Food and Drug Administration
Docket No. FDA-2026-N-1321

Submission of Amgen Inc. And ChemoCentryx, Inc. In Support Of Summary Judgment Or A Hearing In Response To The Food And Drug Administration Center For Drug Evaluation And Research's Notice of Opportunity For A Hearing And Proposal To Withdraw Approval Of TAVNEOS® (Avacopan) Capsule, 10 mg (NDA No. 214487)

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Rheumatologist, Scleroderma, Vasculitis, and Myositis Center of Excellence, Hospital for Special Surgery; Associate Professor of Medicine at Weill Cornell Medicine
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LIST OF ABBREVIATIONS AND TERMS

2019 readjudication	A readjudication of nine (out of 331) patients performed in 2019 as part of the ADVOCATE trial
2026 readjudication	The de novo, independent, fully blinded readjudication recently performed by the Duke Clinical Research Institute
AAV	ANCA-associated vasculitis
AC	Adjudication Committee
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Amgen	ChemoCentryx, Inc. and its parent company, Amgen Inc.
ANCA	Anti-Neutrophil Cytoplasmic Antibody
AST	Aspartate aminotransferase
AVACOSTAR	A Post-Authorization Safety Study To Evaluate The Incidence Of Safety Events Of Interest In Subjects Treated With Avacopan For AAV
BVAS	Birmingham Vasculitis Activity Score
CBE-30	Changes Being Effected in 30 Days
CDER	Center for Drug Evaluation and Research
ChemoCentryx	ChemoCentryx, Inc.
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic Kidney Disease
CRBSI	Catheter-Related Bloodstream Infection
CRO	Clinical Research Organization
DCRI	Duke Clinical Research Institute
DILI	Drug-Induced Liver Injury
DILIrank	Drug-Induced Liver Injury Rank
DSC	Drug Safety Communication
EDC	Electronic Data Capture
ENT	Ear, Nose And Throat
ERDC	Eosinophilic & Rare Disease Cooperative
eTMF	Electronic Trial Master File
EULAR	European Alliances of Associations for Rheumatology
FDA Briefing Document	May 6, 2021 Advisory Committee Meeting Briefing Document

FDAMA	Food and Drug Administration Modernization Act of 1997
FDCA	Food, Drug, and Cosmetic Act
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GCs	Glucocorticoids
GPA	Granulomatosis with Polyangiitis
HCP	Healthcare Providers
HHF	Hospitalization for Heart Failure
HLA	Human Leukocyte Antigen
ICH	International Conference on Harmonization
IR	Information Request
ISS	Investigator-Sponsored Study
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MPA	Microscopic Polyangiitis
MPO	Myeloperoxidase
NI	Non-Inferiority
NDA	New Drug Application
NOOH	Notice of Opportunity for a Hearing
PAS	Prior Approval Supplement
PASS	Post-Authorization Safety Study
PBC	Primary Biliary Cirrhosis
PCP	Pneumocystis Pneumonia
PGHD	Pediatric Growth Hormone Deficiency
PMR	Post-Marketing Requirement
PMS	Post-Marketing Surveillance
PNH	Paroxysmal Nocturnal Hemoglobinuria
PR3	Proteinase 3
QC	Quality Control
RWD	Real-World Data
RWE	Real-World Evidence
SAP	Statistical Analysis Plan
SOC	Standard of Care

SRAP	Study Results Analysis Plan
USPI	U.S. Prescribing Information
VBDS	Vanishing Bile Duct Syndrome
Walton Report	A securities litigation-generated report from Dr. Marc Walton

I. INTRODUCTION AND EXECUTIVE SUMMARY

Amgen's mission is to serve patients. That mission is directly implicated by the April 30, 2026 proposal by the Center for Drug Evaluation and Research ("CDER") to withdraw approval of TAVNEOS® (avacopan), an orphan drug approved to address a critical unmet need for the treatment of adult patients with a rare disease, severe active anti-neutrophil cytoplasmic antibody ("ANCA")-associated vasculitis ("AAV"). People living with ANCA-AAV face a rare, serious and potentially life-threatening disease that can cause irreversible organ damage and has limited treatment options. For these patients, reducing exposure to steroids, with their known and serious toxicities, and sustaining remission remain important treatment goals. Since its approval, more than 8,000 people have been treated with TAVNEOS in the United States. The goal of our submission is to ensure that FDA has the fullest, most up-to-date scientific evidence for consideration before making a decision which directly impacts rare disease patients and their families.

In this submission, Amgen demonstrates that the totality of evidence—including a recently completed independent readjudication of the clinical trial at issue here, along with sensitivity analyses, real-world, and post-marketing evidence, and recently developed manuscripts—strongly supports that TAVNEOS plays a critical and otherwise unmet role in treating AAV and that CDER's withdrawal proposal should be rejected. Amgen is committed to supporting the patients who rely on TAVNEOS. We urge the Agency to take a forward-looking approach that focuses on the totality of the evidence of efficacy, which remains compelling.

Recognizing the significant consequences of taking TAVNEOS away from the patients who live with AAV, and given the legal impediments with CDER's position, Amgen respectfully submits that CDER should rescind its withdrawal proposal. Short of rescission, Amgen respectfully submits that judgment as a matter of law be issued in Amgen's favor or, in the alternative, that there are genuine and substantial questions of material fact and issues of exceptional public interest justifying a hearing. Amgen remains committed to working with FDA and CDER to find a path forward to ensure that TAVNEOS remains available to patients with AAV.

* * * * *

TAVNEOS was developed by ChemoCentryx, Inc. ("ChemoCentryx") and approved in the United States on October 7, 2021. Amgen Inc. acquired ChemoCentryx (together with Amgen Inc., "Amgen") on October 20, 2022, and is now its parent company.

The Role Of TAVNEOS In Treating A Serious, Life-Threatening Rare Disease

TAVNEOS is an orphan drug indicated for the treatment of adult patients with severe active AAV (granulomatosis with polyangiitis and microscopic polyangiitis)—a serious, life-threatening condition with profound unmet patient need. AAV is a group of rare autoimmune diseases that can strike at any age and affect virtually any organ system. It is associated with recurrent relapses, permanent organ damage, treatment-related toxicities, frequent hospitalizations, and significantly decreased health-related quality of life. Among other significant complications, AAV often irreversibly affects the kidneys and significantly increases

a patient's risk of dying. AAV can also traumatize the lungs, resulting in acute life-threatening events, such as diffuse alveolar hemorrhage with respiratory failure, and chronic respiratory impairment, such as interstitial lung disease. It can attack the eyes and ears, rendering patients blind and deaf.

Without treatment, mortality rates from AAV have been estimated to exceed 80-90% after the first year. There is no cure for AAV.

Prior to the approval of TAVNEOS, standard treatments focused on inducing remission by broadly suppressing a patient's immune system. These treatments were associated with significant risks, including cytopenias (e.g., life-threatening neutropenia), severe infection, malignancies, hemorrhagic cystitis, infertility, fatal infusion-related reactions, progressive multifocal leukoencephalopathy, bowel obstruction, and adverse cardiovascular reactions. These risks were compounded by the extensive use of glucocorticoids (steroids) to manage the disease. Though a traditional mainstay of AAV management, glucocorticoids present independent and serious risk of toxicities, including diabetes, dyslipidemia, hypertension, arrhythmia, osteoporosis, fracture, avascular necrosis, cataracts, glaucoma, adrenal insufficiency, anxiety, and depression.

This concern is underscored by the FDA's acknowledgement at the time of TAVNEOS's approval that a significant unmet need existed for patients with AAV. Specifically, the Agency acknowledged that, while some patients may initially respond to existing treatment options, "there remain patients who fail to achieve remission or who relapse after remission. In addition, there are significant toxicities associated with current treatments" such as "infection, myelosuppression, infertility, and malignancy."[1] As such, the Agency stated during its review of the NDA for TAVNEOS that "there remains an unmet need for additional therapeutic options for those who do not respond to currently available therapies, as well as a need for alternatives with fewer toxicities."[2] The same is true today.

Since its approval in 2021, TAVNEOS has facilitated a significant change in the AAV treatment paradigm and represents a meaningful improvement over the prior treatment options, such that it has become a part of the standard of care for the management of AAV. Reversion to the pre-TAVNEOS treatment paradigm, which would further limit treatment options for the AAV patient community, would disrupt continuity of patient care and place patients who currently rely on TAVNEOS at increased risk of relapses, progressive disease, and significant side effects and toxicities from alternative treatments, overall presenting serious clinical challenges. Taking TAVNEOS away from patients who rely on it would, in short, be detrimental to the thousands of patients who currently rely on it to control their debilitating disease—it would make managing this serious disease more difficult, not easier, and be a disservice to the very patients the healthcare system is meant to protect.

Agency leadership has recognized the need for flexibility in the context of rare diseases, explaining that "developing drugs for rare diseases can make it difficult or even impossible to

[1] CDER, *Multi-Disciplinary Review* (NDA 214487) at 40-41, 48 (Oct. 12, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214487Orig1s000MultidisciplineR.pdf ["CDER Multi-Disciplinary Review"].
[2] *Id.* at 35.

generate substantial evidence of safety and efficacy—as required by statute—using multiple traditional clinical trials. Instead, rare disease drug developers and the FDA must work together to identify alternative methods for meeting the statutory standard that are both rigorous and viable for rare disease populations."[3] The Agency should continue to exercise such flexibility here.

Withdrawal Is Not Warranted On Either Ground Raised By CDER

On April 30, 2026, CDER published a Notice of Opportunity for a Hearing ("NOOH") proposing to withdraw approval of the new drug application (NDA 214487) for TAVNEOS (avacopan) capsule, 10 milligrams (mg). CDER rests its proposal on two grounds. First, CDER invokes Section 505(e)(3) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), contending that new information, evaluated together with the evidence available at the time of TAVNEOS's approval, shows a lack of substantial evidence of effectiveness. Second, CDER invokes FDCA Section 505(e)(5), contending that the TAVNEOS New Drug Application ("NDA") submitted by ChemoCentryx contained untrue statements of material fact.

Importantly, CDER does not propose withdrawal on the basis of safety.

CDER asserts that the data from the ADVOCATE trial, which was the single registrational trial supporting approval, can no longer be relied on to provide evidence of effectiveness. CDER cannot meet the statutory criteria on which its withdrawal proposal relies. Section 505(e)(3) requires examining the totality of the evidence to establish effectiveness. Here, that evidence includes not only the ADVOCATE trial, in which a readjudication of nine (out of 331) patients was performed in 2019 as part of the trial ("2019 readjudication"), but also the readjudication recently performed by the Duke Clinical Research Institute ("DCRI"), which is part of the Duke University School of Medicine ("2026 readjudication"). It also includes sensitivity analyses from the ADVOCATE trial, real-world evidence ("RWE") and post-marketing experience, and must consider the serious unmet need in AAV. Taken together, the totality of the evidence does not support CDER's position. Nor can CDER satisfy the criteria for withdrawal under Section 505(e)(5). That section of the FDCA requires CDER to identify an actual untrue statement of material fact in the TAVNEOS NDA, not merely dispute the methodology or processes used or disagree with how prespecified data review was conducted or described. CDER cannot make this showing either. In this submission, Amgen provides evidence—including new manuscripts[4] and expert declarations—that further demonstrates Amgen's entitlement to judgment as a matter of law or that, at a minimum, there are genuine and substantial questions of material fact and an overwhelming public interest justifying a hearing.

First, Amgen disagrees with CDER's contention that there is a lack of substantial evidence of effectiveness for TAVNEOS. As extensively detailed in this response, the totality of the evidence supports the continued availability of TAVNEOS based on substantial evidence of

[3] FDA, *FDA Advances Rare Disease Drug Development with New Evidence Principles* (Sept. 3, 2025), https://www.fda.gov/news-events/press-announcements/fda-advances-rare-disease-drug-development-new-evidence-principles.
[4] *See infra* Section II.D.

its efficacy.[5] The ADVOCATE trial was adequate and well controlled and the data it generated remain valid. The results of ADVOCATE demonstrated that TAVNEOS was at least as effective as the prednisone taper for induction and maintenance of remission through 52 weeks, and that patients receiving TAVNEOS had lower risk of relapse and better kidney and quality of life outcomes, while receiving substantially less glucocorticoid exposure and experiencing clinically meaningful reductions in glucocorticoid toxicity when compared to those treated with a standard prednisone taper. Contrary to CDER's allegations, those results were not "manipulated." Rather, the 2019 readjudication followed a prespecified procedure to correctly and consistently apply prespecified trial rules to potentially erroneously classified data. No underlying clinical data were altered. The question presented to the blinded adjudication committee at that time was whether the protocol's prespecified endpoint definitions were properly applied to the unaltered patient data. Additionally, since TAVNEOS was approved in 2021, a growing body of real-world evidence and patient experience further demonstrate effectiveness consistent with the results of the ADVOCATE trial.

The results of the recently completed 2026 readjudication by an independent well-respected organization strengthen confidence in TAVNEOS's efficacy by demonstrating non-inferiority at both Week 26 and Week 52. In this analysis, the treatment effect of TAVNEOS at Weeks 26 and 52 was similar to the results of the 2019 readjudication, which again supports that the trial is providing reliable evidence of effectiveness.

The non-inferiority finding indicates that "TAVNEOS can achieve comparable disease control while avoiding months-long exposure to glucocorticoids and their associated side effects and toxicities"—such as obesity from weight gain, diabetes, hypertension, and fracture—"making TAVNEOS valuable for patient care," as stated in the Declaration of Dr. Lindsay S. Lally, Rheumatologist in the Scleroderma, Vasculitis, and Myositis Center of Excellence, Hospital for Special Surgery and Associate Professor of Medicine at Weill Cornell Medicine.[6] The 2019 readjudication—which involved a total of nine patients from both trial arms (out of the 331 total patients in ADVOCATE)—does not diminish or alter the value of TAVNEOS for patient care. Instead, this readjudication applied prespecified trial rules for primary endpoint measurement that were set out in the protocol and Statistical Analysis Plan ("SAP"). These trial documents, along with documentation of the changes, were included in the electronic Trial Master File ("eTMF"), which is available for review. It is unfortunate that information about the 2019 readjudication—which Amgen did not learn about until years later in private securities litigation—was not also communicated in the NDA submission. Amgen acknowledges that the 2019 readjudication, which occurred prior to Amgen's acquisition of ChemoCentryx, would not

[5] Appendix A further provides "an analysis of the data upon which [Amgen] relies" pursuant to 21 C.F.R. § 314.200(d)(3). Amgen incorporates by reference its prior submissions to the Agency and materials that are part of the Agency's files for the TAVNEOS NDA, including (1) NDA 214487 and all supplements, information request responses, raw data, protocols, and financial certification or disclosure statements submitted to the NDA; (2) all Agency approval letters, review documents, and approved labeling; (3) Amgen's August 22, 2025 Response to FDA Requests Dated July 23, 2025, and all associated exhibits; and (4) all materials from the May 6, 2021 Advisory Committee Meeting, including FDA's Briefing Document and the Erratum that FDA published with respect thereto. *See* 21 C.F.R. § 314.200(c)(1)(ii), (2), (d). Appendix E provides, for studies identified as in progress in the Request for Hearing, a brief status report of the studies, and the protocols and lists of participating investigators are attached pursuant to 21 C.F.R. § 314.200(c)(2).

[6] *See* Declaration of Lindsay S. Lally, M.D. (July 21, 2026) (Appendix B.1.) ["Lally Declaration"].

align with the approach Amgen would have taken. That does not, however, justify CDER's current position or amount to an untrue statement in the NDA. Importantly, the 2019 readjudication was conducted to correct a small number of errors in the applications of prespecified trial rules (including one manual transcription error).

In January 2026, when CDER asked Amgen to voluntarily withdraw TAVNEOS, Amgen offered to have the ADVOCATE trial data readjudicated, anew and independently. CDER did not agree that a readjudication of the ADVOCATE data could address the questions the Center had regarding the efficacy of TAVNEOS. Amgen disagreed, and commenced a de novo, independent, fully blinded readjudication of the ADVOCATE primary endpoint data conducted by DCRI. As detailed in Appendix A (Table 1) and by Dr. Robert D. Gibbons—Blum-Riese Professor of Biostatistics and Pritzker Scholar at the University of Chicago, Director of the Center for Health Statistics at the University of Chicago, and fellow of the American Statistical Association, where he co-founded the Mental Health Statistics section—the 2026 adjudication does not render the ADVOCATE trial statistically unreliable; nor does the 2026 readjudication introduce Type 1 error.[7] As explained by Dr. Gibbons, the independent readjudication that DCRI conducted is fundamentally distinct from the standard multiplicity issues encountered in repeated analyses of clinical trial data, and multiplicity concerns are not relevant in this case, because there was no unplanned hypothesis test for the primary endpoint.[8]

Moreover, in other circumstances, CDER has acknowledged the proper role of readjudications of clinical data with appropriate safeguards[9] and has relied on readjudicated data for regulatory decision-making, including decisions to approve therapeutic products, for instance, where concerns were identified with respect to the reliability of the original adjudication.[10] In certain cases, CDER has gone further and even conducted the readjudication process itself, then using that CDER-conducted readjudication to inform new drug approval. We are aware of no evidence in publicly available review packages demonstrating that CDER required multiplicity adjustments or even raised multiplicity concerns in precedents in which readjudicated results supported a determination of efficacy. Consideration of the 2026 readjudication to inform an assessment of the efficacy of TAVNEOS is equally appropriate here, and failure of CDER to do so arbitrarily risks inconsistency with precedent and making a consequential regulatory decision on the basis of less than the totality of the evidence.

As demonstrated in this submission, the totality of the evidence supports the efficacy of TAVNEOS. The ADVOCATE trial, including the results of the 2026 readjudication, was an adequate and well controlled study that provides substantial evidence of effectiveness, rendering CDER's concerns about the 2019 readjudication moot. The totality of the evidence, including real-world evidence and post-marketing patient experience—as reflected in, among other things, recently developed manuscripts and patient and provider testimonials—further supports this conclusion. Since approval, more than 8,000 U.S. patients with AAV have been treated with avacopan. Real-world evidence across comparative studies, large cohorts, and post-marketing

[7] *See* Declaration of Robert D. Gibbons, Ph.D. at 22-23 (July 22, 2026) (Appendix B.2) ["Gibbons Declaration"].
[8] *See id*. at 5, 22-23.
[9] CDER, Manual of Policies and Procedures 6010.6: *The Use of Clinical Source Data in the Review of Marketing Applications* (Oct. 18, 2010), https://www.fda.gov/files/about%20fda/published/The-Use-of-Clinical-Source-Data-in-the-Review-of-Marketing-Applications.pdf.
[10] *See infra* Section IV.A.2.d.

studies consistently provides data supporting TAVNEOS's role in achieving remission, reducing relapse, minimizing glucocorticoid exposure, and supporting kidney recovery. At a minimum, the scientific disagreements outlined in this submission, and the needs of the 3,500 American patients who currently depend on TAVNEOS,[11] demonstrate that there is a genuine and substantial issue of material fact on this issue, and it is in the public interest to grant a hearing so that the scientific disagreements can be fully evaluated and addressed.

Importantly, CDER has not sought withdrawal on the basis of safety, a separate ground under the statute, and withdrawal on that basis would be similarly unsupportable. The safety profile of TAVNEOS is well characterized and manageable, as explained in the Declaration of Dr. Naga P. Chalasani, David W. Crabb Professor of Gastroenterology and Hepatology and Adjunct Professor of Anatomy, Cell Biology & Physiology at Indiana University School of Medicine.[12] Hepatotoxicity risks, including Drug-Induced Liver Injury ("DILI"), have been known since prior to approval, and since approval, have been included on the FDA-approved labeling, along with appropriate guidance for managing and monitoring these risks.

When vanishing bile duct syndrome ("VBDS") cases emerged in the post-marketing setting outside the United States,[13] Amgen proactively submitted, in April 2024, a prior approval supplement ("PAS") providing a proposed labeling update to include VBDS in TAVNEOS's labeling.[14] Although CDER acknowledged the submission six months later, in October 2024, and requested additional information, which Amgen submitted in November 2024,[15] CDER did not act on the PAS. In fact, CDER did not take any action on this issue until almost a year and a half later on March 31, 2026—and even then only after it had already communicated that it would seek to withdraw TAVNEOS on grounds other than safety[16]—when CDER issued a Drug Safety Communication ("DSC") regarding serious liver injuries reported in non-U.S. patients taking TAVNEOS.[17] Notably, the March 2026 DSC cited only data through October 2024. While CDER did not require or request any update to TAVNEOS's label, Amgen has since implemented labeling changes addressing VBDS by its own initiative through a Changes Being

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[11] As of February 2026.

[12] Declaration of Dr. Naga P. Chalasani (July 22, 2026) (Appendix B.3) ["Chalasani Declaration"].

[13] VBDS cases are rare and concentrated in Japan, where Amgen is not the marketing authorization holder; no confirmed VBDS cases have been reported to date from the United States or Europe. As described by Dr. Chalasani, it is hypothesized that certain populations may have a genetic propensity impacting susceptibility to liver injury. In addition, historical labeling differences in monitoring and stopping criteria between the Japan labeling for TAVNEOS and the labeling that has always been in force in the U.S. could play a role in the differences seen in the frequency or severity of hepatic events in the Japanese population.

[14] *See* Amgen, *Prior Approval Supplement* (NDA 214487) (Apr. 24, 2024) (proposing amendment to USPI to include risk of vanishing bile duct syndrome).

[15] *See* Amgen, *Response to 28 October 2024 Information Request Regarding VBDS PAS* ["Vanishing Bile Duct Syndrome Prior Approval Supplement"] (NDA 214487/S-05) (Nov. 27, 2024) (responding to FDA Information Request).

[16] As explained in greater detail in Section II.F, CDER first requested over a teleconference on January 16, 2026, that Amgen voluntarily withdraw the TAVNEOS NDA. On January 28, 2026, Amgen informed CDER that it respectfully declined to voluntarily withdraw and waive its right to request a hearing.

[17] *See* FDA, *FDA Identifies Cases of Serious Liver Injury in Patients Taking Tavneos (avacopan) for Severe Active Anti-neutrophil Cytoplasmic Autoantibody (ANCA)-associated Vasculitis* (Mar. 31, 2026), https://www.fda.gov/drugs/drug-safety-communications/fda-identifies-cases-serious-liver-injury-patients-taking-tavneos-avacopan-severe-active-anti.

Effected in 30 Days ("CBE-30") supplement, which went into effect on May 29, 2026.[18] And when CDER issued a follow-up question about the CBE-30 in June—after the new label had already gone into effect—Amgen responded eight days later. In any event and notwithstanding its March 2026 DSC, as noted above, CDER has not sought to withdraw TAVNEOS on the basis of safety.

Second, Section 505(e)(5) applies only if "the [TAVNEOS new drug] application contains any untrue statement of material fact."[19] But, as detailed below, none of the statements identified by CDER is untrue. And to the extent CDER is asserting that certain information should have been included in the NDA or other documents, there are no regulations (and CDER points to none) that required ChemoCentryx to do so.[20] ChemoCentryx made all required disclosures. CDER's position thus fails as a matter of fact and law.

In The Interest Of Doing What Is Right For Patients, CDER Should Take A Forward-Looking Approach, Engage With The Applicant To Discuss The 2026 Readjudication, And Rescind The NOOH

Amgen respectfully requests that CDER reconsider the NOOH in light of the 2026 readjudication, which confirms efficacy, along with the totality of the evidence. Accordingly, CDER should rescind the NOOH and instead engage in a science- and patient-focused dialogue with Amgen. Amgen remains hopeful that such a process still could obviate the need for a hearing. Rather than moving forward with withdrawal, or even with a hearing, the far better course in the interest of patient care would be for FDA to rescind the NOOH and engage in a productive exchange about the totality of the evidence supporting continued approval.

The Agency previously has rescinded NOOHs based on information that becomes available after issuance of the NOOH; in one case, explicitly concluding that rescission was appropriate because submission of additional data regarding an application rendered the application approvable and "effectively moot[ed] the request for hearing."[21] Here, CDER initially requested withdrawal based only on its view of the purported lack of evidence of efficacy—not a position that the NDA contained untrue statements.[22] Amgen sought to engage with CDER to identify a productive path forward, requesting that CDER await the results of the 2026 readjudication.[23] CDER summarily declined Amgen's proposal and added the alleged

[18] Because the labeling updates contained in the CBE-30 supplement superseded those provided in Amgen's 2024 PAS, Amgen withdrew the PAS.
[19] 21 U.S.C. § 355(e)(5).
[20] *See infra* Section IV.B.2.
[21] *See, e.g.*, 43 Fed. Reg. 14739, 14739 (Apr. 7, 1978) ("In response to this notice, the firm filed a hearing request . . . . The firm also filed additional data. Subsequently, on the basis of the additional data, the NDA was approved by letter . . . . This action effectively moots the request for hearing.").
[22] Email from Susie Choi, Pharm.D., Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation, to [redacted], Amgen (Jan. 16, 2026) (citing 21 U.S.C. § 355(e)(3) only).
[23] Letter from Jay Bradner, M.D., Executive Vice President, Research & Development, to Tracy Beth Høeg, M.D., Ph.D., Acting Director, CDER (Jan. 28, 2026) ["January 28 Letter"]. Unfortunately, this was a period of perhaps unprecedented turmoil within CDER, and thus there has been an apparent lack of continuity in this dialogue. *See* Melody Schreiber, *FDA Turmoil Deepens as Top Drug Chief Departs Claiming She Was Fired*, THE GUARDIAN (May 15, 2026), https://www.theguardian.com/us-news/2026/may/16/fda-tracy-beth-hoeg-drug-chief-departs; Lizzy

FDCA 505(e)(5) misstatements ground for withdrawal to the NOOH only *after* Amgen declined to waive its Due Process right to dispute the withdrawal.[24] If the additional ground truly reflected a genuine and independent basis for withdrawal, it is unclear why it was not raised as part of the Center's initial request to the company to voluntarily withdraw, given that it is grounded in the same information that the Agency already had.

It is also worth noting that CDER unfortunately rushed to publish the NOOH without observing fundamental Due Process and Freedom of Information Act ("FOIA") protocols, including granting a reasonable opportunity to propose appropriate redactions, despite having been notified by Amgen that the NOOH contained (1) confidential commercial information and (2) patient information. Although Amgen had informed CDER of the ongoing 2026 readjudication, the Center elected to disclose, in the NOOH, ADVOCATE patient ID numbers, patient treatment group assignments, and adjudication results, despite Amgen's efforts to inform the Agency that this information should be redacted to avoid the risk of unblinding and biasing the 2026 readjudication. While Amgen acted quickly to secure confirmation that DCRI remained fully blinded, the degree to which CDER risked jeopardizing Amgen's efforts to generate further data regarding TAVNEOS's benefit-risk profile was surprising and disappointing. Finally, Amgen is concerned that the tone of the NOOH is inconsistent with the impartial consideration that should accompany Amgen's exercise of its Due Process and FDCA rights to request a hearing and to have these important issues addressed by the Agency. Patients, physicians, and Amgen deserve a fair and impartial process that focuses on the science and what is in the best interest of patients. Accordingly, the most productive path forward would be for CDER to rescind the NOOH and to engage in a science- and patient-focused consideration of the totality of the evidence.

If CDER Does Not Rescind The NOOH, Amgen Is Entitled To Judgment As A Matter Of Law Or To A Hearing Before An Advisory Committee

Because CDER cannot satisfy the statutory criteria for either of the bases it cites for withdrawal, Amgen is entitled to judgment as a matter of law on both grounds. In the alternative, and at a minimum, Amgen's submission plainly establishes multiple genuine and substantial issues of material fact and significant public interest warranting a hearing on both grounds for withdrawal set forth by CDER in its NOOH:

- Whether the totality of the evidence supports the continued positive benefit-risk profile of TAVNEOS in light of the needs of the rare-disease patients who use it
- Whether the ADVOCATE trial and other available evidence provide substantial evidence of effectiveness following readjudication
- Whether continued approval is warranted based on the 2026 readjudication confirmation of efficacy

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Lawrence, *FDA Leadership Shakeup Widens Following Makary's Departure*, STAT+ (May 15, 2026). https://www.statnews.com/2026/05/15/fda-leadership-vacuum-tracy-beth-hoeg-resigns-drug-center-post/.

[24] *See* 91 Fed. Reg. 23278, 23279 (Apr. 30, 2026) (citing both 21 U.S.C. § 355(e)(3) and 21 U.S.C. § 355(e)(5)).

- Whether the NDA contained an untrue statement of material fact

- Whether the 2026 readjudication and totality of the evidence give sufficient reassurance of efficacy to maintain patient access

- Whether the interests of rare-disease patients who have relied on TAVNEOS for years, and the unmet need that would result in the event of a withdrawal, warrant maintained approval

In addition, even assuming purely for the sake of argument that there was no genuine and substantial issue of fact, a hearing still would be warranted given the overwhelming public interest in this issue.[25] FDA has emphasized the importance of regulatory flexibility to meet the needs of rare-disease patients, and CDER's NOOH presents a significant public health question of whether this therapy should be taken away from patients in light of the confirmation of efficacy in the 2026 readjudication and the totality of the evidence. CDER's rationale for withdrawal does not outweigh the compelling public health interests, including the needs of physicians and patients who have long relied on TAVNEOS. At a minimum, CDER's NOOH raises a genuine issue that warrants full consideration, as withdrawal of TAVNEOS would recreate a significant unmet need in this patient population.

Having established its entitlement to a hearing by showing genuine and substantial issues of fact[26] and compelling public interest, Amgen respectfully exercises its option to "request . . . [a] hearing before a public advisory committee under part 14" as an alternative form of hearing.[27] This request is submitted "in the form of a waiver of the right to request a hearing *conditioned on an alternative form of hearing*."[28] A Part 14 hearing is warranted given the significant public interest in having an advisory committee consider these crucial and life-altering issues for rare-disease American patients living with AAV. Amgen's submission of a request "in the form of a citizen petition" as required by 21 C.F.R. Part 12 is provided as Appendix D.[29]

II. BACKGROUND

A. AAV Is A Severe Rare Disease With Ongoing Unmet Patient Need

AAV is a group of rare and serious diseases in which the immune system attacks blood vessels and can damage major organs. The two most common types of AAV are granulomatosis

[25] *See* 21 C.F.R. § 314.200(g)(6).
[26] *See Vanda Pharms., Inc. v. FDA*, 150 F.4th 563, 567 (D.C. Cir. 2025).
[27] 21 C.F.R. § 12.32(a)(2); *cf.* Letter from Namandjé N. Bumpus, Ph.D, Chief Scientist, FDA, to David M. Fox, Hogan Lovells LLP, and Donna Katz, Office of the Chief Counsel, FDA (Docket No. FDA-2021-N-0874) (Mar. 24, 2023), https://www.regulations.gov/document/FDA-2021-N-0874-0070 (granting a request for a public hearing before an advisory committee in lieu of a formal evidentiary hearing) ["March 2023 Letter from Dr. Bumpus"].
[28] 21 C.F.R. § 12.32(b)(3)(ii) (emphasis added).
[29] *See* 21 C.F.R. § 12.32(b)(2); *see also* March 2023 Letter from Dr. Bumpus, *supra* note 27 (clarifying that FDA interprets the requirement to submit in the form of a citizen petition as a requirement of form only that does not necessitate creation or consideration of a separate citizen petition docket).

with polyangiitis ("GPA") and microscopic polyangiitis ("MPA").[30] Severe AAV can be life-threatening, with five-year mortality rates over 20%. Without treatment, mortality rates have been estimated to exceed 80-90% after the first year.[31] Even with treatment, many patients face ongoing health problems and major impacts on daily life. AAV is associated with significant and permanent organ damage, treatment-related toxicities, frequent hospitalizations, recurrent relapses, and significantly decreased health-related quality of life.[32] AAV has high mortality and morbidity, and there remains no cure for the disease. It is a disease with significant, ongoing unmet medical need.

As detailed in Appendix A (Section 4.1), AAV can strike at any age, though patients are most commonly diagnosed with AAV in mid-to-late adulthood (around 50-60 years old). Diagnosis itself is challenging and typically occurs only after a prolonged and complex process, as early symptoms are vague and often mistaken for common conditions such as infections or allergies. Most patients initially present in primary care and are referred across multiple specialists, including ear, nose and throat ("ENT"), pulmonology, nephrology, or rheumatology, depending on their symptoms. Because AAV is a chronic, life-long condition, diagnosis also marks the beginning of ongoing disease management, including long-term monitoring, maintenance therapy, and the risk of relapse even after remission is achieved.

The clinical burden of AAV is profound and multisystemic, with kidney involvement representing a key determinant of long-term outcomes. Kidney involvement is nearly universal in MPA and occurs in approximately 70% of patients with GPA.[33] It can progress to chronic kidney disease ("CKD") and end-stage kidney disease, and is associated with excess mortality. AAV can traumatize the lungs. Pulmonary complications include acute and life-threatening events such as diffuse alveolar hemorrhage and interstitial lung disease, which may both lead to respiratory failure. In addition, neurologic, ocular, and cutaneous disease further contribute to functional impairment, frequent hospitalization, and irreversible damage. Relapse remains a defining feature of AAV, with 30-50% of patients relapsing within five years despite maintenance therapy; each relapse can result in organ damage and typically necessitates renewed immunosuppression using glucocorticoids. As described in greater detail in Section II.B, below, glucocorticoids are associated with significant treatment-related toxicities impacting patient quality of life.

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[30] Baptiste Chevet et al., *Diagnosing and Treating ANCA-Associated Vasculitis: An Updated Review for Clinical Practice*, 62 RHEUMATOLOGY 1787 (2023).

[31] Beatriz Sánchez Álamo, *Long-Term Outcomes and Prognostic Factors for Survival of Patients with ANCA-Associated Vasculitis*, 38 NEPHROLOGY DIALYSIS TRANSPLANTATION 1655, 1656 (2023); Ju Ann Tan et al., *Mortality in ANCA-Associated Vasculitis: A Meta-Analysis of Observational Studies*, 76 ANNALS RHEUMATIC DISEASES 1566 (2017).

[32] Baptiste Chevet et al., *supra* note 30; Loïc Guillevin et al., *Rituximab Versus Azathioprine for Maintenance in ANCA-Associated Vasculitis*, 371 NEJM 1771 (2014); A. Richard Kitching et al., *ANCA-Associated Vasculitis*, 6 NAT. REVS. DISEASE PRIMERS 71 (2020); Luca Degli Esposti et al., *Profile, Healthcare Resource Consumption, and Related Costs in ANCA-Associated Vasculitis Patients: A Real-World Analysis in Italy*, 40 ADVANCES THERAPY 5338 (2023); Karina Raimundo et al., *Clinical and Economic Burden of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in the United States*, 42 J. RHEUMATOLOGY 2383 (2015).

[33] Renato A. Sinico et al., *Renal Involvement in Anti-Neutrophil Cytoplasmic Autoantibody Associated Vasculitis*, 12 AUTOIMMUNITY REVS. 477 (2013).

In addition to organ damage, AAV is associated with marked and persistent impairment in health-related quality of life. Patients commonly report reduced physical functioning, fatigue, pain, and limitations in social and occupational participation, even during periods of clinical remission. Psychological comorbidities such as anxiety and depression are frequent and further amplify disease burden. Taken together, irreversible organ injury, high relapse rates, treatment-related toxicity, and impairment of quality of life underscore the substantial unmet medical need in AAV and the importance of therapeutic strategies that achieve disease control while minimizing the adverse long-term effects of glucocorticoid exposure.

B. TAVNEOS Offers A Significant Improvement Over Other Treatment Options

Prior to the approval of TAVNEOS in 2021, standard treatment of severe AAV focused on inducing disease remission[34] to prevent irreversible organ damage by suppressing a patient's immune system through use of glucocorticoids, which are powerful tools for immunosuppression, and either rituximab or cyclophosphamide. Among the most consequential side effects of glucocorticoids on patients' emotional and physical well-being are their metabolic effects, including weight gain and lipodystrophy; psychiatric effects, including anxiety, depression, and insomnia; and dermatologic effects, including thinning of the skin, skin tears, and easy bruising. Beyond these, other common toxicities associated with glucocorticoids include diabetes, dyslipidemia, hypertension, arrhythmia, osteoporosis, fracture, avascular necrosis, cataracts, glaucoma, and adrenal insufficiency. In addition to these treatment-related toxicities, many patients on these treatments fail to achieve sustained remission and experience high rates of AAV relapse as well as limited improvement in kidney function.

TAVNEOS represents a significant shift in the AAV treatment paradigm and a meaningful improvement over prior treatment options. Since its approval in 2021, the use of TAVNEOS in the management of AAV has become well established. As described in greater detail in Appendix A (Section 4.3), major international clinical guidelines—including the European Alliances of Associations for Rheumatology ("EULAR") recommendations,[35] Kidney Disease Improving Global Outcomes ("KDIGO") 2024 Clinical Practice Guideline for the management of AAV,[36] and most recently, the Kidney Disease Outcomes Quality Initiative ("KDOQI") commentary[37]—recognize the role of avacopan in contemporary AAV management and reflect growing expert consensus that such therapies capable of reducing cumulative glucocorticoid exposure while maintaining disease control are critical in the treatment paradigm for AAV.[38] These guidelines highlight the important role of TAVNEOS in the treatment

[34] Remission has been variably defined but is typically characterized by the absence of disease activity (as measured by the Birmingham Vasculitis Activity Score ("BVAS")) on minimal (*e.g.*, ≤ 5 mg/day) or no glucocorticoids.
[35] Bernhard Hellmich et al., *EULAR Recommendations for the Management of ANCA-Associated Vasculitis: 2022 Update*, 83 ANNALS RHEUMATIC DISEASES 30 (2024).
[36] Jürgen Floege et al., *KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis*, 105 KIDNEY INT'L S71 (2024).
[37] Salem Almaani et al., *KDOQI US Commentary on the KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis*, 87 AM. J. KIDNEY DIS. 597 (2026).
[38] *See also* Bernhard Hellmich et al., *EULAR Recommendations for the Management of ANCA-Associated Vasculitis: 2022 Update*, 83 ANNALS RHEUMATIC DISEASES 30 (2024).

armamentarium for AAV as a safe and effective therapy capable of reducing cumulative glucocorticoid exposure while maintaining disease control.

Approximately 3,500 patients in the United States[39] currently rely on TAVNEOS to treat their AAV. Reversion to the prior treatment paradigm would place these patients at increased risk of these significant side effects, disrupt their continuity of care, and present serious clinical challenges.

C. The ADVOCATE Trial

ChemoCentryx, the NDA holder for TAVNEOS and the sponsor of the ADVOCATE trial, is a biopharmaceutical company, founded in 1997, that focused on developing new medications to treat autoimmune diseases, inflammatory disorders, and cancer. At the time of its acquisition by Amgen on October 20, 2022, ChemoCentryx was a small company of fewer than 200 employees. ChemoCentryx served as the sponsor throughout avacopan's clinical development program. In May 2014, avacopan received orphan drug designation for the treatment of AAV. In March 2017, following completion of two Phase 2 trials, ChemoCentryx initiated the ADVOCATE trial, the pivotal trial to support approval of avacopan. The ADVOCATE trial (Protocol CL010_168) was a Phase 3, randomized, double-blind, double-dummy, active-controlled, multi-center trial. Its primary objective was to evaluate the efficacy of avacopan.

1. ADVOCATE Trial Design

The ADVOCATE trial design is described below. In addition, a more detailed description of why ADVOCATE is an adequate and well-controlled study with the required characteristics described at 21 C.F.R. § 314.126 is set forth in Appendix A (Table 1: "ADVOCATE Study Design Meets the Definition of an Adequate and Well-controlled Study (21 CFR 314.126)"), hereto. Appendix A (Section 5) also provides a more detailed recitation of the ADVOCATE trial design, as well as associated efficacy outcomes, pursuant to 21 C.F.R. § 314.200(d)(3), along with Amgen's August 2025 IR Response to FDA's July 23, 2025 Information Request and exhibits thereto.[40]

The primary efficacy endpoints in the study were the proportion of patients achieving disease remission at Week 26 and sustained remission at Week 52. Disease remission and sustained remission determinations first required assessment of a subject's Birmingham Vasculitis Activity Score ("BVAS"), a validated measure of AAV disease activity. In order to be in remission, a BVAS score of 0 was required. The BVAS is a complex measure that considers (1) a list of items from nine organ systems that reflect the typical features of active systemic vasculitis and (2) whether those items are caused by active vasculitis.[41] At Week 26, remission

[39] As of February 2026.
[40] *See* Response to FDA Requests Dated July 23, 2025 (Aug. 22, 2025) ["August 2025 IR Response"].
[41] *See The Birmingham Vasculitis Activity Score (BVAS)*, OXFORD UNIV. INNOVATION (Nov. 17, 2023), https://innovation.ox.ac.uk/licence-details/birmingham-vasculitis-activity-score-bvas. ADVOCATE used BVAS Version 3 as described in the protocol. *See* 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 (Protocol Amendment 4.0) at 108-11 (Jan. 18, 2019), https://cdn.clinicaltrials.gov/large-

determinations also required a determination that patients had not taken glucocorticoids *for treatment of AAV* within four weeks prior to the Week 26 assessment. At Week 52, sustained remission was defined as achieving remission at Week 26 without relapse to Week 52, a BVAS score of 0 at Week 52, and not taking glucocorticoids, again *for treatment of AAV*, within four weeks prior to the Week 52 assessment.[42]

The protocol SAP also prespecified that glucocorticoid use for certain reasons *unrelated to the treatment of AAV* was permitted and would not affect the assessment of whether patients were in remission at Week 26 and in sustained remission at Week 52.[43]

- **Adrenal Insufficiency:** The protocol prespecified that replacement glucocorticoids for adrenal insufficiency would be permitted in doses that "should not exceed 10 mg prednisone equivalent per day."[44] The protocol instructed investigators to document the adverse event of adrenal insufficiency and replacement glucocorticoid treatment for this event to ensure it did not improperly disqualify subjects from a remission evaluation. Subjects receiving low-dose oral glucocorticoids for treatment of adrenal insufficiency could therefore be classified as responders for purposes of the primary efficacy endpoint assessment, provided all other requirements for remission were met.[45]

- **Pre-Medication for Rituximab:** Glucocorticoid use was permitted as pre-medication for the four planned infusions of rituximab if rituximab was selected as the background immunosuppressant instead of cyclophosphamide/azathioprine.[46] Standard practice is to administer glucocorticoids prior to rituximab infusions to reduce the risk of infusion reactions, as indicated in the label for rituximab.[47] Glucocorticoid use for this purpose did not therefore disqualify subjects from a remission determination at Week 26 and Week 52 for the purpose of evaluating the primary efficacy endpoint.

- **Other Conditions, Not AAV:** The protocol and SAP further prespecified that oral glucocorticoid use was permitted for other conditions as well, such as allergic reaction, and that subjects taking glucocorticoids for these permissible, non-AAV uses "will be classified as responders for purposes of assessment of the primary endpoints if all other

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docs/27/NCT02994927/Prot_000.pdf ["Protocol Amendment 4.0"]; *see* CDER Multi-Disciplinary Review, *supra* note 1, at 98.

[42] Protocol Amendment 4.0, *supra* note 41, at 41; Statistical Analysis Plan, 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 (NCT02994927) at 11 (Oct. 28, 2019), https://cdn.clinicaltrials.gov/large-docs/27/NCT02994927/SAP_001.pdf ["SAP Version 2.0"].

[43] *See* SAP Version 2.0, *supra* note 42, at 15; *see also* 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 (Protocol Amendment 1.0) at 120 (June 21, 2017) ["Protocol Amendment 1.0"].

[44] Protocol Amendment 4.0, *supra* note 41, at 124; *see also* SAP Version 2.0, *supra* note 42, at 26.

[45] *See* Protocol Amendment 1.0, *supra* note 43, at 5.

[46] *See* Protocol Amendment 4.0, supra note 41, at 127.

[47] *See* Genentech, Inc., *RITUXAN® (rituximab) Prescribing Information* (Apr. 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103705s5453lbl.pdf.

requirements for response are met."[48] Investigators were instructed to code the reason for the glucocorticoid use along with the dosage and timing.

Given the complexity of these endpoint evaluations—including the BVAS scoring itself and the assessment of whether a subject's glucocorticoid use was for the prespecified, permitted uses described above—the ADVOCATE protocol established an adjudication committee to perform a blinded, independent adjudication of BVAS scores and to determine whether patients were in remission.[49] ChemoCentryx established this Adjudication Committee pursuant to a charter referenced in the protocol,[50] and consistent with FDA recommendations in guidance, which notes that "[s]uch committees are particularly valuable when endpoints are subjective and/or require the application of a complex definition."[51] The Adjudication Committee Charter in effect at the time (Version 4.0) is dated June 21, 2019, with an addendum dated October 8, 2019.[52] The Adjudication Committee Charter also provided for blinded, independent adjudication of Vasculitis Damage Index ("VDI"),[53] a secondary endpoint measure of vasculitis damage that is comprised of 64 items of damage grouped into 11 organ-based systems or categorizations.[54]

The SAP also provided rules for determining remission status for patients who missed scheduled visits. In general, the SAP treated patients with "missing data" by default as "not achieving remission."[55] Participants could permissibly be deemed in remission, however, if they attended an unscheduled or early termination visit within the permissible assessment windows, defined as between Day 149 and Day 228 for a Week 26 visit and between Day 320 and Day 420 for a Week 52 visit.[56] For example, if a patient missed their scheduled Week 26 visit, but still saw an investigator during an unscheduled visit between Days 149 and 228, the Adjudication Committee would consider the data from this unscheduled visit for the purpose of a Week 26 primary endpoint adjudication.[57]

The ADVOCATE trial results are described in detail in Appendix A (Section 5.3). Those results make clear that TAVNEOS provides effective disease control, reduces the risk of relapse, improves kidney outcomes, improves quality of life, and reduces glucocorticoid exposure and toxicity.

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[48] SAP Version 2.0, *supra* note 42, at 15.
[49] *See* Protocol Amendment 4.0, *supra* note 41, at 81; SAP Version 2.0, *supra* note 42, at 17.
[50] *See generally* ChemoCentryx, Inc., *BVAS and VDI Adjudication Committee Charter* (Version 4.0) (June 21, 2019) and Addendum (Oct. 8, 2019) ["Adjudication Committee Charter"].
[51] FDA, *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Data Monitoring Committees* at 7 (Mar. 2006), https://www.fda.gov/media/75398/download.
[52] The initial version of the Adjudication Committee Charter (Version 1.0) went into effect on July 14, 2017. *See* Adjudication Committee Charter, *supra* note 50, at 9.
[53] Adjudication Committee Charter, *supra* note 50, at 8.
[54] *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* (NCT02994927), NAT'L LIBR. MED. (Mar. 24, 2025), https://clinicaltrials.gov/study/NCT02994927.
[55] SAP Version 2.0, *supra* note 42, at 22.
[56] SAP Version 2.0, *supra* note 42, at 23 ("If a scheduled visit is not available, unscheduled . . . visits will be assigned to analysis visits . . .").
[57] SAP Version 2.0, *supra* note 42, at 21-22.

2. 2019 ADVOCATE Trial Adjudication

All parties involved in the trial were blinded during the study, including: the investigators, Adjudication Committee members, sponsor personnel involved in administering the trial, patients, study monitors, biostatisticians, data managers, data monitoring committee, and the clinical research organization ("CRO"), Medpace. ChemoCentryx took measures to protect the blinding throughout the study, including using a double-dummy design under which placebo capsules were identical in appearance to the avacopan capsules.

ChemoCentryx and Medpace followed the procedures outlined in the Study Results Analysis Plan ("SRAP") for conducting the database lock and selectively unblinding only authorized personnel to the data, granting them restricted access to the unblinded data to perform quality control ("QC") and validation of the top-line study results.[58] The SRAP established these measures in advance of dissemination of study results to ensure that the analysis was conducted in accordance with the SAP and that the results were internally consistent.

The SAP specified that the adjudication committee was responsible for adjudication of "Achievement of disease remission at Week 26 (Primary Endpoint)" and "Achievement of sustained disease remission at Week 52 (Primary Endpoint)."[59] The Adjudication Committee Charter set forth the process for readjudication of data, even after initial adjudication by the Adjudication Committee. "[T]he [Adjudication Committee (AC)] Chair or designee may be provided with listings of data changes from Data Management and/or Biostatistics [i.e., Medpace] and determine if a patient requires readjudication."[60] Importantly, those listings "may also incorporate questions, observations, or comments from the Sponsor . . . based on their review of adjudication data."[61] Per the Charter, any readjudication decisions "will be filed in the eTMF."[62] It further outlined the following process that would apply if a patient "require[d] readjudication":

- "[Medpace's] Data Management or Biostatistics [teams] will notify Medpace Clinical Endpoints (CE) if a patient needs to be re-adjudicated.
- Biostatistics will provide an updated patient profile.
- CE will provide the updated patient profile to the AC Chair and/or designee AC member(s) along with copies of the previously completed AC forms.
- AC Chair or designee will review and determine if any updates are required.
- If updates are required, the AC Chair or designee will make edits to the original copy of the scanned/copied form (no wet-ink signatures or forms required).

[58] *See generally* Letter from Susan Burwig, Executive Vice President, Operations, Medpace (Apr. 29, 2026) (Appendix C.1) (confirming that "the Medpace team followed Medpace SOPs during the conduct of the study").
[59] SAP Version 2.0, *supra* note 42, at 48.
[60] Adjudication Committee Charter, *supra* note 50, at § 4.3.3.
[61] *Id*.
[62] *Id.*

- AC Chair or designee will re-sign and date the AC forms (after/around the original signature/date) and return to CE via email/fax/mail. Forms do not need to be resigned/dated if no changes are required.

- The original AC forms in EDC will be updated with the edits made by the AC Chair or designee.

- The original TMF case file will be revised to include the updated AC forms and new patient profile, if any of the AC forms required updates. If no updates were made to the forms, the TMF case file will not be revised."[63]

November 2019 was not the first time that the sponsor questioned inconsistencies in the adjudication decisions. For example, in August 2019, for two patients, adjudication documentation showed that the Adjudication Committee checked the box indicating that they disagreed with the investigators' scoring of BVAS, but there was no apparent difference between the investigator and Adjudication Committee in BVAS scoring. As a result, the sponsor asked for clarification from the Adjudication Committee.[64]

Pursuant to the prespecified procedures described in the SRAP and Data Management Plan, Medpace and ChemoCentryx completed two pre-lock checklists on November 4 and 5, 2019: the Biostatistics Database Pre-Lock Checklist and the Data Management Database Lock Checklist.[65] Following completion of the checklists, Medpace completed the Request to Break Randomization Code and a Database Lock Approval Form, which were both documented in the eTMF.[66]

According to the SRAP, three ChemoCentryx personnel—Cass Kelleher, Pirow Bekker, and Huibin Yue—were to conduct a "QC review for completeness and internal consistency."[67] The QC review identified a limited number of errors in the application of prespecified trial rules among patients across both trial arms. Accordingly, the primary endpoints for nine patients[68] were readjudicated by the blinded Adjudication Committee Chair in the following cases:

- **Misapplication of trial rule regarding glucocorticoid use:** Six participants (440-002, 702-001, 751-001, 852-001, 854-001, 957-002) had an Adjudication Committee-adjudicated BVAS score of 0, had patient records stating that glucocorticoids were used for purposes other than the treatment of AAV within the four weeks prior to the scheduled Week 26 or Week 52 assessment visit, and where applicable did not experience a relapse between Week 26 and Week 52, but were nonetheless marked as not in remission. These cases warranted readjudication because the adjudicated remission

[63] *Id*.
[64] *See* August 2025 IR Response, *supra* note 40, at Exhibit 55.
[65] *See id.* at Exhibit 3 (Biostatistics Database Pre-Lock Checklist), Exhibit 4 (Database Lock Checklist).
[66] *See id.* at Exhibit 5 (Request to Break Randomization Code Form), Exhibit 6 (Database Lock Approval Form).
[67] *See* Memorandum: Study Results Analysis Plan, *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* (Protocol CL010_168) (Version 1.0) at 4 (Nov. 4, 2019) ["SRAP Version 1.0"].
[68] The cases listed here reflect nine unique patients because patient 957-002 was included in both the glucocorticoid-use and missing-data categories, as shown above.

determination did not appear to comply with the prespecified rules in the protocol and SAP with respect to use of glucocorticoids. And as described below, the misapplication of the trial rule for four of these participants (440-002, 702-001, 852-001, and 854-001) was identified prior to the database lock as early as October 2019, but these four patients were not sent for readjudication by Medpace and therefore were identified again during this QC review.[69]

- **Misapplication of trial rule regarding handling of missing data:** Three participants (428-001, 534-001, and 957-002) were identified as having unscheduled visits that were within the assessment window but nonetheless appeared to have been considered as not meeting remission because of missing data. As described above, the SAP set forth the rule that subjects who attended an unscheduled or early termination visit within the prespecified assessment window would not be considered to have missing data.

- **Manual data entry error:** One participant (466-003) had an error in the remission determination because he/she did not have glucocorticoid use in the four weeks prior to Week 26 or 52, had BVAS scores of 0 at Week 26 and Week 52, and did not have a relapse between Week 26 and Week 52, but was nonetheless recorded as "not in remission" at Week 26 and "not in sustained remission" at Week 52. This appeared to be a manual data entry error.

Appendix A (Table 3) illustrates the changes to the remission/sustained remission status for each readjudicated participant and the reason for the change. These readjudications included participants in both the drug and control arms, were grounded in and supported by source data, and were fully documented in both the electronic data capture ("EDC") system and the eTMF. The Adjudication Committee Chair, who was charged with and conducted the readjudication, remained fully blinded throughout that process.

Notably, four of the nine patients listed above had previously been identified by Medpace and a ChemoCentryx individual as early as October 2019 as having adjudication errors, but these patients were not sent for readjudication at that time. On October 24, 2019, Medpace sent Dr. Bekker a spreadsheet requesting review of remission outcomes with respect to patients who had used glucocorticoids for non-AAV reasons within four weeks prior to measurement.[70] In sending this request, Medpace noted that these four patients (440-002, 702-001, 852-001, and 854-001) had used glucocorticoids within the four-week window for something other than AAV.[71] Dr. Bekker agreed that the patients could be considered in remission/sustained remission because they received glucocorticoids for treatment of conditions other than AAV.[72] These patients' remission/sustained remission outcomes were, however, not readjudicated at the time and the same four patients were identified again after November 5, 2019.

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[69] *Cf.* Adjudication Committee Charter, *supra* note 50, at § 4.3.3 (specifying that Medpace "Data Management or Biostatistics will notify Medpace Clinical Endpoints (CE) if a patient needs to be re-adjudicated," and the Medpace CE team is to "provide the updated patient profile to the AC Chair and/or designee AC member(s) along with copies of the previously completed AC forms").

[70] Email from P. Bekker to [redacted] RE: Patient Status Spreadsheet (Oct. 25, 2019).

[71] *Id.*

[72] *Id.*

Like a judge applying a preexisting legal standard to an unchanged evidentiary record, the November 2019 readjudication of the nine patients affected how primary endpoints were classified under prespecified trial rules and *did not change underlying clinical data or BVAS scores*. Without the readjudication of the nine patients—including the four patients above whose initial adjudications had previously been identified as requiring correction—the prespecified primary endpoint definitions and handling of missing data would not have been correctly or consistently applied across the patient population in the study. For example, there were several patients, outside of these nine, who had used glucocorticoids for reasons other than the treatment of AAV in the four weeks prior to Week 26 and/or 52 and had been *correctly* adjudicated as in remission at Week 26 and/or sustained remission at Week 52, prior to November 5, 2019. These patients are identified and described in detail in Amgen's August 2025 IR Response.[73]

3. 2026 DCRI ADVOCATE Trial Readjudication

The results of the recently completed 2026 readjudication further support that TAVNEOS was at least as effective as a prednisone taper for induction and maintenance of remission through 52 weeks. Non-inferiority was demonstrated at both Week 26 and Week 52, which is also consistent with the 2019 readjudication. As detailed below, non-inferiority remains important for patient care given the advantages of reducing steroid use given their toxicities. The proportion of patients experiencing relapse after achieving remission was consistent with the original analyses from the ADVOCATE trial, and favored TAVNEOS.

With respect to the primary endpoint, TAVNEOS demonstrated non-inferiority to prednisone for remission at Week 26 (67.1% versus 68.1%; difference 2.2%, 95% CI −7.5 to 11.9) and sustained remission at Week 52 (61.4% versus 52.4%; difference 9.8%, 95% CI −0.3 to 19.9), with all lower confidence bounds remaining well above the prespecified non-inferiority margin of −20%. Non-inferiority was supported by highly statistically significant one-sided p-values (<0.0001). Superiority was not demonstrated at either Week 26 (p=0.3301) or Week 52 (p=0.0282) at the prespecified statistical threshold (0.025). As illustrated above, however, the results at Week 52 demonstrated a nearly 10 percentage point numerical difference favoring TAVNEOS. As described in detail in Section IV.A.2.c, multiplicity was not a concern in the readjudication.

As further detailed in Appendix A, significantly, the rate of relapse was lower in the TAVNEOS group, and the median steroid exposure in participants in the TAVNEOS group was more than 80% lower than in the control arm, with substantially lower steroid toxicity. These data substantially increase confidence that TAVNEOS can induce and sustain remission, with reduced need for prednisone use, which is a known driver of morbidity in patients with AAV.

4. ADVOCATE Trial's Safety Data

The ADVOCATE trial demonstrated an acceptable safety profile for TAVNEOS, as described in detail in Appendix A (Section 7.1). In the study, patients in the avacopan arm experienced fewer adverse events, serious adverse events, and infections compared to the

[73] *See generally* August 2025 IR Response, *supra* note 40.

prednisone control arm.[74] In approving TAVNEOS on the basis of ADVOCATE, CDER expressly recognized the acceptable safety profile demonstrated by the study data and that the observed safety findings were manageable in light of TAVNEOS's demonstrated benefits as well as the seriousness of AAV and the risks associated with available alternative therapies.

In particular, CDER noted at the time of approval that the ADVOCATE data had identified "potential safety risks of hepatotoxicity and hypersensitivity"[75] but concluded that this risk could be effectively mitigated and managed by labeling and post-marketing studies, stating "[t]hough the safety data is small, these risks (hepatotoxicity and hypersensitivity) are also seen in other drugs in the therapeutic armamentarium and can be managed through labeling and a PMR to further characterize these safety risks."[76] TAVNEOS was therefore approved with labeling containing information and warnings regarding hepatotoxicity (section 5.1 Warnings and Precautions) and hypersensitivity (section 5.2 Warnings and Precautions and section 2.1 Dosage and Administration), which was "[c]onsistent with other immunosuppressive therapies used for AVV [*sic*] such as cyclophosphamide and methotrexate" according to CDER.[77] For example, rituximab also has warnings with respect to infusion reactions and HBV as it relates to hepatotoxicity, and healthcare providers managing GPA/MPA often manage other medications associated with hepatotoxicity requiring close monitoring (e.g., methotrexate, azathioprine). Nephrologists also often manage other complement inhibitors requiring close monitoring and risk mitigation actions (e.g., SOLIRIS (eculizumab)).

D. TAVNEOS Post-Approval Efficacy And Safety Data

Nearly five years of post-marketing evidence reinforces the efficacy and safety profile of TAVNEOS for AAV patients established in the ADVOCATE trial. The robust body of post-marketing evidence is described in greater detail in Section IV.A and Appendix A (Sections 6 and 7)—including the results of recent manuscripts. For example, a recent meta-analysis based on effectiveness and safety data from 71 studies of TAVNEOS use in routine clinical practice observed that "[i]n real-world clinical practice, avacopan is associated with high remission rates, low relapse rates, and a consistent GC-sparing effect, with effectiveness comparable to standard-of-care regimens," and that "[f]indings support its clinical use with appropriate safety monitoring."[78] Additional data regarding efficacy and safety is provided below.

1. Efficacy

The consistent findings across numerous real-world studies, including seven comparative effectiveness studies, more than 20 observational cohort studies, and an ongoing Japan Post-Marketing Surveillance ("PMS") study as well as the AVACOSTAR observational study in

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[74] CDER Multi-Disciplinary Review, *supra* note 1 ("In the pivotal study, generally similar or fewer number of patients in the avacopan arm compared to the prednisone arm experienced deaths (2 vs. 4 patients), SAEs (42% vs. 45%), AEs leading to discontinuation (16% vs. 17%), and TEAEs (99% vs. 98%).").
[75] *Id.* at 36.
[76] FDA, *Risk Assessment and Risk Mitigation Review(s)* (NDA 214487) at 14 (Oct. 6, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214487Orig1s000RiskR.pdf.
[77] *Id.* at 3.
[78] Elizabeth Ibiloye et al., *Real-World Effectiveness and Safety of avacopan in ANCA-Associated Vasculitis: A Systematic Literature Review and Meta-analysis*, MEDRXIV (June 17, 2026), https://www.medrxiv.org/content/10.64898/2026.06.17.26355805v1#p-5.

Europe, support the efficacy of TAVNEOS-based regimens in line with the efficacy observed in ADVOCATE. The totality of data from RWE reinforce the value of TAVNEOS added to standard of care in achieving remission, minimizing relapse, and supporting favorable kidney outcomes, while reducing glucocorticoid exposure and toxicity. These studies represent a heterogeneity of designs and patient populations, and the favorable results, reviewed in detail in Appendix A (Section 6), provide additional evidence that the benefits of TAVNEOS are robust and span the breadth and depth of GPA and MPA, including in patients with newly diagnosed and relapsing disease, severely impaired kidney function, refractory disease, and multi-organ involvement. These post-marketing studies and their results are itemized in Tables 10, 11, and 12, below, for ease of review.

A recent manuscript highlights that real-world evidence is important for evaluating the effectiveness of medicines when used in day-to-day practice.[79] Directionally, the findings from this large comparative effectiveness study that used administrative claims data are consistent with the broader evidence base: patients treated with TAVNEOS and standard of care ("SOC") had fewer relapses (weighted hazard ratio [95% CI]: 0.81 [0.59 to 1.13]) at 12 months and meaningfully lower steroid exposure (weighted difference −559.7 mg [−814.2, −1.9]) at six months when compared to the SOC alone group. As in ADVOCATE, patients treated with TAVNEOS and SOC in real world practice experienced faster steroid tapering, had significantly less steroid exposure, and, despite less steroid treatment, fewer relapses when compared to SOC alone. There were rare serious hepatic events observed in patients treated with TAVNEOS as well as those who received SOC alone. Collectively, these findings support the favorable benefit-risk profile of TAVNEOS.

2. Safety

a. Post-marketing studies and pharmacovigilance data

As detailed in Appendix A (Section 7), post-marketing safety data for TAVNEOS is largely consistent with the safety findings observed during the clinical development program. Since its first approval in Japan in September 2021, followed by approvals in the United States, European Union, and other countries, TAVNEOS has accumulated substantial post-marketing exposure, both through post-marketing studies as well as real-world use. As of January 2026, estimated real-world exposure exceeds 25,000 patient-years globally, consisting of over 6,500 in the United States and 19,000 abroad.

As further detailed in Section IV.A.4.b, below, post-marketing safety studies conducted worldwide to date similarly provide results consistent with the known safety profile of TAVNEOS:

- A Post-Authorization Safety Study ("PASS") to Evaluate the Incidence of Safety Events of Interest in Subjects Treated with Avacopan for AAV (AVACOSTAR):[80] In this ongoing, non-randomized, non-interventional observational PASS in Germany and the United Kingdom, an interim analysis has

[79] *See* Lauren Dang et al., *Effectiveness and Safety of avacopan in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis*, MEDRXIV (July 22, 2026), https://www.medrxiv.org/content/10.64898/2026.07.20.26358270v1.
[80] *See* Appendix A (Section 7.3.1).

been conducted based on a data cut-off date of September 11, 2025, supporting the important role TAVNEOS plays in reducing glucocorticoid exposure in patients with GPA and MPA. Liver injury events, mostly liver laboratory abnormalities, were reported for 8.3% of patients in the TAVNEOS group. The exposure-adjusted unique incidence rate of liver injury events was 0.075 per patient-year with TAVNEOS. All events were graded as mild to moderate in severity. One event was reported as serious (alanine aminotransferase increased); TAVNEOS was briefly paused and then restarted, with no recurrence of significant liver test abnormalities.

- Japan Post-Marketing Surveillance Study:[81] An interim analysis (cutoff date of September 26, 2025) revealed the rate of serious hepatic abnormalities to be similar to ADVOCATE (5.4% in ADVOCATE vs. 5.3% in the study), the majority being liver laboratory abnormalities, supporting the known safety profile of TAVNEOS.

Across TAVNEOS's clinical development program and subsequent real-world use, the overall safety profile has generally remained consistent with trial experience. Hepatotoxicity was seen during clinical development and was easily identified through frequent liver laboratory testing and reversible after discontinuing the drug, with no fatal events. Since approval, however, VBDS—a rare, severe condition where the small bile ducts inside the liver are progressively destroyed and disappear—has been seen outside of the United States, with cases concentrated in Japan. Liver safety, therefore, has become the most clinically important TAVNEOS-related safety risk and is discussed further below in Section IV.A.4. As discussed therein and by Dr. Chalasani, the substantial safety data available on TAVNEOS indicates that the drug has a well-characterized hepatotoxicity risk, which can be further managed by physicians in accordance with information in the TAVNEOS label.[82]

b. Liver injury events

The need for hepatic monitoring with TAVNEOS is not unique in the context of modern therapeutics. More than 200 drugs in the U.S. Food and Drug Administration Drug-Induced Liver Injury Rank ("DILIrank") dataset are categorized as "Most DILI-concern." Notably, many of these medications are those routinely used by rheumatologists and/or nephrologists (such as azathioprine, methotrexate, leflunomide, sulfasalazine, infliximab, allopurinol, and febuxostat) or are used to treat conditions that are not serious or life-threatening (such as acetaminophen, nonsteroidal anti-inflammatory drugs ("NSAIDs"), or antibiotics). As such, the potential for clinically significant liver injury is not uncommon among approved therapies, and healthcare providers ("HCPs") are accustomed to following structured risk mitigation strategies. Nevertheless, the emergence of VBDS and the occurrence of fatal hepatic events in the post-marketing setting has heightened focus and warrants close examination.

As noted above, in April 2024—two years before FDA's DSC—Amgen proactively submitted a PAS to CDER to include VBDS in TAVNEOS's label. Six months later, CDER

[81] *See* Appendix A (Section 7.3.2).
[82] Chalasani Declaration, *supra* note 12, at 4.

issued an IR, to which Amgen provided a response in November 2024, but the Center did not otherwise take action on this submission. After FDA issued the DSC, Amgen again moved on its own initiative to implement corresponding labeling changes through a CBE-30 supplement, which was submitted on April 29, 2026 and went into effect on May 29, 2026. On June 2, 2026, after the new TAVNEOS label took effect, CDER issued an IR relating to the CBE-30 supplement, to which Amgen responded timely on June 10, 2026.

As described in a recent manuscript, the accumulating post-approval experience provides an opportunity to further characterize the safety profile of TAVNEOS beyond the setting of controlled clinical trials.[83] As of January 20, 2026, serious liver injury events in patients receiving TAVNEOS have been reported to Amgen at a rate of approximately 31 events per 1,000 patient-years.[84] Most reported hepatic events were reversible laboratory abnormalities. The most serious hepatic events, including fatal cases, were mainly reported from Japan, frequently in elderly females, and included hepatic function abnormality, liver disorder, drug-induced liver injury, hepatic enzyme increased, jaundice, and VBDS. A causal link between TAVNEOS and these events has not been confirmed in some cases due to limited information or other confounding drugs or medical conditions.

As of January 20, 2026, no VBDS cases were reported from the United States or European Union. Thirty-one VBDS cases have been reported, including 27 from Japan, two from Canada (one patient of Chinese race, the other unknown), and two literature reports from China. Fifteen cases were confirmed on biopsy; nine were fatal, one had not recovered, one recovered, and four were recovering at last follow-up. Time to onset in the biopsy-confirmed cases ranged from 22 to 76 days after TAVNEOS initiation, with a median of 46 days. Sulfamethoxazole/trimethoprim was a co-suspect drug in eight biopsy-confirmed cases, and several fatal cases had relevant confounders, limiting causal attribution. All fatal cases of VBDS were reported from Japan, in patients over the age of 65.

Patients of Japanese descent appear to be more susceptible to liver injury. The reason for this geographic variance is not known, but may be due to differences in pharmacogenetic susceptibility, clinical practice, or background therapy. For instance, as described in greater detail in Section IV.A.4.d, certain alleles that are more common in East Asian populations may contribute to susceptibility in liver injuries. In addition, differences in Japanese labeling for TAVNEOS at the time of approval until May 2026 in monitoring and stopping criteria could play a role in the differences seen in the frequency and/or seriousness of hepatic events in the Japanese population.

Notably, the U.S. prescribing information ("USPI") included information on liver monitoring and treatment discontinuation guidance since its approval in 2021.

Table 1 compares hepatic-safety labeling and monitoring recommendations for TAVNEOS in the United States and Japan from the time of approval until January 2026, when the health authorities in Japan decided to update the Japanese prescribing information to include detailed information on liver test monitoring and treatment discontinuation rules, resulting in

[83] *See* Punam Bharania et al., *A Post-Marketing Evaluation of avacopan Safety with a Focus on Hepatic Adverse Events*, MEDRXIV (July 22, 2026), https://www.medrxiv.org/content/10.64898/2026.07.20.26358315v1.
[84] This is the most recent date for which the analyses described herein were available at the time of submission.

content that more closely aligns with the USPI. It shows that the TAVNEOS USPI provides more specific liver-safety guidance, including a named hepatotoxicity warning; required baseline testing of alanine aminotransferase ("ALT"), aspartate aminotransferase ("AST"), alkaline phosphatase ("ALP"), and total bilirubin; and repeat monitoring every four weeks for the first six months followed by testing as clinically indicated. The USPI also gives explicit management thresholds, advising prompt evaluation and possible interruption and discontinuation. In contrast, the TAVNEOS label in Japan states more generally that hepatic dysfunction may occur and recommends liver-function testing before and periodically during treatment, but it does not specify exact analytes, monitoring cadence, or numeric thresholds; if abnormalities occur, it advises discontinuation or other appropriate measures.

Table 1. Hepatic-Safety Labeling and Monitoring Comparison for TAVNEOS in the United States and Japan Until January 20, 2026[85]

Domain	U.S. TAVNEOS PI	Japan TAVNEOS PI
Warning and Precautions	Named hepatotoxicity warning stating that serious cases of hepatic injury have occurred; guidance to obtain ALT, AST, ALP, and total bilirubin before treatment; repeat every 4 weeks for 6 months, then as clinically indicated.	Important Precautions: hepatic dysfunction may occur; perform liver-function tests before and periodically during treatment. Recommends close monitoring of patients. Exact analytes and cadence are not specified in the cited PI text.
Management of Abnormal Liver Tests	ALT/AST >3 x ULN: evaluate promptly and consider interruption. ALT/AST >5 x ULN, or >3 x ULN with bilirubin >2 x ULN: discontinue until drug-induced liver injury is ruled out.	If an abnormality is observed, discontinue treatment or take other appropriate measures; no numeric thresholds are given

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; AST, aspartate aminotransferase; AUC, area under the curve; Cmax, maximum plasma concentration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PI, prescribing information/package insert; PK, pharmacokinetic; ULN, upper limit of normal; VBDS, vanishing bile duct syndrome.

As part of TAVNEOS's approval in Japan, a post-marketing surveillance study of TAVNEOS is being conducted in that country. A total of 451 patients were included in the interim safety analyses (data cutoff September 26, 2025). Safety data showed that 97 of 451 patients (21.5%) experienced hepatic function disorder adverse drug reactions during the first 12 months, including 24 serious cases (5.3%), three drug-induced liver injury cases (0.7%), and one VBDS case (0.2%). Most events occurred early: 90% within 112 days and 54% within 56 days.

In the ongoing AVACOSTAR post-marketing study interim analysis (data cutoff September 11, 2025), 254 TAVNEOS users and 250 non-users with new or relapsing GPA/MPA were enrolled in Germany and the United Kingdom, with most participants also receiving rituximab and/or cyclophosphamide. As noted above, liver injury events occurred in 21 TAVNEOS users (8.3%) and five non-users (2.0%). The exposure-adjusted unique incidence rate was 0.075 per patient-year with TAVNEOS versus 0.012 per patient-year without TAVNEOS. After propensity score adjustment for baseline differences, the estimated exposure-adjusted incidence rate ratio was 6.91, although channeling bias and residual confounding remain

[85] The table does not reflect changes in the TAVNEOS labeling effective May 2026 in the U.S. and Japan.

important limitations. No VBDS events have been reported in the AVACOSTAR study, and there have been no fatal events related to liver injury, as detailed in Appendix A.

As detailed above, AAV is a serious and severe disease with associated mortality, and patients living with this condition have benefited from the use of TAVNEOS. Hepatotoxicity continues to be an important safety issue in real-world use. Most hepatic abnormalities are aminotransferase elevations and appear reversible after interruption or discontinuation, but serious liver injury and rare VBDS, with fatal outcomes, have been reported, with a concentration of cases in Japan and early onset after treatment initiation. No VBDS cases were reported from the United States or European Union. These findings support continued liver function monitoring, heightened vigilance during the first one to three months of therapy especially for patients of Japanese descent, and prompt discontinuation of TAVNEOS in the event of potential hepatotoxicity or VBDS. In addition, ongoing pharmacovigilance will continue to refine risk factors and guide mitigation strategies.

The TAVNEOS USPI includes warnings and precautions for hepatotoxicity, hypersensitivity reactions, hepatitis B virus reactivation, and serious infections. In April 2024, Amgen proactively submitted a proposed label update to FDA to include VBDS in TAVNEOS's label. Amgen provided additional information in November 2024, but CDER did not take any action on this submission. Acting on its own initiative, on April 29, 2026, Amgen submitted a CBE-30 labeling supplement to update the USPI section 5.1 (Hepatotoxicity) and section 6.2 (Postmarketing Experience) to further support safe prescribing. The CBE-30 filing amends the hepatotoxicity warning language in the label to provide more information on cases of VBDS that have been observed in the post-marketing setting, including that cases with fatal outcomes have been reported, and modifies language regarding liver panel testing and treatment discontinuation rules. This label update became effective on May 29, 2026, and CDER subsequently issued an IR to Amgen on June 2, 2026. Amgen duly responded to this IR on June 10, 2026.

E. Regulatory History

ChemoCentryx submitted the NDA for approval of avacopan (NDA 214487) on July 7, 2020, based primarily on the efficacy and safety of avacopan as demonstrated in ADVOCATE. During the course of the NDA review, FDA issued, and ChemoCentryx responded to, multiple Information Requests ("IRs") targeting the basis for the remission determinations by the Adjudication Committee, and later the difference between investigator-scored and adjudicated BVAS. FDA also issued several IRs raising questions related to the use of glucocorticoids, including the timing, dose, and reasons for non-study supplied glucocorticoid use. In response to these requests, ChemoCentryx provided that information, along with the remission determinations for each patient, showing that patients who used glucocorticoids for the treatment of conditions other than AAV were still considered responders.[86] ChemoCentryx also provided

[86] *See* ChemoCentryx, *Clinical Information Amendment*, NDA 214487 (FDA) ["IR 3 Response"]; ChemoCentryx, *Clinical: Response to Information Request #4*, NDA 214487 (FDA) ["IR 4 Response"]; ChemoCentryx, *Clinical: Response to Information Request #8*, NDA 214487 (FDA) ["IR 8 Response"]; ChemoCentryx, *Clinical: Response to Information Request #9*, NDA 214487 (FDA) ["IR 9 Response"]; ChemoCentryx, *Clinical & Statistics: Response to Information Request #11*, NDA 214487 (FDA) ["IR 11 Response"]; ChemoCentryx, *Clinical: Response to Information Request #13*, NDA 214487 (FDA) ["IR 13 Response"]; ChemoCentryx, *Clinical: Response to*

information on the rules governing missing data, including that unscheduled or early termination visits that fell within an analysis visit window would be used where the scheduled analysis visit was missed. *See* Appendices A and D hereto for a more detailed discussion of this background.

On May 6, 2021, FDA convened a meeting of the Arthritis Advisory Committee to discuss NDA 214487.[87] The Agency released its briefing document for the advisory committee meeting on May 4, 2021 ("FDA Briefing Document").[88] Among other topics, the FDA Briefing Document detailed the prespecified rules governing remission determinations and how those rules were applied to the ADVOCATE data; the differences between adjudicator and investigator BVAS scores and FDA's independent analysis of those differences; and the use of glucocorticoids in patients deemed to be in remission at Week 26 or sustained remission at Week 52. FDA subsequently issued an erratum revising the discussion of the regulatory history in the FDA Briefing Document to acknowledge ChemoCentryx's incorporation of the Agency's feedback into the ADVOCATE trial design as well as other errors, such as characterization of a subgroup analysis in patients with stages of kidney disease based on eGFR—which was included in the SAP—as post hoc.[89]

Notably, the FDA Briefing Document acknowledged that "glucocorticoid use was not protocol-specified but could be administered for reasons as previously described (vasculitis, adrenal insufficiency, and other conditions)."[90] The FDA Briefing Document also explained that patients in ADVOCATE who received glucocorticoids for other conditions "were to be considered responders if all other requirements for meeting the endpoints were met."[91] The FDA Briefing Document acknowledged that some of the specific "other conditions" for which glucocorticoids were prescribed during the trial included "asthma, allergic reaction, arthritis, [and] gout."[92] FDA also analyzed the reasons for non-study supplied glucocorticoid use and compared the reasons for non-study supplied glucocorticoid use across the first and second halves of the study.[93] Table 16 of the FDA Briefing Document analyzed the use of non-study supplied glucocorticoids by reason for prescription and included the number of patients who received glucocorticoids for "[t]reatment of other disorder, not vasculitis."[94] Additionally, Table 30 in the FDA Briefing Document reflected that FDA analyzed patients who received non-study supplied glucocorticoids but were still counted as responders.[95]

Information Request #14, NDA 214487 (FDA) ["IR 14 Response"]; ChemoCentryx, *Clinical: Response to Information Request #15*, NDA 214487 (FDA) ["IR 15 Response"].

[87] FDA, *Final Summary Minutes of the Arthritis Advisory Committee Meeting* at 1 (May 6, 2021), https://web.archive.org/web/20241108190628/https://www.fda.gov/media/150534/download.

[88] FDA, *FDA Briefing Document, Arthritis Advisory Committee Meeting* (NDA 214487) at 1, 5 (May 6, 2021), https://web.archive.org/web/20250227051641/https:/www.fda.gov/media/148176/download ["FDA Briefing Document"].

[89] *See* FDA, *Erratum to the FDA Briefing Document, Arthritis Advisory Committee Meeting* (NDA 214487) at 1-2 (May 6, 2021), https://web.archive.org/web/20241108234503/https://www.fda.gov/media/148177/download.

[90] FDA Briefing Document, *supra* note 88, at 48.

[91] *Id.* at 34.

[92] *Id.* at 9.

[93] *See id.* at 51-54 & tbl. 16.

[94] *Id.* at 53 tbl. 16.

[95] *Id.* at 84 tbl. 30 (listing specific examples of patients who were counted as responders and received non-study-supplied glucocorticoids).

The FDA Briefing Document confirmed that, under these prespecified rules, ADVOCATE met its primary endpoints of non-inferiority at 26 weeks and superiority at 52 weeks.[96] In confirming that ChemoCentryx's primary endpoint results were correct, FDA replicated the primary endpoint analyses based upon adjudicated remission determinations and the prespecified rules in the SAP.[97] The advisory committee voted 10 to 8 that the benefit-risk profile of avacopan was adequate to support approval.[98]

Following the Advisory Committee meeting, ChemoCentryx submitted information on June 18, 2021 (during the NDA review), including a revised proposed indication statement clarifying that avacopan does not eliminate glucocorticoid use, a summary of available safety and efficacy data from ADVOCATE, and a proposal for post-approval studies.[99] On October 7, 2021, avacopan received FDA approval as an adjunctive treatment of adult patients with severe AAV (GPA and MPA) in combination with standard therapy including glucocorticoids.[100]

Consistent with FDA's longstanding approach to rare disease, CDER found that there was substantial evidence of efficacy and approved avacopan based upon a totality of evidence. As is typical of rare disease approvals, the approval of TAVNEOS reflected a multi-faceted rationale and was not limited to the superiority outcome in ADVOCATE. In fact, the FDA review team originally recommended a Complete Response. However, consistent with FDA's totality of evidence approach particularly with respect to rare disease the Division Director cited "additional considerations [that] ameliorate and outweigh those concerns," including:

- AAV is "a serious, potentially organ- and life-threatening rare disease with a limited therapeutic armamentarium."[101] In light of the small rare-disease patient population and the "compelling need to treat to remission when patients present with serious manifestations," "requiring a second phase 3 study may delay access while not providing the desired additional clarity with respect to avacopan's ultimate role in the therapeutic armamentarium."[102]

- The fact that TAVNEOS did not demonstrate superiority (but did demonstrate non-inferiority) at Week 26 "does not preclude a conclusion that avacopan has a beneficial treatment effect"—for example, because "the point estimate of the results for the avacopan group was very similar to that of the prednisone control group (72.3% vs. 70.1%, respectively), suggesting that avacopan had some level of treatment benefit toward remission rates at Week 26, albeit difficult to quantify."[103]

- While "[e]xploratory analyses across multiple secondary endpoints were not consistently favorable," "results for the clinically important endpoint of rates of relapse did favor

[96] *Id.* at 7.
[97] *Id.* at 41-42.
[98] *Id.* at 7.
[99] ChemoCentryx, NDA 214487 Clinical Information Amendment (June 18, 2021).
[100] ChemoCentryx, Inc., *TAVNEOS (avacopan) Prescribing Information* (Oct. 2021) https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214487s000lbl.pdf ["Oct. 2021 USPI"].
[101] CDER Multi-Disciplinary Review, *supra* note 1.
[102] *Id.*
[103] *Id.* at 235-36.

avacopan," and those results "clearly support the clinical activity of avacopan *beyond that demonstrated by the primary endpoint analyses*."[104] In addition, "[t]he heterogeneity of results among the secondary endpoints is expected in conditions where patients experience a wide range of manifestations and severity, such as . . . AAV."[105]

- The Phase 2 studies "are difficult to interpret and do not provide clear support for the single phase 3 study; however, they also do not conflict with a finding of efficacy in the phase 3 study."[106]

Similarly, the Office Director pointed to considerations beyond the ADVOCATE superiority outcome, including:

- AAV "is a rare, potentially life-threatening condition."[107] While achieving remission has become more feasible as treatments have advanced, "disease relapse continues to pose a burden to patients" and "[m]orbidity related to disease-related organ damage and adverse effects of therapies to manage the disease negatively impact quality of life."[108]

- In ADVOCATE, "exploratory analyses suggest that fewer avacopan-treated patients relapsed after remission as compared to patients on the comparator arm."

- Additional "[s]upportive evidence of avacopan efficacy is derived from mechanistic considerations, from nonclinical studies (e.g., involving C5a-induced neutropenic cynomolgus monkeys, and a transgenic mouse ANCA disease model)."[109]

- The data from the Phase 2 studies "do not conflict with the treatment effects seen in [ADVOCATE]."[110]

TAVNEOS is subject to a post-marketing requirement ("PMR") and post-marketing commitment consisting of a randomized, controlled clinical trial with a planned duration of at least five years to evaluate comparative safety and efficacy outcomes, respectively (4155-1 and 4155-3). When CDER requested that Amgen withdraw TAVNEOS, it expressly indicated that this study would be allowed to continue and the study is currently ongoing.[111]

F. CDER's Withdrawal Request And NOOH

CDER's current interest in the readjudications traces to July 2025, when plaintiffs' lawyers pursuing a class action lawsuit against ChemoCentryx provided CDER with a report

[104] *Id.* at 237 (emphasis added).
[105] *Id.*
[106] *Id.* at 238.
[107] *Id.* at 240.
[108] *Id.*
[109] *Id.*
[110] *Id.*
[111] *A Study to Evaluate Avacopan in Participants With ANCA-associated Vasculitis* (NCT06072482), NAT'L LIBR. MED. (July 16, 2026), https://clinicaltrials.gov/study/NCT06072482?term=NCT06072482&viewType=Card&rank=1.

from one of their paid experts, Dr. Marc Walton (the "Walton Report").[112] Shortly after receiving the Walton Report, on July 23, 2025, CDER issued an information request to Amgen, asking for a comprehensive account of the events described in the report regarding the November 5, 2019 database lock (hereafter, referred to as the "November 5 initial lock" or "initial lock") in ADVOCATE and readjudication of the nine participants. Amgen timely submitted its response on August 22, 2025, explaining the events in detail and that the readjudications were documented in the eTMF which remained available for regulatory review.

Five months later, on January 16, 2026, the then-acting CDER Director, Dr. Tracy Beth Høeg, requested in a teleconference that Amgen voluntarily withdraw the TAVNEOS NDA, giving the company seven business days, until January 28, 2026,[113] to do so and requesting that Amgen waive its Due Process right to a hearing. As part of that request, Dr. Høeg stated that the Center viewed ADVOCATE study results as unreliable for regulatory decision-making and cited an alleged lack of substantial evidence of efficacy—under only Section 505(e)(3) of the FDCA—as the basis for withdrawal. When Amgen offered to have the trial data readjudicated anew, CDER dismissed the idea out of hand. The Center did not invoke the additional ground of untrue statement of a material fact under Section 505(e)(5) as a basis for its request for a voluntary withdrawal.[114]

On January 28, 2026, Amgen informed CDER that it respectfully declined to voluntarily withdraw TAVNEOS from the U.S. market and would not waive its right to request a hearing. Amgen explained that it remained confident in TAVNEOS's favorable risk-benefit profile and reaffirmed its commitment to TAVNEOS patients.[115] To address CDER's concerns, Amgen again offered to conduct a new, independent, fully blinded readjudication of the ADVOCATE

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[112] It is notable that the negative characterization of the events surrounding the 2019 readjudication that CDER now raises arose through and echoes the claims of plaintiffs' class action attorneys in a private litigation that brought securities fraud claims against ChemoCentryx and its former CEO, Dr. Thomas Schall. Plaintiffs' lawyers filed that lawsuit on May 5, 2021, in the United States District Court for the Northern District of California. Notably, the lawsuit was filed a day before a pre-approval Advisory Committee Meeting took place and months before FDA approved TAVNEOS. Ultimately, the court granted summary judgment to ChemoCentryx and Dr. Schall on all challenged statements, and denied a motion for partial summary judgment the plaintiffs had brought, finding that the plaintiffs failed to establish falsity. In late June 2025, plaintiffs' lawyers sent the Walton Report to FDA. That report relies on an incomplete set of record documents and even then was generated in the curated context of a private litigation. For example, Dr. Walton admitted he reviewed and relied on the set of documents listed in his report, which had been provided by plaintiffs' lawyers. The documents he reviewed do not include the underlying ADVOCATE trial procedures governing the review process at issue or even the eTMF for the TAVNEOS NDA that contained the records surrounding the readjudications. Plaintiffs' lawyers did not provide Dr. Walton with statements from ChemoCentryx personnel or the Adjudication Committee Chair that they followed trial procedures. In addition, plaintiffs' lawyers apparently provided to Dr. Walton only the first day of deposition testimony from Petrus J. Bekker, M.D., Ph.D., but not the second day, in which Dr. Bekker more fully addressed the readjudication process. *See* Expert Report of Marc Walton, M.D., PhD, *Homyk v. ChemoCentryx, Inc.*, No. 4:21-cv-03343 (N.D. Cal. 2024) ["Walton Report"], Tr. 35:5-17 (appendix b), Tr. 361:6-12 (patient files), Tr. 363:14-17 (eTMF), Tr. 333-350 (on violations) (Reference 3 to 91 Fed. Reg. 23278 (Apr. 30, 2026)).

[113] Monday, January 19, 2026, was a federal holiday.

[114] Email from Susie Choi, Pharm.D., Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation, to [redacted] (Jan. 16, 2026) ("If we do not receive a withdrawal request from you citing 314.150(d) by Wednesday, January 28, 2026, CDER will pursue withdrawal of approval under section 505(e)(3) of the Food, Drug, and Cosmetic Act and agency regulations").

[115] January 28 Letter, *supra* note 23.

data in all 331 study participants. Amgen explained that it would implement several measures to minimize bias, including using the original data packages in the manner they were provided to the original Adjudication Committee, and providing that the new adjudication committee would not have any knowledge of adjudication decisions made by the original Adjudication Committee. Amgen advised the Center that it expected the de novo readjudication to be completed within approximately three months and asked that the Center, in the best interests of patients who rely on TAVNEOS, consider and review all available data—including the new readjudication results—before initiating any withdrawal proceeding.

On March 26, 2026, Amgen provided CDER with an update that it had engaged the DCRI Clinical Event Classification Unit to conduct the new readjudication, and submitted the new readjudication-associated statistical analysis plan and charter to FDA.[116] Amgen explained that the DCRI adjudication committee would be blinded to treatment assignments and prior adjudication decisions and would be trained on assessment of BVAS and VDI assessment under a renowned and widely adopted program, developed by Oxford University and already in use for Amgen's Phase IV post-marketing requirement study. Amgen reiterated its request that the Center review the 2026 readjudication data before initiating a withdrawal proceeding, given the relevance of such data and the importance of TAVNEOS for AAV rare-disease patients.

CDER did not respond to Amgen's request and did not engage with Amgen in a dialogue about the 2026 readjudication or other options to generate data that could further inform TAVNEOS's benefit-risk profile. On April 30, 2026, CDER published in the Federal Register its proposal to withdraw TAVNEOS's marketing approval and NOOH. For the first time, the Center articulated an additional ground—a claimed untrue statement of a material fact under FDCA Section 505(e)(5)—on top of the only previously cited efficacy ground (505(e)(3)) as the basis for withdrawal.

Much of CDER's allegations for withdrawal under both sections rely on the Walton Report. That report, however, does not appear to have considered all relevant parts of the record from the securities litigation. For example, although the securities litigation deposition of ChemoCentryx's Chief Medical Officer, Pirow Bekker, M.D., Ph.D., occurred over two days—Friday, July 26, 2024, and Monday, July 29, 2024—Dr. Walton references only the Friday transcript and does not address additional context provided in the Monday transcript.[117] In addition, the NOOH did not acknowledge responses that Amgen provided to the July 2025 Information Request.

In addition, CDER did not follow the 10-day FOIA review process before making the NOOH public.[118] The NOOH, which was published on CDER's website on April 27, 2026,[119] and in the Federal Register on April 30, 2026,[120] did not contain redactions and included confidential commercial information and personal privacy information. Notably, although

[116] Letter from Jay Bradner, M.D., Executive Vice President, Research & Development, to Tracy Beth Høeg, M.D., Ph.D., Acting Director, CDER (Mar. 26, 2026).
[117] *See* Walton Report, *supra* note 112, Appendix B: Documents Relied Upon.
[118] 21 C.F.R. § 20.61(e).
[119] Letter from Tracy Beth Høeg, M.D., Ph.D., Acting Director, CDER, to Dr. Nicole Cheung, Amgen (Apr. 27, 2026), https://www.fda.gov/media/192160/download?attachment.
[120] 91 Fed. Reg. at 23278.

Amgen had informed the Center of the ongoing 2026 readjudication, the Center elected to disclose in the NOOH ADVOCATE patient ID numbers, patient treatment group assignments, and adjudication results without redactions, notwithstanding Amgen's efforts to inform the Agency that these redactions should be made to avoid the risk of unblinding and biasing the ongoing readjudication conducted by DCRI.[121] The Center released this information publicly, with no process for review or redaction.

After Amgen requested that the Center pause publication and allow it an opportunity to propose appropriate redactions, CDER invoked the normal FOIA process of allowing a 10-day period for Amgen to propose redactions before making confidential commercial information or other protected materials public with respect to certain attachments to its NOOH.[122] Amgen did so, submitting proposed redactions on May 18, 2026.

III. LEGAL FRAMEWORK

A. Standards For Withdrawal

CDER's NOOH invokes two separate provisions of the FDCA as a basis for withdrawal—Section 505(e)(3) and Section 505(e)(5).

1. Section 505(e)(3) Requires Consideration Of The Totality Of The Evidence Of Effectiveness

Section 505(e)(3) addresses whether, on the basis of new information evaluated together with the evidence available at the time of approval, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in labeling.[123] Section 505(e)(3) focuses on the evidentiary basis for effectiveness.

a. Substantial evidence

Under the FDCA, sponsors are required to demonstrate "substantial evidence" of effectiveness for approval of an NDA.[124] Historically, FDA expected sponsors to demonstrate "substantial evidence" through two adequate and well-controlled trials in humans. In the Food and Drug Administration Modernization Act ("FDAMA") of 1997, Congress amended the FDCA to clarify that the substantial evidence standard may be met with "data from *one* adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after

[121] Amgen was able to avoid this risk by acting quickly to have DCRI require adjudicators to attest that they had not viewed the patient information published by the Agency in the NOOH.
[122] Letter from Howard Philips, Director, Division of Information Disclosure Policy, Office of Regulatory Policy, to Nicole Cheung, Manager, Global Regulatory Affairs, Amgen (May 7, 2026).
[123] *See* 21 U.S.C. § 355(e)(3); 21 C.F.R. § 314.150(a)(2)(iii).
[124] *See* 21 U.S.C. § 355(d). "Substantial evidence" is defined in the provision as "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." *Id.*

such investigation)."[125] In February 2026, FDA leadership reiterated the Agency's statutory authority to grant approvals on the basis of one adequate and well-controlled clinical trial with confirmatory evidence and emphasized that "a one-trial requirement will be the FDA's new default standard."[126] The February 2026 statement also highlighted that FDA has exercised "disease-by-disease flexibility" in considering the body of evidence required to demonstrate efficacy for a particular drug.[127]

FDA regulations and guidance acknowledge that there are a range of clinical trial designs that can be considered "adequate and well-controlled" and are sufficient to establish efficacy.[128] These include, among other things, "active treatment concurrent control."[129] In addition, the Agency acknowledges that "the clinical context is critical to informing the approach to establishing substantial evidence of effectiveness," including whether regulatory flexibility may be warranted, and "[c]onsiderations include, for example, disease severity, unmet need, and disease rarity."[130]

> These clinical considerations should not be considered individually, but rather holistically, as more than one consideration will often be relevant. For example, many rare diseases are life-threatening and lack available therapy. In general, all relevant clinical considerations (e.g., disease severity, unmet need, and disease rarity) should inform the extent and types of flexibilities that may be appropriate. For example, certain flexibilities might be more acceptable for a rare disease that is life-threatening and lacks available therapies than another rare disease with less severe consequences with multiple therapeutic options already available. Both of these scenarios, however, present a very different clinical context than a common, nonserious disease with several available treatment options.[131]

Non-inferiority trials against an active control are a credible and FDA-recognized path to demonstrating drug effectiveness that offer meaningful comparisons against standard of care:

> Establishing superiority to a randomized concurrent control group (whether an active control or placebo) generally provides strong evidence of effectiveness. Other types of designs can support effectiveness in certain circumstances. For example, designs intended to show non-inferiority (NI) against an active control can be credible and appropriate in situations in which the active control

[125] Pub. L. No. 105-115, 111 Stat. 2296, 2313 (1997) (current version at FDCA Section 505(d)) (emphasis added).
[126] Vinay Prasad, M.D., M.P.H. & Martin A. Makary, M.D., M.P.H., *One Pivotal Trial, the New Default Option for FDA Approval—Ending the Two-Trial Dogma*, 394 NEJM 815, 815 (2026).
[127] *See id.*
[128] FDA, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry* at 4 (June 2026), https://www.fda.gov/media/133660/download ["Substantial Evidence Draft Guidance 2026"]; *see also* 21 C.F.R. § 314.126(b).
[129] Substantial Evidence Draft Guidance 2026, *supra* note 128, at 4.
[130] *Id.* at 14.
[131] *Id.*

> has shown a consistent and large effect in prior superiority trials conducted in a patient population and clinical setting similar to the trial being planned. NI trials provide relevant comparisons against standard of care and can facilitate collection of long-term controlled data to inform the benefit-risk assessment.[132]

When "there is an effective treatment that provides an important benefit (e.g., life-saving or preventing irreversible injury) available to patients for the condition to be studied in the trial[]" a non-inferiority active control study design may be used instead of a superiority design.[133]

FDA has approved drugs for treatment of rare diseases, including AAV, on the basis of single adequate and well-controlled trials demonstrating non-inferiority. For example:

- In April 2011, orphan-designated RITUXAN (rituximab) received approval for use in combination with glucocorticoids for the treatment of patients with Wegener's Granulomatosis ("WG") and MPA,[134] two forms of AAV. Approval was "based on a single clinical efficacy and safety study," the Rituximab in ANCA-Associated Vasculitis ("RAVE") trial, which was "a randomized, double-blind, active-controlled, multicenter, non-inferiority study."[135] The "pre-specified non-inferiority margin was a treatment difference of 20%," and "the study demonstrated non-inferiority of Rituxan to cyclophosphamide for complete remission at 6 months [approximately 26 weeks]."[136] The CDER review team highlighted the unmet patient need and seriousness of the disease in explaining the rationale for the non-inferiority trial design: "Currently, there are no medications approved for WG and MPA, and because of the serious course of the disease, a placebo controlled trial would not be ethical. Thus, the use of a NI design is reasonable."[137] The review package reflects that "the applicant provided [a] rationale for the study design of non-inferiority and justified a single efficacy study in the submission, thereby demonstrating that the quality and quantity of efficacy data were appropriate for rituximab to be efficacious."[138]

- In June 2024, orphan-designated PIASKY (crovalimab-akkz) received approval for treatment of paroxysmal nocturnal hemoglobinuria ("PNH") based on "[s]ubstantial evidence of effectiveness . . . established based on one adequate and well-controlled clinical study," a "randomized, open-label, active-controlled [], *noninferiority*, multicenter trial," plus confirmatory evidence.[139] The CDER review team noted that PNH "is a rare, serious, life-threatening disease" and explicitly recognized (1) that "[i]t is

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[132] *Id.* at 4.
[133] FDA, *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry* at 7 (Nov. 2016), www.fda.gov/media/78504/download.
[134] CDER, *Supplement BLA Approval* (BLA 103705/S-5344) (Apr. 19, 2011), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/103705s5344ltr.pdf.
[135] CDER, *Approval Package* (BLA 103705/S-5344) at PDF 40, 49 (Apr. 19, 2011), https://www.accessdata.fda.gov/drugsatfda_docs/bla/2011/103705Orig1s5344.pdf.
[136] *Id.* at PDF 40.
[137] *Id.* at PDF 64, 81.
[138] *Id.* at PDF 175.
[139] CDER, *Integrated Review* (NDA 761388) at PDF 33 (June 20, 2024), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/761388Orig1s000IntegratedR.pdf (emphasis added).

reasonable in this situation to establish effectiveness based on one adequate and well-controlled study plus confirmatory evidence" and (2) that the non-inferiority trial submitted in support of approval was "an adequate and well-controlled study that provides persuasive evidence of . . . effectiveness."[140]

- Similarly, in explaining the August 2021 approval of orphan-designated SKYTROFA (lonapegsomatropin-tcgd) for treatment of pediatric growth hormone deficiency ("PGHD") on the basis of a Phase 3 non-inferiority trial, the CDER review team noted that "[g]iven the history of this class of products *and because PGHD is a rare disease*, FDA has accepted a single adequate and well-controlled study for the approval of hGH products . . . for the PGHD indication."[141]

- In addition, in April 2013, orphan-designated PROCYSBI (cysteamine bitartrate) received approval for treatment of nephropathic cystinosis on the basis of one Phase 3 non-inferiority trial, which "serve[d] as the lone adequate and well controlled study of [the] clinical development program."[142] Despite challenges identifying the appropriate non-inferiority margin, the CDER review team commented that the trial design "m[et] the regulatory requirements for adequate and well-controlled trials as delineated in 21 CFR 314.126."[143] The review team also explicitly acknowledged the role that rare-disease status played in evidence generation during the clinical development program, explaining that "[d]ue to the orphan status of nephropathic cystinosis, there was only one small clinical safety and efficacy study conducted by [the sponsor] prior to [the Phase 3 trial]."[144] Thus, in practice, CDER has exercised regulatory flexibility with respect to the body of evidence required to support approval of rare-disease therapies, including by accepting a non-inferiority trial as a single adequate and well-controlled trial providing substantial evidence of efficacy with confirmatory evidence.

b. Totality of the evidence

FDA uses the totality of the evidence approach when considering the quantity and quality of evidence to support effectiveness for new drugs.[145] Many types of data can be used as

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[140] *Id.* at PDF 76.
[141] CDER, *Summary Review* (NDA 761177) at PDF 3-4 (July 30, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761177Orig1s000SumR.pdf (emphasis added).
[142] CDER, *Statistical Review(s)* (NDA 203389) at PDF 4, 26 (Apr. 30, 2013), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203389Orig1s000StatR.pdf ["PROCYSBI Clinical Review"].
[143] CDER, *Medical Review(s)* (NDA 203389) at PDF 50 (Apr. 26, 2013), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203389Orig1s000MedR.pdf.
[144] PROCYSBI Clinical Review, *supra* note 142, at PDF 7.
[145] *See generally* FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998), https://www.fda.gov/media/71655/download ["Clinical Evidence Guidance 1998"]; *see also* FDA, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry* at 2 (Apr. 2015), https://www.fda.gov/media/82647/download ("The totality-of-the-evidence approach that FDA will use to review applications for biosimilar products, consistent with a longstanding Agency approach to evaluation of scientific evidence . . . The guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* provides insight into the concept of the *totality-of-the-evidence* approach in a different context (i.e., considerations of both the quantity and quality of the evidence to support effectiveness for drugs and biological products)" (emphasis in original)); FDA, *Developing Targeted Therapies in Low-Frequency*

"confirmatory" evidence to supplement the single adequate and well-controlled trial, and FDA guidance provides as many as seven examples, including real-world data ("RWD") or RWE.[146] The confirmatory evidence may even consist of studies other than the pivotal study, such as earlier-phase studies and "supportive data outside of a controlled trial."[147] The February 2026 statement and June 2026 draft guidance document further emphasized that confirmatory evidence can come from a range of sources, including "mechanistic science, data from a related indication, animal models, information from other drugs of the same class, real-world evidence, or a second adequate and well-controlled study."[148]

FDA's use of the totality of the evidence approach is also evident in its assessment of a new drug's benefit-risk profile. According to FDA, its benefit-risk assessment of a product for its proposed indication is a case-specific determination that requires not only an assessment of the evidence of safety and effectiveness submitted in the NDA, but also "careful consideration of a complex set of factors, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks."[149] This approach is consistent with FDA regulations at 21 C.F.R. Part 312, Subpart E, which are intended to speed the availability of new therapies to patients with serious conditions, especially when there are no satisfactory alternative therapies. As stated therein:

> [W]hile the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The [FDA] has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely debilitating illnesses, than they would accept from products that treat less serious illnesses. *These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated*.[150]

Molecular Subsets of a Disease: Guidance for Industry at 4 (Oct. 2018), https://www.fda.gov/media/117173/download ("As with all new drug approvals, the FDA will consider the totality of evidence in weighing the benefits and risks of the drug").

[146] *See FDA*, *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence: Guidance for Industry* (Sept. 2023), https://www.fda.gov/media/172166/download ["Draft Substantial Evidence Guidance 2023"].

[147] *See* Substantial Evidence Draft Guidance 2026, *supra* note 128, at 4.

[148] Prasad & Makary, *supra* note 126, at 815; *see* Substantial Evidence Draft Guidance 2026, *supra* note 128, at 15-16.

[149] FDA, *Benefit-Risk Assessment for New Drug and Biological Products: Guidance for Industry* at 12-14 (Oct. 2023), https://www.fda.gov/media/152544/download ["Benefit-Risk Assessment Guidance 2023"].

[150] 21 C.F.R. § 312.80 (emphasis added). For example, FDA used its totality of the evidence approach in a recent approval involving PAPZIMEOS (zopapogene imadenovec-drba), the first immunotherapy for recurrent respiratory papillomatosis, a rare, chronic disease that causes recurrent growth of benign tumors in the respiratory tract. FDA,

c. Particular considerations for rare-disease therapies

Under the 21st Century Cures Act, FDA has recognized the high level of unmet medical need in rare-disease patient populations and affirmed its commitment to supporting the development of treatments for rare diseases, which by their nature require regulatory flexibility.[151] Specifically, in the rare-disease context, FDA has stated that its "regulations provide flexibility in how the regulatory standard [for demonstrating evidence of efficacy] may be met," and that "[t]his flexibility extends from the early stages of development to the design of adequate and well-controlled clinical investigations required to demonstrate effectiveness to support marketing approval and to establish safety data needed for the intended use."[152] A 2024 GAO report on rare diseases further confirms this approach by the Agency. As noted in the report, although "[r]are disease drugs must meet the same standards as other drugs to be marketed," "FDA regulations provide flexibility in determining the evidence needed to meet that standard."[153]

In addition, FDA has prioritized incorporating patient perspectives into its benefit-risk assessments in recent years, including for rare-disease treatments, in light of the congressional directive in the 21st Century Cures Act to issue guidance "regarding the collection of patient experience data, and the use of such data and related information in drug development."[154] In 2023 guidance, FDA noted that "[d]ifferent types of patient experience data can inform nearly every aspect of FDA's benefit-risk assessment," and explained that even as FDA must conduct its own benefit-risk assessment, "FDA carefully weighs and considers the patient perspective including available patient experience data. *When patients indicate that a benefit is important to them in the treatment of their condition, this informs FDA's assessment of the extent of*

FDA Approves First Immunotherapy for Recurrent Respiratory Papillomatosis (Aug. 14, 2025), https://www.fda.gov/news-events/press-announcements/fda-approves-first-immunotherapy-recurrent-respiratory-papillomatosis. Prior to approval of PAPZIMEOS, patients lacked access to any approved medical therapies that could eliminate the need for repeated surgical procedures. *Id.* Approval was based on results from a single-arm, open-label trial. *Id.* In the accompanying press release, Agency leadership emphasized that "[t]he FDA will always demand the correct clinical study for the specific medical product and disease. Our requirements for products given to tens of millions of healthy people will be different than products given to at most hundreds or thousands of patients with unique diseases." *Id.* The PAPZIMEOS review team further explained that "[t]his comprehensive approach balanced the urgent unmet medical need for this life-threatening rare condition against study limitations, ultimately determining that the substantial treatment effect . . . in a previously untreatable condition justified approval with appropriate post-marketing oversight while maintaining scientific rigor." *Summary Basis for Regulatory Action* (BLA 125832) at 16-17 (Aug. 14, 2025), https://www.fda.gov/media/188592/download?attachment.

[151] *See*, *e.g.*, FDA, *FDA Rare Disease Innovation Hub* (Apr. 20, 2026), https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/fda-rare-disease-innovation-hub ["FDA Rare Disease Innovation Hub"]; FDA, *Accelerating Rare Disease Cures (ARC) Program* (May 26, 2026), https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program; FDA, *Rare Diseases Team* (Aug. 29, 2023), https://www.fda.gov/about-fda/accelerating-rare-disease-cures-arc-program/rare-diseases-team.

[152] FDA, *Rare Diseases: Considerations for the Development of Drugs and Biological Products: Guidance for Industry* at 3 (Dec. 2023), https://www.fda.gov/media/119757/download.

[153] U.S. Gov't Accountability Off., *RARE DISEASE DRUGS: FDA Has Steps Underway to Strengthen Coordination of Activities Supporting Drug Development*, GAO 25-106774 (Nov. 2024), https://www.gao.gov/assets/gao-25-106774.pdf.

[154] Pub. L. No. 114-255, § 3002(a), 130 Stat. 1084 (2016); 21 U.S.C. § 360bbb-8c note (Patient-Focused Drug Development Guidance).

benefit."[155] To that end, FDA has undertaken multiple initiatives to ensure consideration of patient perspectives, including Patient-Focused Drug Development, which is "a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation,"[156] and the Rare Disease Innovation Hub, which reflects FDA's view that "[f]undamental to the mission of the [Agency] is to engage patients and caregivers—to understand their unique perspectives and experiences and keep these front of mind as we review medical products for rare disease patients."[157]

FDA has considerable discretion in determining the type and quantity of data and information that a drug intended for a rare disease must provide to meet the regulatory standards. FDA also prioritizes rare-disease patient perspectives when considering the benefit-risk profile of therapeutic options for rare diseases.

For example, regarding the March 25, 2026 approval of the rare-disease drug AVLAYAH (tividenofusp alfa-eknm), FDA leadership explicitly acknowledged: "The FDA is capable of doing two things: one, exercising regulatory flexibility; and two, complying with our obligation under the law to approve drugs based on 'substantial evidence' of effectiveness. We will continue to do everything we can to accelerate treatments for rare diseases."[158] Similarly, the Agency explained that its March 10, 2026 expansion of the approval for WELLCOVORIN (leucovorin calcium) for treatment of a rare genetic condition "reflects the agency's commitment to accelerating cures and expanding treatment options including for patients with serious and unmet needs."[159] There, FDA exercised regulatory flexibility by granting approval "based on a systematic review of the published literature on the topic, including published case reports with patient-level information, as well as mechanistic data."[160] As Agency leadership explained, the approval "demonstrates the FDA's commitment to rapidly identifying effective treatments for ultra rare diseases while maintaining the same evidentiary standards for approval" and "provides a good example of how observational or 'real world' evidence can lead to an FDA approval."[161]

2. Section 505(e)(5) Requires An Untrue Statement Of Material Fact In The Application

Section 505(e)(5) addresses whether "the application contains any untrue statement of a material fact,"[162] and FDA's implementing regulation at 21 C.F.R. § 314.150(c)(2)(iv) provides

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[155] *See* FDA, *Benefit-Risk Assessment for New Drug and Biological Products: Guidance for Industry* at 12-14 (Oct. 2023), https://www.fda.gov/media/152544/download (emphasis added).
[156] FDA, *CDER Patient-Focused Drug Development* (May 15, 2026), https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.
[157] FDA Rare Disease Innovation Hub, *supra* note 151.
[158] FDA, *FDA Approves Drug to Treat Neurologic Manifestations of Hunter Syndrome* (Mar. 25, 2026), https://www.fda.gov/news-events/press-announcements/fda-approves-drug-treat-neurologic-manifestations-hunter-syndrome.
[159] FDA, *FDA Approves First Treatment for Patients with Cerebral Folate Transport Deficiency* (Mar. 10, 2026), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-cerebral-folate-transport-deficiency.
[160] *Id.*
[161] *Id.*
[162] 21 U.S.C. § 355(e)(5); *see also* 21 C.F.R. § 314.150(a)(2)(iv) (containing an identical limitation).

for notice and an opportunity for a hearing where the Center contends that "the application . . . contains any untrue statement of a material fact."[163] The text of both the statute and regulation are unambiguous:[164] Both apply only when an application contains a statement that is "untrue."

Starting with the text of the statute, untrue simply means "not according with the facts; false."[165] The structure of the FDCA similarly confirms that Congress intended for Section 505(e)(5) to reach only literally untrue—false—statements. It does not include language on "misleading" statements like other provisions of the FDCA. Section 502(a)(1) deems a drug misbranded when its labeling is "false or misleading in any particular," and Section 201(n) expressly provides that failures to reveal material facts in light of representations made are considered "misleading."[166] Later, Congress added labeling that is "false or misleading in any particular" as a basis for withdrawing a drug application.[167] Other statutes have a similar structure: they reach both "false or misleading representation[s] of fact,"[168] as well as material omissions.[169] Yet, in drafting Section 505(e)(5), it did not use such language. Instead, Congress used the narrower language in Section 505(e)(5): an "untrue statement of material fact." That choice must be given meaning. As discussed in Section IV.B below, the TAVNEOS application did not contain untrue statements; the statements identified by CDER are true, and ChemoCentryx was not required to provide the narrative now demanded by the Center.

B. Standards For Judgment As A Matter Of Law And A Hearing

As an initial matter, CDER can and should rescind the NOOH. CDER has the option to rescind the NOOH and discontinue the proceeding if further information provided by the hearing requestor demonstrates that the proceeding is no longer necessary.[170] For example, CDER's predecessor, the Bureau of Drugs, rescinded a NOOH because the applicant for an NDA initially deemed not approvable submitted "additional data" that led to approval.[171] There, the Director of

[163] 21 C.F.R. § 314.150(a)(2)(iv).
[164] *Cf. Groff v. DeJoy*, 600 U.S. 447, 468 (2023) ("[S]tatutory interpretation must begin with, and ultimately heed, what a statute actually says.").
[165] *See Untrue*, Merriam-Webster's Third New International Dictionary 2513 (1976) (capitalization omitted).
[166] *See* 21 U.S.C. §§ 352(a)(1), 321(n).
[167] *See* 21 U.S.C. § 355(e)(3).
[168] 15 U.S.C. § 1125(a)(1) (emphasis added).
[169] *E.g.*, 7 U.S.C. § 6b(e)(2) (making it unlawful "to make any untrue statement of a material fact or to omit to state a material fact necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading"); 15 U.S.C. § 7241(a)(2) (requiring the principal executive officer's certification that financial reports do not contain "any untrue statement of material fact or omit to state a material fact necessary in order to make the statement made, in light of the circumstances in which such statements were made, not misleading").
[170] 43 Fed. Reg. 14739, 14739 (Apr. 7, 1978) ("In response to this notice, the firm filed a hearing request . . . . The firm also filed additional data. Subsequently, on the basis of the additional data, the NDA was approved by letter . . . . This action effectively moots the request for hearing."); *see also* 85 Fed. Reg. 43852, 43853 (July 20, 2020) (rescinding, prior to reissuance, a NOOH that proposed to withdraw approval of carbadox, a new animal drug, citing that the Agency had "reviewed information submitted by the drug sponsor, including some studies submitted in response to the April 2016 NOOH, and determined that the current approved method for detecting residues of carcinogenic concern does not meet the [regulatory requirements]").
[171] 43 Fed. Reg. at 14739.

the Bureau of Drugs explained that the hearing requestor's submission of additional information "effectively moot[ed] the request for hearing."[172]

In addition, if the applicant's submission shows that the grounds cited in the NOOH are not valid—for example, that substantial evidence of effectiveness exists or the application does not contain an untrue statement of material fact—"the Commissioner will enter summary judgment for the person requesting the hearing, and rescind the notice of opportunity for hearing."[173]

Where summary judgment for the applicant is not entered, FDA regulations require that a hearing be granted if "there exists a genuine and substantial issue of fact" or if "the Commissioner concludes that a hearing would otherwise be in the public interest."[174] To establish the existence of a genuine and substantial issue of fact, the hearing requestor must "set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing."[175] That threshold showing is not a requirement that the requestor prove the ultimate merits of its position in the hearing request itself. Rather, as the D.C. Circuit recently confirmed in *Vanda Pharmaceuticals, Inc. v. FDA*, FDA may use summary-decision procedures to deny a hearing only when no material facts are genuinely disputed.[176]

Accordingly, in determining whether a hearing is warranted, the task is not to choose between competing scientific judgments or to require the application holder to conclusively prove the merits. A hearing may be denied only when "it appears conclusively from the applicant's 'pleadings' that the application cannot succeed."[177] In other words, FDA must identify a "conclusive deficiency" in the applicant's submissions to deny a hearing.[178] FDA therefore must give adequate consideration to all relevant record evidence and may not use summary disposition simply to resolve competing, reasoned scientific views against the applicant.[179]

The rigor of that "conclusive deficiency" inquiry depends on the precision of the governing standard. In *Hynson*, the Supreme Court explained that FDA could use summary-decision procedures where the statutory standard had been particularized by precise regulations that gave manufacturers "full and precise notice" of what their submissions had to contain.[180] In

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[172] *Id.*

[173] 21 C.F.R. § 314.200(g)(4); *see also* Fresenius USA, Inc., et al.; Withdrawal of Approval of 216 Abbreviated New Drug Applications, 86 Fed. Reg. 58675 (Oct. 22, 2021) (rescinding proposal to withdraw approval of three abbreviated new drug applications because sponsor had requested a hearing and shown previously submitted annual reports for the applications).

[174] 21 C.F.R. § 314.200(g)(6) (emphasis added); *see* 21 C.F.R. § 12.24(b).

[175] 21 C.F.R. § 314.200(g) (emphasis added).

[176] 150 F.4th 563, 567, 571-73 (D.C. Cir. 2025).

[177] *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 621 (1973); *Vanda*, 150 F.4th at 576-77; *Am. Cyanamid Co. v. FDA*, 606 F.2d 1307, 1315 (D.C. Cir. 1979) ("[O]ur function is not to choose among expert opinions but to determine whether FDA's evaluation of the study conclusively establishes" its invalidity.).

[178] *See Vanda*, 150 F.4th at 573; *Am. Cyanamid Co.*, 606 F.2d at 1313.

[179] *Vanda*, 150 F.4th at 573, 575, 577; *Am. Cyanamid Co.*, 606 F.2d at 1319.

[180] *Hynson*, 412 U.S. at 622. Indeed, *Hynson* cautioned that summary disposition against an applicant may not be proper where the operative standards are imprecise and "call for the exercise of discretion or subjective judgment,"

American Cyanamid Co. v. FDA, the D.C. Circuit acknowledged that limitation, explaining that when a statute or regulation uses broad judgmental concepts without particularization, "it is difficult to demonstrate that a submission is conclusively deficient."[181] And more recently, in *Vanda*, the D.C. Circuit explained that its review is more searching where FDA relies on a "more general standard that provides less precise guidance."[182]

Thus, when the requestor identifies specific facts, data, or expert evidence that, if credited, could affect the outcome, and FDA's contrary position turns on scientific or evidentiary judgment under a broad standard, the submission is not "conclusively deficient." *Vanda* illustrates the kinds of record showings that can necessitate a hearing.

- *First*, FDA may not avoid a hearing by mischaracterizing reasoned record evidence as "conclusory."[183] In *Vanda*, the applicant offered expert testimony that was "specific, reasoned, and rooted in evidence"—the experts "fully explained their reasons" for their conclusions and "cited studies from their field to support that position." Because that testimony addressed FDA's objections, FDA could not dismiss the applicant's position as an unsupported assumption without adequately explaining a conclusive flaw in the evidence demonstrating that no dispute existed.[184]

- *Second*, FDA disagreement with the scientific weight or applicability of a sponsor's evidence generally does not justify summary disposition unless FDA identifies a conclusive defect. In *Vanda*, FDA attempted to undermine the applicant's experts by questioning the validity and applicability of the studies on which they relied. The D.C. Circuit explained that this argument "only helps to prove Vanda's point" because it showed a genuine dispute over the strength of the scientific evidence.[185]

- *Third*, and relatedly, credible expert disagreement is the kind of factual and scientific dispute that ordinarily demonstrates a genuine and substantial issue of material fact for a hearing. *Vanda* emphasized that, where FDA and the applicant's experts offered conflicting, nonconclusory views on scientific questions, "the dispute remains a battle of experts who offer conflicting and nonconclusory views—and that is exactly the type of dispute our precedent says is inappropriate for resolution without a hearing."[186] That principle is consistent with *American Cyanamid*, which held that FDA may not deny a hearing merely by choosing among competing expert interpretations unless the applicant's showing is conclusively deficient so as not to require resolution at a hearing.[187]

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because qualitative terms such as "adequate" and "suitable" "do not lend themselves to clear-cut definition." *Id*. at 621 n.17.

[181] *Am. Cyanamid Co.*, 606 F.2d at 1312-13.

[182] *Vanda*, 150 F.4th at 573.

[183] *Id.* at 574-75, 576 & n.1, 577.

[184] *Id.* at 573-75.

[185] *Id.* at 575 (internal citations omitted).

[186] *Id.* at 576 n.1.

[187] *Am. Cyanamid Co.*, 606 F.2d at 1315-16; *Vanda*, 150 F.4th at 577.

Vanda therefore highlights that when the sponsor provides evidence, which may include expert testimony, that is specific, reasoned, and contrary to FDA's position, in the absence of any "conclusive flaw" that renders that evidence facially irrelevant, the Agency *must* grant a hearing to resolve the factual disputes that the sponsor has raised.[188]

FDA's prior actions further illustrate the evidence that the Agency has deemed sufficient to justify a hearing in other contexts. For example, in 2021, in the accelerated approval context, FDA granted a hearing to Covis Pharma Group/Covis Pharma GmbH ("Covis") on the Agency's proposal to withdraw approval of MAKENA (hydroxyprogesterone caproate injection) on efficacy grounds. There, the Commissioner's designee found that the evidence Covis provided had justified a hearing, explaining: "Covis's response provides *specific challenges to the factual and scientific bases underlying CDER's proposal and includes or describes data and information in support of those challenges*. I find that, *taken as a whole*, Covis's response raises genuine and substantial issues of fact appropriate for a hearing . . . ."[189] Consistent with the *Vanda* court's observation that FDA must "give[] adequate consideration to all relevant evidence in the record,"[190] the Agency's rationale for granting Covis's request for a hearing emphasizes that the assessment of whether the sponsor has raised a genuine and substantial issue of fact justifying a hearing is based on the totality of the evidence.

C. New Drug Application And Approval Standards

Section 505(b) of the FDCA generally requires an NDA to include full reports of investigations showing whether the drug is safe and whether it is effective for use, a full list of the drug's components, manufacturing information, samples, specimens of proposed labeling, as well as other information required by FDA.[191] Section 505(d) directs FDA to refuse approval of an NDA if, among other grounds, the investigations submitted in the application do not include substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in labeling.[192]

FDA's regulations implement those provisions. For example, the regulations at 21 C.F.R. § 314.50 discuss the general format and content of an NDA.[193] FDA regulations at 21 C.F.R. § 314.126 discuss the characteristics of adequate and well-controlled studies that support substantial evidence, including "adequate" measures to minimize bias and an "adequate" analysis of the study results.[194]

FDA also has published guidance documents to assist sponsors of NDAs with clinical-trial conduct and statistical analysis. This includes: (1) International Conference on Harmonization ("ICH") E9, *Statistical Principles for Clinical Trials*, which advises on statistical

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[188] *Vanda*, 150 F.4th at 575.
[189] Letter from RADM Denise M. Hinton, Chief Scientist, FDA, to Rebecca K. Wood, Sidley Austin LLP, at 5 (Docket No. FDA-2020-N-2029-0072) (Aug. 18, 2021), https://www.regulations.gov/document/FDA-2020-N-2029-0072 (emphasis added).
[190] *See Vanda*, 150 F.4th at 573 (quoting *Pharm. Mfg. Rsch. Servs.*, 957 F.3d at 266).
[191] 21 U.S.C. § 355(b).
[192] 21 U.S.C. § 355(d).
[193] *See* 21 C.F.R. § 314.50(c), (d).
[194] *See* 21 C.F.R. § 314.126(b)(5), (7).

principles for clinical trials submitted in marketing applications;[195] and—in September 2025—(2) ICH E6(R3), *Good Clinical Practice*, which advises on, among other things, trial conduct, data quality, investigator and sponsor responsibilities, maintenance of records, data handling, and randomization and unblinding.[196] As codified in FDA's Good Guidance Practice regulation, "[g]uidance documents do not establish legally enforceable rights or responsibilities" and "do not legally bind the public."[197] Courts have recognized the non-binding nature of FDA guidance documents, declining to "transform[] the FDA's non-binding guidelines into strict requirements based only on hindsight."[198]

IV. ARGUMENT

CDER has not demonstrated—and cannot demonstrate—that withdrawing the approval of TAVNEOS is warranted under either Section 505(e)(3) or Section 505(e)(5).

First, CDER's claim under 505(e)(3) is misplaced. The totality of the evidence gives confidence in the efficacy of TAVNEOS. The ADVOCATE study provides substantial evidence regarding the efficacy of TAVNEOS as an adequate and well-controlled clinical trial. The 2026 readjudication confirms the non-inferiority of TAVNEOS. The treatment effect favored TAVNEOS at Week 52 and statistical significance for superiority was narrowly missed (by one patient). Thus, the results support the original findings and provide ample evidence of efficacy in the unique context of rare-disease patients presented here. Substantial evidence of effectiveness is not undermined by the 2019 readjudication. What the Center has characterized as "data manipulation" was a prespecified quality control process that is not prohibited by FDA regulations. Despite Amgen's acknowledgement that the process would not occur in an Amgen-run study, CDER's position is not justified: ChemoCentryx did not invent data, alter source records, or override a blinded adjudicator's clinical judgment during that process. It identified nine patients, from both trial arms, with endpoint classifications inconsistent with prespecified trial rules—including errors that had been identified previously but not corrected—and provided them for blinded readjudication. It is not appropriate to disqualify the ADVOCATE trial results in their entirety from contributing to substantial evidence of effectiveness.

The 2026 readjudication, which was conducted by DCRI, addresses CDER's concerns with the handling of the primary endpoint data in 2019 and further contributes to the totality of the evidence supporting substantial evidence of effectiveness. In addition, supportive and corroborative results from Phase 2 studies and the totality of evidence from the post-marketing setting, which has encompassed more than 25,000 patient-years of exposure, provides ample support and confirmatory evidence for substantial evidence of effectiveness. Real-world evidence across comparative studies, large cohorts, and post-marketing studies consistently provides data supporting TAVNEOS's role in achieving remission, reducing relapse, minimizing glucocorticoid exposure, and supporting kidney recovery. These results show that clinicians are using TAVNEOS to effectively control disease while minimizing steroid use, which can confer

[195] FDA, *E9 Statistical Principles for Clinical Trials: Guidance for Industry* (Sept. 1998), https://www.fda.gov/media/71336/download ["ICH E9 Guidance"].
[196] FDA, *E6(R3) Good Clinical Practice: Guidance for Industry* (Sept. 2025), https://www.fda.gov/media/169090/download ["ICH E6(R3) Guidance"].
[197] 21 C.F.R. § 10.115(d).
[198] *See, e.g.*, *In re Ocugen, Inc. Sec. Lit.*, 659 F. Supp. 3d 572, 590-91 (E.D. Pa. 2023).

significant benefits to patients by reducing their risks for steroid-related side effects and toxicities.

Second, CDER's claim under 505(e)(5) is likewise misplaced. Section 505(e)(5) applies only if "the application contains any untrue statement of material fact."[199] CDER identifies several statements related to the ADVOCATE readjudication that it claims were untrue. In fact, those statements were accurate. And to the extent CDER is asserting that ChemoCentryx should have included additional narrative regarding the readjudication process in the TAVNEOS NDA, CDER identifies no regulatory or other legal requirement mandating the disclosure it now demands.

Amgen is therefore entitled to judgment as a matter of law under 21 C.F.R. § 314.200(g)(4). At a minimum, Amgen must be afforded the opportunity to correct CDER's one-sided—and erroneous—characterization of the facts in a hearing. That is especially true where CDER's allegations rest on disputed scientific, statistical, regulatory, and factual issues. Those disputes present genuine and substantial issues of fact under 21 C.F.R. §§ 12.24(b) and 314.200(g)(6). A hearing is also warranted given the compelling patient need for this rare-disease treatment and totality of the circumstances. Accordingly, a hearing would otherwise be in the public interest under 21 C.F.R. § 314.200(g)(6).

A. The Totality Of The Evidence Supports Continued Approval Of TAVNEOS

CDER's core rationale for withdrawing TAVNEOS under FDCA Section 505(e)(3) is that the "new information regarding data manipulation, along with the evidence available to CDER when the application was approved, [mean] there is a lack of substantial evidence that TAVNEOS will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling."[200] After its recounting of selected aspects of the 2019 readjudication, which it erroneously labels as "data manipulation," CDER declares that "in light of the facts outlined above, CDER can no longer conclude that there is, or ever has been, a valid demonstration of substantial evidence of effectiveness for TAVNEOS."[201]

Amgen disagrees. First, the ADVOCATE study provides substantial evidence regarding the efficacy of TAVNEOS as an adequate and well-controlled clinical trial. The new independent 2026 readjudication provides confidence in the study results. Second, the totality of evidence presented at the time of approval and supplemented by data from Phase 2 trials and post-marketing real world evidence shows consistency in the effects of TAVNEOS and provides ample confirmatory evidence for substantial evidence of efficacy. The importance of the issues presented here are underscored by the accompanying declarations which further demonstrate the genuine and substantial issues of fact for resolution.

[199] 21 U.S.C. § 355(e)(5).
[200] 91 Fed. Reg. at 23279.
[201] *Id.* at 23287.

1. ADVOCATE Is An Adequate And Well-Controlled Study That Provides Substantial Evidence Of Effectiveness

ADVOCATE continues to provide substantial evidence of effectiveness. ADVOCATE was a Phase 3, randomized, double-blind, double-dummy, active-controlled, multi-center trial. Its primary objective was to evaluate the efficacy of avacopan. Because of the complexity of the patient population and concomitant medications, ADVOCATE's primary endpoints of remission and non-remission at Week 26 and Week 52 were adjudicated by an Adjudication Committee operating under an Adjudication Committee Charter. The criteria for adjudication of patients were prespecified in trial documents, including the Protocol, SAP, and Adjudication Committee Charter. The ADVOCATE results demonstrate the efficacy of TAVNEOS. The ADVOCATE trial results are described in detail in Appendix A (Section 5.3).

The 2026 readjudication addresses CDER's concerns with the handling of the primary endpoint data in 2019 and further contributes to the totality of the evidence supporting substantial evidence of effectiveness. The results of the 2026 readjudication demonstrated consistency in results favoring avacopan. Non-inferiority for disease remission and sustained remission was statistically significant at Weeks 26 and 52. Although superiority results for sustained remission at Week 52 from the 2026 readjudication did not meet statistical significance, the results showed, as confirmed by Dr. Gibbons, that the difference between treatment groups for sustained remission at Week 52 was 9.8% (95% CI: -0.3%, 19.9%; 1-sided p-value 0.0282), favoring TAVNEOS.[202] It should be acknowledged that the ADVOCATE study was originally powered to show an 18% treatment difference and was therefore underpowered to show statistical significance for a treatment difference of 10%. Nonetheless, the 2026 readjudication achieved borderline significance with a clear, consistent, clinically meaningful, and notable numerical increase in achievement of sustained remission at Week 52.

Dr. Gibbons similarly concluded that the 2026 readjudication demonstrated consistency favoring avacopan, explaining in his Declaration that the p-value for the superiority test at Week 52 (p=0.028) is only slightly higher than the prespecified threshold (p=0.025), and that "such a marginal miss in the pre-specified significance level is not indicative of the drug being any less efficacious than indicated by the data that was the basis for the drug's original FDA approval."[203] According to Dr. Gibbons, statisticians widely recognize that a p-value just above a threshold is not meaningfully different from one just below it and FDA is also known to not always adhere strictly to a prespecified threshold for statistical significance in its drug approval decisions.[204] Moreover, the estimated 9.8% treatment effect of TAVNEOS noted above is statistically similar to the estimated treatment effect size that was the basis for the drug's original FDA approval (i.e., 12.5% with 95% confidence interval [2.6%, 22.3%]).[205] By comparison, Dr. Gibbons's analysis of the DCRI's remission determinations finds only a slightly smaller treatment effect size—9.8% versus 12.5%—and an overlapping 95% confidence interval of -0.3% to 19.9%.

As noted above, and as Dr. Gibbons explains in his Declaration, FDA has previously approved drugs where the pivotal trial missed the prespecified significance threshold by a

[202] Gibbons Declaration, *supra* note 7, at 26.
[203] *Id.* at 24.
[204] *Id.* at 24-26.
[205] CDER Multi-Disciplinary Review, *supra* note 1, at 26.

similarly small margin. For example, in 2017, FDA approved betrixaban (a prophylaxis treatment for blood clots) based on clinical trial results where the statistical test for the primary endpoint had a p-value of 0.054, even though the prespecified p-value threshold for statistical significance was 0.05.[206] Similarly, in 2018, FDA approved migalastat for the treatment of Fabry disease despite failing to reach statistical significance (p-value of 0.30 versus the prespecified p-value of 0.05) in the general intention-to-treat population of the pivotal clinical trial.[207] In 2021, FDA approved viloxazine as a treatment for attention deficit hyperactivity disorder for children and adolescents (ages 6–17) despite a statistical near-miss in Study 304, where the 600-mg treatment arm failed to achieve significance, yielding a two-sided p-value of 0.071 against the pre-specified threshold of 0.05.[208] More recently, in 2023, FDA approved an additional indication for secukinumab (a monoclonal antibody that reduces inflammation in autoimmune diseases) despite the drug failing to reach the prespecified statistical significance level for the primary efficacy endpoint in the SUNSHINE trial, one of the two pivotal trials.[209] Thus, the Agency has not previously viewed borderline statistical significance as a barrier to approval.

Overall, the level of concordance between the 2019 and 2026 analyses of the trial data was strong. Both reached the same conclusions regarding the first, second, and fourth primary endpoints. And with respect to the third endpoint (superiority at Week 52), both sets of analyses are very consistent in terms of treatment effect and similar in statistical significance. The strong concordance supports the reproducibility and reasonableness of the first adjudication and weighs against outcome-driven bias. Because endpoint determinations required application of clinical judgment to complex patient profiles and clinical records, it is expected that reasonable experts could reach different conclusions for some patients—for example, regarding whether a reported sign or symptom reflected active AAV, residual damage, or another condition. And although with respect to the third endpoint (superiority at Week 52), results fell marginally outside the prespecified significance threshold according to the 2026 analysis, both sets of analyses are very consistent in terms of treatment effect and similar in statistical significance.[210]

In November 2019, the Adjudication Committee readjudicated eight Week 26 endpoint determinations and five Week 52 endpoint determinations related to nine patients total. DCRI agreed with six of eight endpoint determinations at Week 26 and with four of five endpoint determinations at Week 52. Overall, for the nine patients, the DCRI readjudication confirmed seven of the nine patients' disease remission results at Week 26 and eight of the nine patients' sustained remission results at Week 52. The two patients for whom DCRI's assessment differed—patients 440-002 and 854-001—were identified as having used glucocorticoids for

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[206] Kennedy-Shaffer, *When the Alpha is the Omega: P-Values, 'Substantial Evidence,' and the 0.05 Standard at FDA*, 72 FOOD & DRUG L.J. 595 (2017).
[207] CDER, *Multi-Discipline Review* (NDA 208623) (2018), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208623Orig1s000MultidisciplineR.pdf.
[208] CDER, *Integrated Review* (NDA 211964) at 33, 37 (2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211964Orig1s000IntegratedR.pdf.
[209] CDER, *Approval Package* (BLA 125504/s063) at 91 (2023), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/125504Orig1s063.pdf.
[210] Concordance analyses demonstrated high agreement between adjudications performed by the DCRI Adjudication Committee and prior assessments, with agreement rates of 93.9% and 92.7% and Cohen's kappa values of 0.86 and 0.85 for Week 26 and Week 52 endpoints, respectively, indicating strong and reproducible endpoint classification. Collectively, these findings provide robust and internally consistent evidence supporting the non-inferiority results and the reliability of the adjudication process.

non-AAV reasons during the blinded October 2019 review, as described in Section II.C.2, and again during the November 2019 readjudication. The differences for both patients in the 2026 readjudication appear to have turned on clinical judgments regarding whether the conditions for which glucocorticoids were used (arthromyalgia and arthralgia/gout) were manifestations of AAV or separate, non-AAV conditions.

- For patient 440-002, the Investigator recorded the prednisone use as treatment for arthromyalgia "not vasculitis," with the November 2019 readjudication agreeing. DCRI appears to have disagreed with the Investigator, interpreting those symptoms as attributable to active AAV.[211]

- For patient 854-001, the Investigator recorded the prednisone use as treatment for arthralgia or gout, not AAV, with the November 2019 readjudication agreeing. DCRI appears to have disagreed with the Investigator, attributing the joint symptoms and prednisone use to active AAV.[212]

The results are highly impactful for patients and healthcare providers, as discussed further in Section IV.C, below. The median steroid exposure in the participants in the avacopan group was more than 80% lower than in the control arm, with substantially lower steroid toxicity. In addition, participants in the avacopan group had fewer relapses, better quality of life, and improved kidney function over 52 weeks when compared to the prednisone group.

In order to show consistency of efficacy from ADVOCATE, the discussion in Appendix A (Section 5.3) includes ADVOCATE results: (1) *before* readjudication of nine participants; (2) *after* readjudication of nine participants (as submitted in the NDA); (3) *excluding* the participants whose status was changed to "in remission" at Week 26 or 52 following readjudication; and (4) results based on the 2026 readjudication. As discussed above in Section IV.A.2.c, the 2026 readjudication does not constitute a new hypothesis test, and there are no different or new endpoints being tested; the objective of the DCRI's readjudication is simply to ensure an accurate and consistent assessment of the same, previously prespecified endpoints using the same, previously prespecified statistical methods. As confirmed by Dr. Gibbons, such readjudication does not introduce Type 1 error. Collectively, these findings provide consistent evidence of non-inferiority of TAVNEOS versus prednisone for disease remission and support the reliability of the adjudication process.

The key data and analyses specific to the primary efficacy endpoint at Weeks 26 and 52 are included below. Additional data and analyses for additional endpoints, including secondary endpoints, are provided in Appendix A (Section 5). At Weeks 26 and 52, TAVNEOS consistently demonstrated non-inferiority to prednisone across all analyses (Tables 2 and 6). The non-inferiority results provide strong evidence that TAVNEOS is at least as effective as the prednisone taper in achieving sustained remission. Furthermore, the positive treatment effect estimates (TAVNEOS minus prednisone taper) consistently favors TAVNEOS, providing additional evidence of a treatment benefit relative to the prednisone taper group.

[211] *See* Amgen Response to July 2025 IR, *supra* note 40, Exhibit 29.
[212] *See* Amgen Response to July 2025 IR, *supra* note 40, Exhibit 33.

Contrary to CDER's position in the NOOH, achievement of non-inferiority in the ADVOCATE study compared with the prednisone taper active control group contributes to the totality of the evidence demonstrating substantial evidence of effectiveness for TAVNEOS and supports continued approval. Whereas CDER claims in its NOOH that "FDA informed ChemoCentryx in 2016 that TAVNEOS *would not be considered for approval* unless the ADVOCATE study demonstrated superiority on week 52 sustained remission results,"[213] minutes from the November 1, 2016 Type C meeting that CDER cites and the July 14, 2016 End-of-Phase 2 meeting that preceded it clarify that the Agency's view at the time was that "a non-inferiority study would not be sufficient *to show that [avacopan] can replace glucocorticoids*."[214]

Importantly, the regulatory history reflects that CDER moved away from this earlier view and instead its approval decision in 2021 invoked the totality of the evidence, the context of rare disease, and unmet patient need. As noted in Section II.E above, the Division Director and Office Director cited the totality of the evidence, including:

- AAV is "a serious, potentially organ- and life-threatening rare disease with a limited therapeutic armamentarium."[215] In light of the small rare-disease patient population and the "compelling need to treat to remission when patients present with serious manifestations," "requiring a second phase 3 study may delay access while not providing the desired additional clarity with respect to avacopan's ultimate role in the therapeutic armamentarium."[216]

- AAV "is a rare, potentially life-threatening condition."[217] While achieving remission has become more feasible as treatments have advanced, "disease relapse continues to pose a burden to patients" and "[m]orbidity related to disease-related organ damage and adverse effects of therapies to manage the disease negatively impact quality of life."[218]

- The fact that TAVNEOS did not demonstrate superiority (but did demonstrate non-inferiority) at Week 26 "does not preclude a conclusion that avacopan has a beneficial treatment effect"—for example, because "the point estimate of the results for the avacopan group was very similar to that of the prednisone control group (72.3% vs 70.1%, respectively), suggesting that avacopan had some level of treatment benefit toward remission rates at Week 26, albeit difficult to quantify."[219]

- While "[e]xploratory analyses across multiple secondary endpoints were not consistently favorable," "results for the clinically important endpoint of rates of relapse did favor avacopan," and those results "clearly support the clinical activity of avacopan *beyond*

[213] *See* 91 Fed. Reg. at 23281 (emphasis added).
[214] FDA, *Memorandum of Type C Meeting Minutes* (IND 120784) at 2 (Nov. 30, 2016) (emphasis added) ["Type C Meeting Minutes"]; *see* FDA*, Memorandum of End of Phase 2 Meeting Minutes* (IND 120784) at 6 (Aug. 9, 2016) ("A non-inferiority study would not be sufficient to show that [avacopan] *can replace glucocorticoids*." (emphasis added)).
[215] CDER Multi-Disciplinary Review, *supra* note 1, at 238.
[216] *Id.* at 239.
[217] *Id.* at 240.
[218] *Id.*
[219] *Id.* at 235-36.

that demonstrated by the primary endpoint analyses."[220] In addition, "[t]he heterogeneity of results among the secondary endpoints is expected in conditions where patients experience a wide range of manifestations and severity, such as . . . AAV."[221]

- The Phase 2 studies "are difficult to interpret and do not provide clear support for the single phase 3 study; however, they also do not conflict with a finding of efficacy in the phase 3 study" and "do not conflict with the treatment effects seen."[222]

- In ADVOCATE, "exploratory analyses suggest that fewer avacopan-treated patients relapsed after remission as compared to patients on the comparator arm."

- Additional "[s]upportive evidence of avacopan efficacy is derived from mechanistic considerations, from nonclinical studies (e.g., involving C5a-induced neutropenic cynomolgus monkeys, and a transgenic mouse ANCA disease model)."[223]

It is also important to understand that the ADVOCATE study, as conducted, did not evaluate whether avacopan could replace glucocorticoids, as discussed with CDER in 2016. The context is important here. Rituximab had been approved for AAV based on results from the 26 week non-inferiority RAVE trial, and ChemoCentryx's proposed design in 2016 would have explored whether avacopan could replace glucocorticoids in treating AAV as an adjunctive treatment with either rituximab or cyclophosphamide. Notably, however, because ADVOCATE allowed for concomitant use of glucocorticoids in both treatment arms according to prespecified rules, glucocorticoids were regularly utilized in both the avacopan and the active control arms of the study either as prednisone study medication and at low doses for treatment of adrenal insufficiency or treatment of other conditions, e.g., allergic reaction. These protocol-driven uses of glucocorticoid meant that, in fact, ADVOCATE did not evaluate whether avacopan could replace glucocorticoids, as was originally described by CDER in 2016, but rather, as CDER made clear at the May 6, 2021 meeting of the Arthritis Advisory Committee, "as a result of the widespread steroid use on both arms, the comparison in this trial is more accurately described as a comparison of avacopan plus lower dose glucocorticoids vs. higher dose glucocorticoids."[224]

The changed characterization of the study was the subject of further discussion between CDER and ChemoCentryx including during the review process[225] and, notably, resulted in labeling for TAVNEOS that does not claim that avacopan can replace glucocorticoids. In fact, TAVNEOS's labeling, both now and upon initial approval, explicitly states that TAVNEOS is "indicated as an adjunctive treatment" and "*does not eliminate glucocorticoid use*."[226] This

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[220] *Id.* at 237 (emphasis added).
[221] *Id.*
[222] *Id.* at 238, 240.
[223] *Id.*
[224] CDER, *FDA Pre-Recorded Presentation Transcript for the May 6, 2021 Meeting of the Arthritis Advisory Committee* (May 6, 2021), https://web.archive.org/web/20241108235041/https://www.fda.gov/media/148179/download.
[225] Amgen Response to July 2025 IR, *supra* note 40, Exhibit 35 (FDA Clarification Meeting Post Advisory Committee Meeting (June 2, 2021)).
[226] Oct. 2021 USPI, s*upra* note 100, at 1 (emphasis added); Amgen Inc., *TAVNEOS (avacopan) Prescribing Information* (May 2026), https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c93cbc0b-29a3-46a5-9c85-41815ea5cf4a (emphasis added) ["Current Labeling"].

language reflects ChemoCentryx's submission of a June 18, 2021 major amendment in response to feedback from CDER that revised the indication to specify that ADVOCATE ultimately did not evaluate whether avacopan could eliminate glucocorticoid use.

TAVNEOS is therefore neither approved nor intended for use as a therapeutic that replaces glucocorticoids, as CDER had described during the 2016 discussions. Importantly, as illustrated above, it is clear from CDER's summary review that the 2021 approval decision cited and relied upon ***the totality of evidence***, including the non-inferiority results, and not only the superiority result for sustained remission.

As illustrated in the tables below, for disease remission at Week 26, avacopan consistently demonstrated non-inferiority to prednisone across analyses for all adjudication scenarios (i.e., based on the November 5, 2019 database lock, after the 2019 readjudication, excluding participants with a change in remission status at Week 26 after the 2019 readjudication, and based on the 2026 readjudication). In an ad hoc Bayesian analysis, the posterior probability that avacopan is non-inferior to prednisone was 100% for the -20% margin and ≥ 98.4% for the more stringent -10% margin.

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Table 2. Disease Remission at Week 26 (ITT Population)

	Prednisone Group	Avacopan Group	p-value for Difference Between Groups[a]
Before Readjudication (05 Nov 2019 DBL), N	164[e]	166	< 0.0001 (non-inferiority) 0.3646 (superiority)
Remission[b] at Week 26, n (%)	112 (68.3)	115 (69.3)	
Estimate of common difference in percentages (2-sided 95% CI)	--	1.7 (-8.0, 11.4)	
After 2019 Readjudication (CSR Results), N[c]	164	166	< 0.0001 (non-inferiority) 0.2387 (superiority)
Remission[b] at Week 26, n (%)	115 (70.1)	120 (72.3)	
Estimate of common difference in percentages (2-sided 95% CI)	--	3.4 (-6.0, 12.8)	
Excluding 8 Originally Readjudicated Participants[d], N	161	161	< 0.0001 (non-inferiority) 0.2692 (superiority)
Remission[b] at Week 26, n (%)	112 (69.6)	115 (71.4)	
Estimate of common difference in percentages (2-sided 95% CI)	--	3.0 (-6.6, 12.6)	
2026 Readjudication, N	164	166	< 0.0001 (non-inferiority) 0.3301 (superiority)
Remission[b] at Week 26, n (%)	110 (67.1)	113 (68.1)	
Estimate of common difference in percentages (2-sided 95% CI)	--	2.2 (-7.5, 11.9)	

CSR = Clinical Study Report; DBL = database lock; ITT = intent-to-treat.

Note: Two-sided 95% confidence intervals are calculated for the difference in proportions (Avacopan minus Prednisone) adjusted for randomization strata (newly diagnosed or relapsed AAV, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide (IV or oral) standard of care treatment) using the stratified Summary score test and estimate for the common difference in proportions.

ITT population = all participants who were randomized and received at least 1 dose of study drug.

[a] One-sided p-values to be compared with a one-sided significance level (type I error rate) of 0.025.

[b] Remission, based on assessment by the blinded Adjudication Committee, was defined as having a BVAS of zero at Week 26 and not having received any glucocorticoids for ANCA-associated vasculitis within the 4 weeks prior to the Week 26 visit.

[c] Source: Phase 3 Study CL010_168 (ADVOCATE) CSR Table 14.2.1.1

[d] Excluding 8 participants with a change in remission status at Week 26 after readjudication.

[e] Of 331 enrolled patients, one patient 'was withdrawn from the study by the Investigator since upon re-review, the renal biopsy did not clearly indicate the presence of vasculitis.'" ChemoCentryx, Inc., Clinical Study Report: 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 (CL010_168), at 72 (June 1, 2020).

Source: Post hoc Table 14.2.1.11.a and Table 14-4.2.1

Table 3. Sensitivity Analysis of the Proportion of Participants With Disease Remission at Week 26 Assessed by the Adjudication Committee - Defining High Non-Study Supplied GC Users as Non Remitters (ITT Population)

Treatment Group	N	n	(%)	95% CI	Difference in %	Estimate of Common Difference in %	2-sided 95% CI for Common Difference	Non-inferiority p-value	Superiority p-value
05 November 2019 Database Lock									
Prednisone Group	164	109	(66.5)	(58.7, 73.6)					
Avacopan Group	166	107	(64.5)	(56.7, 71.7)	-2.0	-1.1	(-11.0, 8.8)	< 0.0001	0.5864
2026 Readjudication									
Prednisone Group	164	105	(64.0)	(56.2, 71.4)					
Avacopan Group	166	105	(63.3)	(55.4, 70.6)	-0.8	0.7	(-9.2, 10.6)	< 0.0001	0.4457

ITT = intent-to-treat; GC = glucocorticoid

Note 1: The Adjudication Committee assessed remission based on BVAS = 0 at Week 26, and having not received any GC treatment for treatment of AAV during the 4-week period preceding and including the Week 26 visit.

Note 2: Participants who used more than 1460 mg prednisone equivalent within the first 26 weeks of the study were considered not to have achieved the BVAS remission at Week 26 endpoint.

Note 3: N = number of participants in the analysis population for the specified treatment group; n = number of participants with disease remission; % = 100*n/N.

Note 4: Confidence intervals for treatment proportions are calculated using the Clopper and Pearson Method. Two-sided 95% confidence intervals are calculated for the difference in proportions (avacopan minus prednisone) adjusted for randomization strata (newly diagnosed or relapsed AAV, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide (IV or oral) standard of care treatment) using the stratified Summary score test and estimate for the common difference in proportions.Non-inferiority and superiority nominal p-values are one-sided and were compared with the nominal 1-sided 0.025 threshold for descriptive purposes.

Source: Table 14.2.1.3.S1 and Table 14-4.3.1

Table 4. Sensitivity Analysis of the Proportion of Participants With Disease Remission at Week 26 Assessed by the Adjudication Committee - Excluding Participants With High Non-Study Supplied GC Use (ITT Population)

Treatment Group	N	n	(%)	95% CI	Difference in %	Estimate of Common Difference in %	2-sided 95% CI for Common Difference	Non-inferiority p-value	Superiority p-value
05 November 2019 Database Lock									
Prednisone Group	136	109	(80.1)	(72.4, 86.5)					
Avacopan Group	131	107	(81.7)	(74.0, 87.9)	1.5	2.2	(-7.6, 12.0)	< 0.0001	0.3304
2026 Readjudication									
Prednisone Group	136	105	(77.2)	(69.2, 84.0)					
Avacopan Group	131	105	(80.2)	(72.3, 86.6)	2.9	3.7	(-6.2, 13.7)	< 0.0001	0.2302

ITT = intent-to-treat; GC = glucocorticoid

Note 1: The Adjudication Committee assessed remission based on BVAS=0 at Week 26, and having not received any GC treatment for treatment of AAV during the 4-week period preceding and including the Week 26 visit.

Note 2: Participants who used more than 1460 mg prednisone equivalent within the first 26 weeks of the study were excluded from the analysis.

Note 3: N=number of participants in the analysis population for the specified treatment group excluding high non-study supplied GC users (See Note 2); n=number of participants with disease remission; %=100*n/N.

Note 4: Confidence intervals for treatment proportions are calculated using the Clopper and Pearson Method. Two-sided 95% confidence intervals are calculated for the difference in proportions (avacopan minus prednisone) adjusted for randomization strata (newly diagnosed or relapsed AAV, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide (IV or oral) standard of care treatment) using the stratified Summary score test and estimate for the common difference in proportions. Non-inferiority and superiority nominal p-values are one-sided and were compared with the nominal 1-sided 0.025 threshold for descriptive purposes.

Source: Table 14.2.1.4.S1 and Table 14-4.3.2

Table 5. Proportion of Participants Achieving BVAS=0 at Week 26 Assessed by the Adjudication Committee - Independent of Non-Study Supplied GC Use (ITT Population)

Treatment Group	N	n	(%)	95% CI	Difference in %	Estimate of Common Difference in %	2-sided 95% CI for Common Difference	Non-inferiority p-value	Superiority p-value
05 November 2019 Database Lock									
Prednisone Group	164	135	(82.3)	(75.6, 87.8)					
Avacopan Group	166	144	(86.7)	(80.6, 91.5)	4.4	4.0	(-4.1, 12.2)	< 0.0001	0.1672
2026 Readjudication									
Prednisone Group	164	129	(78.7)	(71.6, 84.7)					
Avacopan Group	166	137	(82.5)	(75.9, 88.0)	3.9	3.0	(-5.6, 11.6)	< 0.0001	0.2485

ITT = intent-to-treat; GC = glucocorticoid

Note 1: Achievement of BVAS = 0 at Week 26 is based on the Adjudicated BVAS score.

Note 2: N = number of participants in the analysis population for the specified treatment group; n = number of participants with disease remission; % = 100*n/N.

Note 3: Confidence intervals for treatment proportions are calculated using the Clopper and Pearson Method. Two-sided 95% confidence intervals are calculated for the difference in proportions (Avacopan minus Prednisone) adjusted for randomization strata (newly diagnosed or relapsed AAV, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide (IV or oral) standard of care treatment) using the stratified Summary score test and estimate for the common difference in proportions. Non-inferiority and superiority nominal p-values are 1-sided and were compared with the nominal 1-sided 0.025 threshold for descriptive purposes.

Source: Table 14.2.1.5.S1 and Table 14-4.4.1

In addition, analyses of sustained remission support the conclusion that TAVNEOS is effective. In order to minimize the influence of non-study glucocorticoid use on the efficacy results, analyses were performed in which these participants were considered non-responders. These include analyses where participants who used high doses of GCs (> 560 mg from Week 26 through Week 52) were defined as non-responders (Table 7), where participants were excluded from the analysis if they used high doses of GCs (> 560 mg from Week 26 through Week 52) (Table 8), and an analysis of the proportion of participants who achieved BVAS = 0 irrespective of GC use (Table 9). The non-inferiority p-values were < 0.0001 for all these sensitivity analyses. The superiority p-values were > 0.025 for all sensitivity analyses apart from the BVAS = 0 irrespective of glucocorticoid use analysis from the November 5, 2019 database lock, which reached statistical significance at a 1-sided 0.025 level (p = 0.0223). In summary, these results support the conclusion that TAVNEOS is at least as effective as the prednisone taper and show trends for superiority in sustained remission.

Table 6. Sustained Disease Remission at Week 52 (ITT Population)

	Prednisone Group	Avacopan Group	p-value for Difference Between Groups[a]
Before Readjudication (05 Nov 2019 DBL), N	164	166	< 0.0001 (non-inferiority)
Sustained Remission[b] at Week 52, n (%)	90 (54.9)	104 (62.7)	
Estimate of common difference in percentages (2-sided 95% CI)	--	8.4 (-1.7, 18.5)	0.0513 (superiority)
After 2019 Readjudication (CSR Results), N[c]	164	166	< 0.0001 (non-inferiority)
Sustained Remission[b] at Week 52, n (%)	90 (54.9)	109 (65.7)	
Estimate of common difference in percentages (2-sided 95% CI)	--	12.5 (2.6, 22.3)	0.0066 (superiority)
Excluding 5 Originally Readjudicated Participants[d], N	164	161	< 0.0001 (non-inferiority)
Sustained Remission[b] at Week 52, n (%)	90 (54.9)	104 (64.6)	0.0130 (superiority)
Estimate of common difference in percentages (2-sided 95% CI)	--	11.3 (1.4, 21.3)	
2026 Readjudication, N	164	166	< 0.0001 (non-inferiority)
Sustained Remission[b] at Week 52, n (%)	86 (52.4)	102 (61.4)	
Estimate of common difference in percentages (2-sided 95% CI)	--	9.8 (-0.3, 19.9)	0.0282 (superiority)

CSR = Clinical Study Report; DBL = database lock; ITT = intent-to-treat.

Note: Two-sided 95% confidence intervals are calculated for the difference in proportions (Avacopan minus Prednisone) adjusted for randomization strata (newly diagnosed or relapsed AAV, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide (IV or oral) standard of care treatment) using the stratified Summary score test and estimate for the common difference in proportions.

ITT population = all participants who were randomized and received at least 1 dose of study drug.

[a] One-sided p-values to be compared with a one-sided significance level (type I error rate) of 0.025.

[b] Sustained remission, based on assessment by the blinded Adjudication Committee, was defined as remission at Week 26 and remission at Week 52 (BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 52) and without relapse between Weeks 26 and 52.

[c] Source: Phase 3 Study CL010_168 (ADVOCATE) CSR Table 14.2.2.1

[d] Excluding 5 participants with a change in sustained remission status at Week 52 after readjudication.

Source: Post hoc Table 14.2.2.11.2 and Table 14-4.2.6

Table 7. Sensitivity Analysis of the Proportion of Participants With Week 52 Sustained Disease Remission Assessed by the Adjudication Committee - Defining High Non-Study Supplied GC Users as Non-Remitters (ITT Population)

Treatment Group	N	n	(%)	95% CI	Difference in %	Estimate of Common Difference in %	2-sided 95% CI for Common Difference	Non-inferiority p-value	Superiority p-value
05 November 2019 Database Lock									
Prednisone Group	164	86	(52.4)	(44.5, 60.3)					
Avacopan Group	166	100	(60.2)	(52.4, 67.7)	7.8	8.4	(-1.7, 18.6)	< 0.0001	0.0508
2026 Readjudication									
Prednisone Group	164	84	(51.2)	(43.3, 59.1)					
Avacopan Group	166	99	(59.6)	(51.8, 67.2)	8.4	9.3	(-0.8, 19.4)	< 0.0001	0.0359

ITT = intent-to-treat; GC = glucocorticoid

Note 1: Sustained disease remission at Week 52 is based on assessment by the blinded Adjudication Committee that disease remission has been achieved at Week 26, that disease remission has been achieved at Week 52, and that no relapse has occurred between Week 26 and Week 52. The Adjudication Committee assessed Week 26 remission based on BVAS = 0 at Week 26, and having not received any GC treatment for treatment of AAV during the 4-week period preceding and including the Week 26 visit. Similarly, the Adjudication Committee assessed remission at Week 52 based on BVAS = 0 at Week 52, and having not received any GC treatment for treatment of AAV during the 4-week period preceding and including the Week 52 visit.

Note 2: Participants who used more than 560 mg prednisone equivalent from Week 26 through Week 52 were considered not to have achieved the BVAS sustained remission at Week 52 endpoint.

Note 3: N = number of participants in the analysis population for the specified treatment group; n = number of participants with sustained disease remission; % = 100*n/N.

Note 4: Confidence intervals for treatment proportions are calculated using the Clopper and Pearson Method. Two-sided 95% confidence intervals are calculated for the difference in proportions (Avacopan minus Prednisone) adjusted for randomization strata (newly diagnosed or relapsed AAV, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide (IV or oral) standard of care treatment) using the stratified Summary score test and estimate for the common difference in proportions. Non-inferiority and superiority nominal p-values are 1-sided and were compared with the nominal 1-sided 0.025 threshold for descriptive purposes.

Source: Table 14.2.2.3.S1 and Table 14-4.3.4

Table 8. Sensitivity Analysis of the Proportion of Participants With Week 52 Sustained Disease Remission Assessed by the Adjudication Committee - Excluding Participants With High Non-Study Supplied GC Use (ITT Population)

Treatment Group	N	n	(%)	95% CI	Difference in %	Estimate of Common Difference in %	2-sided 95% CI for Common Difference	Non-inferiority p-value	Superiority p-value
05 November 2019 Database Lock									
Prednisone Group	119	86	(72.3)	(63.3, 80.1)					
Avacopan Group	138	100	(72.5)	(64.2, 79.7)	0.2	1.3	(-9.5, 12.0)	< 0.0001	0.4097
2026 Readjudication									
Prednisone Group	119	84	(70.6)	(61.5, 78.6)					
Avacopan Group	138	99	(71.7)	(63.5, 79.1)	1.2	2.3	(-8.5, 13.1)	< 0.0001	0.3383

ITT = intent-to-treat; GC = glucocorticoid

Note 1: Sustained disease remission at Week 52 is based on assessment by the blinded Adjudication Committee that disease remission has been achieved at Week 26, that disease remission has been achieved at Week 52, and that no relapse has occurred between Week 26 and Week 52. The Adjudication Committee assessed Week 26 remission based on BVAS = 0 at Week 26, and having not received any GC treatment for treatment of AAV during the 4-week period preceding and including the Week 26 visit. Similarly, the Adjudication Committee assessed remission at Week 52 based on BVAS = 0 at Week 52, and having not received any GC treatment for treatment of AAV during the 4-week period preceding and including the Week 52 visit.

Note 2: Participants who used more than 560 mg prednisone equivalent from Week 26 through Week 52 were excluded from the analysis.

Note 3: N = number of participants in the analysis population for the specified treatment group excluding high non-study supplied GC users (see Note 2); n = number of participants with sustained disease remission; % = 100*n/N.

Note 4: Confidence intervals for treatment proportions are calculated using the Clopper and Pearson Method. Two-sided 95% confidence intervals are calculated for the difference in proportions (Avacopan minus Prednisone) adjusted for randomization strata (newly diagnosed or relapsed AAV, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide (IV or oral) standard of care treatment) using the stratified Summary score test and estimate for the common difference in proportions. Non-inferiority and superiority nominal p-values are 1-sided and were compared with the nominal 1-sided 0.025 threshold for descriptive purposes.

Source: Table 14.2.2.4.S1 and Table 14-4.3.5

Table 9. Proportion of Participants Achieving BVAS=0 at Week 26 and Week 52 Assessed by the Adjudication Committee - Independent of Non-Study Supplied GC Use (ITT Population)

Treatment Group	N	n	(%)	95% CI	Difference in %	Estimate of Common Difference in %	2-sided 95% CI for Common Difference	Non-inferiority p-value	Superiority p-value
05 November 2019 Database Lock									
Prednisone Group	164	114	(69.5)	(61.9, 76.5)					
Avacopan Group	166	130	(78.3)	(71.3, 84.3)	8.8	9.3	(0.2, 18.5)	< 0.0001	0.0223
2026 Readjudication									
Prednisone Group	164	107	(65.2)	(57.4, 72.5)					
Avacopan Group	166	125	(75.3)	(68.0, 81.7)	10.1	9.3	(-0.1, 18.7)	< 0.0001	0.0267

ITT = intent-to-treat; GC = glucocorticoid

Note 1: Achievement of BVAS=0 at Week 26 and Week 52 is based on the Adjudicated BVAS score. Participants having a relapse between Week 26 and 52 are considered as not achieving response.

Note 2: N = number of participants in the analysis population for the specified treatment group; n = number of participants with sustained disease remission; % = 100*n/N.

Note 3: Confidence intervals for treatment proportions are calculated using the Clopper and Pearson Method. Two-sided 95% confidence intervals are calculated for the difference in proportions (Avacopan minus Prednisone) adjusted for randomization strata (newly diagnosed or relapsed AAV, anti-PR3 or anti-MPO ANCA, and IV rituximab or cyclophosphamide (IV or oral) standard of care treatment) using the stratified Summary score test and estimate for the common difference in proportions. Non-inferiority and superiority nominal p-values are 1-sided and were compared with the nominal 1-sided 0.025 threshold for descriptive purposes.

Source: Table 14.2.2.5.S1 and Table 14-4.4.2

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As shown above and in Appendix A, the totality of the evidence—including the 2026 readjudication—confirms efficacy and should give the Agency confidence in maintaining approval for patients living with AAV. Specifically, the 2026 readjudication further contributes to the totality of the evidence establishing substantial evidence of effectiveness. It is not appropriate to disqualify the ADVOCATE trial results in their entirety from contributing to substantial evidence of effectiveness.

Accordingly, it is unnecessary to focus on CDER's second ground for withdrawal. As explained below, however, the 2019 readjudication also does not undermine efficacy.

2. Substantial Evidence Of Efficacy Is Not Undermined By The 2019 Readjudication

In its NOOH, CDER has mislabeled the result of prespecified quality control as "manipulation." The robust evidence supporting the efficacy of TAVNEOS is not undermined by the readjudication of primary endpoints for nine patients in 2019 because, quite simply, there was no data manipulation or falsification.

a. FDA regulations do not prohibit the readjudication procedure

Importantly, FDA regulations did not prevent ChemoCentryx from conducting the 2019 readjudication in the manner CDER now criticizes. CDER points to language in 21 C.F.R. § 314.126(b)(5) and (b)(7) to support its claim that ADVOCATE was not adequate and well-controlled. But those provisions require only that "adequate measures" be taken to minimize bias and that "[t]he protocol and report of the study" describe those measures, "such as blinding."[227] As discussed above, ChemoCentryx did so here by ensuring that the prespecified rules in the protocol were correctly applied to the final study data. And the Adjudication Committee Chair—who actually conducted the readjudications—remained fully blinded according to the ADVOCATE protocol. If CDER believes those measures were inadequate, then that alone is a genuine issue of fact underlying the NOOH that requires a hearing to resolve.

CDER's reliance on non-binding, sub-regulatory guidance—one of which was enacted years after the NDA submission here—underscores the absence of any regulatory requirement binding ChemoCentryx. The Center cites two guidance documents—*E9 Statistical Principles for Clinical Trials* ("ICH E9") and *E6(R3): Good Clinical Practice: Guidance for Industry* ("ICH E6(R3)") for the proposition the readjudications were improper. CDER is mistaken.

First, CDER cites to ICH E9 in support of its contention that blinding "is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial."[228] Amgen agrees that limiting bias in the conduct and interpretation of a clinical trial is critical, and that blinding is an important means of doing so. But the Center's reliance on ICH E9 is incomplete. ICH E9 does not impose a categorical prohibition on limited access to treatment codes by sponsor personnel.[229]

Second, CDER cites ICH E6(R3) for the proposition that certain post-unblinding events "should" be documented and justified. According to ICH E6(R3):[230]

> Deviations from the planned statistical analysis or changes made to the data after the trial has been unblinded (where applicable) should be clearly documented and justified and should only occur in exceptional circumstances (e.g., data discrepancies that must be

[227] *See* 21 C.F.R. § 314.126(b)(5).
[228] *See* 91 Fed. Reg. at 23285 (citing ICH E9 Guidance, *supra* note 195, at 10, 12).
[229] ICH E9 Guidance, supra note 195, at 11 ("If any of the sponsor staff who are not involved in the treatment or clinical evaluation of the subjects are required to be unblinded to the treatment code (e.g., bioanalytical scientists, auditors, those involved in serious adverse event reporting), the sponsor should have adequate standard operating procedures to guard against inappropriate dissemination of treatment codes.").
[230] ICH E6(R3) Guidance, *supra* note 196, at 42.

> resolved for the reliability of the trial results). Such data changes should be authorized by the investigator and reflected in an audit trail. Post-unblinding data changes and deviations from the planned statistical analyses should be reported in the clinical trial report.

Critically, FDA did not finalize ICH E6(R3) until September 2025—nearly *five years* after submitting the NDA. In fact, FDA did not even adopt the draft version of that guidance until June 2023, almost *two years* after TAVNEOS NDA approval.[231] And the version of the guidance in effect prior to the approval of TAVNEOS—ICH Good Clinical Practice Guidance, ICH E6(R2)—did not include the language quoted above. Thus, the quoted language did not exist in any FDA-adopted guidance during the relevant period and could not have provided contemporaneous advice regarding the 2019 readjudications.

Even if the quoted language from ICH E6(R3) had existed in 2019, it would not support CDER's position. First, ChemoCentryx did not engage in "data changes" contemplated by the guidance. The recommendation in ICH E6(R3) that the investigator authorize "data changes" confirms that the changes contemplated by the quoted guidance language are to data for which the investigator has responsibility. The ADVOCATE protocol called for investigators to initially evaluate BVAS scores.[232] Thereafter, the Adjudication Committee was responsible for determining whether patients were in remission.[233] *The BVAS scores, data regarding glucocorticoid use and patient visits, and relapse status all remained unchanged after the November 5, 2019 database lock.* The only question presented to the blinded adjudication committee was whether the protocol's prespecified endpoint definitions applied to those unchanged facts. That readjudication was documented in the eTMF. CDER's assertion in a footnote that "other than the correction of a manual error, the errors to be corrected were not mere data 'discrepancies'"[234] is therefore contrary to the factual record. Allowing these known discrepancies to persist in the endpoint dataset would have quantifiably reduced the reliability of the trial results.

Third, the guidance itself recognizes that post unblinded data changes, though rare, may be permissible in certain circumstances, including to "data discrepancies that must be resolved for the reliability of the trial results."[235] Accordingly, the limited, and documented, action taken here was not inconsistent with the later-issued guidance.

In any event, FDA guidance documents, including the ICH Guidelines cited in CDER's NOOH, have not undergone the notice-and-comment rulemaking process, do not have the force

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[231] *See id.*; FDA, *Good Clinical Practice (GCP) E6(R3), Draft version* (May 19. 2023), https://web.archive.org/web/20240225050830/https://www.fda.gov/media/169090/download.

[232] *See* Protocol Amendment 4.0, *supra* note 41, at 81 ("BVAS data recorded by investigators will be adjudicated, according to an adjudication charter" and the "adjudicated data will be used in the final analysis."); SAP 2.0 Version 2.0, *supra* note 42, at 15 ("The proportion of subjects achieving sustained disease remission at Week 52 will be based on assessment by the blinded AC [Adjudication Committee] that disease remission has been achieved at Week 26, that disease remission has been achieved at Week 52, and that no relapse has occurred between Week 26 and Week 52.").

[233] *See supra* note 232.

[234] *See* 91 Fed. Reg. at 23284 n.9.

[235] *Id.*

of law, and are non-binding.[236] FDA's policies and procedures for developing, issuing, and using guidance documents, codified in the Agency's Good Guidance Practice regulation, make clear that "[g]uidance documents do not establish legally enforceable rights or responsibilities" and "do not legally bind the public."[237] Specifically, in response to the question whether "you . . . [are] required to follow a guidance document," the regulation answers, "No."[238] Instead, stakeholders, including industry, "may choose to use an approach other than the one set forth in a guidance document" so long as it "compl[ies] with the relevant statutes and regulations."[239] Courts have also recognized the non-binding nature of FDA guidance documents, declining to "transform[] the FDA's non-binding guidelines into strict requirements based only on hindsight,"[240] including in the context of an FDA-adopted ICH Guidelines, which (like other FDA guidance) "FDA characterizes . . . as nonbinding," is "published in the Federal Register, not the Code of Federal Regulations," and "does not have actual binding effect."[241] The same considerations apply to the non-binding guidance documents cited in the NOOH.[242]

b. Readjudication of nine patients followed prespecified protocol

CDER may disagree with the 2019 readjudication, but disagreement does not establish that the ADVOCATE data were manipulated or that the controls were insufficient to minimize bias.

First, what CDER characterizes as "data manipulation" consisted of quality checks performed pursuant to the ADVOCATE Study Results Analysis Plan (SRAP). CDER asserts that Dr. Bekker and Dr. Yue manipulated the results of the study by "look[ing] for cases that could alter the study results to indicate TAVNEOS achieved statistically superior outcome on the primary endpoint of sustained remission."[243] The upshot of CDER's allegation is that Dr. Bekker and Dr. Yue looked for incorrect endpoint application that would improve efficacy outcomes, while ignoring potential incorrect endpoint application that would negatively impact efficacy outcomes.

That accusation is unsupported. The SRAP prespecified that identified ChemoCentryx personnel would complete a "QC review for completeness and internal consistency" and "[r]eview of topline data," during which "access to un[bl]inded data will be strictly limited to authorized (pre-identified) individuals."[244] According to Dr. Bekker and Dr. Yue, there was a

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[236] By definition, guidance documents "do not have the force and effect of law." *Perez v. Mortgage Bankers Ass'n*, 575 U.S. 92, 97 (2015) (quoting *Shalala v. Guernsey Mem'l Hosp.*, 514 U.S. 87, 99 (1995)).
[237] 21 C.F.R. § 10.115(d).
[238] *Id.*
[239] *Id.* § 10.115(d)(2); *see also* FDA, *Guidances* (Jan. 17, 2025), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidances ("[G]uidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited").
[240] *See, e.g.*, *In re Ocugen, Inc. Sec. Lit.*, 659 F. Supp. 3d 572, 590-91 (E.D. Pa. 2023).
[241] *See Vanda Pharms., Inc. v. FDA*, 436 F. Supp. 3d 256, 270 (D.D.C. 2020).
[242] *See* ICH E9 Guidance, *supra* note 195, at 1 (explaining that the guidance "does not operate to bind FDA or the public"); FDA, *E3 Guideline for Industry: Structure and Content of Clinical Study Reports* at 1 n.1 (July 1996), https://www.fda.gov/media/71271/download ["ICH E3 Guidance"] (explaining that this guidance "does not operate to bind FDA or the industry"); ICH E6(R3) Guidance, *supra* note 196, at 1 (explaining that this guidance "is not binding on FDA or the public").
[243] 91 Fed. Reg. at 23281.
[244] *See* SRAP Version 1.0, *supra* note 67, at 4 (capitalization omitted).

review of the BVAS remission outcomes in the patient data across all patients in both treatment arms at both their Week 26 and Week 52 visits to determine whether the remission status was correctly applied.[245] After the November 5, 2019 database lock, Dr. Yue, Dr. Bekker, and Dr. Kelleher were provided access to the unblinded data for the purpose of conducting a "QC review for completeness and internal consistency."[246] These individuals were subject to strict confidentiality requirements in connection with their review and analysis of the results for the purpose of conducting a QC review and ensuring consistency in the topline results.[247] All other individuals at ChemoCentryx and the Adjudication Committee remained blinded during the prespecified QC review process between November 5, 2019 and November 21, 2019.[248]

According to Dr. Bekker and Dr. Yue, they reviewed whether the remission definitions were correctly and consistently applied across *all* patients in the study and whether the primary endpoint results were analyzed according to the rules in the protocol and SAP.[249] In doing so, they did not change any underlying data. Instead, they identified misapplication of the study protocol endpoints to established data for nine patients—including data relating to unscheduled visits and early termination of the study, as well as data regarding the use of glucocorticoids in the four weeks before a primary endpoint assessment.[250]

[245] *See* Deposition of Petrus Bekker, M.D. at 182, *Homyk v. ChemoCentryx, Inc.*, No. 4:21-cv-03343 (N.D. Cal. July 26, 2024) (Appendix C.2) ["Bekker Deposition Day 1"]; ; Deposition of Huibin Yue at 219, *Homyk v. ChemoCentryx, Inc.*, No. 4:21-cv-03343 (N.D. Cal. May 10, 2024) (Appendix C.4) ["Yue Deposition"]; Amgen Response to July 2025 IR, *supra* note 40, at Exhibits 13, 14, 15.

[246] Amgen Response to July 2025 IR, *supra* note 40, at 9-10; *see also* SRAP Version 1.0, *supra* note 67, at 4.

[247] Amgen Response to July 2025 IR, *supra* note 40, at 10.

[248] *Id.*

[249] ; Yue Deposition, *supra* note 245, at 219; Amgen Response to July 2025 IR, *supra* note 40, at Exhibits 13, 14, 15.

[250] Amgen Response to July 2025 IR, *supra* note 40, at 12-16; Exhibits 13, 14, 15.

[redacted]

After the data were reviewed, Dr. Bekker explained that he emailed Dr. Yue a table of nine patients whose adjudication decision was inconsistent with the study rules.[252] This included three patients in the prednisone arm who were readjudicated as in remission at Week 26.[253] Dr. Yue, in turn, provided the table to Medpace.[254] Notably, four of these nine patients had been previously identified in October 2019 as not being appropriately categorized under the protocol; however, those categorizations had not been corrected at the time and were therefore identified again during this QC review.[255] [redacted] Medpace sent the Adjudication Committee Chair a request for readjudication pursuant to the procedure set forth in the Adjudication Committee Charter, Section 4.3.3, with a listing of the nine patients and patient files.[257] As required by the study protocol and Adjudication Committee Charter, the Adjudication Committee Chair remained blinded, and the materials shared with him did not identify the treatment groups of patients nor did they identify the proposed readjudication determination.[258] Instead, the materials identified the basis for the readjudication request under the prespecified remission determination rules.[259]

In the case of these nine patients, QC review found that the rules had not been correctly or consistently applied across the patient population in the study. Thus, without the readjudication, the resulting primary endpoint dataset would have been incorrect with respect to the nine patients, resulting in inaccurate interpretation of the trial data.[260]

Despite this comprehensive process, CDER asserts Dr. Bekker's and Dr. Yue's review was "biased" because they "appeared to focus primarily on a subpopulation of patients who had a BVAS of zero and were adjudicated as not in remission due to missing data or recent glucocorticoid use for a reason other than treatment of AAV."[261] According to contemporaneous emails, however, Dr. Bekker and Dr. Yue examined objective criteria—i.e., patient visit dates and glucocorticoid use as defined in the study protocol—and applied it to data from both the avacopan and prednisone arms to identify clear errors, appropriately minimizing any bias consistent with FDA regulations.[262] Dr. Bekker and Dr. Yue did not change any underlying data

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[251] [redacted]
[252] Amgen Response to July 2025 IR, *supra* note 40, at Exhibit 15.
[253] *Id.*
[254] Amgen Response to July 2025 IR, *supra* note 40, at Exhibit 17.
[255] Email from P. Bekker to [redacted] RE: Patient Status Spreadsheet (Oct. 25, 2019).
[256] [redacted]
[257] Amgen Response to July 2025 IR, *supra* note 40, at 16.
[258] *Id.*
[259] *Id.*
[260] *Cf. E6(R2): Good Clinical Practice: Guidance for Industry* at 28 (May 2023), https://web.archive.org/web/20230612201321/https://www.fda.gov/media/169090/download ("Quality control should be applied to each stage of the data handling to ensure that data are reliable and have been processed correctly.").
[261] 91 Fed. Reg. at 23285-86.
[262] *See* 21 C.F.R. § 314.126(b)(5) (stating that an adequate and well-controlled study takes "adequate measures . . . to minimize bias on the part of the subjects, observers, and analysts of the data."); *see also* Amgen Response to July 2025 IR, *supra* note 40, at Exhibits 14 and 15.

during this process. In contrast, the quality review that CDER suggests should have been employed—such as reviewing the accuracy of BVAS scores—would have required Dr. Bekker and Dr. Yue to second-guess subjective clinical determinations. The readjudications at issue are therefore distinct from substantive changes to study conduct or to the planned analyses, such as "dropping a treatment group, changing the entry criteria or drug dosages, [or] adjusting the sample size," that FDA recommends in guidance should be described in a clinical study report.[263]

[redacted]

[redacted][269]

[263] *See* ICH E3 Guidance, *supra* note 242.

[264] [redacted]

[265] [redacted]

[267] [redacted]

[268] [redacted]

[269] CDER also alleges that Dr. Bekker excluded patient 534-001 while blinded for missing a Week 26 assessment and then identified that patient for readjudication while unblinded because of misapplication of the prespecified rule for handling missing data. 91 Fed. Reg. at 23283. To the extent CDER characterizes this an example of bias,

Second, contrary to CDER's assertion, limited unblinding occurred to conduct a quality control review of data according to prespecified procedures, with limited, unchanged data provided to the Adjudication Committee Chair—who was responsible for the readjudications—to readjudicate that data while fully blinded. Specifically, ChemoCentryx and its CRO Medpace followed the detailed procedures outlined in the SRAP for conducting the database lock and selectively unblinded only authorized personnel to the data, granting them restricted access to carry out a series of predefined activities in a predetermined sequence. The SRAP established these measures in advance of dissemination of study results to ensure that the analysis was conducted in accordance with the study protocol and SAP and that the results were internally consistent. In accordance with recommendations in contemporary FDA guidance, all members of the Adjudication Committee were "blinded to the assigned treatments when performing their assessments," including during the 2019 readjudication.[270] The prespecified QC review pursuant to the SRAP did not result in decisions modifying the planned analysis, such as "the exclusion of subjects or data from the analysis sets" or definition of outliers, that FDA recommends doing under a blinded review.[271]

Third, CDER contends that, even if permitted by the SRAP, the unblinded quality review violated the terms of the Adjudication Committee Charter.[272] Specifically, CDER asserts that "sending blinded BVAS listings and other remission-related data to Dr. Jayne for readjudication after the database had been unblinded violated the terms of the Adjudication Committee Charter and therefore went beyond the 'QC review for completeness and accuracy' permitted under the SRAP after database lock."[273] Although the Adjudication Committee Charter provides that "[t]here will be no blinded BVAS listings for review after unblinding,"[274] it does not prohibit all post-unblinding quality control, all post-unblinding readjudication, or all review of remission-related endpoint classifications. CDER effectively concedes the point, acknowledging that the provision "appears limited to BVAS listings."[275]

Finally, the 2019 readjudication was fully documented for nine patients. After the readjudication was complete, the results were recorded on the same form as the initial adjudication for eight of those patients such that each form clearly reflected the readjudication, as required by the Adjudication Committee Charter.[276] For the ninth patient, no Adjudication Committee form had been previously completed so a new adjudication form was provided.[277] The data subsequently were entered into the EDC and the eTMF by Medpace. Documentation was shared with Vifor Fresenius Medical Care Renal Pharma (the marketing authorization holder

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CDER's characterization is misplaced. DCRI found that patient 534-001 was in sustained remission at Week 52, which would support Dr. Bekker's finding of an error and sending the patient for blinded readjudication.

[270] *See* ICH E6(R3) Guidance, *supra* note 196, at 27.

[271] *See* ICH E9 Guidance, *supra* note 195, at 30 ("This pre-analysis review, blinded to treatment, should cover decisions concerning, for example, the exclusion of subjects or data from the analysis sets; possible transformations may also be checked, and outliers defined; important covariates identified in other recent research may be added to the model; the use of parametric or non-parametric methods may be reconsidered.").

[272] *See* 91 Fed. Reg. at 23283.

[273] *Id.* at 23284 (citing Adjudication Committee Charter, *supra* note 50, at § 4.3.3).

[274] Adjudication Committee Charter, *supra* note 50, at § 4.3.3.

[275] 91 Fed. Reg. at 23283.

[276] August 2025 IR Response, *supra* note 40, at 17.

[277] *Id.*

for TAVNEOS in the European Union), and Kissei Pharmaceutical Company (the marketing authorization holder for TAVNEOS in Japan).

c. Multiplicity is not an issue with respect to the readjudication

CDER argues that ChemoCentryx engaged in "multiple unplanned hypothesis tests for the primary endpoints" of the trial that would lead to "'not properly controlled' Type 1 error."[278] In other words, the Center claims that the 2019 readjudication was a reanalysis of data with improper multiplicity controls. That argument is misplaced.

As Dr. Gibbons explains in his Declaration, multiplicity is not a concern with respect to the readjudication. Multiplicity "refers to scenarios where multiple endpoints, or different analyses using different statistical approaches, are evaluated as part of the same study, and just by chance one would expect treatment effects to be statistically significant for some number of endpoints."[279] The concern is that "[i]n such scenarios, while the probability of a false positive result for each test viewed individually may be controlled at the prespecified level, the probability of *one or more* false positive results across all tests can rise above that level."[280]

Dr. Gibbons makes clear that this concern does not apply to the 2019 readjudication because there are no different or new endpoints being tested. Instead, the readjudication was carried out to mirror prespecified analyses in the original SAP and applied prespecified trial rules for endpoint measurement.[281] Dr. Gibbons explains that the 2019 readjudication "simply involved implementing corrections to the remission outcomes of trial participants following a prespecified re-adjudication process."[282] Indeed, "the only hypothesis tests for the primary endpoints that the company conducted were the ones prespecified in the SAP, and the Type 1 error on these tests was in fact controlled through the prespecified gatekeeping procedure" in the SAP.[283]

CDER also raises multiplicity concerns with the 2026 readjudication, claiming that it "is no way to redeem the ADVOCATE study" and that "each re-analysis, without procedures to control multiplicity that are specified before the data are locked, will increase the risk of a false positive."[284] But the 2026 readjudication likewise does not have an issue with multiplicity because, as explained by Dr. Gibbons, that readjudication "is fundamentally distinct from the standard multiplicity issues encountered in repeated re-analyses of clinical trial data."[285]

As detailed in Appendix A (Table 1), readjudication of disease remission at Week 26 and sustained disease remission at Week 52 by an independent blinded external committee does not

[278] 91 Fed. Reg. at 23285.
[279] Gibbons Declaration, *supra* note 7, at 22-23; *see, e.g.*, Gary G. Koch et al., *Statistical Considerations for Multiplicity in Confirmatory Protocols*, DRUG INFO. J. 523, 524 (1996) ("The main theme concerning multiplicity is that multiple assessments lead to multiple opportunities for finding to be due to chance and so need control. . . . One area for multiplicity is the presence of multiple primary response variables.").
[280] Gibbons Declaration, *supra* note 7, at 23.
[281] *Id.* at 5, 17.
[282] *Id.* at 17.
[283] *Id.* at 17.
[284] 91 Fed. Reg. at 23286.
[285] Gibbons Declaration, *supra* note 7, at 22.

constitute a new hypothesis test but rather a refinement of outcome ascertainment within the originally prespecified estimand and analysis framework. As explained by Dr. Gibbons:[286]

> there are no different or new endpoints being tested. Indeed, the Supplemental Statistical Analysis Plan ("SSAP") that documents the statistical analyses planned based on the DCRI's re-adjudication explicitly notes that any such statistical analyses would mirror the prespecified analyses in the original SAP. More specifically, the SSAP does not contemplate using any new statistical methods or statistical analyses of any new endpoints.

In conclusion, multiplicity concerns are neither relevant for the 2019 readjudication nor the 2026 readjudication, and CDER's argument is unfounded.

d. FDA has relied on readjudicated results in approval decisions

FDA previously has approved therapeutic products based upon readjudicated results that have provided increased confidence in efficacy, including where readjudication was conducted following database lock.

For example, in its review of the osteoporosis drug TYMLOS (abaloparatide), CDER explained that although "[a]djudication of clinical fractures based on source data was conducted by the Applicant prior to database lock in Dec. 2014," "[d]uring finalization of the CSR [for pivotal Phase 3 study BA058-05-003] in Sept. 2015, discrepancies were noted in locations of some fractures between the eCRF 'fractures page' and the AE tables."[287] As a result, "a complete readjudication (again, treatment-blinded) of all fractures was conducted, including review of all source data and x-ray re-interpretation."[288] The clinical review team nonetheless concluded that "[t]he phase 3 studies BA058-05-003 and BA058-05-005 (extension) were adequate and well controlled studies that unequivocally establish the efficacy of abaloparatide in reducing [postmenopausal osteoporosis] related fractures,"[289] and TYMLOS received approval in 2017.[290]

In addition, in 2021, ENTRESTO (sacubitril; valsartan) was approved for an expanded indication based on a single Phase 3 trial, PARAGON-HF, with support from readjudication data.[291] The primary efficacy endpoint was the rate of the composite of total (first and recurrent)

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[286] *Id.* at 23.
[287] CDER, *Medical Review(s)* (NDA 208743) at 56 (Dec. 8, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208743Orig1s000MedR.pdf.
[288] *Id.*
[289] *Id.* at 15.
[290] CDER, *Approval Letter* (NDA 208743) (Apr. 28, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208743Orig1s000Approv.pdf. In another example, the protocol for the pivotal trial supporting approval of an efficacy supplement for CUBICIN (daptomycin) provided that patient data "that had undergone final lock procedures at the CRO" could be referred for readjudication by the Independent External Adjudication Committee if "changes made to these data after this time" warranted it, and FDA itself conducted outcome readjudications as part of its medical review. *See* CDER, *Approval Package* (NDA 021572/S-008) at 136 (May 25, 2006), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/021572Orig1s008.pdf.
[291] CDER, *Supplement Approval Package* (NDA 207620/S-018) at 19 (Feb. 16, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/207620Orig1s018.pdf.

hospitalization for heart failure ("HHF") and cardiovascular death.[292] Certain investigator-reported events relevant to the primary efficacy analysis were eliminated during the trial's initial adjudication process, however, and the sponsor

> argued that the adjudication process, in an effort to maximize specificity for the primary efficacy endpoint, resulted in the rejection of events that could have been positively adjudicated. Investigator assessment of events as endpoints were reportedly adjudicated as non-events because of missing data that were required by the adjudication charter (e.g., chest x-ray, lab, physical findings[)]. The PARAGON-HF study governance opined that such missing data would not have reversed an investigator-based endpoint diagnosis during the adjudication if more clinical judgement flexibility was provided in the adjudication process.[293]

Accordingly, the sponsor "was asked [by FDA] to convene a new independent adjudication committee to re-assess negatively adjudicated endpoints and assign a probability that these endpoints may have been positive."[294] The readjudication encompassed all 566 negatively adjudicated HHF events and resulted in addition of approximately 104 events to the ENTRESTO arm and 124 events to the active control arm.[295] Ultimately, although the trial did not support "the first-ever claim in a fundamentally different form of heart failure," the review team concluded that the trial *did* support "an expansion of [the drug's] prior claim," citing—among other things—"data that incorporated *an independent blinded re-adjudication of originally negatively adjudicated events* by assigning a probability that such events may be positive."[296] The review team explained, in part, that "[a]lthough PARAGON-HF narrowly missed statistical significance for the primary composite endpoint, additional prespecified exploratory and post-hoc analyses support a treatment effect."[297] Thus, readjudication of results with respect to the PARAGON-HF primary efficacy analysis supported approval for an expanded efficacy claim.

That same year, in 2021, FDA conducted a readjudication of clinical trial data to support approval of DEFENCATH (taurolidine and heparin) based on a single Phase 3 trial, LOCK-IT-100.[298] The primary efficacy endpoint was time to catheter-related bloodstream infection ("CRBSI") in patients with kidney failure receiving hemodialysis.[299] Because relatively few CRBSI events were captured during the trial, the protocol was modified while the trial remained blinded to, among other things, introduce a clinical adjudication committee responsible for identifying protocol-defined CRBSIs by reviewing subjects' medical records.[300] The drug met

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[292] *Id.* at 30.
[293] *Id.* at 12, 31.
[294] *Id.* at 12.
[295] *Id.* at 47-48.
[296] *Id.* at 10-11 (emphasis added).
[297] *Id.* at 14.
[298] CDER, *Multi-Discipline Review* (NDA 214520) at 18 (Feb. 26, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/214520Orig1s000MultidisciplineR.pdf.
[299] *Id.*
[300] *Id.*

the primary endpoint of time to CAC-adjudicated CRBSIs in the final analysis.[301] FDA clinical reviewers then "conducted a readjudication of the cases reviewed by the CAC and performed a sensitivity analysis based on the results."[302] While the Agency's readjudication "showed a few differences as compared with the CAC-adjudicated CRBSI cases," the review team nonetheless concluded that "the overall results of the FDA readjudication were consistent with the CAC-adjudicated results."[303] As part of its rationale for accepting a single adequate and well-controlled trial, the review team specifically cited the readjudication, explaining that "[r]esults based on FDA readjudication of the CRBSI cases were consistent with the results based on CAC-adjudication of the CRBSI cases."[304] While approval was delayed due to manufacturing and supplier issues unrelated to the clinical efficacy data,[305] approval was granted in 2023 based on the LOCK-IT-100 trial.[306]As detailed in Dr. Gibbons's Declaration, Dr. Gibbons has also identified additional precedent where CDER—as well as the Center for Biologics Evaluation and Research ("CBER")—have relied on readjudicated clinical trial results to evaluate a drug product's efficacy.[307] These precedents reflect a cross-center institutional practice of accepting readjudicated clinical data as reliable evidence of efficacy.

Accordingly, FDA has not previously categorically opposed consideration of readjudicated clinical trial data to support approval on the basis of multiplicity or other methodological concerns, and it is not in the best interest of patients to do so here, in the context of a rare disease with ongoing unmet medical need. We are aware of no evidence in publicly available review packages demonstrating that CDER required multiplicity adjustments or even raised multiplicity concerns in these precedents in which readjudicated results supported a determination of efficacy. CDER's insistence on multiplicity adjustments in this case thus risks being arbitrary and inconsistent with precedent.

3. Post-Marketing Evidence Supports Substantial Evidence of Efficacy

Multiple real-world evidence studies as well as post-marketing studies from around the world align with clinical experience and provide confirmatory evidence of the efficacy of TAVNEOS, consistent with that observed in ADVOCATE in achieving and sustaining disease control, as detailed in the accompanying Appendix A (Section 6) and summarized in the tables below. Significantly, data from comparative effectiveness studies reinforce, among other things, that TAVNEOS added to SOC versus SOC alone reduces relapse and glucocorticoid exposure. Additional cohort studies demonstrate that TAVNEOS, when added to SOC can help patients achieve remission and improve kidney outcomes, while reducing glucocorticoid exposure. Importantly, the heterogeneity of designs and patient populations across these studies suggests

[301] *Id.* at 100-01.
[302] *Id.* at 18.
[303] *Id.* at 100.
[304] *Id.* at 16-17.
[305] *See* CorMedix, *CorMedix Receives Complete Response Letter from FDA for Defencath Catheter Lock Solution* (Mar. 1, 2021), https://cormedix.com/cormedix-receives-complete-response-letter-from-fda-for-defencath-catheter-lock-solution/; CorMedix, *CorMedix, Inc. Announces Regulatory and Manufacturing Updates* (Aug. 8, 2022), https://cormedix.com/cormedix-inc-announces-regulatory-and-manufacturing-updates/.
[306] *See* CDER, *Approval Letter* (NDA 214529) (Nov. 15, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/214520Orig1s000ltr.pdf; *Approved Labeling* (NDA 214529) at 8-9 (Nov. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214520Orig1s000lbl.pdf.
[307] Gibbons Declaration, *supra* note 7, at 20-22.

that the benefits of TAVNEOS are robust and span the breadth and depth of GPA and MPA including in patients with newly diagnosed and relapsing disease, severely impaired kidney function, refractory disease, and multi-organ involvement. Together, these data provide additional support that there is substantial evidence of efficacy of TAVNEOS in AAV management.

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Table 10. Overview of Real World Comparative Effectiveness Studies

Author, Country, Year	Data source	Control Cohort	N		Remission^			Relapse Over 12mo			Cumulative GC Exposure			eGFR improvement at 12mo†		
			Ava	Ctrl	Ava	Ctrl		Ava	Ctrl		Ava	Ctrl		Ava	Ctrl	
Dang et al., US, 2026	Claims	RTX or CYC SOC	183	4096				24.3%	28.1%	HR = 0.81 (0.59, 1.13)	6mo: 1755mg; 12mo: 2273mg	6mo: 2315mg. 12mo: 2907mg	6mo: Difference (95% CI): -560mg (-814, -2); 12mo: Difference (95% CI): -633mg (-985, 18)			
Draibe, Spain, 2025	EHR	Historical cohort	29	39				14%	26%	p=0.36	6mo: 2201mg 12mo: 2345mg	6mo: 3650mg 12mo: 4732mg	6mo: p=0.02 12mo: p<0.01	+14	+16	p=0.61
Faguer, France, 2025	EHR	Historical cohort	20	50										+19	+24	p=0.44
Hussain, UK, 2026	EHR	Historical cohort	70	56	93%*	91%*		6%	11%	p=0.45	12mo: 390mg	12mo: 3535mg		+21	+18	p=0.32
Thiele et al., Germany, 2026	EHR	Historical cohort	35	70	86%*	68%*	p=0.11	16%	51%	p=0.003	until ≤5mg/d: 3266mg	until ≤5mg/d: 4288mg	p=0.008	+18	+7	
Ushio et al., Japan, 2025	EHR	Historical cohort	14	52	100%#	87%#	p=0.33	0%	5.8%	p=1.00	6mo: 1978mg	6mo: 2972mg	p<0.001			
Wood, UK, 2025	EHR	Historical cohort	61	62	63%#	NR	OR 2.92 (95% CI 1.34-6.35); p=0.007									

Ava = avacopan; Ctrl = control; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; EHR = electronic health record; GC = glucocorticoid; HR = hazard ratio; mo = month; NR = not reported; OR = odds ratio; RTX = rituximab; SOC = standard of care; UK = United Kingdom; US = United States

Blank cells indicate unreported data/definitions from the study. All cumulative GC use and eGFR results are presented as mean/median as presented in the article. In cases where both are presented, what was featured in the text was included in the table.

^ Remission definitions vary across studies.

† eGFR outcomes are expressed in mL/min/1.73m2 units.

Remission at 6 months

* Remission at 12 months

Table 11. Overview of Real World Cohort Studies Assessing Avacopan Effectiveness in Large Cohorts

Author, Country, Year	Study Design	Number of Avacopan Patients	AAV Type	Baseline Organ involvement	Induction Therapy	Remission Definition‡	Remission	Relapse	GC outcomes	Kidney outcomes†
Assmann, Germany, 2026#~	Retrospective cohort - EHR	30	GPA: 20 (67%) MPA: 10 (33%)	Kidney: 30 (100%) - eGFR <15: 6 (20%) - Dialysis: 5 (17%) Lung: 26 (87%) ENT: 18 (60%)	RTX/CYC: 30 (100%)	Remission-BVAS=0; Complete remission-BVAS=0 and no GCs	6mo: 30 (100%) Complete 6mo: 17 (58%) Complete 12mo: 23 (82%)	1 (3%)		eGFR 6mo: +15 4/5 (80%) dialysis liberation
de Koning, Europe, 2026~+	Retrospective cohort - EHR	132	GPA: 79 (60%) MPA: 53 (40%)	Kidney: 96 (73%) Lung: 78 (59%) ENT: 66 (50%)	RTX: 108 (82%) CYC: 34 (26%)	Remission-BVAS=0	3mo: 80% 6mo: 87% 12mo: 85%		GC ≤5mg/d - 3m: 84% - 6mo: 90% - 12mo: 96%	
Hussain, UK, 2026~+	Retrospective cohort - EHR	70	PR3+: 39 (55%) MPO+: 31 (45%)	Kidney: 56 (80%) Lung: 25 (36%) ENT: 22 (31%)	RTX: 59 (84%) CYC: 10 (14%)		Sustained 12mo: 66 (93%)	4 (6%)	All rapid taper 30mg x 1 week, 20mg x 1 week, discontinue Cumm GC 390mg	eGFR 12mo: +20
Meade-Aguilar, US, 2026~+	Retrospective cohort- EHR	64	GPA: 41 (64%) MPA: 23 (36%)			Remission-BVAS=0; Complete remission BVAS=0 and no GCs	Remission: 60 (94%) - Median 2.6mo Complete remission: 45 (70%) - Median 4.3mo	14 (22%) - 6 minor - 8 major	GC free: 47 (73%) - Median time 4mo	eGFR 6mo: +8 eGFR 12mo: +10
Patel, US, *(under review)*~^	Retrospective cohort- EHR	159	GPA: 92 (58%) MPA: 67 (42%)	Kidney: 74 (47%) - eGFR<20: 17 (10%) - Dialysis: 13 (8%) Lung: 72/148 (49%) - DAH: 13 (8%) ENT: 66/149 (44%)	RTX: 97 (61%) CYC: 5 (3%) RTX/CYC: 50 (31%)	Remission-BVAS=0 and ≤5mg/d GC within 1mo; Complete remission-BVAS=0 and no GCs within 1mo	6mo: 102/148 (69%) Sustained 12mo: 96/148 (65%) Complete 6mo: 77/148 (77%) Sustained complete 12mo: 73/148 (49%) BVAS=0 at 12mo: 139/148 (94%)	29 (20%) patients 38 events - 11 minor - 27 major	Cumm GC 12-mo: 1199mg 14 (10%) no GCs Discontinued GC - 2mo: 38% - 6mo: 64% - 12mo: 80%	eGFR 12mo: +20 7/12 (58%) dialysis liberation
Scholes, Australia, 2026~+	Retrospective cohort- EHR	44	GPA: ~40% MPA: ~60% EGPA: ~1%	Kidney: 31 (71%) - eGFR<15: 7 (16%) Lung: 11 (25%) ENT: 10 (23%)	RTX: 36 (82%) CYC: 14 (32%) RTX/CYC: 12 (27%)		6mo: 23/30 (77%) 12mo: 12/16 (75%)	4 (9%)	GC free - 6mo: 22/36 (61%) - 12mo: 13/21 (62%)	eGFR 6mo: ~+4 eGFR 12mo: ~+8

Author, Country, Year	Study Design	Number of Avacopan Patients	AAV Type	Baseline Organ involvement	Induction Therapy	Remission Definition‡	Remission	Relapse	GC outcomes	Kidney outcomes†
Thiele et al., Germany, 2026	Retrospective cohort- EHR	35	GPA: 19 (55%) MPA 16 (45%)	Kidney: 31 (89%) - eGFR<15: 11 (31%) Lung: 15 (43%) ENT: 15 (43%)	RTX:12 (34%) CYC: 2 (6%) RTX/CYC: 21 (60%)	Remission- BVAS=0 and GC ≤5mg/d	6mo: 18/26 (69%) 12mo: 18/21 (86%)	4/25 (16%)	Cumm GC until ≤5mg/d: 3266mg	
Wood, UK, 2025~	Retrospective cohort- EHR	61		Kidney - eGFR<15: 11 (18%)	Unknown immuno-suppression: 17 (28%) RTX/CYC: 14 (23%)	Remission- BVAS<3 and GC≤5mg/d Complete remission BVAS=0 and no GC	6mo: 31/49 (63%) Complete 6mo: 7/49 (14%)	2/16 (13%)	GC free: - 12mo: 18/49 (37%)	7/9 (78%) pt with eGFR <15 at baseline had eGFR >15 at 6mo
Zimmerman, Germany, 2024#~	Retrospective cohort- EHR	39	PR3+: 22 (56%) MPO+: 15 (38%) MPO+/anti-GBM: 2 (5%)	Kidney: 33 (85%) - eGFR<15: 15 (38%) - Dialysis: 7 (18%) Lung: 20 (51%) ENT: 12 (31%)	RTX: 24 (62%) CYC: 15 (39%)	Remission- BVAS=0 and GC≤7.5mg/d	6mo: 28/32 (88%) Sustained 12mo: 21/23 (91%)	4 (10%) - 4 major	Cumm GC: 3090mg	eGFR 6mo: +7 eGFR 12mo: +14 Among eGFR<15 at baseline - eGFR 6mo: +25 - eGFR 12mo: +30 5/6 (83%) dialysis liberation
Zonozi, US, 2024b#~*^	Retrospective cohort- EHR	92	PR3+: 25 (27%) MPO+: 66 (72%) ANCA-: 1 (1%)	Kidney: 71 (77%) - eGFR<15: 15 (38%) - Dialysis: 9 (10%) Lung: 48 (52%) ENT: 27 (29%)	RTX: 44 (47%) CYC: 2 (2%) RTX/CYC: 43 (47%)	Remission: no signs/ symptoms and GC≤5mg/d	6mo: 61/68 (90%) 12mo: 32/38 (84%)	3 (3%)	GC free: 64/89 (72%) - Mean time 97d after induction - Mean time 52d after avacopan Cumm GC exposure - 6mo: 1797mg - 12mo: 2212mg	eGFR 6mo: +12.2 eGFR 12mo: +19.8 Among eGFR<15 at baseline - eGFR 6mo: +19.5 - eGFR 12mo: +25.1 5/9 (56%) dialysis liberation

AAV = ANCA-associated vasculitis; ANCA = anti neutrophil cytoplasmic autoantibody; BVAS = Birmingham vasculitis activity score; BVAS/WG = BVAS/Wegener's Granulomatosis; CKD = chronic kidney disease; Cumm = cumulative; CUP = compassionate use program; CYC = cyclophosphamide; DAH= diffuse alveolar hemorrhage; EAP = early access program; eGFR = estimated glomerular filtration rate; EGPA = eosinophilic GPA; EHR = electronic health record; ENT = ear, nose and throat; GBM = glomerular basement membrane; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; mo = month; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase 3; RTX = rituximab; UK = United Kingdom; US = United States

Blank cells indicate unreported data/definitions from the study. All cumulative GC use and eGFR results are presented as mean/median as presented in the article. In cases where both are presented, what was featured in the text is included in the table.

Included in the meta-analysis by Berke et al., 2026.

~ Included in the Amgen-sponsored meta-analysis (Ibiloye et al., 2026).

* Included in the systematic literature review by Kronbichler et al., 2026.

^ Includes 31 overlapping patients.

+ Data abstracted from both abstracts and posters.

‡ The terms “remission” and “complete remission” were aligned in this table and may not match exact terms used in each study. Sustained remission required no relapse between timepoints.
† eGFR outcomes are expressed in mL/min/1.73m^2 units.

Table 12. Overview of Real World Cohort Studies Assessing Avacopan Effectiveness in Special Populations

Author, Country, Year	Study Design	Number of Avacopan Patients (special population)	AAV Type	Baseline Organ involvement	Induction Therapy	Remission Definition‡	Remission	Relapse	GC outcomes	Kidney outcomes†
Chalkia, UK, 2024#~*	Retrospective cohort - EHR	8 (DAH)	PR3+: 3 (38%) MPO+: 5 (63%)	Kidney: 7 (88%) - Dialysis: 3 (38%) Lung: 8 (100%) - DAH: 8 (100%) - Mechanical Vent: 4 (50%)	RTX: 3 (38%) CYC: 1 (13%) RTX/CYC: 4 (50%)	Remission-clinical remission per provider	6mo: 8 (100%)	0 (0%)	1mo: median: 5mg/d	1/3 (33%) dialysis liberation
Draibe, Spain, 2025#~	Retrospective cohort - EHR	29 (EAP)	GPA: 10 (34%) MPA: 18 (62%) EGPA: 1 (3%)	Kidney: 24 (79%) Lung: 9 (31%) ENT: 9 (31%)	RTX: 14 (48%) CYC: 2 (7 %) RTX/CYC: 12 (41%) Other: 1 (3%)	Remission-BVAS=0	3mo: 27/28 (96%) Sustained 6mo: 25/28 (89%) 12mo:13/13 (100%) 18mo: 4/4 (100%)	4 (13%) 3 minor 1 major		eGFR 12mo: +13.7 4/5 (80%) dialysis liberation
Eisinger, US, 2025#~	Retrospective cohort - EHR	15 (avacopan use beyond 52 weeks)	PR3+: 5 (33%) MPO+: 10 (67%)	Kidney: 14 (93%) Lung: 10 (67%) ENT: 3 (20%)	RTX: 12 (80%) CYC: 1 (7%) RTX/CYC: 2 (13%)	Remission-BVAS <3	6mo: 13 (87%) 12mo: 15 (100%)	1 (6%)	GC free: 15 (100%) median time 30d Cumm GC 6mo: 1220mg Cumm GC 12mo: 1220mg	eGFR 6mo: +15 eGFR 12mo: +18
Falde, US, 2024#~	Retrospective cohort - EHR	15 (DAH)	GPA: 8 (53%) MPA: 7 (47%)	Kidney: 9 (60%) - Dialysis: 2 (13%) Lung: 15 (100%) - DAH: 8 (100%)	RTX: 14 (94%) CYC: 3 (20%)	Remission-BVAS/WG=0; Complete Remission-BVAS/WG=0 and no GCs	Remission: 14 (93%) Median 52d Complete remission: 10 (67%) Median 52d	0 (0%)	GC free - 4wks: 3 (20%) - 12wks: 9 (60%)	
Gabilan, France, 2025#~*	Retrospective cohort - EHR	31 (EAP requiring GC contraindication)	PR3+: 9 (29%) MPO+: 20 (6%) Dual+: 1 (3%) ANCA–: 1 (3%)	Kidney: 30 (97%) - Dialysis: 2 (6%) Lung: 7 (23%) - DAH: 5 (16%) ENT: 6 (19%)	RTX: 27 (87%) CYC: 2 (6%) RTX/CYC: 2 (6%)	Remission-BVAS=0	6mo: 29 (94%)	2 (6%)	GC free - 3mo- 28 (90%) - Median time <1mo Cumm GC: 700mg	eGFR 12mo: +16 1/2 (50%) dialysis liberation
van Leeuwen, The Netherlands, 2021#~	Case series	8 (Compassionate Use)	PR3+: 4 (50%) MPO+: 4 (50%)	Kidney: 5 (63%) Lung: 4 (50%) ENT: 4 (50%)	RTX: 3 (38%) RTX/CYC: 5 (63%)	Remission-BVAS=0	6mo: 8 (100%)	1 (13%)	GC free: 5 (63%)	4/8 (50%) pt eGFR improvement (+4 to +9)

AAV = ANCA-associated vasculitis; ANCA = anti neutrophil cytoplasmic autoantibody; BVAS = Birmingham vasculitis activity score; BVAS/WG = BVAS/Wegener's Granulomatosis; CKD = chronic kidney disease; Cumm = cumulative; CUP = compassionate use program; CYC = cyclophosphamide; DAH= diffuse alveolar hemorrhage; EAP = early access program; eGFR = estimated glomerular filtration rate; EGPA = eosinophilic GPA; EHR = electronic health record; ENT = ear, nose and throat; GBM = glomerular basement membrane; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; mo = month; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase 3; RTX = rituximab; UK = United Kingdom; US = United States

Blank cells indicate unreported data/definitions from the study. All cumulative GC use and eGFR results are presented as mean/median as presented in the article. In cases where both are presented, what was featured in the text is included in the table.

[#] Included in the meta-analysis by Berke et al., 2026.
[~] Included in the Amgen-sponsored meta-analysis (Ibiloye et al., 2026).
***** Included in the systematic literature review by Kronbichler et al., 2026.
^ Includes 31 overlapping patients.
‡ The terms “remission” and “complete remission” were aligned in this table and may not match exact terms used in each study. Sustained remission required no relapse between timepoints.
† eGFR outcomes are expressed in mL/min/1.73m^2 units.

Post-approval safety studies provide further support for substantial evidence of effectiveness. Interim effectiveness findings from the Japan PMS study, which has been ongoing since June 2022, underscore TAVNEOS's efficacy in providing durable disease control and preserving kidney function in patients with GPA or MPA. An interim effectiveness analysis based on a recent data cutoff date of September 26, 2025 included 448 patients, 325 patients with active disease and 123 patients with non-active disease at TAVNEOS initiation. Significantly, by one year after starting TAVNEOS, the vast majority of patients (410 patients) remained relapse-free while 8.5% of patients (38 of 448) experienced a relapse. Among patients with active disease at the time of TAVNEOS initiation, the disease was no longer active for 75.8% (185/244) at six months and 81.4% (144/177) at one year. Overall, these findings indicate a low relapse rate consistent with previously published data, along with a progressive decrease in active disease status during TAVNEOS treatment.

In an interim analysis of AVACOSTAR, in particular, a consistent GC-sparing effect was observed, with substantially higher proportions of glucocorticoid-free subjects in the TAVNEOS arm versus SOC at both six months (62.8% versus 27.5%) and 12 months (71.6% versus 37.9%). While estimated improvements in eGFR at Month 12 were numerically higher in the TAVNEOS group compared with SOC across all populations and model specifications, the differences did not reach statistical significance, and the corresponding LSM differences confidence intervals included zero. More details on these studies' interim analyses are available in Appendix A (Section 6.4).

In conclusion, multiple supportive RWE and post-marketing studies across a number of geographies confirm that TAVNEOS has a clinically meaningful benefit in patients living with AAV.

4. TAVNEOS Has A Well-Characterized, Manageable Safety Profile

Although CDER has not invoked safety as a basis for seeking the withdrawal of TAVNEOS, Amgen addresses the well-characterized, manageable safety profile at length in Appendix A (Section 7). The risk-benefit profile of TAVNEOS thus remains positive.

a. CDER recognized TAVNEOS's acceptable safety profile in approving TAVNEOS based on the ADVOCATE trial

The ADVOCATE trial demonstrated an acceptable safety profile for TAVNEOS. In the study, patients in the TAVNEOS arm experienced fewer adverse events, serious adverse events, and infections compared to the prednisone control arm.[308] In approving TAVNEOS on the basis of this trial, CDER expressly recognized the acceptable safety profile demonstrated by the study data and that the observed safety findings were acceptable in light of TAVNEOS's demonstrated benefits as well as the seriousness of the indicated disease and the risks associated with available alternative therapies.

[308] CDER Multi-Disciplinary Review, *supra* note 1, at 45 ("In the pivotal study, generally similar or fewer number of patients in the avacopan arm compared to the prednisone arm experienced deaths (2 vs. 4 patients), SAEs (42% vs. 45%), AEs leading to discontinuation (16% vs. 17%), and TEAEs (99% vs. 98%).").

As suggested in the NOOH,[309] CDER noted at the time of approval that the ADVOCATE data had identified "potential safety risks of hepatotoxicity and hypersensitivity."[310] TAVNEOS was therefore approved with labeling containing information and warnings regarding hepatotoxicity and hypersensitivity. According to CDER this was "[c]onsistent with other immunosuppressive therapies used for A[A]V such as cyclophosphamide and methotrexate."[311]

Notably, the Center neither required a boxed warning in TAVNEOS labeling nor concluded a "REMS [Risk Evaluation and Mitigation Strategies] is . . . needed to ensure the benefits of avacopan outweigh its risks."[312] In doing so, CDER implicitly determined that the risks of TAVNEOS could be managed through routine risk minimization. The prescribers of TAVNEOS are generally specialists with substantial experience treating patients with this disease[313] and therefore familiar with the comparable risk profile of other therapies used in this setting. The Center also took into consideration the risk profiles of available alternatives and the gravity of AAV, itself, noting that the alternative treatments of glucocorticoids and immunosuppressant are "associated with significant toxicities such as infection, myelosuppression, hepatotoxicity, endocrine and metabolic disruptions, and hypersensitivities which may limit therapeutic options in patients who are intolerant or have inadequate response to therapies."[314] In fact, as the Center acknowledged that, prior to TAVNEOS, therapy-related causes accounted for the largest share of deaths for AAV patients.[315] These factors all weighed in favor of TAVNEOS's approval because the substantial toxicities and risks associated with these existing AAV therapies highlighted "an unmet need for alternative options, and for therapies with less toxicities" for AAV patients.[316]

b. Post-marketing data supports manageable safety profile

As detailed in Appendix A (Section 7), the post-marketing safety data is largely consistent with the safety findings observed during clinical development program and further supports the safety profile of TAVNEOS. Since its first approval in Japan in September 2021, followed by approvals in the U.S., European Union, and other countries, TAVNEOS has accumulated substantial post-marketing exposure, both through post-marketing studies as well as real-world use. As of January 2026, estimated real-world exposure exceeds 25,000 patient-years globally, consisting of approximately 6,500 in the U.S. and 19,000 abroad. This growing body of experience provides a valuable insight into TAVNEOS's safety profile beyond the controlled setting of clinical studies conducted prior to approval.

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[309] 91 Fed. Reg. at 23279 ("We note that hepatotoxicity was identified as a key safety risk in the original NDA review.").
[310] CDER Multi-Disciplinary Review, *supra* note 1, at 35, 39.
[311] *Id.* at 3.
[312] *Id.*
[313] *Id.* ("The review team from DRM and the Division of Rheumatology and Transplant Medicine (DRTM) determined a REMS is not needed to ensure the benefits of avacopan outweigh its risks. The primary prescribing population are rheumatologists but may include other specialists such as neurologists, nephrologists, pulmonologists, dermatologists, and urologists, who are experienced in treating patients with AVV.").
[314] *Id*. at 12.
[315] *Id.*
[316] *Id.*

Post-marketing safety studies conducted worldwide to date similarly provide results consistent with the known safety profile of TAVNEOS: [317]

- A Post-Authorization Safety Study ("PASS") To Evaluate The Incidence Of Safety Events Of Interest In Subjects Treated With Avacopan for AAV ("AVACOSTAR"): In this ongoing, non-randomized, non-interventional observational PASS in Germany and the United Kingdom, an interim analysis conducted with data cut-off date of September 11, 2025, revealed liver injury events for 8.3% of patients in TAVNEOS group versus 2% of the patients in the non-TAVNEOS group. The exposure adjusted unique incidence rate of liver injury events was 0.075 per patient year with TAVNEOS. All events were graded as mild to moderate in severity. One event was reported as serious (alanine aminotransferase increased); TAVNEOS was briefly paused and then restarted, with no recurrence of significant liver test abnormalities. As Dr. Chalasani notes in his Declaration, these hepatotoxicity data are not greater than that observed with that of many other FDA-approved drugs.[318]

- Japan Post-Marketing Surveillance Study: An interim analysis (cutoff date of Sept. 26, 2025) revealed the rate of serious hepatic abnormalities to be similar to ADVOCATE (5.4% in ADVOCATE vs. 5.3% in the study), supporting the known safety profile of TAVNEOS.

c. Hepatotoxicity risks are highly manageable

As described in detail in Appendix A (Section 7) and below, hepatotoxicity risks associated with TAVNEOS are not only well-characterized, but also are highly manageable in real-world practice. TAVNEOS's labeling sets out clear, concrete instructions for clinicians: it specifies which liver analyte tests must be performed before initiation of therapy (i.e., ALT, AST, ALP, and total bilirubin), the precise monitoring cadence during treatment (i.e., every four weeks after start of the therapy for the first six months), and the numeric thresholds at which treatment should be paused or discontinued. These measures are not onerous and generally consistent with clinical practice. As Dr. Lally explains, the requirement to monitor monthly for the first six months of TAVNEOS treatment is neither outside typical practice nor unduly burdensome for patients or prescribers, particularly in a population that already undergoes frequent blood testing.[319] Patients being treated with cyclophosphamide for AAV, for example, typically require labs every two weeks. Further, as a rheumatologist, many of the medications that she prescribes to manage other rheumatic diseases require laboratory monitoring at some regular cadence.[320] Dr. Chalasani also states that it is not uncommon for drugs treating serious conditions, such as cancer, infectious diseases, or nervous system disorders, to have similar warnings for liver monitoring.[321]

[317] *See* Appendix A (Section 7.3).
[318] *See* Chalasani Declaration, *supra* note 12, at 6, 8, 11, 16.
[319] Lally Declaration, *supra* note 6, at 24.
[320] *Id.*
[321] Chalasani Declaration, *supra* note 12, at 14.

The clinical context in which TAVNEOS is used further makes the hepatotoxicity risk easier to manage. AAV is rare and is generally treated by rheumatologists and other medical specialists (e.g., nephrologists, pulmonologists, and/or otolaryngologists).[322] KDIGO, as Dr. Lally notes, recommended in 2024 that AAV patients be managed in health centers with experience in vasculitis, ensuring that treating physicians are familiar with both the disease and its therapeutic options.[323] In the U.S., the Vasculitis Clinical Research Consortium ("VCRC")—which in turn is part of the Rare Diseases Clinical Research Network that is funded by the National Institutes of Health—includes 18 academic institutions, to which local physicians commonly refer newly diagnosed AAV patients so that they can benefit from care by disease experts.[324] The prescribing community for AAV is thus relatively small and concentrated at academic centers with vasculitis centers.[325] In this environment, prescribers are well-positioned to understand TAVNEOS's hepatotoxicity profile, apply the monitoring instructions in the labeling rigorously, and respond promptly to emerging signals.

Moreover, Amgen's actions as TAVNEOS's sponsor demonstrate that these risks are actively managed. When VBDS first emerged in the post-marketing setting outside the U.S., Amgen proactively submitted a safety label update via a PAS to CDER to add further information on VBDS to the labeling. In response, CDER issued an Information Request, to which Amgen submitted a response in November 2024, but the Center did not take further action on this submission. After FDA issued a Drug Safety Communication on March 31, 2026[326]—once CDER had already communicated that it would seek to withdraw TAVNEOS—Amgen again moved on its own initiative to implement corresponding labeling changes through a CBE-30 supplement, which was submitted on April 29, 2026, and went into effect on May 29, 2026. The CBE-30 amended Section 5.1 (Hepatotoxicity) of the PI to provide more information and heightened monitoring recommendations in response to the VBDS cases, including fatal cases, that have been reported in the post-marketing setting. This history shows a consistent, responsible stewardship of the labeling and willingness and ability to update it promptly as the pharmacovigilance record evolves.

Real-world clinical experience also confirms that these hepatotoxicity warnings and monitoring provisions have served as risk management tools, not barriers to prescribe or use TAVNEOS. As Dr. Lally observes, neither the existing hepatotoxicity warnings nor the associated monitoring instructions have served as an impediment to the appropriate use of TAVNEOS in patients with AAV.[327] Physicians have incorporated these measures into their

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[322] *See* FDA, *FDA Approves Add-on Drug for Adults with Rare Form of Blood Vessel Inflammation* (Oct. 13, 2021), https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-add-drug-adults-rare-form-blood-vessel-inflammation; FDA, *Risk Assessment and Risk Mitigation Review(s)* (NDA 214487) at PDF 4 (Oct. 6, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214487Orig1s000RiskR.pdf; Sharon A. Chung et al., *2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis*, 73 ARTHRITIS & RHEUMATOLOGY 1366, 1366–83 (2021).
[323] Lally Declaration, *supra* note 6, at 12.
[324] *Id.* at 13.
[325] *Id.* at 13-14.
[326] *See* FDA, *FDA Identifies Cases of Serious Liver Injury in Patients Taking Tavneos (avacopan) for Severe Active Anti-neutrophil Cytoplasmic Autoantibody (ANCA)-associated Vasculitis* (Mar. 31, 2026), https://www.fda.gov/drugs/drug-safety-communications/fda-identifies-cases-serious-liver-injury-patients-taking-tavneos-avacopan-severe-active-anti.
[327] Lally Declaration, *supra* note 6, at 22, 24.

routine practice without difficulty, and the enhanced labeling introduced through Amgen's recent CBE-30 is similarly not expected to deter prescribing. In short, TAVNEOS is being used by experienced specialists under a robust labeling that timely detects and appropriately manages hepatotoxicity risk.

d. DILI risks are manageable and VBDS has not been observed in U.S. patients

CDER's NOOH notes the recent Drug Safety Communication issued by the Agency and states that serious cases of hepatotoxicity have been reported post-marketing, including DILI and VBDS cases.[328] As detailed in Amgen's accompanying Appendix A, these observed DILI and VBDS events have largely involved patients of Japanese descent and appear to be driven by discrete, manageable causes—rather than indicating a safety concern in the U.S. patients.

Furthermore, as Dr. Chalasani explains, DILI can present in many different ways (from asymptomatic elevations in liver biochemistry to serious adverse events such as jaundice or liver failure), making it difficult to distinguish DILI caused by a specific medication from other causes of liver injuries.[329] In addition, AAV patients are already prone to a higher incidence of elevated liver enzymes, likely due to the disease itself as well as comorbidities and concomitant medications.[330] Dr. Chalasani notes that based on his review of the Council for International Organizations of Medical Sciences ("CIOMS") forms for VBDS events, at least a few patients were taking other medications such as sulfamethoxazole/trimethoprim (an antibiotic combination for pneumocystis pneumonia ("PCP") prophylaxis), amoxicillin/clavulanate acid, and/or azithromycin (for pneumonia), which can also cause cholestatic liver injury and VBDS.[331]

Significantly, as made clear in FDA's DSC as well, most DILI and VBDS cases reported to date have arisen from Japan.[332] According to Amgen Global Safety Database, as of January 20, 2026, 191 cases have been reported that met the DILI criteria. Among these DILI cases, the majority were reported from Japan (n=165), followed by the United Kingdom (n=5), France (n=5), Germany (n=4), the United States (n=3), Canada (n=2), Switzerland (n=2), and Italy (n=2), with single cases reported from Australia, Luxembourg, and Belgium. As for VBDS, 31 cases have been reported, which include 27 from Japan, two from Canada (one patient of Chinese heritage, the other unknown), and two literature reports from China. Notably, no VBDS cases have been reported from the U.S. or Europe All fatal cases of VBDS were reported from Japan, in patients over the age of 65.

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[328] *See* 91 Fed. Reg. at 23279-23280.
[329] Chalasani Declaration, *supra* note 12, at 4.
[330] *Id.* at 10.
[331] *Id.* at 18-19.
[332] *See* FDA, *FDA Identifies Cases of Serious Liver Injury in Patients Taking Tavneos (avacopan) for Severe Active Anti-neutrophil Cytoplasmic Autoantibody (ANCA)-associated Vasculitis* (Mar. 31, 2026), https://www.fda.gov/drugs/drug-safety-communications/fda-identifies-cases-serious-liver-injury-patients-taking-tavneos-avacopan-severe-active-anti ("Most cases (n=66) were reported from Japan, followed by the United States (n=5), Europe (n=4), and Canada (n=1). Of the 76 cases, 7 reported biopsy-confirmed VBDS as a complication of DILI with reasonable evidence of a causal association with avacopan use. Cases were reported from Japan (n=6) and Canada (n=1).").

Amgen's analysis of these events is detailed in Appendix A (Section 7.2.1). The imbalance in the number of cases from Japan may be attributable to several factors, including differences in pharmacogenetic susceptibility as well as regional differences in labeling language and monitoring practices. For instance, human leukocyte antigen ("HLA") DRB1*0901-DQB1*0303 is another allele common in East Asian populations, but rare in European populations.[333] The allele is not only associated with both myeloperoxidase ("MPO") ANCA-positive MPA[334] and primary biliary cirrhosis ("PBC"), but a risk factor for DILI. A reasonable hypothesis is therefore that Japanese patients are more susceptible to TAVNEOS liver injury, including VBDS because HLA-DRB1*09:01* is a risk factor for both the disease being treated and the liver injuries produced by the treatment.[335]

As Dr. Chalasani explains, there are several examples of medications where adverse drug reactions are found clustered in certain geographic areas, including Asian populations. For example, severe cutaneous adverse reactions ("SCAR") from carbamazepine are concentrated in Han Chinese, nevirapine hypersensitivity is concentrated in Africa and Australia, and allopurinol SCARs are found mostly in Asia.[336] Similarly, interstitial lung disease associated with gefitinib has been found to be far more prevalent in Japanese cohorts than Western cohorts.[337]

In addition, regional differences in the prescribing information for TAVNEOS between the United States and Japan (where Amgen is not the marketing authorization holder) and how patients are monitored between the U.S. and Japan may offer a further explanation for the disproportionate liver injury events observed in the latter. As noted in Table 1 above, in the U.S., TAVNEOS label has contained a dedicated hepatotoxicity warning in Section 5 (Warnings and Precautions) since approval, requiring patients to undergo baseline testing of ALT, AST, ALP, and total bilirubin before initiating the therapy, and to repeat this testing every four weeks for the first six months of therapy and thereafter as clinically indicated.[338] The label has also specified concrete thresholds for when providers should consider pausing or discontinuing the treatment.[339]

In contrast, the TAVNEOS labeling in Japan noted only in general terms that hepatic dysfunction may occur and recommends testing before and during treatment, but does not specify which tests should be conducted, how often they should be performed, and what numeric triggers should prompt action, including discontinuation of treatment.

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[333] Amgen, 1.11.3 Clinical Information Amendment (June 2, 2026).
[334] MPA accounts for the vast majority of AAV in Japan.
[335] Amgen, 1.11.3 Clinical Information Amendment (June 2, 2026).
[336] Chalasani Declaration, *supra* note 12, at 17-18.
[337] *Id.* at 18.
[338] Oct. 2021 USPI, supra note 100 ("Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS, every 4 weeks after start of therapy for the first 6 months of treatment and as clinically indicated thereafter.").
[339] *Id*. ("If a patient receiving treatment with TAVNEOS presents with an elevation in ALT or AST to >3 times the upper limit of normal, evaluate promptly and consider pausing treatment as clinically indicated. If AST or ALT is >5 times the upper limit of normal, or if a patient develops transaminases >3 times the upper limit of normal with elevation of bilirubin to >2 times the upper limit of normal, discontinue TAVNEOS until TAVNEOS-induced liver injury is ruled out.").

The robust monitoring framework present in the U.S. labeling since TAVNEOS was first marketed in the United States could have therefore contributed to earlier detection of liver injury signals and prompting timely dose interruption or discontinuation, reducing the likelihood that those signals progressed to serious adverse clinical events.

* * * * *

In sum, the totality of the evidence detailed here and in Appendix A demonstrates the continuing substantial evidence of effectiveness, and a positive risk-benefit profile for indicated rare disease patients. At a minimum, multiple disputed issues of material fact and the overwhelming public interest in rare-disease patient access to this therapy amply justifies a hearing.

B. CDER's Allegations That There Are Untrue Statements Of Material Fact In The NDA Fail As A Matter Of Law, Are Unsupported By The Requisite Evidence, And At A Minimum Involve Genuine And Substantial Issues Of Fact Warranting A Hearing

CDER also argues that it can withdraw approval pursuant to Section 505(e)(5), which applies only if "the application contains any untrue statement of material fact."[340] The Center identifies several statements related to the readjudication that it claims were untrue. In fact, those statements are true. Moreover, to the extent CDER is asserting that certain information should have been included in the NDA or other documents, there are no regulatory requirements that mandate the narrative that CDER demands. Because CDER has not identified untrue statements made to FDA, Amgen is entitled to judgment as a matter of law, or, at a minimum, a hearing because there are genuine factual disputes that must be resolved.

1. The NOOH does not identify any untrue statements

First, CDER asserts that ChemoCentryx failed to disclose an earlier lock, unblinding, analysis, and readjudication process, and, therefore, the application "falsely conveyed" a single database lock, a single unblinding, and a single analysis of ADVOCATE. CDER does not identify any statement in the application saying that there was "only" one analysis, "only" one database lock, no earlier analysis, no earlier lock, or no readjudication activity.

CDER points instead to statements that the ADVOCATE database was locked on November 20, 2019. That is not false; CDER itself states that "the database was locked for a second time on November 20, 2019." A true statement does not become untrue merely because CDER contends that the applicant should have provided additional information.

CDER further alleges that, in response to December 9, 2020 Information Request (IR 11), ChemoCentryx falsely characterized the study database lock as a single event when stating "the freeze of the study database" occurred on November 20.[341] But CDER's information request specifically focused on the question of whether "the SAP was not submitted for review prior to unblinding of the data" and requested that ChemoCentryx "provide any relevant

[340] 21 U.S.C. § 355(e)(5).
[341] 91 Fed. Reg. at 23286-87.

documentation . . . to provide evidence *that the SAP was finalized before the data unblinding*."[342] ChemoCentryx's statements in response were true: The response stated "[t]he final version of the SAP (version 2) was approved on 29 October 2019" prior to unblinding and provided a link to that version of the SAP.[343] Because the final version of the SAP was approved on October 29, 2019, it was finalized prior to any unblinding, regardless of whether the database lock occurred on November 5, 2019, or November 20, 2019.

Second, CDER's challenge to the reported p-value appears to be about the alleged reliability and evidentiary weight, not falsity. CDER states that the original post-November 5 analysis produced a two-sided p-value of 0.1025 and that the post-readjudication analysis submitted in the NDA produced a two-sided p-value of 0.0132.[344] CDER does not allege that the 0.0132 value was fabricated, miscalculated from the final corrected dataset, or different from the value generated under the prespecified analysis. Its objection is that the value should not be treated as valid because of the readjudication. That is an argument about whether the p-value supports substantial evidence of effectiveness. It does not provide proof that the reported p-value was an untrue factual statement.

Third, CDER alleges that the following statement in the CSR is untrue: "[t]reatment assignments for individual subjects remained blinded to the study team, Investigators, and subjects until after the study database had been cleaned and locked."[345] CDER contends that this statement is true if it refers to the initial lock but "patently false" if it refers to the November 20 lock.[346] However, as discussed above, only limited unblinding occurred on November 5, 2019. From November 5 to November 20, 2019, the treatment assignments for individual subjects remained blinded to the study team, Investigators, and subjects; only those members of Medpace and ChemoCentryx who were permitted to QC data pursuant to the SRAP had access to the data.

Fourth, and finally, CDER asserts that, "[g]iven the material omissions and untrue statements in the application, the applicant has falsely certified that the data and information in its application submissions for NDA 214487 were 'true and accurate.'"[347] But that assertion depends entirely on CDER's predicate contention that the application contained untrue statements. As explained above, the statements CDER has identified are not untrue.

A certification cannot supply the untrue statement that CDER has otherwise failed to identify. If it could, every alleged omission from an NDA would automatically become a Section 505(e)(5) case simply because the application included a true-and-accurate certification.

[342] *See* IR 11 Response, *supra* note 86, at 1 (emphasis added).
[343] *Id.*
[344] 91 Fed. Reg. at 23281, 23286.
[345] 91 Fed. Reg. at 23287.
[346] *Id*.
[347] 91 Fed. Reg. at 23287.

2. FDA regulations did not require ChemoCentryx to provide the information that CDER demands

FDA regulations impose no requirement that obligates ChemoCentryx to explain the 2019 readjudication.[348] CDER points to the requirement in 21 C.F.R. § 314.50 that, "as a general matter . . . an NDA contain reports of all investigations of the drug product and 'all other information about the drug pertinent to an evaluation of the NDA.'"[349] In addition, CDER cites the requirements that an NDA "contain a summary of the NDA in enough detail that the reader may gain a good general understanding of the data and information in the NDA, including an understanding of the quantitative aspects of the data"[350] and include (1) "the results of statistical analyses of the clinical trials," (2) "a description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product," and (3) "a description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies."[351] ChemoCentryx disclosed all this information. Section 314.50 does not require extensive narratives where the sponsor followed a prespecified QC process that was set forth in the trial documents and information about any data corrections was fully documented and available in the eTMF.

In the absence of any regulatory requirement, CDER once again relies on non-binding regulatory guidance. CDER cites in the NOOH to two guidance documents in support of its position. First, the Center cites to ICH E9 in support of its statement "that any intentional or unintentional breaking of the blinding should be reported and explained to the Agency."[352] But the language about reporting the blind breaking appears in ICH E9 in the context of a single subject when necessary for a contemporaneous clinical care determination.[353] As explained in Section II.C.2, there was limited unblinding of the ADVOCATE study on November 5, 2019 to conduct a prespecified procedure to ensure endpoints were consistently and correctly applied to the completed study data. No underlying data were changed.

CDER also cites ICH E6(R3) for the proposition that certain post-unblinding events "should" be reported, stating that "[p]ost-unblinding data changes and deviations from the planned statistical analyses should be reported in the clinical trial report."[354] However, as explained in Section IV.A.2.a, that language did not exist in 2019; it does not support CDER's position, as ChemoCentryx did not engage in "data changes" involving investigator information

[348] To the extent that CDER is relying on alleged omissions or statements that it considers misleading, but not false, to justify withdrawal under Section 505(e)(5) for an "untrue statement," that reliance is misplaced. Assuming purely for the sake of argument the NDA could be so characterized—Amgen does not agree that it can—as discussed in Section III.A.2 above, Section 505(e)(5) requires CDER to identify an affirmative factual statement in the application and show that the untrue fact was material. Because CDER fails to demonstrate that any statement was affirmatively false, it fails to demonstrate that withdrawal is required under Section 505(e)(5).
[349] 91 Fed. Reg. at 23286 (quoting 21 C.F.R. § 314.50).
[350] *Id.* (quoting 21 C.F.R. § 314.50(c)(1)).
[351] *Id.* (quoting 21 C.F.R. § 314.50(c)(2)(viii), (d)(5)(iv), (d)(6)).
[352] *Id.* at 23285 (citing ICH E9 Guidance, *supra* note 195, at 10, 12).
[353] ICH E9 Guidance, supra note 195, at 12.
[354] ICH E6(R3) Guidance, *supra* note 196, at 42.

contemplated by the guidance; and FDA guidance documents cannot create a binding NDA-reporting obligation.

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For all of these reasons, Amgen is entitled to judgment as a matter of law or, at a minimum, to a hearing to address genuine and substantial disputed issues of fact.

C. The Unique Needs Of The Rare-Disease Patient And Medical Communities Create A Significant Public Interest In Holding A Hearing On TAVNEOS

In addition to the numerous areas of factual disagreement described in this submission, which entitle Amgen to a hearing on the basis of having demonstrated a genuine and substantial issue of material fact, Amgen respectfully submits that a hearing is further justified in all events because it would "otherwise be in the public interest."[355]

1. Current Congressional And FDA Rare-Disease Policy Is Patient Focused And Emphasizes Regulatory Flexibility In Order To Bring And Maintain Access To Beneficial Therapies

As described in greater detail in Section III.A.1.c, Congress has made clear its commitment to rare-disease patients through the 21st Century Cures Act, which was "designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently."[356] FDA and rare-disease communities alike have recognized the Act as an important step in prioritizing rare diseases, including through incorporation of rare-disease patient perspectives and experiences in drug development.[357] One component of the Agency's strategy to support rare-disease patients since passage of the Act has been to exercise "flexibility in how the regulatory standard [for demonstrating evidence of efficacy] may be met," in light of the unique challenges facing rare-disease drug development.[358]

FDA's recent approvals of rare-disease drugs demonstrate the Agency's ability to exercise regulatory flexibility on behalf of rare-disease patients. Implicit in recent approvals of rare-disease drugs such as AVLAYAH and WELLCOVORIN, described in Section III.A.1.c, is a shared understanding that making additional therapeutic options available to rare-disease patients is both in the public interest and consistent with FDA's public-health mission.

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[355] 21 C.F.R. § 314.200(g)(6).
[356] FDA, *21st Century Cures Act* (Jan. 31, 2020), https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act.
[357] *See, e.g.*, FDA, *Work Plan and Proposed Funding Allocations of FDA Innovation Account: Required by Section 1002 of the 21st Century Cures Act (Public Law 114-255)* (June 6, 2017), https://www.fda.gov/media/105635/download; *21st Century Cures Passed*, NAT'L ORG. FOR RARE DISORDERS (Dec. 7, 2016), https://rarediseases.org/senate-passes-landmark-21st-century-cures-act/.
[358] FDA, *Rare Diseases: Considerations for the Development of Drugs and Biological Products: Guidance for Industry* at 3 (Dec. 2023), https://www.fda.gov/media/119757/download.

2. The Patient Community Would Suffer If Returned To Pre-TAVNEOS Treatment Regime As A Result Of Market Withdrawal

Standard AAV treatments prior to approval of TAVNEOS carried significant risks of treatment-related toxicities, and many patients on those treatments did not achieve sustained remission. During the nearly five years since approval in October 2021, no other therapy has been approved for AAV. TAVNEOS has been recognized as a valued addition to the AAV treatment armamentarium,[359] and TAVNEOS has been used to treat more than 8,000 patients in the United States to date.

Faced with CDER's proposal to withdraw approval, patients who rely on TAVNEOS report that the patient community would suffer if denied access to the drug and returned to the pre-TAVNEOS treatment regime. For example, as Eosinophilic & Rare Disease Cooperative ("ERDC"), a patient- and care-partner-run non-profit advocacy organization that represents the rare-disease community, explains:

> Across more than 40,000 people impacted by ANCA vasculitis that we interact with on a regular basis; we have heard directly and repeatedly from people for whom TAVNEOS has been beneficial. Real world evidence is essential in evaluating the benefit and risk of a medication. In this case, real world evidence and experience dramatically points to ensuring this medication remains available. These are not benefits in the abstract — they are demonstrated in specific, concrete terms that reflect how this medication helps them manage a chronic, often debilitating, sometimes deadly, relapsing disease.[360]

Numerous individual patients have commented that TAVNEOS has changed—even saved—their lives. For example, patients have explained:

- "I consider Avacopan (Tavneos) to be a miracle drug for my treatment of GPA and MPA."[361]
- "Tavneos was a godsend to me, having ANCA Vasculitis MPA."[362]
- "I genuinely believe TAVNEOS saved my life."[363]

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[359] *See* Lally Declaration, *supra* note 6, at 3, 27-28.
[360] Comment from Eosinophilic & Rare Disease Cooperative, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0028 ["ERDC Comment"].
[361] Comment from Eddie Jones, Dkt. No. FDA-2026-N-1321 (Apr. 30 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0010.
[362] Comment from Kathleen Tomamichel, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0014.
[363] Comment from Taylor Carlson, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0009.

- "Please keep this drug. I feel like it literally saved my daughter."[364]

- "For people like my wife, it is a drug that performed a miracle. It gave her back a fairly normal life when she was about to give up any hope of one."[365]

- "Please please do not remove TAVNEOS from the approved drug list. This drug has saved my daughter's life."[366]

Since FDA's announcement of its proposed withdrawal, patients have expressed fears of life-altering harm if TAVNEOS were to become unavailable to them:

- "These drugs saved my life and I am currently in remission. . . . I don't know what will happen to my disease if Avacopan were to be taken off of the FDA list of approved medications. I am not sure I want to find out. What I do know is that I have been given a chance to live - work, travel, be a mom."[367]

- "Don't remove one of the only methods we have of living a normal life by removing its approval. For rare diseases that's incrementally unfair. We would have to choose between predniso[n]e and death. Don't do it."[368]

- "I don't know what I would've done without Tavneos."[369]

- "Tavneos is a god send. Please don't remove this from the market. I can't go back to the hell I had with Prednisone."[370]

- "Taking avacaopan away and putting me back on steroids will be depressing. I will l[]ose hope. I will watch my liver but I need the hope of living a good life which I did not get on prednisone."[371]

[364] Comment from Joanna Thomson, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0029.
[365] Comment from Timothy Hahn, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0059.
[366] Comment from Teresa Sawyer, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0062.
[367] Comment from Melanie Nigro, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0037.
[368] Comment from Jennifer K. Stevenson, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0061.
[369] Comment from Kristine Viancourt, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0016.
[370] Comment from Laurie Huntley, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0055.
[371] Comment from K Carson, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0063.

- "I am very concerned about the thought of losing the medicine that is starting to give me my life back."[372]

Patients have also described their experiences managing the treatment-related toxicities associated with standard AAV treatment prior to approval of TAVNEOS, expressing that removal of TAVNEOS as a treatment option "will affect a lot of people who will have to take other harsher medications and/or steroids which help but also have harder side effects."[373] One patient reports that since stopping steroid use, "[m]assive weight gain and deformities have all retreated and I am able to live and work a normal life."[374] Another patient similarly shares: "Prednisone/steroids, although effective, ravage the body. I was able to wean off of them because of Avac[o]pan."[375] Another patient details the impact of treatment-related toxicities on daily life: "When I was on steroids, I could not sleep. I was gaining weight in my face and my belly and I was concerned about my osteoarthritis and cataracts getting worse . . . . Rituximab keeps me immunocompromised so I wear a mask and can't go to church or crowds."[376] ERDC summarizes the potential harms of reversion to a pre-TAVNEOS treatment paradigm as follows:

> Withdrawing TAVNEOS leaves people with ANCA vasculitis with fewer options — all of them carrying significant toxicity and mortality risks that are well-established and serious. Because each person uniquely manifests the disease (i.e., the extent and severity of the combination of organs impacted), treatment plans are best determined by the person and their medical professional. ANCA vasculitis is not a one-size-fits-all systemic rare disease.[377]

Similarly, the Vasculitis Foundation ("VF"), a national patient-focused nonprofit organization dedicated to improving the lives of people affected by vasculitis, explains:

> Any benefit-risk assessment of TAVNEOS must be conducted with clear-eyed recognition of what patients face in its absence. The existing standard of care for AAV carries well-established, serious, and sometimes fatal risks.
>
> Current AAV treatment relies primarily on non-specific immunosuppressants (cyclophosphamide or rituximab) combined with prolonged courses of high-dose glucocorticoids.

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[372] Comment from Corrin C, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0046.
[373] Comment from Anonymous, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0022 ("If you take it off the market, it will affect a lot of people who will have to take other harsher medications and/or steroids which help but also have harder side effects.").
[374] Comment from Jennifer Stevenson, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0008.
[375] Comment from Kristine Viancourt, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0016.
[376] Comment from K Carson, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0063.
[377] ERDC Comment, *supra* note 360.

> Glucocorticoid use is associated with a significant side-effect burden including serious infections (which can be fatal in immunocompromised patients), diabetes mellitus, osteoporosis, weight gain, adrenal suppression, and substantially reduced quality of life. *These are not rare complications; they are the lived reality of the majority of patients with AAV*.
>
> TAVNEOS was the only FDA-approved targeted oral treatment for severe active GPA and MPA. *Its removal from the market does not leave patients with safer options. It leaves them with fewer options, all of which carry their own serious and well-documented risks.*[378]

As one patient summarized: "A medication that allows people to reduce or avoid long-term steroid use is not a luxury. It is a meaningful reduction in cumulative harm."[379]

Importantly, the patient community is aware of TAVNEOS's risk profile, and patients who choose TAVNEOS express that they have done so considering available risk information and the potential mitigating impact of close monitoring according to the FDA-approved labeling.[380] Like many rare-disease patient communities, the AAV patient community recognizes that all treatment options carry risks and weighs the benefit-risk profile of TAVNEOS against the benefit-risk profiles of pre-TAVNEOS treatments and the significant risks of allowing AAV to progress untreated. As ERDC explains:

> Rare disease patients routinely and reasonably accept significant risk in exchange for meaningful benefit. That is not a failure of judgment — it is a rational response to a disease that, left untreated or undertreated, causes organ failure and death. The people in our community are capable of making that calculus. They need the options for add on treatments to remain available in order to make it.[381]

The VF further explains that in order for rare-disease patients and their physicians to exercise agency in making a benefit-risk determination, they must have access to treatment options:

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[378] Comment from Vasculitis Foundation, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0060 (emphasis added) ["Vasculitis Foundation Comment"].
[379] Comment from Sara Jones, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0045.
[380] *See* Comment from Sarah Jennings, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0002 ("We both were well aware of the risk of liver problems, but the risks vs benefits with Tavneos far outweighed risks of side effects and problems with prednisone. This risk was already known when it was approved."); Comment from Anita Matson, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0040 ("We were informed about the potential side effects of the medication and understood that she might not tolerate the treatment. We also knew that close monitoring and regular bloodwork would be necessary throughout the process.")
[381] ERDC Comment, *supra* note 360.

> Rare disease patients, and the physicians who treat them, routinely and reasonably accept significant risk in exchange for meaningful clinical benefit. *That calculus requires having options*. The FDA's benefit-risk framework is designed to weigh exactly this kind of tradeoff, and we ask that it do so fully here.[382]

It is clear that the community of individuals living with AAV strongly opposes FDA's proposal to take away a potentially "lifesaving" treatment option from patients with significant unmet medical need whose treatment options are already limited. It is equally clear that the Agency should "ensure that patient perspectives are formally incorporated into the benefit-risk determination for this decision, not as an afterthought, but as a substantive input."[383]

Furthermore, in an independent assessment conducted by Amgen and described in Appendix A (Section 8), participants provided feedback emphasizing the importance to patients of minimizing glucocorticoid toxicity. Eight adult patients in the United States living with GPA or MPA were selected based on disease status and other relevant characteristics, with the goal of achieving representation across GPA and MPA populations, as well as a range of age and sex categories. Treatment-related insights were gathered through qualitative interviews.

Most participants (seven of eight) were currently receiving treatment, including steroid therapy, and the majority had experienced a prior disease relapse (five of eight). Across interviews, participants described a substantial ongoing disease burden and a strong desire for treatment options that reduce or eliminate the need for glucocorticoids. While participants acknowledged that steroids can be effective for controlling disease activity and managing symptoms, participants stated that the negative impact of steroid-related adverse effects outweighed their benefits. Steroid tapering was frequently described as difficult, with participants reporting worsening symptoms, physical discomfort, and emotional challenges during dose reductions. Reduction or elimination of steroid use was identified as a highly important treatment goal in seven of eight participants, and all eight participants expressed strong interest in therapies that could enable a faster steroid taper than currently available options.

When presented with hypothetical treatment options, seven of eight participants indicated that a treatment approach that enabled more rapid steroid reduction compared with the current guideline-recommended taper was very important or extremely important, citing avoidance of steroid-related side effects and improved quality of life as key drivers of preference. Furthermore, within the context of hypothetical treatment scenarios, participants indicated a willingness to accept risks including severe allergic reactions (seven of eight), liver injury (mild, seven of eight; severe, five of eight) and blood clots (six of eight) in exchange for a treatment that would enable more rapid steroid reduction. These findings suggest that, for many patients with GPA and MPA, the burden of prolonged steroid exposure is an important factor influencing their willingness to accept certain treatment-related risks when evaluating therapeutic options.

[382] Vasculitis Foundation Comment, *supra* note 378 (emphasis added).
[383] *See id.*

3. The Medical Community Supports Continued Access To TAVNEOS For AAV Patients

Physicians and health care providers involved in caring for patients with AAV continue to support access to TAVNEOS for their patients.

As stated in her declaration, Appendix B.1, Dr. Lally relies on TAVNEOS as a core component of the limited set of available treatment options for AAV. Dr. Lally is a seasoned AAV clinician, with the majority of her practice devoted to patients with a form of systemic vasculitis, including AAV. She explains that TAVNEOS "has significant benefits for AAV patients compared to existing treatment paradigms that incorporate prolonged high-dose steroids regimens," reporting that she is able to rapidly taper patients with newly diagnosed severe AAV off of glucocorticoids over the course of four-six weeks, instead of the six or more months that is typical of the existing standard of care. Tapering off glucocorticoids in weeks versus months confers significant benefit to patients, including reducing their risks for glucocorticoid-related weight gain, insomnia, diabetes, hypertension, and fracture.

Dr. Lally explains that TAVNEOS is also useful in treating AAV patients suffering from relapses or flares of their disease, "who are often most concerned about the need to go back onto high doses of glucocorticoids." The ability to treat severe relapses with TAVNEOS has allowed her to "limit additional prolonged courses of glucocorticoids in this vulnerable population, many of whom have already experienced glucocorticoid-related damage from their first course of treatment." In this context, Dr. Lally makes clear that TAVNEOS's demonstration of non-inferiority over the comparator prednisone group still "carries substantial clinical value" because it shows that "TAVNEOS can achieve comparable disease control while avoiding months-long exposure to glucocorticoids and their associated side effects and toxicities." Ultimately, Dr. Lally explains that since its approval "TAVNEOS has been a welcome option for AAV patients and has been adopted by many rheumatologists as part of a first line treatment strategy" for AAV patients with severe, active disease, and withdrawal would meaningfully reduce the ability to lessen patients' reliance on glucocorticoids and would "leave AAV patients with fewer therapeutic options."[384]

Healthcare providers have voiced similar perspectives in response to CDER's NOOH. For example, one physician with more than 20 years of experience treating AAV patients explains:

> The traditional medications used in the care of ANCA vasculitis have significant side effects, especially the high dose steroids. With the availability of avacopan, I have been able to aggressively reduce the amount of steroids that my patients receive. This has had tremendous effect on their ability to maintain remission as well as quality of life.[385]

[384] Lally Declaration, *supra* note 6, at 3.

[385] Comment from Ankit Mehta MD, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0006; *See also* Comment from Anonymous, Dkt. No. FDA-2026-N-1321 (Apr. 30, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0022 ("If you take it

Another physician commenter emphasizes the role that TAVNEOS has played for his patients given the rare-disease treatment landscape with few other options:

> Tavneos use in my patients has been very beneficial. It treats a disease group that not only is difficult to control but is potentially fatal. With so few options to treat, removing this product based on information that is yet to be understood would be irresponsible and detrimental to patients. *It IS saving lives*. Knowing this liver concern will help prevent poor outcomes and consequences in the future but eliminating its availability will harm more than it will protect. . . . This medication needs to remain an option and used responsibly.[386]

These and the overwhelming majority of comments from healthcare providers attest to the significant role that TAVNEOS has come to play in the treatment landscape. Only one healthcare practitioner (who was anonymous) expressed skepticism about the use of TAVNEOS in their patients.[387] Amgen believes patients and their physicians should have access to a range of treatment options so they can make individualized decisions based on each patient's medical needs and treatment goals. Amgen believes that TAVNEOS remains an important option that the medical community can access for treatment of this life-threatening disease based on physicians' expertise and individualized assessments of what is appropriate for each patient.

4. There Is A Strong Public Interest In Holding A Hearing Given The Profound Impact On Rare-Disease Patients

As demonstrated by numerous public comments from AAV patients, caregivers and treating physicians, some of which are highlighted above, CDER's proposal to withdraw approval of TAVNEOS has generated significant public interest among rare-disease patients and those who support them. These comments highlight that the question of whether to take away a therapeutic option on which rare-disease patients have relied for nearly five years is not merely a legal or regulatory question—it is a real-world question impacting actual patients and their families. Similarly, the National Kidney Foundation has likewise recognized the importance of FDA holding a hearing prior to any withdrawal.[388] If CDER will not rescind the NOOH, a hearing would represent these stakeholders' best opportunity to voice their concerns before the Agency decides if they lose access to a drug that many patients report benefits them. The question presented here is clearly a matter of public interest.

Importantly, Amgen's request for a hearing is distinct from the recent precedent in which the Agency declined to grant a hearing on public-interest grounds related to its refusal to approve

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off the market, it will affect a lot of people who will have to take other harsher medications and/or steroids which help but also have harder side effects.").

[386] Comment from Mark Diehl, Dkt. No. FDA-2026-N-1321 (June 11, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0058 (emphasis added).

[387] Comment from Anonymous, Dkt. No. FDA-2026-N-1321 (May 28, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0005.

[388] Comment from National Kidney Foundation, Dkt. No. FDA-2026-N-1321 (June 18, 2026), https://www.regulations.gov/comment/FDA-2026-N-1321-0077.

an opioid product designed to deter abuse by injection. In its request for hearing following a complete response letter, the sponsor argued, in part, that a hearing would be in the public interest "in order to resolve broader policy issues related to opioid abuse."[389] But the Chief Scientist denied the hearing, reasoning that while the sponsor's "submissions raise arguments relevant to FDA's regulation of opioid products and to the crisis of opioid abuse, generally," "[t]he Agency continues to take a variety of steps to address the public health crisis created by opioid abuse and the resulting addiction and death."[390] The D.C. Circuit agreed with the Agency's "determination that a hearing on one manufacturer's new drug application is not the appropriate forum to address these important public health issues," in light of the "numerous fronts on which [FDA] is working to tackle the pervasive crisis of prescription opioid addition and abuse."[391]

Here, by contrast, Amgen does not seek a hearing "on issues of policy and law."[392] Nor does Amgen seek a hearing in an area in which the Agency "continues to take a variety of steps."[393] While rare disease policy—in general—is an area in which the Agency has recently addressed, Amgen respectfully submits that AAV specifically, unlike the opioid epidemic, has not been an area of focus. As the Agency is aware, TAVNEOS was approved as an orphan drug, highlighting a high level of patient need that persists today. And unlike in the case of the opioid crisis, Amgen is not aware of any initiatives underway at the Agency to benefit this specific rare-disease patient population or to ensure that patients are not harmed by a return to the pre-TAVNEOS treatment regime. Under these circumstances, the Agency cannot point to meaningful alternative ways for AAV patients, the population who will "bear the direct consequences of this decision every day," to make their voices heard.[394] Where, as here, the question is whether a rare-disease patient community should lose access to a therapeutic option and be reverted to the standard of care of nearly five years prior—with its known treatment-related toxicities—"a hearing on a specific new drug application" is *precisely* the "appropriate forum."[395] Amgen respectfully submits that it—and, more importantly, AAV patients—is entitled to a hearing in the public interest on this additional basis.[396]

V. AMGEN IS ENTITLED TO JUDGMENT AS A MATTER OF LAW OR, AT A MINIMUM, A HEARING

Particularly in light of the results of the 2026 readjudication, the most sensible course in the best interest of patient care would be for CDER to recognize, consistent with precedent, that the "additional information" provided by Amgen in this submission "effectively moots" the underlying proceeding by confirming that ADVOCATE continues to provide substantial evidence of effectiveness supporting approval.[397] On that basis, Amgen respectfully requests that CDER rescind the NOOH and consider the 2026 readjudication. Amgen welcomes the

[389] 83 Fed. Reg. 54598, 54603 (Oct. 30, 2018).
[390] *Id.*
[391] *Pharm. Mfg. Rsch. Servs., Inc. v. FDA*, 957 F.3d 254, 266-67 (D.C. Cir. 2020).
[392] *See id.* at 266 (citing 21 C.F.R. § 12.24(b)(1)).
[393] *See* 83 Fed. Reg. at 54603.
[394] *See* ERDC Comment, *supra* note 360.
[395] *Cf. Pharm. Mfg. Rsch. Servs., Inc.*, 957 F.3d at 259.
[396] *See* 21 C.F.R. § 314.200(g)(6).
[397] *See* 43 Fed. Reg. at 14739.

opportunity to engage with CDER to identify a productive path forward to continue to serve rare-disease patients.

In the alternative, for all of the reasons described above, Amgen is entitled to judgment as a matter of law. At a minimum, Amgen has amply established a genuine and substantial issue of material fact and that the public interest justifies a hearing before taking away this treatment from rare-disease patients.

Consistent with *Vanda Pharmaceuticals, Inc. v. U.S. Food & Drug Administration*, which established that a showing of a genuine and substantial issue of material fact creates an entitlement to a hearing,[398] and recent precedent in MAKENA, which exemplified the Agency's practice of granting a hearing when the sponsor raises "specific challenges to the factual and scientific bases underlying CDER's proposal" and provides "data or information in support of those challenges,"[399] Amgen has established a genuine and substantial issue of material fact requiring a hearing.[400] Granting a hearing is also in the public interest and consistent with the Agency's commitment to rare-disease patients.[401]

Amgen's submission demonstrates that a hearing is required in the public interest and to resolve at least the following genuine and substantial issues of fact:

- Whether the totality of the evidence supports the continued positive benefit-risk profile of TAVNEOS in light of the needs of the rare-disease patients who use it
- Whether the ADVOCATE trial and other available evidence provide substantial evidence of effectiveness following readjudication
- Whether continued approval is warranted based on the 2026 readjudication confirmation of efficacy
- Whether the NDA contained an untrue statement of material fact
- Whether the 2026 readjudication and totality of the evidence give sufficient reassurance of efficacy to maintain patient access
- Whether the interests of rare-disease patients who have relied on TAVNEOS for years, and the unmet need that would result in the event of a withdrawal, warrant maintained approval

[398] 150 F.4th 563, 567 (D.C. Cir. 2025).
[399] Letter from RADM Denise M. Hinton, Chief Scientist, FDA, to Rebecca K. Wood, Sidley Austin LLP, at 5 (Docket No. FDA-2020-N-2029-0072) (Aug. 18, 2021), https://www.regulations.gov/document/FDA-2020-N-2029-0072.
[400] *See* 21 C.F.R. §§ 314.200(g), 12.24(b).
[401] 21 C.F.R. § 314.200(g)(6).

In light of these significant disputes presented in this submission, Amgen is eager to exercise its legal right to a hearing to advocate for continued access to TAVNEOS on behalf of rare-disease patients.

VI. CDER SHOULD MAKE FULL DISCLOSURES REGARDING ITS DECISION-MAKING

Amgen respectfully requests that CDER make available to Amgen and to all interested parties its full files regarding its decision to withdraw approval for TAVNEOS. Such disclosures should include "[a]ll documents in the director's files containing factual information, whether favorable or unfavorable to the director's position, which relate to the issues involved in the hearing." 21 C.F.R. § 12.85(a)(2). At a minimum, CDER should disclose:

(1) All documents or communications related to the question of whether a non-inferiority clinical trial design could support approval of TAVNEOS, including, but not limited to, documents generated related to the Phase 2 trials, the Phase 3 trial, the May 6, 2021 meeting of the Arthritis Advisory Committee to discuss NDA 214487, and/or the review of TAVNEOS;

(2) All documents or communications related to FDA's publication of errata to the FDA Briefing Document for the May 6, 2021 meeting of the Arthritis Advisory Committee to discuss NDA 214487;

(3) All documents or communications related to CDER's review of the major amendment that ChemoCentryx submitted to NDA 214487 on June 18, 2021; and

(4) All documents or communications related to correspondences between FDA and plaintiffs' counsel in the litigation *Homyk v. ChemoCentryx*, No. 21-cv-03343 (N.D. Cal.), including, but not limited to, emails, memoranda, letters, meeting minutes, or other communication records.

Absent such disclosures by CDER, Amgen will not have a full or fair opportunity to understand and to contest the basis for CDER's rationale.

VII. CONCLUSION

Rare disease patients deserve all treatment options available to them. Ultimately, this submission is about ensuring that people living with ANCA-associated vasculitis continue to have access to an important treatment option. For patients living with a rare, life-threatening disease with limited therapeutic options, decisions of this magnitude should be guided by the totality of the evidence and a shared commitment to preserving appropriate treatment choices.

Amgen urges the Agency to take a forward-looking approach that focuses on the totality of the evidence of efficacy, which remains compelling, and to engage in productive discussions about the best path forward for patients living with this rare disease.

For all of these reasons, we urge CDER to withdraw the NOOH and engage in a science- and patient-focused discussion of a path forward to retain patient access. In the alternative,

judgment should be granted to Amgen as a matter of law or, at a minimum, a hearing should be granted because (1) there exists a genuine and substantial issue of fact and (2) a hearing would otherwise be in the public interest.

Respectfully submitted,

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