NDA 217686

CORRECTED NDA APPROVAL

Idorsia Pharmaceuticals Ltd.
c/o: Idorsia Clinical Development US Inc.
Attention: Bradford Kirk Perry, PharmD, RPh
Director, US Drug Regulatory Affairs
1820 Chapel Avenue West
Suite 150
Cherry Hill, NJ 08002

Dear Dr. Perry:

Please refer to your new drug application (NDA) dated December 19, 2022, received December 19, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tryvio (aprocitentan) tablets.

We also refer to our approval letter dated March 19, 2024, which contained the following error:

> On page 5, under **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**, the Medication Guide was identified incorrectly as part of the REMS.

This corrected action letter incorporates the correction of the error. The effective action date will remain March 19, 2024, the date of the original letter.

We acknowledge receipt of your major amendment dated September 6, 2023, which extended the goal date by three months.

This NDA provides for the use of Tryvio (aprocitentan) tablets, in combination with other antihypertensive drugs, for the treatment of hypertension, to lower blood pressure in adult patients who are not adequately controlled on other drugs.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217686**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Tryvio (aprocitentan) tablets shall be 24 months from the date of manufacture when stored at 20 °C to 25 °C (68 ºF to 77 ºF). Excursions are permitted from 15 ºC to 30 ºC (59 ºF to 86 ºF).

ADVISORY COMMITTEE

Your application for Tryvio was not referred to an FDA advisory committee because:

(1) The application did not raise significant public health questions on the role of the drug in the treatment of hypertension.

(2) Outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients with hypertension and is not likely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of embryo-fetal toxicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4600-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Tryvio (aprocitentan) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you submitted on March 4, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2024
Final Protocol Submission:	5/2025
Interim Report Submission #1:	5/2027
Interim Report Submission #2:	5/2029

Interim Report Submission #3:	5/2031
Interim Report Submission #4:	5/2033
Interim Report Submission #5	5/2035
Study Completion:	5/2036
Final Report Submission:	11/2036

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 122772 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Tryvio (aprocitentan) to ensure the benefits of the drug outweigh the risk of embryo-fetal toxicity.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Tryvio (aprocitentan) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of embryo-fetal toxicity listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers are specially certified
- Pharmacies or practitioners that dispense the drug are specially certified

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified.

Your proposed REMS, submitted on September 6, 2023, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Tryvio (aprocitentan) into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:
For each metric, provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

REMS Implementation and Operations:

1. REMS Website
   a. Date REMS Website went live (first assessment report only)
   b. Number of total visits and number of unique visits to the REMS Website
   c. Number and type of REMS materials downloaded or printed for each material

d. Summary of outages or problems with the operation of the REMS Website

2. REMS Implementation (first assessment report only)
   a. Date of first commercial availability of Tryvio
   b. Date of Tryvio REMS launch
   c. Date that each stakeholder (e.g., healthcare providers, pharmacies, wholesaler/distributors) could become certified/authorized
   d. Date when the REMS Coordinating Center was established and fully operational

3. REMS Infrastructure and Performance
   a. REMS Coordinating Center
      i. Number of contacts by stakeholder type (e.g., patients, healthcare providers, pharmacies, wholesaler/distributors, other)
      ii. Summary of reasons for calls (e.g., authorization to dispense, enrollment question, location of a pharmacy) and by stakeholder type (e.g., healthcare providers, pharmacies, wholesaler/distributors, patients, authorized representative, other). Limit the summary to the top five reasons for calls by each stakeholder group
      iii. If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues, and how these issues were resolved
      iv. Summary of frequently asked questions (FAQs) by stakeholder type

4. REMS Certification and Enrollment
   a. Certified Pharmacies
      i. Number and percentage of newly certified pharmacies, stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)
      ii. Method of pharmacy certification (i.e., online, fax)
      iii. Total number of certified pharmacies at the end of the reporting period, stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)
      iv. Number and percentage of active certified pharmacies (i.e., have dispensed Tryvio), stratified by pharmacy type (e.g., inpatient, outpatient-retail, and outpatient-specialty)

   b. Certified Healthcare Providers
      i. Number and percentage of newly certified healthcare providers, stratified by medical specialty (e.g., cardiology, internal medicine, etc.)
      ii. Method of healthcare provider certification (i.e., online, fax)
      iii. Total number of certified healthcare providers at the end of the reporting period
      iv. Number and percentage of active certified healthcare providers (i.e.,

have prescribed Tryvio)

c. Authorized Wholesaler/Distributors
   i. Number of newly contracted wholesaler/distributors
   ii. Number of active (i.e., have shipped Tryvio) wholesaler/distributors

5. REMS Utilization
   a. Number of tablets sent to certified prescribers, certified pharmacies, stratified by type of pharmacy

6. REMS Compliance
   a. Audits: Provide a report of audit findings for each stakeholder (i.e., certified inpatient pharmacies; certified outpatient pharmacies; authorized wholesalers/distributors) including but not limited to:
      i. A copy of the audit plan for each stakeholder
      ii. The number of audits expected, and the number of audits conducted
      iii. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for group of audited stakeholders
      iv. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan
      v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
      vi. Confirm documentation of completion of training for relevant staff
      vii. Verify the existence of documented processes and procedures for complying with the REMS
      viii. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

   b. Non-Compliance: Provide a summary of the non-compliance identified, including but not limited to:
      i. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
      ii. The number of instances of non-compliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:
         1. The unique identifier (ID(s)) of the stakeholder(s) associated with the non-compliance event or deviation to enable tracking over time
         2. The source of the non-compliance data
         3. The results of the root cause analysis
         4. What action(s) were taken in response and whether any follow

up is planned

iii. Number and percentage of certified healthcare providers that were non-compliant with the REMS requirements
   1. Number of certified healthcare providers that had certification suspended or revoked. Include the reasons for the action.

iv. Number and percentage of authorized wholesaler/distributors that were non-compliant with the REMS requirements
   1. Number of shipments sent to non-certified pharmacies. Include the source of the report, corrective actions taken to prevent future occurrences, and the outcome of such actions

v. Number and percentage of certified pharmacies that were non-compliant with the REMS requirements, stratified by setting (e.g., inpatient, outpatient)
   1. Number of certified pharmacies that had certification suspended or revoked. Include the reasons for the action

vi. Outpatient pharmacy-related REMS Dispense Authorizations (RDAs) compliance
   1. The number of RDAs issued
   2. The number of RDA requests that were not authorized because the prescriber is not certified
   3. Summary of RDA compliance issues (e.g., pharmacy did not request RDA, pharmacy dispensed without RDA, etc.) identified in audits, corrective actions, and resolution.

vii. For certified inpatient and outpatient pharmacies that are audited: the number and percentage of patients who received the patient material, Risk of Birth Defects with Tryvio, stratified by pharmacy type (inpatient, outpatient specialty, outpatient retail)

viii. For all other non-compliance with the REMS requirements, provide source of non-compliance report, and the corrective action taken

Knowledge

7. Post-training Knowledge Assessment
   a. Number of healthcare providers who completed post-training knowledge assessment. Include method of completion and number of attempts needed to complete.
   b. Number of healthcare providers who did not pass the knowledge assessment.
   c. A summary of the most frequently missed questions.
   d. A summary of potential comprehension or perception issues identified with the knowledge assessment (first assessment report only)

8. Evaluation of Knowledge of the Tryvio REMS and Risks of Tryvio
   a. An evaluation of certified healthcare providers' knowledge, attitudes, and behaviors (to be conducted annually from the date of REMS approval) related to:
      i. The risks of embryo-fetal toxicity associated with Tryvio

ii. The need to counsel patients who can become pregnant about:
    1. The risks of embryo-fetal toxicity associated with Tryvio
    2. The recommendation for pregnancy testing prior to initiating treatment, monthly during treatment, and for one month after discontinuing treatment
    3. The need for patients who can become pregnant to use acceptable contraception

b. Qualitative evaluation (e.g., focus group, comprehension study, etc.) assessing patient comprehension of the "Risk of Embryo-Fetal Toxicity with Tryvio" (to be conducted once initially).

Health Outcomes and/or Surrogates of Health Outcomes

9. An estimation of the percent pregnancy rate per reporting period and cumulatively, reported as:
    a. Percentage pregnancy rate, calculated as the number of pregnancies reported divided by the number of women of reproductive age who were exposed to Tryvio
    b. Pregnancy incidence rate (in person-years), calculated as the number of pregnancies reported divided by the amount of person-time that women of reproductive age were exposed to Tryvio

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan **and** non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the certified healthcare providers' knowledge survey for FDA review within 90 days of this letter.

iii. Submit your proposed protocol for the qualitative evaluation (e.g., focus group, comprehension study, etc.) assessing patient comprehension of the "Risk of Embryo-Fetal Toxicity with Tryvio" for FDA review within 90 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 217686 REMS ASSESSMENT METHODOLOGY**
> (insert concise description of content in bold capital letters, e.g., **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY**)

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the

REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 217686 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 217686 /S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 217686/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 217686/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 217686/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 217686

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]
As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5]
Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REQUESTED PHARMACOVIGILANCE

We request that for a period of 5 years, you submit all serious cases of hepatotoxicity from your global safety database and the published medical literature as 15-day Alert Reports [as described under 21 CFR 314.80(c)(1)]. Provide comprehensive summaries and analyses of serious cases of hepatotoxicity reported from clinical studies and post-marketing reports in your periodic safety report [i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report (PBRER) format]. These analyses should show cumulative data relative to the date of approval of Tryvio (aprocitentan) tablets, as well as relative to prior periodic safety reports.

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

[7] https://www.uspnf.com/

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, MD
Deputy Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
03/22/2024 10:16:29 AM