Slide 1

Slide 2

Hello. My name is Tom Schall, and I am the President at ChemoCentryx and also the scientific founder some 24 years ago.

Accordingly, I present my brief remarks as the scientific lead of the avacopan program from its inception to the present day.

We're pleased to present our data that support the approval of avacopan.

Slide 3

Avacopan is a first-in-class, targeted therapy for patients with ANCA-associated vasculitis – a rare, severe, and often fatal autoimmune disease with anti-neutrophil cytoplasmic auto-antibodies, or ANCA, involved in the pathogenesis.

ANCA-associated vasculitis is characterized by inflammation of small blood vessels and can affect any organ, but commonly affects a patient's kidneys.

Currently, patients are treated with broad immunosuppression including high doses of glucocorticoids that are associated with significant toxicities and even death.

Despite currently available therapies, more than 1 in 10 patients die within the first year of diagnosis. And many more sustain organ damage either from the disease itself or from the toxicities that come with glucocorticoid use.

Slide 4

C5a and its receptor, the C5aR, which is the molecular target of avacopan, have a central role in the pathogenesis of ANCA-associated vasculitis.

- C5a primes neutrophils and enhances ANCA-induced neutrophil activation.
- Neutrophils activate the alternative complement pathway through endogenous properdin secretion
- Neutrophils also release C5a when stimulated by inflammatory cytokines such as tumor necrosis factor-α.
- C5a, acting on the C5aR, is a potent neutrophil chemoattractant and agonist which triggers neutrophil aggregation.
- C5a decreases neutrophil deformability, particularly in the presence of ANCA, leading to increased neutrophil aggregation.
- Lastly, C5a activates endothelial cells, promoting retraction and increased vessel permeability.

Slide 5

Avacopan is a highly potent and selective C5aR inhibitor. With this precise targeted mechanism of action it avoids the long-term biological consequences of 'upstream' complement inhibition.

Unlike C5 inhibitors such as eculizumab, avacopan, as a selective C5a receptor inhibitor, does not block C5b-9 production, leaving the critical host defense mechanism, known as the membrane attack complex, or MAC, entirely in place. MAC is important to protect against encapsulated bacterial infection, such as Neisseria meningitidis.

Importantly, avacopan blocks the pro-inflammatory effects mediated through C5aR, but preserves the beneficial anti-inflammatory effect of the C5L2 pathway.

Therefore, avacopan's approach targeting the 'downstream' complement pathway has several advantages.

In short, avacopan is a precisely targeted therapy for ANCA-associated vasculitis. It's mechanism of action specifically blocks the inflammatory processes that destroy the vasculature in this disease, and could provide a valuable alternative to existing current therapy options.

Slide 6

Next, I would like to introduce Dr. Pirow Bekker, the Clinical Lead for the avacopan clinical development program. Dr. Bekker has been doing clinical development for 31 years and has been involved in the development of avacopan for ANCA-associated vasculitis from the start.

Slide 7

Thank you, Dr. Schall.

Our proposed indication for avacopan is for the treatment of adult patients with ANCA-associated vasculitis, and includes the 2 types of ANCA-associated vasculitides: granulomatosis with polyangiitis and microscopic polyangiitis.

Our proposed dose is 30 mg taken twice daily with food. This dose regimen was shown to be effective in Phase 2 and 3 studies.

Let's look at our clinical development program…

Slide 8

We conducted a robust clinical development program including seven Phase 1 studies, and 2 Randomized, placebo-controlled, 24-week, Phase 2 studies. The Phase 2 studies, CL002 and CL003, included 109 patients and are considered as supportive evidence of efficacy.

Our pivotal Phase 3 study, CL010, known as ADVOCATE, was a 60-week, randomized, controlled clinical trial comparing avacopan to prednisone in patients with newly diagnosed or relapsing ANCA-associated vasculitis.

ADVOCATE enrolled patients in 18 countries and included 331 patients.

As you will hear today, the ADVOCATE study demonstrated the substantial evidence of efficacy and safety to support our proposed indication.

Avacopan received orphan drug designation in 2014, and our NDA was filed in July of 2020.

Slide 9

Regarding the Phase 3 study design, ChemoCentryx held several discussions with the FDA and European Medicines Agency in 2016 in advance of starting the ADVOCATE study.

Recall ANCA-associated vasculitis is an orphan disease, and owing to the rare nature of the disease, trials in ANCA-associated vasculitis are constrained by factors including limited patient availability and complex standard treatment regimens.

For example, a new therapy license for rituximab was primarily based on results from a single trial called RAVE.

RAVE had approximately 200 patients, and was designed as a non-inferiority comparator trial over 26 weeks.

Accordingly, based on the RAVE precedence, in July 2016 ChemoCentryx initially proposed a 26-week randomized, double-blind trial comparing avacopan to prednisone in 232 patients receiving either rituximab or cyclophosphamide.

In Europe the EMA agreed to a non-inferiority study, with demonstration of superiority in a secondary endpoint such as glucocorticoid toxicity,

But in the US a 26-week non-inferiority study was deemed not to be sufficient.

To address both FDA and EMA comments, ChemoCentryx revised the study to be a 52-week study in ~300 patients with superiority assessment built in as well.

In Nov 2016, the sponsor and FDA agreed on this proposal.

At the End of Phase 2 meeting, FDA also agreed that a single Phase 3 study might be sufficient to support the indication if it was a multicenter trial, with a clinically and statistically persuasive treatment effect, and consistency of effect among endpoints, and at the pre-NDA meeting FDA agreed that the single Phase 3 study was sufficient for approval.

Slide 10

A diagram of the Phase 3 study design is shown here. Dr. Merkel will discuss the design in detail. However, I would like to briefly discuss a key aspect, namely glucocorticoid use.

There were two treatment groups.

The avacopan group did not receive a daily oral prednisone taper, as was the case in the prednisone group.

Our goal in the ADVOCATE study was to eliminate the daily oral prednisone.

However, it was not possible to avoid additional glucocorticoid use in both groups, for example, as pre-medication for rituximab, or as taper following glucocorticoids given pre-study.

Let’s briefly review the potential sources of glucocorticoid use…

Slide 11

Scheduled daily oral prednisone constitutes the biggest burden in glucocorticoid load when being treated for either a new diagnosis of acute ANCA-associated vasculitis or a relapse. This first source of glucocorticoids is what we attempted to eliminate in this trial.

It is important to note that it is impossible to do a completely glucocorticoid-free trial in patients with ANCA-associated vasculitis.

This could be a source of some confusion which I will try to clarify here.

There are three additional sources of glucocorticoid in our trial.

As second source, many forget that glucocorticoids are required as pre-medication for rituximab infusions to prevent allergic reactions to rituximab.

It is important to remember that 65% of all patients in ADVOCATE received rituximab as background therapy so these patients inevitably had approximately 500 mg of prednisone equivalent within the first 4 weeks of the trial.

This source alone would constitute a large portion of the ~80% incidence of glucocorticoid exposure in the trial. This was true of both treatment groups.

Thirdly, in addition to daily prednisone, some 'spillover glucocorticoid exposure' occurs from pre-randomization therapy, which for safety reasons, had to be tapered to avoid an adrenal crisis.

The final category of 'other glucocorticoids' is that which was prescribed either for reasons other than ANCA-associated vasculitis, for controlled short bursts of non major flares, or as rescue therapy. Such use is defined in the protocol. Keep in mind that patients with excess glucocorticoid use typically were treatment failures in both treatment groups.

When all sources of glucocorticoid use is taken into account, it is clear that most of the glucocorticoid use would be within the first 4 weeks of the trial. This is consistent with the data we will present later.

We will also later discuss the patient incidence of glucocorticoid use by study period, but note that the overall incidence of any glucocorticoid use may be misleading when one ultimately considers the total glucocorticoid exposure in the two treatment groups.

Slide 12

More relevant than overall patient incidence of glucocorticoid use, is the reduction in total glucocorticoid dose observed in the study as will be discussed later.

The overall median glucocorticoid dose was reduced 86% and the mean dose 63%

This substantial reduction in glucocorticoid dose translated into a significant reduction in glucocorticoid toxicity, as will be shown later.

Slide 13

Our presentation will show that avacopan allows patients to achieve and sustain remission while eliminating daily oral prednisone and reducing the toxicities associated with glucocorticoids.

The primary endpoints were met in the Phase 3 pivotal trial.

The sustained remission rate at Week 52 was higher in the avacopan group compared to the prednisone group with a reduced risk of relapse, and greater improvements in kidney function and health-related quality of life.

The safety profile is favorable, with lower toxicity in the avacopan group compared to the prednisone group in several key areas, such as infection.

Overall, the clinical data demonstrate avacopan's positive benefit-risk profile and show that treatment with avacopan can fulfill many of the medical needs that are not met with currently available therapies for ANCA-associated vasculitis.

Let me take you through the agenda for the rest of our presentation.

Slide 14

First, Dr. David Jayne will discuss the disease background and current unmet medical need.

Next, Dr. Peter Merkel will present the avacopan efficacy results, followed by Dr. Jayne reviewing the safety profile.

And finally, Dr. Merkel will provide his clinical perspective and conclude.

Slide 15

We have additional experts to help address your questions. All external responders have been compensated for their time and expenses.

Thank you, and I will now turn the presentation to Dr. Jayne.

Slide 16

Hello. My name is David Jayne. I'm a nephrologist based in Cambridge, in the United Kingdom. I'm the Director of the Vasculitis and Lupus Service at Addenbrooke's Hospital and President of the European Vasculitis Society or EUVAS.

I've dedicated my career to vasculitis research and treating patients with vasculitis. And I'm here today because patients with ANCA-associated vasculitis need treatment options that address the significant unmet medical needs of current therapies.

I'll begin with some background…

Slide 17

ANCA-associated vasculitis is a heterogenous group of systemic autoimmune diseases. They are characterized by necrotizing vasculitis, which predominantly affects the small to medium-sized blood vessels.

The recurring inflammation of the vessels can ultimately accrue into irreversible organ damage and death.

ANCA-associated vasculitis comprises 2 main subgroups: granulomatosis with polyangiitis, or GPA, formerly known as Wegener's, and microscopic polyangiitis, or MPA. These conditions demonstrate distinct pathological profiles yet have significant overlap of clinical characteristics and are often studied together.

Slide 18

ANCA-associated vasculitis is a rare, serious and life-threatening disease.

Based on recent studies, the incidence in the US is 3.3 cases per 100,000 adults every year.

The clinical features of ANCA-associated vasculitis vary depending on disease stage, the specific organ involved, disease severity, and the extent of damage to the involved organ.

Although almost any organ can be affected, the kidneys and respiratory tract are frequent targets. 80 to 90% of patients present with renal or another organ-threatening manifestation.

An estimated 11% of patients die within the first year after diagnosis, and nearly 60% of these are a result of the medications used, including glucocorticoids.

Slide 19

Patients with ANCA-associated vasculitis have a decreased chance of survival.

This recent study from Sweden shows the greater risk of early mortality of these patients. But even over time, the gradient is steeper than the health, age, and sex-matched control group.

So, how do we treat ANCA-associated vasculitis?

Slide 20

The primary goals of managing ANCA-associated vasculitis start with a rapid diagnosis and prompt treatment initiation.

Once treatment is started, we strive for our patients to achieve early remission to prevent organ damage.

Then, we need to limit treatment-related toxicity while maintaining disease remission and preventing relapses. Limiting toxicity has been challenging because many patients have required chronic glucocorticoid and immune suppressive treatment.

Slide 21

The initial phase of treatment includes high-doses of glucocorticoids – typically tapered over a period of 5 to 6 months to try to manage toxicity associated with chronic use– combined with immunosuppressants to induce remission. These include the alkylating agent cyclophosphamide given orally or intravenously for about 13 weeks; alternatively, the B-cell depleting biologic treatment rituximab is given intravenously weekly for 4 weeks.

This is followed by other immunosuppressive drugs to sustain remission, which may include glucocorticoids, azathioprine, methotrexate, mycophenolate mofetil or repeated administration of rituximab.

Overall, these regimens can be successful in controlling the acute vasculitis crisis and have enhanced short-term survival, but they have substantial limitations, leaving the patient with significant unmet needs. They are not always effective at preventing relapse and have both short and long-term side effects.

Despite current therapies, many patients die or sustain damage from disease activity or the toxicities associated with these therapies.

Slide 22

Therefore, significant concerns remain with the current treatment of patients with ANCA-associated vasculitis.

These include high relapse rates, limited efficacy on renal function, detrimental or no effects on quality of life and high levels of toxicity – especially with glucocorticoid use.

I'll discuss each of these in more detail…

Slide 23

First is that current treatments provide low rates of sustained remission and high relapse rates after remission has been achieved.

Once our patients achieve remission, we need to prevent relapse. Not only are relapses associated with increased tissue and organ damage, but when patients relapse, they're often treated with glucocorticoids. This can result in more cumulative organ damage.

In the RAVE study, at 18 months only 39% of patients maintained relapse-free remission following 4 weeks of rituximab treatment compared to 33% in the cyclophosphamide/azathioprine comparison group.

This tells us that induction with rituximab without maintenance therapy is unlikely to prevent future relapses in most patients.

Subsequent studies have shown a reduced relapse rate with chronic rituximab treatment. However, concerns associated with hypogammaglobulinemia in many patients may limit its use.

We need safe treatment options that can not only achieve- but sustain – remission with a low risk of relapse.

Slide 24

The next issue is that current treatments have limited efficacy on renal function.

Renal involvement is the most common severe manifestation in patients with GPA or MPA, occurring in over 70%, and patients with renal involvement have a worse prognosis.

A post hoc analysis of the RAVE study showed limited efficacy on estimated glomerular filtration rate over time that was similar in the rituximab and cyclophosphamide/azathioprine groups.

Since renal involvement is an important factor in a patient's prognosis, successful treatment should focus on improvement in renal function.

Turning next to quality of life…

Slide 25

Patients with ANCA-associated vasculitis often have impaired health-related quality of life – as shown here by Physical and Mental Composite Scores and 8 domains of the Medical Outcomes Survey Short Form 36.

The scale ranges from 0 to 100, with 100 indicating perfect health. In this meta-analysis of 4 EUVAS trials, patients with ANCA-associated vasculitis had a median score of around 25 for the Physical Component Score and around 40 for the Mental Component Score.

Across all 8 of the domains, patients reported low quality of life.

These domains remain depressed long term. We've been trying to understand why patients are restricted in what they can do and why they feel a lack in energy.

Slide 26

Glucocorticoids are associated with salient emotional, physical, and social effects.

Because glucocorticoid treatment typically starts with high doses, patients often experience euphoria initially, which affects sleeping patterns. This may lead to fatigue during the day.

Other patients report depression, anxiety, and irritability. Social interactions may be affected because of the mood swings and irritability.

Glucocorticoids may cause myopathy with loss of muscle strength and reduced physical function.

And often, glucocorticoid use leads to weight gain and changes in appearance. Hunger and increasing appetite are widely reported, which inevitably lead to increased weight. Patients often develop a so-called moon face, and these changes in appearance may bring unwanted attention to the underlying ANCA-associated vasculitis. These may lead to decreased social functioning.

Slide 27

This leads to the last concern I will cover – the high level of toxicity associated with current therapies.

Glucocorticoid use is associated with an increased risk of infection, new onset or worsening of diabetes, hyperlipidemia, hypertension and cardiovascular disease, myopathy, osteoporosis, skin and neuropsychiatric disorders, among other debilitating side effects.

Slide 28

Highlighting the level of toxicity with current treatment, this figure shows the most common treatment-related damage items on the Vasculitis Damage Index. It includes nearly 300 patients from the 4 EUVAS studies I previously mentioned – at approximately 7 years after trial entry.

5 of the 14 most common items were related to Glucocorticoids – emphasizing why we need safer therapies.

Slide 29

In summary, patients with ANCA-associated vasculitis need better treatment options that address the unmet needs from current treatment.

Successful alternative therapies should suppress disease activity long-term, reduce relapse rates, improve renal function and health-related quality of life, and minimize treatment-related toxicity.

It is also important for patients to be able to reduce or eliminate their daily oral glucocorticoid treatment to diminish their detrimental effects.

Thank you. I'll now turn the presentation to Dr. Merkel.

Slide 30

Good morning. I'm Dr. Peter Merkel. I'm the Chief of Rheumatology and a Professor of Medicine and Epidemiology at the University of Pennsylvania.

I've been involved in research in vasculitis and caring for patients with vasculitis for more than 20 years. I also have the privilege of being the Principal Investigator and Director of the Vasculitis Clinical Research Consortium – an international vasculitis research network.

I was co-principal investigator of the ADVOCATE Phase 3 pivotal trial with Dr. Jayne, and today I'll be presenting the efficacy data which show that avacopan allows patients to achieve and sustain remission while reducing the toxicities associated with prednisone.

I will start with the study design…

Slide 31

The pivotal Phase 3 ADVOCATE study was designed to evaluate the efficacy and safety of avacopan, in the context of eliminating daily glucocorticoid treatment.

It was a randomized, double-blind, double-dummy, active-controlled clinical trial.

Eligible patients were required to have

- A diagnosis of granulomatosis with polyangiitis or microscopic polyangiitis, and
- A positive test for ANCA; with either antibodies to proteinase-3 or myeloperoxidase, and
- Active disease; either newly-diagnosed or relapsing vasculitis.

Slide 32

The study included a 52-week treatment period.

Patients were randomized 1:1 into two groups: avacopan or prednisone

166 patients were randomized to receive avacopan 30 mg orally twice a day plus a matching prednisone placebo.

164 patients were randomized to receive prednisone and avacopan-matching placebo twice a day.

The prednisone scheduling included a starting dose of 60 mg/day which was steadily tapered off to zero over 20 weeks.

Additionally, both groups received background standard of care therapy of cyclophosphamide followed by azathioprine,

or rituximab.

The primary endpoints were measured at Weeks 26 and 52 and both were analyzed at the end of the study.

Slide 33

In discussions with the FDA, a study arm with only rituximab and cyclophosphamide with no glucocorticoids and no avacopan was proposed as a control group. This was discussed with experts and not considered feasible.

The glucocorticoid taper in the control arm was blinded (i.e., through a double-dummy design) and standardized to limit site-to-site and patient-to-patient variability. This tapering regimen was also selected according to best medical practice and expert consensus.

It is impossible at the current time to conduct a trial in ANCA-associated vasculitis without allowing some glucocorticoids, for example as pre-medication for rituximab.

Background therapy of cyclophosphamide and rituximab was also given according to best practices and prescribing information at the time.

Slide 34

Rituximab re-treatment was not given to patients in the rituximab stratum.

This is consistent with the treatment practice at the time the study was launched. At that time, rituximab was only approved as initial 4-week treatment for induction of remission.

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

Importantly, not giving any additional rituximab to patients in the rituximab stratum allowed for an assessment of the efficacy of avacopan as monotherapy against a blinded placebo control group, a design generally considered the gold standard for assessment of efficacy in randomized controlled clinical trials.

Slide 35

Patients were stratified based on three factors:

- Background immunosuppressive therapy: whether they were assigned at the time of randomization at the investigator's discretion to receive rituximab, IV cyclophosphamide, or oral cyclophosphamide.
- ANCA type: proteinase 3 or myeloperoxidase.
- Newly-diagnosed or relapsing ANCA-associated vasculitis.

This stratification ensured balance across treatment groups for key factors that might affect treatment outcomes.

Slide 36

The ADVOCATE study had 2 primary endpoints: remission at Week 26 and sustained remission at Week 52.

Both endpoints were based on the Birmingham Vasculitis Activity Score – or BVAS – a validated instrument that is the standard tool used in trials to capture disease activity in patients with vasculitis.

Slide 37

The BVAS consists of 9 organ systems and includes symptoms that are typical of each organ's involvement in systemic vasculitis.

Scores range from 0 to 63, with a higher score indicating greater disease activity.

In ADVOCATE, remission and sustained remission were defined as having a BVAS of 0 and not taking any glucocorticoids for the treatment of vasculitis within 4 weeks prior to the visit of interest – either Week 26 or Week 52.

If a patient relapsed after remission had been achieved at Week 26, sustained remission could not have been achieved at Week 52.

Relapse was defined as having a return of disease activity based on having at least one major BVAS item, OR at least 3 non-major items, OR 1 or 2 non-major BVAS items for at least 2 consecutive study visits.

To ensure accuracy and consistency across study centers, it was pre-specified in the protocol and statistical analysis plan that the investigator-assessed scores were to be adjudicated by a blinded Adjudication Committee, consistent with FDA guidance on Endpoint Committees and consistent with previous studies in the field.

Adjudicated data were used for primary endpoint analyses according to the protocol and the pre-specified Statistical Analysis Plan.

Slide 38

I will now outline how the primary endpoints were analyzed.

We tested the two primary endpoints for non-inferiority and superiority using a gatekeeping procedure to maintain the Type I error at 0.05.

The testing order was:

- Non-Inferiority at Week 26,
- and then Non-Inferiority at Week 52,
- followed by Superiority at Week 52,
- and then Superiority at Week 26.

A non-inferiority margin of minus 20 percentage points was derived according to the FDA guidance, elaborated in the Briefing document.

The study was to be declared successful if, at minimum, the first test was met.

Slide 39

Key secondary endpoints included several clinically-important patient outcomes including relapse of disease activity after achieving remission.

We also measured glucocorticoid toxicity, kidney function including estimated GFR and albuminuria, and health-related quality of life.

Slide 40

I will now review the patient disposition…

A high proportion of patients completed the study to Week 60:

91% in each treatment group.

The Intent-To-Treat and Safety populations included all randomized patients who received at least one dose of study medication. Only one of the randomized patients were excluded in the ITT and Safety populations. This patient, who had been in the prednisone group, did not take any study medication.

Twice as many patients in the prednisone group were withdrawn from the study early due to an adverse event.

I will now describe the baseline demographics and clinical characteristics of the study population, which were all consistent with what we would expect for a study of this type - and size - in ANCA-associated vasculitis.

Slide 41

Treatment groups were relatively well balanced at baseline.

The mean age was 61 years, and there were slightly more males than females in the study.

Most patients were White, and approximately 10% were Asian.

Approximately 4% of patients were Hispanic.

Slide 42

Baseline disease characteristics confirmed that stratification was successful in balancing the treatment groups.

Approximately 70% of patients had newly-diagnosed disease in both the prednisone and avacopan groups.

In the overall study population myeloperoxidase-ANCA was the more common ANCA type and granulomatosis with polyangiitis was the more common disease sub-type, but both factors were balanced between groups.

Approximately 65% of patients received rituximab as background standard of care therapy.

The mean BVAS was 16 in each group at baseline. Major items of the BVAS, such as red blood cell casts or glomerulonephritis, typically have a score of 6, and minor items a score of 1 or 2. Therefore, on average, patients had several BVAS items and many patients had multi-organ involvement at baseline.

The estimated glomerular filtration rate at baseline was around 50 mL/min, indicating Stage 3 kidney disease on average.

Slide 43

The organ system involvement at baseline based on the BVAS is shown on this slide.

Approximately 81% had renal involvement…

with General, Ear Nose and Throat, and Chest also commonly involved.

The study population reflected both other study cohorts and the spectrum of patients seen in routine practice.

Now let’s look at the results of the ADVOCATE trial…

Slide 44

The primary endpoint was met for remission at Week 26 with the avacopan group statistically non-inferior to the prednisone group.

Specifically, 72% of avacopan-treated patients achieved clinical remission compared to 70% in the prednisone group.

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

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

As anticipated, superiority was not met at Week 26 due to the expected high remission rate in the prednisone standard of care control group, which was in line with previous trials.

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

Slide 45

For sustained remission at Week 52, the avacopan group achieved both non-inferiority and superiority compared to the prednisone group.

66% of patients in the avacopan group achieved sustained remission compared to 55% in the prednisone group, a difference that is both statistically significant and clinically meaningful. Note that at Week 52 only 6% of the total number of patients in the avacopan group lost the remission between Week 26 and 52.

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

Slide 46

Other than the Intent to Treat primary analyses, a series of pre-specified sensitivity analyses were conducted to evaluate the robustness of the study outcome. This includes Per Protocol population analyses.

As shown here, results of the Per Protocol population sensitivity analyses for the Week 26 remission endpoint

and the Week 52 sustained remission endpoint were consistent with the Intent to Treat analyses.

Slide 47

The primary endpoint findings for the whole study population were also seen when we examined the remission results across pertinent sub-groups.

At Week 26, avacopan was effective across subgroups, including

- those with newly-diagnosed or relapsed disease,
- those with PR3+ or MPO+ ANCA-associated vasculitis,
- those receiving cyclophosphamide or rituximab,
- and those with granulomatosis polyangiitis, GPA or those with microscopic polyangiitis, MPA.

Keep in mind that even though the treatment groups had a similar remission rate, patients treated with avacopan still received benefit from lower glucocorticoid use.

These findings were also seen when we examined the rates of remission at Week 52 by these same important clinical sub-groups.

Slide 48

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

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

This placebo-controlled comparison of avacopan provides clear evidence of avacopan's efficacy and indicates that after remission has been achieved, remission can be sustained with avacopan without any other maintenance treatment.

I'll now report on the data regarding relapses of vasculitis in the trial….

Slide 49

Relapse was assessed in patients who achieved a BVAS of 0 at any point after baseline. Even though this was a conditioned analysis, that is, based on achieving a BVAS of 0, note that the vast majority of patients, 96%, achieved a BVAS of 0; therefore, the fact that this population is not exactly the same as the randomized population is clinically immaterial.

A Kaplan-Meier graph of time to relapse in the two treatment groups is shown here.

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

To further support this outcome, the FDA conducted an exploratory analysis evaluating the proportion of patients who never achieved remission, or achieved remission but had a relapse, and also found a higher rate in the prednisone group (24.4%) vs 14.5% in the avacopan group, with the 95% confidence interval not including 0.

I'll now report on the data regarding use of glucocorticoids

Slide 50

It is important to clearly understand the nature of glucocorticoid use by patients in the trial.

This figure shows the average daily oral glucocorticoid use by study week for the two treatment groups. It includes both study prednisone as well as oral glucocorticoid use other than study prednisone.

This shows that there was an almost complete elimination of oral glucocorticoid use in the avacopan compared to the prednisone group.

Slide 51

You will recall that Dr. Bekker showed you that it is impossible to do an entirely glucocorticoid-free trial in ANCA-associated vasculitis.

We eliminated the scheduled daily prednisone in the avacopan group of the study.

Let me show you the details of the total glucocorticoid load from all sources and the difference between the groups.

Slide 52

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

During the 52-week treatment period, there was a 63% reduction in the average glucocorticoid dose

and an 86% reduction in the median glucocorticoid dose in the avacopan group compared to the prednisone group.

Most of the glucocorticoid use in the avacopan group occurred within the first 4 weeks of the study.

Approximately 40% of the total dose within the first 4 weeks was the oral taper after the screening period, 40% was IV pre-medication for rituximab, and approximately 20% was IV use not as pre-medication.

Slide 53

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

Note that the majority of patients used this extra glucocorticoids during the first 4 weeks of the study, 83% in the avacopan group and 86% in the prednisone group. This is consistent with results shown in the previous slide.

During the Week 4 through 26 period, 31% of patients in the avacopan group vs. 34% in the prednisone group used extra glucocorticoids.

In the second part of the treatment period, Week 26 to 52, when sustained remission was assessed, 27% of patients in the avacopan group vs. 39% in the prednisone group used extra glucocorticoids.

Based on these data, if anything, there would be a bias in favor of the prednisone group regarding additional glucocorticoid use.

Slide 54

In summary, the daily oral prednisone use was successfully eliminated in the avacopan arm of the study.

Overall total mean glucocorticoid dose was reduced by approximately two-thirds in the avacopan group compared to the prednisone group, and

Most extra glucocorticoid use occurred within the first 4 weeks of the study, mainly as pre-medication for rituximab or the taper from pre-study glucocorticoid use.

Now, let's look at glucocorticoid toxicity results…

Slide 55

The Glucocorticoid Toxicity Index, or GTI, is a standardized, weighted, validated instrument that measures change in glucocorticoid toxicity.

It was created by an international group of 19 experts representing eleven subspecialties, including rheumatology, pulmonary medicine, and nephrology, among others.

In developing the GTI, the investigators used methods conventionally employed in multiple Classification Criteria efforts funded by the American College of Rheumatology and the European League Against Rheumatism. These methods include multi-criteria decision analysis facilitated by the1000Minds software, and validation in real patients.

Slide 56

The GTI was designed as a clinician-facing instrument that relies on patient input.

Several domains require direct patient interaction and consideration of the impact of glucocorticoid toxicity on patients lives. Examples include:

- The myopathy domain where the patients' muscle strength is assessed and its impact on day-to-day function is determined,

- The skin toxicity domain where patients are examined for cutaneous findings of glucocorticoid toxicity, and where the potential impact on activities of daily living is assessed, and

- The neuropsychiatric effects domain where – through discussion with the patients, the degree to which patients' lives and day-to-day functioning are impacted by, for example, insomnia, depression, and glucocorticoid-induced violence is assessed.

Other GTI domains are quantitative measures that also reflect toxicities important to patients, including body mass index, blood pressure, glucose metabolism, and lipid metabolism.

Lastly, infections and weight changes are also included in the GTI, both important to patients.

Slide 57

There are two components of the GTI.

The Cumulative Worsening Score, or CWS, of the GTI, captures cumulative glucocorticoid toxicity over time.

In the Aggregate Improvement Score, or AIS, toxicities are removed if they improve and can be added if they are new or worsen.

With both the CWS and AIS, if a study medication is effective at decreasing glucocorticoid toxicity over time, the scores will be lower in the study medication arm.

Slide 58

In the ADVOCATE study, both GTI scores demonstrated that glucocorticoid toxicity was reduced in the avacopan group compared to the prednisone group. Dr. Jayne will expand further on glucocorticoid toxicity in the safety section.

At the two timepoints where the GTI was measured, Weeks 13 and 26, the mean Cumulative Worsening Score, was lower in the avacopan group compared to the prednisone group. Recall that a higher score on this measure indicates greater toxicity.

The avacopan group also had a lower Aggregate Improvement Score compared to the prednisone group, indicating lower toxicity with avacopan.

Of note, the difference in mean CWS and AIS between the prednisone and avacopan groups was greater than 10 points, at both weeks 13 and 26. This difference is considered the minimum clinically important difference in ANCA-associated vasculitis.

GTI was not measured after Week 26, because the prednisone taper stopped at 20 weeks, and the goal of using this instrument was to quantify the glucocorticoid toxicity mainly related to study prednisone.

Slide 59

Here the components of the GTI Cumulative Worsening Score are shown for the two treatment groups at Weeks 13 and 26.

Lower scores, indicating lower toxicity, was observed for the avacopan group compared to the prednisone group across these components, except for blood pressure. This is probably not surprising, because many factors other than glucocorticoid use have an effect on blood pressure.

The same pattern was observed for the GTI Aggregate Improvement Score, which is shown in the Briefing document.

Next I will report on outcomes measuring renal function….

Slide 60

It has been notoriously difficult historically to improve kidney function with medications.

A meta-analysis of 47 trials in more than 60,000 patients conducted by Inker and colleagues in 2019 showed that a difference as small as 0.75 mL/min/year between treatment groups is clinically relevant in patients with chronic kidney disease.

Patients with ANCA-associated vasculitis often have renal vasculitis. Approximately 81% of patients in our study had evidence of renal disease at baseline. Therefore, it was relevant to evaluate the changes in renal function, as measured by the estimated glomerular filtration rate.

The mean eGFR at baseline was approximately 45 mL per minute in both treatment groups, indicating Stage 3 kidney disease on average.

At both Week 26 on the left, and Week 52 on the right, there was a greater improvement in eGFR in the avacopan group compared to the prednisone group.

The difference in eGFR between treatment groups was approximately 3 mL per minute. This exceeds the clinically relevant difference of 0.75 mL/min.

Slide 61

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

These data show that the avacopan treatment effect on renal function over 52 weeks was particularly notable among this subset of patients.

There was a continued trend in improvement in eGFR between Week 26 and Week 52, a period when the prednisone taper in the prednisone group was completed, and avacopan was thus being compared directly to placebo.

At Week 52, the mean difference of 5.5 mL/min between groups is clinically important in these patients with Stage 4 kidney disease.

Slide 62

Looking at another measurement of kidney function, the urinary albumin to creatinine ratio.

Albuminuria is common in patients with ANCA-associated vasculitis and is a prognostic factor at baseline for poor renal outcome.

At Week 4, the urinary albumin to creatinine ratio, or UACR, improved 40% on average in the avacopan group compared to no change in the prednisone group.

The overall improvement in UACR was similar between treatment groups at Week 52.

I will now move on to outcomes related to health-related quality of life…

Slide 63

Looking first at the SF-36…

Patients in the study had impaired quality of life at baseline. The Mental and Physical Component Summary scores were approximately 40 – on a 0 to 100 scale – at baseline in both groups.

Scores were consistently low across all the individual domains that make up the two summary scores.

Slide 64

This graph shows the mean change from baseline to Week 26 and Week 52 in the Physical Component Score and the four domains that make up this summary score.

You can see that the changes were greater in the avacopan group compared to the prednisone group in the Physical Component Score and all 4 domains at both timepoints. Notably, General Health Perception worsened in the prednisone group at Week 26 following the prednisone taper, compared to an improvement in the avacopan group.

Slide 65

This graph shows the mean change from baseline to Week 26 and Week 52 in the Mental Component Score and the four domains that make up this summary score.

At Week 26, the improvements in the Role Emotional and Vitality scores were greater in the avacopan group compared to the prednisone group.

Slide 66

The other health-related quality of life measure used in this trial, the EQ-5D-5L, also demonstrated advantages for patients in the avacopan group compared to the placebo group.

At Week 52, the avacopan group had significantly greater improvements from baseline compared to the prednisone group in both

the Visual Analogue Scale, shown on the left

and on the Index Score, shown on the right.

Overall, these significant improvements in health-related quality of life, as measured by both of these two validated instruments (SF-36 and EQ-5D-5L), demonstrate a clinically meaningful benefit of treatment with avacopan for patients with ANCA-associated vasculitis.

Slide 67

In summary, the ADVOCATE study demonstrated avacopan's statistically significant and clinically meaningful efficacy in treating patients with ANCA-associated vasculitis.

Both pre-specified primary endpoints were met as patients in the avacopan group achieved clinical remission at Week 26 at the same rate as patients in the prednisone group

and

at Week 52 the rate of sustained remission was statistically superior among patients in the avacopan group compared to patients in the prednisone group.

We also saw a significantly lower risk of relapse with avacopan compared to prednisone.

Importantly, these results were coupled with significantly less glucocorticoid toxicity in avacopan-treated patients compared to the prednisone group.

We also saw greater improvements in kidney function, in the avacopan group compared to the prednisone group, which was particularly evident in patients with Stage 4 kidney disease at baseline, those who are at highest risk of progressing to end-stage renal disease.

Finally, patients treated with avacopan reported greater improvements in health-related quality of life, particularly in the physical domains, compared to the prednisone group.

Overall, treatment with avacopan can fulfill many of the unmet medical needs seen with currently available therapies and provide patients with ANCA-associated vasculitis an effective therapy while reducing the toxicities associated with glucocorticoids.

Thank you. I'll now return the microphone back to my colleague, Dr. Jayne.

Slide 68

Thank you. I'll now review the safety data from the Phase 3 ADVOCATE study demonstrating that the safety profile in the avacopan group was favorable compared to the prednisone group.

Slide 69

Overall, the clinical development program included more than 1000 patients who received at least one dose of avacopan,

with 239 in the Phase 2 and Phase 3 randomized controlled studies in ANCA-associated vasculitis.

166 patients received Avacopan up to 52 weeks in the Phase 3 pivotal trial, ADVOCATE - where I will focus the presentation.

Starting with the overall safety profile….

Slide 70

The Phase 3 study was larger and of longer duration compared to the Phase 2 studies. Therefore, the main safety analyses focused on the Phase 3 study.

Nevertheless, integrated analyses were conducted for completeness.

This slide shows high level results for the integrated analysis, and shows that the incidence of adverse events, severe adverse events, serious adverse events and discontinuation of study medication due to adverse events was similar between treatment groups.

There were fewer life-threatening adverse events and deaths in the avacopan compared to the prednisone group.

Let's now look at the Phase 3 study results….

Slide 71

In the Phase 3 study, a similar proportion of patients reported at least one adverse event in both treatment groups; however, the number of adverse events was lower in the avacopan group compared to the prednisone group.

Approximately a quarter in each group experienced a severe AE, with 71 events in the avacopan group compared to 94 in the prednisone group.

The number of serious adverse events was 116 in the avacopan group compared to 166 in the prednisone group.

Life-threatening AEs occurred in 5% of patients in the avacopan group, and 9% of patients in the prednisone group.

There were 2 deaths in the avacopan group and 4 in the prednisone group. I'll provide more detail regarding these cases later in my presentation.

The percentage of patients who discontinued study medication due to an adverse event was similar between treatment arms.

Let's look at the reported adverse events…..

Slide 72

The most commonly reported Adverse Events in either treatment group are often seen within this disease setting.

Overall, the number of adverse events was lower in the avacopan group, with nearly 1800 events compared to more than 2100 events in the prednisone group.

Nausea, headache and vomiting were reported more in the avacopan group. These were typically transient and not serious.

Several adverse events occurred less frequently in the avacopan group compared to the prednisone group.

Slide 73

No deaths occurred in the Phase 1 or Phase 2 studies. There were 7 deaths during the Phase 3 study, with 1 occurring during the screening period due to acute myocardial infarction.

2 patients died in the avacopan group, and 4 patients died in the prednisone group.

The adverse events leading to death for the 2 patients in the avacopan group were granulomatosis with polyangiitis and pneumonia.

The first patient was a 70-year-old male with newly diagnosed PR3-positive GPA who died on Day 315 from severe worsening of his disease. The last dose of avacopan was taken on Day 236, 79 days before his death.

The second avacopan patient was a 70-year-old woman with newly diagnosed, MPO-positive MPA, who died from broncho-pneumonia due to aspergillus superinfection on Day 160. Her last dose of avacopan was on Day 50.

Both events were assessed by the investigator as probably not related to study medication.

Now moving to other serious adverse events…

Slide 74

Most of the reported serious adverse events were related to underlying ANCA-associated vasculitis or standard therapies and align with rates in previously published trials.

The most commonly reported SAEs are shown here.

The most common serious adverse event was worsening of ANCA positive vasculitis, including GPA and MPA, with 10% in the avacopan and 14% in the prednisone groups.

Now moving to discontinuations.

Slide 75

The overall incidence of adverse events leading to discontinuation of study medication were similar between treatment groups demonstrating that the adverse event profile is manageable and allows most patients to remain on study treatment. Again, the rates align with previous studies.

The most common adverse event leading to study medication discontinuation was ANCA positive vasculitis, with 2% in the avacopan and 5% in the prednisone groups.

The two cases of latent tuberculosis were identified based on screening results, which violated an exclusion criterion of the study. Study medication was stopped in both patients on Day 7. Therefore, there was no association of avacopan with TB.

Turning next to glucocorticoid toxicity….

Slide 76

Adverse events considered possibly related to glucocorticoid use were based on EULAR search term criteria. The incidence of these events was lower in the avacopan group, 66% compared to 81% in the prednisone group. The 95% confidence interval around the group difference does not include 0, indicating a significant difference between groups overall.

The organ cluster analysis indicated a lower incidence in the avacopan group particularly regarding dermatologic and endocrine/metabolic events.

When evaluating individual adverse events, the difference between treatment groups was mainly due to adverse events of weight increase, insomnia, hyperlipidemia, adrenal insufficiency, blood glucose increase, and irritability. These are likely related to glucocorticoid use.

Next, I'll review pre-specified adverse events of interest….

Slide 77

Adverse events of interest were pre-specified based on experience from the Phase 2 clinical studies and in consideration of potential adverse events based on biologic plausibility.

Let's start with adverse events of infection…

Slide 78

There was a lower number of infections and serious infections in the avacopan group compared to the prednisone group.

The incidence of serious opportunistic infections was lower in the avacopan group: 4% compared to 7% in the prednisone group.

One patient in the avacopan group reported a life-threatening infection during the follow-up period, when avacopan was not given. This case of hepatitis B reactivation was considered possibly related to 2 additional rituximab infusions given prior to the event – on Days 225 and 239. Such reactivation is a known risk of use of rituximab.

2 patients in the prednisone group reported life-threatening infections – one with Cryptococcal meningitis, and one with sepsis.

One fatal infection of broncho-pneumonia was reported in the avacopan group, and 2 patients in the prednisone group had fatal infections – one with a generalized fungal infection and one with empyema.

Slide 79

Here we see the serious infections that occurred in at least 2 patients in any group.

Two device-related serious infections were reported in the avacopan group: both had central venous catheter-related infections; neither was considered related to avacopan by the Investigator, and both resolved with no action taken regarding study medication.

No Neisseria meningitidis infections were observed, which is consistent with the fact that avacopan does not block the formation of the membrane attack complex, i.e., C5b-9.

Serious herpes zoster, infectious pleural effusion, and respiratory syncytial virus infection, each was reported in no patient in the avacopan group and two patients in the prednisone group.

Turning to AEs associated with hepatic test elevations….

Slide 80

Overall, 22 patients in the avacopan and 19 patients in the prednisone group had hepatic test adverse events.

Regarding serious events, Grade 4 elevations in ALT or AST occurred in 1 patient in the avacopan and 2 patients in the prednisone groups. The rest of the cases were Grade 2 or 3. One patient in the avacopan group had a positive re-challenge with study medication.

Bilirubin increases, in the same timeframe as liver enzyme elevations, occurred in 2 patients in the avacopan and 1 patient in the prednisone groups.

There were no cases that met the definition of Hy's Law. Hy's Law states--among other requirements– that "no other reason could be found for increases in aminotransferase and serum bilirubin". This was clearly not true in any patient in this trial.

It is to be noted that all patients in both groups were required to have prophylaxis for pneumocystis, consistent with the FDA requirement for this trial. The most common agent for this, co-trimoxazole, was used in over 90% of patients in the trial, which was balanced between groups. Co-trimoxazole has well documented hepatic toxicity.

Alcohol was causative in at least one patient, azathioprine in another, and patients also received acetaminophen, statins, and repaglinide, which could have caused or contributed to the events.

Importantly, all patients recovered with the withdrawal of study medication and other potentially hepatotoxic drugs.

Next, we look at adverse events of neutropenia and lymphopenia…

Slide 81

The incidence of adverse events associated with neutropenia or lymphopenia were lower in the avacopan than the prednisone group.

19% of patients in the avacopan and 24% in the prednisone groups had adverse events associated with low white blood cell counts.

Of these events, 4 patients in the avacopan group had SAEs compared to 8 in the prednisone group.

Grade 3 or 4 events of leukopenia or neutropenia were uncommon. However, as anticipated based on the mechanism of action of rituximab and cyclophosphamide, lymphopenia was

commonly observed in both groups. Grade 3 lymphopenia events were observed in 28% in the avacopan and 30% of the prednisone groups, Grade 4 events occurred in 2% in the avacopan and 8% in the prednisone groups.

Moving now to hypersensitivity….

Slide 82

The majority of hypersensitivity events occurred in the Skin and subcutaneous tissue disorders system organ class.

Even though "rash" appeared to be slightly more common in the avacopan group, when rash was examined across all Phase 2 and 3 studies, the incidence was similar with 22% in the avacopan group and 23% in the prednisone group.

Two skin serious hypersensitivity adverse events were reported in the avacopan group. One patient with angioedema recovered without sequelae and an AE of skin necrosis was not considered a hypersensitivity reaction to avacopan (necrotic foot ulcer due to secondary infection of purpura).

A second adverse event of angioedema was observed in the avacopan group. Study medication was paused and the patient recovered. However, the event did not recur upon re-challenge with study medication.

Slide 83

Adverse events of blood creatine phosphokinase increase occurred in 6 patients in the avacopan and 1 in the prednisone groups.

Two of the events in the avacopan group were Grade 3. One patient was on a statin and the other took colchicine for gout. The rest of the events were Grade 1 or 2.

None of the AEs were serious, and there were no cases of rhabdomyolysis or myositis.

Slide 84

In summary, the safety profile in the avacopan group was favorable compared to the prednisone group.

Fewer adverse events, serious adverse events, life-threatening adverse events, and deaths were observed in the avacopan compared to prednisone groups.

The avacopan group also had a lower incidence of adverse events of interest for infection and neutropenia or lymphopenia.

There was a slightly higher incidence of hepatic test adverse events and angioedema in the avacopan vs. prednisone group. These are manageable with patient monitoring.

Adverse events considered possibly related to glucocorticoid use were significantly lower in the Avacopan Group and are consistent with the GTI efficacy results.

Overall, avacopan was well-tolerated and provided patients with significantly less glucocorticoid-associated toxicity. These results demonstrate that avacopan could be a valuable treatment for patients with ANCA-associated vasculitis.

Thank you. I'll now turn the presentation back to Dr. Merkel.

Slide 85

Thank you, Dr. Jayne.

I'm happy to now provide my clinical perspective on avacopan's benefit-risk profile and describe what this treatment would mean to my patients with ANCA-associated vasculitis

Slide 86

Let me describe a typical clinical scenario to help highlight how avacopan could directly help patients with ANCA-associated vasculitis:

Imagine a 51 year-old woman presents for medical attention after several weeks of increasing fatigue, cough, bloody nasal discharge, and a serum creatinine of 3.4 mg/dl.

CT scans demonstrate the presence of sinusitis and several pulmonary nodules,

and she has a positive test for proteinase 3-ANCA.

A kidney biopsy is consistent with ANCA-associated vasculitis.

Following the receipt of the biopsy results, treatment for ANCA-associated vasculitis is begun with prednisone 60 mg/day and plans for a course of rituximab. Over the next several months the patient does fairly well from the standpoint of her vasculitis with resolution of her upper airway and lung problems. Her serum creatinine improves but never goes below 2.2 mg/dl. Additionally, as a result of her using prednisone for several months she requires treatment for diabetes mellitus, she gains 25 pounds, and she is quite unhappy with her personal appearance.

Unfortunately, 8 months after starting treatment, the patient experiences a relapse of ANCA-associated vasculitis requiring re-initiation of glucocorticoids and other treatments.

This may seem like a dramatic example, but I assure you this is an extremely common situation.

Although our treatments are certainly helpful to a patient like this, this case illustrates the point that we can do better.

Slide 87

As we heard earlier from Dr. Jayne, despite currently available therapies, there remain significant unmet needs regarding treatment for ANCA-associated vasculitis.

Even though progress has been made, the risk of relapse remains high. Current treatments have limited effects on renal function with residual and important renal impairment a common problem.

Furthermore, patients with ANCA-associated vasculitis continue to suffer reduced quality of life, even after treatment has been provided.

Finally, the current approaches to treatment are associated with substantial toxicity, especially due to use of glucocorticoids.

Our patients need safer, more effective treatments that can control their disease activity, safely maintain remission, improve their kidney function, positively affect their quality of life, and avoid the many toxicities associated with treatment of this disease.

Slide 88

For as long as I've been treating patients with ANCA-associated vasculitis, glucocorticoids have been the backbone of therapy.

Although these drugs are effective at reducing inflammation, they have substantial short- and long-term toxicities.

Therefore, in addition to dealing with a life-threatening autoimmune disease, patients with ANCA-associated vasculitis must endure the harsh physical and emotional side effects of treatment with daily high-dose prednisone.

A goal I have for all of my patients is to reduce glucocorticoid use and the inevitable toll these drugs have on patients' health and well-being. I cannot emphasize enough – from a patient's perspective – how meaningful it is to meet this goal.

Slide 89

The selective C5a receptor inhibitor, avacopan represents the first potential alternative to daily oral prednisone for ANCA-associated vasculitis.

The data from the ADVOCATE trial I presented earlier clearly demonstrates avacopan's efficacy in treating patients with ANCA-associated vasculitis.

Importantly, avacopan fulfills many of the unmet needs that remain despite current therapy.

First, both primary endpoints were met, with statistical non-inferiority at Week 26 for the avacopan versus prednisone group, without the need for daily glucocorticoid treatment, and statistical superiority in sustained remission at 52 weeks. We also saw a significantly lower risk of relapse with avacopan compared to the prednisone group. Avacopan may also be given to sustain remission without the need for additional immunosuppressants such as rituximab.

Second, the avacopan group had significantly greater improvements in kidney function compared to the prednisone group, which was particularly evident in patients with Stage 4 kidney disease at baseline.

Third, patients treated with avacopan reported greater improvements in health-related quality of life compared to the prednisone group. We saw this particularly in the physical domains, but also in important mental domains such as vitality (that means fatigue), one of the most devastating aspects of ANCA-associated vasculitis.

Fourth, avacopan-treated patients had a statistically and clinically significant reduction in glucocorticoid toxicities as measured by the GTI and adverse event assessments.

Slide 90

Of course, we must always weigh the benefits of any therapy against any potential risks. The safety data has shown that avacopan was well tolerated and had a favorable safety profile compared to the prednisone group.

In the ADVOCATE study, there was a lower number of adverse events in the avacopan group compared to the prednisone group.

The incidence of adverse events of infections, that are commonly observed in patients receiving treatment for ANCA-associated vasculitis was lower in the avacopan group compared to the prednisone group.

Hepatic AEs and angioedema are manageable with monitoring, which is part of routine medical care for these patients.

Overall, avacopan, with its targeted mechanism of action, was well tolerated and provides an important safety advantage over glucocorticoids.

Slide 91

Returning to the patient example I started this section with, we can have a good sense of how use of avacopan could potentially have helped this patient.

Avacopan could have been used instead of the daily oral glucocorticoid taper to help the patient achieve remission without experiencing the substantial side-effects of glucocorticoids, her residual renal function may have been better, and she would have had a better chance of staying in remission with continued avacopan use.

Her probability of relapse may have been reduced and her quality of life also may have improved with avacopan use.

Slide 92

Thus, in summary, if approved for use in ANCA-associated vasculitis, avacopan would be a major advance in our field.

Avacopan, as a selective C5a receptor inhibitor, has a novel mechanism of action that targets disease-specific pathophysiology.

It will provide patients with clinically-meaningful benefits without having to endure the substantial toxicities associated with use of glucocorticoids.

Thank you.

Slide 93