CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214487Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 28, 2021
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 214487
Product Name and Strength:	Tavneos (avacopan) capsules, 10 mg
Applicant/Sponsor Name:	Chemocentryx
OSE RCM #:	2020-1483-1
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 27, 2021 for Tavneos. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Tavneos (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Vee, S. Label and Labeling Review for Tavneos (NDA 214487). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 FEB 10. RCM No.: 2020-1483.

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 16, 2021
To:	Susie Choi, PharmD Regulatory Project Manager Division of Rheumatology and Transplant Medicine (DRTM)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Kyle Snyder, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TAVNEOS (avacopan)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 214487
Applicant:	Chemocentryx, Inc.

1 INTRODUCTION

On July 7, 2020, Chemocentryx, Inc. submitted for the Agency's review an original New Drug Application (NDA) 214487 for TAVNEOS (avacopan) capsules, for oral use. The proposed indication for TAVNEOS (avacopan) is for treatment of anti-neutrophil cytoplasmic antibody associated vasculitis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rheumatology and Transplant Medicine on August 6, 2020, and July 24, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TAVNEOS (avacopan) capsules for oral use.

2 MATERIAL REVIEWED

- Draft TAVNEOS (avacopan) MG received on July 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 7, 2021.
- Draft TAVNEOS (avacopan) Prescribing Information (PI) received on July 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 7, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 10, 2021

To: Susie Choi, Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for TAVNEOS (avacopan) capsules, for oral use

NDA: 214487

In response to DRTM's consult request dated July 24, 2020, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), and carton and container labeling for the original NDA submission for TAVNEOS (avacopan) capsules, for oral use.

Labeling: OPDP's comments on the proposed Prescribing Information are based on the draft labeling received by electronic mail from DRTM on September 3, 2021, and are provided below.

OPDP comments on the proposed Medication Guide will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DRTM on September 9, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2020345
NDA Number/ Referenced IND for NDA:	214487/120784
Applicant:	ChemoCentryx, Inc.
Established Name/Trade Name:	Avacopan (CCX168)
Indication:	Treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis
Review Division:	Division of Rheumatology and Transplant Medicine
Clinical Reviewer	Suzette Peng
Clinical Team Leader (TL)	Rachel Glaser
Review Division Project Manager:	Susie Choi
COA Reviewer:	Ji Li
COA Director:	David Reasner
Date Consult Request Received:	August 6, 2020
Date COA Briefing Package/Submission Received:	July 7, 2020
Date COA Review Completed:	March 19, 2021
Date COA Review Addendum Completed:	September 3, 2021

Please check all that apply: ☒Rare Disease/Orphan Designation
☐Pediatric

This Clinical Outcome Assessment (COA) Addendum is related to review of health-related quality of life (HRQoL) assessments, i.e., the Medical Outcomes Survey Short Form-36 version 2 (SF-36 v2) and EuroQOL-5D-5L (EQ-5D-5L), in the drug development program of Avacopan (CCX168) capsules (i.e., NDA 214487). Both the SF-36 v2 and EQ-5D-5L were completed by study patients to measure changes from baseline in HRQoL in the phase 3 trial, i.e., Study CL010_168.

SF-36

The SF-36v2 acute version is a 36-item self-administered generic health status instrument designed to measure functional health and well-being from patient perspective in eight domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Items are rated based on a 1-week recall period using Likert scales with varying lengths. Domain scores range from 0 to 100, with higher scores representing better levels of function and/or better health. All 8 domain scores are combined, normalized, and z-transformed to calculate two summary scores, i.e., physical component summary (PCS) and mental component summary (MCS) scores. These two component summary scores provide global measures of physical and mental functioning and well-being, and have normative scores of 50 with a standard deviation (SD) of 10 based on the 2009 U.S. general population. A single overall score for the SF-36 is not applicable.

The applicant provided existing literature to support inclusion of the SF-36 for use as a key secondary endpoint measure for regulatory purposes. We acknowledge that the submitted literature supports the wide use of the SF-36 in clinical research. However, as the SF-36 is a generic measure developed to assess universal health concepts, the instrument appears to capture health concepts that are not specific to a particular disease, condition, or treatment. Upon review of the applicant's literature references, we do not believe that there is sufficient information to determine whether the SF-36 is fit for purpose in AAV-specific drug development program(s). Additional qualitative and quantitative data from patients with AAV are required to demonstrate that the SF-36 assesses the most important and relevant concepts in a reliable way within this patient population. Some specific concerns include:

1. The item stem, e.g., "Does your health now limit you in …? If so, how much?" appears to not specifically ask patients to focus on AAV-related concepts. It is unclear whether patients may consider other aspects of their health unrelated to AAV when answering these questions. In addition, we are concerned that the term "during a typical day" is not a well-defined time frame that may have different interpretation by patients.
2. The SF-36 does not have a response option to select if patients do not perform an activity (e.g., lifting or carrying groceries, climbing several flights of stairs, walking more than a mile). We are concerned that the patients' responses to hypotheticals are not reliable and may not reflect their degree of limitation when actually doing these activities.
3. Emotional impacts represent aspects of life that can be affected by many external factors in addition to the underling disease and treatment (e.g., psychosocial factors). Assessment of these impacts may not clearly describe a direct clinical benefit and interpretation of change is challenging.

In conclusion, we acknowledge that the SF-36 has been widely deployed to measure HRQoL in clinical research and the Agency has accepted the instrument in certain contexts of use. However, in the AAV patient population, we believe that there is insufficient evidence of content validity either from the literature or in the avacopan program-specific research to ensure adequate interpretation of HRQoL in the proposed context. The SF-36 is a measure of general health status, which makes it difficult to ascertain the effect of treatment on the underlying disease or condition under treatment. Given the complexity of HRQoL, (b) (4) a robust outcome on the primary endpoint, a clear estimand, and an *a priori* endpoint model with appropriate control for multiplicity are necessary considerations for regulatory decision-making.

<u>EQ-5D-5L</u>
There is no regulatory precedent of utilizing EQ-5D-5L to support regulatory decision-making (b) (4) The EQ-5D-5L is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses and (b) (4) we acknowledge that the EQ-5D-5L may be necessary for other regulatory authorities and/or payers.

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Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	214487
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Avacopan (CCX168)
Indication	ANCA associated vasculitis
Applicant	Chemocentryx, Inc.
Requesting Division	Division of Rheumatology and Transplant (DRTM)
Primary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	June 14, 2021

Context: The DHN DILI Team was asked by DRTM for "assistance in evaluating a potential liver safety signal" with Avacopan (AVP).

AVP is a new molecular entity (NME) that prevents complement 5a binding and studied in placebo-controlled trials of patients with the rare disease, ANCA associated vasculitis (AAV). One phase 3 and two phase 2 studies form the basis for this NDA. Approximately 250 patients were exposed to AVP in the 3 studies. There was an increase in liver associated AEs in the active arm compared to placebo (13.3% versus 11.6%). This imbalance persisted in liver related SAE's (5.4% versus 3.7%). A total of 10 patients receiving AVP had SAEs related to liver test abnormalities. One patient had peak transaminases over 3 times upper limit of normal with concurrent jaundice and only modest alkaline phosphatase elevation (Hy's Law criteria).

The DILI Team sent its consult document to DRTM Apr 17, 2021. The Team had regular discussions with DRTM and was present at the Advisory Committee (AC) on May 6, 2021. The AC split on adequacy of efficacy (9 yes; 9 no), safety (10 yes, 9 no) and benefit-risk (10 yes, 8 no). We also had discussions with DRTM about the sponsor's IR-25 response of May 24, 2021.

Executive Summary: AVP can cause liver injury, but the risk of severe injury is unclear. AAV patients took other potentially hepatotoxic medications that hindered clear assessment of DILI severity in this NDA. The low number of patients exposed and one possible Hy's Law case is concerning. While this case is highly like DILI, there was a plausible competing medication making it impossible to implicate AVP with confidence. There were 4 liver related SAE cases that were more clearly due to AVP, but none of these became jaundiced. All cases improved back to baseline with stopping AVP.

Without clear attribution of a Hy's Law case to AVP, we think a path toward approval can be forged, if efficacy and need are clear. Close monitoring of liver tests would be recommended, if approval is given. Please see Section 5.0 for our full assessment.

Full Consultation Sections:

Section 1.0 - Rationale: Target disease, rationale and mechanism of action.
Section 2.0 – ADME, metabolites, hepatic metabolism pertinent to DILI
Section 3.0 - Non-clinical data: In vitro, in silico, animal data pertinent to DILI.
Section 4.0 - Clinical data: Trial summary and DILI case level assessments
Section 5.0 – Summary & Recommendations.
Section 6.0 -- References

Abbreviations:
AAV: ANCA associated vasculitis
ADaM: Analysis Data Model
ALP: alkaline phosphatase
ALT: alanine aminotransferase
ANA: anti-nuclear antibody
ANCA: antineutrophil cytoplasmic antibody
ASMA: anti-smooth muscle antibody
AST: aspartate aminotransferase
AVP: Avacopan or CCX168
C5a: complement 5a
DILI: drug-induced liver injury
IR: Information request
ISS: Integrated Summary of Safety
MOA: mechanism of action
NME: new molecular entity
STDM: Study Data Tabulation Model
Sulfa-TMP: Sulfamethoxazole-Trimethoprim (e.g. Bactrim)

1.0 Rationale for Use:

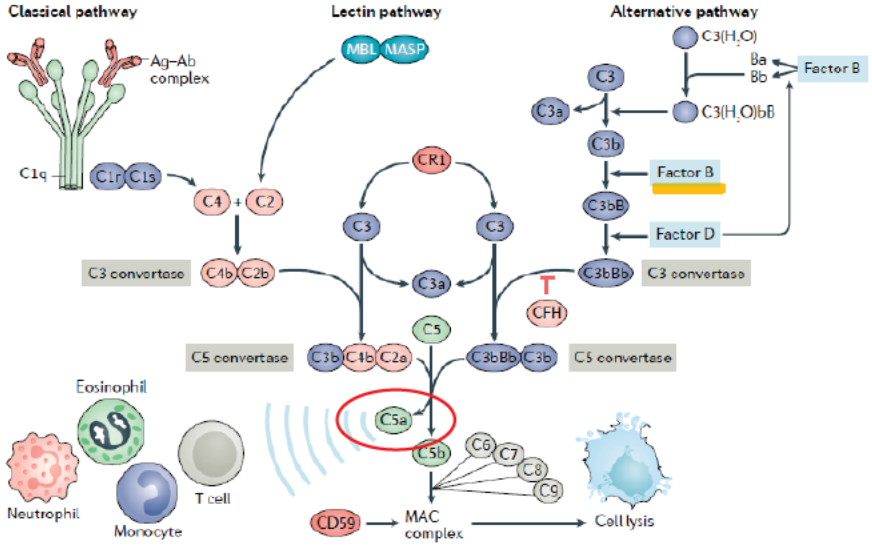
1.1 Targeted Disease: Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) encompasses a group of rheumatologic disorders that involve small vessel vasculitis. The sponsor indicates AAV is a group of orphan diseases with an estimate US incidence of 1.1 per 100,000 person-years. These disorders are associated with autoantibodies including neutrophil-expressed antigens myeloperoxidase and proteinase 3.

It effects primarily older persons but is diagnosed in all age groups. It occurs more in Caucasians, but large cohorts in Asia are also reported. Disease involvement includes the lungs, kidneys, skin, eyes, nervous system, ears, nose and throat. Without treatment, mortality can be 80% at 2 years.

Treatment with cyclophosphamide, rituximab and corticosteroids lowers this rate substantially to 11% in the first year, but the therapies come with significant side effects. Moreover, the disease control is incomplete and mortality remains 9 fold higher than age matched healthy controls. In particular, current treatments have limited ability to slow deterioration in renal function.

1.2 Mechanism of Avacopan (AVP) Action: AVP is new molecular entity that inhibits binding of complement 5a (C5a) to its receptor, thus preventing C5a's downstream effects of enhancing inflammation by priming neutrophils and other cells involved in the inflammatory response. Complement activation and C5a production is considered central to the pathophysiology of ANCA associated vasculitis (Figure 1). Elevated levels of C5a are seen in AAV patients, and an Anti-MPO mouse model for AAV suggests AVP can prevent ANCA-induced renal disease.

Figure 1: Complement Cascade Showing the Classical, Lectin, and Alternative Pathways



2.0 Absorption, Distribution, Metabolism and Excretion (ADME) Overview

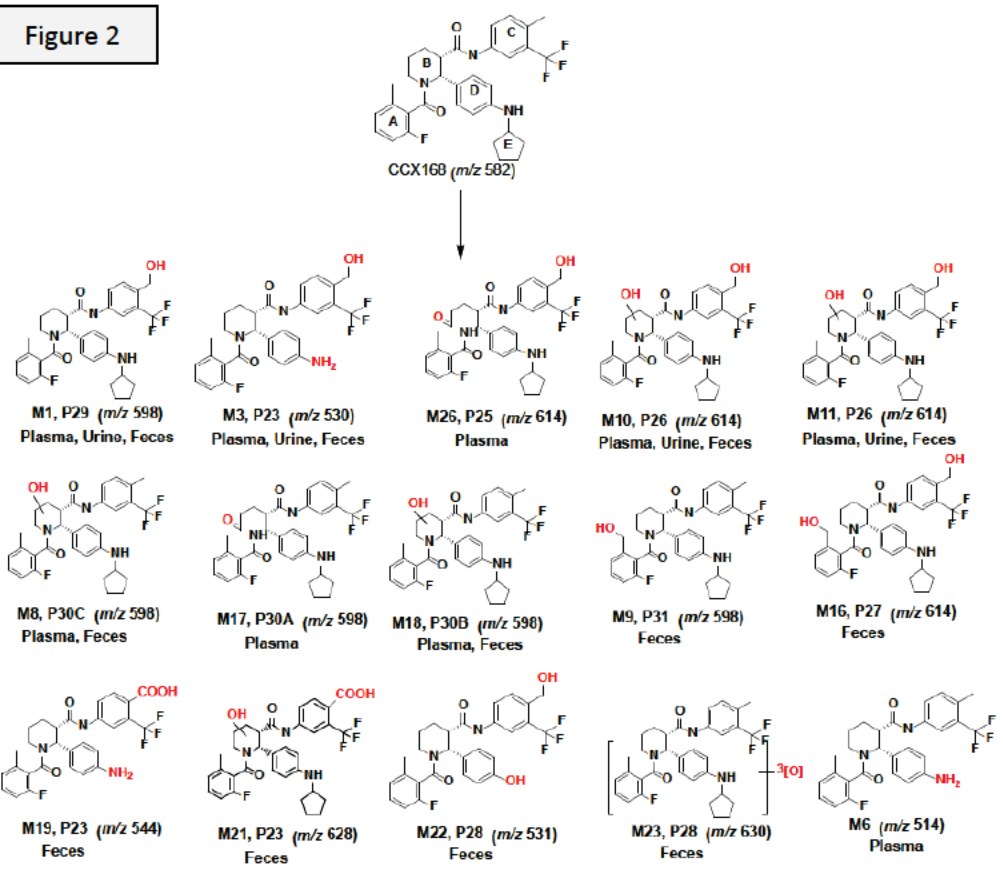
2.1 Absorption and Distribution: Absorption of oral AVP is high at 93% when delivered in liquid form. Peak plasma concentrations occur in 2.5 hours. AVP is nearly 100% albumin and alpha1-acid glycoprotein bound in plasma. Volume of distribution is 5600 L. It is widely distributed in rats, taking 14 days to drop below limits of quantification.

2.2 Metabolism and Excretion: AVP is metabolized primarily by CYP3A4 mediated oxidation. Carbon-14 studies indicate that the main excretion is by "numerous Phase I metabolites" via bile and feces. There is limited excretion by the kidneys. AVP is the main circulating form, but it is minimally found in urine or feces (1% and 7%). The main metabolite, CCS168-M1, accounts for

12% of plasma exposure and has about the same activity as AVP in terms of C5a inhibition. AVP's structure and proposed human metabolites are shown in Figure 1. Only M1 is found to take up >10% of the circulation species. Exact half-life values in humans are not provided in the Clinical Overview or Safety Summary but is referred to as "long" in the Clinical Overview (2.5 Clinical Overview, page 7). In mice, it is 2.5 hours while in dogs it is 14.2 hours (2.4 Non-clinical Overview, page 19). AVP is a weak inhibitor of CYP3A4, increasing midazolam and celecoxib AUCs by 81% and 15% respectively. AVP is a weak inducer with a 3-4-fold increase in CYP3A4 gene expression but no increase in activity. (Study Report No. PC0635_168_a, Report IVAL1300-020714; Table 4)

2.2.1 AVP Chemical Structure and Proposed Metabolites:

Figure 2



3.0 Non-clinical data related to DILI

3.1 Animal studies: The sponsor conducted several short and long-term dosing studies in Sprague-Dawley rats and Cynomolgus monkeys (2.6.6, Toxicology Written Summary, Table 1). Long-term dosing was 26 and 44 weeks in rats and monkeys, respectively. Maximum dosing were 200 mg/kg and 15-25 mg/kg per day respectively. Increase liver weights were document in several studies, but no liver histopathology changes were seen in any animal models.

3.2 In vitro and/or in silico studies: The sponsor did transporter interaction studies for AVP (CCX168) and CCX168-M1. They found weak inhibition of the basolateral/sinusoidal transporters OAT1 and OAT1B1 only. There was no inhibition of MDR1, or BSEP. There was no mention of MRP2. This reviewer found no other in vitro or in silico studies related to DILI by searching the Non-Clinical Overview (Seq 0001, 2.4) and Toxicology Written Summary (Seq 0001, 2.6.6) for the following terms: liver, microsome, glutathione, trapping, mitochondria, hepatocyte, layer, sandwich, cell culture, culture, microphysiology, microphysiologic, chip, liver-on-a-chip (with or without dashes), in silico, DILISym, quantitative system.

4.0 Clinical Data related to DILI

4.1 Studies: One phase 3 (CL010-168) and two phase 2 studies (CL002-168, CL003-168) form the basis for this NDA. The phase 3 study exposed 166 patients to AVP with target length of 52 weeks (Figure 3). The phase 2 studies exposed 73 patients to AVP for a target length of 12 weeks (Figures 4 & 5). A total of 239 patients were exposed and reached target dosing of 30 mg BID. The sponsor mentions another 13 patients receiving 10 mg BID, but in which study or studies these 13 participated is not clear to this reviewer (Clinical Overview, Seq 001, 2.5, page 24). Therefore, of 440 patients enrolled, 239 to 252 were exposed to AVP.

Figure 3: CL010_168 (Phase 3)

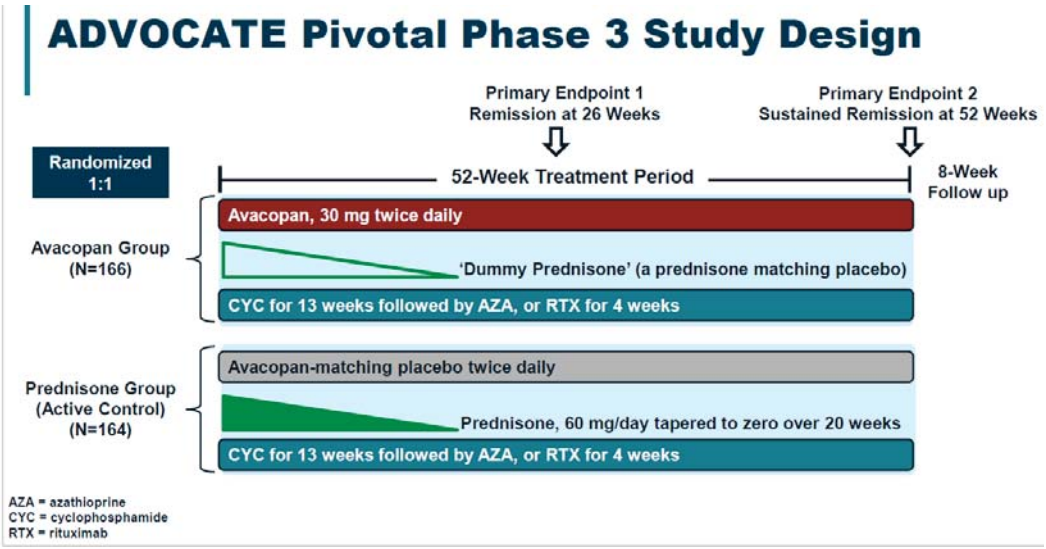


Figure 4a: CL002_168 steps 1 & 2 (Phase 2)

Figure 1. Study Design for Steps 1 and 2

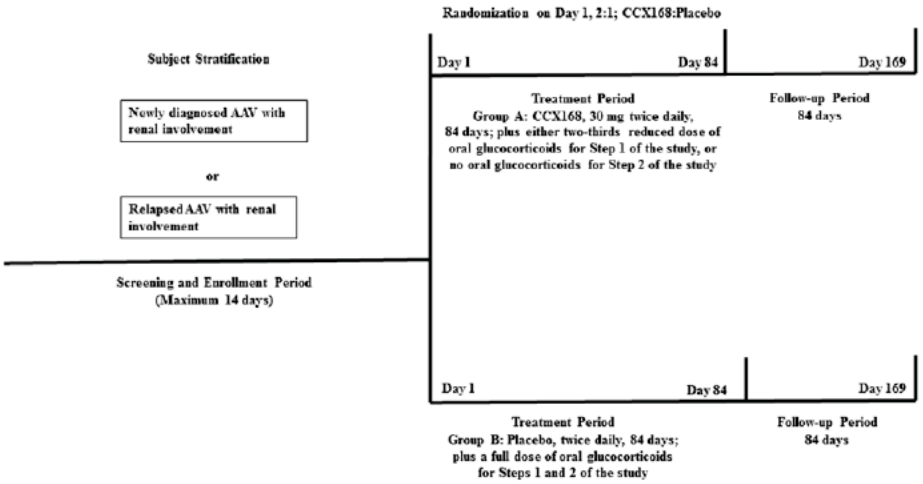


Figure 4b: CL002_168, step 3 (Phase 2)

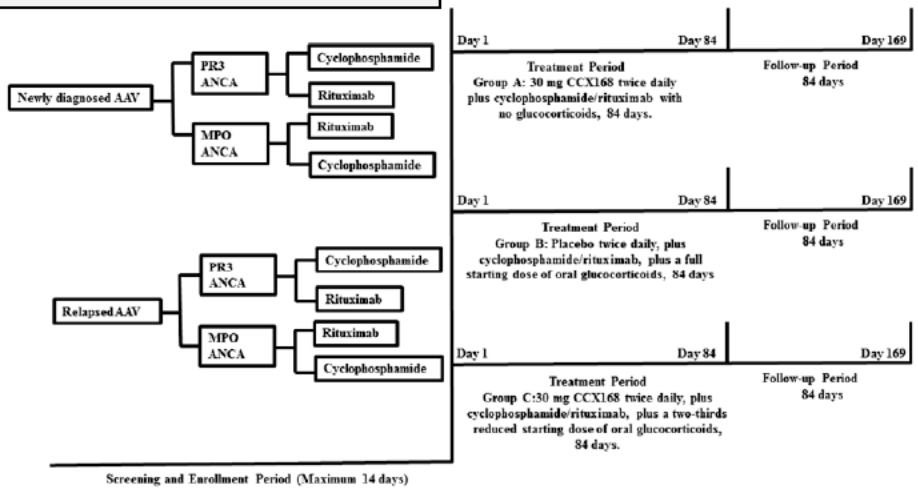
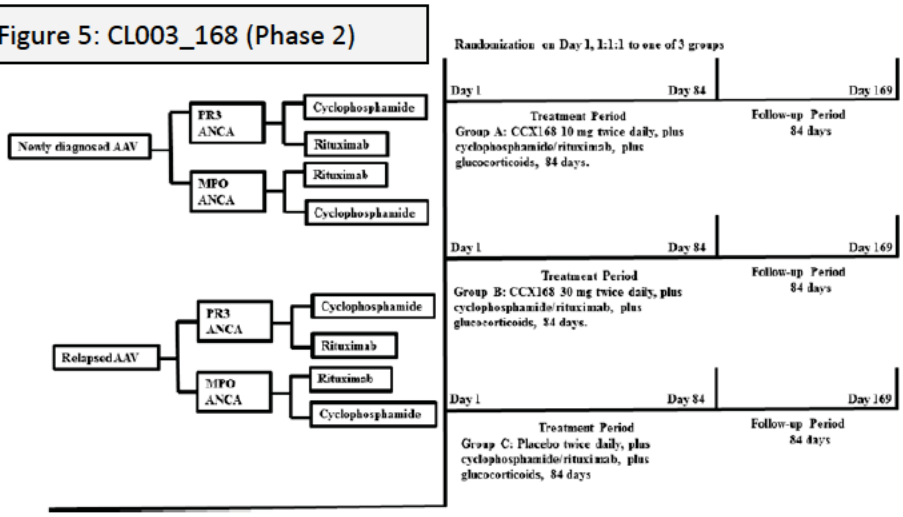
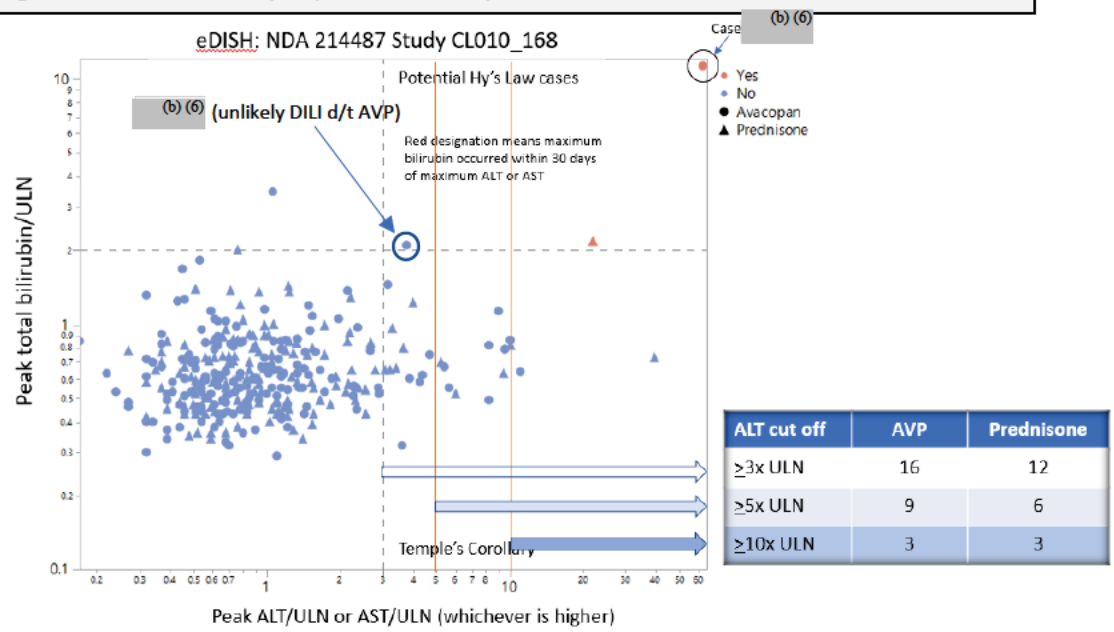


Figure 5: CL003_168 (Phase 2)



4.2 eDISH Scatterplots: The eDISH suggests two cases in the right upper quadrant that were on study drug (Figure 6). Only of the two had the bilirubin peak occur with 30 days of peak transaminase (Case (b) (6), red dot). This case is discussed in detail in section 4.4. The other case (b) (6) had an unrelated bilirubin rise 6 months after transaminase rise. There were more cases with maximum transaminase >3x and >5x ULN in the study arm, but equal number with >10x ULN. Thus, there were 8 AVP cases with maximum transaminase >5x ULN and 1 case with jaundice and maximum transaminase >3x ULN. These 9 cases with transaminase are discussed in Section 4.3 along with one other case in the Phase 2 trials.

Figure 6: eDISH Scatterplot, Phase 3 Study CL010-168



ALT cut off	AVP	Prednisone
≥3x ULN	16	12
≥5x ULN	9	6
≥10x ULN	3	3

4.3 Ten liver related SAE cases: The sponsor initially identified 10 patients with SAEs related to elevated liver enzymes with or without jaundice, 9 cases in phase 3 and 1 case in phase 2. All patients were on AVP. Case narratives are given for all 10, but tabular data including outside labs are provided for only the 9 phase 3 patients. The DILI Team reviewed all 10 cases in detail. Of the 10, three (cases (b) (6)) were considered unlikely AVP hepatotoxicity due to alternate causes being more likely (azathioprine liver injury, bile duct obstruction and gallstone disease). Summary data and assessment scores for the remaining 7 are shown below (Table 1). Three cases were considered probable and 1 case highly likely DILI due to AVP. The remaining 3 cases were considered possible due to competing diagnoses.

In a Clinical Response to IR-25, the sponsor also identified case (b) (6) as falling in Hy's Law quadrant, but felt unlikely DILI due to AVP. We had already assessed this case as unlikely DILI. Narrative information was provided and this reviewer agrees. The AVP continued and the enzyme and bilirubin elevations where were 6 months apart both resolved. Bactrim may be considered a competing cause.

Table 1: Liver related SAE cases considered at least possible DILI due to AVP by DHN DILI Team

ID	Study	Causality Score	Alternate diagnosis	Age	Sex	Race	Hy's Law	Symptoms	Latency from start drug	Latency from stop drug	ALT peak	AST peak	ALP peak	Bilirubin peak	R value peak
(b) (6)	CL010_168	4	Reflex liver injury	65	F	White	No	No	49	-2	336	163	314	0.7	3.0
	CL010_168	4	Simvastatin liver injury	62	F	White	Yes	Yes	112	-34	1933	1708	196	13.6	27.9
	CL010_168	2		80	F	White	No	No	36	0	355	158	321	0.5	3.1
	CL010_168	3		54	F	White	No	No	69	-27	380	229	130	0.9	8.3
	CL010_168	3		79	F	Asian	No	No	48	0	336	224	190	0.4	5.0
	CL010_168	3		81	F	Asian	No	No	28	-14	207	117	1503	1.7	0.4
	CL002-168	4	Bactrim liver injury	80	M	White	No	Yes	20	-4	277	201	633	15.4	1.2
			Mean	*71.6*					*51.7*	*-11.6*	*546*	*400*	*470*	*4.7*	*7.0*
			Std. Dev.	*10.2*					*28.7*	*12.9*	*569*	*535*	*449*	*6.2*	*8.9*
			Median	*79.0*					*48.0*	*-4.0*	*336*	*201*	*314*	*0.9*	*3.1*
			Max	*81.0*					*112.0*	*0.0*	*1933*	*1708*	*1503*	*15.4*	*27.9*
			Min	*54.0*					*20.0*	*-34.0*	*207*	*117*	*130*	*0.4*	*0.4*

Causality scores based on the Drug-induced Liver Injury Network categories and percent likelihoods[1]: 1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate; Symptoms: Symptoms were not always mentioned in the narrative as a pertinent negative. In these cases, DILI Team reviewer assumed no symptoms.

4.4 Five cases of Interest:

4.4.1 **Case (b) (6) (Possible DILI due to AVP)**: This case is of special interest because it is the only one that meets Hy's Law criteria. While it was highly likely hepatocellular DILI, simvastatin competes with AVP, hence the score of 4 (possible) for DILI due to AVP.

Summary: This is a 62-year-old white woman with AAV who developed elevated transaminases 4 months after AVP start and while on drug. She became jaundiced with this episode.

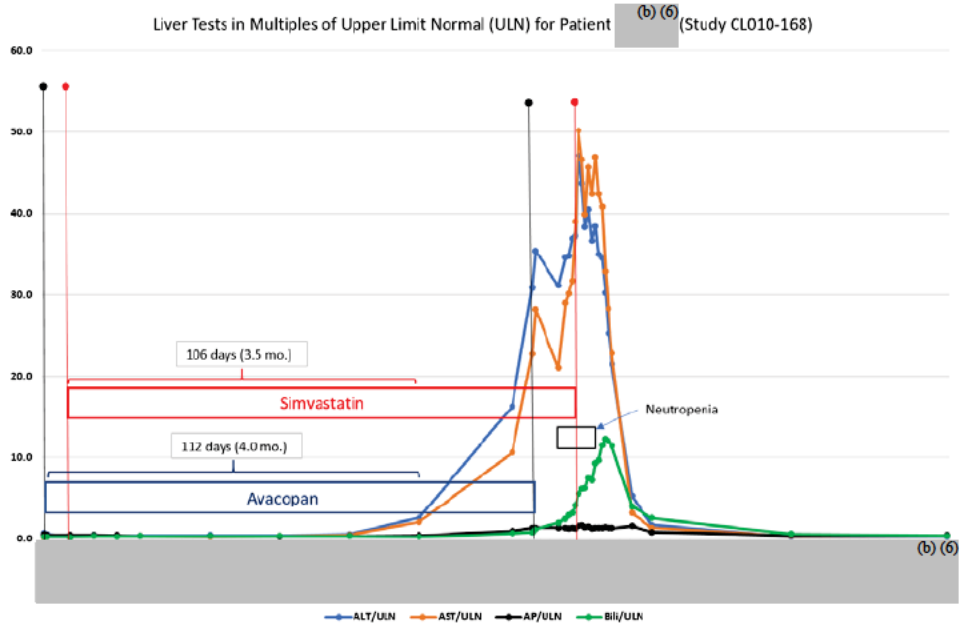
She had no liver disease and normal liver tests at baseline. No mention of alcohol. On (b) (6) 112 days into AVP therapy, her transaminase increased to 2-3x ULN. AVP continued, but enzymes rose more acutely in April. By (b) (6) ALT was >500 but bilirubin still normal. AVP was stopped on (b) (6) Transaminases remained quite high for the next 2 weeks with bilirubin rising to 13.6 in mid-May. She was admitted for evaluation. CT scan was unrevealing for cause. Viral serologies negative including cytomegalovirus (CMV) and Epstein Barr viruses (EBV). However, no mention of hepatitis C virus (HCV) RNA or hepatitis E virus (HEV) testing. Anti-nuclear antibody (ANA) was 1:80. Anti-smooth muscle antibody (ASMA) negative. No mention of fever or

rash. Liver biopsy showed chronic hepatitis like picture with mixed infiltrate and piecemeal necrosis; no viral hepatitis changes seen. Stage F2 fibrosis. No fat or Mallory bodies.

About a week before peak ALT but with ALT already >1000, neutropenia developed. Bone marrow confirmed central decreased production of neutrophils. No liver related symptoms mentioned except jaundice would be obvious.

Patient eventually recovered with liver tests back to normal baseline (Figure 7). No treatments given. Concomitant medications are well described. Simvastatin/ezetimibe given from (b) (6) (b) (6) She did not receive cyclophosphamide.

Figure 7



Assessment: We assessed this as highly DILI and meeting Hy's Law, but we considered simvastatin more likely than AVP (Simvastatin 3-probable; AVP 4-possible). Latency is long for AVP compared to other cases found (Table 1) and stopping AVP did not trigger a consistent washout. While simvastatin DILI is rare, it is well-described in the literature. In case (b) (6) latency is typical for simvastatin[2] and the peak ALT occurs 1 day after simvastatin stop with rapid washout thereafter. Evaluation included a liver biopsy and no viral changes were seen. (+) ANA could fit with a hypersensitivity DILI due to statins that has been described but is not typical. Neutropenia is unexplained. There was no association between neutropenia with AVP over placebo in this ISS, but the total exposed

is low. Simvastatin is metabolized via CYP3A4. AVP is a weak inhibitor of this CYP, so important drug-drug interaction is speculated.

4.4.2 Case (b) (6) (Highly likely DILI due to AVP):

Summary: This is an 80-year-old white woman with AAV who developed elevated liver enzymes in a mixed pattern without jaundice 36 days after starting AVP and while still on drug.

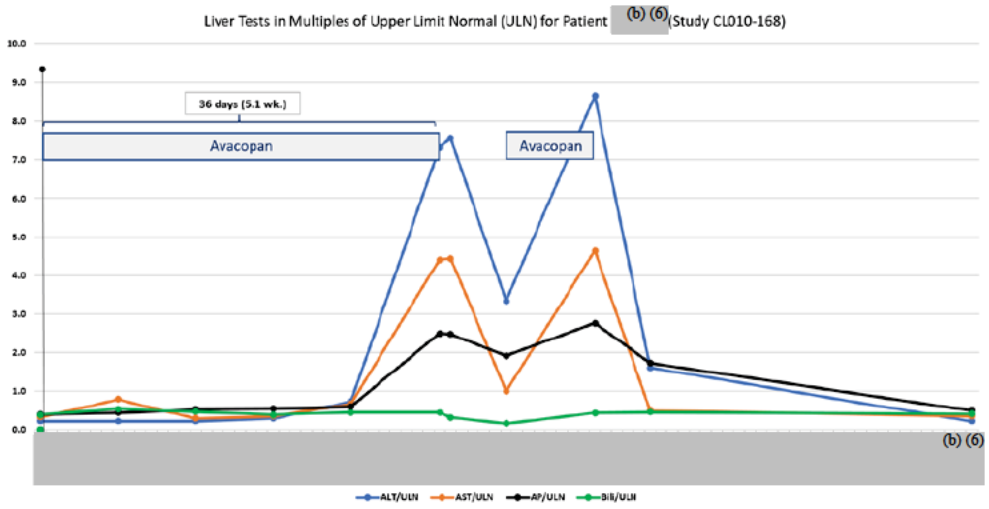
She had no liver disease and her liver tests were normal at baseline. She had a history of alcohol use disorder, pancreatitis and gallstones.

She was noted to have elevated liver tests 5 weeks after drug start. She was admitted for evaluation. AVP and sulfamethoxazole-trimethoprim (Sulfa-TMP) were both held. Liver ultrasound was "normal". No mention of gallstones or symptoms of cholecystitis. Hepatitis A through E, CMV, EBV serologies all "negative". She was on rituximab and not cyclophosphamide. Liver biopsy was not done.

Her enzymes fell significantly (ALT 137, AST 34), and AVP was restarted (b) (6) (study day 43). This restart was followed by a increase in liver enzymes. AVP was stopped permanently with last dose (b) (6) Thereafter her liver enzymes fell to baseline.

Assessment: The DILI Team felt this was highly likely (score of 2) DILI from AVP based on the evaluation, positive re-challenge and complete washout to baseline after stopping AVP permanently (Figure 8).

Figure 8



4.4.3 **Case** [redacted] **(Probable DILI due to AVP)**:

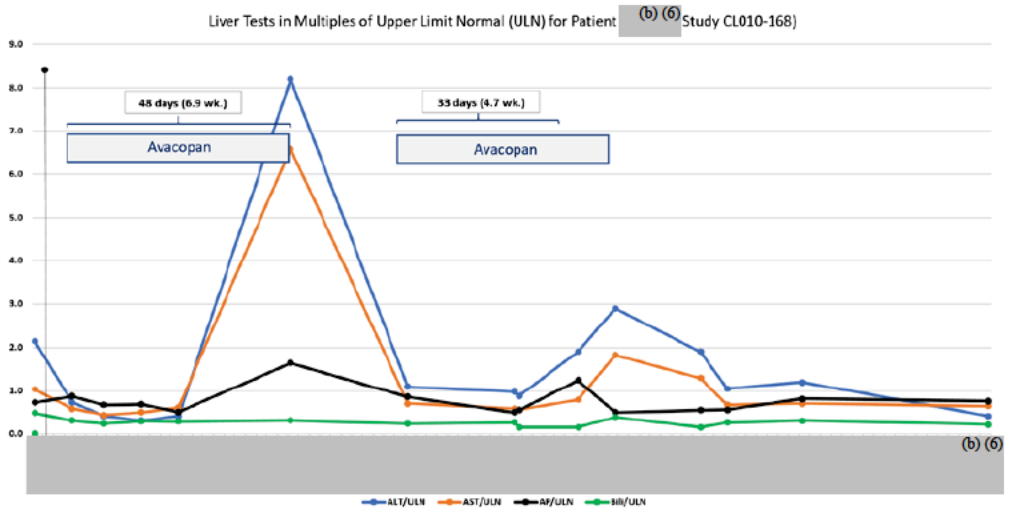
Summary: This is a 79 Asian woman with AAV. She had elevated liver enzymes in a hepatocellular pattern without jaundice 6-7 weeks after AVP start and while still on drug.

The patient's Sulfa-TMP prophylaxis was started 5 days prior to AVP. No liver tests provided for the day of Sulfa-TMP start. However, on Day 1 (start day of AVP), her ALT was 88, AST 35. Bilirubin and ALP were normal. The ALT and AST fell quickly to normal and then less than 20. They stayed down until [redacted] when they elevated substantially. Both Sulfa-TMP and AVP were held. Liver tests fell within 22 days to normal range, but they did not get back to the less than 20 range.

AVP was restarted on [redacted] and bactrim restarted [redacted] By [redacted] enzymes were on the rise again. Bactrim was held. By [redacted] they were higher still, and the AVP was held. Thereafter, enzymes returned to normal range and then less than 20 for rest of follow-up. There is no mention of evaluation testing.

Assessment: We assessed this case as probable (score of 3) DILI due to AVP because of probable positive re-challenge (Figure 9). Sulfa-TMP competes some but latency is a bit long for this drug and washout began more abruptly after AVP stop. Cyclophosphamide was given [redacted] so it continued through enzyme washout. No evaluation testing hurts the case. If imaging and other tests were done and negative, then this would be highly likely DILI due to AVP.

Figure 9



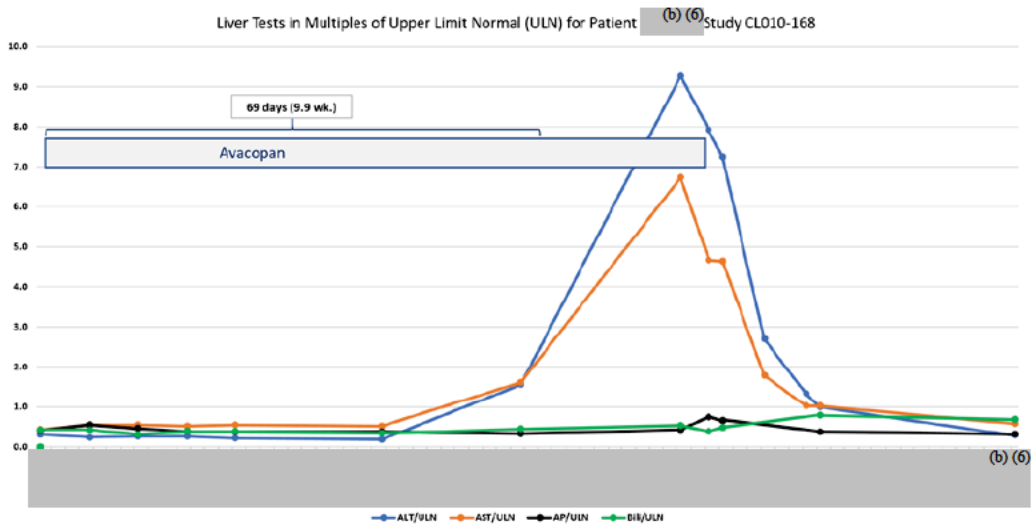
4.4.4 Case (b) (6) (Probable DILI due to AVP):

Summary: This is a 54-year-old white woman with microscopic angiitis who developed elevated transaminases without jaundice 13 weeks after AVP start and while still on AVP.

She had no liver disease. Liver enzymes were normal at baseline. She developed modestly elevated ALT and AST at study day 70. There was no change in AVP dosing, and by study day 92 the ALT and AST climbed to 380 and 229. AVP was stopped on Mar 20, 2018. Viral studies complete and negative. Concomitant mediations were without obvious culprits in time frame. No AIH markers or imaging done. She was asymptomatic. Her liver tests rapidly improved back to normal after stopping AVP.

Assessment: We felt this case was probably DILI due to AVP due to the latency being acceptable and rapid washout after stopping AVP (Figure 10). Cyclophosphamide competes poorly because the latency would be long for that drug.[2] Common viral serologies addressed. Autoimmune hepatitis competes poorly with rapid washout without treatment. No imaging done, but gallstone disease seems less likely without symptoms.

Figure 10



4.4.5 Case (b) (6) (Probable DILI due to AVP):

Summary: This is an 81-year-old Asian woman with AAV. She developed a cholestatic liver injury 4 weeks after starting AVP and while still on drug.

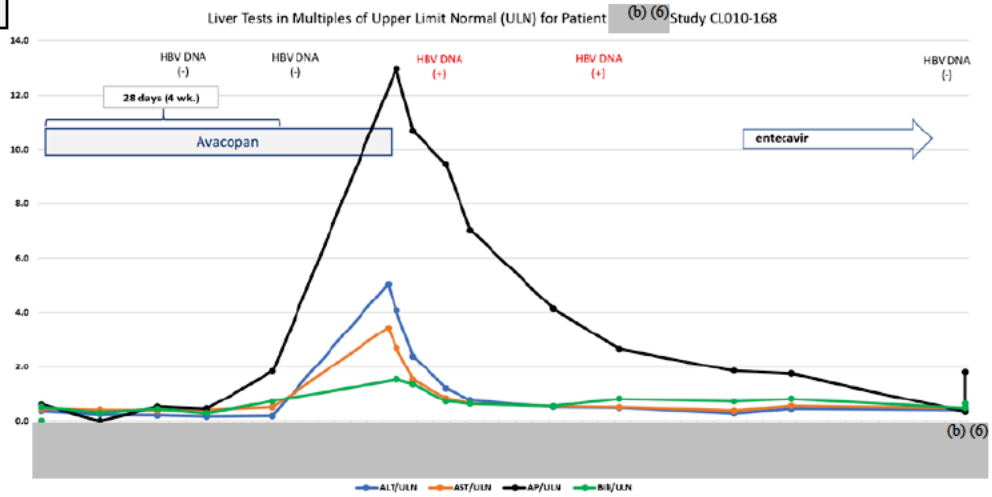
Her liver tests were normal at baseline. However, HBV DNA's were being check so presumably she had (+) HBV serologies at baseline. No details given on this matter. On (b) (6) her ALP rose to 213. By (b) (6) ALT and AST had increased, and on (b) (6) (b) (6) her ALP was >1000. AVP and Sulfa-TMP were stopped. The patient was hospitalized for evaluation. US was negative for gallstone disease. No other findings mentioned. HBV DNA was found to be positive on (b) (6) but at low titer. On (b) (6) Sulfa-TMP was restarted and continued thereafter. Entecavir was finally started on (b) (6) well after AP had fallen substantially. Hepatitis C and E were not tested. No other evaluation testing discussed. No symptoms mentioned.

She did receive rituximab but not until after injury was already resolving (starting (b) (6)). Enzymes gradually resolved after stopping AVP.

Assessment: We felt this cholestatic liver injury was probably related to AVP, making it an outlier by its prominent ALP elevation. She was never jaundiced. Imaging was negative for gallstone disease or biliary obstruction. No symptoms were mentioned. Sulfa-TMP was restarted shortly after peak injury and washout continued. Cyclophosphamide liver injury is typically not so ALP predominant.[2]

No other drugs in her history compete well. The hepatitis B is not causal but of interest in that reappearance of HBV DNA was documented shortly after AVP was held. Therefore, no other causes compete well here.

Figure 11



5.0 **Summary and Recommendations**: AVP is an NME blocking C5a binding. It is under NDA review for the treatment of ANCA associated vasculitis (AAV), and the DILI Team was asked to assess a potential liver safety signal. This DILI Team consultation was done in conjunction with our colleague, Mark Avigan, MD, CM, Associate Director, OPE/OSE.

Assessing DILI in AAV patients is difficult because these patients often take other medications known to have DILI potential (e.g. Sulfa-TMP and other antibiotics, cyclophosphamide). AAV patients are typically older raising the risk of polypharmacy related DILI in general[3] and non-DILI related liver injury. Nevertheless, available case level data in this NDA support AVP as being able to cause liver injury. The degree of injury and risk of liver failure is less clear. The 10 cases reviewed do not include a clear case of AVP liver injury meeting Hy's Law criteria. One case (b) (6) comes close. If we feel this case is attributable to AVP, then it would be a worrisome rate of 1 Hy's Law case in approximately 250 patients exposed, a rate well above the threshold typically predictive of safe marketing. Other drugs with lower rates of severe DILI such as troglitazone (1 in 3000 to 10,000)[4, 5] and ximelagatran (3.7 in 2000)[6-8] have been removed or not marketed in the US for liver injury concerns. Moreover, the low number of patients with AAV makes it difficult to assess DILI risk in these smaller registration trials.

Therefore, much hinges on how we assess case (b) (6) in the context of the other liver related SAE cases. At this point, we view (b) (6) as only possibly related to AVP because simvastatin competes. While rare, some characteristics support

simvastatin liver injury over AVP here. Latency would be typical of simvastatin injury. Washout was established only after simvastatin was held. The AVP had already been stopped 13 days prior without definite washout (Figure 7). If this is AVP injury, this case's latency is an outlier at 112 days compared to a mean of just 52 days for the at least possible (Table 1) and 45 days for the at least probable AVP DILI cases. On the other hand, the case was complicated by concurrent neutropenia which is not reported in simvastatin injury. If AVP is associated with neutropenia, then AVP may considered more likely than simvastatin. There was no neutropenia association was seen in the ISS data, but the number of patients exposed is relatively low. AVP is a weak inhibitor of CYP3A4 which metabolizes simvastatin. Thus drug-drug interaction could be a part of this case's liver injury.

We assessed 4 other cases with liver related SAEs as more clearly linked to AVP, but none had jaundice; all recovered with stopping AVP. Two cases (b) (6) (b) (6) probably had positive re-challenges strengthening the link to AVP. One other case (b) (6) developed detectable HBV DNA at low titer after being undetectable earlier in the trial. While hepatitis B was not the cause of the cholestatic liver injury, it raises concerns for HBV reactivation with AVP particularly when given with other immune suppressing agents (e.g. prednisone, cyclophosphamide). This patient did not receive rituximab. The complement cascade is important to the humoral response[9], so screening for HBV prior to treatment should be done if AVP is approved, particularly if it is given with cyclophosphamide. Monitoring for reactivation or prophylactic treatment should be done depending on HBV serologies and status.

There was no significant liver injury signal in the sponsor's animal studies. In vitro and in silico studies related to DILI were limited to transporter studies which were not informative. Therefore, mechanism of AVP injury is unclear. This lack of mechanistic data is unfortunate because the clinical signature for this injury is also not clear. Hepatocellular and cholestatic injury were both seen. While AVP is an NME, marketed eculizumab also targets C5. It is a humanized monoclonal anti-C5 antibody used for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS). Hayes, et al., reported several cases of DILI due to this agent[10], but only a couple are convincing. Also, the injury is clinically different from what we see in this NDA. All eculizumab cases had mixed or cholestatic injury (R-values 2.8-4.9) and short latencies (10-29 days). Therefore, DILI from this biologic is distinct from AVP DILI. Inhibition of the complement cascade has been postulated to be hepatoprotective[11], but there are animal data suggesting inhibition could hinder hepatocyte regeneration.[12] Whether such inhibition could lead to worsening liver injury from another insult (e.g. simvastatin injury) is speculative. Further research into mechanisms of AVP liver injury would be helpful.

At this point, we think a path toward approval can be found, if efficacy and need are clear. Close monitoring of liver tests is recommended, if approval is given.

5.1 Recommendations / Plan:

a. Further research into possible mechanisms of liver injury from AVP and its metabolites (e.g., glutathione trapping, mitochondrial toxicity assays, and intra-hepatic accumulation in animal models).
b. If AVP is approved, the following should be considered for labeling:
    - Safety labeling should clearly describe the risk of hepatic injury associated with Avacopan. At a minimum, we recommend hepatic injury to be listed in Warnings and Precautions.
    - Liver enzyme and bilirubin monitoring (e.g. monthly for 6 months) and stop AVP if ALT or AST over 3 times upper limit of normal or baseline without other cause.
    - Exclusion of patients with active, untreated and/or uncontrolled chronic liver disease (e.g. chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis).
    - Exclusion of patients with cirrhosis
    - Monthly HBV DNA monitoring or prophylactic treatment with a direct acting anti-viral for hepatitis B surface antigen negative, anti-hepatitis B core positive patients throughout AVP treatment and 3-6 months after AVP stop. If rituximab is used with AVP, then prophylactic treatment should be given.
    - Prophylactic treatment with a direct acting anti-viral for hepatitis B surface antigen positive patients.

6.0 References:

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Paul H. Hayashi -S

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Paul H. Hayashi, MD, MPH
DILI Team Lead, Division of Hepatology and Nutrition
CDER/OND

Joseph G. Toerner -S

Digitally signed by Joseph G. Toerner -S
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Joseph Toerner, MD, MPH
Director, Division of Hepatology and Nutrition
CDER/OND

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/s/

PAUL H HAYASHI
06/15/2021 03:23:07 PM

COA Tracking ID: C2020345
NDA Number/Referenced IND for NDA: 214487/120784

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2020345
NDA Number/ Referenced IND for NDA:	214487/120784
Applicant:	ChemoCentryx, Inc.
Established Name/Trade Name:	Avacopan (CCX168)
Indication:	Treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis
Review Division:	Division of Rheumatology and Transplant Medicine
Clinical Reviewer	Suzette Peng
Clinical Team Leader (TL)	Rachel Glaser
Review Division Project Manager:	Susie Choi
COA Reviewer:	Ji Li
COA TL:	Onyeka Illoh
COA Acting Deputy Director:	Elektra Papadopoulos
Date Consult Request Received:	August 6, 2020
Date COA Briefing Package/Submission Received:	July 7, 2020
Date COA Review Completed:	March 19, 2021

Please check all that apply: ☒Rare Disease/Orphan Designation
☐Pediatric

Contents

1 EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 214487 for Avacopan (CCX168) capsules. The applicant has completed two randomized controlled phase 2 clinical studies (CL002_168 and CL003_168) and a randomized, double-blind, double-dummy, active-controlled international phase 3 study (CL010_168) for this drug development program and has submitted applications for regulatory approval. The proposed indication is the treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) (i.e., granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]).

The phase 3 trial (Study CL010_168) evaluated the safety and efficacy of avacopan in 331 subjects with newly diagnosed or relapsing active AAV on background standard therapy of rituximab or cyclophosphamide/azathioprine. The primary endpoint measure was a clinician-reported outcome (ClinRO) of AAV activity and severity, i.e., the Birmingham Vasculitis Activity Score (BVAS).

At the request of the Division of Rheumatology and Transplant Medicine (DRTM) dated August 6, 2020 (DARRTS Reference ID: 4653418), this review is limited to a secondary endpoint derived from the Glucocorticoid Toxicity Index (GTI), a ClinRO to assess the concept of "toxicity due to corticosteroids/glucocorticoids" (see Appendix A for a copy of the instrument).

This review concludes that the evidence submitted by the applicant does not support a conclusion that the GTI-derived endpoint is fit-for-purpose[1] to measure glucocorticoid-related toxicities and glucocorticoid-sparing effects for the context of use of this drug development program. We have concerns regarding the interpretability of the GTI Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS) used to derive the secondary endpoint as these scores combine biomarkers with clinical outcomes related to glucocorticoid toxicity (e.g., neuropsychiatric toxicity). We also have concerns regarding the scoring algorithms of both the GTI and its upgraded version, i.e., the GTI 2.0 which was used to quantify changes in glucocorticoid toxicity in the final analysis (see Appendix B for a copy of the GTI 2.0 instrument).

2 REVIEW CONCLUSIONS

At this time, we do not agree that the GTI is fit-for-purpose[1] to measure glucocorticoid-related toxicities or glucocorticoid-sparing effects for the context of use of this drug development program. We have the following concerns:

Issue 1: Measure not comprehensive of the intended claim

- There is insufficient evidence (i.e., documentation of the development history, evidence on content validity of GTI, and patient interviews).

[1] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/)

- As qualitative research with patients was lacking during the development of GTI, it is unclear whether the domains and/or items included in the Composite GTI may adequately measure the important and relevant concepts of signs that are the most clinically meaningful in terms of treatment benefit to this specific patient population from the patients' perspectives.
- To be comprehensive, (b) (4) glucocorticoid-related toxicity would include patients' perspectives, which may be best evaluated using a well-defined and reliable patient-reported outcome (PRO)-derived endpoint measure to supplement the GTI, a ClinRO-derived endpoint measure.
- We also note that the GTI-derived endpoint measure omitted the osteoporosis domain as well as rare but serious events on the Specific List of the GTI, and thus is not comprehensive.

Issue 2: Score interpretability

- There is insufficient evidence to support the underlying weighting and scoring algorithms of both the Composite GTI and the Specific List items (see Appendix C). Similarly, there is insufficient information provided for the weighting and scoring algorithms of the GTI 2.0 that the applicant used to calculate the GTI CWS and AIS for use as key secondary endpoint measures.
- The scoring combines both biomarkers and clinical events which makes the total score difficult to interpret clinical meaningfulness, as it is unclear what a score represents and how the biomarkers and their weighting may translate into how patients feel, function or survive in daily life.
- The applicant confirmed that the Specific List items were not part of the GTI score calculation, indicating that certain rare but serious events, particularly those of the "endocrine", "gastrointestinal", "musculoskeletal", and "ocular" domains, may be omitted from the glucocorticoid-related toxicity measures, i.e., the GTI CWS and AIS. In addition, it is unclear whether and how glucocorticoid-related adverse events apart from the GTI items were recorded and analyzed.

Issue 3: Clinically meaningful within-patient change

Even if we agreed that there was sufficient evidence to support the CGI-derived endpoint as a comprehensive measure of glucocorticoid toxicity, we do not have evidence (e.g., anchor-based methods) to support clinically meaningful within-patient change and thus the meaningfulness of the treatment effect is unclear.

Issue 4: Study design

The review concludes the following:

- The objective of assessing glucocorticoid toxicity is unclear in this study as the control group, but not the avacopan group, received glucocorticoid therapy. However, this assessment is potentially biased, because while the comparator arm had toxicity systematically assessed in the endpoint, the investigational arm did not have a comparable measure of its potential toxicity profile for comparison, e.g., hepatotoxicity. (b) (4)

- Given the differential toxicity profiles of the two treatment groups, unblinding toxicities may functionally unblind the raters of the GTI leading to bias in their ratings.

Issue 5: Adjustment for multiplicity

- The GTI-derived endpoint measure was not adjusted for multiplicity. See the biostatistical review.

3 BACKGROUND AND MATERIALS REVIEWED

Regulatory Background:
Avacopan (CCX168) was granted Orphan Drug Designation for the treatment of ANCA-associated vasculitides by the Agency on May 19, 2014. The drug development program for avacopan was exempt from the requirement for a Pediatric Study Plan as confirmed in the Agency's Written Responses to the Type C Meeting dated January 23, 2020 (DARRTS Reference ID: 4550563). The applicant submitted an original New Drug Application (NDA) for avacopan capsules for the proposed indication of treatment of AAV on July 7, 2020. The applicant's submission documents included clinical study protocol dated January 18, 2019, clinical overview received on July 7, 2020, and summary of clinical efficacy received on July 7, 2020.

Previous COA Reviews:
None

Disease Background:
AAV is a group of multisystem autoimmune small vessel vasculitides, which has three different forms, i.e., GPA, MPA, and eosinophilic granulomatosis with polyangiitis. The signs and symptoms of AAV vary by the affected organs, and may include sinus pain, nasal discharge, ear pain, deafness, cough, shortness of breath, wheeze, fatigue, numbness, difficulty walking, etc. Currently, cyclophosphamide plus glucocorticoids or rituximab plus glucocorticoids are considered the standard therapy for AAV. As per the applicant, due to low sustained remission rate, high rate of relapse after remission, and adverse effect and toxicity of conventional therapies, there are unmet medical needs in the treatment of patients with AAV.

Investigational Product:
Anaphylatoxin C5a, a potent neutrophil chemoattractant and agonist, may play an important role in homotypic neutrophil aggregation via interactions of the TNF-activated αMβ2 (Mac-1)-integrins with ICAM-3 or iC3b on bystander neutrophils. Avacopan was developed as an antagonist of the human complement 5a receptor (C5aR), which may selectively inhibit the binding of C5a to C5aR and hinder C5a-induced cell signaling pathways. As per the applicant, while it may alleviate necrotizing vasculitis by inhibiting vascular endothelial cell retraction and permeability, avacopan does not interfere with the host defense mechanism.

Other materials reviewed:

- Type B Pre-NDA Clinical Meeting Background/Briefing Materials dated February 18, 2020
- Study CL010_168 Protocol Amendment 4.0 dated January 18, 2019
- Clinical Overview received on July 7, 2020
- Summary of Clinical Efficacy received on July 7, 2020
- Synopsis of Individual Studies received on July 7, 2020

4 CONTEXT OF USE

4.1 Clinical Trial Population

The target population for Study CL010_168 are males and females aged at least 18 years, or where approved, adolescents (12 to17 years old), with newly-diagnosed or relapsed AAV who received a background standard therapy of rituximab or cyclophosphamide/azathioprine.

A complete list of the inclusion and exclusion criteria is summarized in Study CL010_168 Protocol Amendment 4.0 dated January 18, 2019.

Reviewer's comment(s): *As per the Summary of Clinical Efficacy received on July 7, 2020, a total of three adolescent patients were enrolled in the pivotal phase 3 study. Two of them were discontinued early from treatment. To be eligible for participation, patients need to present at least one major item, or at least 3 minor items, or at least the 2 renal items of proteinuria and hematuria in the BVAS. It is unclear whether this disease severity threshold at enrollment was representative of the target patient population for this study.*

4.2 Clinical Trial Design

Study CL010_168 was a double-blind, randomized, active comparator-controlled, non-inferiority study of 52 weeks duration. The study also had an 8-week follow-up period.

Refer to the clinical study protocol for more details on the clinical trial design.

Reviewer's comment(s): *The pivotal phase 3 study was conducted at 143 study centers in 18 countries in North America, Europe, Australia, New Zealand, and Japan. It is unclear whether COAs including the GTI were culturally adapted and adequately translated for use. As per the Study Protocol Amendment 4.0 dated January 18, 2019, the applicant conducted both non-inferiority and superiority analyses. In addition, given the differential toxicity profiles of the two treatment groups, e.g., hepatotoxicity in the avacopan group, unblinding toxicities may functionally unblind the raters of the GTI, which may lead to bias in the ratings.*

4.3 Endpoint Position, Definition, and Assessment Schedule

The primary endpoint was derived from the Birmingham Vasculitis Activity Score (BVAS), a ClinRO.

The first secondary endpoint was the change from baseline in GTI over the first 26 weeks. The GTI was assessed at Day 1 (baseline), Weeks 13 and 26.

Reviewer's comment(s): *There is insufficient evidence to demonstrate that each of the components assessed in GTI was important and relevant to the patients with AAV in this study. According to the Miloslavsky et al. 2017, the Composite GTI was designed to capture common glucocorticoid toxicities for a typical clinical trial of a duration of 6 months to 3 years. As per the applicant, as the last assessment of GTI was administered at Week 26, the osteoporosis component was not included in GTI for analyses. In addition, the applicant confirmed that the Specific List items were not part of the GTI score calculation. Omissions of both the bone density domain and the Specific List items from the calculation of the GTI CWS and AIS indicate that the GTI-derived endpoint measures are not comprehensive to support the intended claim.*

4.4 (b) (4)

The applicant has proposed (b) (4)

(b) (4)

Reviewer's comment(s): *We defer to the Statistical Reviewer on this. It is unclear* (b) (4)

(b) (4)

5 CLINICAL OUTCOME ASSESSMENT OVERVIEW

The Glucocorticoid Toxicity Index (GTI) is a ClinRO intended to measure morbidity related to the use of corticosteroids/glucocorticoids. The GTI 2.0 is an upgraded version of the original GTI instrument, which captures improvement and worsening in certain glucocorticoid toxicity with the same absolute weight.

GTI consists of two parts, i.e., a Composite GTI and a Specific List. The Composite GTI is a weighted scale, and includes 9 domains (i.e., BMI, glucose tolerance, blood pressure, lipids, bone density, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection) and 31 items. The Composite GTI provides a quantitative assessment of both worsening and improvement.

The Specific List includes 11 domains and 23 items, which is intended to capture rare but important glucocorticoid-related adverse events not included in the Composite GTI. The adverse

events of the Specific List are not scored and thus not used for calculating the Composite GTI score.

Reviewer's comment(s): *The Composite GTI combines biomarker and symptom items, which makes the interpretation of its clinical meaningfulness difficult.*

6 SCORING ALGORITHM

All 9 domains of the Composite GTI have improvement items. If an adverse event of the Specific List occurs, the most severe item in the Composite GTI is scored correspondingly. According to the author's recommendation, the bone density component was excluded as the last GTI assessment was Week 26 and the duration was insufficient to detect a change.

The applicant did not provide detailed information on the weighting and scoring algorithms of the GTI 2.0 that were used to calculate the GTI CWS and AIS. As per Appendix B, the GTI 2.0 assigns the same absolute weight to an improvement as well as a worsening of glucocorticoid toxicity. According to the literature the applicant cited, i.e., Ehlers et al. 2019 and McDowell et al. 2019, the GTI CWS is a sum of all GC-toxicities that occur to a patient, while the GTI AIS considers both improvement and worsening.

Reviewer's comment(s): *The applicant did not provide adequate rationale for the scoring algorithms of the GTI and GTI 2.0 used in this study. The Miloslavsky et al. 2017 article states that the most severe corresponding item in the Composite GTI will be scored when observing a Specific List item. However, as per the applicant's response to the Information Request received on March 18, 2021, the Specific List items were not part of the GTI score calculation in this study. As such, certain rare but serious events, particularly those in the "endocrine", "gastrointestinal", "musculoskeletal", and "ocular" domains, may be omitted from the GTI CWS and AIS. As per the Summary of Clinical Efficacy received on July 7, 2020, the applicant presented results at Weeks 13 and 26 based on both total and domain-specific scores.*

7 CONTENT VALIDITY

The applicant provided literature (Miloslavsky et al. 2017) as supportive evidence to support the measurement properties of the GTI. Detailed qualitative and quantitative reports of the development and validation of the scale were not provided. We note that testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity.

Reviewer's comment(s): *As per the Miloslavsky et al. 2017 article, the GTI was developed based on input from international clinical experts on glucocorticoid use and outcome measures from multiple specialties, i.e., rheumatology, pediatrics rheumatology, pulmonology, nephrology, neurology, ophthalmology, dermatology, infectious disease, and psychiatry. As qualitative research with patients was lacking during the development of GTI, it is unclear whether the domains and/or items included in the Composite GTI may adequately measure the important and*

relevant concepts of signs that are the most clinically meaningful in terms of treatment benefit to this specific patient population from the patient perspectives. To obtain patient perspectives on corticosteroid toxicity, the GTI may be supplemented with a well-defined and reliable PRO. Additionally, the pre-specified endpoint measure excluded the osteoporosis domain of the GTI.

8 OTHER MEASUREMENT PROPERTIES

As previously stated, the applicant provided literature (Miloslavsky et al. 2017; Ehlers et al. 2019; McDowell et al. 2019) as supportive evidence to support the measurement properties of the GTI. As per the Miloslavsky et al. 2017 article, the inter-rater reliability ranged between 0.88-0.90. The Ehlers et al. 2019 and McDowell et al. 2019 articles collected quantitative data demonstrating prospective use of the GTI in patients with vasculitis and glucocorticoid-dependent asthma, respectively.

However, detailed qualitative and quantitative reports of the development and validation of the scale were not provided. It also does not appear that anchor-based analyses were provided for the evaluation of clinically meaningful within-patient change in the score.

Reviewer's comment(s): *Results from quantitative analyses (i.e., psychometric properties and measurement performance) cannot be interpreted without first establishing that an instrument has content validity. Testing other measurement properties does not overcome our concerns with content validity as described elsewhere in this review.*

9 INTERPRETATION OF SCORES

The applicant did not provide information to aid in determination of clinically meaningful within-patient changes in GTI scores (e.g., anchor-based analyses) or other information.

Reviewer's comment(s): *The applicant did not provide results from anchor-based analysis and/or exit interviews (or surveys) to aid in determination of clinically meaningful within-patient changes in GTI-derived scores.*

10 APPENDICES

Appendix A: The Glucocorticoid Toxicity Index (GTI) from the Study Protocol Amendment 4.0
Appendix B: The GTI Version 2.0 from Type B Pre-NDA Meeting Background/Briefing Materials
Appendix C: The Specific List items of the GTI from Type B Pre-NDA Meeting Background/Briefing Materials

Appendix A: The Glucocorticoid Toxicity Index (GTI) from the Study Protocol Amendment 4.0

Composite GTI [1]	Item Weight	Specific List [2]
BMI		
Improvement in BMI	-8	Major increase in BMI (>8 units and above 24.9 kg/m^2)
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	-8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose intolerance	32	Diabetic neuropathy
Worsening of glucose intolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	-10	Hypertensive emergency (or posterior reversible encephalopathy syndrome)
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	-9	
No change in lipids	0	
Worsening hyperlipidaemia	10	
Worsening hyperlipidaemia despite treatment	30	
Bone density [3]		
Improvement in bone density	-1	Major decrease in bone density
No change in bone density	0	Insufficiency fracture
Decrease in bone density	29	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy or tendon rupture
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin toxicity		

Composite GTI [1]	**Item Weight**	**Specific List** [2]
No skin toxicity	0	Severe skin toxicity
Mild skin toxicity	8	
Moderate skin toxicity or greater	26	
Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis (hallucinations, delusions, or disorganized thought processes, occurring in the absence of mania, delirium, or depression)
Mild neuropsychiatric symptoms	11	Glucocorticoid-induced violence towards self or others
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade IV infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection (death from infection)
Grade III infection or greater	93	
Endocrine		Symptomatic adrenal insufficiency
Gastrointestinal		Perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use)
		Peptic ulcer disease confirmed by endoscopy (excluding *H. pylori*)
Musculoskeletal		Avascular necrosis
		Tendon rupture
Ocular		Central serous retinopathy
		New onset or worsened elevation of intraocular pressure requiring treatment or change in treatment.
		Posterior subcapsular cataract (or history of the same)
Total	**-35 to 410**	

[1] See Section 12.5.1 for definitions of each item in the GTI.

[2] See Section 12.5.2 for definitions of each specific list item.

[3] Since the last assessment of the GTI will be performed at Week 26, and bone density assessments are typically performed annually, the osteoporosis component will not be included in the GTI for this study, according to the authors' recommendation.

Appendix B: The GTI Version 2.0 from Type B Pre-NDA Meeting Background/Briefing Materials

Feature/Body System	Item Weight
Body Mass Index (BMI)	
Decrease of ≥5 BMI units	-36
Decrease of >2 but <5 BMI units	-21
No significant change in BMI (±2 BMI units)	0
Increase of >2 to <5 BMI units	21
Increase of 5 or more BMI units	36
Glucose tolerance	
Improvement in HbA1c AND decrease in medication	-44
Improvement in HbA1c OR decrease in medication	-32
No significant change	0
Increase in HbA1c OR increase in medication	32
Increase in HbA1c AND increase in medication	44
Blood pressure	
Improvement in BP AND decrease in medication	-44
Improvement in BP OR decrease in medication	-19
No significant change in blood pressure	0

Feature/Body System	Item Weight
Increase in BP OR increase in medication	19
Increase in BP AND increase in medication	44
Lipids	
Decrease in LDL AND decrease in medication	-30
Decrease in LDL OR decrease in medication	-10
No significant change in lipids	0
Increase in LDL OR increase in medication	10
Increase in LDL AND increase in medication	30
Steroid myopathy[1]	
Moderate weakness to none	-63
Moderate to Mild weakness	-54
Mild weakness to none	-9
No significant change	0
None to mild weakness	9
Mild to moderate weakness	54
None to Moderate weakness	63
Skin toxicity[1]	
Decrease in Skin Toxicity - Moderate to None	-26
Decrease in Skin Toxicity - Moderate to Mild	-18
Decrease in Skin Toxicity - Mild to None	-8
No significant change	0
Increase in Skin Toxicity - None to Mild	8
Increase in Skin Toxicity - Mild to Moderate	18
Increase in Skin Toxicity - None to Moderate	26
Neuropsychiatric (NP) toxicity[1]	
Decrease in NP Toxicity - Moderate to None	-74
Decrease in NP Toxicity - Moderate to Mild	-63
Decrease in NP Toxicity - Mild to None	-11
No significant change	0
Increase in NP Toxicity - None to Mild	11
Increase in NP Toxicity – Mild to Moderate	63
Increase in NP Toxicity - None to Moderate	74
Infection[1]	
No significant infection	0
Oral/vaginal candidiasis or uncomplicated zoster	19
Grade 3, 4 or 5 infection	93
[1] See Section 12.5.1 of the protocol for definitions of steroid myopathy, skin toxicity, neuropathy, and infection.	

Appendix C: The Specific List items of the GTI from Type B Pre-NDA Meeting Background/Briefing Materials

Feature/Organ System	Specific List
Body Mass Index	Major increase in BMI (>8 units and above 24.9 kg/m^2)
Glucose Tolerance	Diabetic retinopathy Diabetic nephropathy Diabetic neuropathy
Blood pressure	Hypertensive emergency (or posterior reversible encephalopathy syndrome) Posterior reversible encephalopathy syndrome
Steroid myopathy	Severe steroid myopathy or tendon rupture
Skin toxicity	Severe skin toxicity
Neuropsychiatric toxicity	Psychosis (hallucinations, delusions, or disorganized thought processes, occurring in the absence of mania, delirium, or depression) Glucocorticoid-induced violence towards self or others Other severe neuropsychiatric symptoms
Infections	Grade IV infection Grade V infection (death from infection)
Endocrine	Symptomatic adrenal insufficiency
Gastrointestinal	Perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use) Peptic ulcer disease confirmed by endoscopy (excluding *H. pylori*)
Musculoskeletal	Avascular necrosis Tendon rupture Insufficiency fracture
Ocular	Central serous retinopathy New onset or worsened elevation of intraocular pressure requiring treatment or change in treatment. Posterior subcapsular cataract (or history of the same)

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ELEKTRA J PAPADOPOULOS
03/26/2021 04:32:44 PM

Division of Cardiology and Nephrology Consult

Date:	March 12, 2021
From:	Kimberly Smith, Clinical Team Leader Rekha Kambhampati, Medical Officer Division of Cardiology and Nephrology
Through:	Aliza Thompson, Deputy Director Division of Cardiology and Nephrology
To:	Susie Choi, Regulatory Project Manager, Division of Rheumatology and Transplant Medicine
Subject:	Kidney-related efficacy of avacopan (NDA 214487)

Background

Avacopan is a selective antagonist of the complement 5a receptor (C5aR) that is expected to reduce the pro-inflammatory effects of complement component C5a. On July 7, 2020, the Division of Rheumatology and Transplant Medicine (DRTM) received a new NDA for avacopan for the treatment of adults with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). In support of the proposed indication, the applicant conducted trial CL010_168, "A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/ Azathioprine" (ADVOCATE). (b) (4) (b) (4) (b) (4) DRTM has asked the Division of Cardiology and Nephrology (DCN) to assist with interpretation of the kidney-related trial data, particularly the clinical meaningfulness of the findings (b) (4) (b) (4)

Material Reviewed

1. Clinical Study Protocol for Study CL010_168, version 4.0, dated January 18, 2019
2. Statistical Analysis Plan for Study CL010_168, version 2.0, dated October 28, 2019
3. BVAS and VDI Adjudication Committee Charter, version 4.0, dated June 21, 2019
4. Clinical Study Report (CSR) for Study CL010_168 dated June 1, 2020
5. Proposed label
6. Applicant's response to December 9, 2020, February 8, 2021, and February 24, 2021 Information Requests

Overview of ADVOCATE

Overall Study Design

ADVOCATE was a randomized, double-blind, active-controlled, phase 3 study in 330 patients with newly-diagnosed or relapsed GPA or MPA requiring treatment with cyclophosphamide/azathioprine or rituximab. After a screening period of no more than 14 days, patients were randomized 1:1 to avacopan 30 mg twice daily for 52 weeks or prednisone 60 mg/day tapered over 20 weeks to 0 mg in a double-dummy design. All patients also simultaneously started cyclophosphamide/azathioprine or rituximab. Randomization was stratified by whether the disease was newly-diagnosed or relapsing, ANCA-positivity status, and background therapy (intravenous cyclophosphamide, oral cyclophosphamide, or rituximab).

The primary objective was to evaluate the efficacy of avacopan compared with prednisone to induce and sustain remission in subjects with ANCA-associated vasculitis when used with cyclophosphamide/ azathioprine or rituximab. The trial had two primary endpoints that assessed disease remission based on

the Birmingham Vasculitis Activity Score (BVAS) and the need for glucocorticoids for the treatment of ANCA-associated vasculitis, one at Week 26 and one at Week 52. The endpoints were to be tested sequentially for non-inferiority at Week 26, non-inferiority at Week 52, superiority at Week 52, and superiority at Week 26.

Pertinent/Kidney-related Eligibility Criteria

Key Inclusion Criteria:

1. ≥ 18 years of age. Where allowed, the minimum age was lowered to 12 years.
2. Clinical diagnosis of GPA or MPA consistent with Chapel-Hill Consensus Conference definitions.
3. At least one major or three minor BVAS items from any organ system (general, cutaneous, mucous membrane/eyes, ENT, chest, cardiovascular, abdominal, renal, nervous system, and "other") or at least the minor renal BVAS items (see below) of proteinuria (>1+ or >0.2 g/g creatinine) and hematuria (≥10 RBCs/hpf).
4. Estimated glomerular filtration rate ≥15 mL/minute/1.73 m^2 (MDRD for adults; modified Schwartz for adolescents) at screening.

Key Exclusion Criteria:

1. Any other known multi-system autoimmune disease including eosinophilic granulomatosis with polyangiitis (Churg-Strauss), systemic lupus erythematosus, IgA vasculitis (Henoch-Schönlein), rheumatoid vasculitis, Sjögren's syndrome, anti-glomerular basement membrane disease, or cryoglobulinemic vasculitis.
2. Dialysis or plasma exchange within 12 weeks prior to screening.
3. Kidney transplant.

Birmingham Vasculitis Activity Score (BVAS)

The BVAS completed by investigators at screening was used to determine study eligibility and to identify patients with "renal disease at baseline" for key efficacy analyses. According to instructions in the protocol, investigators were to "record only symptoms/signs ascribed to the presence of active AAV (GPA or MPA) on the form." The specified criteria relevant to kidney involvement were in the "renal" and "other" categories as follows (major criteria are in bold and italics[1]):

8. Renal
    - Hypertension
    - Proteinuria >1+ or >0.2 g/g creatinine
    - Haematuria ≥10 RBCs/hpf
    - Serum creatinine 125-249 µmol/L
    - Serum creatinine 250-499 µmol/L
    - Serum creatinine ≥500 µmol/L
    - ***Rise in serum creatinine >30% or fall in creatinine clearance >25%***

10. Other
    - ***RBC casts and/or glomerulonephritis***

[1] The published BVAS Version 3 (Mukhtyar 2009) includes hematuria and creatinine ≥500 µmol/L as major items and does not specify items in the "other" category.

According to the applicant's response to an information request, patients who met BVAS criteria for renal disease at baseline were identified programmatically based on the investigator's assessment of the BVAS renal criteria recorded in the eCRF at screening, and "investigators were provided with training on the BVAS" at the start of the study. According to the applicant's response, the following guidance was also provided to investigators (copied verbatim from response):

- *Hypertension: Check if diastolic blood pressure was >95 mm Hg and the hypertension was considered related to ANCA-associated vasculitis.*
- *Proteinuria: Check if there is >1+ on urinalysis or >0.2 g/g creatinine on a urine sample sent to the laboratory.*
- *Hematuria: Check if there is >1+ blood on urinalysis or ≥10 RBC per high power field upon microscopy.*
- *Check elevated serum creatinine at first assessment for the following levels:*
  - *Serum creatinine 125-249 µmol/L (1.41-2.82 mg/dL)*
  - *Serum creatinine 250-499 µmol/L (2.83-5.64 mg/dL)*
  - *Serum creatinine ≥500 µmol/L (5.65 mg/dL)*
- *Score a >30% rise in creatinine or >25% fall in creatinine clearance*

Reviewer's comments:

1. *Screening and follow-up BVAS criteria were adjudicated; however, the adjudication of the screening BVAS was just to determine whether the adjudicator agreed with the investigator's scoring and, if not, the adjudicator was to complete a new form. As we understand, the investigator-reported and adjudicated BVAS renal criteria did not differ significantly for the screening assessment, and investigator-reported criteria were used to identify the population with renal disease at baseline.*
2. *We do not have experience with use of the BVAS to identify patients with kidney involvement; however, we have the following general observations regarding the use of the specified BVAS criteria to identify a population with significant kidney involvement at baseline:*
   - *It is not clear why hypertension was based only on diastolic blood pressure or how an investigator was to determine the elevation was "related to ANCA-associated vasculitis."*
   - *The BVAS criterion for hematuria provided in training (>1+ blood on urinalysis or ≥10 RBC per high power field) differed from the BVAS criterion (≥10 RBC per high power field).*
   - *The BVAS criteria for "elevated serum creatinine," as written, would not differentiate between acute kidney injury related to ANCA-vasculitis from pre-existing chronic kidney disease (CKD).*
   - *The criterion for a rise in serum creatinine or fall in creatinine clearance do not provide guidance on time course for the change or the measurements that should be compared to make the determination.*
   - *We were unable to locate any additional information on the definition of the "other" criterion "RBC casts and/or glomerulonephritis" in the protocol, SAP, or training materials.*

   If anything, we would expect these issues to result in noise rather than bias; however, they make it more challenging to understand the level of kidney involvement in patients identified as having "renal disease at baseline" and to understand the nature of the benefit and the clinical importance of the trial's findings.

Concomitant Therapies
Patients could receive additional glucocorticoids or other immunosuppressive agents during the trial, as needed, to treat the underlying disease. Patients requiring additional therapy could continue study drug and were to remain in the study.

Patients received sulfamethoxazole 400 mg-trimethoprim 80 mg daily or sulfamethoxazole 800 mg-trimethoprim 160 mg every second day according to local practice as prophylaxis against *Pneumocystis jirovecii*. The protocol did not address the use of other concomitant medications that could affect serum creatinine/eGFR or proteinuria (e.g., ACE inhibitors, ARBs, SGLT2 inhibitors, NSAIDS).

Kidney-related Efficacy Assessments
Serum creatinine was collected during screening, on Day 1 pre-dose, weekly until Week 4, every 3 weeks from Weeks 7 to 16, every 6 weeks from Weeks 20 to 52, and at 8 weeks post-treatment. Spot urine samples for albumin and creatinine were collected on Day 1 pre-dose, at Weeks 1, 2, 4, 13, 26, 39, 52, and 8 weeks post-treatment.

Kidney-related Endpoints
As noted above, the trial included two primary endpoints based on disease remission. In addition, there were eight specified secondary endpoints, two of which were intended to assess a kidney benefit:

- change in eGFR from baseline over 52 weeks
- percent change in urinary albumin: creatinine ratio (UACR) from baseline over 52 weeks

According to both the original protocol and SAP, which was not submitted to the Agency until after unblinding of the trial data, baseline eGFR and UACR were defined as the last pre-dose value, and both endpoints were to be assessed in patients with "renal disease at baseline (based on the BVAS renal component)." The protocol did not otherwise define "renal disease at baseline." In the SAP, "renal disease at baseline" was defined as having one or more of the following components of the BVAS at screening (copied verbatim from SAP):

- Hypertension
- Proteinuria >1+ or >0.2 g/g creatinine
- Hematuria ≥10 RBCs/hpf
- Elevated serum creatinine (≥ 125 µmol/L)
- Rise in serum creatinine >30% or fall in creatinine clearance >25% from previous assessment.

Of note, the SAP did not specify that patients meeting the "other" BVAS criterion specified in the protocol ("RBC casts and/or glomerulonephritis") would be included in the subgroup of patients with renal disease at baseline.

According to the SAP, the population for the UACR analysis was specified as patients with "albuminuria at baseline, defined as a UACR of at least 10 mg/g creatinine."

Reviewer's comment: Albuminuria is generally defined as a UACR ≥30 mg/g; therefore, it was not clear why the applicant selected a value of ≥ 10 mg/g to identify a subset of patients with baseline albuminuria. In response to an information request, the applicant cited a publication by Levey et al. in which "normal UACR was defined as a level <10 mg/g." Generally speaking, the clinical significance of reducing albuminuria in patients with a normal or near-normal UACR is unclear.

Key Statistical Considerations [2]

Control of Type 1 Error

The trial's two primary endpoints based on the BVAS and need for glucocorticoids for the treatment of ANCA-associated vasculitis at Weeks 26 and 52 were to be tested sequentially for both non-inferiority and superiority using a gatekeeping procedure to preserve the overall type 1 error rate at 0.05. None of the secondary endpoints were included within a pre-specified testing strategy.

Analyses of eGFR and UACR

As noted above, analyses of the secondary endpoints based on eGFR and albuminuria were limited to the subset of the ITT population (all randomized patients) who met criteria for "renal disease at baseline." The population was defined in the SAP, as noted above. The SAP further specified the population for the UACR analyses as patients with UACR ≥ 10 mg/g creatinine at baseline.

According to the SAP, both the eGFR and UACR analyses were to use a mixed effects model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and baseline as covariates.[3]

Data missing for any reason were not to be imputed and were considered missing at random, even in situations such as loss-to-follow-up or study withdrawal, where missingness may be informative (i.e., related to worsening of disease). The protocol and SAP did not explicitly address how intercurrent events (e.g., premature discontinuation of study drug, initiation of additional therapies for ANCA-vasculitis, initiation of renal replacement therapy, or death) would be handled for the eGFR and UACR analyses. In response to an information request, the applicant did not provide additional details but noted that the potential impact was "considered to be small." They also stated that no sensitivity analyses were pre-specified in the protocol or SAP.

Key Trial Results

Baseline Characteristics

The treatment arms were generally well-balanced (Table 1). The mean age was 61 years, and nearly all patients were ≥18. Most patients were male (57%), white (84%), and had newly diagnosed disease (69%). Slightly more had GPA (55%) than MPA (45%) and received a rituximab-based regimen (65%) compared with intravenous (31%) or oral (4%) cyclophosphamide. At randomization, 64% had an eGFR below 60 mL/min/1.73 m^2 and 47% had a UACR >300 mg/g. Approximately 19% of patients were taking an ACE inhibitor and 15% were taking an ARB at baseline.

[2] According to the review team, the applicant did not provide the SAP for Agency review before unblinding the trial and aspects of the analyses conducted differed from those specified in the protocol, raising concerns that the analytic plan could have been influenced by knowledge of trial data.

[3] The model specified in the protocol also included randomization strata as a covariate, but this was excluded from the model in the SAP. In response to an information request regarding this discrepancy, the applicant cited the restricted sample size for this population (patients with renal involvement at baseline) and concerns related to convergence of the model if too many covariates were included.

Table 1: Demographics and baseline characteristics

	Avacopan N=166	**Prednisone** N=164
Age (yrs)		
Mean (SD)	61 (15)	61 (15)
<18 years of age (n (%))	2 (1)	1 (1)
Race (n (%))		
White	138 (83)	141 (86)
Asian	17 (10)	15 (9)
Black	3 (2)	2 (1)
Other	8 (5)	6 (4)
Male (n (%))	98 (59)	89 (54)
Baseline eGFR[1] (mL/min/1.73 m^2)		
Mean (SD)	51 (31)	53 (33)
>59 (n (%))	55 (33)	58 (35)
30-59 (n (%))	56 (34)	57 (35)
<30 (n (%))	52 (31)	48 (29)
Not assessed (n (%))	3 (2)	1 (<1)
Baseline UACR[1] (mg/g)		
Mean (SD)	710 (993)	543 (795)
Median (Min, Max)	354 (2, 6461)	254 (2, 5367)
<10 (n (%))	11 (7)	15 (9)
10-300 (n (%))	57 (34)	66 (40)
>300 (n (%))	82 (49)	74 (45)
Not assessed	16 (10)	9 (6)

Source: Clinical Study Report

[1]eGFR and UACR categories based on subgroups specified in SAP.

A total of 81% of patients were classified as having "renal disease at baseline" based on meeting one or more BVAS renal criteria (Table 2). The median number of criteria met was three. The most common criteria met were proteinuria >1+ on urinalysis or UACR >0.2 g/g (66%), a serum creatinine-based criterion (56%), hematuria (44%), and RBC casts and/or glomerulonephritis (36%). Of note, "RBC casts and/or glomerulonephritis" was not a criterion included in the definition of "renal disease at baseline" specified in the SAP, but it appears that the applicant included these patients in the secondary endpoint analyses (five avacopan and two prednisone qualified only based on this criterion).

Table 2: Summary of BVAS renal criteria met at baseline (ITT population)

	Avacopan N=166	**Prednisone** N=164
Population with renal disease by BVAS	134 (81)	134 (82)
Baseline eGFR mean (SD)	45 (28)	46 (27)
Number of BVAS renal or "other" criteria met		
Mean	2.8	2.7
Median	3.0	3.0
1 (n [%])	21 (13)	21 (13)
2 (n [%])	25 (15)	41 (25)
3 (n [%])	53 (32)	38 (23)
4 or more (n [%])	35 (21)	34 (21)
Criteria met		
Hypertension (n [%])	21 (13)	23 (14)
Proteinuria (n [%])	110 (66)	107 (65)
Hematuria (n [%])	77 (46)	68 (42)
Serum creatinine 125-249 µmol/L (n [%])	60 (36)	61 (37)
Serum creatinine 250-499 µmol/L (n [%])	26 (16)	20 (12)
Serum creatinine ≥500 µmol/L (n [%])	1 (1)	0 (0)
Rise in serum creatinine >30% or fall in creatinine clearance >25% (n [%])	17 (10)	20 (12)
RBC casts and/or glomerulonephritis (n [%])	60 (36)	59 (36)
Criterion met for patients meeting only one		
Hypertension (n [%])	2 (1)	1 (1)
Proteinuria (n [%])	6 (4)	5 (3)
Hematuria (n [%])	8 (5)	12 (7)
RBC casts and/or glomerulonephritis (n [%])	5 (3)	2 (1)

Source: Applicant's response to February 8, 2021 information request.

It was not clear from the information provided in the NDA submission whether patients had evidence of chronic kidney disease before the current diagnosis/flare of ANCA-vasculitis. In response to an information request, the applicant clarified that no pre-study eGFR or UACR data are available. They provided analyses of the available medical history data; however, it is not clear whether the diagnoses pre-dated the ANCA-vasculitis diagnosis/flare or were associated with the ANCA-vasculitis itself. "Renal disease-related conditions" reported in at least 10% of patients in each group are shown in Table 3, specifically hypertension, hematuria, proteinuria, and "chronic kidney disease."

Table 3: Medical history of "renal disease-related conditions" at baseline

	Avacopan N=166	**Prednisone** N=164
Hypertension	91 (55)	87 (53)
Hematuria	39 (24)	38 (23)
Proteinuria	36 (22)	31 (19)
Chronic kidney disease	23 (14)	25 (15)

Source: Applicant's response to February 8, 2021 information request.

Disposition

A total of 166 patients were randomized to avacopan and 165 to placebo (Table 4), and all but one was treated and included in the ITT population. Just under 10% of patients in each treatment group withdrew from the study early and did not complete study follow-up assessments, most commonly because of adverse events or patient/investigator decision. Approximately 20% of patients prematurely discontinued study drug in both treatment arms, most often citing an adverse event. Fewer than 3% of patients in each group died and fewer than 3% in each group required renal replacement therapy during the trial.

Table 4: Subject disposition

	Avacopan	Prednisone
Randomized	166 (100)	165 (100)
ITT population	166 (100)	164 (99.4)
Completed Week 52	151 (91)	152 (92)
Early withdrawal from study	15 (9)	13 (8)
Adverse event	3 (1.8)	6 (3.6)
Investigator decision	3 (1.8)	4 (2.4)
Subject decision	6 (3.6)	3 (1.8)
Lost to follow-up	1 (0.6)	0
Other	1 (0.6)	0
Prematurely discontinued study drug	37 (22)	35 (21)
Adverse event	26 (16)	29 (18)
Investigator or sponsor decision	6 (4)	4 (2.4)
Subject decision	3 (1.8)	0
Lost to follow-up	1 (0.6)	0
Other	1 (0.6)	1 (0.6)
Died	2 (1.2)	4 (2.4)
Required renal replacement therapy	3 (1.8)	4 (2.4)

Source: Clinical Study Report Table 5.

Key Concomitant Medications Administered During Trial

As shown in Table 5, nearly 90% of patients received additional IV and oral glucocorticoids during the trial and 20% received other immunosuppressive agents. Approximately half received an ACE inhibitor or ARB.

Table 5: **Key Concomitant Treatments**

	Avacopan N=166	Prednisone N=164
Non-study supplied oral or IV glucocorticoids (n [%])	145 (87)	149 (91)
Non-protocol specified treatments for ANCA-associated vasculitis[a] (n [%])	29 (18)	36 (22)
ACE inhibitors or ARBs (n [%])	93 (56)	76 (46)

Source: Clinical Study Report

[a]Includes non-protocol specified rituximab, azathioprine, cyclophosphamide, mycophenolate, methotrexate, methotrexate, cyclosporine, tacrolimus, alemtuzumab, belimumab, abatacept, or other immunosuppressants

Endpoints

Primary Endpoint

For the trial's primary endpoints, avacopan was non-inferior to prednisone on disease remission at Weeks 26 and 52 and was superior at Week 52 but not at Week 26 (Table 6).[4]

Table 6: **Primary Endpoint Analyses (ITT)**

	Avacopan (% (95% CI)) N=166	**Prednisone (% (95% CI)) N=164**	**Difference (% (95% CI)**	**Non-inferiority p-value**	**Superiority p-value**
Primary Endpoint 1: Disease Remission at Week 26	72 (65, 79)	70 (63, 77)	2 (-6, 13)	<0.0001	0.24
Primary Endpoint 2: Sustained Disease Remission at Week 52	66 (58, 73)	55 (47, 63)	11 (3, 22)	<0.0001	0.01

Source: Clinical Study Report

Kidney-related Secondary Endpoints

As noted above, secondary endpoints were not included in plans to control the overall type 1 error rate, and the trial was not successful on the fourth analysis specified in the primary endpoint testing hierarchy; however, we have summarized analyses below that the applicant believes support claims related to 1) improvements in kidney function in patients meeting BVAS criteria for renal disease at baseline and 2) changes in albuminuria in patients meeting BVAS criteria for renal disease at baseline and with a UACR ≥10 mg/g.

eGFR

As shown in Table 7, mean eGFR for patients meeting BVAS criteria for renal disease at baseline improved in both treatment arms over time, with a least squares (LS) mean increase in eGFR from baseline to Week 52 of 7.3 and 4.1 mL/min/1.73 m^2 for the avacopan and prednisone groups, respectively (LS mean difference of 3.2 [95% CI 0.3, 6.1; nominal p-value 0.029]).

For patients with a baseline eGFR <30 mL/min/1.73 m^2, (b) (4) (b) (4) the LS mean increase in eGFR from baseline to Week 52 was 13.7 mL/min/1.73 m^2 and 8.2 mL/min/1.73 m^2 for the avacopan and prednisone groups, respectively (LS mean difference of 5.6 [95% CI 1.7, 9.5; nominal p-value 0.005]).

[4] The sequence of testing was noninferiority at Week 26 then Week 52, followed by superiority at Week 52 then Week 26.

Table 7: Change in eGFR from baseline to Week 52

	Avacopan	Prednisone
Patients meeting BVAS renal criteria at baseline		
N	134 (100)	134 (100)
Data available at both baseline and Week 52 (n [%])	119 (89)	125 (93)
eGFR at baseline (mean [SD])	45.5 (28)	46.2 (27)
eGFR at Week 52 (mean [SD])	53.2 (24)	50.5 (22)
LS mean change from baseline (95% CI)	7.3 (2.1, 6.1)	4.1 (5.2, 9.4)
LS mean difference (95% CI; p-value)	**3.2 (0.3, 6.1; 0.029)**	
Patients with eGFR <30 mL/min/1.72 m^2 at baseline		
N	52 (100)	48 (100)
Data available at both baseline and Week 52 (n [%])	45 (87)	42 (88)
eGFR at baseline (mean [SD])	21.0 (4)	21.6 (4)
eGFR at Week 52 (mean [SD])	35.2 (14)	30.8 (10.4)
LS mean change from baseline (95% CI)	13.7 (11.0, 16.4)	8.2 (5.4, 11)
LS mean difference (95% CI; p-value)	**5.6 (1.7, 9.5; 0.005)**	

Source: Clinical Study Report Tables 14.2.7.1.1, 14.2.7.1.2

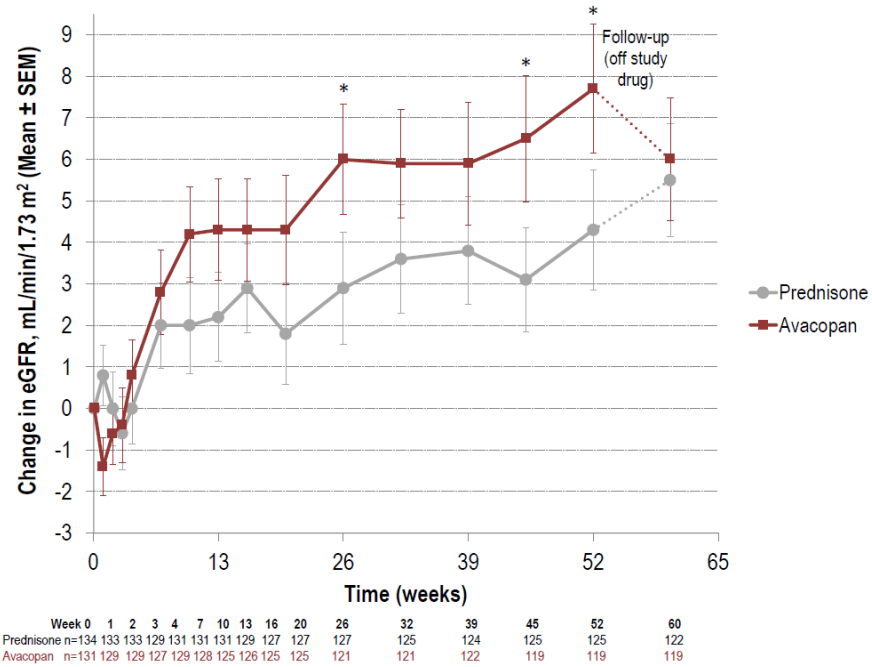
Of note, at the 8-week post-treatment follow-up assessment, there was no difference in eGFR between the treatment arms (Table 8).

Table 8: Change in eGFR from baseline to Week 60 (8 weeks post-treatment) in patients meeting BVAS renal criteria at baseline

	Avacopan n=134	Prednisone N=134
Data available at both baseline and Week 60 (n [%])	119 (89)	122 (91)
eGFR at baseline (mean [SD])	45.7 (28)	45.6 (26)
eGFR at Week 60 (mean [SD])	51.7 (23)	51.0 (23)
LS mean change from baseline (95% CI)	6.0 (3.7, 8.4)	5.4 (3.1, 7.8)
LS mean difference (95% CI; p-value)	**0.6 (-2.7, 3.9; 0.72)**	

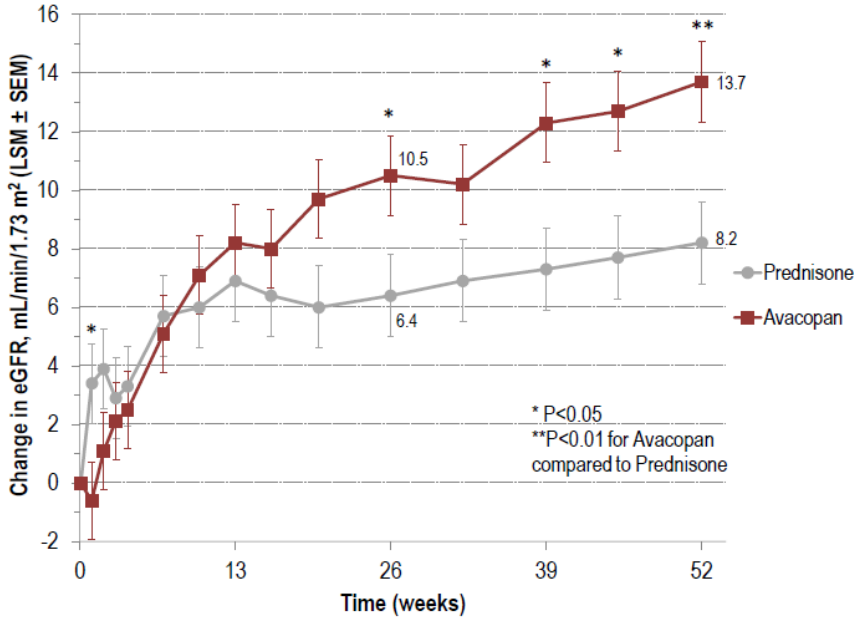
Figures 2 through 5 shown change from baseline in eGFR over time in patients meeting BVAS renal criteria at baseline and in patients meeting BVAS renal criteria at baseline by eGFR subgroups. Of note, there is no evidence of a difference between treatment arms at the 8-week follow-up visit in the overall population meeting BVAS renal criteria at baseline (Figure 2). It is not clear why a difference between treatment arms, if reflective of a true benefit of avacopan over prednisone on the underlying disease, would dissipate so quickly following discontinuation of study drug. In addition, there is no evidence of a difference between treatment arms in the subgroup with an eGFR >59 mL/min/1.73 m^2, with eGFR declining in both treatment groups during the study (Figure 5).

Figure 1: Change from baseline in eGFR over time in patients meeting BVAS renal criteria at baseline (ITT Population)



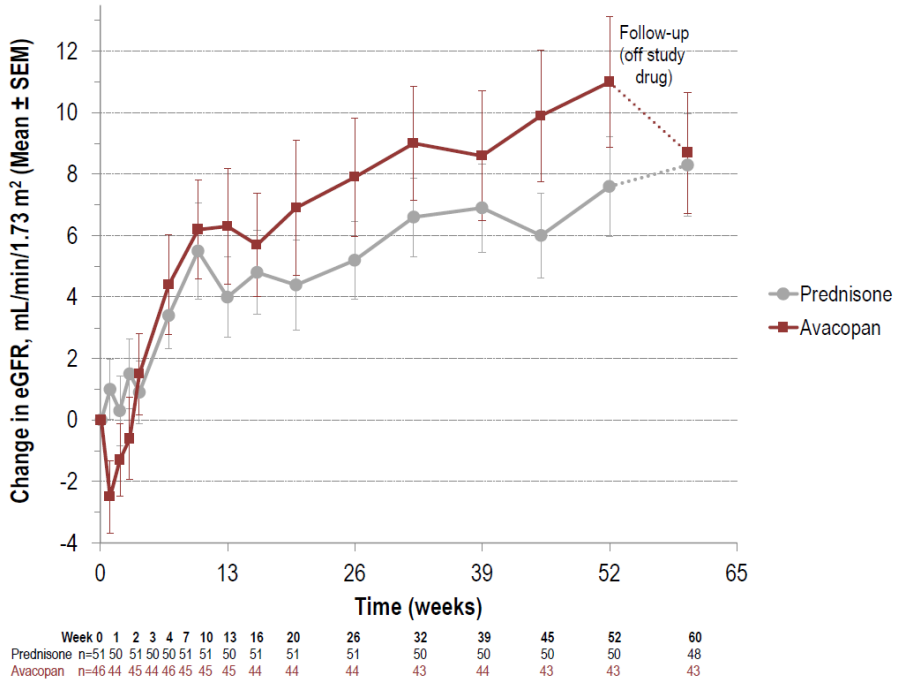
Source: Applicant's response to February 8, 2021 information request.

Figure 2: Change from baseline in eGFR over time for patients with a baseline eGFR <30 mL/min/1.73 m² (ITT Population)



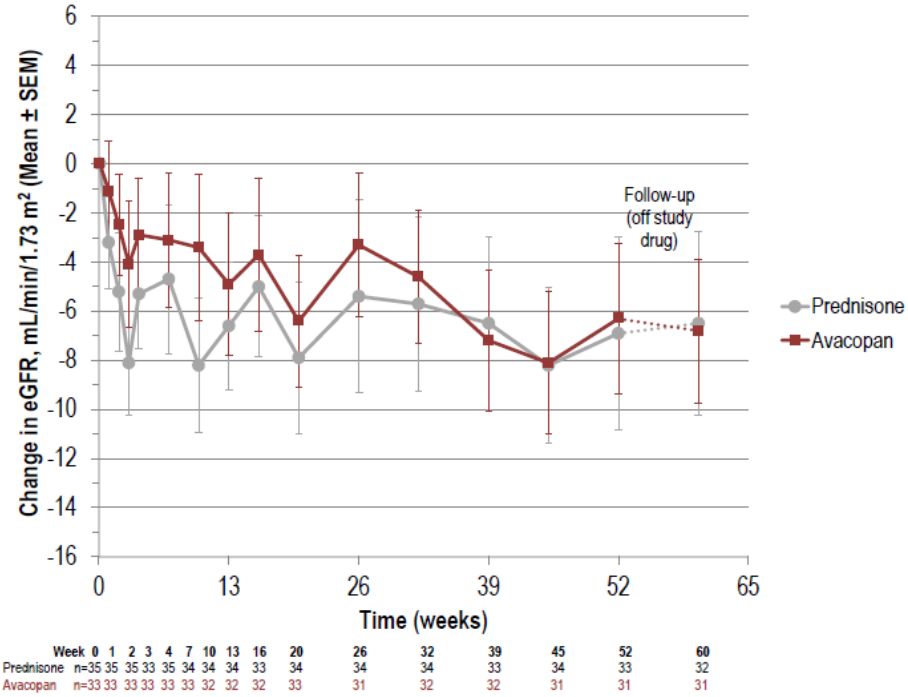
Source: [redacted] (b) (4).
Note: Applicant did not include data from post-treatment follow-up visit (Week 60) in the figure. According to CSR Table 14.2.7.1.2, the LSM difference at Week 60 was 4.2 (SEM 2.6; 95% CI -0.9, 9.3).

Figure 3: Change from baseline in eGFR over time for patients with a baseline eGFR 30 to 59 mL/min/1.73 m² (ITT Population)



Source: Applicant's response to February 8, 2021 information request.

Figure 4: Change from baseline in eGFR over time for patients with a baseline eGFR >59 mL/min/1.73 m² (ITT Population)



Source: Applicant's response to February 8, 2021 information request.

Albuminuria

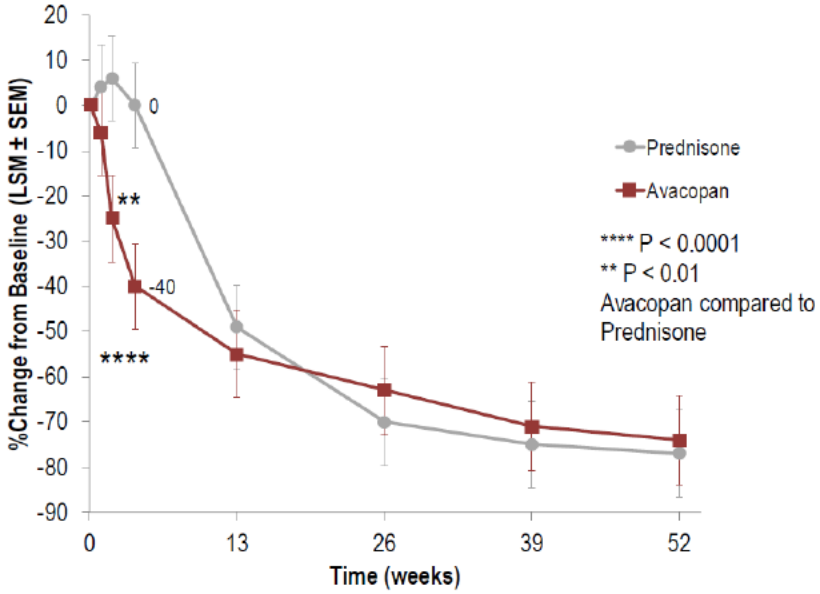
As shown in Table 9 and Figure 1, the applicant provided an analysis of percent change from baseline in UACR for the subset of patients meeting BVAS criteria for renal disease at baseline who also had a UACR ≥10 mg/g. The applicant highlights a reduction in UACR from baseline to Week 4 of 40% in the avacopan group and 0% in the prednisone group; however, by Week 52, UACR values in the two arms were similar with improvements in proteinuria seen in both treatment arms. Of note, it is challenging to interpret the clinical significance of percent change in albuminuria in a population that includes patients with near-normal albuminuria levels at baseline.

Table 9: Change in proteinuria for patients meeting BVAS renal criteria and with UACR ≥ 10 mg/g at baseline (ITT population)

	Avacopan (N=125)	Prednisone (N=128)
Week 4		
Included in analysis (n [%])	121 (97)	124 (97)
UACR at baseline (mean [SD])	833 (435)	638 (304)
UACR at Week 4 (mean [SD])	634 (255)	740 (310)
LS mean UACR ratio Week 4:baseline (95% CI)	0.6 (0.5, 0.72)	1.0 (0.84, 1.19)
LS mean ratio (95% CI; p-value)	**0.6 (0.47, 0.78; <0.0001)**	
Week 52		
Included in analysis (n [%])	109 (87)	114 (89)
UACR at baseline (mean [SD])	798 (430)	643 (316)
UACR at Week 52 (mean [SD])	320 (113)	252 (75)
LS mean UACR ratio Week 52:baseline (95% CI)	0.26 (0.22, 0.31)	0.23 (0.19, 0.28)
LS mean ratio (95% CI; p-value)	**1.12 (0.86, 1.45; 0.4)**	

Source: Clinical Study Report Table 14.2.9.1.1

Figure 5: Change from baseline in UACR in patients meeting BVAS criteria for renal disease at baseline and with a baseline UACR ≥10 mg/g (ITT Population)



Source: Clinical Study Report Figure 12

Consult Question

Question: For the pivotal trial evaluating avacopan (CCX168) in ANCA-associated vasculitis, Chemocentryx evaluated parameters of renal disease including estimated glomerular filtration rate (eGFR), albuminuria, and urinary excretion of monocyte chemoattractant protein-1 (MCP-1) in patients with active renal disease at baseline. (b) (4) (b) (4) (b) (4) Please assist with interpretation of these data, particularly the clinical meaningfulness of these assessments (b) (4) (b) (4)

DCN Response:

(b) (4) (b) (4) *We believe the data submitted* (b) (4) *are challenging to interpret because the analyses were not specified in plans to control the overall type 1 error rate; the trial's SAP was submitted late and key aspects of the analytic plan were first specified in the SAP, had been changed from the plan specified in the protocol, or were not specified in adequate detail;* (b) (4) (b) (4) *In addition, for the following reasons it is not clear whether the eGFR and UACR findings are real or whether the magnitude of the changes seen are clinically meaningful:*

1. *Population: We do not have experience with the use of BVAS criteria to identify a population that is likely to have clinically important kidney-related events (e.g., need for acute or chronic renal replacement therapy or an irreversible loss of kidney function); however, for the reasons described in the body of this review, it is not clear whether the specified criteria for "renal disease at baseline" identified a population with significant kidney involvement or how to characterize the level of kidney involvement such that we can readily interpret the nature and clinical importance of the effects on eGFR and UACR.*
2. *Size of the treatment effect on eGFR: The mean difference between treatment arms on eGFR at Week 52 was small (3.2 mL/min/1.73m^2), and it is not clear that such an effect would be considered clinically meaningful.*
3. *Durability of the eGFR effects: Even if the treatment benefit on kidney function for avacopan compared with prednisone is believed to be both real and clinically meaningful, we do not understand why the effect would dissipate within 8 weeks of study drug discontinuation, raising additional questions about the durability and clinical importance of the findings.*
4. *Importance of the UACR Findings: The applicant highlights an early reduction in UACR from baseline to Week 4 in the subset of patients meeting BVAS criteria for renal disease at baseline who also had a UACR ≥10 mg/g; however, UACR decreased in both treatment arms during the trial, and there was no difference at Week 52, the prespecified timepoint. It is often challenging to interpret the clinical importance of treatment effects on UACR, and we generally review the available data in the population of interest to understand whether treatment effects on UACR at a specific timepoint and of a certain magnitude are likely to predict clinical outcomes of interest. Although the applicant did not provide data supporting the use of UACR as a surrogate for clinical outcomes in ANCA-associated vasculitis, it seems unlikely that the difference seen at Week 4 but not at later timepoints would predict a meaningful clinical benefit of avacopan over prednisone.*

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 10, 2021
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 214487
Product Name, Dosage Form, and Strength:	Tavneos (avacopan) capsules, 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Chemocentryx
FDA Received Date:	July 7, 2020 and October 9, 2020
OSE RCM #:	2020-1483
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Tavneos (avacopan) capsules, 10 mg the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, container labels, and carton labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We identified some areas of concern for the proposed PI, container label, and carton labeling. We provide our recommendations below in Section 4.1 for the Division and Section 4.2 for Chemocentryx.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division.

4.1 RECOMMENDATIONS FOR DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE (DRTM)

A. Prescribing Information

1. Dosage and Administration Section

a. Revise [redacted] To read "Recommended dose of [PROPRIETARY NAME] is 30 mg twice daily with food."

2. How Supplied/Storage and Handling Section

   a. Storage information: Several temperatures statements are missing unit of measure. Add the appropriate unit of measure to each temperature statement.

4.2 RECOMMENDATIONS FOR CHEMOCENTRYX

We recommend the following be implemented prior to approval of this NDA:

B. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.
2. [redacted] We recommend the use of [redacted] for the proposed proprietary name and the strength statements.
3. Relocate the quantity statement away from the strength statement and decrease the prominence so that it does not compete with strength statement.
4. Storage information: Several temperatures statements are missing unit of measure. Add the appropriate unit of measure to each temperature statement.
5. To ensure consistency with the Prescribing Information, revise the statement, [redacted] to read "Recommended Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tavneos received on October 9, 2020 from Chemocentryx.

Table 2. Relevant Product Information for Tavneos	
Initial Approval Date	N/A
Active Ingredient	avacopan
Indication	for the treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Route of Administration	oral
Dosage Form	capsules
Strength	10 mg
Dose and Frequency	30 mg twice daily
How Supplied	HDPE bottle and child-resistant induction seal closure containing 180 capsules or 30 capsules.
Storage	Store at 68-77°F (20-25°C); excursions permitted to 59-86°F (15-30°C) [see USP Controlled Room Temperature].

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Tavneos labels and labeling submitted by Chemocentryx.

- Container label received on July 7, 2020
- Carton labeling received on July 7, 2020
- Prescribing Information (Image not shown) received on October 9, 2020, available from \\CDSESUB1\evsprod\nda214487\0009\m1\us\114-label\1141-draft-label\proposed.docx

G.2 Label and Labeling Images

(b) (4)

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Clinical Inspection Summary

Date	January 4, 2021
From	Tina Chang, M.D., Reviewer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Suzette Peng, M.D., Medical Officer Rachel Glaser, M.D., Clinical Team Leader Susie Choi, PharmD, Regulatory Project Manager Division of Rheumatology and Transplant Medicine (DTRM)
NDA/BLA #	214487
Applicant	ChemoCentryx, Inc.
Drug	Avacopan (CCX168)
NME (Yes/No)	Yes
Therapeutic Classification	Complement 5a receptor (C5aR) selective antagonist
Proposed Indication(s)	Treatment of Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis
Consultation Request Date	August 5, 2020
Summary Goal Date	June 7, 2021
Action Goal Date	July 7, 2021
PDUFA Date	July 7, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single study (Protocol CL010_168) was submitted to the Agency in support of a New Drug Application (NDA 214487) for avacopan to treat adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. Clinical inspections of Dr. Peter Merkel and Dr. John Niles were conducted in support of this application. Based on the results of these inspections, the study (Protocol CL010_168) appears to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of the respective indication.

II. BACKGROUND

Avacopan is a selective antagonist of the human complement 5a receptor (C5aR) and blocks the binding of complement 5a (C5a) to C5aR for the treatment of adult patients with Anti-Neutrophil Cytoplasmic (ANCA)-associated vasculitis. The proposed dosing for avacopan is 30 mg or three 10 mg capsules twice daily.

The applicant, ChemoCentryx, Inc., submitted the data from a randomized, double-blind, active-controlled trial (Protocol CL010_168), to evaluate the safety and efficacy of avacopan in patients with ANCA-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine in male and female subjects aged 18 years or older with a clinical diagnosis of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. The following describes briefly the Protocol CL010_168.

Protocol CL010_168

Study Title: A Randomized, Double-Blind, Active-Controlled, Phase 3 Study to Evaluate the Safety and Efficacy of CCX168 (Avacopan) in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Treated Concomitantly with Rituximab or Cyclophosphamide/Azathioprine

The primary study objective was to evaluate the efficacy of avacopan to achieve and sustain remission in subjects with active ANCA-associated vasculitis, when used with cyclophosphamide followed by azathioprine, or with rituximab.

The co-primary efficacy endpoints were the following:

1. The proportion of subjects achieving disease remission at Week 26.
   Disease remission at Week 26 was defined as:
   i. Achieving a BVAS of 0 as determined by the Adjudication Committee (AC);
   ii. No administration of glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26;
   iii. No BVAS >0 during the 4 weeks prior to Week 26 (if collected for an unscheduled assessment).

2. The proportion of subjects achieving sustained disease remission at Week 52. Sustained remission at Week 52 was defined as:
   i. Disease remission at Week 26 as defined above;
   ii. Disease remission at Week 52 defined as a BVAS of 0 at Week 52 as determined by the AC and no administration of glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 52;

The study randomized 331 subjects from 143 sites in North American, Europe, Australia, New Zealand, and Japan.

The first subject was enrolled on 15 March 2017 and the last subject completed the study on 1 November 2019.

Rationale for Site Selection

The clinical investigators Dr. Peter Merkel and Dr. John Niles were selected for clinical site

inspections using risk-based approach that also considers numbers of enrolled subjects, treatment effect (b) (4)

III. RESULTS:

1. **Dr. John Niles**
   Massachusetts General Hospital
   101 Merrimac Street
   Boston, MA 02114
   Inspection dates: October 15-20, 2020

   For study CL010_168, this site screened 18 subjects and enrolled 15 subjects. Among the 15 enrolled subjects, 14 completed the study treatment. All 15 subjects that were enrolled in the study were reviewed comprehensively during the inspection.

   The inspection evaluated the following documents: subject medical records, correspondence between the Clinical Investigator (CI) and the sponsor/Contract Research Organization (CRO), correspondence between the CI and the Institutional Review Board (IRB), the sponsor monitoring log, all informed consent forms and revisions, selective source records to compare to case report forms, adverse event records, and accountability for the study drug.

   Source documents used to assess the co-primary efficacy endpoint data were verifiable at the study site. There was no evidence of underreporting of adverse events.

   This clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

2. **Dr. Merkel, Peter**
   University of Pennsylvania
   3400 Spruce Street Fl 5
   Philadelphia, PA 19104
   Inspection dates: November 16-20, 2020

   For study CL010_168, this site screened and enrolled eight subjects. Among the eight enrolled subjects, eight completed the study treatment. All eight subjects that were enrolled in the study were reviewed comprehensively during the inspection.

   The inspection evaluated the following documents: informed consent forms, IRB approval letters and correspondence, delegation logs, FDA form 1572s, financial disclosure forms, investigational product (IP) accountability logs, site training documents, subject source documents for efficacy, adverse event reports and monitoring logs.

   Source documents used to assess the co-primary efficacy endpoint data were verifiable at

the study site. There was no evidence of underreporting of adverse events.

This clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

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Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
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Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/

OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214487
Submission Number	001
Submission Date	7/7/2020
Date Consult Received	8/7/2020
Drug Name	Avacopan (CCX168)
Indication	Anti-neutrophil cytoplasmic antibody-associated vasculitis
Therapeutic dose	30 mg twice daily
Clinical Division	DRTM

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 8/7/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-120784 dated 07/06/2016 in DARRTS (link);
- Previous IRT review under IND-120784 dated 10/25/2016 in DARRTS (link);
- Previous IRT review under IND-120784 dated 03/28/2019 in DARRTS (link);
- Previous IRT review under IND-120784 dated 09/11/2019 in DARRTS (link);
- Previous IRT review under IND-120784 dated 10/09/2019 in DARRTS (link);
- Previous IRT review under IND-120784 dated 01/30/2020 in DARRTS (link);
- Sponsor's clinical study protocol # CL014 168 (SN0001; link);
- Sponsor's clinical study report # CL014 168 (SN0001; link);
- Sponsor's QT assessment report # CL014_168 (SN0001; link);
- Sponsor's statistical analysis plan # CL014 168 (SN0001; link);
- Sponsor's proposed product label (SN0000; link);
- Investigator's brochure under IND-120784 (SN0000; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0003; link).

1 SUMMARY

No significant QTc prolongation effect of avacopan was detected in this QT assessment.

The effect of avacopan was evaluated in a thorough QT study (Study # CL014_168). This was a randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy subjects. The highest dose evaluated was 100 mg twice daily, which covers the worst-case exposure scenario (CYP3A inhibition, Section 3.1). The assay sensitivity was established using oral moxifloxacin.

The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that avacopan is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	**Treatment**	**Concentration** (ng/mL)	**ΔΔQTcF** (msec)	**90% CI** (msec)
QTc	Avacopan* 100 mg (twice daily)	779.8	0.8	(-2.8 to 4.5)

**Avacopan was administered as twice daily dose for 7 days. For further details on the FDA analysis, please see section 4.*

The findings of this analysis are further supported by the available categorical analysis (Section 4.4).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the label submitted to SDN001. Our proposal is highlighted below (addition, ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At the maximum approved recommended dose, <Tradename> does not prolong the QT interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

ChemoCentryx is developing avacopan for the treatment of anti-neutrophil cytoplasmic autoantibody-associated vasculitis and microscopic polyangiitis (NDA-214487; IND-120784). [redacted] (b) (4)

(b) (4) (b) (4) Avacopan (CCX168; MW: 581.6) is human complement 5a receptor (C5aR) antagonist.

The product is formulated as immediate-release capsule (b) (4) (b) (4) formulation containing 10 mg avacopan for oral administration. The proposed therapeutic dose for the present indication is 30 mg twice daily under fed condition. The peak concentrations of 350 ± 170 ng/mL (Tmax: 2 to 3 h; half-life: ~300 to 500 h) are expected at steady-state with the anticipated therapeutic dose in target population (Half-life Pop-PK Predicted). Significant accumulation is expected at steady-state with the proposed therapeutic dose (30 mg twice daily; Racc: ~4-fold). Due to its extremely poor aqueous solubility, avacopan is formulated as a liquid filled hard gelatin capsule (10 mg) with Cremophor RH40 and PEG-4000. Previously, the sponsor highlighted that higher systemic exposures of avacopan are not achievable as PEG-4000 administration may lead to diarrhea at high oral doses. Highest does up to 100 mg avacopan twice daily have been studied and was found to be tolerable.

Avacopan exhibits a positive food effect with a 1.7-fold increase in exposure (Cmax: no significant change for 30 mg single dose) was observed following its administration with a high-fat and high-calorie meal compared to that under fasting condition (Study # CL007_168). The product is intended to be administered under fed condition. The studies indicate that avacopan is extensively metabolized mainly by CYP3A4 forming a major metabolite (M1: a mono-hydroxy metabolite of avacopan; ~12% of the total drug-related materials in plasma). The human mass balance study indicates that ~77% (~7% as unchanged drug) of the radioactive dose is excreted in feces, and ~10% (>1% as unchanged drug) in urine (Study # CL004_168). Concomitant administration of avacopan with a strong inhibitor of CYP3A4 resulted in increased exposures of avacopan (Cmax: ~2-fold; 262 ±52 to 484 ±100 ng/mL; Study # CL008_168). Considering 2-fold increase exposure (Cmax) of avacopan with concomitant administration of CYP3A4 inhibitor, the mean steady-state peak concentrations (~650 ng/mL) are expected with 30 mg twice daily regimen in patients (318 ng/mL; Pop-PK based). The sponsor recommends caution during concomitant administration of avacopan with the strong inhibitors of CYP3A4.

The sponsor claims that mild or moderate hepatic impairment had no clinically significant impact on the pharmacokinetics of avacopan or its M1 metabolite. However, no formal study was conducted by the sponsor to assess the pharmacokinetics of avacopan in subjects with severe hepatic impairment (Child-Pugh Class C). No dose adjustment is described on the product label for subjects with renal impairment and subjects with mild and moderate hepatic impairment.

Previously, the IRT reviewed the meeting package (IND-120874, SQ:046) and the report for phase-1, food-effect, and cardiac safety (Study # CL007) study submitted by the sponsor as a substitution request for thorough QT study. The IRT review indicated that the data submitted by the sponsor is adequate as a substitute for thorough QT study (Dt: 07/06/2016, 03/18/2019, and 09/11/2019). Considering the formulation limitations in achieving sufficiently high exposures, the IRT suggested that the sponsor conducts a separate study using exposure-response relationship as the primary analysis.

Subsequently, the sponsor submitted their study protocol for review (Study # CL014_168). Overall the proposed study design and analysis plan were acceptable to the IRT for characterizing the effects of avacopan on the QTc interval. General comments on data modeling and submission were provided to the sponsor (Dt: 10/09/2019).

It was a randomized, double-blinded, placebo- and active-controlled study evaluating the risk of QTc prolongation associated with avacopan in healthy subjects (Protocol # CL014_168 / CEYP3-962). The sponsor proposed a double-dummy, parallel group, multiple dose study with a nested crossover comparison between avacopan, moxifloxacin and placebo. Subjects (n=56; 28 per cohort) were planned to be randomized (2:1:1) to receive 1) avacopan (Cohort 1; n ≥ 24), or 2) moxifloxacin / placebo (Cohort 2A; single dose Moxifloxacin on Day 1), or 3) placebo / moxifloxacin (Cohort 2B; single dose Moxifloxacin on Day 15).

In cohort 1, the sponsor proposed to use 30 mg twice daily (3 capsules; as therapeutic levels) dosing for 7 days followed by 100 mg twice daily (10 capsules; as supratherapeutic levels) dosing for additional 7 days. Study drug was planned to be administered following an overnight fast on Days 1, 7, 14, and 15. This was expected to result in 2-fold increase in avacopan concentrations (on Day 14; ~800 ng/mL) over peak concentrations of avacopan at therapeutic doses.

In cohort 1, PK samples (for determination of avacopan and its metabolite) were planned on Days 1, 7, and 14: Pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, and 24 hours post-dose with additional pre-dose samples on Days 4, 5, 6, 11, 12, and 13. In cohort 2, PK samples (for determination of moxifloxacin) were planned on Days 1, and 15: Pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, and 24 hours post-dose. ECG sample (Holter extractions) collection was planned on Days 1, 7, 14 and 15: at pre-dose (-1 h), and 0.5, 1, 2, 3, 4, 5, 6, 9, 12, and 24 hours post-dose and on Day -1 (baseline) at corresponding time points.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety and previous IRT review under IND-120784 dated 09/11/2019 in DARRTS (link);

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for avacopan was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: The largest upper bound of 90% CI for ΔΔQTcF in sponsor's analysis is less than 10, but greater than 10 in reviewer's assessment. The reviewer's results were fitted using unstructured covariance structure and that yields wider confidence intervals comparing to sponsor's confidence intervals fitted using compound symmetric covariance structure. In addition, the sponsor did not adjust baseline covariate in the analysis. The reviewer adjusted baseline covariate in the reviewer's analysis. Please see section 4.3 for more details.

3.2.1.1 Assay Sensitivity

The study included oral moxifloxacin (400 mg) as a positive control to detect small increases from baseline for QTcF in this study. The sponsor performed exposure-response analysis for assay sensitivity assessment. The results of the sponsor's analysis indicate that the study demonstrated assay sensitivity (the lower bound of the 2-sided CI of the predicted QT effect 14.8 ms [90% CI: 9.65 to 19.97] at the geometric mean peak moxifloxacin concentration i.e., 1951 ng/mL was above 5 ms). In addition, the assay sensitivity was also established using by time analysis.

Reviewer's comment: The results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Sections 4.5.1.1 and 4.3.1.1 for additional details.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 beats/min) and QRS (>120 msec and 25% over baseline). One subject experienced PR >200 msec and 25% over baseline.

Reviewer's comment: Sponsor's results are consistent with reviewer's results. One subject experienced maximum PR 251.67 msec and the corresponding change from averaged baseline is 23% and the change from time matched baseline is 28.4%. Therefore, the subject is not included in reviewer's categorical output. Please see section 3.2.2.

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between plasma concentration of avacopan (and its M1 metabolite) and ΔQTcF (change from baseline in QTcF) using a linear mixed-effects model. The sponsor's analysis included ΔQTcF as the dependent variable, time-matched concentrations of avacopan and M1 as the explanatory variates (0 for placebo), study drug (active = 1 or placebo = 0) and time (i.e., post-baseline time point, including the single pre-dose time point and all post-dose time points on Days 1, 7, and 14) as fixed effects, and a random intercept and slope per subject. The sponsor's full model included both analytes (avacopan and its M1 metabolite).

The model predicted ΔΔQTcF (upper confidence interval) values of 0.82 (4.05) msec at the mean peak concentrations of avacopan for the highest studied dose (100 mg twice daily; geomean Cmax ~780 ng/mL) following oral administration. The sponsor highlights that a QTc effect exceeding 10 ms can be excluded within the observed plasma concentration ranges of avacopan and M1, up to ~1220 and ~335 ng/mL, respectively. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the highest studied dose.

Reviewer's comment: Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.

3.2.4 Safety Analysis

There were no deaths or subject discontinuations due to AEs reported in the study. One (1) subject in Cohort 2A (receiving avacopan placebo and moxifloxacin) experienced a serious adverse event (SAE) of transverse myelitis requiring hospitalization that occurred 31 days following study discharge.

The percentage of subjects reporting AEs was 38% following multiple supratherapeutic doses of avacopan and 21% following multiple therapeutic doses. The most commonly reported AE following avacopan administration was headache (21% of subjects). The majority of AEs following avacopan administration were mild in severity and considered possibly study drug-related.

No treatment- or dose-related trends were observed with respect to clinical laboratory, vital sign, ECG, or physical examination safety assessments.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

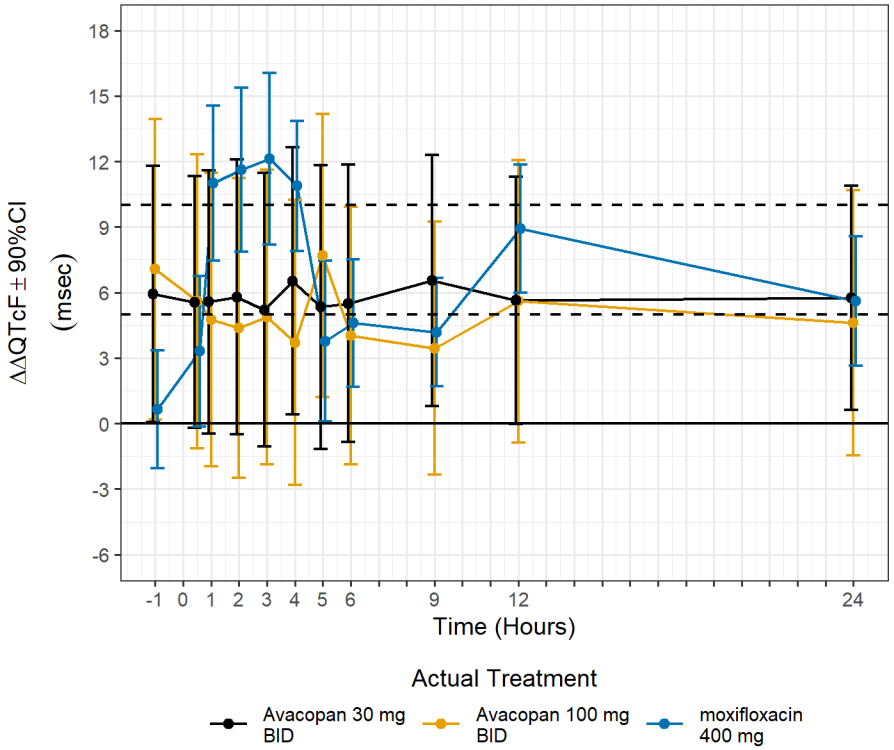
The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).



4.3.1.1 Assay sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure response analysis. Please see section 4.5.1.1 for details.

The same linear mixed model was used to analyze moxifloxacin effect by time for ΔQTcF. The time-course of changes in ΔΔQTcF is shown in Figure 1, and the expected mean effect with the largest lower bound is above 5 msec after Bonferroni adjustment for 4 time points as shown in Table 2.

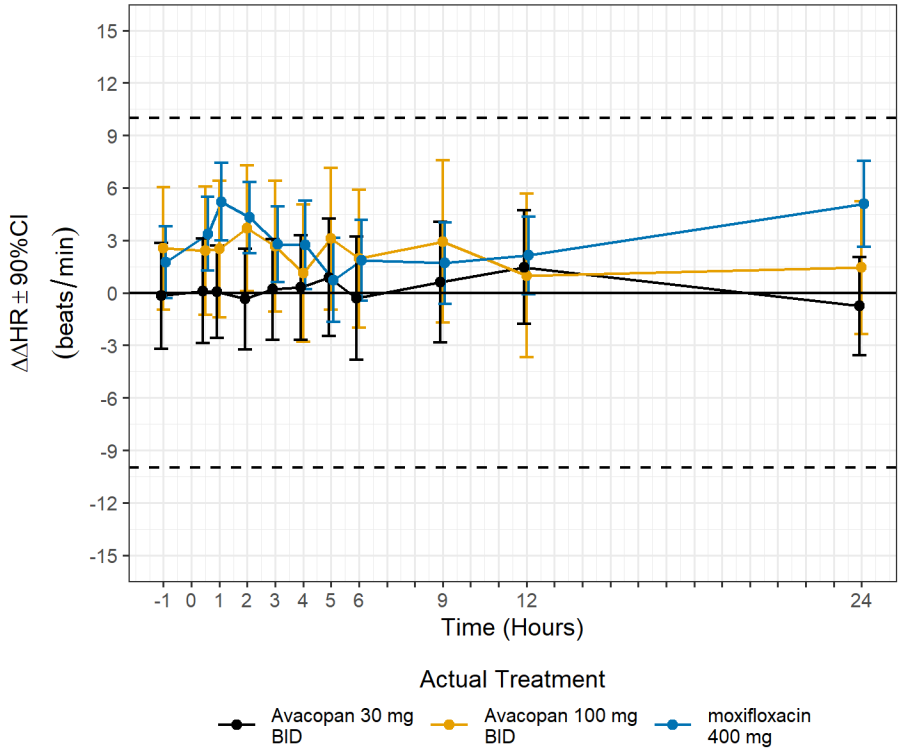
Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTcF (msec)	90.0% CI (msec)	97.5% CI (msec)
moxifloxacin 400 mg	29 / 28	4.0	10.9	(7.9 to 13.9)	(6.7 to 15.0)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

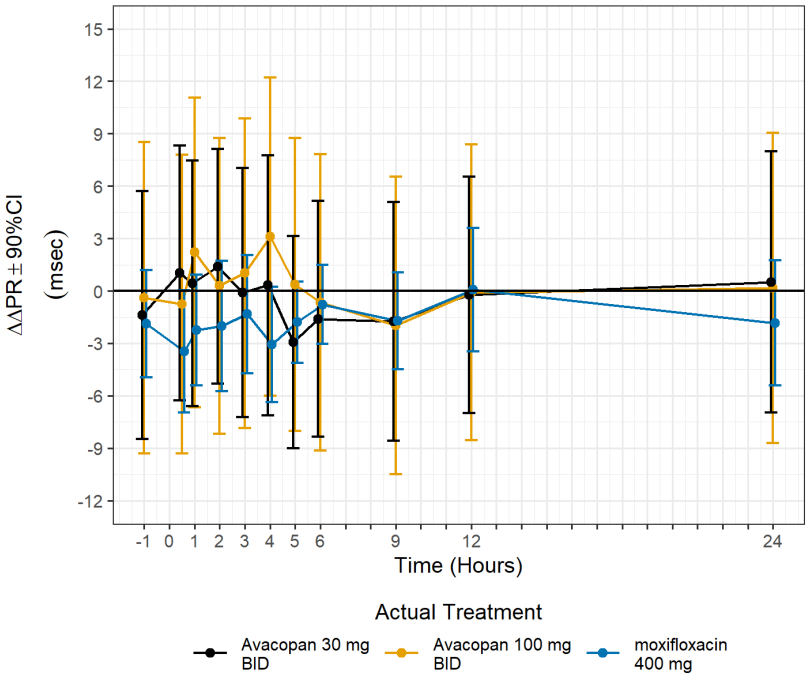
Figure 2: Mean and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

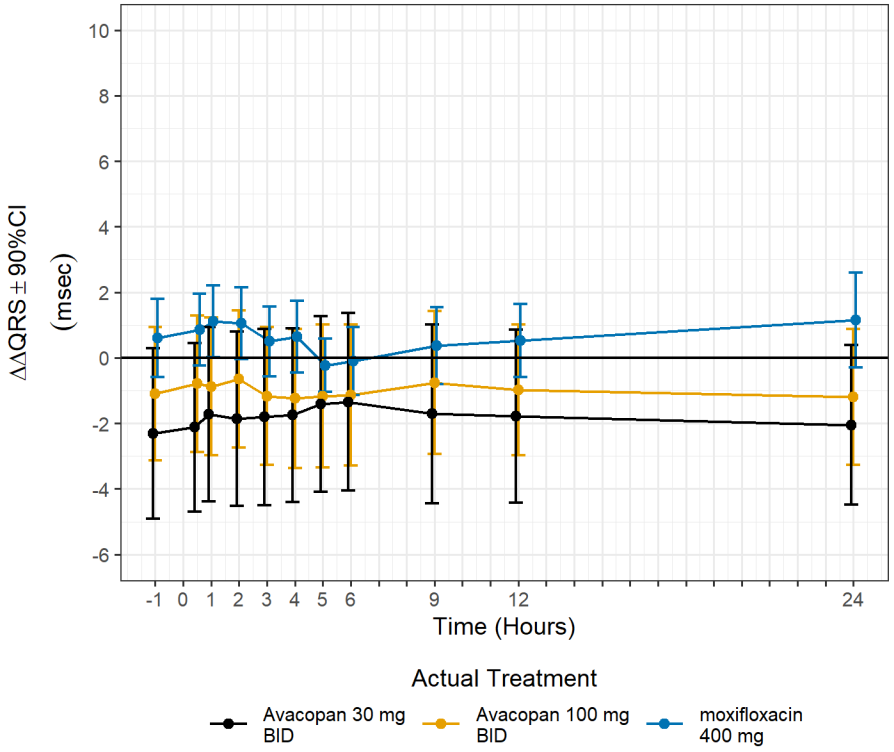
Figure 3: Mean and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

No subjects experienced QTcF above 480 msec or ΔQTc above 60 msec after receiving avacopan 30 mg BID or 100 mg BID.

4.4.2 HR

No subjects experienced HR above 100 bpm after receiving avacopan 30 mg BID or 100 mg BID.

4.4.3 PR

No subjects experienced PR above 220 msec with at least 25% increase over baseline after receiving avacopan 30 mg BID or 100 mg BID.

4.4.4 QRS

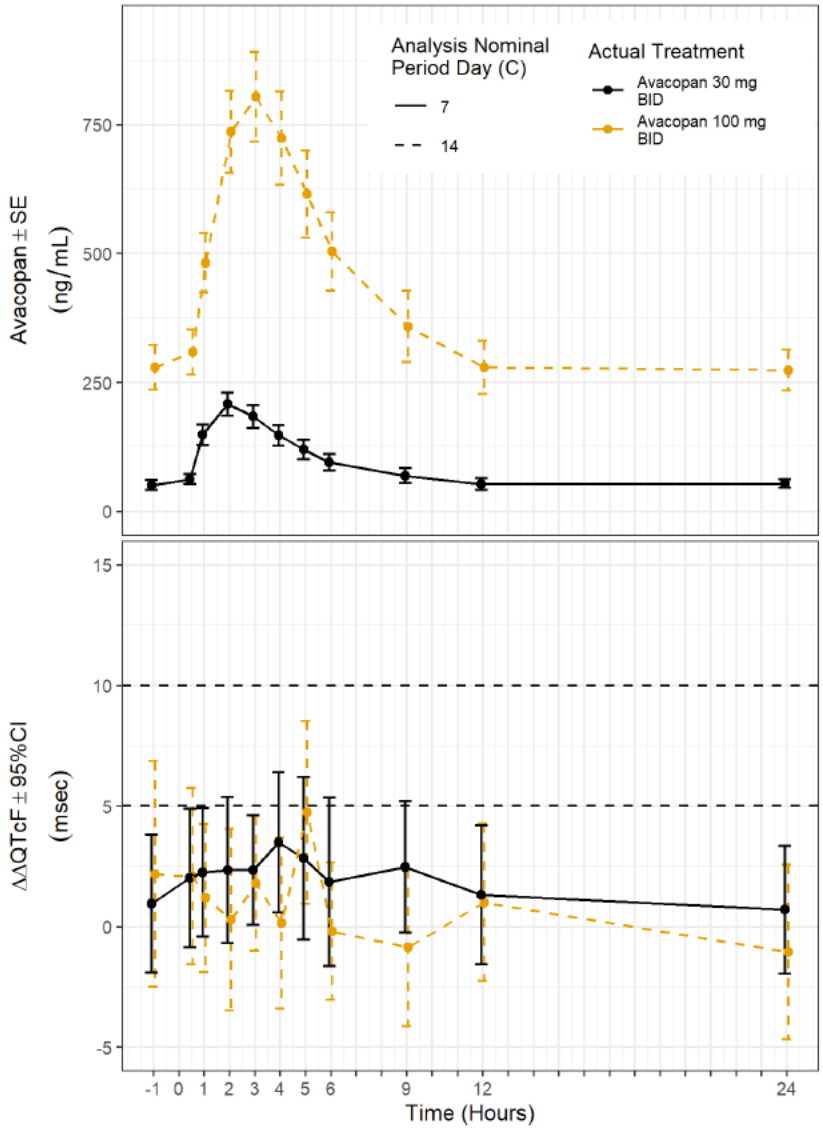
No subjects experienced QRS above 120 msec with at least 25% increase over baseline after receiving avacopan 30 mg BID or 100 mg BID.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of avacopan (and its M1 metabolite) and ΔQTcF. Exposure response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between avacopan (and its M1 metabolite) concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between avacopan concentration and ΔQTc and 3) presence of non-linear relationship.

Figure 5: Time course of drug concentration (top) and QTc (bottom)



An evaluation of the time-course of avacopan concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of avacopan (or its M1 metabolite) indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 8 bpm (Sections 4.3.2 and 4.4.2).

After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between avacopan concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship

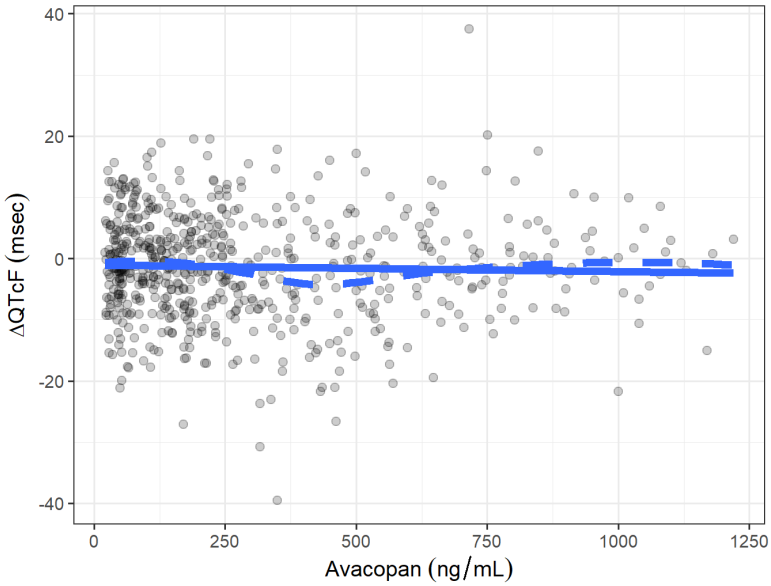
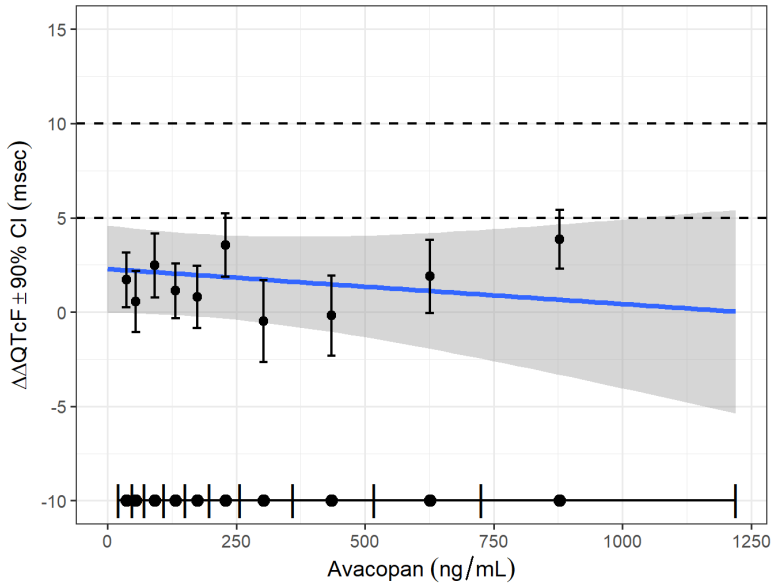


Figure 7: Goodness-of-fit plot for QTc



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 1 and Table 3.

Table 3: Predictions from concentration-QTc model

Actual Treatment	Analysis Nominal Period Day (C)	Avacopan (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Avacopan 30 mg BID	7	203.0	1.9	(-0.3 to 4.1)
Avacopan 100 mg BID	14	779.8	0.8	(-2.8 to 4.5)

Actual Treatment	Analysis Nominal Period Day (C)	Avacopan (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Avacopan 30 mg QD (per label)	*Predicted*	349.0	1.6	(-0.7 to 4.0)

Significant accumulation is observed at steady-state with the proposed therapeutic dose (30 mg twice daily; Racc: ~4-fold; Half-life: ~510 h) with the time to steady-state of ~13 weeks. Since the concentrations observed in the present study with 30 mg twice daily dose on Day 7 are lower than the expected the steady state concentrations under fed condition (~2.4-fold in 7 days vs. ~4-fold at steady-state; effective half-life: ~1.5 days), the effects were interpolated at the expected the steady state concentrations with the proposed maximum therapeutic dose (i.e., 350 ng/mL; Table 3). The peak concentration (Cmax: 780 ng/mL) observed with highest dose studied (i.e., 100 mg twice daily dose; for 7 days) offers ~2-fold margin over the therapeutic exposures (Cmax: ~350 ng/mL) associated with the maximum proposed dose at the steady-state and covers the worst-case scenarios.

4.5.1.1 Assay sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin and moxifloxacin placebo on Day 1 and Day 15 in a nested crossover design. The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (*data not shown*).

Figure 8: Goodness-of-fit plot for ΔΔQTc for moxifloxacin

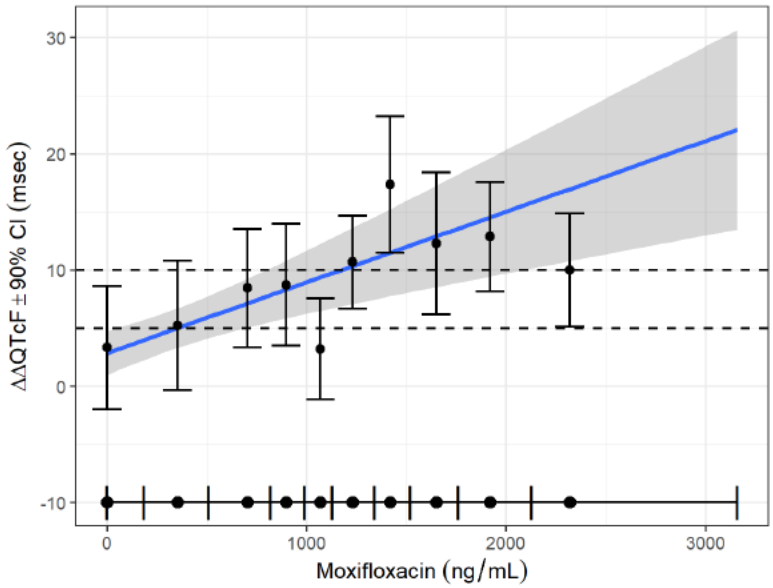


Table 4: Predictions from concentration-QTc model for moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	1,950.6	14.7	(9.5 to 19.9)

Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔQTcF and the plasma concentration of moxifloxacin. The goodness-of-fit plot for moxifloxacin is shown in Figure 8 and the predicted QTc at the geometric mean Cmax is listed in Table 4. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established.

Assay sensitivity was also established using by time analysis. Please see section 4.3.1.1 for additional details.

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/s/

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10/13/2020 04:42:04 PM

MICHAEL Y LI
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CHRISTINE E GARNETT
10/14/2020 08:46:18 AM