TABLE 1—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]—Continued

21 CFR section; activity	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
120.14(a)(2), (c), and (d) and 120.12(b); importers of fruit or vegetable juices, or their products used as ingredients in beverages, have written procedures to ensure that the food is processed in accordance with our regulations in part 120.	308	1	308	4	1,232
120.8(a), 120.8(b), and 120.12(a)(3), (b), and (c); written HACCP plan.	1,560	1.1	1,716	60	102,960
Total			21,980,369		461,426

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Based on a review of the information collection since its last OMB approval, we have made no adjustments to our burden estimate.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

[FR Doc. 2026–08417 Filed 4–29–26; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2026–N–1321]

ChemoCentryx, Inc.; Proposal To Withdraw Approval of New Drug Application for TAVNEOS (Avacopan) Capsule, 10 Milligrams; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration's (FDA, Agency, or we) Center for Drug Evaluation and Research (CDER) is proposing to withdraw approval of the new drug application (NDA) for TAVNEOS (avacopan) capsule, 10 milligrams (mg), held by ChemoCentryx, Inc., One Amgen Center Dr., Thousand Oaks, CA 91320 (ChemoCentryx or applicant), and is announcing an opportunity for the applicant to request a hearing on this proposal. The grounds for the proposal are twofold: (i) on the basis of new information before FDA, evaluated together with the evidence available to FDA when the application was approved, 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 its labeling; and (ii) the application contains untrue statements of material fact.

DATES: The applicant may submit a written request for a hearing by June 1, 2026 and submit all data, information, and analyses in support of the hearing request by June 29, 2026. Others may submit electronic or written comments by June 29, 2026.

ADDRESSES: The request for a hearing may be submitted by the applicant by either of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments to submit your request for a hearing. Comments submitted electronically to *https://www.regulations.gov,* including any attachments to the request for a hearing, will be posted to the docket unchanged.

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- Because your request for a hearing will be made public, you are solely responsible for ensuring that your request does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. The request for a hearing must include the Docket No. FDA–2026–N–1321 for ''ChemoCentryx, Inc.; Proposal to Withdraw Approval of New Drug Application for TAVNEOS (Avacopan) Capsule, 10 Milligrams; Opportunity for a Hearing.'' The request for a hearing will be placed in the docket and publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday. The applicant may submit all data and analyses upon which the request for a hearing relies in the same manner as the request for a hearing except as follows:
- Confidential Submissions—To submit any data analyses with confidential information that you do not wish to be made publicly available, submit your data and analyses only as a written/paper submission. You should submit two copies total of all data and analyses. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of any decisions on this matter. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov* or available at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday. Submit both copies to the Dockets Management Staff. Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law.

Comments Submitted by Other Interested Parties: For all comments submitted by other interested parties, submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to

the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*

• If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

• *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

• For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2026–N–1321 for ''ChemoCentryx, Inc.; Proposal to Withdraw Approval of New Drug Application for TAVNEOS (Avacopan) Capsule, 10 Milligrams; Opportunity for a Hearing.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

• Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Joan Dailey, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6248, Silver Spring, MD 20993, 301–796–6357, *joan.dailey@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Proposal to Withdraw Approval of NDA 214487

A. Summary

CDER proposes to withdraw approval of TAVNEOS (avacopan), NDA 214487, because of new information, which was withheld from FDA and did not become known to FDA until more than three years after approval, indicating that there is a lack of substantial evidence of effectiveness for the drug, and the application contains untrue statements of material facts.

Section 505(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355(e), states that the Secretary of Health and Human Services shall withdraw approval of a drug on certain grounds after due notice and opportunity for hearing to the applicant. Under section 505(e)(3) of the FD&C Act and 21 CFR 314.150(a)(2)(iii), approval of a drug shall be withdrawn if, on the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application was approved, there is a lack of substantial evidence from adequate and well-controlled investigations 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. In addition, under section 505(e)(5) of the FD&C Act and 21 CFR 314.150(a)(2)(iv), approval of a drug shall be withdrawn if FDA finds that the application contains any untrue statement of a material fact.

New information shows that the applicant's unblinded study personnel manipulated endpoint results for the phase 3 study, CL010_168, referred to as the ADVOCATE study, which was the sole study used to establish substantial evidence of effectiveness for approval of TAVNEOS.[1] That manipulation was designed to change results that were not statistically significant and make the product look effective when the original analysis did not support that conclusion. If the data as originally analyzed according to the prespecified statistical analysis plan had been submitted to the Agency, the study would not have been viewed as establishing substantial evidence of effectiveness, which is a legal requirement for approval of an NDA. However, in contravention of fundamental principles of good clinical practice regarding the reporting of clinical results as well as FDA's regulations regarding what must be submitted in an NDA, the applicant did not submit this data and original analysis to the Agency. Based on the new information regarding data manipulation, along with the evidence available to CDER when the application was approved, 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. Accordingly, CDER is proposing to withdraw approval of TAVNEOS under section 505(e)(3) of the FD&C Act and 21 CFR 314.150(a)(2)(iii).

We note that hepatotoxicity was identified as a key safety risk in the original NDA review. In addition, serious and sometimes fatal cases of hepatotoxicity have been reported postmarketing, and recent post-market safety reports suggest that avacopan may also be associated with vanishing bile duct syndrome (VBDS), a serious and, at the time of approval, unexpected

[1] See *ClinicalTrials.gov* number NCT02994927, available at *https://clinicaltrials.gov/study/NCT02994927#more-information* (accessed Apr. 24, 2026); see also Ref. 1.

adverse event. In light of our finding that there is a lack of substantial evidence of efficacy, there is no demonstrated benefit to balance the risks associated with TAVNEOS.

In addition, new information shows that the NDA for TAVNEOS contains untrue statements of material fact, including statements regarding when and how many times database lock and unblinding occurred and inaccurate representations regarding the analyses that were used to evaluate the ADVOCATE study. Because of these untrue statements, FDA was unaware that the ADVOCATE study's primary endpoint data could not be reliably interpreted as part of NDA approval and therefore the data did not establish substantial evidence of effectiveness, which must be demonstrated for approval under section 505(d) of the FD&C Act. Instead, the approval of TAVNEOS was based on untrue statements regarding the analyses of manipulated data, which is unreliable for approval. Therefore, these untrue statements are material; as a result, CDER is proposing to withdraw approval of TAVNEOS under section 505(e)(5) of the FD&C Act and 21 CFR 314.150(a)(2)(iv).

B. General Background

On October 7, 2021, FDA approved NDA 214487 for TAVNEOS (avacopan) capsule, 10 mg, for the adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) in combination with standard therapy including glucocorticoids. The drug is included as a treatment option in recent medical practice guidelines for AAV treatment. Standard therapies for AAV include rituximab, cyclophosphamide, glucocorticoids, and other immunosuppressants such as methotrexate and azathioprine.

The CDER review team identified a variety of issues that might preclude approval of the product during the initial NDA review. Following public discussion of these issues at a May 2021 advisory committee meeting (Ref. 2), a shareholder lawsuit was filed that same month against ChemoCentryx alleging securities fraud. In 2022, Amgen, Inc. (Amgen) acquired TAVNEOS with its purchase of ChemoCentryx.

On May 29, 2025, plaintiffs in the securities fraud litigation filed with the court the expert report from Marc Walton, M.D., Ph.D. (Walton Report), (Ref. 3). The Walton Report stated that a statistical analysis of the ADVOCATE study was conducted after database lock and that the initial analysis had found that the avacopan treatment group did not achieve a statistically significant superiority outcome on the primary endpoint of sustained remission compared with the control group. The Walton Report stated that, upon reviewing these results, unblinded ChemoCentryx personnel had selected nine ADVOCATE study subjects for readjudication following the initial blinded analysis, including five avacopan patients whose clinical outcome would be changed from ''not in sustained remission'' to ''sustained remission.'' The Walton Report further stated that, before sending the patient data for readjudication, ChemoCentryx personnel confirmed that changing the remission outcomes for the five avacopan patients would change the study results to reflect that avacopan demonstrated statistically significant superiority over therapy in the control arm. Finally, the Walton Report stated that the five avacopan patients were readjudicated to ''sustained remission,'' and the revised statistical analysis was submitted to FDA in the NDA without disclosing this readjudication of the pivotal study results. Specifically, the Walton Report noted that the applicant did not disclose the original statistical analysis of the study, the unblinded selection of subjects for readjudication after the clinical database was locked, or that the post-database lock changes changed the study result from not statistically significant to statistically significant.

After learning about the Walton Report, CDER sent an information request on July 23, 2025, seeking detailed information regarding the handling of unblinded data in the ADVOCATE study. On August 22, 2025, Amgen responded to the information request on behalf of the applicant (Ref. 4). Amgen's response confirmed the key factual allegations outlined above from the Walton Report. Amgen nevertheless claimed in its response that the data in the NDA are accurate and that the readjudications were appropriate. As explained below, FDA disagrees.

On August 15, 2025, the court dismissed the shareholders' lawsuit, granting summary judgment in favor of ChemoCentryx. The court's opinion did not acknowledge or address the data manipulation allegations in the Walton Report and does not have any bearing on the status of the NDA or enforcement of the FD&C Act.

This Notice of Opportunity for a Hearing omits certain information that is not publicly available at this time.

C. ADVOCATE Study and Data Manipulation

1. Study Background

The ADVOCATE study randomized 331 subjects with AAV to avacopan 30 mg twice daily or a protocol-specified prednisone taper in a 1:1 ratio; all subjects were treated with background immunosuppressive therapy of rituximab or cyclophosphamide. Because glucocorticoids are used to treat AAV, minimizing their use by study subjects would ensure that efficacy outcomes were interpretable and not inflated. The study protocol (Ref. 5), statistical analysis plan (Ref. 6), and clinical study report (Ref. 7) state that glucocorticoids not supplied as a study drug must be avoided ''as much as possible during the study.'' [2] According to the protocol, study subjects were permitted to receive ''low doses'' of oral glucocorticoids (no more than 10mg/day) for treatment of adrenal insufficiency or for other conditions (Ref. 5 at 124). Non-study supplied glucocorticoids were permitted only in low doses for adrenal insufficiency, but this rule was liberalized over time to also permit glucocorticoid use at any dose by study subjects for conditions other than adrenal insufficiency (*e.g.,* allergic reaction) if they were not prescribed for treatment of AAV.[3] The protocol and statistical analysis plan are each internally inconsistent on this point; on the one hand, they require non-study supplied glucocorticoids to be avoided as much as possible, but on the other hand permit such glucocorticoid use at any dose with no impact on remission determinations.

Patients were followed for 52 weeks for a disease remission endpoint evaluated using the Birmingham Vasculitis Activity Score (BVAS), a standardized, clinician reported outcome measure of disease activity in patients with vasculitis. The primary endpoints for the ADVOCATE study were remission at week 26 and sustained remission at week 52. According to the study protocol, study subjects were considered in remission at weeks 26 and 52 if they had a BVAS of zero and had not received glucocorticoids for treatment of AAV within 4 weeks prior to the week 26 or week 52 assessment, respectively. Sustained remission was defined as remission at weeks 26 and 52 with no intervening relapse. The study protocol and statistical analysis plan set forth a prespecified method for handling

[2] Ref. 5 at 17, 50, and 123; Ref. 6 at 26; Ref. 7 at 31, 35.

[3] See Ref. 8 at 8.

missing data, under which subjects whose remission or sustained remission status was not evaluated within a specified window of time would be imputed as not in remission (week 26) or sustained remission (week 52) (Ref. 4 at 6; Ref. 6 at §§ 5.4, 5.5).

BVAS, remission at week 26, and sustained remission at week 52 were determined by a blinded adjudication committee. The adjudication committee's activities were governed by an adjudication committee charter (AC Charter). The AC Charter prohibited readjudication of remission status after database unblinding (Ref. 8, Addendum 2 § 4.3.3).

ChemoCentryx originally proposed a study design in which the primary endpoint of sustained remission at week 52 would be analyzed for non-inferiority compared to glucocorticoids. 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 in the avacopan arm of the study compared to the control arm (Ref. 9 at 2, 4).

2. Data Manipulation

FDA takes seriously allegations of scientific misconduct that threaten the integrity of the drug approval process and patient safety. Upon reviewing the Walton Report, FDA became concerned that the data submitted to the NDA were biased and that the ADVOCATE study did not provide reliable evidence of the effectiveness of TAVNEOS. Accordingly, FDA requested that the applicant provide a comprehensive account of the events described in the Walton Report and the handling of unblinded adjudication data in the ADVOCATE study. FDA also requested emails, raw data, and other documents relevant to the data manipulation described in the Walton Report.

Amgen's response to CDER's July 2025 information request (Amgen Response) chronicled the facts regarding the handling of data in the ADVOCATE study. The Amgen Response states that the contract research organization, Medpace, Inc. (Medpace), conducted prespecified procedures to ''clean'' the ADVOCATE study database to ensure the data, including the primary endpoint data, were accurate and complete before the database was locked for analysis.[4] Specifically, on November 4, 2019, the Medpace lead biostatistician completed a biostatistics pre-database lock checklist verifying, among other things, that the database and datasets were ready for analysis, the statistical analysis plan had been approved, and the statistical programs had been validated (Ref. 4, Exh. 3). On November 5, 2019, the Medpace data coordinator and data manager signed a database lock checklist, confirming among other things that all clinical data had been entered, all edit checks applied, all queries resolved, source data verified, all records locked from editing, and all other necessary steps completed as a prerequisite for the database to be declared clean and ready to be locked (Ref. 4, Exh. 4). The study database was then locked and unblinded on November 5, 2019.

Between November 5, 2019, and November 7, 2019, Medpace took a database snapshot and generated datasets and tables, listings, and figures (TLFs) for unblinded review and validation by select ChemoCentryx personnel (Ref. 4 at 10). With respect to efficacy data, the Study Results Analysis Plan (SRAP), which was signed on November 4, 2019, permitted two ChemoCentryx employees to receive unblinded data after database lock for the purposes of conducting a quality control (QC) review ''for completeness and internal consistency'': Dr. Huibin Yue, Director of Biostatistics, and Dr. Pirow Bekker, Chief Medical Officer (Ref. 4 at 9–10 and Exh. 2). In addition, Dr. Chao Wang, an independent statistical consultant retained by ChemoCentryx, was responsible for assisting in the validation of topline TLFs (Ref. 4 at 10).

On November 8, 2019, in accordance with the SRAP, the unblinded datasets and top-line efficacy TLFs were transferred to Dr. Bekker. Those results showed that the primary endpoint of sustained remission at week 52 had failed to achieve statistical significance, returning a two-sided p-value of 0.1025, which is above the significance threshold specified in the statistical analysis plan.[5] The applicant did not include these results in the NDA or otherwise disclose them to FDA during the Agency's review of the application.

On November 9, 2019, Dr. Bekker emailed Dr. Yue requesting that Dr. Yue and Dr. Wang verify the week 52 sustained remission results: ''Regarding sustained remission at Week 52 it is, of course, of *paramount importance that the data are correct* (especially the *p-value for superiority*). Chao and you must verify these results ASAP. We cannot afford to miss a superiority outcome here'' (Ref. 4, Exh. 11 (emphasis in original)). On November 11, 2019, Dr. Yue emailed the Medpace lead biostatistician to request a blinded data quality check to confirm whether all adjudicated remission determinations in the electronic data capture (EDC) system match those on paper case report forms (CRFs). His email noted that ''[w]e cannot afford to miss a superiority outcome,'' that ''[t]he p-value is close to be[ing] significant,'' and that ''[w]e need to make sure that both the data and analysis are correct'' (Ref. 4, Exh. 12). The email further noted that Dr. Yue was awaiting Dr. Wang's validation of the statistical analysis. The lead biostatistician replied by email, dated November 12, 2019, that the quality check had been completed ''with no findings.'' Dr. Wang validated the TLF analysis on November 12, 2019.

After being informed that there was nothing wrong with either the data or the analysis, Drs. Bekker and Yue looked for cases that could alter the study results to indicate TAVNEOS achieved a statistically superior outcome on the primary endpoint of sustained remission. On November 12, 2019, Dr. Yue ran a targeted, unblinded search of the clinical database to identify all subjects with a BVAS of zero who used glucocorticoids in the four weeks prior to the week 26 or week 52 remission assessments and who were originally adjudicated as not in remission (Ref. 4, Exh. 14). He forwarded the resulting unblinded data spreadsheet to Dr. Bekker. In addition, Drs. Yue and Bekker reviewed unblinded data to determine whether data from early termination or unscheduled visits was included in the primary endpoint analysis consistent with the statistical analysis plan (Ref. 4 at 12; Ref. 4, Exh. 13). Together, they identified nine subjects—three from the prednisone arm and six from the avacopan arm—for readjudication. Most were identified for readjudication because Drs. Bekker and Yue believed their primary endpoints were inconsistent with the prespecified protocol provisions related to glucocorticoid use or missing data, or both. One subject was identified for

[4] See Ref. 4 at 7–8. Database cleaning addresses problems with incomplete, invalid, or inconsistent data caused by improper data recording or data entry (Ref. 10). Database cleaning activities may include reconciliation of entered data and datasets, rectification of data errors, and addressing the impact of noncompliance issues, including protocol deviations. Ref. 11 at 47. The sponsor should ensure that blinding is maintained during the process of cleaning the database prior to its release for analysis (Ref. 12 at 11).

[5] Ref. 13. The statistical analysis plan specified a procedure to preserve the overall Type I error rate at a 5% level with a one-sided p-value threshold of 0.025 (Ref. 6 at 30–31). For equivalent comparison to a two-sided 5% significance level (*i.e.,* two-sided p-value threshold of 0.05) and alignment with current labeling, two-sided p-values are presented in this document.

readjudication due to a manual data entry error in which the subject was categorized as not in remission or sustained remission despite satisfying the relevant criteria.

On November 13, 2019, Dr. Bekker forwarded to Dr. Yue a table identifying the nine subjects, their previously adjudicated remission determinations, and the rationale for a potential revised adjudication decision (Ref. 4, Exh. 15). That same day, Dr. Yue asked Dr. Wang to rerun the primary endpoint analyses and calculate new p-values based on a hypothetical dataset accounting for the anticipated results of the readjudication of the nine subjects. Specifically, the dataset anticipated that five of the six subjects in the avacopan arm would be readjudicated to sustained remission, and none of the three subjects in the control arm would be readjudicated to sustained remission. On November 13, 2019, Dr. Wang replied that the new p-value showed statistical significance.

On November 14, 2019, Dr. Yue forwarded to Medpace personnel the table identifying the subjects for potential readjudication. Later the same day, Dr. Bekker spoke with the ADVOCATE study's Adjudication Committee (AC) Chair, Dr. David Jayne, regarding the readjudications (Ref. 4, Exh. 18). On November 14, 2019, after receiving confirmation from Dr. Bekker that Dr. Jayne was expecting cases for readjudication, Medpace sent Dr. Jayne a data package (''patient profile'') for each of the nine subjects to be readjudicated. Each patient profile included the subject's original adjudication form, BVAS and other remission-related data, and the same table Dr. Bekker forwarded to Dr. Yue the previous day, minus the rationale for a potential revised adjudication decision for each subject (Ref. 4, Exh. 18). The table directed Dr. Jayne's attention to the specific facts for each subject that were relevant to review (*i.e.,* unscheduled visit within assessment window and glucocorticoid use). In preparation for potential database changes to record readjudicated remission determinations, Dr. Yue and Medpace personnel signed a post-datalock change approval form on November 15, 2019 (Ref. 4, Exh. 69).

Dr. Jayne conducted a blinded readjudication of all nine subjects. Among other reclassifications, Dr. Jayne reclassified five of the six avacopan subjects as in sustained remission. Table 1 summarizes the adjudication and readjudication decisions: [6]

TABLE 1—EFFECT OF READJUDICATION

Treatment arm and subject ID	Before readjudication		After readjudication*	
	Week 26 remission	Week 52 sustained remission	Week 26 remission	Week 52 sustained remission
Control arm (prednisone):				
428–001	No	No (ET)	**Yes**	No (ET)
852–001	No	No	**Yes**	No
957–002	No	No (ET)	**Yes**	No (ET)
Treatment arm (avacopan):				
440–002	No	No	**Yes**	**Yes**
466–003	No	No	**Yes**	**Yes**
534–001	No	No	**Yes**	**Yes**
702–001	No	No	**Yes**	**Yes**
751–001	Yes	No	Yes	**Yes**
854–001	No	No	**Yes**	No

ET: early termination; remission at week 52 imputed as nonresponse.
*Bold text in the two columns under the ''After Readjudication'' heading indicates readjudicated determinations; unbolded text in the same two columns indicates no readjudication was requested (*e.g.*, because of early termination or excessive glucocorticoid use).

The endpoint determinations were changed in the database accordingly, and the database was locked for a second time on November 20, 2019. At that point, the primary efficacy analysis was rerun, and this time generated statistically significant results. These were the only primary endpoint analysis results submitted in the NDA to support the demonstration of substantial evidence of effectiveness for approval.

3. Study Documents Prohibited Readjudications After Database Lock

None of the nine readjudications was justified or permitted under the terms of the AC Charter. According to the AC Charter, readjudications should be rare. Specifically, the AC Charter states that if an adjudication form is complete, the remission time point will be considered adjudicated and ''[t]he form will not be presented to the AC again at a later time'' (Ref. 8, § 4.3.2). This makes sense because all data packages presented to the AC must be ''100% cleaned,'' having relevant data sources verified, manual/auto edits run, and queries resolved (Ref. 8, § 4.1, Addendum 2, § 4.3.3). Under the terms of the AC Charter, readjudication should occur only when the original adjudication decision could be affected by data changes made by investigative sites after adjudication, such as changes to BVAS or other data relevant to remission status (Ref. 8, Addendum 2, § 4.3.3). Medpace was responsible for tracking post-adjudication data changes and providing the AC Chair or designee with periodic listings of data changes (Ref. 8, Addendum 2, § 4.3.3). In this case, there were no underlying ''data changes'' that precipitated this request for readjudication—only a desire for changes that would alter the study results to indicate avacopan was effective when the original analysis of the study failed to find such an effect.

Moreover, the AC Charter indicates that no readjudications can occur after unblinding—a key provision to prevent bias in the study conduct, analysis, and results. Specifically, the AC Charter states that ''no changes may be entered into EDC after data base lock'' (Ref. 8, Addendum 2, § 4.3.3). EDC was the electronic data capture system used to enter adjudication decisions (Ref. 8, § 4.3). The AC Charter further states that ''[t]here will be no blinded BVAS listings for review after unblinding''

[6] The Amgen Response erroneously identified subject 852–001 as in the treatment arm (Ref. 4 at 14). According to the ChemoCentryx response to an information request submitted during NDA review, this subject was in the control arm (Ref. 14 at 13). Table 1 reflects readjudication decisions by Dr. Jayne and should not be interpreted as FDA's agreement that these readjudication decisions were properly determined.

(Ref. 8, Addendum 2, § 4.3.3).[7] Although this provision appears limited to BVAS listings, it essentially prohibits any readjudication after database unblinding because every determination of remission status involves an assessment of BVAS data, among other factors. Indeed, every patient profile sent for adjudication must include not only BVAS listings, but also a variety of other information relevant to remission status, including prior and concomitant medications (including ''non-study-supplied glucocorticoid medications''), relapse information, and previously adjudicated BVAS, VDI, remission, and relapse data, if applicable (Ref. 8, § 4.1.1). Thus, 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 AC Charter and therefore went beyond the ''QC review for completeness and accuracy'' permitted under the SRAP after database lock (Ref. 4, Exh. 2).

The time to correct errors in study data is before unblinding, which eliminates the potential to introduce bias in the data and analysis as a result of knowing the assignment of subjects to the control or treatment arms of a study. Before the ADVOCATE study database was locked and unblinded on November 5, 2019, ChemoCentryx had many opportunities to correct errors in study data, including those involving the nine subjects identified for readjudication after unblinding. For example, the purported incorrect application of the prespecified provisions regarding missing data and glucocorticoid use should have been identified and corrected as part of the patient profile data cleaning conducted before the initial adjudication of any study subject. In addition, any purported misapplication of the study provisions regarding glucocorticoid use or missing data should have been caught over the course of the trial and certainly during database cleanup prior to unblinding.

Another opportunity for correcting errors, including those involving remission status for subjects with missing data, was the blinded data review meeting held on October 24, 2019, with Medpace and ChemoCentryx staff, including Drs. Bekker and Yue.[8] Among other things, the purpose of the meeting was to identify significant protocol deviations that would require excluding subjects from the per protocol study analysis. At this meeting, Dr. Bekker identified four subjects for exclusion from the per protocol population ''because their response could not be assessed at week 26 and are therefore non-responders.'' (Ref. 4, Exh. 56). After unblinding, Drs. Bekker and Yue identified one of the four subjects—avacopan subject 534–001—for readjudication on the grounds that the prespecified method for handling missing data had not been applied accurately. Prior to unblinding Dr. Bekker was aware of the rules for handling missing data and concluded that this subject was a non-responder. Only after unblinding did Dr. Bekker take a different position so that the subject could be readjudicated. That subject was readjudicated as being in remission, which contributed to changing the study outcome. This purported error—as well as any other errors involving misapplication of the prespecified method for handling missing data—could have been identified before or at the blinded data review meeting, or during the QC reviews performed prior to database lock and unblinding.

Finally, as required by the AC Charter, BVAS and other data related to remission, as well as ''[t]he 52 week adjudications,'' should have been cleaned before database lock, which occurred on November 5, 2019. That was the applicant's last chance to correct adjudication decisions because the AC Charter prohibited changes to adjudication decisions after database lock (Ref. 8, Addendum 2, § 4.3.3). Other data errors or inconsistencies, such as the manual data entry error involving one of the readjudicated subjects (subject 466–003), should have been identified during the various QC checks conducted immediately before database lock and unblinding, if not earlier.

The applicant's conduct cannot be considered ''quality control''; rather, sponsor personnel engaged in data manipulation that distorted the study results as reported in the NDA, which were material to the review of the NDA. As more fully explained in section I.E.1 below, the conduct biased the study results reported in the NDA to the extent that the pivotal study cannot be relied upon to support a demonstration of substantial evidence of effectiveness.

D. NDA Review Based on Manipulated Primary Endpoint Results

In the NDA submission, the applicant represented that the ADVOCATE study demonstrated (1) superiority for sustained remission at week 52 (avacopan versus prednisone treatment difference 12.5 percent with 95 percent confidence interval (CI) [2.6 percent, 22.3 percent] and two-sided p-value = 0.0132 for superiority at week 52); and (2) noninferiority, but not superiority, for remission at week 26 (avacopan versus prednisone treatment difference 3.4 percent with 95 percent CI [-6.0 percent, 12.8 percent], two-sided p-value < 0.0001 for noninferiority at week 26).

The CDER review team sent several information requests to the applicant during the NDA review to better understand the adjudication process and results. However, the applicant never disclosed the readjudications that occurred after the initial database lock and that they were prompted by both an unblinded review of the study database and knowledge that the readjudications would change the study result from not statistically significant to statistically significant. In a December 9, 2020, information request, CDER inquired about ''document finalization and unblinding dates'' in an effort to establish whether the study's statistical analysis plan had been finalized before data unblinding (Ref. 15). Noting that the specified data analyses in the statistical analysis plan differed from those in the original study protocol, CDER expressed concern that perhaps the choice of analyses specified in the statistical analysis plan was influenced by viewing trial data after unblinding, which would have introduced significant bias and inflated Type 1 error (*i.e.,* the chance of a false positive, which is a finding of a significant difference between drug and control when there really is none). The applicant's response indicated that the statistical analysis plan was finalized before the study database was frozen (*i.e.,* locked) on November 20, 2019 (Ref. 16). The response falsely characterized this as the only date on which the database was locked, because it refers to ''the freeze of the study database, which occurred on 20 November 2019.'' ChemoCentryx omitted any information regarding the database lock and unblinding that occurred on November 5, 2019. Moreover, the applicant's response omitted the crucial point that its own personnel reviewed unblinded primary efficacy endpoint data before the November 20, 2019, database lock. Nor did the applicant disclose that its unblinded personnel caused the readjudication of primary endpoint data for nine study subjects, which ultimately changed the result from not

[7] Similar language appears in the study protocol, which states that ''BVAS data recorded by investigators will be adjudicated, according to an adjudication charter, before data finalization and unblinding. The adjudicated data will be used in the final analysis'' (Ref. 5, § 7.1.1).

[8] Ref. 4, Exh. 56. The SAP required this meeting to be held prior to database lock and unblinding (see Ref. 6 at 24).

statistically significant to statistically significant. At no point did the applicant disclose any information about the first database lock, including its failed topline efficacy results, and that nine patients' endpoint determinations were readjudicated in response to a request from unblinded study personnel.

The applicant's failure to disclose these facts is contrary to well-established internationally recognized good clinical practice (GCP) guidelines established for the conduct of clinical trials, including principles for appropriate statistical analysis. These principles serve as a foundation for helping to ensure that data and statistical analysis are free from biases that make the study results uninterpretable (Ref. 11 at 42, Ref. 12 at 10–12). FDA has reiterated these principles in several FDA guidance documents. For example, FDA guidance states that changes made to data after unblinding should occur only in exceptional circumstances, should be clearly documented and justified, and reported in the clinical study report (CSR).[9] The CSR submitted to the NDA for the ADVOCATE trial made it seem like the applicant followed accepted statistical analysis practices when they did not. Specifically, the CSR did not disclose that adjudication data were changed after the database was initially locked and after unblinding, nor did it disclose that the post-unblinding readjudication of primary endpoint data reversed the failed study results in the original analysis (Ref. 7).

Documents submitted to the NDA describe the November 20, 2019, database lock and resulting unblinding and statistical analysis as if it were the only one that occurred. For example, in the previously described response to CDER's December 9, 2020 information request, the applicant characterized the study database lock as a single event: ''the freeze of the study database, which occurred on 20 November 2019'' (Ref. 16 at 1). The CSR states that ''[t]he database was frozen on November 20, 2019'' to conduct the primary efficacy endpoint analysis (Ref. 7 at 53), omitting the critical fact that the database had been frozen earlier to conduct the original analysis. In contrast, the CSR discloses elsewhere that ''minor'' errors regarding vasculitis damage index (VDI) scores were discovered after database lock, and the report includes original and revised listings and tables for VDI scores (Ref. 7 at 64–65). The CSR further states that ''[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'' (Ref. 7 at 34). That is untrue with respect to the November 20, 2019, database lock date, which was represented to FDA to be the sole database lock date.

Protecting the study blinding is an expected element of proper statistical planning and analysis. Indeed, the study documents recognize the importance of maintaining the study blinding before the database was locked for analysis. For example, the statistical analysis plan set forth safeguards against unblinding of study data ''prior to database freeze.'' The applicant appears to have followed these provisions of the statistical analysis plan and study protocol when it locked the study database on November 5th and then shared unblinded data with applicant staff. However, the applicant violated the statistical analysis plan and acceptable statistical practices once it decided to unlock the database, use unblinded data to request that nine patients be readjudicated in violation of the adjudication committee charter, reanalyze the data post readjudication, and submit those results to FDA as though the first database lock and analysis had never occurred.

Before approval, whether the applicant submitted sufficient evidence in its NDA to demonstrate TAVNEOS had its intended effect was debatable across the FDA reviewers and independent advisory committee members. The 18-member advisory committee FDA convened to provide expert advice regarding the evidence submitted in the TAVNEOS NDA were split about whether the data were sufficient to demonstrate that the product was effective, safe, or that the benefits outweighed the risks (Ref. 17). Moreover, after considering the application, including the applicant's responses to information requests, the study protocol, statistical analysis plan, and clinical study report, the primary review team did not recommend approval of TAVNEOS. In other words, even without knowledge of the data manipulation by unblinded personnel, the primary review team had significant concerns regarding whether there was a demonstration of substantial evidence of effectiveness (Ref. 18 at 33).

Importantly, the purported statistically significant superiority for sustained remission at week 52 was a key factor in the recommendation to approve the NDA made by the Director of the Division of Rheumatology & Transplant Medicine and the decision to approve the NDA made by the Director of the Office of Immunology & Inflammation (Ref. 18 at 33–35). In addition, the Division Director relied on what he was led to believe were study data and results that reflected appropriate adherence to the study plan documents. Specifically, the Division Director believed that as a large, global, multicenter trial, with procedures in place to ensure trial quality, the ADVOCATE study would be less vulnerable to certain biases, such as selection or measurement bias (Ref. 18 at 34). In recommending approval, the Division Director also considered the clinical context, noting that AAV is a rare disease with an unmet need for additional therapeutic options and a need for treatment alternatives with fewer toxicities (Ref. 18 at 35). Under the circumstances, the Division Director believed additional flexibility was warranted with respect to the acceptability of the uncertainties highlighted by the primary review team, and the Office Director concurred (Ref. 18 at 35). The Division Director did not know that the facts on which he was relying were untrue—that absent manipulation, the study results were not statistically significant on the superiority analysis at week 52, and the procedures in place to ensure trial quality were violated. Had the Division Director known these facts, he would not have recommended approval. These facts and the Division Director's recommendation would have been material to the review of the application by the Office Director and her decision to approve it.

Because of the limited safety data in the original NDA, the Agency required a postmarketing study (PMR 4155–1) to evaluate safety outcomes, including hepatotoxicity, DILI, and serious hypersensitivity reactions (Ref. 19). The same study is also assessing efficacy outcomes to fulfill a postmarketing commitment agreed to during NDA review (Ref. 18 at 231). According to the applicant's most recent annual report for this ongoing study, only 21 of the planned 300 patients have been enrolled.

E. Impact of Data Manipulation and Untrue Statements

Immediately upon learning that the results of the sole study intended to support a demonstration of effectiveness

[9] Ref. 11 at 42. ''Exceptional circumstances'' may include ''discrepancies that must be resolved for the reliability of the trial results.'' *Id.* Here, other than the correction of a manual error, the errors to be corrected were not mere data ''discrepancies,'' such as transcription errors or discrepancies between source documents and case report forms recorded in the study database. In addition, the manner in which the errors were resolved here—which was contrary to the express terms of the AC Charter and not disclosed to FDA—only reduced the reliability of the study results.

were not positive and knowing this would almost certainly result in a failure to obtain approval, key personnel took multiple steps to manipulate the results to change the study result from not statistically significant to statistically significant and hide that manipulation from the Agency by making untrue statements in the NDA.

Although Amgen states the readjudications corrected errors in the study data, the applicant's actions were improper and rendered the results biased and unreliable. No further analysis of the data can rectify this problem. Adequate and well-controlled clinical investigations are designed, among other things, to minimize the risk of a false positive conclusion (Type 1 error).[10] Statistical analyses are prespecified and controlled to minimize this risk. When a study entails multiple analyses of a primary endpoint, statistical procedures are used to control the increased risk of false positives. Without such procedures, the risk of false positives will increase. The ADVOCATE study was not designed to control for the multiple unplanned hypothesis tests for the primary endpoints that the applicant conducted. Therefore, the Type 1 error risk was not properly controlled, and the primary endpoint of sustained remission at 52 weeks presented in the NDA cannot be reliably interpreted.

The ADVOCATE study cannot be considered adequate and well-controlled. For example, FDA regulations at 21 CFR 314.126(b)(5) require ''an analysis of the results of the study adequate to assess the effects of the drug.'' The applicant conducted a reanalysis of the data that did not control for multiplicity, and therefore the analysis could not adequately assess the effects of the drug. Moreover, under 314.126(b)(5), a study must ensure that ''adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.'' After the applicant's analysts knew that the study failed to achieve statistical significance, it used unblinded data to select certain subjects for readjudication with the goal of changing the statistical significance of the study outcome. Therefore, the study conduct did not adequately minimize bias on the part of the analysts of the data. Accordingly, the ADVOCATE study cannot support a demonstration of substantial evidence of effectiveness. The only interpretable analysis of the primary endpoint of sustained remission at 52 weeks was the original analysis based on the November 5, 2019, database lock, which was conducted in accordance with the prespecified analysis plan after the data were checked and confirmed to be accurate before unblinding. That analysis was not statistically significant and would not have supported a demonstration of substantial evidence of effectiveness during the NDA review.

1. Impact of the Data Manipulation

The applicant's manipulation of data in the ADVOCATE study irreconcilably biased the study result on sustained remission and renders that result uninterpretable for regulatory decision making. Minimizing bias in clinical research is essential to ensure that study results are reliable and reflective of a medical product's safety and effectiveness. Bias can arise in many ways, including through clinical trial design and conduct, as well as the analysis and evaluation of study results.

Blinding is one of the most important design techniques for avoiding bias in clinical trials (Ref. 12 at 10). Blinding is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence that the knowledge of treatment may have on a number of factors, including the assessment of endpoints, the exclusion of data from analysis, and more (Ref. 12 at 10). Maintaining the blinding until all opportunities for bias have passed is critical. Regardless of how bias is introduced—whether consciously or unconsciously, from lack of blinding, improper unblinding, selective outcome reporting, etc.—it distorts findings and reduces the reliability of study results.

a. Biased Study Results

In its August 22, 2025 response to FDA, Amgen claimed that the readjudications were statistically appropriate to preserve the accuracy of the underlying trial data (Ref. 4 at 28). Amgen's claim is incorrect. While it may be generally acceptable to conduct *blinded* data quality assurance checks, the unblinded review of study data to inform patient selection for readjudication and reanalyses—and the failure to disclose it—was a significant deviation from core scientific and statistical principles and good clinical practices for clinical trials.[11] In any double-blind study, such as the ADVOCATE study, neither the subject nor any of the investigators or sponsor staff—including those evaluating endpoints—should be aware of the treatment received (Ref. 12 at 11). Moreover, this level of blinding must be maintained throughout the conduct of the trial; ''only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded'' (Ref. 12 at 11). FDA guidance further states the fundamental principle that any intentional or unintentional breaking of the blinding should be reported and explained to the Agency, regardless of the reason for its occurrence (Ref. 12 at 12). In addition, post-unblinding data changes and deviations from the planned statistical analyses should be reported in the clinical study report (Ref. 11 at 42), which is included in the NDA submission.[12]

As discussed in section I.C.3 above, the ADVOCATE study had several procedures designed to correct study data before database unblinding. However, the correction of study data after unblinding and analysis can introduce substantial conscious and unconscious bias. Here, the evidence shows that the applicant and its service providers conducted a quality control review of the data before the database was locked on November 5, 2019 and identified no concerns.

What the applicant did is exactly what the AC Charter was designed to prevent: the introduction of bias in the study results due to selective readjudication of study subjects after unblinding. In the absence of any evidence of erroneous data, sponsor personnel used unblinded data specifically to find subjects whose readjudication would change the results of the trial. The evidence shows that the goal of this behavior was to alter the results of the original analysis. If the original analysis had been positive, Drs. Bekker and Yue would likely not have searched for subjects to readjudicate.

Knowledge of the study results permitted the applicant to conduct a biased search for subjects to readjudicate where the readjudication would change the study results from negative to positive. Although the Amgen Response indicates that Drs. Bekker and Yue analyzed remission data for all patients in the study, 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

[10] See 21 CFR 314.126.

[11] See, for example, discussion of bias and the importance of blinding in section II.C of the guidance for industry entitled ''E9 Statistical Principles for Clinical Trials'' (Ref. 12). See also the guidance for industry entitled ''E6(R3) Good Clinical Practice'' (Ref. 11).

[12] See 21 CFR 314.50(a) (requiring an NDA to ''contain reports of all investigations of the drug product sponsored by the applicant''); see also Ref. 20.

other than treatment of AAV (Ref. 4 at 11–14; Ref. 4, Exh. 14). This targeted review would not detect misapplication of other prespecified protocol provisions affecting remission determinations, such as the definition of disease relapse or the accuracy of BVAS assessments, in subjects that had been adjudicated as in remission or sustained remission. Their targeted data review was biased in favor of finding more patients—specifically more avacopan patients—whose remission status could be changed to support the desired trial outcome.

In addition, knowledge of treatment assignments appears to have biased which study subjects were referred for readjudication. We note that the remission determinations selected for readjudication were heavily weighted in favor of generating a statistically significant result on sustained remission for subjects in the avacopan arm of the ADVOCATE study. For example:

- All subjects identified for readjudication were believed to have been incorrectly adjudicated as not in remission at week 26 or week 52 or both;
- Twice as many subjects in the avacopan arm were selected for readjudication compared to the control arm (six versus three); and
- The three control arm patients selected for readjudication could not have made a difference in the analysis of the superiority claim at week 52 because two of the three terminated too early to be evaluated for sustained remission, and glucocorticoid use by the third control subject precluded a sustained remission determination.[13] In fact, readjudication of the week 52 remission status for the three control arm subjects was not even requested.[14]

Bias in the selection of subjects for readjudication could not be mitigated by the fact that Dr. Jayne conducted the readjudications in a blinded fashion. The AC charter rightly prohibits readjudication after study unblinding because of the potential for bias. In addition, bias is not overcome because the applicant also included three prednisone control subjects for readjudication at week 26. As noted above, at the time these subjects were selected for readjudication, it was obvious that readjudication of their week 26 remission status would have no effect on the week 52 sustained remission results for that study arm.

b. The Study Results are Uninterpretable and Cannot Be Salvaged with Further Analyses

The applicant's improper actions forever taint the study results reported in the NDA and render them uninterpretable. Further analyses of the ADVOCATE study cannot salvage this drug approval. If not controlled and prespecified, the risk of a false positive increases with every subsequent analysis, making the results less reliable. The ADVOCATE study's statistical analysis plan did not plan for repeat analyses of the primary endpoint. This is expected because it is improper to change the data after an unfavorable analysis and reanalyze the same endpoint. Therefore, the ADVOCATE study results submitted in the NDA cannot be considered statistically significant.

Under the ADVOCATE study's statistical analysis plan, the overall Type I error rate was controlled at 5% significance level (Ref 8 at 30). The original statistical analysis of the study database after database lock on November 5, 2019, was not significant, returning a two-sided p-value of 0.1025, which is above the significance threshold. The statistical analysis submitted for NDA review, which was performed after changing the study data to reflect the readjudication of five avacopan subjects, returned a two-sided p-value of 0.0132, suggesting that avacopan was superior to the control arm and the result was statistically significant. But as explained below, it was not.

The p-value the applicant reported in the NDA for avacopan was not controlled for Type I error, but the applicant never disclosed that. The applicant conducted a second analysis of the primary endpoint after it changed the data and without controlling for the risk of a false positive result. The p-value reported in the NDA is therefore meaningless and uninterpretable.

There is no way to redeem the ADVOCATE study by permitting the applicant to conduct a new, independent, blinded review and adjudication of the study data. As stated previously, each re-analysis, without procedures to control multiplicity that are specified before the data are locked, will increase the risk of a false positive. This is exactly what guidelines and regulations around the conduct of clinical trials are designed to prevent—continuously reanalyzing data until you get a positive result. Moreover, different adjudications, even based on the same data, may produce different results because of the selection and training of the adjudicators, among other things. In the present case, there may also be biases associated with knowledge of the study results from prior analyses. With enough readjudication, the study may inappropriately appear to have statistical significance even if the drug is not effective. Again, the only analysis that should be evaluated as part of the TAVNEOS NDA is the original analysis following database lock on November 5, 2019, which did not demonstrate statistical significance.

2. Untrue Statements in the Application

The applicant withheld and mischaracterized information about when and how often the study database was locked, unblinded, analyzed, and altered. These distortions violated various FDA requirements regarding the content of NDAs and constituted untrue statements of material fact that affected FDA's decision to approve the application.

For example, FDA regulations require, as a general matter, that 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'' (21 CFR 314.50). These regulations specifically require, among other relevant data and information: (1) ''the results of statistical analyses of the clinical trials'' (§ 314.50(c)(2)(viii)); (2) a ''description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies'' (§ 314.50(d)(6)) ; and (3) a ''description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product'' (§ 314.50(d)(5)(iv)). Furthermore, the NDA ''is required to 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'' (§ 314.50(c)(1)).

Despite these obligations, the applicant did not disclose in the NDA that the database was locked, unblinded, and statistically analyzed more than once, nor did the applicant describe or otherwise note the original, failed primary endpoint analysis. Instead, the applicant repeatedly and falsely conveyed that there was a single analysis of the ADVOCATE study, and that it achieved a certain p-value indicating that the results were statistically significant. In response to an information request from FDA after

[13] See Ref. 4 at 12–14 regarding subjects 428–001, 957–002, and 852–001. We note that subject 852–001 was erroneously characterized in that document as being in the avacopan treatment arm. This subject was in the control arm of the ADVOCATE study (Ref. 14 at 13).

[14] See Ref. 4, Exh. 18.

the NDA was submitted, the applicant then falsely characterized the study database lock as a single event (''*the* freeze of the study database'') occurring on November 20, 2019. For example, as described in section I.D, the applicant's response to CDER's December 9, 2020, information request asserts that the ADVOCATE study database was frozen (*i.e.* locked) on November 20, 2019 (Ref. 16 at 2, 3). Similarly, the CSR states that database lock occurred on November 20, 2019 (Ref. 7 at 4). The CSR further states that ''[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'' (Ref. 7 at 34). That statement is only true if the database lock referenced is the November 5, 2019, database lock; it is patently false if the database lock referenced is the November 20, 2019, lock—the only database lock referenced in the NDA.

Given 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.'' The applicant's omissions and untrue statements were material to the review of NDA 214487, including the determination of substantial evidence of effectiveness, the overall benefit-risk assessment, the recommendation of the Director of the Division of Rheumatology & Transplant Medicine to approve the NDA, and the decision of the Director of the Office of Immunology & Inflammation to approve the NDA.

F. Withdrawal of Approval is Appropriate

In light of the facts outlined above, CDER can no longer conclude that there is, or has ever been, a valid demonstration of substantial evidence of effectiveness for TAVNEOS. The post hoc nature of the database changes and involvement of unblinded study personnel, combined with the resulting change in statistical significance, irrevocably compromises the credibility of the study results and thus the demonstration of substantial evidence of effectiveness that supported the original approval.

The original analysis based on the November 5, 2019, database lock was not statistically significant. Additional readjudication or reanalysis of the same data, blinded or unblinded, cannot overcome the finding of the original analysis. Every additional readjudication or reanalysis reduces the reliability of the result because of the increased risk of chance findings. Thus, substantial evidence of effectiveness of TAVNEOS can no longer be demonstrated with the existing data.

Furthermore, we are increasingly concerned about the safety profile of TAVNEOS. In a review of postmarketing data from the applicant's global safety database, the medical literature, and CDER's Office of Surveillance and Epidemiology review of FDA's Adverse Event Reporting System (FAERS) through October 9, 2024, CDER identified 76 cases of DILI, of which 72 cases were possibly, and 4 cases were probably causally associated with, avacopan use. Importantly, 7 of the 76 cases of DILI reported biopsy-confirmed VBDS, a serious and unexpected adverse event for avacopan. Seventy-four cases reported a serious outcome, including hospitalizations (n=54) and deaths (n=8). Without certain demonstration of benefit to balance the serious risks associated with avacopan, including the risk of hepatotoxicity, the drug's benefits cannot outweigh its known risks for the conditions of use for which it is approved.

Accordingly, CDER proposes to withdraw approval of TAVNEOS (avacopan) capsule, 10 mg, because, on the basis of new information, evaluated together with the evidence available to FDA when the NDA was approved, there is a lack of substantial evidence of effectiveness that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling. This absence of demonstrated benefit is further aggravated by the drug's known serious risks of hepatoxicity. In addition, CDER proposes to withdraw approval of the drug because the application contained untrue statements of material fact, as described in Section I.E.

We are mindful that TAVNEOS is indicated as an adjunctive treatment of a serious rare disease associated with high morbidity and mortality. We also recognize that there are limited therapeutic options for the condition, and that those options (glucocorticoids) are often not well tolerated. On the other hand, there are serious safety risks associated with avacopan, including the risk of hepatotoxicity, with no demonstration of benefit.

Withdrawing a drug under these circumstances is critical to protect the public health and the integrity of the drug approval process. Otherwise, applicants would be incentivized to deceive FDA and, if the deception is discovered by FDA after approval, claim the drug should remain on the market while the applicant gets another chance to reanalyze data and hope for a positive result.

II. Notice of Opportunity for a Hearing

In accordance with § 314.200 (21 CFR 314.200), notice is hereby given to the applicant and to all other interested persons that the Director of CDER proposes to issue an order, under sections 505(e)(3) and 505(e)(5) of the FD&C Act, and 21 CFR 314.150(a), withdrawing approval of NDA 214487 and all amendments and supplements thereto.

In accordance with section 505 of the FD&C Act and 21 CFR 314.200, the applicant is hereby provided an opportunity for a hearing to show why the approval of the NDA should not be withdrawn.

If the applicant decides to seek a hearing, it must file the following: (1) a written notice of participation and request for a hearing (see **DATES** and **ADDRESSES**) and (2) the data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of fact that requires a hearing (see **DATES** and **ADDRESSES**). Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for a hearing, notice of participation and request for a hearing, the information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in § 314.200 and in 21 CFR part 12.

The failure of the applicant to file a timely written notice of participation and request for a hearing, as required by § 314.200, constitutes an election by the applicant not to avail itself of the opportunity for a hearing concerning CDER's proposal to withdraw approval of the NDA and constitutes a waiver of any contentions concerning the legal status of the drug product. FDA will then withdraw approval of the NDA, and the drug product may not thereafter be lawfully introduced or delivered for introduction into interstate commerce. Any new drug product introduced or delivered for introduction into interstate commerce without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request that there is no genuine and substantial issue of material fact, or if a request for a hearing is not made in the required format or with the required analyses, the

Commissioner of Food and Drugs will enter summary judgment against the person who requests the hearing, making findings and conclusions, and denying a hearing.

If you choose to submit confidential information under this notice of opportunity for a hearing, it must be a paper submission filed in two copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen at the Dockets Management Staff (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *https://www.regulations.gov*.

This notice is issued under section 505(e) of the FD&C Act, 21 CFR part 314, and under authority delegated to the Director of CDER by the Commissioner of Food and Drugs.

III. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES** [1]) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov*. References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2026–P–0655]

Determination FENOGLIDE (Fenofibrate) Tablets, 40 Milligrams and 120 Milligrams, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) has determined that FENOGLIDE (fenofibrate) tablets, 40 milligrams (mg) and 120 mg, was not withdrawn from sale for reasons of safety or effectiveness. This determination means that FDA will not begin procedures to withdraw approval of abbreviated new drug applications (ANDAs) that refer to this drug product, and it will allow FDA to continue to approve ANDAs that refer to the product as long as they meet relevant legal and regulatory requirements.

FOR FURTHER INFORMATION CONTACT: Heather Dorsey, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6269, Silver Spring, MD 20993–0002, 301–796–3600, *Heather.Dorsey@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION: Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) allows the submission of an ANDA to market a generic version of a previously approved drug product. To obtain approval, the ANDA applicant must show, among other things, that the generic drug product: (1) has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and (with certain exceptions) labeling as the listed drug, which is a version of the drug that was previously approved, and (2) is bioequivalent to the listed drug. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

Section 505(j)(7) of the FD&C Act requires FDA to publish a list of all