a screening subgroup to look for any variability in outcomes with the primary endpoints, and what you can see on the slide is when we look at those only with heart failure, in the top panel, we can see that the entire difference is driven by that population. So in other words, if you remove those with, for example, diastolic dysfunction by medical history who didn't have a clinical syndrome heart failure, you see that those uncertain clinical variables weren't important in the imbalance that was observed.

So actually, to counter, perhaps, the comment that was made, it's the fourth term that dilutes rather than vice versa. It's the history of heart failure group where the imbalance is derived.

Then I think your comment was about a value for a hazard ratio point estimate that's perhaps different from the 1.22 we see here, so I'd just

like to pull up our core presentation, slide 50, and just clarify the reason for that. This relates to a difference between looking at hospitalization for heart failure alone, which is the green arrow in the top panel. So that's looking at those with a history of heart failure in the dialysis population, and then looking at hospitalization for heart failure.

What we observed is that the ESA comparator had more deaths, so you had a slightly increased number of hospitalizations in the daprodustat arm, but you had more deaths in the ESA arm. And these are deaths in patients with CKD and heart failure, and actually what we observed is that they had a higher number of sudden deaths, which one would consider plausibly would be related to the underlying heart failure. So when we account for survival in the bottom green arrow, we see those point estimates come back down to unity.

DR. WANG: Okay.

DR. LEWIS: Dr. Kasper?

I'm sorry, Dr. Wang. Did that answer your

question?

DR. WANG: That's fine. Thank you, yes.

DR. LEWIS: Dr. Kasper?

DR. KASPER: Ed Kasper. My questions have been answered. Thank you.

DR. LEWIS: Dr. Soergel?

DR. SOERGEL: My questions have been answered. Thank you.

DR. LEWIS: Dr. Packer?

DR. PACKER: Yes. Could you put up the slide that you just put up just a moment ago? I was going to ask a question about it, and I'm really glad that you put it up.

There are good reasons and not so good reasons to combine mortality together with hospitalizations for heart failure. One good reason is mortality represents a competing risk, but the really not so good reason is if you have a lot of deaths that are not related to cardiovascular disease, what you do is you just drown out the signal.

So in this case, you have a substantial

number of events which are not cardiovascular and unknown deaths which are included in all-cause mortality, and that just drives the estimate to the null. So I think the most reliable estimate of hospitalizations for heart failure or worsening heart failure events is the top part of this panel.

I did want to ask just two more brief questions. Is it true that your non-dialysis and dialysis patients, that the dialysis patients were at higher risk? When I look at all of the numbers on all the slides, and I look at the event rate, and I'm trying to correct for the total number of patients, your non-dialysis patients and dialysis patients had about the same risk.

Is that an incorrect conclusion?

DR. VAN ADELSBERG: I believe that I'm getting my statistical colleagues to pull up the precise estimates. I believe that the yearly MACE rate in the dialysis patients was 11 and change per 100 patient-years, whereas in the non-dialysis patients, it was 10 and change. So the rates were higher in the dialysis patients.

DR. PACKER: Yes, I think that that's about right. I guess a lot of us would have assumed that the difference between dialysis and non-dialysis would have been much larger than that, but I think you've got it right. There's a little bit greater severity of illness in the dialysis patient, but it's not marked.

I just want to ask one last question. You had expert panels review some of your events. You had an expert panel that reviewed gastrointestinal erosions and acute kidney injury. Can I just ask, was the purpose of the expert panels to look at the individual events and determine whether they were related to treatment?

DR. VAN ADELSBERG: Let me clarify a bit about our reviews and our external reviews. We had prespecified reviews or adjudication of our cardiovascular events. However, for the general safety events that we observed once the studies were unblinded, we had blinded but expert review of the cases that we identified. So these are quite different in terms of what data was available for

review.

I would like to speak to the -- or actually to have Dr. Vlado Perkovic speak to the comments on the drowning out of the signal involved in the hospitalization for heart failure and all-cause mortality --

(Crosstalk.)

DR. PACKER: Before you do that --

DR. LEWIS: Excuse me. It's Dr. Lewis.

I think Dr. Packer made a comment. I don't think it needs a counterpoint, and we are short on time, and we have --

DR. PACKER: Okay.

DR. LEWIS: -- three more people to question, because, Dr. Packer, I don't think you were asking a question. I think you were making a statement on that end of it.

Dr. Bagiella?

DR. BAGIELLA: Yes. Hi. I just have a practical question, I guess. I'm not a physician. My question is, what kind of a hemoglobin monitoring would the patient taking this medication

need? Is that something they can do at their own doctor office or do they have to report to the hospital to do that? Would their personal physician be able to give them the appropriate dosage of the medication so it does not become toxic for them?

DR. VAN ADELSBERG: To address your question about, really, the difference between administration of a parenteral therapy versus monitoring of the hemoglobin, I'd like to call on Dr. Kirsten Johansen.

DR. JOHANSEN: Hi. Kirsten Johansen.

Yes. I'm a nephrologist, as you know. I take care of these kind of patients all the time, and currently they come to our clinic for both their monitoring and their injections. The beauty of having an oral drug would be that they could get their monitoring done -- there's just a lot more flexibility available for monitoring.

For example, where I work, we have only one kidney clinic downtown, but we have several satellite clinics where people could go to get

their bloods drawn, and then those results would come right to me. Alternatively, yes, I already coordinate with primary care doctors, so this would be also a way where on a visit to a primary care doctor, they could get that monitoring, which could then be transmitted to the nephrologist or whoever is doing that.

I don't know about other health systems, but I do know that there are a lot of external laboratories where people could go. There are just a lot more ways you could get hemoglobin drawn than there are ways and places where you can get an injectable treatment.

DR. BAGIELLA: I'm sorry, but how often would they have to do that?

DR. JOHANSEN: Our recommendation is that hemoglobin monitoring should be as is currently recommended for the treatment with the standard of care, ESA, so it would be the same.

DR. BAGIELLA: Thank you.

DR. LEWIS: Dr. Bairey Merz?

DR. BAIREY MERZ: Thank you, Dr. Lewis.

This is a question for the FDA.

Dr. Lewis mentioned in her first question about there were two others in this new class of presumably novel mechanisms. The sponsor demurred, obviously talking about other medications in development, but perhaps the FDA can share any safety signals that were seen in these other two drugs and the category. Thank you.

DR. WROBLEWSKI: Hi. This is Tanya Wroblewski with the FDA. Thank you for question. As you know, the FDA had an advisory committee regarding roxadustat in 2021. That is public information and is available for review. But at this point, the real focus is on the safety findings with this application, and I will also see if GSK has any additional comments regarding the two other products in development.

DR. VAN ADELSBERG: We can't comment on somebody else's development program.

DR. BAIREY MERZ: Thank, and I understand that.

DR. LEWIS: Thank you --

DR. BAIREY MERZ: As a non-nephrologist, hearing -- I believe Dr. Lewis said that these other two were not approved. That's potentially meaningful in terms of safety signals just in terms of not being -- as a cardiologist, I wouldn't necessarily know that those drugs were not approved.

DR. LEWIS: Dr. Farrell, can you comment on the complete response letters that the FDA issued, just say what they were and it happened; confirm it?

DR. FARRELL: No. Our complete response letters are not publicly available, and until a --

DR. LEWIS: No. I'm sorry; not on the contents of them, but that they were issued.

DR. FARRELL: Yes. That has been in the press that there were two issued, and we did take roxadustat to an advisory committee in July of 2021 and discussed the thrombosis and effects on MACE.

DR. LEWIS: And the second one did not go to the advisory committee but got a complete response correct?

DR. FARRELL: Correct, and that's in the press.

DR. LEWIS: Yes. Thank you.

DR. BAIREY MERZ: Thank you.

DR. LEWIS: Dr. Bairey Merz, does that answer your question?

DR. BAIREY MERZ: Yes. Thank you.

We're a little bit, three minutes, past time. I'm going to give Dr. Nachman the last question.

DR. NACHMAN: Patrick Nachman. Again, thank you, Dr. Lewis.

My question to GSK is if you were to set up a mitigating program for heart failure -- I know you mentioned education and information, but would there be specific parameters that you have in mind that you would implement in terms of who should not receive this drug? The term "heart failure" is all encompassing and affects a lot of our patients. Do you have any specific parameters in mind?

DR. VAN ADELSBERG: To speak to what our current recommendations are for managing the risk

of heart failure, I'm going to call on Dr. Heather Stein. But I do want to emphasize, before she speaks, that correctly and safely using this drug and advising patients and physicians of their options and their risk is of paramount importance to the FDA -- sorry, to us as well as the FDA, and defining the appropriate use and making sure that that's in the labeling would be a major topic of conversation with the agency should daprodustat be approved.

DR. LEWIS: Thank you.

DR. STEIN: This is Heather Stein --

DR. LEWIS: I'm sorry. You had another comment?

DR. STEIN: Yes. We were going to comment, but it was really a repeat of the information that we provided on CO-71 about our current recommendations for how we would manage the risk, so I think no additional comments.

DR. LEWIS: Thank you.

I actually am going to go ahead and let Mr. Conway go ahead, and then we have Dr. Parsa,

but then I will call it then.

Mr. Conway?

MR. CONWAY: Thank you very much, Dr. Lewis; just a quick question actually to FDA, a point for clarification, and then a question.

Our role today is strictly focused on this particular drug, correct, not a class of drugs? I mean, that's what we're taking a look at, is a particular drug, not a class of drugs; correct?

DR. WROBLEWSKI: Good afternoon. Yes. This is Tanya Wroblewski with the FDA. Yes, this AC is convened to discuss daprodustat and not the class of drugs.

MR. CONWAY: Thank you. And then I have one quick follow-up, which is GSK indicated that they had collected some patient preference information. So my question is, was that submitted to FDA, number one; and number two, did FDA asked for that? Thank you.

DR. VAN ADELSBERG: Clarifying from GSK, this is in the literature. This was not part of the application, so it's a patient preference study

of whether patients preferred oral or injectable therapies, but not read for publication, not a part of the submission.

MR. CONWAY: Okay. Thank you.

DR. LEWIS: Thank you.

Dr. Parsa?

DR. PARSA: This is Afshin Parsa from NIDDK. This is a question for the manufacturer.

On your briefing document, figure 22, page 104, it shows the quintiles of dosing and their association with the amount of MACE outcome, and for the ASCEND-ND, there's quite a striking increase -- some of it's obviously expected due to confounding -- of the amount of MACE events, as the dose went up.

Would that have played a role or suggest in terms of different capping of the maximal dose in the non-dialysis population?

DR. VAN ADELSBERG: To discuss these analyses, I'm going to call on Dr. Alex Cobitz.

DR. COBITZ: Hello. This is Dr. Alex Cobitz here. I assume you're talking about where

we -- well, let me put this slide up. It's slide A, I believe.

We're having some issues here, but I can speak to this. I assume you're talking about the slide where we're actually looking at categories of dosing, and here it is. Yes. This is the slide. And the question is, in terms of any issues with regard to imbalances between the groups? Is that what your question --

DR. PARSA: Or reconsideration of what a maximal dose should be in the non-dialysis population.

DR. COBITZ: Well, first off, what this actually shows is we've actually gone into the number of categories trying to maintain the number of patients in each category via dose, and we've gone through here, looking at what happens in terms of the MACE events. And as you can see, and I think you've already intrinsically said, that as you go to the higher categories, you see more of an issue in terms of MACE, however, this is actually not just with daprodustat, but which is within ESA,

as the FDA has already said.

In terms of what the maximal dose is with regard to dialysis patients, our maximal dose is actually 24 milligrams with regard to them. And given the issues we've actually seen in the past -- for instance in the TREAT study looking at this, where you've got this basically confounded because you're looking at a post-randomization cohort here -- the very thought is that what we're seeing here is not something intrinsic to the drug but something that's actually part of what you would see because of the post-randomization cohort. That is to say that these individuals who require more drug are typically more sick.

DR. PARSA: Thank you.

Questions to the Committee and Discussion

DR. LEWIS: Okay. Thank you. I'm going to call it there for time sake, and I apologize if anyone had any other comments.

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 number 1. Discuss the benefits of daprodustat in adults with non-dialysis-dependent chronic kidney disease.

Are there any questions or issues about the wording of the question?

(No response.)

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

Dr. Abbott?

DR. ABBOTT: I'm muted. Yes, I just unmuted. Thank you.

I just want to revisit the issue that the

items of concern appear to be outcomes that were not the primary outcomes of the studies, and for that reason the studies were not randomized or powered specifically for those outcomes. We spent a lot of time talking about the statistical methods to account for that, including focusing only on the U.S. population as part of the studies.

I just wanted to make sure, as we visit the issue of the reports of higher risk, that this has been dealt with as rigorously as we think is possible, and that these outcomes should be a driving factor for this decision. Thank you.

DR. LEWIS: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: I was just going to respond to the question, which is the benefit, not the risk. We've spent a lot of time on risk, so maybe we can cut this short since most people don't have much to say. But I thought that it was appropriately framed, the questions. I think the totality of evidence in the primary outcomes demonstrated noninferiority, and I would leave it

at that for this question.

DR. LEWIS: Mr. Conway?

MR. CONWAY: Thank you, Dr. Lewis.

I don't think I'm left without words on this one. Just to be really frank, I understand full well what it's like to go through this, and I have to tell you, to have an anemia is a kick in the pants, to say the least.

I remember sitting in Richmond, Virginia, working for the governor and staging my work during the week for after I had my ESA therapy on Sunday, knowing that I could think clearly through Wednesday, and that because of the governor and the Secretary of Health at the time, I could coast in on Thursday and Friday, and just read and not have to think and prepare 30 or 40 decision packages for the governor or for the secretary, all in terms of detail.

I can't imagine what it's like for folks that work in the trades, and in construction, and things like that, to have to manage all those things. But as the numbers clearly show, this is a

condition that is not being treated and not being treated that well. For many people, it's being treated with transfusions, which we're taught as a patient, stay healthy and do not get a transfusion; try to avoid it, especially if you want to get a transplant and live longer. That's what my instructions were.

So when I take a look at this issue and we try to figure out what the benefits are, there are many of them. One of them is patient care choice. You have a choice of therapies, and the SF-36 here is not a precise instrument. Many patient advocates don't like it because it's very transactional and it's not aspirational about what you want to do, but you have a choice.

The second thing is you can avoid going into a medical setting, and there's a great article that just came out in CJASN about this, about COVID-19 outcomes based on dialysis modalities. I don't think anybody in their right mind right now would want to be recommending less options for patients, whether they are CKD, pre-dialysis, or patients

that are on dialysis, that would force them to have to keep going into a medical setting. I think that's nonsensical to taxpayers and to patients.

Then the third thing that I think is very important, and it should not be dismissed, is convenience. It's time out of work. It's a caregiver's time out of work. It's your ability to plot and plan and live your life and manage your kidney disease as opposed to living your life around kidney disease and facing the prospect of greater unemployment, greater reliance on disability, or SSI. I think there are many, many benefits to non-dialysis-dependent patients. Thank you.

DR. LEWIS: Okay. I do have a comment on benefit. I do think that there is a minority of patients for whom this would represent all those things, especially the ones who live very far away and can't get to the doctor easily, but I will make a couple points.

Home dialysis patients are required to have monthly visits with their physician. Now, if there

has been a recent change, some of those can occur by telemed, but it still is probably ideal for them to come and see the whole team for their monthly visits. Point-of-care hemoglobins can be done at the time of the monthly visit and ESAs administered subcutaneously. So for the majority of the home dialysis patients, it is not going to make a major difference.

For CKD-5 patients, they're a stronger population. It would be a convenience, and also give them another choice, and avoid going to the medical center. But again, many recommendations are for CKD-5 patients who are the ones that have the most frequent anemia, who are not yet on dialysis, for monthly, or maybe every 6 weeks, as is due to access planning and monitoring them for uremic symptoms.

In the dialysis population, the average dialysis patient is currently taking 13 unique oral medications, I will [indiscernible] say, rounding in dialysis units, probably 20 times a month. The medication list and clarifying what the patient's

actually taking versus what we might think they're taking is an ongoing challenge.

So I do think there are some benefits, but I think the population that it's a benefit for is small. I also think it's surprising, the lack of benefit that we didn't see that may be expected. Lower ESA levels that are endogenous seem to have offered no superiority to the drug, nor the absence of using IV iron. Also, with less IV iron and not delivering a drug intravenously in the dialysis population, there was no benefit on infection.

I'm going to close since no one else has a comment, and we will move on to question number 2. I will read question number 2.

Discuss the benefits of daprodustat in adults with dialysis-dependent CKD.

Are there any issues or questions about the wording of the question?

(No response.)

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

Dr. Butler?

DR. BUTLER: Thank you, Dr. Lewis.

This is a comment, which is an extension to your last comment that most of the benefit that has been discussed, or at least in part, is convenience, and logistics, and not needing to come to the centers. On the other hand, there is an alternate perspective as well, and that is that there are for some other disease therapies that are being developed to give sub-Q and IV because adherence and compliance with daily medications in multi-morbid patients taking multiple medications is a huge problem, and people don't get the full benefit of the therapies that are available. Thank you.

DR. LEWIS: Thank you.

Dr. Abbott?

DR. ABBOTT: I apologize. I should lower my hand. Sorry.

DR. LEWIS: Okay. So there are no other comments on the benefits -- oh, Dr. Thadhani? Thank you.

DR. THADHANI: Thank you, Dr. Lewis.

A couple of points. One is we heard a discussion about why would there be a benefit in this population given the standard of care, and dialysis includes subcutaneous or IV. These individuals are coming to a dialysis unit 3 times a week, and I certainly can understand why one would argue an oral agent in that context would not be necessarily beneficial, or advantageous; let's put it that way.

That said, I think we all, at least those individuals who practice on a day-to-day basis, know the stress and strain currently going on in dialysis units; the labor challenges we have; the amount of work going on; the ratios that are being challenged in terms of technicians, and nurses, and physicians to patients.

Anything we can do to lower that burden, which in this case would include an oral medication, in my opinion would actually go a long way, especially given all the challenges we're having today in dialysis units. I would say that's

number one.

Number two, if indeed there is a drug effect on heart failure, gastric erosions, and such, which was seen in this population, in addition of course to the non-dialysis population, here at least you have a population that is being seen on a routine basis. They're being rounded upon heart failure, although can be masked on dialysis. It certainly can be managed much more easily on dialysis.

So I think there are benefits of an oral agent on dialysis, and I don't think necessarily sub-Q and IV medications in the United States -- which by the way we're the exception, given what's going on in the world, to that practice -- would continue, especially as we continue to have labor challenges in the dialysis unit. Thank you.

DR. LEWIS: Thank you, Dr. Thadhani.

Mr. Conway?

MR. CONWAY: Thanks, Dr. Lewis. I just wanted to come back on one thing. I don't think this is simply a matter of logistics, and I want to

go back to one of the points that I made previously to patient care choice. It's a shared decision, but sometimes patients have opinions about how they want to take their care that may not mesh with what their doctor wants, or it may not mesh with what the doctor agrees with, and then they have a conversation.

The goal here is to provide the highest quality care, and that's as defined by patients as therapies and care that's available that aligns with your aspirations for how you want to live, not the convenience of the doctor, or the dialysis facility.

So I think having additional options for patients, whether it's a matter of logistics or their choice, is just as important as any other factor that's being deliberated. And that's why I was actually pushing very hard on this issue of PROs because I was very disappointed in what I saw on the slide from FDA, where I believe that was being made a statement instead for patients without talking to patients, and I talk to a lot of them.

We're the largest in the country, and I can tell you that having the flexibility of being able to work with your doctor and giving your doctor additional flexibilities how to work out a treatment with you is the number one concern of patient advocates, and it's the number one reason why we push for innovations in this space. Thank you.

DR. LEWIS: Thank you, Mr. Conway.

If there are no other questions, I'll summarize. There was an initial comment that the driving factor should be the primary outcomes, if I understood that correctly, and a benefit in the non-dialysis, and I presume the dialysis population as well, is the noninferiority for the two co-primary outcomes was met.

Mr. Conway has expressed the patient's point of view eloquently about how disabling anemia is that patient choice is important. And avoid going into a medical center, I think we all recall that, after COVID, is important, and convenience is a very valuable thing.

It was also noted that oral agents have been considered to be burdensome and that there is some movement towards sub-Q and other alternatives than swallowing many pills, I assume. Challenges in the hemodialysis unit were also stated; that staffing issues, and the time and staff it takes to administer the IV injections or subcutaneous injections of the ESA is a factor to take into consideration, and that that is a benefit of the oral and the dialysis-dependent population.

We'll next go on to question number 3, and I'll read that. Discuss the risks of --

DR. PARSA: This is Afshin Parsa. I'm sorry. I had my hand up. I just wanted to --

DR. LEWIS: Oh, I'm sorry.

DR. PARSA: That's ok.

DR. LEWIS: Dr. Parsa, I'm sorry.

DR. PARSA: Yes. Afshin Parsa from NIDDK. I just want to reiterate what Mr. Conway briefly brought up in terms of the concern of the stated benefit for the dialysis units.

Is that extending a little bit beyond what

we should be evaluating? I mean, it's discuss the benefits of daprodustat in adults with dialysis, not benefits for a dialysis unit. I think that creates a potential bias, and I think, as also stated, the total burden being so high, and compliance with dose is actually a downfall of this doing by mouth for dialysis versus in dialysis unit. I'm just uncomfortable with that being discussed as a benefit to the patient.

DR. LEWIS: Well, just to make it a little bit of a discussion, recently I commented I was working on something that was going to help increase billing or something. I said the reason to do that is so that we provide more resources that can be applied to our patients. So if our dialysis nurses aren't busy drawing up ESA, they could be spending their time talking to patients, interacting with patients, finding out how they've been doing at home, et cetera. So although it is not an apparent direct benefit, it's sort of an indirect benefit, arguably.

The other thing I'll comment on is the SF-36

is a well-established, probably best established, PRO ever used, and it has involved in its development many, many patient-focused, patient-voiced analyses. So I'm not sure that it's fair to say that you can't estimate anything from the SF-36 because it doesn't have patient voices, because it did in its development. So it's a matter of when you take a group of patients' voices and compare it to another group of patients' voices, how many voices difference means that there's really a difference in the agent?

Anyhow, we'll go on to question 4 now.

Question 4 I'll read. Discuss the risks of daprodustat in the dialysis population, including the risks of heart failure -- I'm sorry; question number 3.

Discuss the risks of daprodustat in adults with non-dialysis CKD, including cardiovascular harm, gastric erosion/hemorrhage, and acute kidney injury.

Are there any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: If not; if there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Abbott?

DR. ABBOTT: Just on some of the outcomes that were mentioned here, for acute kidney injury, I appreciate that it's 40 percent decrease in GFR, however, this is not a whole lot more than what we expect to see from the physiologic action of ACE, or ARB, or SGLT2 inhibitors.

I would be interested in more information. I realize it's limited, but how many of these episodes are hospitalized? How many were dialysis requiring? And, as my colleague, Dr. Parsa, pointed out, the time frame of these studies was relatively short, so it was difficult to draw any conclusions as to whether there was any impact on CKD progression. So in my opinion, we had some incomplete information on the acute kidney injury.

Then on the gastrointestinal erosions/

hemorrhage, the data presented appeared to show that despite this, there was still no net difference in the number of transfusions required or all-cause death, which is what would be associated with the gastrointestinal erosions. So I think we've talked about the MACE and the other issues, and I'll let others address that, but those are the two outcomes I had questions for. Thank you.

DR. LEWIS: Dr. Nachman?

DR. NACHMAN: Thank you, Dr. Lewis.

Patrick Nachman --

DR. LEWIS: Oh, I'm sorry. I'm sorry. Nope, I didn't.

Dr. Nachman?

DR. NACHMAN: Thank you.

I wanted to make more of a comment about the risk of thrombosis, especially of the vascular access thrombosis, and I think this has been mentioned or written about in the sponsors' draft.

I'm not convinced at all from the data that there is an increased risk of vascular access

thrombosis. Because of all the complexity of how to measure that in a pre-dialysis population, I haven't seen any analysis of what kind of access we're talking about. Is it an AV graft? Is it an AV fistula? It's pretty difficult to tease out what we're measuring here, and that's my comment. Thanks.

DR. LEWIS: Thank you.

Dr. Packer?

(No response.)

DR. LEWIS: Dr. Packer?

(No response.)

DR. LEWIS: We'll go on to Dr. Wang.

DR. WANG: Yes. Thank you.

I want to address this question of the class effect, which has been raised. I certainly acknowledge that the question at hand is regarding a specific medication, but I think the issue of class effect relates to the question of prior probability since a lot of the potential harms that we're talking about represents signals in secondary analyses in which, as was pointed out, the issue of

multiple testing is an issue. Prior probability for me is an important consideration to provide context to these secondary analysis signals.

In that regard, I would point out, because it is part of the public record, that there are some striking consistencies between what we're seeing with this drug and other drugs in the class, including the signal or possible signal of MACE in the non-dialysis population. In fact, in the roxadustat ADCOM in 2021, it was really the same question because the signal was mostly in the on-treatment analysis, and I would point out that the hazard ratio was nearly identical.

So while that could be coincidence or due to some other factor, I think we should also acknowledge the possibility that there could be class effect, and that there are now multiple drugs in this class, specifically in the non-dialysis population, for which there is the possibility of a MACE signal.

I would point out secondly, that the heart failure, at least, also seems fairly robust in this

population. And lastly, I would agree with the point made earlier by Dr. Packer that the merging of the hospitalization for heart failure endpoint with all-cause mortality is potentially perilous and I think could mask what otherwise appears to be a relatively clear signal for excess heart failure risk. That's all.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Yes. Thank you.

I want to just --

DR. LEWIS: Would you say your name for the record, Dr. O'Connor?

DR. O'CONNOR: Yes. Chris O'Connor here. I want to just amplify what Dr. Wang has said.

One of the concerns I have, particularly in the non-dialysis study, is that when we look at the cardiovascular endpoints, the seventh, all the hazard ratios are greater than 1, and this is in comparison to darbepoetin, which probably has a hazard ratio of 1.2 for many of these endpoints versus placebo. So what we're looking at is a drug

that only 10 to 12 percent of the population with non-dialysis-dependent CKD are on an ESA. So we're talking about this drug being initiated in essentially patients who haven't been on anything, so I think these hazard ratios may actually be underestimating the risk.

So I wanted to voice that concern, that if this was really compared to placebo, that these hazard ratios might be higher. Thank you.

DR. LEWIS: Thank you.

Dr. Cook?

DR. COOK: Yes. Thomas Cook, and I'm speaking purely from a statistical point of view.

It's clear to me from the primary analyses that this drug, with respect to those outcomes, is noninferior to ESAs. Virtually, every other analysis that I've seen is subject to confounding, and it isn't clear to me that it represents an actual signal. For example, I guess what was just raised was looking at heart failure alone, ignoring non-heart failure deaths.

The issue of competing risks is a real one,

and to argue that somehow we can just simply throw them away and recover an analysis that's looking at the direct causal effect of the treatment of heart failure is naive in my opinion. And if you want to tease that out, you've got to do something more sophisticated, and it's not even clear to me that such method actually exists.

The on-treatment analyses are not compelling because we know that on-treatment analyses are fundamentally broken, and they don't tell us what we imagine that they're telling us. We've looked at lots of potential adverse harm, but again, like someone mentioned, there's no real adjustment for multiplicity, and it isn't clear if simply these are things that were identified as being, by chance, higher in the active arm than in the control arm.

So I am at this point convinced that there's noninferiority with respect to ESA on the primary, and it's unclear to me if there's compelling evidence that there is actual harm with respect to other endpoints. Thank you.

DR. LEWIS: I'm sorry, Dr. Cook. Can I ask you for a clarification of what you said?

DR. COOK: Go ahead.

DR. LEWIS: You think it's unclear if there is any harm?

DR. COOK: It is unclear to me that the signals we've seen that suggest harm are, in fact, signals of real harm.

DR. LEWIS: Thank you.

Ms. Alikhaani?

MS. ALIKHAANI: Yes. Jacqueline Alikhaani here. My apologies. I've been having a lot of technical problems.

I can appreciate there's some uncertainty on a lot of issues still, and I really am concerned that this drug seems to offer something for patients that I can appreciate because my mother has this issue with her dialysis treatments. The convenience of an oral therapy, I think that's really special, but at the same time this is complicated for me because I'm concerned about the general risk of the ESAs, and then there's

additional risk factors that come into play.

Someone said something about needing more long-term outcomes data, and I really agree with that. More long-term outcomes data relating to the risk factors I think would be really helpful.

DR. LEWIS: Thank you.

Dr. Packer, welcome back.

DR. PACKER: Thank you, Julia. I lost my internet connection, and then I'm still struggling with it. I do want to make some comments about what others have said.

When one does a noninferiority with a primary endpoint of MACE, and one achieves noninferiority with that, there are so many other data points that one collects along the way, and if there are imbalances in other safety issues, one can't simply set those aside simply because one has achieved noninferiority on MACE. To say that one can set those aside is to say that one should never have collected all of the safety data in the first place. All one had to do was just collect MACE, and if you achieve noninferiority in MACE, then

that's it; you're done.

The imbalances that we are seeing -- and I'm particularly concerned about those imbalances in the non-dialysis patient population -- are increased heart failure; increased gastric erosions; acute kidney injury; thrombotic events; and there's also worsening blood pressure, which we haven't talked about today. Those imbalances I am not looking at through a pure statistical eye, but those imbalances are not biased. Those are intention-to-treat imbalances. There may be informative censoring because of mortality, but mortality was not different between the two treatment groups.

My concern is that for some of these, particularly heart failure hospitalization, the signal here is not just with this drug, but with other drugs of this class that have come up with the same signal. And when you see the same signal across multiple members of a drug class, you don't need very impressive statistical analyses to know that there's a pattern here that we can't ignore.

So I'm personally concerned about the imbalances that we are seeing that the FDA has pointed out, particularly in the non-dialysis patient population. And given the fact that those signals are seen consistently and are seen with other members of drug classes, and in some cases are supported by preclinical observations, I don't think we can ignore that.

DR. LEWIS: I'll give it a moment to see if anyone else has any questions or has any comments.

(No response.)

DR. LEWIS: Okay. I will try to summarize.

DR. COOK: Julia, I had my hand up by mistake, and then I tried to put it back up so I could respond to Milton Packer's comment. Is that ok?

DR. LEWIS: This is Dr. Cook?

DR. COOK: Yes.

DR. LEWIS: Dr. Cook, could you identify yourself?

DR. COOK: Okay. Yes, this is Tom Cook.

I fully appreciate Dr. Packer's comment, but

if there is a systematic association between mortality and the other outcomes that induces an apparent imbalance, that could easily be replicated throughout trials because it's intrinsic to the underlying phenomena, but it doesn't necessarily mean that it's a causal effect of treatment on the risk of interest. So just the fact that it might appear in multiple trials in drugs of the same class doesn't necessarily imply that it's additional evidence of a causal association. Thank you.

DR. LEWIS: Dr. Packer, do you want to comment?

DR. PACKER: Yes. Maybe I should ask Dr. Cook a question.

If this drug were to cause a meaningful increased risk of heart failure, or gastric erosions, or other problems, what would convince you to believe that they were real in a trial that exceeds noninferiority on MACE? In other words, is there anything that we can learn from this trial about other safety issues other than the primary?

DR. COOK: Yes. Thomas Cook.

That's a good question, and I don't know that I have a good answer for it. All I'm suggesting here is that there are alternative explanations for what we're seeing that don't imply that this drug is causing increased risk, a purely statistical comment.

DR. PACKER: Julia, can I just respond?

DR. LEWIS: Yes.

DR. PACKER: Because I think Dr. Cook's -- this is really an important question because if we cannot learn anything about imbalances in the non-primary endpoint, one wonders why we collect all of that additional safety data if we're going to simply say that when we see imbalances, and those imbalances are seen with other members of the drug class, that we're simply going to say, "Well, we just can't interpret it so we're not going to reach any conclusions about it," I'm concerned about that because for many of these imbalances, these are really important safety issues, and they occur with a significant

frequency.

The number of heart failure events here is like 2 to 400 heart failure events. That's a lot of data, and when you see imbalances in a serious effect of heart failure, and you see it with other members of the drug class, I don't know how one could say, "Gee, I don't know how to interpret that." I think I do know how to interpret that.

DR. LEWIS: Thank you, Dr. Packer.

I do also have a comment, and it's a kind of practical concern that I think is a potential risk.

I think we probably all are in agreement that rapid excursions of hemoglobin or hemoglobins that rise far above 11.5, there's a significant body of evidence to suggest that those may increase cardiovascular risk, and I want to point out that we don't really know what real-world application of this drug would be.

In the first 12 months of this trial, these patients came every 4 weeks for a visit, and their hemoglobins were checked, their drugs were adjusted, and that is, if you will, almost a

training session. I realize in the subsequent months of the study, they were seen less frequently, but there's been no comment made of any consideration of putting a restriction on, for example, what they did in the first 12 months of this study, a 1-month supply; and if you don't get your hemoglobin checked, you don't get your next month's supply.

Again, there are lots of reasons patients don't get things done. People talked about a lot of the burden of getting your hemoglobin checked. How many patients who are not study patients, who are kind of a preselected population, who haven't gone through a year of training, if you will, in how to manage this drug, will not get their hemoglobin checked for months at a time and continue on the oral medications that they have at home? So I consider that a significant risk in anybody who's not having it monitored in a medical setting in some way.

Dr. Parsa?

DR. PARSA: Afshin Parsa, NIDDK. Thanks for

bringing that point up. I was just about to do the same because I very much share the same concern in terms of what happens in a real-world application with a drug like this.

Now, to me that doesn't mean that this should directly affect the vote for approval, but in terms of how or conditions for it, I think it is important. What I have scribbled down in my notes, part of you already got to, but measures such as limiting duration of treatment per prescription; not allowing for prescription refills, as you have to write a new prescription to people to continue treatment, and/or perhaps requiring documentation of hemoglobin levels before a new prescription; or some sort of measures to account for that; because undoubtedly, an amount of errors for only prescription will happen quite a bit, and the consequences of it.

This, as was noted historically, is quite high, where you go from beneficial to harmful, as the target hemoglobin levels go up. I think it is an important matter to address.

DR. LEWIS: Dr. Parsa, I will add to that comment. I think for the non-nephrologists on the panel, nephrologists have a very good example of this with tolvaptan, which is the medication that had a -- actually, probably its major risk was liver necrosis, so it's under a special REMS where the physicians prescribing had special training, and the supply of it is limited if the patient doesn't get their liver function tests checked initially on a monthly basis; so I think as nephrologists because we've seen it and are familiar with that working.

I think we have a couple more hands up.

Dr. Bagiella?

DR. BAGIELLA: Yes. Hi. Emilia Bagiella.

So I think that this goes back in this discussion that we're having to what my question was before. And again, how closely can these patients be really monitored and left in the hands of a personal physician who might not be so familiar with the drug and not be able to calibrate it to dose it properly?

DR. LEWIS: Thank you.

I think, Dr. Soergel.

DR. SOERGEL: Yes. Thanks, Dr. Lewis. David Soergel, industry representative.

I wanted to come back to the back and forth between Dr. Cook and Dr. Packer for a second because I think during the Q&A, we heard an example of some skepticism about how to interpret thromboembolic events, for example, in the non-dialysis-dependent study. So I think that would be an example of what Dr. Cook was getting at, how it's a little difficult to understand how to interpret some of these events.

I'd come back to Dr. Packer's point, which I think was around the heart failure finding, which I think the sponsor recognizes and was suggesting an approach to be able to manage. So I'm curious about Dr. Packer's interpretation of the sponsor's review and the FDA's answer to the question about how to interpret the heart failure hospitalization raised in the pre-existing heart failure population. Thank you.

DR. LEWIS: Dr. Packer, I think that was a question to you.

DR. PACKER: Yes, I'd be happy to. I'm sorry. I'm only able to connect by phone and not by my laptop, but I'll do my best.

I think the sponsor's analysis of heart failure is correct, and I think by looking at heart failure and recognizing that there is an increase in heart failure hospitalizations, the sponsor agrees with the fact that we can look at non-MACE events, and we can interpret them.

The sponsor, and the FDA, and I think the committee has agreed that there is an increase in heart failure hospitalizations. The question is whether it's confined to the patient population that has a history of heart failure, and the sponsor has presented analyses that suggests that it is confined to the group with a history of heart failure.

The problem is that was a checkbox, and it's really hard to know how to apply that in a clinical setting where so many of these patients have heart

failure, or volume overload, systolic function, or diastolic function. It is really hard to say what represents or doesn't represent a history of heart failure, but I am personally convinced that the heart failure signal is really most prominent in the non-dialysis patient population and less prominent in the dialysis population. And the dialysis population also doesn't have all the other safety signals for non-gastrointestinal events.

So I'm in agreement with the sponsor about the heart failure risk. I'm not comfortable that we know how to identify that risk, but I do think that's a risk that's primarily in the non-dialysis population. I do want to emphasize this is a comparison with ESAs that are also already known to increase cardiovascular risk, so this is a risk on top of a class of drugs that increases cardiovascular events.

DR. LEWIS: Thank you.

Dr. Abbott?

DR. ABBOTT: That addressed my question. I was going to follow up and ask about the issue of

whether the risk of heart failure only applied to those with a history of heart failure, so I think that previous answer addressed that. Thank you.

DR. LEWIS: Thank you.

Dr. Nachman?

DR. NACHMAN: Yes. Thank you, Dr. Lewis. Patrick Nachman here.

I, too, feel that the heart failure question is probably, in my mind, the most compelling concern. We have several cardiologists on the panel here, and my cardiology colleagues manage very severe heart failure at home by doing frequent monitoring, phone calls, and adjusting medication based on weight.

I just want to say that, for me, the difficulty in maybe handling this potential complication does not necessarily mean that the drug should not be allowed to go through, or be used, or to come back to Mr. Conway's term, to empower and help patients to manage their disease in an informed way.

I mean, again, heart failure is difficult,

and many of the severe, low EF patients manage it at home through us physicians doing the better job of not denying them the access to a potential treatment.

DR. LEWIS: I will comment, Dr. Nachman, though, that there are some differences in that a patient would have to actually do a test to tell what their hemoglobin was. They wouldn't necessarily know it like a heart failure would -- feeling short of breath or being edematous -- but it is true that we manage some dangerous drugs at home. I would agree with that.

DR. NACHMAN: The point is that we can learn to help our patients do it.

DR. LEWIS: Okay. Dr. Nachman, you want to put your hand down, I think.

Dr. Bagiella, is your hand meant to be up or are you ready to put it down?

DR. BAGIELLA: No. I have a question, and I'm unsure that this is the right group to ask it.

If this medication were to go on the market, would it have the same boxed warnings as the ESA?

DR. LEWIS: I think I'm going to let the FDA make a comment on that. I mean, they're not going to be able to answer it directly, but maybe just comment whether they want to comment on it. You're right; none of us can.

DR. FARRELL: This is Dr. Farrell. I think we would defer any labeling conversation until after the advisory committee. Thank you.

DR. LEWIS: Okay. Thank you.

Dr. Wang?

DR. WANG: Thanks very much. I just wanted to briefly respond to Dr. Nachman's comment. I certainly appreciate his thoughts.

I would respond, though, that of course heart failure is a very morbid event, and although it is true that at times, heart failure and volume overload can be managed at home, one, we're talking about hospitalization for heart failure, which is highly morbid and highly dangerous as well. As the sponsor themselves acknowledged, frequently it can lead to cardiovascular death, and as the sponsor is acknowledging that sometimes from deaths that are

otherwise unclassified as a heart death.

So although I know Dr. Nachman is not suggesting that we take these endpoints lightly, I just wanted to reinforce that this is something that I think any drug with potential excess risk of heart failure is a drug for whom the safety profile would have to seriously be considered. And certainly the morbidity and mortality from heart failure is at least as much as that of anemia, and the indication that we're evaluating this drug for.

DR. LEWIS: We have two more discussions. It is our break time. We could cut our break from 10 minutes to 5 minutes.

Does anyone object to that?

(No response.)

DR. LEWIS: Okay.

Dr. Packer?

DR. PACKER: Yes. I just wanted to reinforce what Dr. Wang just said. Heart failure specialists and people who take care of heart failure recognize that heart failure hospitalization, it's a very serious event. It's

not just the immediate morbidity. It indicates a progression of the disease. It uses an endpoint for progression of heart failure for drugs that are being developed and are developed for the treatment of heart failure.

So heart failure hospitalization is not a little bit of fluid overload that's treated either with diuretics or intensification of dialysis. Heart failure hospitalization is a major, major event, both in terms of understanding what's happening with progression of the underlying heart disease and the prognosis of the patients. An imbalance in heart failure hospitalizations is something that we worry about all the time. There are lots of drugs that contribute to that, and it's not something that is just tweaked with a little bit of change in volume management.

DR. LEWIS: Thank you, Dr. Packer.

Mr. Conway?

MR. CONWAY: Thank you, Dr. Lewis.

I just wanted to go back to what Dr. Nachman said, because I think, in many ways, at least from

my perspective, this comes down to the trust and competence, the trust you invest in the doctor and their competence to work with you to manage some of these issues.

For me, I don't think it's the pivot point for either dialysis or non-dialysis patients. I think Dr. Nachman's right in the sense that you look to your medical team to manage these things with you and to make you aware them, and then you have the ability to make a choice, and I think that's fundamentally important, so thank you.

DR. LEWIS: Thank you.

We will now take a five-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break. We will resume at 4:18.

(Whereupon, at 4:13 p.m., a recess was taken.)

DR. LEWIS: Okay. I'm now going to try to summarize our discussion of question 3.

I think I'll begin by just saying that there were two concerns that the safety risks might be

underestimated, one, because that it was not compared to placebo in either of the two main trials, and we know that ESAs, which were the comparator arm, had a very high risk of these safety events to start with. So if this drug had been compared to ESAs, it would have been, say, at a much higher safety signal.

Also, I think an underestimate of the risk could come from the non-real-world application of supply visits and monitoring that was used in the study since there's so far not been a proposal to alter that; so then, how the patients got in this study wouldn't reflect what would be happening in the real world, and there could be much greater safety problems in that setting.

Our statistician shared the point of view that they won on noninferiority and that the analysis that suggested safety all had potential flaws, the OT, the subgroup risk, et cetera, and that although the data from other drugs in the class may show similar signals, that there are alternate explanations for that potentially, aside

from a class effect.

I think we also heard a strong voice that there was consistent cardiovascular safety data across the class of agents, which increases the prior probability that any safety signal seen in this trial might be relevant and that merging ACM and HF could be a perilous thing to do. The CHF signal was thought to be robust by several of the panelists. Particularly in non-dialysis patients, there were important safety signals.

The severity of a CHF hospitalization was also emphasized by panel members, and it was also, on the other hand, emphasized that a heart failure would be an example of a serious drug that can sometimes be managed in the home setting, and that it's possible to manage the risks of this drug in the home setting as well, with careful physician and patient involvement. I think there was a voice to give the patients and the physicians the individual choice to make an educated decision about how they wanted to manage that risk.

We will now move on to question 4. Discuss

the risks of daprodustat in the dialysis population, including the risks of heart failure and gastric erosions and hemorrhages.

Are there any issues or questions about the wording of the question?

Mr. Conway, do you have your hand up about a question about the wording?

MR. CONWAY: My apologies. I'll put it right down. Thanks.

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

Dr. O'Connor?

DR. O'CONNOR: Yes. Chris O'Connor.

In contrast to what we saw in the non-dialysis-dependent populations, the cardiovascular endpoint analysis provided by the FDA, from slide 68, I feel it's more favorable. Only 1 out of 7 have a hazard ratio greater than 1, and it's 1.1, and it's in that heart failure space that we're concerned about, but I think there would be an opportunity to mitigate that risk.

But this to me feels more comfortable regarding the cardiovascular safety endpoints. One of the, I think, challenges we're having is looking through the lens of efficacy versus safety, and we're looking at what typically cardiologists look as efficacy endpoints. We're now looking at them as safety endpoints. I think what Dr. Packer said is correct. We look at the totality of information and if it's going in one direction or not, and I feel in this particular trial and population, this feels more comfortable with respect to the cardiovascular endpoints. Thank you.

DR. LEWIS: Thank you.

Dr. Abbott?

DR. ABBOTT: I was going to follow up with Dr. Pendel's [ph] slide 33. Maybe I don't understand the slide, but this was the one which showed the achieved hemoglobin between the groups, darbo and ESAs. It may not be statistically significant, but in the ASCEND-D trial, visually at least, it looked like the achieved hemoglobin was higher in the dapro group than in the epo group.

This was not in the high hemoglobin range of the CHOIR study, but assuming the continuous relationship, is it feasible that -- the disparity in achieved hemoglobin, visually it seems much greater in the dialysis bar than in the non-dialysis bar. It was stated that this showed that the results were not due to differences in achieved cumulative event [indiscernible], but I just wanted to revisit that question.

DR. LEWIS: Thank you.

Are there any other discussion comments?

Dr. O'Connor, do you have another comment or is your hand still up?

DR. O'CONNOR: Sorry. I'll pull that down.

DR. LEWIS: That's ok.

Dr. Abbott, your hand's still up as well.

Dr. Thadhani? And I'm sorry. I might have not known whether it was Dr. Thadhani or Dr. Wang, but we'll have time for both of you.

Dr. Thadhani?

DR. THADHANI: Great. Thank you.

Just to point out, the gastric erosions,

gastric bleeding, there was a difference, of course, between the ASCEND-D and the ASCEND-non-D, where the curves separated quite quickly in the non-dialysis population. The dialysis population, the curves separated well after 2 years. That's not to say there wasn't an effect; it just was a very small effect.

I think the comments were made on heart failure. Now certainly, among those individuals with a history of heart failure, the point estimate was a little further to the right, but overall, the cardiovascular effects were different than what we saw in non-dialysis. Thank you.

DR. LEWIS: Thank you, Dr. Thadhani.

Dr. Wang?

DR. WANG: Yes. Thank you. Thomas Wang.

I just wanted to amplify the comment that Dr. O'Connor made. For me, the statistical data extending down to the secondary endpoints are more reassuring for this population than they were for the ND population. Secondly, I'd like to again point out that when you look at the publicly

available data for other drugs in this class, in fact, a similar pattern can be seen where the dialysis population seems to have less signal for possible cardiovascular harm. So again, recognizing the debate that took place earlier, I think that, for me, again, raises a higher probability that some of these findings could be real.

Lastly, as has been pointed out, for some of these potential harms like volume overload, notwithstanding the comment I made earlier about the severity of heart failure, it does seem that the dialysis population, because it's seen and monitored more frequently and for whom volume status can also potentially be managed more easily, that it may be easier to address some of these risks; that they do in fact appear. Thank you.

DR. LEWIS: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: Yes. Just to elaborate on those comments, as well as Dr. O'Connor, we have such amazing good heart failure drugs now, when we

have patients that see us regularly, it's really chronic disease management at this point for many of them. I'm not saying they don't ever die, but I suspect that the reason -- or I'm not surprised that the dialysis group has done better, in general, for all of these at-risk endpoints.

I would maybe make the case -- and maybe this was where you were going, Chris -- there may be an increasing group of dialysis patients that will want an oral formulation because they will increasingly, with all of our remote monitoring and management hastened by the pandemic -- and I think we should keep that in mind that that might be happening, and an oral formulation might be relevant to that group in the future. Thank you.

DR. LEWIS: Although, it may be that their monitoring in the in-center is actually, in some way, improving the safety. It's really hard to know. We don't have an answer to that question.

DR. BAIREY MERZ: Absolutely. Yes. Thank you.

DR. LEWIS: Dr. Butler?

DR. BUTLER: I echo all the comments recently made about the dialysis population signal being more favorable. On the other hand, I'm struggling whether that's where the real unmet need is because, as was the stated in the beginning, most of these patients are getting the therapy, the alternate therapy anyway, and the benefit of not needing to come to the healthcare center is not that relevant in this group.

DR. LEWIS: Thank you.

Dr. Packer?

(No response.)

DR. LEWIS: Dr. Thadhani and Dr. Wang, I don't know if you have more comments or you just haven't put your hands down.

Dr. Packer, are you on the phone still? It looks like you've got an internet connection. Oh, you're muted in Adobe. There you go.

DR. PACKER: Julia, I'm so sorry. I was muted.

DR. LEWIS: That's ok.

DR. PACKER: I'm so sorry.

DR. LEWIS: That's ok.

DR. PACKER: I'm very pleased. There are a number of heart care specialists on this panel that contributed amazingly to the field, and it is nice to know that, yes, we have some nice heart failure drugs. The sad thing is, one, most people with heart failure don't receive them, and the second is even if you get great heart failure drugs, your annual mortality for heart failure is greater than most forms of cancer.

I would not want the committee to assume that, "Oh, gee, someone has heart failure. We can take care of it; it's not a problem." Having heart failure is a real problem.

DR. LEWIS: Dr. Butler?

DR. BUTLER: Just to expand on that, heart failure therapies, for which we have had a lot of progress recently, are either contraindicated in patients with advanced CKD in dialysis or there is no data for the efficacy in this patient group.

DR. LEWIS: Thank you.

If there are no further comments, I'll go

ahead and try to summarize question 4. I think several of the speakers note that there is less of a cardiovascular safety risk in the dialysis population, and that they are more comfortable with the totality of the data for the dialysis population.

However, there were some questioning voiced -- I'm hearing a bit of an echo, but I don't have my sound on, so I apologize if anybody else is hearing it. But there were some questionary statements that even though there's less CV risk for the in-center population, there's less of an unmet need since they are going to the medical facility 3 times a week; and that although heart failure on the one hand is an extremely serious complication with a high mortality rate, there are therapies for it to make it more of a chronic disease, but then that's complicated by the fact that many of those therapies were not a proven benefit in the dialysis population.

In terms of some of the gastric erosion safety signal, there was a comment that its curve

separated quickly in the non-dialysis population and separated not until 2 years in the dialysis population. So again, that might be indicating a real difference; then just a concern about the achieved hemoglobin being higher in the daprodustat group even though they were still within the therapeutic range than the control group, and CHOIR had shown a signal with the higher achieved hemoglobin.

We will now move on to the next question, which is a voting question. Dr. Jessica Seo will provide the instructions for the voting.

DR. SEO: Thank you, Dr. Lewis.

Question 5 and 6 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 question 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 are a voting member, you will 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, either 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 will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, 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 to. 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. LEWIS: Dr. Packer, I think your hand is left up from before.

I will read question 5. Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults not on dialysis? Provide a rationale for your vote. If you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment.

Are there any issues or comments concerning the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 5.

DR. SEO: 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. SEO: Voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. SEO: 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.

There were 5 yeses, 11 noes, and zero abstentions.

Dr. Lewis?

DR. LEWIS: Dr. Parsa, please state your name.

Thank you. We will 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. Parsa.

DR. PARSA: Hi. This is Afshin Parsa, NIDDK. I voted yes. I would like to provide a short commentary, though.

In summary, I still have some definite concerns regarding some of the signals for potential increased risk. None of those -- apart from the use in individuals with a history of heart failure -- to me do not convey a clear unacceptable risk level for every individual or circumstance.

Given this and the potential benefit to individuals with CKD and limited access to clinic injections, my assessment is that much of the concerns and appropriateness for use can be managed by individual healthcare providers and their patients as long as appropriate warnings, and education, and other reasonable safety measures are put in place. These would, for example, include boxed warnings for individuals with a history of CHF; warning for GI bleed or ulcers; and careful postmarketing studies, looking at the risk of AKI, thromboembolism, and other risk factors that have been noted earlier.

Lastly, I would also suggest limiting the prescription, number of refills, and requirements for it, and perhaps requiring documentation of hemoglobin levels before putting in such prescriptions. Thanks.

DR. LEWIS: Dr. Bairey Merz?

DR. BAIREY MERZ: Yes. Thank you, Dr. Lewis. I voted no. I felt like, again, we met the primary outcome. It is noninferior for efficacy for the important outcomes. And while I don't think that we feel confident that it has increased risk, I do think that the data we reviewed today leaves us feeling very uncertain about increased risk, as currently on the market. The risks were only identified later after approval and widespread use. Thus, I think we need more information about the risk. My suggestion would be to, if possible, do a meta-analysis of the other two products within this category to determine, or at least gain some knowledge about whether or not this is a class effect of these safety signals, or whether or not they aren't there with additional

power.

I also would suggest looking more carefully -- there are things that count that we cannot count. And to pick up on where Dr. Butler was going, there may be something about daily versus every other day, versus less frequent dosing orally that is in some way different. It poses more risk. We certainly see this in Coumadin. Even though we dose Coumadin appropriately, despite that, it still has a less safety record compared to other pharmaceuticals now on the market.

So those would be my two suggestions because I'm otherwise enthusiastic about having an oral preparation for all of the good reasons stated. Thank you.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Dr. Chris O'Connor. I voted no, and the reason, the risk of the cardiovascular safety endpoints I believe outweigh the benefit in this population, especially the heart failure safety signal, given the data we had showed a risk

above ESAs, which have an inherent risk above, already, placebo.

I think a path forward would be a US-focused trial in this population with an expanded MACE endpoint, including heart failure in the MACE endpoints, and expanded PRO analysis endpoints. I think there's real potential for the future of this oral medication in this population, but not with the data presented today. Thank you.

DR. LEWIS: Thank you.

Dr. Bagiella?

DR. BAGIELLA: Yes. I voted yes. I believe that the data across the two studies are not consistent. It is unclear why in more severe groups you have a lower risk signal. I agree with Dr. Cook that the statistical analysis probably cannot really get into the true estimate of these rates.

DR. LEWIS: Thank you.

Ms. Alikhaani?

MS. ALIKHAANI: Jacqueline Alikhaani. I voted no. I think that after all of the really

informative and educational discussion we had today, there's still a lot of uncertainty about a lot of the safety issues. I'm really concerned about that.

I was really enthusiastic about hoping to provide more convenience for kidney failure patients. Unfortunately, I don't think that we had enough evidence to go forward to approve this drug today the way I would have been more comfortable with; just too many added risk factors. I think we need more long-term research outcomes data. We need more and more diverse PRO feedback, and we need more long-term data to supplement that.

DR. LEWIS: Thank you.

Dr. Butler?

DR. BUTLER: Javed Butler. I voted no for the concerns related to cardiovascular safety and also the differential signal in the U.S. population. Thank you.

DR. LEWIS: Dr. Julia Lewis. I voted no, largely for the reasons that have already been stated. I have two main concerns. One is that I

do think there's prior probability from the other drugs studied. I don't know if a meta-analysis or some sort of data across all three studies for safety would be helpful, but from a statistical point of view, I know it would have limitations. But I think we need more data before we release this into the non-dialysis population in unlimited quantities.

Dr. Abbott?

DR. SEO: I apologize.

Dr. Lewis, this is Jessica. I believe we skipped Dr. Kasper. If we could go back to Dr. Kasper's vote.

DR. LEWIS: Oh, I apologize. Thank you, Jessica.

Dr. Kasper?

DR. KASPER: Thank you, and no need to apologize. I'm not hurt that you skipped right over me.

I voted no. I, too, am concerned about the hospitalization for heart failure signal, despite the fact that I recognize that anemia of chronic

kidney disease is a real and true burden and that there is real importance to developing an oral treatment for this.

I'm concerned that this is kind of an inherently unstable time. Chronic kidney disease in patients heading towards dialysis I think will be a difficult time to study because it's not unusual for a patient to get admitted once or twice with volume overload before they land on dialysis, and how you're going to separate all that out, I'm not really sure. But at this point, I couldn't support this particular vote. That's it.

DR. LEWIS: Thank you, and I apologize again.

Dr. Abbott?

DR. ABBOTT: I was very torn on this, but I did wind up voting no. Despite the fact there is a tremendous need, if we proceed with the status quo, this leaves the majority of the non-dialysis population right exactly where they are; no better off. But the data, I was swayed that the additional risks for the heart failure, although it

appears to be only for recurrent heart failure and for some of the MACE outcomes, is increased in contrast or comparison to ESAs.

I fully support Dr. O'Connor's proposal that a comparison with placebo or some other analysis with a direct comparison would be essential to know more before we can make a recommendation. I'm still of the opinion that -- I'm not entirely persuaded that the difference in outcomes are not due to a change in hemoglobin, looking at the slides that we saw, and even relatively small differences may lead to disproportionate outcomes as we look in the CHOIR trial.

I was less impressed with the -- I think we need more information, as I said, on the AKI. We need to know the severity, based on hospitalization and dialysis requirement, to know how significant these episodes were. But overall, I think we need a bit more information before I could vote yes on this. Thank you.

DR. LEWIS: Thank you.

Dr. Cho?

DR. CHO: Leslie Cho. I voted no. The most concerning thing for me was that this drug would be used in an unintended way in a lot of patients that are non-dialysis dependent that would have unintended consequences, and I felt how to get this drug safely to the right patient I think was very concerning.

I would again echo Dr. O'Connor's point about trying to do a US-focused study. I was not satisfied with GSK's comment about there being no difference in the U.S. versus non-US non-dialysis patients. They are clearly different. Table 521 of the FDA document -- and I read both GSK's document and the FDA's document -- clearly the FDA's table 521 shows that there is a difference. So I think a US-focused non-dialysis trial would be a good point forward. Thank you.

DR. LEWIS: Thank you.

Dr. Packer?

DR. PACKER: Milton Packer. I voted no. I think the real interesting question here is the way the question is framed, which is benefit versus

risk. We've already spent a meaningful amount of time talking about risks and the imbalances seen in the non-dialysis population. That needs to be weighed against the benefit. The benefit here is on a change in hemoglobin and the accompanying ability to reduce fatigue and reduce blood transfusions.

The FDA has made the point that the effect on fatigue, although it's present, it's a little bit hard to discern how many patients actually have a difference in fatigue, and I had to weigh that benefit against the imbalances seen in the non-dialysis patient population, and the benefit-risk relationship was not favorable. So that's why I voted no.

DR. LEWIS: Thank you.

Dr. Nachman?

DR. NACHMAN: Patrick Nachman. I voted yes. I'm usually a glass half empty person. I'm a little surprised by my vote. But Dr. Absa [ph], really, I want to echo his comments. I'm impressed by the fact that the majority of our patients who

are not on dialysis are currently not treated at all. I'm impressed by the fact that having an oral drug would increase access to care and decrease the burden on patients who are left untreated right now.

I am very cognizant of the concerns about the cardiovascular risk and would really want to emphasize the importance of careful guidelines, safeguards, and monitoring to decrease or mitigate the risk of, notably, heart failure. I believe that if we do have these kinds of monitoring, and guidelines, and safeguards, it can be done effectively to a select patient population that would then benefit from it. Thank you.

DR. LEWIS: Thank you.

Dr. Conway? I mean, Mr. Conway? Sorry.

MR. CONWAY: Thank you for the promotion, though. Thank you, Dr. Lewis.

I voted yes, and I understand the concerns that have been raised about several of the factors here, however, I agree with Dr. Nachman that through restrictions, and guidance, and monitoring,

that could be managed by competent medical professionals. I'm one of those patients who still assume that most of the folks I interact with are, although I do raise my voice, as you would expect, with my team.

The reason why I voted yes was because our national policy since 2019, bipartisan national policy, is to take kidney health upstream. And when you take a look at the population who is not being served, who's suffering under this, it's not ok to say that status quo is fine. That's existed for several decades.

I think we need more tools for doctors and for patients, and when you take a look at this population -- I didn't mean to disparage the SF-36, but I do think it has limits, and I think most advocates do believe it has limits. I understand that, and to academicians and to researchers, it's a reliable tool, but it's a short-term tool. It doesn't ask about aspirations in terms of work, full-time and part-time; do you have the energy to travel; all these types of things, major life

decisions. It doesn't really cover that.

So the point that I'm making here is that for the data that was presented, especially the data on patient-reported outcome, even though it may not seem significant, if you are that patient who gets that energy and has a difference, that is a significant development for you, and I think that's how we have to start taking a look at these things. I do think the risks are important. I do think they can get managed. Thank you.

DR. LEWIS: Dr. Thadhani?

DR. THADHANI: Thank you very much, Dr. Lewis. I voted no, but in fact for the same reasons that Dr. Nachman and Mr. Conway mentioned.

I do believe, given the data and especially the compelling information that Dr. Johansen presented, the number of events that we were able to review in this population sway me to encourage the agency to work closely with the sponsor to figure out ways to develop risk mitigation strategies, identify low-risk populations, and presenting the agency with those plans, revisit

this imbalance of the vote that you see here.

So I voted no in its current format, but I would like to encourage the agency to think of a low-risk population where we may be able to make this available for, again, the compelling reasons that were made by the presenters. Thank you.

DR. LEWIS: Thank you.

Dr. Cook?

DR. COOK: Yes. Thomas Cook, and I voted yes. I can appreciate all of the comments that I have heard so far. I could, in fact, justify voting the other way, but I chose to vote yes because I'm not completely convinced that the evidence that was presented for the risk of this drug have been adequately shown. Thank you.

DR. LEWIS: Thank you.

Dr. Wang [Wong]?

DR. WANG: Thanks.

DR. LEWIS: Wang.

DR. WANG: Thanks. No problem.

I voted no. I voted no despite the fact that I'm not certain whether the cardiovascular

risk signal is all real or not. But that said, I would like more assurance that the signal in this population is neither spurious or very modest. The fact that even a possible modest signal exists on top of ESAs -- which are a class of medication that already has known risks and on which many patients in this population wouldn't be taking at baseline anyway -- does amplify the possible concern.

The second issue is that the possible signal that exists is not in isolation but in the context of other members of this drug class that has elicited similar concerns, so I don't think that this can be ignored. I know it may or may not be a class effect and that there could be biological arguments in either direction, but again, this swayed my vote.

In the end, I agree with others who have said that more data, specifically with regard to heart failure risk in non-dialysis patients with and without a history of heart failure, defined in a standardized manner, would be very useful. Thank you.

DR. LEWIS: Okay. I will try to summarize the vote now.

On the yes side, just separated by yes and no, although there were some residual concerns about the history of heart failure and it wasn't a completely clean safety thing, it was felt that those risks be managed, either managed by the skill set of the professionals caring for the patients or managed by the FDA, putting in boxed warnings, postmarketing studies, restricting refills, and requiring documentation of hemoglobins.

Some of the other reasons that voted for yes was that the data across the two studies weren't consistent, and that they can't get at the true estimate of risk, so that going with the co-primary outcome was the way to go. There was a real concern that the majority of patients in the non-dialysis population are not currently being treated, and that the oral drug would increase access to care, and that it would also address the national goal of taking kidney disease upstream for dialysis in an important way.

On the no side, I think the need for this was recognized, but the discomfort with the potential of increased cardiovascular safety, particularly heart failure, on top of the already existing risk of ESAs, which is significant, was probably the overriding thing.

Some of the suggestions of things that could be done for that were some sort of meta-analysis of the available products in the class; looking at daily versus QOD or 3 times a week delivery, and less frequent dosing; more data in U.S. population, and particularly in the subgroup of African Americans in the U.S. population; more development of confident PROs; comparison with placebo; identifying low-risk populations so that you can mitigate the risk; and of course more data on the heart failure risk; so a suggestion of doing a study, including heart failure, both its pre-enrollment definition, as well as part of the outcome.

Okay. I'm now going to read question number 6. It is also a voting question.

Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults on dialysis? Provide a rationale for your vote. If you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit-risk assessment.

Are there issues or questions about the wording of the question?

(No response.)

DR. LEWIS: I don't see any hands up.

If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 6.

DR. SEO: 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. SEO: Voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. SEO: 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.

There were 13 yeses, 3 noes, and zero abstentions.

Dr. Lewis?

DR. LEWIS: 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.

Dr. Parsa?

DR. PARSA: This is Afshin Parsa. I voted yes. While, in general, I think there is potentially a limited benefit for use on center hemodialysis, I know there are patients who are at home on dialysis and which this could have a potential benefit. There really was a lot less

concern for my end regarding potential risk, based on the data presented in the hemodialysis group or peritoneal dialysis group, and have no overt concerns.

DR. LEWIS: Thank you.

Dr. Merz?

DR. BAIREY MERZ: Noel Bairey Merz. I voted no for the reasons that there appear to be much less benefit in patients already undergoing hemodialysis in terms of convenience and choice, and yet I don't think that we should feel so comfortable about the safety or the lack thereof, or even benefit because we were not convinced of the multiple subgroup analyses and the lack of multiplicity testing; that we didn't feel confident. Many of us voted yes, they weren't worried about safety.

So I don't think we should make any kind of decision on this limited data, and again, I would call for additional data. I would call for analyses of class effect in the dialysis patients, as well as the non-dialysis patients. Thank you.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Dr. O'Connor. I voted yes. First, I want to commend the sponsor for doing very difficult, impressive work in these outcome trials. I felt like in this patient population, efficacy was met. I felt that the safety signals in the cardiovascular space appeared more favorable than the ESA. None of these are statistically significant in isolation, but the totality, 6 out of the 7 cardiovascular endpoints were on the lower side of 1, many of them in the hazard ratio of 0.8, and this could afford potential advantage over ESAs and certainly home dialysis.

I do think the history of heart failure patients needs to be carefully managed and followed, and mitigation strategies. The fact that many of these patients are in dialysis centers allows us to more carefully monitor this drug as it's rolled out. I would encourage the sponsor to consider some mechanistic studies, looking at heart failure in this population to better understand

whether there is actually any measurable injury or effects on heart function. Thank you.

DR. LEWIS: Dr. Kasper?

DR. KASPER: Ed Kasper. I voted yes. I, too, would like to congratulate the investigators and the FDA on a very careful analysis and thoughtful, well-done trial. I think in this population, the benefits do outweigh the risks, and I think that there is a reason to have an oral treatment for anemia in this situation, and that, in general, we should support choice.

I would echo Dr. O'Connor that I think we do have to watch this carefully going forward, but we have that ability because these patients will be seen more frequently than those who are not yet on dialysis.

DR. LEWIS: Thank you.

Dr. Bagiella?

DR. BAGIELLA: Yes. Emilia Bagiella. I voted yes for the same reasons as before. I don't think that there is a clear signal about safety here, and the benefit to the patients are probably

higher than the actual group [indiscernible].

DR. LEWIS: Thank you.

Ms. Alikhaani?

MS. ALIKHAANI: Jacqueline Alikhaani. I voted no. I still think safety is just paramount. It's just really major for me. I think it would be really nice if we could have an oral therapy alternative. I think patients would really appreciate that, and I think there would be benefits to that. But at the same time, I don't think it's very wise to forego concerns about safety. I think we can do better than that, and patients are counting on us to do that.

If we just go ahead and ignore safety concerns, then a lot of patients would be misled, and people can lose their life. I mean, they're losing their lives anyway with this really bad disease. I think we have to work a little bit harder to get things just right, and I think it can be done. Hopefully, we'll get there sooner than later.

I really hope that we can get more diversity

in our clinical trials so we can have the kind of PRO data that would really help us a lot in making better decisions. I think that we need more long-term outcomes data, especially for the PROs.

DR. LEWIS: Thank you.

Dr. Butler?

DR. BUTLER: Javed Butler. I voted no. I struggled with this vote a little bit, and clearly the data here are a little bit different than the non-dialysis population. Eventually, looking at the totality of evidence across these two adjacent populations, the previous data from drugs within the class, the consistency of data on heart failure patients, the lack of data for heart failure effective therapies in this particular population, and also the way the heart failure data were collected in this trial, were all a concern to me.

Now, on the other hand, in terms of the benefit, I was not totally convinced as to the use case with a potential uncertainty in terms of the safety, what the use case is, because these patients are already getting the dialysis and they

are already getting there ESAs otherwise, and in these multi-morbid patients with significant pill burden and adherence being a major issue with chronic diseases, that adding another pill burden may actually have the opposite effect than what we intend for it to be. So for all of these reasons in the net, I voted a no.

DR. LEWIS: This is Julia Lewis. I could have voted yes or no because I think my thought process is the same for either vote, but I swung towards the yes side. I do think this is a highly regulated, highly watched population between the U.S., RDS, and the local state monitoring of dialysis units, hospitalizations, et cetera.

So I voted yes with the caveat that the FDA and the company would work out a true and enforced mitigating data collection to be carefully watching the heart failure, in particular, but all the CV outcomes. I also would caution again that we've had experience with another ESA-like agent that got rolled out. Eighty percent of the dialysis patients in our country are taken care of by two

companies, so if one of those two companies rolls it out, in one week we could have a really excessive safety signal before we need to. So I would also encourage some sort of staged rollout, and I think the dialysis companies would support that. So it's a yes, with a lot of conditions on it.

Dr. Abbott?

DR. ABBOTT: Yes. Kevin Abbott, NIDDK. I voted yes. I was less concerned about the safety data, although certainly there is some signal, but it's not as nearly as convincing as for the non-dialysis-dependent population to me.

Another reason for the rationale of the benefit, something we didn't really discuss today, is a phenomenon of ESA resistance. There is a tail of dialysis patients, hemodialysis patients particularly, who are on truly astronomical doses of ESAs to maintain their hemoglobin levels, and it's a significant problem for them, and markers for other things. So I think it would be very useful in this population to have an alternative

agent that acts through a different mechanism beyond just the idea of an oral agent versus injectable agent.

Just as an aside, I was just going to throw in for the non-dialysis population, the other question is why ESAs can't be made more available. After all, we have patients with diabetes getting salt injections at home and monitored, so I don't see why that can't be expanded to that population. But for the hemodialysis population, I think the issue of ESA resistance and other factors make the case that with the relatively safe findings, it's a rationale for another option. Thank you.

DR. LEWIS: Thank you.

Dr. Cho?

DR. CHO: I voted yes, and the main reason was that these are patients that are highly monitored and highly watched, especially the -- obviously, they're HD patients, but also the peritoneal dialysis patients who have to come in and be seen. This is a patient population that I think is quite different from non-

dialysis-dependent patients.

The other reason I voted yes was because I think, hopefully, FDA will have a pharmacovigilance plan for this drug going forward so that it can be monitored and we can understand the events. Thank you.

DR. LEWIS: Thank you.

Dr. Packer?

(No response.)

DR. LEWIS: Dr. Packer, I'm going to skip and give you a chance to connect your audio.

Dr. Nachman?

DR. NACHMAN: Yes. Thank you, Dr. Lewis.

Patrick Nachman. I voted yes. I voted yes for the non-dialysis, where the safety signals or concerns are higher. So here, for all the reasons that have been mentioned, this issue is less of a worry for me.

I do want to make the point, though, that many of us are working hard trying to bring dialysis to the home, and that hopefully the future will not be that 80 percent of our dialysis

patients will be in in-center hemodialysis. I'm hoping that maybe adding this tool to our toolbox may help us get there as well. Thank you.

DR. LEWIS: Mr. Conway?

MR. CONWAY: Thank you very much, Dr. Lewis. I would echo exactly what Dr. Nachman said, that the status quo right now for in-center dialysis is not the ideal. The ideal was established by national policy, executive order, Advancing American Kidney Health in 2019, which in addition to going upstream says send more people home. And the FDA itself had a significant achievement in that regard when they approved single use of a hemodialysis machine so patients no longer have to have a caregiver at home. I think there's a recognition that that is where technology and where more and more patients want to go. COVID has made that point.

I think that it's a good thing for kidney patients who are on dialysis to have more choices. I think it helps them stay stronger. I think it helps avoid transfusions. I think it makes them

better able to get a transplant. I also think it has not been talked about a lot, but it breaks the cycle of dependency and gives patients more options in terms of not having to look at a 26 percent employment rate if you're on dialysis. If you want to do some work part-time, you may be able to. You may have more energy. The dependency on SSI and the cost to the taxpayer, I think that this is a move that disrupts status quo, and it's a victory for patients. Thank you.

DR. LEWIS: Thanks.

Dr. Thadhani?

DR. THADHANI: Thank you, Dr. Lewis.

I voted yes. First of all, let me just say this is not an easy population to do a clinical trial in, so really, congratulations to the sponsor, but really also bringing in the academic team that knows the space exceedingly well. I believe the benefits outweigh the risks. I think the risks can be managed.

I'll just make two other points. Number one, I do think this represents an opportunity to

change the way we practice. Part of our goal here, of course, is to provide flexibility and opportunities for clinicians, and this kind of agent gives clinicians and dialysis units the opportunity to change the way they practice; hopefully to improve the quality even of the lives of the patients that we care for.

For example, sub-Q is certainly worse than oral for some patients, as an example, and how we practice today is not necessarily how we're going to practice in the future. So with that, I voted yes, and certainly again, congratulations to the sponsor. Thank you.

DR. LEWIS: I'm going to go back to Dr. Packer while we have him.

Dr. Packer?

DR. PACKER: I'm sorry, Julia. I've had technical problems all day.

DR. LEWIS: Would you say your name into the record? Sorry.

DR. PACKER: Yes, no problem.

Milton Packer. I voted yes. I do think

that in the dialysis population, the benefits outweigh the risks. The imbalances on the risk side are muted. It's really interesting to imagine why the dialysis population is different than the non-dialysis population, or at least appears to be. The dialysis patient population is monitored more closely, and it could be that hemoglobin targets in the two patient populations might need to be different.

One of the things I was very impressed by, by the sponsor, was that they took a measured response to achieving their hemoglobin levels. They didn't want them to go up too quickly, they didn't want them to go up too much, and I think that thoughtful process really contributed to its success in the dialysis population.

DR. LEWIS: Thank you.

Dr. Cook?

DR. COOK: Yes. Thomas Cook, and I voted yes because this was a well-conducted study, and I'm convinced that the sponsor met their primary outcome criteria and demonstrated, to the extent

they could, that this drug is sufficiently safe relative to the benefit. Thank you.

DR. LEWIS: Thank you.

Dr. Wang?

DR. WANG: Thanks. Thomas Wang. I voted yes. I also agree that the totality of the data in this population was more reassuring relative to what we saw in the non-dialysis population. I do want to say, though, that there still may be evidence of increased heart failure risk in this population, especially in those with prior heart failure. So as others have recommended, it would be valuable to have continued monitoring of the event and of the possibility of increased risk of heart failure in this population going forward. Thanks.

DR. LEWIS: Thank you.

I will try to summarize. The noes were that there was much less benefit for the majority of the dialysis population, and they still felt very concerned about the safety signals; that safety is paramount, and that the totality of evidence across

the class, the CHF data in both populations was a real concern. There was a suggestion, as I said, for more CV heart failure data, and also more diversity data, and more data in the U.S. subgroup.

Actually, the yeses also had a lot of suggestions. I would say that, overall, the votes for yes reflected the fact that the totality of evidence in this trial was with less of a safety signal in the dialysis population, and there was a consideration that that's a population that is more carefully monitored and followed. I will add that in order for that to be a benefit, it is also going to be important for someone to watch that data on a big scale, not on the single dialysis unit's experience.

The other reasons for yes were that, again, the risks were muted, the totality was more beneficial, and the benefits outweighed the risks, and also a benefit to the ESA-resistant patients.

Before we adjourn, are there any last comments from the FDA?

DR. WROBLEWSKI: This is Tanya Wroblewski.

No, none at this time. Thank you.

Adjournment

DR. LEWIS: Okay.

I'd like to take this moment to thank Dr. Seo and the FDA staff and faculty for insightful and very balanced analyses; the members of the public for lending their perspectives; GSK for a very well-done study, a very impressive follow-up and completion of data, and very clear presentation; and of course, the members of this panel for devoting their time to protect the well-being and safety of the public and being tolerant of me not managing to get us done on time. I deeply apologize, and I really respect you all staying for the extra time.

We will now adjourn the meeting. Thank you.

(Whereupon, at 5:29 p.m., the meeting was adjourned.)