CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217686Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: Expedited ARIA Sufficiency Determination for Pregnancy Safety Concerns
Version: 2018-01-24

Date:	March 18, 2024
Reviewer:	Margie Goulding, PhD Division of Epidemiology 2
Team Leader:	Mingfeng Zhang, MD, PhD Division of Epidemiology 2
Division Director:	Monique Falconer, MD, MS Division of Epidemiology 2
Subject:	ARIA Sufficiency Memo
Drug Name:	Aprocitentan (Tryvio) tablets
Application Type/Number:	NDA 217686
Applicant:	Idorsia
OSE TTT #:	2023-6946

1. BACKGROUND INFORMATION

1.1. Medical Product, Indicated Disease and Disease-Associated Risks in Pregnancy

Aprocitentan is an endothelin receptor antagonist (ERA) and active metabolite of macitentan that is proposed for the treatment of resistant hypertension, i.e. to control high blood pressure (BP) when the patient has had an inadequate response to other anti-hypertensive drugs.

By the 2018 American Heart Association (AHA) definition, approximately 10.8% of US adults ages 20-49 years who are taking anti-hypertensive medication are estimated to have apparent treatment-resistant hypertension[1]. Women who had high blood pressure prior to becoming pregnant or who develop hypertension early in their pregnancy (i.e. with chronic hypertension) account for approximately 0.9-1.5% of pregnant women [2]. During pregnancy, chronic hypertension increases the risk for preterm birth, perinatal death, intrauterine growth restriction, stroke, preeclampsia, acute renal failure, pulmonary edema, and maternal death[3].

1.2. Describe the Safety Concern

An August 2023 Division of Pediatrics and Maternal Health (DPMH) review (by C. Ceresa, Ref ID 5227661) described the non-clinical experience with macitentan as:

> In embryo-fetal development toxicity studies in pregnant rats and rabbits, cardiovascular and mandibular arch fusion abnormalities were observed at all dose levels of macitentan, which included exposures to aprocitentan representing approximately (b) (4) and (b) (4) fold, respectively, of the clinical aprocitentan exposures at the maximum recommended human dose (MRHD) based on the area under the curve (AUC). In pre- and post-natal development studies, female rats given macitentan from late pregnancy through lactation showed reduced pup survival and impairment of the male fertility of the offspring at a macitentan dose of 10 mg/kg/day, where aprocitentan exposures were (b) (4) the clinical exposures at the MRHD based on AUC.

Females of reproductive potential in the trials were required to test for pregnancy and use effective contraception methods. The clinical study data included only one aprocitentan exposed pregnancy. That study participant reported a positive pregnancy test with aprocitentan exposure from their last menstrual period until discontinuation 104 days later. A healthy male infant was delivered with no neonatal illness, no need for resuscitation or ICU admission, and no congenital

anomalies.

The teratogenicity seen in animal reproduction studies has not been seen as major congenital malformations in human case reports, case series with other ERAs and pharmacovigilance data with other ERAs. Nevertheless, teratogenicity remains a concern.

DPMH recommended a descriptive pregnancy safety study because a comparative study with prespecified sample size is not feasible due to the small number of exposed pregnancies that are expected to occur despite the pregnancy contraindication labeling and restrictions under the REMS.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

X No approved indication*, but there is the potential for inadvertent exposure before a pregnancy is recognized

☐ No approved indication, but use in women of childbearing age is a general concern

*: The proposed indication is to treat hypertension, in combination with other anti-hypertensive drugs, to lower blood pressure in patients who are not adequately controlled on other drugs. Use in pregnancy is contraindicated. A Risk Evaluation and Mitigation Strategy (REMS) is required.

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: A protocol-driven single-arm observational study of aprocitentan safety during pregnancy. This study should prospectively and retrospectively collect detailed clinical information to enable complete case narratives of maternal and fetal outcomes after pregnancy exposures to aprocitentan. A comparative study with pre-specified sample size is not feasible because of the low expected number of exposed pregnancies.

2.4. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?

✓ Study Population
☐ Exposures
✓ Outcomes
✓ Covariates
✓ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: ARIA may capture hypertensive patients using diagnosis codes and/or antihypertensive medications. However, very few aprocitentan-exposed pregnancies are expected due to the contraindication and REMS. To increase the likelihood of getting enough cases for interpretable results, the study should capture any exposed pregnancies worldwide, including those outside the US, if other regulatory agencies approve aprocitentan.

Outcomes: The descriptive pregnancy safety study being considered would collect detailed information about the pregnancy outcomes, including spontaneous abortions and any major or minor congenital malformations. A series of well-documented case narratives that present detailed clinical information acquired directly from primary sources (e.g. medical records) might permit credible assessment of the causal significance of adverse events associated with aprocitentan exposures during pregnancy. The requirement for special questionnaires and direct access to medical records invalidate the Sentinel Distributed Database (SDD) as a data source.

Covariates: The descriptive study being considered would also collect detailed information on other factors to aid causality assessment, e.g. outcomes of any prior pregnancies of the mother, and family history of birth defects.

Analytic Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully implemented in post-market surveillance of maternal and fetal outcomes.

2.5. Please include the proposed PMR language in the approval letter.

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.

3. REFERENCES

1. Carey, R.M., et al., *Prevalence of Apparent Treatment-Resistant Hypertension in the United States.* Hypertension, 2019. **73**(2): p. 424-431.
2. Committee, S.f.M.-F.M.P., *Society for Maternal-Fetal Medicine Statement: Antihypertensive therapy for mild chronic hypertension in pregnancy The Chronic Hypertension and Pregnancy trial* 2022, Society for Maternal-Fetal Medicine. p. B24-B27.
3. Bateman, B.T., et al., *Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions.* Am J Obstet Gynecol, 2012. **206**(2): p. 134 e1-8.

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/s/

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

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

Memorandum

Date: March 12, 2024

To: Selena D Deconti, M.D., Medical Officer
Division of Cardiology and Nephrology (DCN)

Sabry Soukehal, Regulatory Project Manager (DCN)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRYVIO™ (aprocitentan) tablets, for oral use

NDA: 217686

In response to DCN's consult request dated April 4, 2023 OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for original NDA for TRYVIO™ (aprocitentan) tablets, for oral use (Tryvio).

PI, MG: OPDP's comments on the proposed labeling are based on the draft version received by electronic mail from DCN on March 5, 2024 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the MG will be completed and sent under separate cover at a later date.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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

PATIENT LABELING REVIEW

Date:	March 8, 2024
To:	Sabry Soukehal, RAC, DCPM Senior Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRYVIO (aprocitentan)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 217686
Applicant:	Idorsia Pharmaceuticals Ltd.

1 INTRODUCTION

On December 19, 2022, Idorsia Pharmaceuticals Ltd. submitted for the Agency's review an original New Drug Application (NDA) 217686 for TRYVIO (aprocitentan) tablets, for oral use. With this submission, the Applicant proposes an indication for the treatment of hypertension, in combination with other antihypertensive drugs, to lower blood pressure (BP) in patients who are not adequately controlled on other drugs.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on April 4, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRYVIO (aprocitentan) tablets.

2 MATERIAL REVIEWED

- Draft TRYVIO (aprocitentan) tablets MG received on December 19, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 5, 2024.
- Draft TRYVIO (aprocitentan) tablets Prescribing Information (PI) received on December 19, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 5, 2024.
- Approved OPSUMIT (macitentan), TRACLEER (bosentan), FILSPARI (sparsentan), and Letairis (ambrisentan) tablets comparator labeling dated May 26, 2023, February 8, 2024, February 17, 2023, and August 23, 2019, respectively.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
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CHARUNI P SHAH
03/08/2024 01:04:42 PM

LASHAWN M GRIFFITHS
03/08/2024 01:21:04 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 5, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217686
Product Name, Dosage Form, and Strength:	Tryvio (aprocitentan) tablets, 12.5 mg
Applicant/Sponsor Name:	Idorsia Pharmaceuticals, Ltd
TTT ID #:	2022-3103-2
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on February 28, 2024 for Tryvio. We reviewed the revised container labels and carton labeling for Tryvio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

(b) (4) the proposed 12.5 mg strength will be approved[b], and as such we have (b) (4) evaluated the revised container labels and carton labeling for the 12.5 mg strength.

2 CONCLUSION

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

[a] Kundreskas, J. Label and Labeling Review for Tryvio (NDA 217686). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 FEB 15. TTT ID No.: 2022-3103-1.

[b] Request for a Teleconference for Tryvio (aprocitentan), NDA 217686. Cherry Hill (NJ): Idorsia Pharmaceuticals, LTD; 2024 FEB 26. Available from: \\CDSESUB1\EVSPROD\nda217686\0048\m1\us\12-cover-letters\cover.pdf.

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/s/

JODY K KUNDRESKAS
03/05/2024 12:58:57 PM

NICOLE F IVERSON
03/05/2024 01:48:53 PM

Office of Prescription Drug Promotion

Internal Consult

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

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

To: Katherine Hyatt Hawkins Shaw, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Tierra Butler, PharmD, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, PharmD, Team Leader, OPDP
Monique Killen, PharmD, Safety Regulatory Project Manager, OSE
Yasmeen Abou-Sayed, PharmD, Team Leader, DRM
Cristen Lambert, PharmD, Risk Management Analyst, DRM
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: March 4, 2024

Re: NDA #217686
Tryvio® (aprocitentan) tablets, for oral use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

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Materials Reviewed

OPDP has reviewed the following proposed REMS materials for TRYVIO:

- Healthcare Provider (HCP) REMS Materials:
  - TRYVIO REMS Prescriber Enrollment Form
  - TRYVIO REMS Outpatient Pharmacy Enrollment Form
  - TRYVIO REMS Inpatient Pharmacy Enrollment Form
  - TRYVIO REMS Prescriber and Pharmacy Guide

- Direct-to-Consumer (Patient) REMS Materials:
  - TRYVIO REMS Patient Guide
  - Risk of Birth Defects with TRYVIO

- TRYVIO REMS Website

The version of the draft REMS materials, including draft product labeling (PI and Medication Guide), used in this review were sent from DRM Katherine Hyatt Hawkins Shaw via email on February 23, 2024. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for TRYVIO.

General Comment

Please remind Idorsia Pharmaceuticals Ltd. (Idorsia) that REMS materials are not appropriate for use in a promotional manner.

OPDP notes that the current TRYVIO PI and Medication Guide (MG) are still being reviewed by DGE. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label for TRYVIO.

OPDP notes the link www.TRYVIOREMS.com and toll-free number (b) (4) OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Idorsia that the REMS specific website should not be the sole source of approved REMS materials.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see “Specific Comment[s]” below):

- TRYVIO REMS Prescriber Enrollment Form
- TRYVIO REMS Outpatient Pharmacy Enrollment Form

- TRYVIO REMS Inpatient Pharmacy Enrollment Form
- TRYVIO REMS Patient Guide

Specific Comment[s]

OPDP considers the following statement[s] promotional in tone and recommends revising them in the REMS piece:

- TRYVIO REMS Prescriber and Pharmacy Guide
- TRYVIO REMS Website
  - Risk
    - We note that the draft TRYVIO PI includes the instruction to "educate and counsel patients who can become pregnant on the use of emergency contraception in the event of unprotected sex or contraceptive failure." We recommend revising these presentations to include this REMS related risk information.

- Risk of Birth Defects with TRYVIO
  - Risk
    - These REMS pieces include information regarding the "risk of birth defects" while taking TRVYIO. This and similar presentations within the REMS pieces in the submission fail to specify the degree of severity of this risk and may misleadingly minimize the risk. Specifically, under **"What is the most important information I should know about TRYVIO?"** (bolded emphasis original) in the draft MG, patients are counseled that "TRYVIO may cause serious birth defects if taken during pregnancy" (underlined emphasis added). We recommend revising these REMS pieces and all similar piece to clarify this is a "serious" REMS related risk.

    - Page one includes the following presentation regarding the risk of TRYVIO:

      - **"TRYVIO™ can cause serious birth defects"**

      This claim omits important REMS related risk information concerning when a patient may experience these serious birth defects. The draft MG states, "TRYVIO may cause serious birth defects if taken during pregnancy" (underlined emphasis added). We recommend revising this claim to include this important information.

    - Page one includes the following presentation regarding the risk of TRYVIO:

- "You should get a pregnancy test one month after treatment with TRVYIO™."

This claim omits important REMS related risk information regarding the need for a pregnancy test one month following discontinuation of TRYVIO. The draft MG states that patients should also use "**acceptable birth control**… for one month after stopping TRYVIO, because the medicine may still be in your body" (bolded emphasis original, underlined emphasis added). We recommend revising these counseling points to include this important REMS related risk information.

- Page two of this REMS piece omits REMS related risk information concerning the role of a physician or gynecologist in counseling patients on acceptable birth control options while taking TRYVIO, as well as instructions on the appropriate way to change the form of birth control used. Specifically, the draft TRVYIO MG states:
  - "Talk with your (b) (4) or gynecologist (a (b) (4) who specializes in female reproduction) to find out about options for acceptable birth control that you may use to prevent pregnancy during treatment with TRYVIO."
  - "If you decide that you want to change the form of birth control that you use, talk with your (b) (4) or gynecologist to be sure that you choose another acceptable form of birth control."

  Additionally, as written, the current presentation of acceptable birth control methods on page two does not include the following information similar to the Prescriber Pharmacy Guide, "Patients must adhere to (at least) any one of the following four Options for contraception."

  We recommend revising this piece to include these REMS related risk information.

- TRYVIO REMS Prescriber and Pharmacy Guide
  - Risk
    - Page one includes the following presentations regarding the risk of TRYVIO:

      - "TRYVIO™ (b) (4) cause embryo-fetal toxicity if taken during pregnancy and should not be prescribed for a pregnant patient."
      - "… TRYVIO™ (b) (4) cause embryo-fetal toxicity when used during pregnancy, including use during **early pregnancy** (first trimester)." (bolded emphasis original)

This and similar claims within the REMS piece use the phrase "may" to communicate the following risk information found in the Boxed Warning of the draft TRYVIO PI, "**TRYVIO can cause major birth defects if used by pregnant patients."** (bolded emphasis original, underlined emphasis added). Therefore, these REMS pieces dissociate the risk of embryo-fetal toxicity from TRYVIO specifically. We recommend revising this piece and all REMS pieces to specify that TRYVIO can cause embryo-fetal toxicity.

- This REMS piece includes the following presentations regarding the risk for TRYVIO (underlined emphasis added):

  - "Counsel patients about acceptable contraception and about medical options in the event of unprotected sex or known or suspected contraceptive failure." (page two)
  - "Prescribers must counsel patients about acceptable contraception and about medical options in the event of unprotected sex or known or suspected contraceptive failure." (page three)

  Although we acknowledge the 'use of emergency contraception using the Patient Guide' is presented on page three, these presentations fail to specify the importance of the use of emergency contraception. We note that the draft TRYVIO PI includes the instruction to "educate and counsel patients who can become pregnant on the use of emergency contraception in the event of unprotected sex or contraceptive failure." We recommend revising these presentations to include this REMS related risk information.

- Page two includes the following presentation regarding the risk of TRYVIO:

  - "Remind patients about pregnancy testing before, during treatment, and for one month after discontinuing treatment."

  We note that the draft TRYVIO MG instructs patients to test for pregnancy "before (b) (4) treatment with TRYVIO, each month during treatment with TRYVIO, and one month after stopping TRYVIO." We recommend revising this presentation to be consistent with the draft MG.

- TRYVIO REMS Website
  - Risk
    - Page 11 of this REMS piece omits REMS related risk information that specifies which patients can become pregnant and a patient-

friendly definition of patients who can become pregnant on the first page of the "Patients" landing page within the REMS website. We acknowledge that this information is found later in the document on pages 40 and 41; however, we recommend revising this landing page to include this important REMS related risk information.

- Page 11 includes the following presentation regarding the risk of TRYVIO on the 'Patients' portion of the website:

  - "You must not become pregnant while taking TRYVIO™, or within one month after stopping TRYVIO™.

  This presentation omits the following important REMS related risk information from the draft TRYVIO MG (bolded emphasis original, underline emphasis added):

  "(b) (4) must not be pregnant when they <u>start taking TRYVIO</u> or become pregnant during treatment with TRYVIO."

  We recommend revising this REMS piece to include this important information.

- Page 15 includes the following presentations regarding the risk of TRYVIO on the 'Prescriber Knowledge Assessment' portion of the website:

  - "6. Before treatment with TRYVIO™, prescribers (b) (4) inform patients who can become pregnant:
    - a. (b) (4)
    - b. To report a missing menstrual period or any suspected pregnancy.
    - c. To have a pregnancy test before and monthly during treatment.
    - d. About the (b) (4) contraception and medical options in the event of unprotected sex or known contraceptive failure."

  Option B of Question 6 in the TRYVIO™ REMS Prescriber Knowledge Assessment fails to specify the complete monitoring parameters in which a patient should report potential pregnancy, and also minimizes the role of a provider in the TRYVIO REMS Program. The draft TRYVIO MG states (bolded emphasis original, underline emphasis added):

“ [redacted] (b) (4)

We recommend clarifying this important concept that patients who become pregnant should report not only a missing, but also a *delayed* menstrual period, *to their doctors* specifically.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 15, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217686
Product Name, Dosage Form, and Strength:	Tryvio (aprocitentan) tablets, 12.5 mg (b) (4)
Applicant/Sponsor Name:	Idorsia Pharmaceuticals, Ltd
TTT ID #:	2022-3103-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 29, 2024 for Tryvio. We reviewed the revised container labels and carton labeling for Tryvio and noted that the submitted revised carton labeling were not suitable for our review due to a (b) (4) displayed across the Principal Display Panel (PDP), which obstructed the view. Additionally, the carton labeling for the 30 count tablets contained the statement " (b) (4) " on the PDP. We sent an information request (IR) via email to Idorsia on January 31, 2024, requesting a clean copy of the revised draft carton labeling for our review as well as a (b) (4) Idorsia responded via email on January 31, 2024, stating that (b) (4) provides the specification information for the carton labeling and is not representative of what will be printed. Additionally, the Applicant confirmed that (b) (4) will not be printed on the carton. Thus, the Applicant submitted clean copies of the revised container labels and carton labeling received on February 2, 2024. We reviewed the clean revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective.

The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. The revised blister carton labeling is unclear that the strength is per single unit (tablet) and the Rx only statement on the blister container labels compete for prominence with other critical information on the label. Additionally, (b) (4)

3 RECOMMENDATIONS FOR IDORSIA PHARMACEUTICALS, LTD

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

A. General Comments (Container labels & Carton Labeling)

1. (b) (4)

B. Blister Carton Labeling

1. It is not immediately clear that the strength (i.e., 12.5 mg) is per single unit (tablet). Failure to clearly express the product strength per single unit may lead to wrong dose errors. We note that the top right of the Principal Display Panel (PDP) has been updated with the statement "(b) (4) ", which can be overlooked. We continue to recommend revising the boxed strength statements to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit compared to the total contents of the entire blister carton. For example, revise the boxed statement of strength from "12.5 mg" to "12.5 mg per tablet". See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

C. Blister Container Labels

1. The "Rx only" statement competes for prominence with other critical information (e.g., proprietary name, established name, strength) the blister labels. The "Rx only" statement should not compete in size and prominence with

[a] Kundreskas, J. Label and Labeling Review for Tryvio (NDA 217686). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JAN 12. TTT ID No.: 2022-3103.

critical information. We continue to recommend debolding the “Rx only” statement.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 2, 2024

Container Labels:

(b) (4)

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JODY K KUNDRESKAS
02/15/2024 08:35:45 AM

NICOLE F IVERSON
02/15/2024 02:55:51 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	January 12, 2024
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 217686
Product Name, Dosage Form, and Strength:	Tryvio (aprocitentan) tablets, 12.5 mg (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Idorsia Pharmaceuticals, Ltd
FDA Received Date:	December 19, 2022
TTT ID #:	2022-3103
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for Tryvio (aprocitentan) tablets, we reviewed the proposed Tryvio Prescribing Information (PI), Medication Guide, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, Medication Guide, carton labeling, and container labels for Tryvio tablets to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed PI, Medication Guide, carton labeling, and container labels that could be revised to improve clarity and readability of important information. For the Division, we recommend adding clarifying statements regarding storage conditions to the PI and Medication Guide and replacing "TRADENAME" with the conditionally acceptable proprietary name "TRYVIO". For the Applicant, we recommend strategic debolding on the carton labeling and container labels to improve visibility of important information, adding clarifying statements to the labels, and replacing "TRADENAME" with the conditionally acceptable proprietary name "TRYVIO". We provide specific recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI, Medication Guide, carton labeling, and container labels for Tryvio tablets may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. General Comments

1. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". We reference our March 16, 2023 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Tryvio, was found conditionally acceptable. We recommend replacing the placeholder "TRADENAME" with the conditionally acceptable proprietary name, Tryvio.

B. Prescribing Information

1. Highlights of Prescribing Information

a. The route of administration is not present. Failure to include the route of administration may result in wrong route errors. In the Dosage and Administration Section, we recommend adding the route of administration, "orally", to the statement "(b) (4) " so that it reads, "(b) (4) ".

2. Full Prescribing Information

a. Dosage and Administration Section

i. The route of administration is not present. Failure to include the route of administration may result in wrong route errors. In Section 2.1 we recommend adding the route of administration "orally" to the first sentence of this section.

b. How Supplied/Storage and Handling Section

i. The Storage and Handling Section is incongruent with the storage information on the carton labeling and container labels. Providing conflicting information may cause storage and handling errors. We recommend adding the statements "Dispense to patient in original container only. Replace cap securely each time after opening. Do not discard desiccant." after the sentence "Store in the original package.".

3. Medication Guide

a. The storage information is incongruent with the storage information on the carton labeling and container labels. Providing conflicting information may cause storage and handling errors. We recommend adding the statements "The TRYVIO bottle contains a desiccant packet to help keep your tablets dry (protect them from moisture). (b) (4) . Tightly close the TRYVIO bottle each time after opening." to the end of the second bullet under "How should I store TRADENAME?"

4.2 RECOMMENDATIONS FOR IDORSIA PHARMACEUTICALS, LTD

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

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our March 16, 2023 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Tryvio, was found conditionally acceptable. Replace all presentations of the placeholder "TRADENAME" with the conditionally acceptable proprietary name "TRYVIO" and use the intend to market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2. The "Rx only" and net quantity statements compete for prominence with other critical information (e.g., proprietary name, established name, strength) on the principal display panel (PDP). The "Rx only" and net quantity statements should not compete in size and prominence with critical information on the PDP. We recommend debolding the "Rx only", and net quantity statements.

B. Bottle Carton Labeling

1. We recommend including a statement to ensure pharmacists and end users are aware the product must be dispensed to the patient in the original container. We recommend revising the statement "Store in the original package." to "Store and dispense in the original package.".
2. The majority of the information presented on the side panels is bolded. Bolding information that is not unique may cause important information to be overlooked. We recommend you consider debolding all the information except for "Store and dispense in the original package. Do not discard desiccant. Protect from light and moisture." as this information is unique and should be bolded so that it is not overlooked.

C. Bottle Container Labels

1. We recommend including a statement to ensure pharmacists and end users are aware the product must be dispensed to the patient in the original container. We recommend revising the statement "Store in the original package." to "Store and dispense in the original package.".
2. The majority of the information presented on the side panels is bolded. Bolding information that is not unique may cause important information to be overlooked. We recommend you consider debolding all the information except for "Store and dispense in the original package. Do not discard desiccant. Protect from light and moisture." as this information is unique and should be bolded so that it is not overlooked.

3. The PDP is cluttered. Visually cluttered labels may cause important information to be overlooked. Consider relocating the statement "(b) (4) " to the side panel to reduce clutter on the PDP.

4. As currently presented, the codes "(b) (4)" and "(b) (4)" are located in close proximity to the lot number on (b) (4) 12.5 mg (b) (4) bottle labels, which could lead to confusion. Numbers or codes located in close proximity to the lot number may be mistaken as the lot number. Consider removing or relocating these codes, if space allows.

D. Blister Carton Labeling

1. It is not clear that the strength (i.e., 12.5 mg) is per single unit (tablet). Failure to clearly express the product strength per single unit may lead to wrong dose errors. We recommend revising the strength statements to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit compared to the total contents of the entire blister carton. For example, revise "12.5 mg" to "12.5 mg per tablet".

2. The "Rx only", "For Hospital Use Only", "Package Not Child Resistant", and net quantity statements compete for prominence with other critical information (e.g., proprietary name, established name, strength) on the PDP. These statements should not compete in size and prominence with critical information on the PDP. We recommend debolding these statements to reduce their prominence.

3. We recommend including a statement to ensure pharmacists and end users are aware the product must be dispensed in the original blister. We recommend revising the statement "Store in the original package." to "Store in the original package and blisters.".

4. The majority of the information presented on the back panel is bolded. Bolding information that is not unique may cause important information to be overlooked. We recommend you consider debolding all the information except for "Store in the original package and blisters. Protect from light and moisture." as this information is unique and should be bolded so that it is not overlooked.

E. Blister Container Labels

1. (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tryvio received on 12/19/2022 from Idorsia Pharmaceuticals, Ltd.

Table 2. Relevant Product Information for Tryvio	
Initial Approval Date	N/A
Active Ingredient	aprocitentan
Indication	TRADENAME, in combination with other antihypertensive drugs, is indicated for the treatment of hypertension, to lower blood pressure (BP) in patients who are not adequately controlled on other drugs.
Route of Administration	oral
Dosage Form	tablets
Strength	12.5 mg (b) (4)
Dose and Frequency	The recommended (b) (4) dose of TRADENAME is 12.5 mg orally once daily (b) (4)
How Supplied	TRADENAME tablets are available as: • 12.5 mg: yellow to orange round, film-coated tablet, debossed with “AN” on one side and plain on the other side. – NDC 80491-125-10, (b) (4) – NDC 80491-125-30, (b) (4) child-resistant closure (b) (4)
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package. Protect from light and moisture.
Container Closure	Bottles: White, opaque, high-density polyethylene (HDPE) 40 mL bottle with child-resistant closure and induction seal liner, containing a (b) (4) desiccant (2 × 1 g (b) (4)). Blisters: 10 units consisting of:

	• Aluminum (b) (4) • Aluminum push-through lidding film

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 23, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, ‘Tryvio’, ‘aprocitentan’, ‘NDA 217686’ and ‘IND 122772’. Our search identified no previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Container label received on December 19, 2022
- Carton labeling received on December 19, 2022
- Prescribing Information (Image not shown) received on December 19, 2022, available from \\CDSESUB1\EVSPROD\nda217686\0001\m1\us\114-labeling\draft\labeling\proposed.pdf
- Medication Guide received on December 19, 2022, available from \\CDSESUB1\EVSPROD\nda217686\0001\m1\us\114-labeling\draft\labeling\proposed.pdf

G.2 Label and Labeling Images

(b) (4)

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

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JODY K KUNDRESKAS
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Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	217686
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Aprocitentan
Indication	Hypertension
Applicant	Idorsia Pharmaceuticals Ltd
Requesting Division	Division of Cardiology and Nephrology (DCN)
Primary Reviewer	Ling Lan, MD, PhD Clinical Analyst, DILI Team, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Other Reviewers	Edwige Chiogo Vouffo, PharmD, PhD Non-clinical analyst, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	George Makar, MD, MSCE Deputy Director (Acting), OND/DHN
Assessment Date	Sept 12, 2023

Context: Aprocitentan (APT) is an oral (12.5 (b) (4) mg/day), endothelin receptor antagonist (ERA) binding both endothelin receptor A (ET_A) and B (ET_B) leading to vascular relaxation and lower blood pressure. This NDA is for the treatment of inadequately controlled primary hypertension. Other ERAs have potential for hepatotoxicity, including bosentan approved for pulmonary hypertension in 2001 and sparsentan approved for IgA nephropathy in 2023; both have box warnings for drug-induced liver injury (DILI) risk. However, two other marketed ERAs have less hepatotoxicity risk, with hepatotoxicity language in Warnings and Precautions only or no labeling for significant DILI risk at all. Elevations in aminotransferases greater than three times upper limit of normal (ULN) were noted in the APT trials, but injury with jaundice was not observed. The Division of Cardiology and Nephrology (DCN) requested the Division of Hepatology and Nutrition (DHN) DILI Team assess the NDA for liver safety and proposed labeling. DCN also seeks opinion on potential need for a risk evaluation and mitigation strategy (REMS).

Executive Summary: We do not see a DILI risk that would preclude approval. APT can cause liver injury, but the injuries seen in this NDA were modest and reversible. The lack of hyperbilirubinemia attributable to APT and relatively high number exposed are encouraging. Nonetheless, the number of people in the US with inadequately controlled hypertension is far greater than the number of APT exposed subjects in this NDA, and a liver injury of clinical significance could arise with wide-spread, post-market use. We do not recommend a box warning or REMS, but labeling should include language

regarding liver injury risk in the Warnings and Precautions section. Our full assessment and detailed recommendations are in Section 5.0.

Consultation Sections:

Section 1.0 Target Disease and Rationale
Section 2.0 ADME pertinent to DILI
Section 3.0 Non-clinical data pertinent to DILI
Section 4.0 Clinical data
Section 5.0 Assessment & Recommendations
Appendix: APT metabolic pathways, study schema and events schedules

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Abbreviations:
ADME: absorption, distribution, metabolism, excretion
ALP or AP: alkaline phosphatase
ALT: alanine aminotransferase
APT: aprocitentan
AST: aspartate aminotransferase
AT: aminotransferase (ALT and/or AST)
BMI: body mass index
CPK or CK: creatine phosphokinase
CYP: cytochrome P450
DB: direct bilirubin
DDI: drug-drug interaction
DILI: drug-induced liver injury
ERA: endothelin receptor antagonist (ERA)
ET: endothelin
ET_A and ET_B: endothelin receptor A and B
MACE: major adverse cardiovascular events
R-value: ALT/ULN ÷ ALP/ULN
REMS: risk evaluation and mitigation strategy
TB: total bilirubin
ULN: upper limit of normal

1.0 Target Disease and Rationale

1.1 Target Disease: Primary hypertension is typically defined as chronic systolic blood pressure over 129 mmHg or diastolic pressure over 79 mmHg without obvious cause.[1] The pathogenesis is unclear, but several mechanisms are probably involved including increased salt absorption resulting in volume expansion, altered renin-angiotensin-aldosterone response, and increased sympathetic nervous activation. These mechanisms increase peripheral resistance and cardiac afterload.[2] Both genetic and

[1] https://www.uptodate.com/contents/overview-of-hypertension-in-adults?search=hypertension&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H9
[2] Iqbal and Syed. Essential hypertension. StartPearls, 2022, https://www.ncbi.nlm.nih.gov/books/NBK539859/

environmental factors are likely involved. For example, increased salt intake and genetically determined abnormal response to a salt load may increase the risk of hypertension.

The number of people between 30-79 years old with hypertension increased from 650 million to 1.8 billion in the last 30 years. In 2019, more than one billion people with hypertension (82% of all people with hypertension worldwide) lived in low- to middle-income countries. An estimated 580 million people with hypertension (41% females and 51% males) are unaware of their condition.[3] Hypertension is associated with major adverse cardiovascular events (MACE).

There are many treatment options for hypertension. Lifestyle modification is advised for all patients.[4] Medications include thiazide-type diuretics, calcium channel blockers, angiotensin-converting enzymes inhibitors, and angiotensin II receptor blockers. Endothelin receptor antagonists (ERAs) are a more recent drug class to enter the market, but the three approved ERAs are for pulmonary hypertension or IgA nephropathy. Aprocitentan (APT) would be the first for primary hypertension.

1.2 Rationale: APT is an oral, dual endothelin (ET) receptor antagonist of both ET_A and ET_B receptors (**Figure 1**). The ET system is involved in controlling vascular tone. ET dysregulation can lead to hypertension, especially salt-sensitive or volume-dependent types that are common in difficult-to-control cases. The Sponsor proposes that APT could be added to other anti-hypertensive drugs, providing an additional mode of action for lowering blood pressure.[5]

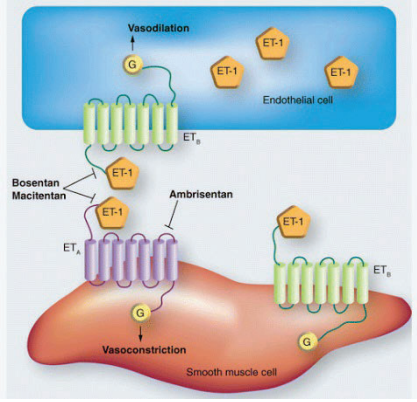

Figure 1: Mechanism of action for ERAs including aprocitentan[6]

2.0 ADME and DDI data pertinent to DILI

2.1 Structure: (**Figure 2**)

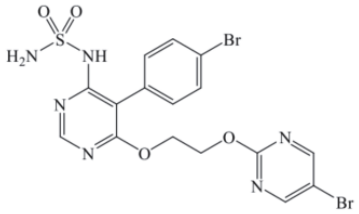

Figure 2: Chemical structure of APT[7]

2.2 Absorption: Aprocitentan (APT) was well absorbed in dogs with a 90% oral bioavailability at clinically relevant doses (0.2-0.3 mg/kg). Slow absorption was noted in rat studies, and the mean bioavailability was

[3] WHO. More than 700 million people with untreated hypertension. 2021
[4] https://www.uptodate.com/contents/overview-of-hypertension-in-adults/print#H27
[5] NDA217686 (217686 - 0003 - (3) - 2023-01-31 - ORIG-1 /Clinical Pharmacology/Response To Information Request) - Nonclinical Overview (#6)
[6] Smith et al. Targeted therapies: endothelin receptor antagonists. Future Medicine. 2013, https://doi.org/10.2217/ebo.13.239
[7] NDA217686 (217686 - 0011 - (11) - 2023-03-24 - ORIG-1 /Quality/Response To Information Request) - Introduction (#2)

41% at higher doses (3 mg/kg). Peak levels occurred in 6-8 hours with quantifiable plasma concentrations 56 hours post dose. Aprocitentan plasma exposure at higher doses decreased after repeated dosing in rats, but the decrease was less consistent in dogs. Hence, APT is well absorbed in dogs with good oral bioavailability. Drug accumulation with repeated doses did not occur.

2.3 Distribution: After oral dosing, total radioactivity of APT was widely distributed in rats. Liver and kidney were among the organs with highest concentrations. However, plasma protein binding was substantial at 98.3 to 99.9% across species (rat, mouse, rabbit, dog, and human, leading to low mean free fraction (0.5% to 1.7%). Thus, APT is highly protein bound, distributed widely but at low tissue concentrations relative to plasma. The liver had higher concentrations compared to most other organs.

2.4 Metabolism: APT is predominantly metabolized via uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase or UGT1) and not the CYP system. In humans, metabolism is primarily by hydrolysis and glycosylation leading to fourteen metabolites (**Appendix**). Parent drug was the most prominent component in rat plasma with M1 being the only metabolite reaching 5% of total compounds found. M1 was subsequently metabolized into M2 and M5 via flavin-containing monooxygenase (FMO)-dependent reactions. M3 was catalyzed by UGT1 and UGT2B7. No substantial concentrations of metabolites were observed in human circulation. Hence, APT is extensively metabolized, but the parent drug is by far the most prominent detectable form. The CYP P450 system is minimally involved.

2.5 Excretion: In rats, APT was excreted in feces and urine with the overall excretion exceeding 88% by 72 hours. Terminal half-life was 8.2 to 9.2 hours in rats and 5 to 11 hours in dogs. In human studies, renal elimination accounted for 52% of the radioactive dose with 25% recovered in feces. Unchanged APT was 6.8% and 0.2% of the radioactive dose in feces and urine respectively. Hence, aprocitentan is eliminated via feces and urine and has a terminal half-life of less than 11 hours in animal studies. Despite parent compound being predominant in plasma, excretion is mostly via metabolites. There was minor enterohepatic recirculation.

2.6 DDI*:* APT is predominantly metabolized via UGT related pathways and not the CYP system. Several drugs including diclofenac, naproxen and benzodiazepines inhibit UGT in vitro,[8] but at least one study suggests such interactions may not be clinically relevant due low levels of inhibition.[9] Metabolism of APT's main metabolite (M1) is FMO dependent which may be affected by inhibitors such as methimazole.[10] However, FMO inhibitors are less numerous than CYP inhibitors. Indeed, FMO metabolism is

[8] Grancharov K, et al. Natural and synthetic inhibitors of UDP-glucuronosyltransferase. *Pharm Thera.* 2001; 89:171-186.
[9] Williams JA, et al. Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed lower exposure (AUCi/AUC) ratios. *Drug Met Disp*. 2004; 32:1201-1208.
[10] Phillips IR, et al. Drug metabolism by flavin-containing monooxygenases of human and mouse*. Exp Op Drug Met Tox.* 2017; 13:167-181.

sometimes seen as a potential advantage in drug development due to less DDI risk.[11] Overall, we do not anticipate DDI that would increase the risk of hepatotoxicity due APT.

High level summary ADME and DDI findings related to DILI risk are in **Table 1**.

Table 1: ADMET summary table[12]

Item	Finding
Absorption	Slow but good oral absorption
Distribution	High protein binding; wide distribution but at low concentrations
Metabolism	Extensive, but not by p450 (CYP); UGT and FMO dependent
Elimination	Urine and feces; half-life: 8-9 hours in rats and 5-11 hours in dogs
DDI	No significant DDI relevant to APT hepatotoxicity expected

3.0 Non-clinical data

3.1 In vitro data: APT inhibited several transporters including OAT1, OAT3, and BCRP, but not BSEP or MDR2. All human metabolites were found in rat and dog making these two animal models relevant for safety assessment. We found no in vitro experiments addressing reactive metabolite formation, mitochondrial toxicity, or hepatocyte toxicity.

3.2 Animal data: NOAEL was 50 mg/kg/day in a 26-week rat study and 5 mg/kg/day in a 39-week dog study. APT's maximum clinical dose is (b) (4) for a US adult male (average weight, 91 kg) and female (average weight, 78 kg), respectively.[13]

3.2.1 *Liver enzymes*: In a 4-week oral dog study, ALP and bile acids increased mildly at 250 mg/kg/day. Increased ALP also occurred in a 13-week oral exposure, and aminotransaminases sporadically increased with 39-week oral dosing. Slight ALT increases occurred in a 26-week oral exposure in rats. Overall, enzyme elevations were mild without hyperbilirubinemia.

3.2.2 *Histology*: In rats, dose-dependent centrilobular hepatocellular hypertrophy occurred in most animals. Increased liver weights, hepatocellular hypertrophy occurred at ≥10 mg/kg/day. Minimal hepatocellular focal necrosis occurred in one rat of each high dose group. Degeneration of hepatocytes with occasional apoptosis occurred mostly in centrilobular regions at 250 mg/kg/day after 26-weeks oral exposure. Hepatocellular vacuolar necrosis and multinucleated hepatocytes also occurred at 250 mg/kg/day.

In dogs, hypertrophy, and increased liver weight but no apoptosis, degeneration, or necrosis occurred at 250 mg/kg/day following a 13-week and a 39-week oral exposure.

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[11] Cashman JR. Role of flavin-containing monooxygenase in drug development. *Exp Op Drug Met Tox*. 2008; 4:1507-1521.
[12] Table made by DILI Team
[13] https://www.cdc.gov/nchs/fastats/body-measurements.htm

For both rats and dogs, increase in liver enzymes often coincided with histology changes. All the findings were fully reversible after the treatment free period in all the above studies.

High level summary of non-clinical data is in **Table 2.**

Table 2: Non-clinical data summary table[14]

Item	Finding
In Vitro Studies	
Major CYPs or other metabolism routes	UGT and FMO dependent; not CYP dependent
Reaction metabolites (i.e., glutathione trapping)	Not done
Mitochondria studies/inhibition	Not done
Time dependent inhibition	No
LogP	2.7 (> 3.0 associated with increase DILI risk)
Covalent binding	Not done
Transporter (BSEP or MRP2 inhibition)	No inhibition of BSEP or MRP2
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	Mild increases in transaminases and ALP
Liver histopathology findings (animal species)	Centrilobular hypertrophy and minimal hepatocellular necrosis; reversible

Overall, the non-clinical data for DILI are mixed but suggest moderate risk for DILI. Low lipophilicity (LogP 2.7), low daily dose, minimal increase in liver analytes and reversible histologic changes in animal studies support a lower risk. However, the histopathologic findings included hepatocellular necrosis (albeit mild), and timely discontinuance with reversibility may not always occur in clinical practice. Also, reactive metabolite formation and mitochondrial injury studies were not done. Lastly, chronic damage with ongoing use is not addressed in non-clinical studies. Substantial DDI relevant to DILI risk is not anticipated.

4.0 Clinical data:

4.1 In class or near class data: There are DILI concerns with endothelin receptor antagonists (ERAs). Three ERAs (bosentan, ambrisentan, macitentan) are approved for pulmonary hypertension. Sparsentan was recently approved for IgA nephropathy. The DILI Team consulted on the sparsentan NDA 216403 but not the others.[15] Labeling language regarding hepatotoxicity for these four ERAs varies widely (**Table 3**). LiverTox® reports that ERAs have been associated with a low, but appreciable rate of serum enzyme elevations during therapy that are generally transient and mild but can cause mild symptoms and require dose modification or discontinuation.[16] Rare instances of clinically significant liver injury are reported.

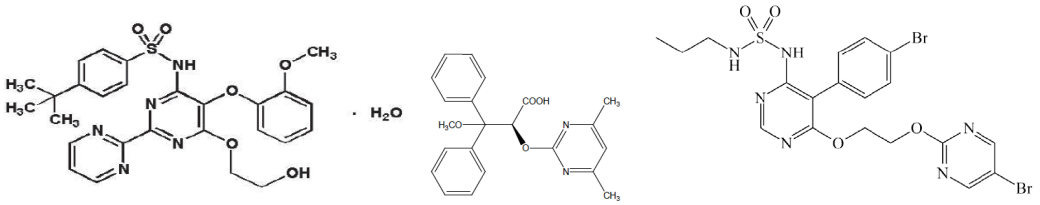
Table 3: DILI labeling and LiverTox assessment for four approved ERAs.

[14] Table made by DILI Team
[15] (Open DARRTS home page to enable link to work.)
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80687781
[16] LiverTox: https://www.ncbi.nlm.nih.gov/books/NBK548723/ accessed on July 29, 2022

ERA (yr. approved)	Indication	Liver injury related labeling	LiverTox®[6]
Bosentan (2001)	Pulmonary hypertension	**Box warning** Warnings and precaution: Check baseline tests and monthly thereafter	7-8% AT elevation; 3-4% drug stop; rare jaundice. Latency 1-6 mo. Likelihood score: C
Ambrisentan (2007)	Pulmonary hypertension	None	0-3% AT elevation; rare severe injury Latency 1-6 mo. Likelihood score: E
Macitentan (2013)	Pulmonary hypertension	Warning and precaution: Check baseline liver tests and monitor as indicated.	0-4% AT elevation; rare clinically significant elevation Latency 1-6 mo. Likelihood score: E*
Sparsentan (2023)	IgA nephropathy	**Box warning** Warning and precaution: Check baseline liver tests and monthly for 12 months	Not yet reviewed

AT = aminotransferase (ALT and/or AST)
LiverTox Likelihood score: C = probably linked to liver injury; E = unlikely cause of liver injury; E* = suspected but unproven (e.g., newly approved without extensive post-market experience)

The structural formulas for the ERAs are varied but share some characteristics such as multiple benzene and/or pyrimidine rings (**Figure 3**).



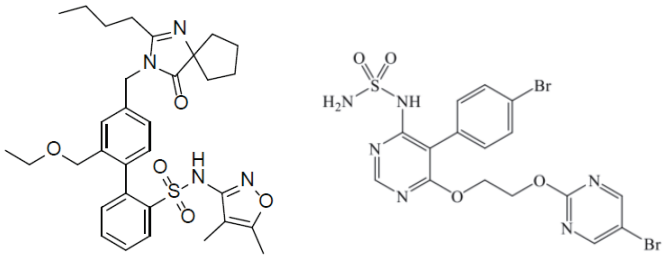


Figure 3: Structural formulas for ERAs
Source: package inserts for bosentan, ambrisentan, macitentan and sparsentan.

[17] NDA217686 (217686 - 0011 - (11) - 2023-03-24 - ORIG-1 /Quality/Response To Information Request) - Introduction (#2)

4.2 Study protocol(s): The aprocitentan (APT) clinical program included ten phase 1 studies, one phase 2 study (Study 201) and one phase 3 study (Study 301). This NDA did not include study level data for each phase 1 study. The Sponsor responded to the DILI Team's information request on March 3, 2023, and adequately clarified that there was no APT related aminotransaminase elevations or jaundice cases in 545 healthy volunteers. Therefore, sections 4.2 and 4.3 focus on Studies 201 and 301 only.

4.2.1 *Study 201* (*Phase 2*): *A multi-center, double-blind, double dummy, randomized, placebo- and active-reference, parallel group, dose-finding study with ACT-132577 in subjects with essential hypertension (Grade 1 and 2)*. This study included four different doses of daily APT versus placebo randomized 1:1:1:1:1 with about 80 subjects in each arm (n = 408; **total exposed to APT = 326**). The study periods included an 8-week double-blinded treatment period followed by a 2-week single-blinded all placebo withdrawal period and a 30-day safety follow up period. Study schematic and events schedule are in the **Appendix**.

Inclusion/exclusion criteria related to liver: Subjects with ALT or AST > 3 × ULN are excluded. Otherwise, there were no liver specific exclusion criteria.

Liver safety plan (study-specific criteria for interruption or premature discontinuation of study treatment included liver aminotransferase abnormalities):

- ALT and/or AST ≥ 3 and ≤ 8 × ULN (interruption of study treatment): Re-test of aminotransferases (ALT and AST), TB, DB and ALP within 48 h was to be done. If the AST and/or ALT elevation was confirmed by the re-test, the re-introduction of study treatment was not to be considered.
- ALT and/or AST > 8 × ULN, ALT and/or AST ≥ 3 × ULN with clinical symptoms of liver injury, ALT and /or AST ≥ 3 × ULN with TBIL ≥ 2 × ULN: Permanent discontinuation of study treatment was to be done. Other diagnoses (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus) and/or etiologies (e.g., acetaminophen-related liver toxicity) were to be addressed by appropriate evaluation testing.

4.2.2 *Study 301 (Phase 3): Multi-center, blinded, randomized, parallel-group, study with aprocitentan in subjects with resistant hypertension (RHT)*. This is a multi-center, randomized, parallel-group, blinded study in 2047 adult RHT subjects. This trial included a 4-week double-blinded period (Part 1) with a randomization ratio of 6:1:2 for daily APT 25 mg, 12.5 mg and placebo arms (n = 1259:243:545; **total exposed to APT = 1502**), respectively. All subjects then entered a single blinded 32-week (Part 2) single arm, 25 mg dose period, followed by a 12-week (Part 3) double-blinded withdrawal period that re-randomized subjects to 25 mg/day or placebo, and ended with a 30-day open label safety follow up period. Study schematic and events schedule are in the **Appendix.**

Inclusion/exclusion criteria: Subjects with ALT or AST > 3 × ULN or severe hepatic impairment were excluded. There were no other liver specific exclusions.

Liver safety plan (study-specific criteria for interruption or premature discontinuation of study treatment included liver aminotransferase abnormalities):

- ALT and/or AST ≥ 3 and ≤ 8 × ULN (interruption of study treatment);
- ALT and/or AST > 8 × ULN, ALT and/or AST ≥ 3 × ULN with clinical symptoms of liver injury, ALT and /or AST ≥ 3 × ULN with TBIL ≥ 2 × ULN (permanent discontinuation of study treatment).
- Aminotransferases, total and direct bilirubin, and alkaline phosphatase levels were to be monitored weekly after study treatment interruption/discontinuation until values return to pre-treatment levels or within normal ranges.

4.3 Study level data

4.3.1 *eDISH/cholestatic plots*

Based on hepatocellular scatterplots (eDISH), there was no imbalance in liver analytes nor cases concerning for significant liver injury in Study 201 (**Figure 4**) and no imbalance in liver analytes during the 4-week double-blinded placebo-controlled phase in Study 301 (**Figure 5**). DILI adjudication of high interest cases identified two highly likely and two possible hepatotoxicity cases attributable to APT (See Section 4.4 for details).

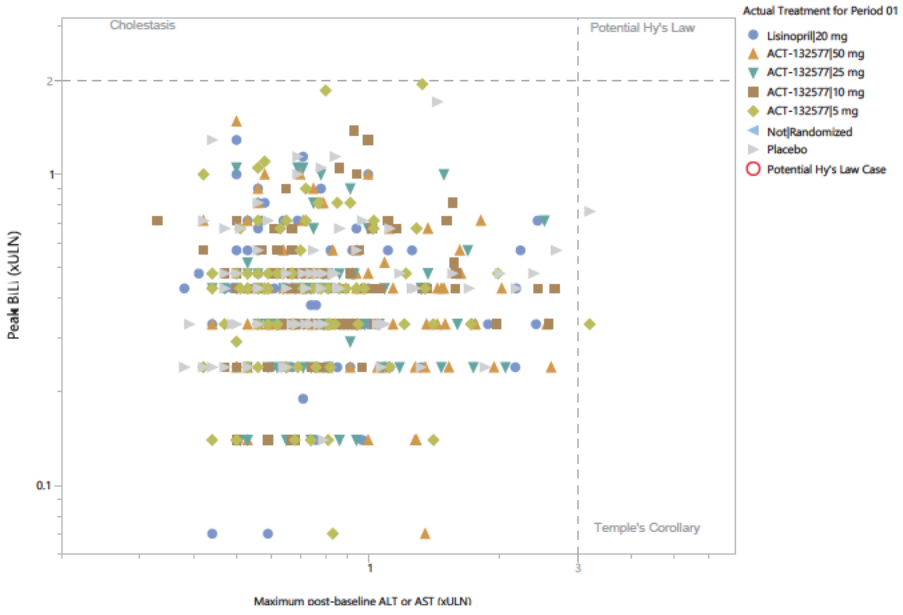


Figure 4: Study 201 (phase 2) eDISH Plot
Source: BIRRS Team using JMP Clinical

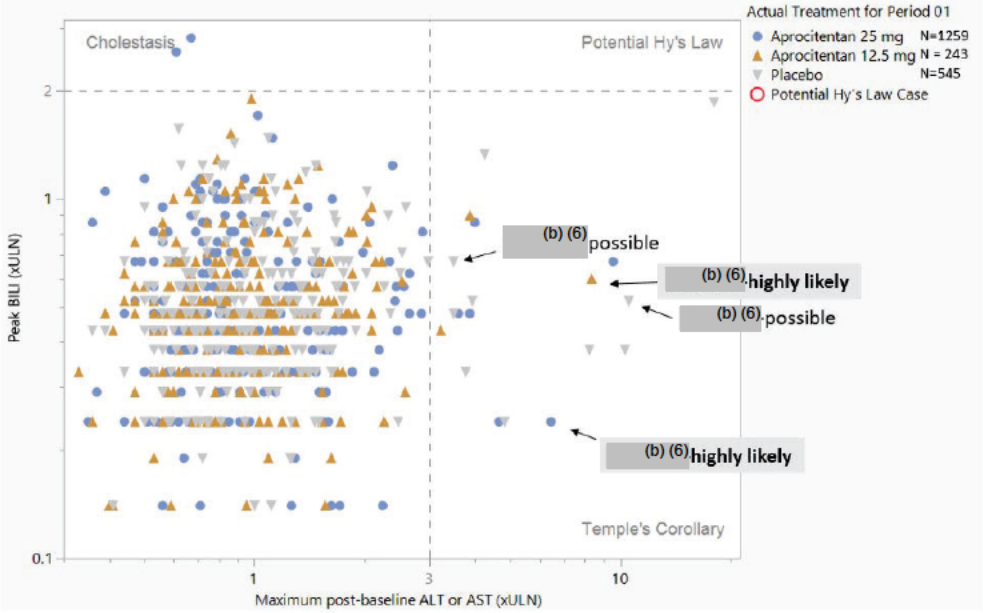


Figure 5: Study 301 eDISH Plot Source: DILI Team based on BIRRS Team's JMP Clinical result

4.4 Case level analyses

4.4.1 *Summary of cases*: We assessed seventeen cases for attribution to APT. These cases included all subjects in Temple's Corollary quadrant of Study 301 eDISH (**Figure 5**) plus subjects identified by liver related adverse event MeDRA terms. Two subjects had highly likely DILI due to APT based on positive rechallenges (See Section 4.2 for details). Two subjects were considered possible and thirteen unlikely DILI due to APT. Alternate diagnoses were varied (**Table 4).** DILI latencies tended to be long (**Table 5).**

Table 4: All adjudicated cases[18]

#	ID	Causality Score*	Alternate diagnosis	Study	Age (yr)	Sex	Race	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)~	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)**
1	(b) (6)	2	NA	ID-080A301	36	F	White	No	139	[8]	220	80	104	0.29	6.47
2		2	NA	ID-080A301	63	F	White	No	205	[4]	284	210	366	0.7	2.37
3		4	Unknown	ID-080A301	32	F	White	No	107	1	119	60	104	0.82	3.50
4		4	Hepatitis B	ID-080A301	54	M	Asian	No	84	[59]	454	158	104	0.53	13.35
5		5	Myopathy	ID-080A301	69	M	White	No	NA	NA	NA	NA	NA	NA	NA
6		5	MAFLD	ID-080A301	55	M	White	No	26	[9]	105	117	104	0.58	3.09
7		5	Myopathy	ID-080A301	31	M	White	No	258	NA	NA	NA	NA	NA	NA
8		5	Infection	ID-080A301	63	F	White	No	279	[6]	280	83	124	0.29	6.91
9		5	Spurious lab	ID-080A301	73	M	White	No	-1	NA	NA	NA	NA	NA	NA
10		5	Myopathy	ID-080A301	37	M	White	No	228	[79]	NA	NA	NA	NA	NA
11		5	Unknown	ID-080A301	42	M	White	No	310	65	NA	NA	NA	NA	NA
12		5	Fatty liver	ID-080A301	70	M	White	No	78	[6]	149	89	104	1.17	4.38
13		5	Unknown	ID-080A301	66	F	White	No	160	[169]	NA	NA	NA	NA	NA
14		5	Unknown	ID-080A301	73	F	White	No	260	[77]	44	53	540	0.47	0.25
15		5	Unknown	ID-080A301	45	M	White	No	280	38	167	111	104	0.76	4.91
16		5	Methotrexate	ID-080A301	66	F	White	No	-1	NA	NA	NA	NA	NA	NA
17		5	Unknown	ID-080A301	72	M	White	No	367	33	NA	NA	NA	NA	NA

NA = not available or not applicable (e.g., obvious non-DILI etiology found; timing inconsiestent with DILI)
MAFLD = metabolic associated fatty liver disease (formerly NAFLD)
R-value = (ALT/ULN) ÷ (AP/ULN); R > 5: hepatocellular; R between 2 & 5 mixed; R < 2 cholestatic
***Causality score for DILI attributable to APT: 1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate**
^For purposes of R-value calculations, the ULN (104) was imputed if AP never rose to > ULN
** ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL
~[ ] day values means the drug continued for that many days *after* injury onset.

[18] Table made by DILI Team

Table 5: At least possible DILI[19]

ID	Causality Score*	Alternate diagnosis	Study	Age (yr)	Sex	Race	Symptoms	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)~	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)**
(b) (6)	2	NA	ID-080A301	36	F	White	No	No	139	[8]	220	80	104	0.29	6.5
	2	NA	ID-080A301 (SB part 2)	63	F	White	No	No	205	[4]	284	210	366	0.7	2.4
	4	Unknown	ID-080A301	32	F	White	No	No	107	1	119	60	104	0.82	3.5
	4	Hepatitis B	ID-080A301 (SB part 2)	54	M	Asian	No	No	84	[59]	454	158	104	0.53	13.4
								Max	*205*	*1*	*454*	*210*	*366*	*0.82*	*13.4*
								Min	*84*	*[59]*	*119*	*60*	*104*	*0.29*	*2.4*

NA = not applicable
R-value = (ALT/ULN) ÷ (AP/ULN); R > 5: hepatocellular; R between 2 & 5 mixed; R < 2 cholestatic
*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate
^For purposes of R-value calculations, the ULN (104) was imputed if AP never rose to > ULN
** ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL
~[ ] day values means the drug continued for that many days *after* injury onset. Thus, the *minumum* latency after drug stop is the highest bracketed number.

4.4.2 *Cases of Interest*: We discuss the two cases with highly likely hepatotoxicity due to APT below.

1. Subject (b) (6); Study ID-080A301: (Highly likely DILI due to APT)

Summary: This is a 63-year-old female, white, with hypertension who developed elevated liver enzymes approximately 205 days after starting aprocitentan (APT). Dose was 12.5 mg daily in part 1 followed by 25 mg daily in part 2 and part 3. She enrolled in (b) (6).

At baseline, her BMI was 41 kg/m^2. Relevant medical history, besides the target disease, included dyslipidemia ((b) (6)), hyperuricemia ((b) (6)), autoimmune thyroiditis-hypothyroidism ((b) (6)), and osteoarthritis ((b) (6)). Alcohol history was not provided. Concurrent medications relative to DILI risk included atorvastatin (20 mg/d; no start date provided). The subject's ALT, AST, AP, and TB were 26 U/L, 24 U/L, 72 U/L, and 0.18 mg/dL, respectively.

The subject started APT on (b) (6) (Day 1). On (b) (6) (Day 27) the study drug dose was changed to 25 mg/day. Liver analytes were normal. On (b) (6) (Day 189), atorvastatin dose increased to 40 mg/day.

On (b) (6) (Day 206; 17 days after statin increase and 179 days after APT increase), ALT, AST, AP, and TB were 284 U/L, 210 U/L, 366 U/L and 0,5 mg/dL, respectively. CK was normal. The subject had no symptoms. The study drug continued without change, but atorvastatin was stopped. On (b) (6) (Day 210), ALT and AST and AP and TB were still up at 235 U/L, 186 U/L, 272 U/L and 0.5 mg/dL, respectively. The subject still had no symptoms. The APT was held that day. Liver tests fell to normal or near normal by (b) (6) (Day 223).

[19] Table made by DILI Team

On [redacted] (b) (6) (Day 253), she re-randomized (part 3 of study) and re-started APT at 25 mg/day. On [redacted] (b) (6) (Day 312; 61 days after re-challenge), ALT and AST were back up at 136 U/L and 83 U/L, respectively. AP rose as well but remained <ULN. TB remained normal throughout. ALT and AST climbed a bit further, and APT was permanently stopped on [redacted] (b) (6) (Day 316). ALT and AST had second peaks of 200 and 132 U/L on [redacted] (b) (6) (Day 328). Thereafter, liver analytes improved with >50% decline from this second peak within twelve days (**Figure 6**). Return to baseline had not yet occurred at last follow-up. Ultrasound showed steatosis, but no obvious etiology for acute liver injury. No viral tests reported. Autoimmune markers were not done. IgG level was not reported.

APPEARS THIS WAY ON ORIGINAL

Figure 6: Liver enzymes and bilirubin by study day for Subject [redacted] (b) (6) [20]

Assessment: We assessed this case as highly likely DILI due to APT because the positive rechallenge strongly suggesting a causal relationship with APT and not the statin. The statin was not restarted. The latencies from APT start, dose increase and rechallenge were 208, 179 and 61 days, respectively. The shorter latency on rechallenge would be consistent with DILI. Both rises in aminotransferases declined to normal or near normal with holding APT. We note that evaluation testing was limited, and so recurrent infection or passage of gallstones could compete. Her sex and obesity increase her risk of gallstones. However, she was asymptomatic, and ultrasound did not report gallstones. The Sponsor suggests the first enzyme peak was due to the statin and the second due to steatosis found on ultrasound. We do not agree. The more logical explanation is a positive APT rechallenge. Her BMI was 40 kg/m^2 at baseline, and there was no mention of marked weight gain followed by weight loss with the second peak. The steatosis is likely chronic and irrelevant to the acute injury.

2. Subject [redacted] (b) (6); Study ID-080A301: (Highly likely DILI due to APT)

Summary: This is a 36-year-old female, white, with hypertension who developed elevated aminotransferases 139 days after starting APT. Dose was 25 mg/day.

[20] NDA217686 (217686 - 0004 - (4) - 2023-02-09 - ORIG-1 /Clinical/Response To Information Request) - Response to 30 January 2023 Request for Information (#26)

At baseline, the subject's BMI was 28 kg/m^2. Relevant medical history included just the targeted disease. Alcohol history was not provided. Concurrent medications relative to DILI risk were nil. The subject's ALT, AST, AP, and TB were 24 U/L, 17 U/L, 50 U/L, and 0.2 mg/dL, respectively.

The subject started APT on [redacted] (b) (6) (Day 1). On [redacted] (b) (6) (Day 140), ALT, AST, AP, and TB were 145 U/L, 75 U/L, 54 U/L and 0.29 mg/dL, respectively. CK was normal. No symptoms were mentioned. The study drug continued without change. On [redacted] (b) (6) (Day 147), ALT and AST peaked at 220 U/L and 80 U/L, respectively. Still no symptoms were mentioned. The study drug was held the next day. The liver enzymes fell to normal or nearly normal by [redacted] (b) (6) (Day 196). On that day, APT was restarted at 25 mg/day. However, on [redacted] (b) (6) (Day 240, and 44 days after re-challenge), ALT and AST were 78 and 37 U/L, respectively. AP and TB remained <ULN throughout both aminotransferase elevations. APT was stopped on [redacted] (b) (6) (Day 247). ALT and AST rose to second peak of 114 and 49 on [redacted] (b) (6) (253). Thereafter, ATs improved with >50% decline from second peak occurring within 27 days, and AST was back to normal. (**Figure 7**) ALT return to baseline had not yet occurred at last follow-up. Evaluation testing was not done.

Figure 7: Liver enzymes and total bilirubin by study day for Subject [redacted] (b) (6) [21]

Assessment: We assessed this case as highly likely DILI due to APT because the positive rechallenge strongly suggesting a causal relationship. The latencies from APT start and from rechallenge were 140 and 44 days, respectively. The shorter latency on rechallenge would be consistent with DILI. Both rises in aminotransferases declined to normal or near normal with holding APT. We note that evaluation testing was limited, and so recurrent infection or passage of gallstones could compete. However, she was asymptomatic. The Sponsor wrote there was an "absence of apparent confounding

[21] NDA217686 (217686 - 0004 - (4) - 2023-02-09 - ORIG-1 /Clinical/Response To Information Request) - Response to 30 January 2023 Request for Information (#35)

factors" and that attribution to APT could not be "ruled out." We agree that there were no obvious competing etiologies but felt the positive rechallenge was highly suggestive a hepatotoxicity due to APT.

5.0 Assessment & Recommendations

5.1 Assessment: Aprocitentan (APT) is oral, endothelin receptor antagonist (ERA) binding both ET_A and ET_B receptors in vascular endothelium. Blocking of these receptors leads to decreased vascular tone, lowering blood pressure. APT is dosed at 12.5 (b) (4) mg daily and being considered for long term treatment of inadequately controlled primary hypertension. It would be the first ERA for this indication, but four other ERAs are approved for pulmonary hypertension or IgA nephropathy. These four ERAs carry varying hepatotoxicity risk from well-established DILI requiring box warnings (e.g., bosentan) to minimal risk without labeling (e.g., ambrisentan). Elevations in aminotransferases without hyperbilirubinemia occurred in the APT pivotal, phase 3 trial, and DCN requested the DILI Team's opinion on overall DILI risk, labeling, and necessity for a REMS.

Non-clinical data for APT liver injury are mixed, but overall suggest a modest DILI risk. Mechanism of such an injury is unclear due to no data on reactive metabolite formation or mitochondrial toxicity. Nevertheless, modest liver enzyme elevations and histologic changes including some hepatocyte necrosis occurred in animals. These changes were all reversable. Low lipophilicity, low clinical daily dose and lack of transporter inhibition associated with DILI argue for a lower risk.

Study level data did not support a substantial DILI risk. There was no imbalance in liver analytes between APT and placebo exposure, but the randomized periods for comparison were relatively short at four to eight weeks. Latencies for other ERA hepatotoxicity can be several months. There were no cases of jaundice and hence no Hy's Law or cholestatic jaundice cases across all study periods. The total number exposed in the phase 2 and 3 studies combined was moderately sized at nearly 2000.

In contrast to study level data, case level analysis established APT's potential to cause liver injury. There were two subjects with highly likely APT related liver enzyme elevations. Both subjects had positive rechallenges. One subject had potential hepatocellular injury (i.e., predominantly aminotransferase elevation) while the other had a mixed injury (i.e., both aminotransferase and alkaline phosphatase elevation). The enzyme elevations were modest without hyperbilirubinemia and resolved or nearly resolved at last follow-up upon APT.

Overall, we do not see a DILI risk that would preclude approval. APT probably caused some liver injuries, but these was modest and reversible in this NDA. The lack of hyperbilirubinemia attributable to APT and relatively large phase 3 trial are encouraging. Nonetheless, the number of people in the US with inadequately controlled hypertension is likely far greater than the number exposed in this NDA, and a liver injury of clinical significance could arise with wide-spread, post-market use. While the data do not

warrant a box warning or REMS, labeling for liver injury risk should be considered based on our case level data and other ERAs with clinically significant DILI potential.

5.2 Recommendations

1) Do not hold up approval for DILI concerns.
2) Labeling considerations: Labeling recommendations are informed by the DILI risk seen with other ERAs and potential for a large number of patients exposed in the post-market setting.
    a. Warnings and Precautions to include language regarding DILI risk for ERAs in general, and for APT.
    b. Liver analytes should be checked at baseline.
    c. Consider recommending monitoring liver analytes for six months after initiation or after dose increase.
    d. Mention that there were cases of aminotransferase elevations attributed to APT based on positive rechallenge.
    e. Included description of aminotransferase elevation rates over three times and five times upper limit of normal in subjects on APT.
    f. Consider restricting or not recommending use in patients with decompensated cirrhosis or acute liver disease.
3) Standard pharmacovigilance post-marketing
4) No need for DILI specific REMS

Ling Lan -S
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Ling Lan, MD, PhD
Clinical Analyst, DILI Team, DHN
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Paul H. Hayashi, MD, MPH
DILI Team Lead, DHN
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George Makar, MD, MSCE
Deputy Director (Acting), DHN
CDER/OND

Appendix

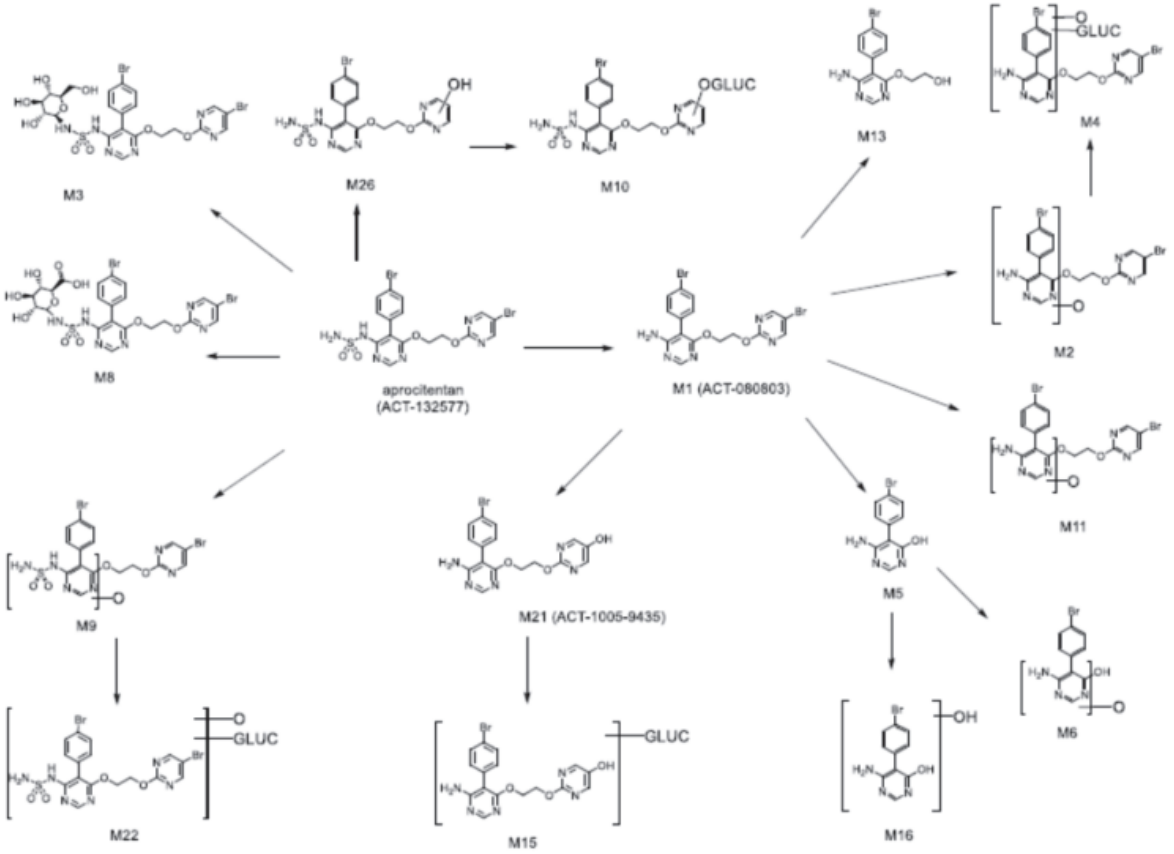
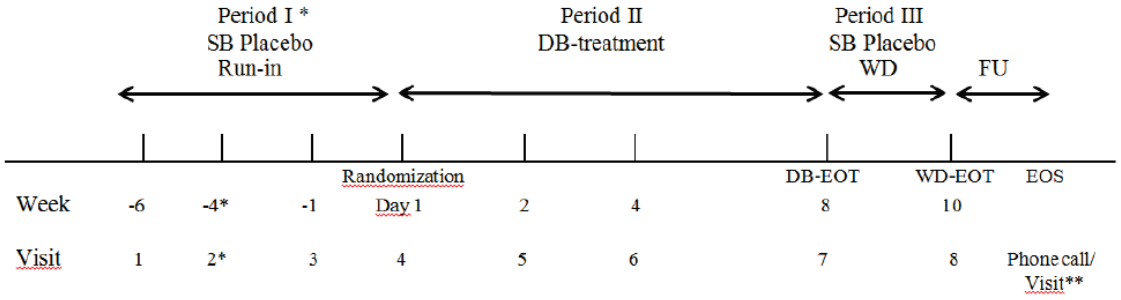


Figure A: Proposed metabolic pathways of aprocitentan[22]

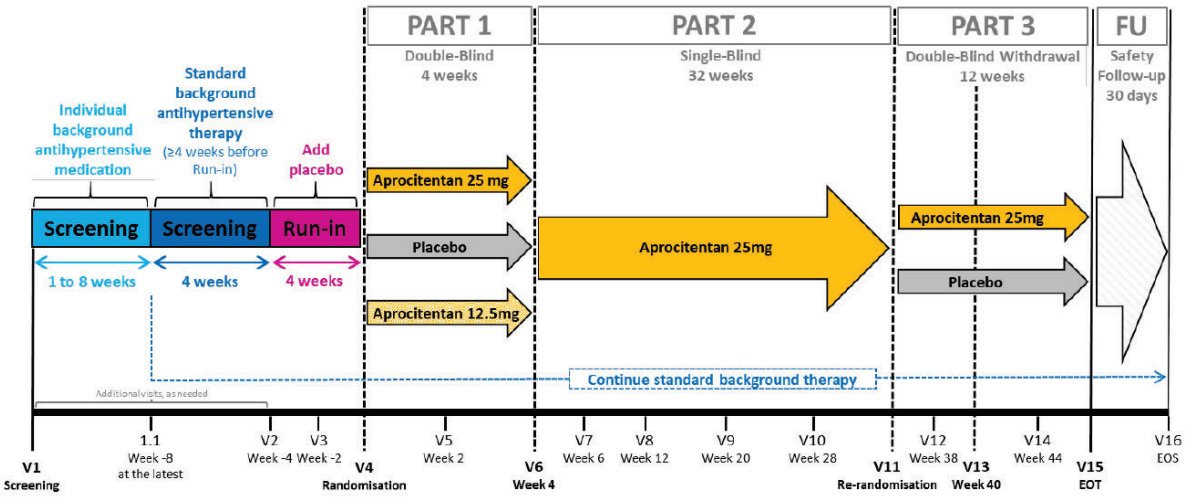
[22] NDA217686 (217686 - 0032 - (32) - 2023-08-24 - ORIG-1 /Clinical/Response To Information Request) - Pharmacokinetics Written Summary (#19)

Study treatment 5 mg	
Study treatment 10 mg	
Study treatment 25mg	
Study treatment 50 mg	
Placebo	
Lisinopril 20 mg	



* SB placebo run-in period is 4 weeks for anti-hypertensive treatment-naïve subjects; Visit 1 is combined with Visit 2 for these subjects.
** Only for women of childbearing potential.
DB = double-blind; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; SB = single-blind; WD = withdrawal.

Figure B: Study 201 schema
Source: Study 201 CSR, page 45



EOT = End-of-Treatment; FU = follow-up; V = visit.

Figure C: Study 301 Schema
Source: Analysis Data Reviewer's Guide for ISS, page 6

Table A: Study 201 Schedule of Events

PERIODS	Name / duration	Period I: Run-in / 4–6 weeks[6]			Period II: Double-blind / 8 weeks				Period III: withdrawal / 2 weeks		Premature EOT		Follow-up
VISITS	Number Name	1[6] Week –6	2[6] Week –4	3 Week –1	4		5 Week 2	6 Week 4	7 Week 8		8 Week 10	9	U1, 2, 3, etc.[10]	Telephone call[9] or visit[11]
	Name	Screening**			Randomization				DB-EOT		WD-EOT	Within 7 d after last study treatment intake	Unscheduled	EOS
	TIME / Week	Day –42	Day –28 (± 3 d)	Day –7 (± 4 d)	Pre-Day –1	Day 1	2 Day 14 (± 3 d)	4 Day 28 (± 3 d)	Part 1 Day 55 (± 5 d)	Part 2 Day 56	10 Day 70 (± 3 d)		Any time	30–33 d after last dose of DB treatment
Informed consent		X												
Eligibility		X	X	X	X									
Medical history		X												
Physical examination		X	X	X	X		X	X	X		X	X	X	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X
HR*, body weight, height[1]		X	X	X	X		X	X	X		X	X	X	
12-lead ECG*		X[4]			X[9]			X	X		X	X[9]	X	
Laboratory incl. pregnancy tests*[2]		X[5]		X[9]	X[9]		X	X	X		X	X[9]	X	X[2]
Urinalysis			X[7, 9]		X[9]		X	X	X		X	X[9]	X	
Office BP measurement*		X	X	X	X		X	X	X		X	X	X	
Home BP device[12]		X	→											
Ambulatory BP measurement*					X				X					
PK and PD sampling[13]							X	X	X					
Compliance with study treatment			X[9]	X[9]	X		X	X	X		X	X	X	
Study treatment dispensing/return		X	X[8]		X	X		X	X	X	X	X	X	

Source: Study 201 protocol Page 73

Table B: Study 301 Schedule of Events

PERIODS	Name / Duration	Screening 4-12 weeks		Run-in 4 weeks			
VISITS[1]	Number	1	1.1[12]	2	3	4	
	Time	Week -16 to Week -8	Week -8 at the latest	Week -4	Week -2	End of Run-in	Randomization
		Additional visits as needed		Day -28 (± 4 d)	Day -14 (± 2 d)	Day –1	Day 1
Informed consent		X					
Eligibility including confirmation of diagnosis of true RHT		X	X	X[13]	X[13]	X[15]	
Demographics / Medical history		X					
Physical examination		X	X	X	X	X	
Concomitant medications		X	X	X	X	X	X
Body weight, height[2]		X	X	X	X	X[16]	
12-lead ECG[3]		X				X[16]	
Laboratory tests[4]		X				X[16,17]	
Serum pregnancy test		X	X	X		X[16,17]	
Urinalysis[5]						X[16]	
Urine sampling to monitor treatment adherence[6]				X	X	X[16]	
AOBPM (incl. HR)		X	X	X	X	X	
Home BP monitoring[7]			→				
ABPM						X[16]	X
Blood sampling for biomarkers[8]		X				X	
Accountability of study treatment and standardized background antihypertensive therapy[9]				X	X	X[16]	
Dispensing/return of study treatment and standardized background antihypertensive therapy[10]			X	X[14]		X	X
SAE[11] and AE[11]		X	X	X	X	X	X

Source: Study 301 protocol Page 180

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/s/

PAUL H HAYASHI
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200

Division of Pediatrics and Maternal Health Review

Date: August 16, 2023 **Date consulted:** April 4, 2023

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH, ORPURM, OND

Lynne P. Yao, MD, Division Director, DPMH, ORPURM, OND

To: Division of Cardiology and Nephrology (DCN)

Drug: Tryvio (aprocitentan) tablets, for oral use

NDA: 217686

IND: 122772

Applicant: Idorsia Clinical Development US Inc.

Subject: Pregnancy and Lactation Labeling Formatting and Recommendations

Proposed Indication: In combination with other antihypertensive drugs, is indicated for the treatment of hypertension, to lower blood pressure (BP) in patients who are not adequately controlled on other drugs.

Materials Reviewed:

- April 4, 2023, DCN consult to DPMH, for aprocitentan, NDA 217686, DARRTS Reference ID 5152788
- December 19, 2022, New Drug Application submission for aprocitentan, NDA 217686
- August 24, 2022, DPMH review for sparsentan, NDA 216403, Katherine Kratz, MD, DARRTS Reference ID 5035058.

Consult Question: "Please review the prescribing information for compliance with the PLLR."

1 INTRODUCTION AND BACKGROUND

On December 19, 2022, Idorsia Clinical Development US Incorporated submitted a 505(b)(1) New Drug Application (NDA) for Tryvio (aprocitentan) tablets to be used in combination with other antihypertensive drugs. Tryvio has the proposed indication of treatment of hypertension, to lower blood pressure (BP) in patients who are not adequately controlled on other drugs. The Division of Cardiology and Nephrology (DCN) consulted the Division of Pediatrics and Maternal Health (DPMH) on April 4, 2023, to assist with the Pregnancy and Lactation subsections of labeling.

Aprocitentan is a endothelin receptor antagonist (ERA). Aprocitentan is an active metabolite of macitentan. ERA-class drugs, including ambrisentan, bosentan and macitentan, as well as sparsentan an ERA and angiotensin receptor (ARB) antagonist, have a Risk and Mitigation Strategy (REMS) to mitigate the risk of embryofetal toxicity. Macitentan and bosentan are approved for the treatment of pulmonary atrial hypertension (PAH); these two drugs are not approved for the treatment of hypertension. Macitentan (10 mg) is administered once daily, and bosentan (16 mg, 32 mg, 48 mg, 62.5 mg, 64 mg or 125 mg; weight based) is administered twice daily. Sparsentan is approved for the reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression and is administered once daily at 200 mg for 14 days and then increased to 400 mg daily as tolerated.

The applicant proposed to mitigate the embryofetal risk of aprocitentan through the combination of labeling and (b) (4) REMS. The applicant's proposed labeling includes a boxed warning for (b) (4) to exclude pregnancy before the start of treatment, monthly during treatment and one month after stopping treatment in addition to the use of highly effective contraception during treatment and for one month after stopping treatment. The applicant's proposed labeling language can be found in Appendix A.

Table 1. Drug Characteristics and Adverse Reactions and Warnings[1]

Drug Class	Endothelin (ET) receptor (ET_A and ET_B) antagonist (ERA)
Mechanism of Action	Aprocitentan inhibits the binding of ET-1 (endothelin) to ET_A and ET_B receptors inhibiting the effects mediated by these receptors in functional assays in cells and isolated organs decreasing mean arterial blood pressure.
Dosage Forms and Administration	12.5 mg (b) (4) once daily dosing
Molecular Weight	546.2 g/mol
Terminal Plasma Half-life	41 hours
% protein binding	>99% bound to plasma proteins primarily albumin
Bioavailability (oral tablet)	Unknown
Adverse Reactions; Warnings and Precautions	Fluid retention, hemoglobin decreased, hepatoxicity, embryo-fetal toxicity

[1] Applicant's prosed labeling verified by DCN review team.

2 REVIEW

PREGNANCY

Hypertension and Pregnancy

- Updated guidelines from the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM), recommend using ≥ 140/90 mm/Hg as a threshold for initiating medical therapy for chronic hypertension during pregnancy.[2] These guidelines were updated after the finalization of the Chronic Hypertension and Pregnancy Study (CHAP).[3,4]
- Chronic hypertension refers to patients who had high blood pressure prior to pregnancy or developed hypertension early in pregnancy before 20 weeks gestation. Hypertension that occurs after the 20th week of gestation is typically caused by pre-eclampsia or gestational hypertension. Chronic hypertension occurs in approximately 0.9-1.5% of pregnant women.[4] According to ACOG, the rate of chronic hypertension in pregnancy increased from 67% to 87% from 2000 to 2009.[3]
- Approximately 10% of cases of hypertension during pregnancy occur secondary to other conditions such as diabetes or thyroid disorders.[5] In a study using hospital discharge data obtained from the Nationwide Inpatient Sample (NIS), part of the Healthcare Cost and Utilization Project, chronic hypertension in pregnancy increases the risk for adverse outcomes, such as preterm birth, perinatal death, intrauterine growth restriction, stroke, preeclampsia, acute renal failure, pulmonary edema, and maternal death.[5]
- In the United States, chronic hypertension resulting in maternal and perinatal morbidity and mortality occurs in approximately 2% of pregnancies .[4,5]
- It is recommended to avoid mineralcorticoid receptor antagonists, angiotensin-converting enzymes (ACE) inhibitors, and angiotensin receptor blockers (ARBs) for hypertension during pregnancy. ACE inhibitors and ARBs should be avoided due to embryofetal toxicity concerns. Mineralcorticoid receptor antagonists should be avoided during pregnancy because they competitively inhibit aldosterone binding to the mineralocorticoid receptor, increasing epithelial sodium channel degradation, reducing sodium reabsorption and potassium excretion, and due to anti-androgen effects observed. Preferred medications include labetalol, nifedipine, hydralazine, or methyldopa.[6]

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[2] American College of Obstetricians and Gynecologists (ACOG). Clinical Guidance for the Integration of the Findings of the Chronic Hypertension and Pregnancy (CHAP) Study. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2022/04/clinical-guidance-for-the-integration-of-the-findings-of-the-chronic-hypertension-and-pregnancy-chap-study. Accessed 30 May 2023.

[3] American College of Obstetricians and Gynecologists (ACOG). Chronic Hypertension in Pregnancy. Practice Bulletin, Number 203. January 2019.

[4] Society for Maternal-Fetal Medicine; Publications Committee. Society for Maternal-Fetal Medicine Statement: Antihypertensive therapy for mild chronic hypertension in pregnancy–The Chronic Hypertension and Pregnancy trial. Volume 227, Issue 2, PB24-B27, August 2022.

[5] Bateman BT, Bansil P, Hernandez-Diaz S, et al. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. Am J Obstet Gynecol 2012;206:134.e1-8.

[6] August, Phyllis. Ed. Lockwood C and Barss V. Treatment of hypertension in pregnant and postpartum patients. UpToDate. May 1, 2023. https://www.uptodate.com/contents/treatment-of-hypertension-in-pregnant-and-postpartum-patients?search=treatment%20of%20hypertension%20during%20pregnancy&sectionRank=1&usage_type=default&anchor=H1980651783&source=machineLearning&selectedTitle=1~150&display_rank=1#H1980651783. 30 May 2023.

- Aprocitentan will not be considered first-line monotherapy but as a treatment option for those who are already on other antihypertensive medications and whose blood pressure is not adequately controlled.

Nonclinical Experience

Aprocitentan is an active metabolite of macitentan. Reproductive toxicity studies were previously reviewed under NDA 204410 for Opsumit (macitentan). Fertility and early embryonic development (FEED) studies were conducted with aprocitentan. In embryo-fetal development toxicity studies in pregnant rats and rabbits, cardiovascular and mandibular arch fusion abnormalities were observed at all dose levels of macitentan, which included exposures to aprocitentan representing approximately (b) (4) and (b) (4)-fold, respectively, the clinical aprocitentan exposures at the maximum recommended human dose (MRHD) based on AUC. In pre- and post-natal development studies, female rats given macitentan from late pregnancy through lactation showed reduced pup survival and impairment of the male fertility of the offspring at a macitentan dose of 10 mg/kg/day, where aprocitentan exposures were (b) (4) the clinical exposures at the MRHD based on AUC.

Genotoxicity and carcinogenicity studies with aprocitentan were negative.

Animal reproduction studies with macitentan

Studies in rabbits and rats revealed cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

The reader is referred to the full Pharmacology/Toxicology review by Srinivasa Raju Datla, Ph.D., DARRTS.

Review of Pharmacovigilance Database

There are currently no available pharmacovigilance data with aprocitentan; however, the applicant submission notes that there have been more than 400 reports of human pregnancies reported with bosentan and macitentan. The applicant provided a summary of data from bosentan periodic safety reports collected from November 20, 2021, through November 19, 2021, as well as data from macitentan periodic safety reports collected from October 18, 2013, through August 19, 2021, and in addition REMS assessment data for both products.

Bosentan Periodic Pregnancy Safety Reports (Sponsor- Actelion)

- 261 pregnancies have been reported for bosentan from November 20, 2001, through November 19, 2021.
- Six of the reported pregnancies included bosentan treatment throughout the entire pregnancy resulting in four healthy infants. and one infant who suffered from neonatal respiratory problems, and one pregnancy that had no reported outcome other than cesarean delivery performed due to fetal distress. There were no congenital anomalies reported. .
- A total of three cases of major congenital anomalies were reported.
    - one case a cleft lip and palate in a baby with a family medical history of cleft lip and palate thought to have an inherited genetic cause.
    - one case of small patent foramen ovale in a premature infant.
    - one case of patent ductus arteriosus and ventricular septal defect (no longer seen on follow-up echocardiograph) which was believed to have been confounded by transmitted genetic factor (Eisenmenger physiology) and prematurity.
- Rates of 1.1% (3/261) major congenital anomalies and 14.6% (38/261) spontaneous abortion. These rates are calculated based on a denominator that includes all reported pregnancies including those lost to follow-up.

Table 2. Pregnancy outcomes reported in female patients with bosentan (corresponds to Table 1, page 11, REMS Justification Document)

Pregnancy Outcome		**Total (n = 261)**
Live births	Congenital anomaly	3
	Other live births[a]	72
Spontaneous abortions		38
Ectopic pregnancies		3
Pregnancy terminations		94
Death of mother and foetus		6
Pregnancy ongoing		10
Unknown/ lost to follow-up		35

a: includes premature or full-term pregnancies with or without neonatal disorders (no congenital anomalies).

Macitentan Periodic Pregnancy Safety Reports (Sponsor- Acelion)

- 115 pregnancies have been reported for macitentan from October 18, 2013, through August 19, 2021.
- A total of 2 cases of congenital anomalies were reported.
  - 1 case of premature birth with bilaterally shortened second digits on hands and feet, diagnosed as chondrodysplasia punctata, confounded by the mother's underlying systemic lupus erythematosus disease and concomitant medications.
  - 1 case of premature infant with secundum-type atrial septal defect.
- Rates of 1.7% (2/115) congenital anomalies and 14.8% (17/115) for spontaneous abortion. These rates are calculated based on a denominator that includes all reported pregnancies including those lost to follow-up.

Reviewer comment: chondrodysplasia punctata is a genetic disorder characterized by skeletal abnormalities, distinctive facial features, intellectual disability and/or respiratory problems. Genetic disorders should not be counted under cases of congenital anomalies.

Table 3. Pregnancy outcomes reported in female patients with macitentan (corresponds to Table 2, page 12, REMS Justification Document)

Pregnancy Outcome		**Total (n = 115)**
Live births	Congenital anomaly	2
	Other live births[a]	25
Spontaneous abortions		17
Ectopic pregnancies		1
Pregnancy terminations		41
Death of mother and foetus		2
Pregnancy ongoing		4
Unknown/ lost to follow-up		23

a: includes premature or full-term pregnancies with or without neonatal disorders (no congenital anomalies).

Summary of bosentan and macitentan pregnancy periodic safety reports

- 102 pregnancy exposures resulting in a live-birth.
- 5 total congenital anomalies reported, 1 with possible genetic component and 1 confounded by concomitant medication and mother's medical history.

Review of Clinical Study Data

In clinical studies with aprocitentan, pregnancy was an exclusion criteria and females of reproductive potential were required to use at least one highly effective method of contraception and undertake pregnancy tests from screening until at least 30 days after randomized study treatment discontinuation.

Overall, 1 case of pregnancy was reported in study 301 and 2 cases reported in study 201.

Study 301

Subject ID (b) (6), a 34-year-old female taking aprocitentan 25 mg for resistant hypertension, estimated exposure from last menstrual period (LMP) through study discontinuation approximately 104 days later when the investigator reported a positive pregnancy test despite 3 methods of contraception (contraceptive pill, spermicide gel and condom). The subject was a former tobacco user and had one previous spontaneous abortion in 2014. The subject also reported a past medical history high blood cholesterol, dyspepsia, anemia, irritable bowel syndrome, anxiety, panic attack, multigravida, headache and rash. Concomitant medication use included nonoxynol, contraceptives for topical use as needed (no additional information was provided), ethinyl estradiol/norethisterone acetate/ferrous fumarate and escitalopram oxalate. At baseline the subject's blood pressure was 157/94 mmHg and weight 93 kg. A healthy male infant was delivered with no neonatal illness, no need to resuscitation and no need for an ICU admission and no congenital anomalies.

Study 201

Subject ID (b) (6) and ID (b) (6)- both pregnancies were reported during the placebo run in a period after 3 days and 2 days of exposure to run-in treatment, respectively. No exposure to aprocitentan.

Review of Literature

Applicant's review of literature

The Applicant conducted a comprehensive search using PubMed and Embase to identify any safety information related to endothelin receptor antagonists (aprocitentan, macitentan, ambrisentan, atrasentan, darusentan, avosentan and sparsentan) from January 1, 2000, through September 18, 2022, regarding pregnancy and lactation. The submission notes that the search did not reveal any new safety issues for aprocitentan or other ERA; however, the submission does reference the following article summarized below.

Hitzerd et al 2019,[7] contains a systematic literature review which identified 18 articles describing 39 cases with ERA exposure during human pregnancy. Data are based on case reports and small case series. The majority of cases involved exposure during the first trimester; however, 5 cases reported exposure late in pregnancy or throughout pregnancy. There were 26 exposures to bosentan (20 first trimester; 4 until delivery, 1 through 2nd trimester and 1 unknown time of exposure); 1 exposure to ambrisentan until 15 weeks gestation, 1 exposed to sitaxentan in 1st trimester and 11 unknown ERA exposures (exact drug unknown). In all, nine cases were reported as healthy live-births, twelve cases (31%) reported elective termination, two cases (5%) reported spontaneous abortion; no congenital anomalies were reported and the remaining were reported as unknown outcomes.

The applicant provided nine published case reports that have been found since the publication of the Hitzerd et al 2019 publication. The publications include 3 reports of pregnancy with ambrisentan , 5 reports with bosentan and 1 report with macitentan. There is no evidence of teratogenicity in any of the 9 published cases. Each case includes short term exposure during the first trimester and two articles describe one case with longer exposure to bosentan during the first two trimesters. High level outcomes measured among the publications include rates of cesarean delivery, changes in pulmonary vascular resistance, worsening PAH and maternal mortality.[8,9,10,11,12,13,14,15,16]

[7] Hitzerd E, Neuman RI, Mirabito Colafella KM, Reiss IKM, van den Meiracker AH, Danser AHJ, et al. Endothelin receptor antagonism during preeclampsia: a matter of timing? Clin Sci (Lond) 2019;133(12):1341-52.
[8] Aspi MTB, Ocsan PMF. The use of point-of-care assessments and advanced hemodynamic monitoring in a patient with Eisenmenger syndrome for cesarean section: A case report. Int J Surg Case Rep. 2021 Dec; 89:106601.
[9] Aamer M, Saeed D, Salman N, Fahim A, Farman S. Pregnancy with a favorable outcome in a patient with MCTD and Pulmonary Arterial Hypertension treated with Bosentan [abstract]. Int J Rheum Dis 2021;24(S2):123-124.
[10] Villaquiran-Torres C, Dueñas-Villamil R, González-Avilés C, Botero Bahamon JD, Saa D, Silva J. Pulmonary Arterial Hypertension and Pregnancy at 2640 Meters Above Sea Level [abstract]. American Thoracic Society 2022 International Conference; doi: 10.1164/ajrccmconference. 2022.205.1_MeetingAbstracts.A4472
[11] Katsurahgi S, Kamiya C, Yamanaka K, Neki R, Miyoshi T, Iwanaga N, et al. Maternal and fetal outcomes in pregnancy complicated with Eisenmenger syndrome. Taiwan J Obstet Gynecol. 2019 Mar; 58(2):183-187.
[12] Kawabe A, Nakano K, Aiko Y, Aramaki S, Onoue T, Okura D, et al. Successful Management of Pregnancy in a Patient with Systemic Lupus Erythematosus-associated Pulmonary Arterial Hypertension. Intern Med. 2018 Jun 1; 57(11):1655-1659.
[13] Dias A, Mineiro A, Pinto L, Lança F, Plácido R, Lousada N. Pregnancy and Pulmonary Arterial Hypertension: A Case Report [letter]. Open Respiratory Archives 2021;3:100135.
[14] Hohmann C, Dumitrescu D, Gerhardt F, Kramer T, Rosenkranz S, Huntgeburth M. High-risk pregnancy in a patient with pulmonary arterial hypertension due to congenital heart disease (PAH-CHD) with temporary shunt inversion and deoxygenation. Pulm Circ. 2019 Apr-Jun;9(2):2045894019835649.
[15] Luknar M Lesny P, Goncalvesova. Twin pregnancy in an undertreated patient with PAH [abstract]. Chest 2022;161 (Suppl.):A599, No. 6, doi: 10.1016/j.chest.2022.04.133.
[16] Condliffe R. Pregnancy in pulmonary arterial hypertension associated with congenital heart disease: an illustrative case study. Journal of Congenital Cardiology 2020;4(Suppl 1):10.

Additionally, Kamp et al 2021,[17] describes a prospective collection of pregnancy outcomes of women with pulmonary artery hypertension (PAH) from the Hannover Medical School between January 2007 and November 2019. The publication reviewed 13 cases of ERA use during pregnancy. The majority of cases involved exposure to macitentan during the first trimester. The outcomes included 3 elective terminations, 2 spontaneous abortions, and 8 healthy infants.

DPMH's review of literature
DPMH conducted a search of published literature in PubMed and Embase using the search terms "aprocitentan and pregnancy," "aprocitentan and pregnant women," "aprocitentan and pregnancy and birth defects," "aprocitentan and pregnancy and congenital malformations," "aprocitentan and pregnancy and stillbirth," "aprocitentan and spontaneous abortion" and "aprocitentan and pregnancy and miscarriage." No data were found specific to aprocitentan exposure during pregnancy.

DPMH previously conducted a review of endothelin receptor antagonists with regard to pregnancy outcomes concluding that placental transfer of ERAs is likely as demonstrated in a study using a perfusion model in the *ex vivo* setting with human placentas.[18] Despite placental transfer of ERAs, the animal reproduction study data and the known mechanism of action of ERAs, no congenital anomalies have been reported in infants exposed to other ERA during pregnancy in published case reports and case series. The reader is referred to the August 24, 2022, DPMH review for sparsentan for NDA 21640 by, Katherine Kratz, MD, DARRTS Reference ID 5035058. An updated search regarding ERA use during pregnancy revealed no new safety data for review.

Reviewer comment: Despite teratogenicity observed in animal reproduction studies, there are no congenital anomalies reported in published data related to pregnancy exposure and ERA exposure in humans. Likewise, there are no reports of congenital anomalies reported among the few pregnancy cases reported in the clinical development program with aprocitentan; however, these results differ slightly from what has been reported in the sponsor's pharmacovigilance database. Refer to the Discussion/Conclusions section of the review for DPMH's conclusion.

LACTATION
Nonclinical Experience
Milk excretion was investigated as part of the macitentan program. Aprocitentan in milk was assessed in lactating rats after a single oral administration of ^{14}C-labeled macitentan dose over a period of 48 hours. Aprocitentan was observed across all collection times in plasma and milk in rats.

The reader is referred to the full Pharmacology/Toxicology review by Srinivasa Raju Datla, Ph.D., DARRTS.

[17] Kamp JC, von Kaisenberg C, Greve S, Winter L, Park DH, Fuge J, et al. Pregnancy in pulmonary arterial hypertension: Midterm outcomes of mothers and offspring. J Heart Lung Transplant. 2021;40(3):229–233.
[18] Hitzerd E, Neuman RI, Broekhuizen M, Simons SHP, Schoenmakers S, Reiss IKM, Koch BCP, van den Meiracker AH, Versmissen J, Visser W, Danser AHJ. Transfer and Vascular Effect of Endothelin Receptor Antagonists in the Human Placenta. Hypertension. 2020 Mar;75(3):877-884.

Review of Pharmacovigilance Database
There are no available lactation pharmacovigilance data for aprocitentan.

Review of Literature
DPMH conducted a review of literature with regard to aprocitentan and use during lactation; no data were found. Likewise, DPMH conducted a search including endothelin receptor antagonists and breastfeeding, and no new data were found. In the 2022, DPMH review[19] for sparsenten, one published case report with bosentan 125 mg given orally twice a day to a 43-year-old female with PAH is summarized. In the case report, the daily infant dosage for a nursing infant exposed to bosentan through human milk of bosentan was calculated to be 0.28 µg/kg/day at day 637, and relative infant dose for an exclusively breastfed infant with an estimated milk intake of 150 ml/kg/day, was calculated to be 0.24% for bosentan. The article concludes that the dosage would also be far below the infant therapeutic dosage of 4 mg/kg; however, the article notes that the infant involved in the study was 21 months old and not exclusively breastfed, therefore, the results may not be applied to younger infants.[20]

There is no available information on aprocitentan or other endothelin receptor antagonists with regard to lactation found in LactMed,[21] Medications and Mothers' Milk[22] or Briggs and Freeman: Drugs in Pregnancy and Lactation.[23]

Reviewer comment: Refer to the Discussion/Conclusions section of the review for DPMH's conclusion.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
In Fertility and Early Embryonic Development (FEED) studies with aprocitentan, gonadal function, mating behavior and reproductive performance was not affected up to 250 mg/kg/day in male rats. Increased incidence in dilation of seminiferous tubules was observed in testes at 250 mg/kg/day. In females, pre-implantation loss was observed at ≥50 mg/kg/day; NOAEL- 10 mg/kg/day ((b) (4) fold of clinical exposure).

The reader is referred to the full Pharmacology/Toxicology review by Srinivasa Raju Datla, Ph.D., DARRTS.

Review of Pharmacovigilance Database
There are no available fertility pharmacovigilance data for aprocitentan.

[19] August 24, 2022, DPMH review for sparsentan for NDA 21640 by, Katherine Kratz, MD, DARRTS Reference ID 5035058.
[20] Nauwelaerts N, Ceulemans M, Deferm N, Eerdekens A, Lammens B, Armoudjian Y, Van Calsteren K, Allegaert K, de Vries L, Annaert P, Smits A. Case Report: Bosentan and Sildenafil Exposure in Human Milk - A Contribution From the ConcePTION Project. Front Pharmacol. 2022 Jun 15;13:881084. doi: 10.3389/fphar.2022.881084. PMID: 35784689; PMCID: PMC9240352.
[21] LactMed. National Library of Medicine. National Center for Biotechnology Information. https://www.ncbi.nlm.nih.gov/books/NBK501922/#IX-E
[22] Hale, Thomas. Medications and Mothers Milk. https://www.halesmeds.com/
[23] Briggs and Freeman: Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Ovid: Ovid: Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.

The applicant provided a summary of data from the bosentan periodic safety reports collected from November 20, 2021, through November 19, 2021, as well as data from macitentan periodic safety reports collected from October 18, 2013, through August 19, 2021.

Bosentan Periodic Safety Reports Regarding Fertility Disorders

- Two cases from spontaneous sources concerning male patients exposed to bosentan for an unspecified indication were reported to the applicant's global safety database.
    - One case reported bosentan discontinuation approximately one year earlier and noted spermiogram was "still really bad." No additional details. Semen analysis and abnormal spermatozoa were not reported.
    - One case in an adult male who received bosentan for several years and was noted to have been trying to have a child. Spermiograms were performed showing infertility (no evidence of sperm). Bosentan was withdrawn and repeat spermiograms showed no improvement. No additional details.

Macitentan Periodic Safety Reports Regarding Fertility Disorders

- Four cases reported from clinical study sources; subject age range from 35 to 45 years.
    - One case of testicular lump treated with levofloxacin antibiotics. No additional details.
    - One case 35-year-old male treated with macitentan for pulmonary hypertension; he and his partner reported difficulty becoming pregnant. Concomitant medication included tadalafil. No additional details.
    - One case of 42-year-old male with esophageal varices treated with macitentan for pulmonary hypertension; concomitant medication included treprostinil sodium and sildenafil. An unspecified duration after initiating treatment with macitentan reported experiencing 3 varicocele bleeds and hospitalization for 10 days. No additional details.
    - One case of semen discoloration. No additional details.

Review of Literature

DPMH conducted a review of available published literature regarding female and male fertility and exposure to aprocitentan, and no data were found.

Reviewer comment: There are no available human data with aprocitentan related to fertility. Although there are reported cases of exposure to other ERAs related to fertility disorders, there is not enough information to confirm any association of ERA drug exposure and effects on human fertility. Refer to the Discussion/Conclusions section of the review for DPMH's conclusion.

Risk Evaluation and Mitigation Strategy (REMS)

The ERA drug class overall has a REMS for embryofetal toxicity. The applicant is proposing to mitigate the risk of embryofetal toxicity with a combination of strict labeling language and a (b) (4) REMS. The applicant's proposal includes a pregnancy contraindication, boxed warning and instructions for physicians on how to manage (b) (4) taking aprocitentan. (b) (4)

Reviewer comment: [redacted] *Despite teratogenicity observed in ERAs in animal studies, teratogenicity has not been observed in case reports and case series reviewed from published literature as well as pharmacovigilance data from bosentan and macitentan exposure during pregnancy. The REMS Oversight Committee (ROC) has met twice to discuss the issuance of a REMS for aprocitentan and at the time of this review DCN was still undecided as to the final decision on the REMS elements. DCN is currently considering a REMS with Elements to Assure Safe Use (ETASU) to include prescribers' specific training/experience or special certifications. The proposed REMS will also require a certification obtained by dispensing pharmacies and healthcare providers.*

3 DISCUSSION AND CONCLUSIONS

Pregnancy

Given the embryofetal risks observed in animal studies with aprocitentan and other ERAs, aprocitentan mechanism of action , and the Risk Evaluation and Mitigation Strategy (REMS) for embryofetal toxicity issued for the other ERAs, DCN will be issuing a REMS for embryofetal toxicity for aprocitentan. DCN is currently considering a REMS with Elements to Assure Safe Use (ETASU) to include prescribers' specific training/experience. The proposed REMS may also require a certification by dispensing pharmacies and healthcare providers that dispense prescriptions for the product. The final decision of the REMS will be included in the final NDA action for aprocitentan.

Teratogenicity was demonstrated in animal reproduction studies with macitentan, aprocitentan is an active metabolite of macitentan. Genotoxicity and carcinogenicity studies with aprocitentan were negative. In embryo-fetal development toxicity studies in pregnant rats and rabbits, cardiovascular and mandibular arch fusion abnormalities were observed at all dose levels of macitentan, which included exposures to aprocitentan representing approximately [redacted] and [redacted]-fold, respectively, the clinical aprocitentan exposures at the maximum recommended human dose (MRHD) based on AUC. In pre- and post-natal development studies, female rats given macitentan from late pregnancy through lactation showed reduced pup survival and impairment of the male fertility of the offspring at a macitentan dose of 10 mg/kg/day, where aprocitentan exposures were [redacted] the clinical exposures at the MRHD based on AUC.

Despite the results of animal reproduction studies, published human data in the form of small case reports, case series with other ERAs, and pharmacovigilance data with other ERAs have not demonstrated a risk of major congenital malformations.

Since pregnancy is not recommended due to animal reproduction studies and the mechanism of action of aprocitentan, there will be a REMS, a pregnancy contraindication and a Warning and Precautions for embryo-fetal toxicity. A pregnancy registry study is unlikely to be able to recruit sufficient numbers of participants to provide interpretable data. DPMH recommends the issuance of a postmarketing requirement (PMR) for a descriptive pregnancy safety study (DPSS) when a drug or biological product will be used in a small population, and it is unlikely that a pregnancy registry or complementary pregnancy study would provide a sufficient number of patients in the study. DPMH recommends DCN consider issuing a descriptive pregnancy safety study for aprocitentan.

Lactation

The presence of aprocitentan in human milk, the effects of aprocitentan on the breastfed infant, and the effects of aprocitentan on milk production are unknown. As aprocitentan is highly protein bound, it is likely to be present in human milk. Subsection 8.2, Lactation, will include the "Risk Summary" subheading with language that is similar to that in other ERA class labeling.

Although aprocitentan will be used in females of reproductive potential, there will be a recommendation to avoid breastfeeding while on aprocitentan based on the drug's adverse event profile. This recommendation is similar to the approach that was taken for other drugs in the ERA and ARB classes. While a milk only lactation study would demonstrate the presence of aprocitentan in human milk, it would not provide information about the extent to which aprocitentan would be transferred to the breastfed infant and would not result in a labeling change. Although a mother-infant pair study could provide information about drug transfer to the infant, aprocitentan labeling will include a recommendation to not breastfeed. Therefore, it would not be feasible to conduct a mother-infant pair lactation study. DPMH does not recommend any postmarketing lactation studies.

Females and Males of Reproductive Potential

In Fertility and Early Embryonic Development (FEED) studies with aprocitentan, gonadal function, mating behavior and reproductive performance was not affected up to 250 mg/kg/day in male rats. Increased incidence in dilation of seminiferous tubules was observed in testes at 250 mg/kg/day. In females, pre-implantation loss was observed at ≥50 mg/kg/day; NOAEL- 10 mg/kg/day ((b) (4) fold of clinical exposure).

Despite limited reports of fertility disorders in males with other ERAs, there is not enough information to associate ERA drug expose to effects on fertility.

Due to concerns for embryo-fetal toxicity with ERAs, pregnancy testing prior to, during, and after treatment with aprocitentan is required. Therefore, subsection 8.3 will include a "Pregnancy Testing" subheading. In addition, subsection 8.3 will include a "Contraception" heading.

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

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CARRIE M CERESA
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CARRIE M CERESA on behalf of MIRIAM C DINATALE
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217686
Submission Number	0001
Submission Date	12/19/2022
Date Consult Received	6/13/2023
Drug Name	TRYVIO (aprocitentan)
Indication	Hypertension, to lower blood pressure in patients who are not adequately controlled on other drugs
Therapeutic Dose	12.5 mg QD, (b) (4)
Clinical Division	DCN
Protocol Review	Link

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

This review responds to your consult dated 6/13/2023 regarding the sponsor's QT/QTc evaluation report. We reviewed the following materials:

- Previous IRT review dated 09/26/2017, 04/12/2019, and 03/03/2022 in DARRTS;
- Clinical study report of study ID-080-108 (NDA 217686/ SN 0001; link);
- QT evaluation checklist (NDA 217686/ SN 0001; link);
- Sponsor's statistical analysis plan (SN 0001; link);
- Highlights of clinical pharmacology and cardiac safety (NDA 217686/ SN 0001; link); and
- Draft label (NDA 217686/ SN 0001; link).

1 SUMMARY

This TQT study showed concentration-dependent QTc prolongation; however, at (b) (4) times the highest therapeutic dose, clinically significant QTc prolongation was not observed as the upper 90% confidence interval of ΔΔQTc was 11 msec – see Table 1 for overall results.

The clinical study ID-080-108 was a prospective, single-center, randomized, double-blind, placebo- and moxifloxacin- controlled, 4-way crossover Phase 1 study to assess the effect of multiple therapeutic and supratherapeutic doses of aprocitentan on the QTc interval duration in healthy subjects. The supratherapeutic dose, which is (b) (4) times the therapeutics dose, provided (b) (4) -fold high clinical exposure.

Data were analyzed using exposure-response analysis as the primary analysis. The upper bound of 90% confident interval of placebo-corrected QTc interval change from baseline is below 10 msec at (b) (4)

(25 mg once daily), but the upper bound of 90% confident interval of placebo-corrected QTc interval change from baseline is greater than 10 msec at steady state exposure of the supratherapeutic dose (100 mg once daily for 10 days), which provided [redacted] (refer to section 3.1.1 and 4.5). The findings of the primary analysis are further supported by by-time analysis (section 4.3). There are no significant outliers for QTc, PR and QRS in categorical analysis (section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☒ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• [redacted]: 3.1-fold C_{max} for an elderly female administered aprocitentan with a high fat meal (section 3.1)
• The maximum geometric mean Cmax in the TQT study was 16.8 µg/mL (100 mg QD on day 10), which is [redacted].
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Period Day</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔΔQTcF</td><td>Aprocitentan 25 mg QD</td><td>1</td><td>1.2</td><td>3.4</td><td>(2.9 to 3.9)</td></tr>
<tr><td>ΔΔQTcF</td><td>Aprocitentan 25 mg QD</td><td>10</td><td>3.7</td><td>4.3</td><td>(3.7 to 4.8)</td></tr>
<tr><td>ΔΔQTcF</td><td>Aprocitentan 100 mg QD</td><td>1</td><td>5.4</td><td>4.9</td><td>(4.2 to 5.5)</td></tr>
<tr><td>ΔΔQTcF</td><td>Aprocitentan 100 mg QD</td><td>10</td><td>16.8</td><td>8.8</td><td>(7.0 to 10.7)</td></tr>
<tr><td>ΔΔQTcF</td><td>High clinical exposure</td><td colspan="3">[redacted]</td></tr>
</table></td></tr>
<tr><td>In vitro/ in vivo findings</td><td>This is not an integrated risk assessment. Nonclinical studies were not evaluated for best practice.</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to NDA 217686/ SN 0001 (link) from the CSS-IRT.

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

(b) (4)

***Reviewer's comment**: Our labeling recommendation is consistent with the draft FDA guidance, "QTc Information in Human Prescription Drug and Biological Product Labeling."*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Aprocitentan is a dual endothelin receptor antagonist (ERA) indicated for the treatment of hypertension in patients who are not adequately controlled on other drugs in combination with other antihypertensive drugs. The (b) (4) dose is 12.5 mg tablet once daily (QD), with or without food (b) (4).

The CS-IRT has reviewed this application before under IND 122772. In review dated 04/12/2019, we reviewed the study design and analysis plan for the thorough QT (TQT) study ID-080-108 and found it acceptable. The review division is asking for our review and comments on the sponsor's cardiac electrophysiology labeling language in section 12.2 and results of their TQT Study Report.

Study ID-080-108 is a Phase 1, randomized, double-blind, placebo- and moxifloxacin - controlled, 4-way crossover TQT study in healthy subjects (n = 48, 40% female). There were 4 periods in which subjects were to receive, under fast condition in a randomly assigned sequence, aprocitentan 25 mg QD x 10 days, aprocitentan 100 mg QD x 10 days, matching placebo QD x 10 days, and matching placebo QD x 9 days + open label 400 mg moxifloxacin on day 10. There were 18 observation days following dosing and minimum of 2 days between each period. Triplicate ECGs were extracted from continuous digital Holter recordings. ECGs were analyzed semi-automatically with

manual verification. Readers were blinded to subject, time point, and treatment. The sponsor's primary analysis is concentration-QTc using white paper model. See previous review (04/12/2019) for more details.

3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety.

The steady state geometric mean Cmax (CV%) following aprocitentan 25 mg QD is 3.68 µg/mL (23) (TQT study ID-080-108). Tmax ~ 4 hr; half-life ~ 45 hr.

Aprocitentan and its metabolites are eliminated both in urine and feces, i.e., 52% and 25%, of the administered dose, respectively. Aprocitentan was excreted unchanged in urine and feces as 0.2 and 7.0% of the administered dose, respectively. The main metabolic pathways are through UGT1A1/UGT2B7 and hydrolysis. In plasma, almost exclusively unchanged aprocitentan was detected (94.3% of the total radioactivity in the sample).

Among all intrinsic factors, sex had the highest impact on Cmax; female subjects had 1.38-fold higher Cmax than male subjects. Cmax was 1.31-fold higher in elderly subjects compared to healthy adults.

Aprocitentan is a substrate of P-gp and BCRP in vitro, however, inhibitors of these transporters are not anticipated to influence the PK of aprocitentan. High-fat, high-calorie meal increased Cmax by 1.73-fold than that of fasted conditions after a single dose. Population PK modeling only indicated minimal impact of food on PK in steady-state conditions.

The worst-case exposure scenario is an elderly female administered aprocitentan with a high-fat meal, with an expected ~3-fold higher Cmax when effects of age, sex, and food effect are combined (1.38 x 1.31 x 1.73 = 3.12). In the Sponsor's population PK modeling, significant covariates included body weight, age, sex, moderate hepatic impairment (HI), eGFR, and food effect. In simulations for a high exposure scenario (female, body weight of 67 kg, moderate HI, severe renal impairment, fed state) versus a reference subject (female, 87 kg, no HI, normal renal function, fasted state), aprocitentan Cmax and AUC were increased ~2-fold.

The maximum geometric mean Cmax in the TQT study was 16.8 µg/mL (100 mg QD on day 10), which is [redacted] (b) (4)

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
[redacted] (b) (4)	25 mg QD, oral tablets	3.7 µg/mL ($C_{max,ss}$)
	3.1-fold Cmax in an elderly female administered aprocitentan with a high fat meal (3.68*1.38*1.31*1.73)	11.5 µg/mL
Highest dose in QT assessment	100 mg QD, oral tablets	16.8 µg/mL

C_{max} Ratio	1.5

3.1.2 Nonclinical Safety Pharmacology Assessments

The potential of aprocitentan to induce QT prolongation was investigated in vitro by the patch clamp technique in HEK293 cells expressing hERG K+ channels and in vivo in conscious Beagle dogs equipped with telemetry.

At concentrations up to 10 µM (5.46 µg/mL), aprocitentan had no effect on repolarizing currents through hERG K+ channels. At concentrations ≥ 10 µM, aprocitentan blocked the currents with an IC50 of 28.6 µM. This concentration is far above the maximum free plasma concentration in humans at the (b) (4) dose of 25 mg. Therefore, aprocitentan is not expected to elicit QT prolongation via hERG inhibition.

In normotensive Beagle dogs, aprocitentan given orally at doses of 10, 50, and 250 mg/kg induced statistically significant decreases in systolic and diastolic BP, and in MAP. The BP effect was associated with a compensatory HR increase. Both effects were seen at all doses. The finding is not considered to be adverse as BP decrease is an expected pharmacological effect of aprocitentan. Treatment with aprocitentan had no effect on atrioventricular or intraventricular conduction velocities, RR or PR intervals, or the duration of the QRS complex at any dose. There was no effect on either QT or corrected QT intervals, indicating that the administration of aprocitentan at oral doses up to 250 mg/kg in dogs has no effect on ventricular repolarization. (b) (4)

Reviewer's comment: *The hERG IC50 is 28.6 µM (MW: 546.2 g/mol); the plasma protein binding is 99%; hERG safety margin over* (b) (4) *. The in vivo study showed no QT/QTc effect at the plasma exposure about* (b) (4) .

3.2 Sponsor's Results

3.2.1 By-Time Analysis

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

In the sponsor's by-time analysis, an increase in ΔΔQTcF can be observed, with the confidence interval crossing the 10 msec threshold on Day 10 in the aprocitentan 100 mg QD treatment group. An increase in ΔΔQTcF of around 5 msec was identified on Day 10 in the aprocitentan 25 mg QD treatment group.

An increase in ΔΔHR was identified but the mean increase was less than 10 bpm. There was no evidence of treatment-emergent changes in PR and QRS intervals.

Reviewer's comment: *The results from the reviewer's by-time analysis were similar to Applicant's results. Please see section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm on Day 10.

Reviewer's comment: *Reviewer's findings are consistent with those reported by the Applicant, please see section 4.5 for details.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline). There was one significant outlier for HR (>100 beats/min and 25% over baseline) in the aprocitentan 100 mg QD treatment group.

Reviewer's comment: *The results of the Applicant's and reviewer's analyses were similar. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper. At the (b) (4) dose of 25 mg daily, day 10 geometric mean C_{max} was 3.68 µg/mL and mean (90% CI) ΔΔQTcF was 3.846 (3.267 – 4.426) msec. At the supratherapeutic dose of 100 mg daily, day 10 geometric mean C_{max} was 16.1 µg/mL and mean (90% CI) ΔΔQTcF was 8.482 (6.554 – 10.411) msec.

Reviewer's comment: *The results of the Applicant's and reviewer's analyses were similar.*

3.2.4 Safety Analysis

All 48 subjects randomized to the study received at least one dose of study treatment. Of these 42, 43, 43, and 41 received at least one dose of 25 mg aprocitentan, 100 mg aprocitentan, placebo, and moxifloxacin.

More TEAEs were reported by subjects after treatment with 100 mg aprocitentan (79%) as compared to other treatments (45, 49, and 39% after treatment with 25 mg aprocitentan, placebo, and placebo/moxifloxacin, respectively). The most frequently reported TEAE was headache, followed by nasal congestion, nausea, and peripheral edema. Cardiac TEAEs reported more than once were palpitations (3 subjects [7%] following 100 mg aprocitentan and 1 subject [2%] following moxifloxacin) and tachycardia (1 subject [2%] following 100 mg aprocitentan).

No deaths or SAEs occurred during this study. 16 subjects (33%) discontinued the study treatment. 7 subjects (15%) discontinued due to an AE. Table 3 listed all these AEs.

Table 3. Treatment Discontinuation due to Adverse Events

Subject	Sex	Treatment	Day	Adverse event
(b) (6)	F	100 mg aprocitentan	8	Cardiac discomfort, intermittent palpitations, and ΔQTcB > 60 msec prior to dosing on day 8.

(b) (6)	F	100 mg aprocitentan	4	Asthenia, bradycardia, feeling hot, nausea, paresthesia, and restlessness
	F	100 mg aprocitentan	1	Dizziness, nausea, vomiting, headache, ear discomfort, and nasal congestion
	F	100 mg aprocitentan	7	Peripheral edema, face edema, seasonal allergy
	F	Placebo	9	Gastroenteritis
	M	Placebo	4	Nausea, pyrexia, and vomiting
	M	Placebo	16	Intermittent headache

Subject (b) (6) is a 39-year-old, White, female healthy subject randomized to treatment sequence ADCB (25 mg aprocitentan -> moxifloxacin-> placebo-> 100 mg aprocitentan). The subject had no recorded medical history and did not take medications at screening.

During Treatment A the subject reported headache. During Treatment A, D, C the subject reported skin rash.

During Treatment B, the subject started 100 mg aprocitentan once daily on Day 1. Prior to dosing QTcB/QTcF of 411/407 msec were recorded. From Day 1 to Day 7, the subject reported headache (Day 1, duration 2 hrs; Day 2, duration 7d20h), attenuated hearing (Day 2, duration 6d19h50m), nasal congestion (Day 3, duration 6d11h), warm sensation in the head and trunk (Day 5, 3d19h50m). On Day 7, 4 h after study treatment administration, the subject reported moderate palpitations and mild feeling of pressure over the heart with a duration of 3 hours. On Day 8, almost 24 h after administration on Day 7 and prior to dosing on Day 8, the subject reported palpitations (duration 1d23h30m). In addition, the QTcB/QTcF recorded pre-dose were 478/450 msec. As QTcB increased by 67 msec from baseline, in combination with the reported AEs, the investigator decided to discontinue study treatment administration. QTcB/QTcF measured On Day 8 approximately 24h30min and 24h40min were 462/431 msec and 427/414 msec. All AEs resolved without sequelae by EOS and were considered related to study treatment by the investigator.

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

Subject (b) (6) *did not report QTcF prolongation. The investigator withdrew her from the study due to increases in QTcB which overcorrects the QT interval for increases in heart rate (palpitations).*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

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

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to subject, time point and treatment. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

Not Applicable.

4.3 BY-TIME ANALYSIS

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

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

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 4.

Figure 1: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

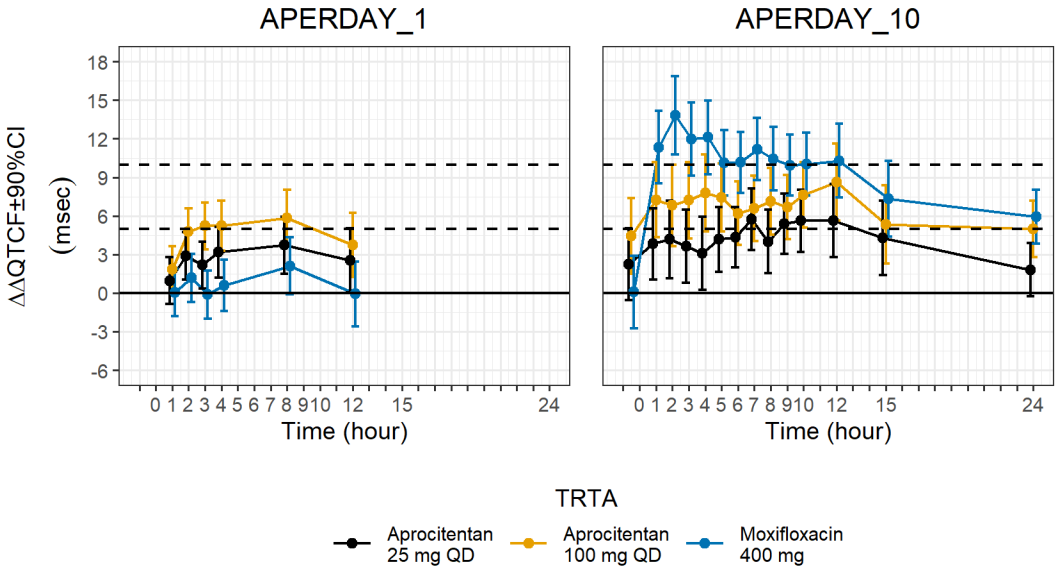


Table 4: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	Nact / Npbo	Time (hour)	ΔΔQTCF (msec)	90.0% CI (msec)
Aprocitentan 25 mg QD	1	42 / 43	8.0	3.7	(1.5 to 5.9)
Aprocitentan 100 mg QD	1	43 / 43	8.0	5.8	(3.6 to 8.0)
Aprocitentan 25 mg QD	10	42 / 41	12.0	5.6	(2.8 to 8.5)
Aprocitentan 100 mg QD	10	36 / 41	12.0	8.6	(5.6 to 11.6)

4.3.1.1 Assay Sensitivity

The same model as described in the primary analyses is used with moxifloxacin treatment for assay sensitivity evaluation. The time-course of changes in ΔΔQTcF is shown in Figure 1 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 3 time points on Day 10 (Table 5).

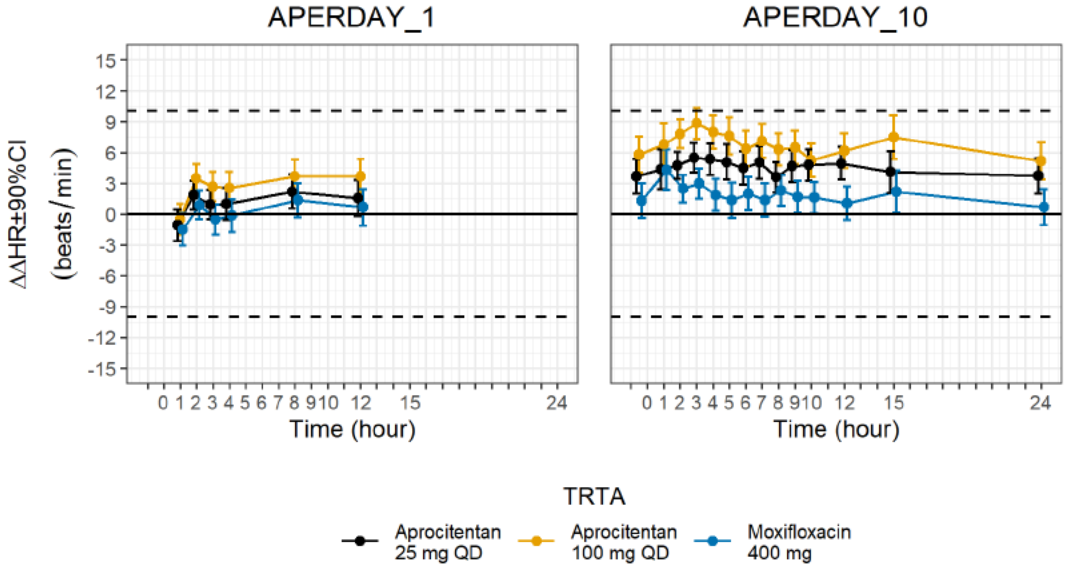
Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	Nact / Npbo	Time (hour)	ΔΔQTCF (msec)	90.0% CI (msec)	96.7% CI (msec)
Moxifloxacin 400 mg	10	41 / 41	2.0	13.8	(10.8 to 16.9)	(9.9 to 17.8)

4.3.2 HR

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

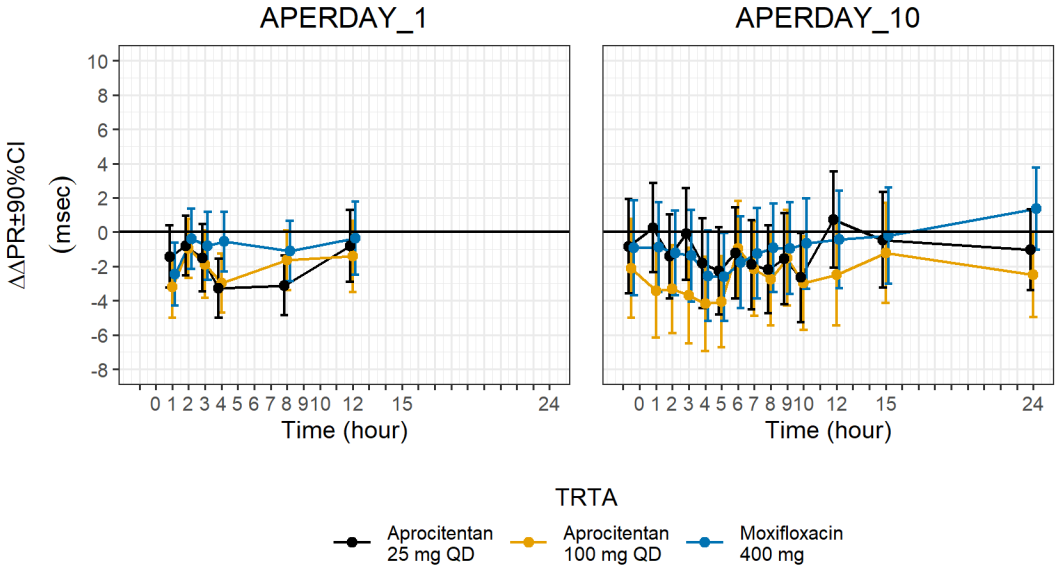
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

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

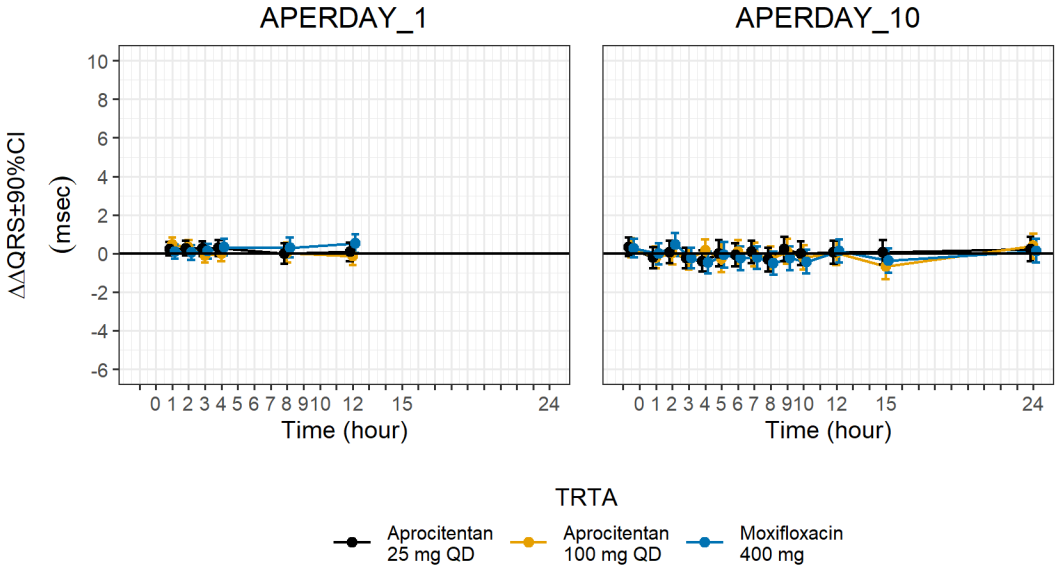
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

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

Figure 4: Mean and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

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

4.4.1 QTc

There were no subjects having observed QTcF above 480 msec or change from baseline above 60 msec.

4.4.2 HR

Table 6 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There was one subject who had observed maximum HR above 100 beats/min with 25% increase over baseline in the aprocitentan 100 mg QD treatment group.

Table 6: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Aprocitentan 25 mg QD	42	840	42 (100.0%)	840 (100.0%)	0 (0%)	0 (0%)
Aprocitentan 100 mg QD	43	762	42 (97.7%)	759 (99.6%)	1 (2.3%)	3 (0.4%)
Placebo	43	832	43 (100.0%)	832 (100.0%)	0 (0%)	0 (0%)

4.4.3 PR

None of the subjects experienced PR >220 msec and 25% increase over baseline in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec in any of the treatment groups.

4.5 Exposure-Response Analysis

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. Four subjects were excluded from the PK set and 9 subjects from the PK/ECG set.

4.5.1 QTc

Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]

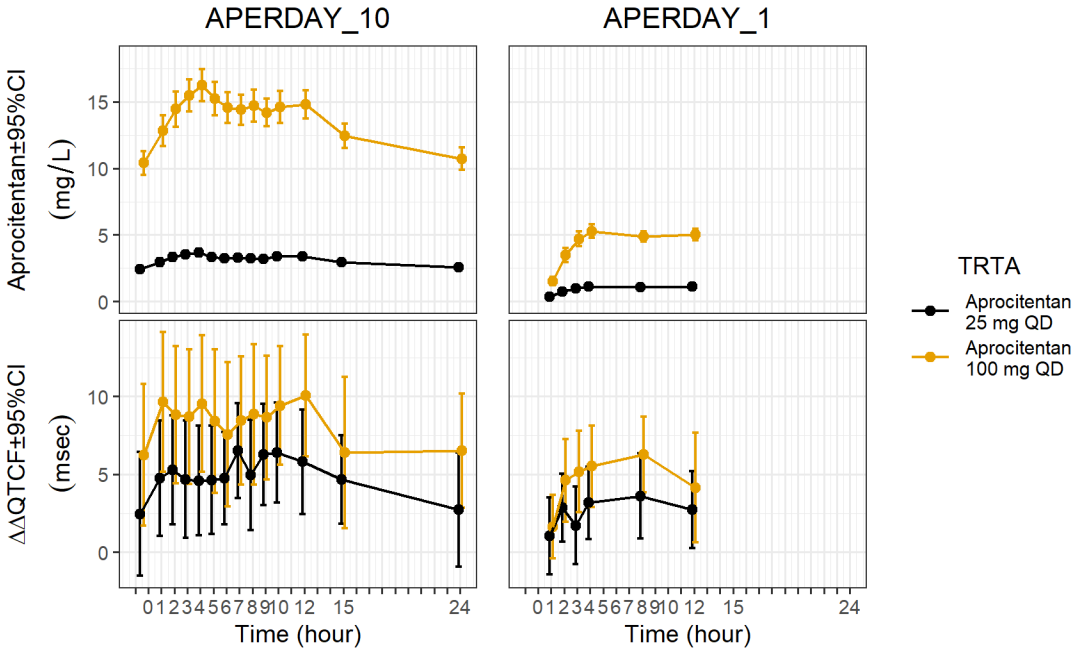
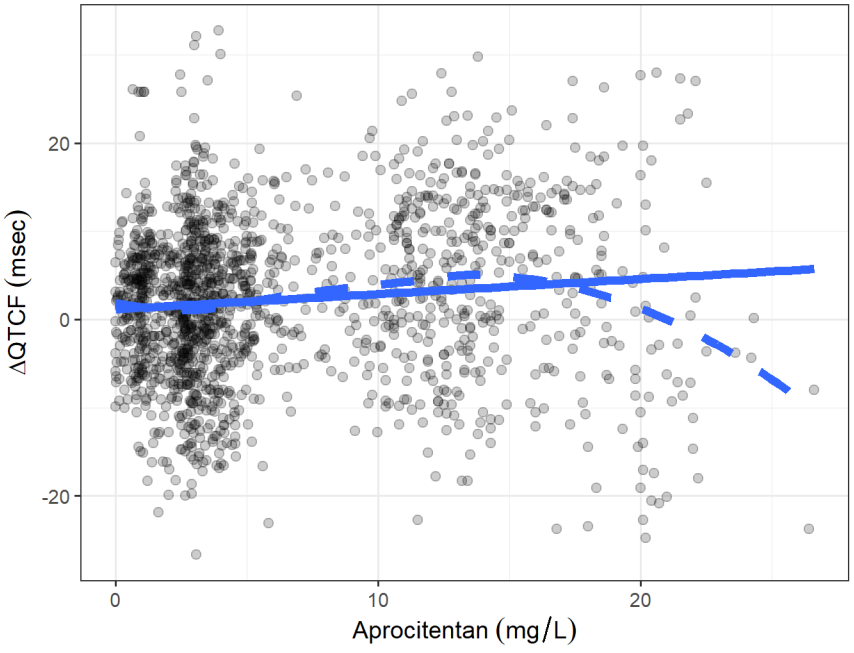


Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

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

Figure 7: Goodness-of-fit Plot for QTcF

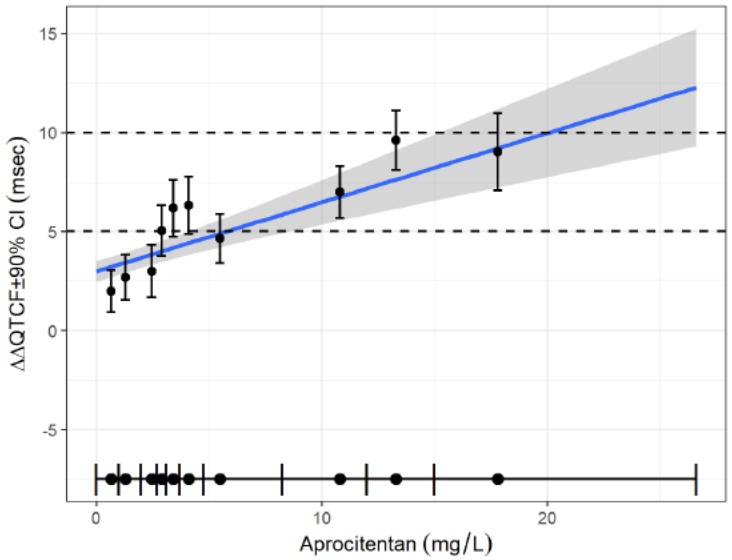


Table 7: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Aprocitentan (mg/L)	ΔΔQTCF (msec)	90.0% CI (msec)
Aprocitentan 25 mg QD	1	1.2	3.4	(2.9 to 3.9)
Aprocitentan 25 mg QD	10	3.7	4.3	(3.7 to 4.8)
Aprocitentan 100 mg QD	1	5.4	4.9	(4.2 to 5.5)
High clinical exposure		(b) (4)		
Aprocitentan 100 mg QD	10	16.8	8.8	(7.0 to 10.7)

4.5.1.1 Assay Sensitivity

Not applicable. No moxifloxacin concentration data were submitted.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

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/s/

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Signing on behalf of Mike as he is OOO

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