CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s000

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: ARIA Sufficiency for DILI Assessment

Date:	February 14, 2023
Reviewer(s):	Margie Goulding, Ph.D., Epidemiologist Division of Epidemiology 2
Team Leader:	Mingfeng Zhang, M.D., Ph.D. Division of Epidemiology 2
Division Director:	Monique Falconer, M.D., M.S. Division of Epidemiology 2
Subject:	ARIA Sufficiency for Assessment of Drug-Induced Liver Injury Risk with Sparsentan
Drug Name(s):	Filspari (sparsentan)
Application Type/Number:	NDA 216403
Applicant/sponsor:	Travere Therapeutics
OSE Record #:	2022-2221

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Sparsentan (NDA 216403) is a first-in-class dual endothelin and angiotensin receptor antagonist (DEARA) for endothelin type A receptor (ETAR) and angiotensin II (Ang II) receptor type 1 (AT1), that is proposed for the treatment of immuno-globulin A nephropathy (IgAN) (b) (4)

1.2. Describe the Safety Concern

According to a DHN consult review[1], during the review of NDA 216403, the Division of Cardiology and Nephrology (DCN) noted, in a clinical study (PROTECT) of patients with IgAN, more hepatic adverse events (Alanine Aminotransferase (ALT) ≥ 5 X *Upper Limit of Normal (ULN))* in sparsentan-treated subjects than an active comparator group of irbesartan-treated subjects (3/202 vs. 0/201, respectively). There was also one severe adverse event (AE) of ALT elevation in a sparsentan-treated patient in another (ongoing) study (DUPLEX) of the treatment of focal segmental glomerulosclerosis (FSGN), (b) (4). Three endothelin receptor antagonists (ERA) related to sparsentan (bosentan, ambrisentan, macitentan) that are approved for treating pulmonary hypertension have been associated with rare, but potentially severe, instances of clinically apparent, acute liver injury. DCN consulted the Division of Hepatology and Nutrition (DHN) to assess sparsentan's hepatotoxicity potential. The key findings of DHN's August 2022 review were:

1. Sparsentan's inhibition of both the bile salt export pump (BSEP) and the multidrug

[1] DHN Consult Review-Clinical 01, Primary Author: Paul Hayashi (OND/DHN), Finalized 9/20/22, Ref ID: 5048166

resistance-associated protein 2 (MRP2), which are important in bile acid and bilirubin secretion (and MRP2 is also important in drug elimination), can have implications for drug-induced liver injury (DILI) due to potential accumulation of bile acids, bilirubin and drugs.

2. A case-level analysis of serum peak ALT and bilirubin levels in PROTECT found that five of the 202 subjects randomized to the sparsentan treatment group had 'probable' DILI associated with the study drug, and three of them had positive re-challenge events.

DHN recommended that if the NDA is to be approved, monthly monitoring of serum liver tests for at least 12-14 months should be required, as well as post-market studies aimed at detecting DILI and liver-related adverse events.

In addition, the NDA review team has determined that, for approval, a Risk Evaluation and Mitigation Strategy (REMS) to educate prescribers and patients about the potential for adverse hepatic events (as well as teratogenicity) with exposure to sparsentan is needed. The enrollment of patients, and monthly serum liver testing during their first year of sparsentan treatment, is planned as part of the REMS.

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

Purpose (place an "X" in the appropriate boxes; >1may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

Statement of Purpose

The study's purpose is to help further characterize the risk of drug-induced liver injury (DILI) in patients treated with sparsentan for IgAN. A descriptive, single arm safety study with 2 year follow-up is needed. The goal is signal refinement. A description of the nature (timing, severity, and reversibility) and frequency of adverse hepatic events, particularly Hy's Law cases, is desired. This study should aim to enroll enough patients such that if 0 events of Hy's law are observed, the upper bound of the 95% confidence interval for the rate of Hy's law will be 1/1000. To assess the causality of the sparsentan exposure to liver injury events, information on any dose changes, discontinuation and restarting the drug, and the timing relative to the liver test results or other signs of injury is needed. The study's results would be used to inform labeling on the DILI risk and the recommendation for liver function monitoring. (Note: A single-arm descriptive study (b) (4) is acceptable because with the natural history of IgAN, we do not expect to observe a lot of hepatic AEs in untreated patients.)

1.4. Effect Size of Interest or Estimated Sample Size Desired

This study should aim to enroll enough patients such that if 0 events of Hy's law are observed, the upper bound of the 95% confidence interval for the rate of Hy's law will be 1/1000.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1. Population

Patients being treated with sparsentan for immuno-globulin A nephropathy.

2.2. Is ARIA sufficient to assess the intended population?

Patients who have been diagnosed with IgAN can be identified with ARIA using ICD-10-CM diagnosis codes (N02.8).

3. EXPOSURES

3.1. Treatment Exposure(s)

Sparsentan is the treatment of interest. Information on the dosing (amount) of sparsentan, the start and stop dates, and timing of any change in sparsentan dose needs to be collected. The patients are expected to be treated with sparsentan in an outpatient setting, to have their liver enzyme levels monitored with monthly testing, and the sparsentan dose to be lowered or cut completely if bad results are seen. It is important to collect the exposure dose and timing information because there is evidence of elevated liver enzymes returning to normal after stopping the sparsentan, and it would be helpful to know more about the timing of discontinuation that is associated with reversals. Also, the information on any changes in dosing and testing results (with dechallenge and rechallenge) will be helpful to assess causality of the drug in any adverse effect.

3.2. Comparator Exposure(s)

A comparator exposure group is not needed. An appreciable frequency of liver enzyme elevations or other signs of liver injury are not expected in the IgAN patient population, so a comparator group is not warranted to estimate the background risk of liver injury associated with the underlying disease.

3.3. Is ARIA sufficient to identify the exposure of interest?

No, ARIA is not sufficient. Changes in the exposure to sparsentan, from temporary changes in the dose taken or temporary discontinuation of the drug, cannot be accurately obtained from prescription refill claims. A temporary dosage cut (pill splitting) or temporary discontinuation of the drug may not be identifiable from the prescription refill data. **Primary data collection is needed to accurately track the exposure over time.**

4. OUTCOME(S)

4.1. Outcomes of Interest

Case-level determination of a drug-induced liver injury (DILI), drawing from three data types:

1. Measures of liver function/injury at pre-defined follow-up time and time points relative to changes of sparsentan exposure (e.g., dose change, challenge and rechallenge). This includes information on:
   a) The liver enzyme test RESULTS (e.g., for ALT/AST, normal, >2X upper limit of normal (ULN),>3X ULN, >5X ULN, or higher), and

b) the amount of time (in days) between the testing and any start/stop/increase/decrease in the sparsentan exposure.
2. Information on alternative exposures or alternative causes of liver injury, and
3. The determination of a (required) Hepatic Adjudication Committee (HAC), made up of physicians who are liver disease experts, on the relationship of sparsentan's exposure to an identified adverse liver event.

4.2. Is ARIA sufficient to assess the outcome of interest?

No, ARIA is not sufficient. Although some laboratory results data are available within ARIA (ALP, ALT, total bilirubin), it cannot be guaranteed that this information would be available in electronic healthcare data at pre-defined times relative to a specific drug exposure. Primary data collection is needed to collect the above case-level information (including determinations of a HAC) to fully characterize the outcome and assess causality.

5. COVARIATES

5.1. Covariates of Interest

Medical history (history of liver disease/impairment, comorbidities, trauma) and other drug exposures that could cause liver injury. This information is essential for the HAC to determine whether liver injuries are associated with sparsentan use.

5.2. Is ARIA sufficient to assess the covariates of interest?

No, ARIA is not sufficient. It would be difficult to create a valid algorithm based on claims data (even with customized programming) to capture the medical history/comorbidities /trauma that could potentially explain adverse liver events. A study with primary data collection on relevant medical history (liver disease/trauma) is necessary to capture rigorous data on these covariates to allow HAC to determine whether liver injuries are attributable to sparsentan use.

6. SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1. Surveillance or Study Design

This is a descriptive study to characterize the frequency and clinical features of DILI risk associated with sparsentan use.

6.2. Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, ARIA analytic tools are sufficient for a descriptive study.

7. NEXT STEPS

If the application moves toward approval, the language for a PMR observational study would need to be finalized. The currently proposed PMR language is:

> Conduct a prospective, single-arm safety study of patients exposed to sparsentan, with 2 years of follow-up to assess and characterize the risk of drug induced liver injury (DILI). This study should analyze the clinical features of DILI cases with sparsentan, such as the injury's severity, type, latency, and specifically evaluate the incidence of Hy's law cases. Information for liver injury cases should be captured with structured follow up (e.g., monthly monitoring of serum liver tests) including dechallenge and rechallenge results. A hepatic adjudication committee (HAC) should assess both the severity of the liver injury and sparsentan's role in its development (i.e., causality). This study should aim to enroll enough patients such that if 0 events of Hy's law are observed, then the upper bound of the 95% confidence interval for the rate of Hy's law will be 1/1000.

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/s/

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MINGFENG ZHANG
02/14/2023 02:27:50 PM

MONIQUE FALCONER
02/14/2023 02:52:52 PM

JUDITH W ZANDER
02/14/2023 03:00:56 PM

PATRICIA L BRIGHT
02/14/2023 03:38:43 PM

ROBERT BALL
02/14/2023 03:58:12 PM

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

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

Memorandum

Date: January 30, 2023

To: Rekha Kambhampati., MD., Clinical Reviewer
Division of Cardiology and Nephrology (DCN)

Anna Park, Regulatory Project Manager (DCN)

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

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for
FILSPARI® (sparsentan), tablets for oral use

NDA: 216403

Background:

In response to DCN's consult request dated April 14, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and Medication Guide (MG for the original NDA for FILSPARI® (sparsentan), tablets for oral use (Filspari).

PI/MG:

OPDP's review of the proposed PI is based on the draft labeling provided via email by DCN on January 17, 2023, and our comments are provided below.

OPDP comments on the proposed MG was sent under separate cover, as a combined OPDP and Division of Medical Policy Programs (DMPP) review on January 26, 2023.

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

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

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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:	January 26, 2023
To:	Anna Park, MS, RPh, RAC 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:	Ruth Mayrosh, 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):	FILSPARI (sparsentan)
Dosage Form and Route:	tablets for oral use
Application Type/Number:	NDA 216403
Applicant:	Travere Therapeutics, Inc.

1 INTRODUCTION

On March 17, 2022, Travere Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 216403 for FILSPARI (sparsentan) tablets. The proposed indication for FILSPARI (sparsentan) tablets is for the treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older.

On October 13, 2022, the Applicant submitted a major amendment to the application; therefore, the Agency extended the goal date by three months in order to provide time for a full review of the submission.

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 15, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for FILSPARI (sparsentan) tablets.

The Risk Evaluation and Mitigation Strategy (REMS) was reviewed by the Division of Risk Management (DRISK) and was provided to DCN under separate cover on December 12, 2022.

2 MATERIAL REVIEWED

- Draft FILSPARI (sparsentan) tablets MG received on March 17, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 17, 2023.
- Draft FILSPARI (sparsentan) tablets Prescribing Information (PI) received on March 17, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 17, 2023.
- Approved OPSUMIT (macitentan) tablets comparator labeling dated October 25, 2021.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible

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

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CHARUNI P SHAH
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LASHAWN M GRIFFITHS
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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, DRM
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Charuni Shah, Regulatory Review Officer, OPDP

CC: Susannah O'Donnell, Team Leader, OPDP
Deveonne Hamilton-Stokes, Safety Regulatory Project Manager, OSE
Yasmeen Abou-Sayed, Team Leader, DRM
Theresa Ng, Risk Management Analyst, DRM
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: January 25, 2023

Re: NDA 216403
FILSPARI® (sparsentan), tablets for oral use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for FILSPARI® (sparsentan), tablets for oral use (Filspari):

- Healthcare Provider (HCP) REMS Materials:
  - Change in Reproductive Status Form
  - Inpatient Pharmacy Enrollment Form
  - Outpatient Pharmacy Enrollment Form
  - Prescriber Enrollment (b) (4) Form
  - Prescriber and Pharmacy Guide

- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Enrollment (b) (4) Form
  - Patient Guide

- FILSPARI REMS Website

The version of the draft REMS materials used in this review were sent from DRM Katherine Hyatt Hawkins Shaw via email on January 13, 2023. The draft REMS materials are attached to the end of this review memorandum.

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

General Comments

Please remind Travere Therapeutics, Inc. (Travere) that REMS materials are not appropriate for use in a promotional manner.

OPDP notes links such as www.FILSPARIREMS.com and toll-free numbers such as 1-833-513-1325. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Travere that the REMS specific website should not be the sole source of approved REMS materials.

Comments are provided using the draft product labeling (PI) for Filspari dated January 17, 2023 and Medication Guide (MG) dated January 23, 2023.

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

REMS Materials

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

- Change in Reproductive Status Form
- Inpatient Pharmacy Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Prescriber Enrollment [redacted] Form
- Prescriber and Pharmacy Guide
- Patient Enrollment [redacted] Form
- Patient Guide
- FILSPARI REMS Website

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS piece:

- Prescriber and Pharmacy Guide

  - **Indications/Use**

    "INDICATION
    FILSPARI is indicated [redacted] (Page one)

    - This claim is an inadequate communication of the indication. Specifically, the Indications and Usage section of the draft product labeling (PI) for Filspari states (underlined emphasis added), "Filspari is…indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥[redacted] g/g." We recommend revising this claim to include the full approved indication from the PI for Filspari.

  - **Risk**

    "RISK OF HEPATOTOXICITY

    [redacted]

    [redacted] " (Page one)

- These claims omit REMS material information from the WARNINGS AND PRECAUTIONS, Hepatoxicity section of the draft PI. Specifically, the draft PI for Filspari states, "Avoid initiation of FILSPARI in patients with elevated aminotransferases (> 3x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult and these patients may be at increased risk for serious hepatotoxicity." We recommend revising these claims to include this material information.

- Patient Guide

  - **Indications/Use**

    "INDICATION
    FILSPARI is a prescription medicine used to (b) (4) " (Page one)

    - This claim is an inadequate communication of the indication. Specifically the **"What is FILSPARI?"** section of the draft Medication Guide (MG) for Filspari states, "FILSPARI is a prescription medicine used to reduce levels of protein in the urine (proteinuria) in adults with a kidney disease called primary immunoglobulin A nephropathy (IgAN), who are at high risk of disease progression." We recommend revising this claim to include the full indication for Filspari.

  - **Risk**

    "WHAT ARE THE SERIOUS RISKS OF FILSPARI?

    FILSPARI can cause serious birth defects if taken during pregnancy." (Page one)

    - This claim omits material information from the draft MG for Filspari. Specifically, the "**What is the most important information I should know about FILSPARI?"** section of the MG states the following (underlined emphasis added): "**FILSPARI can cause serious birth defects** (b) (4) **if taken during pregnancy.**" We recommend revising this claim to include this material information.

    "FILSPARI Tell your healthcare provider right away if you have any of these symptoms of liver problems while taking FILSPARI:

        - **Nausea**
        - **Vomiting**
        - **Fever**
        - [redacted] **tiredness**
        - [redacted]
        - **Yellowing of the skin or the whites of your eyes (jaundice)** (Page seven)

    - OPDP notes that the current version of the draft MG includes additional signs and symptoms for liver problems. We recommend revising the draft patient materials to be consistent with the final approved MG.

- REMS Website

    - We recommend applying the above comments to any and all of the same or similar claims or presentations in the REMS Website.

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

Thank you for your consult.

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CHARUNI P SHAH
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Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	216403
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Sparsentan
Indication	Immunoglobulin A nephropathy (IgAN)
Applicant	Travere Therapeutics
Requesting Division	Division of Cardiology and Nephrology (DCN)
Primary Reviewer	Ling Lan, MD, PhD Clinical Analyst, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Frank Anania Acting Director, OND/DHN
Assessment Date	Sep 15, 2022

Context: Sparsentan is a first-in-class, single molecule that acts as a dual endothelin angiotensin receptor antagonist (DEARA) for endothelin type A receptor (ET_AR) and angiotensin II (Ang II) receptor type 1 (AT1). It is taken orally. (b) (4), the target disease is immunoglobulin A nephropathy (IgAN), and drug induced liver injury (DILI) was an AE of special interest (AESI). The Division of Cardiology and Nephrology (DCN) noted more hepatic events in those treated with SPTN, and one severe AE of ALT elevation in a focal segmental glomerulosclerosis (FSGN) study. DCN requested the DILI Team help assess the SPTN's hepatotoxicity potential, comment on labeling, and identify risk mitigation strategies.

Executive Summary: Sparsentan (SPTN) can lead to hepatocellular liver injury, but there were no Hy's Law cases in this NDA. We can support approval and help with labeling, if efficacy and an unmet need are clear. However, there are significant challenges for assessing and mitigating the risk of severe DILI post-approval. There was an imbalance in AT elevation in Temple's Corollary, including probable DILI cases with positive rechallenges. Moreover, the time from drug start to DILI onset was long, measured in months not weeks, so monitoring for longer periods of time will need consideration. The liver injuries were usually modest resolving when SPT was withheld, but the number of chronic kidney disease subjects exposed to SPTN in the ISS was only 500. This size is well below the desired threshold of a few thousand which can provide a 95% chance of detecting a 1 in 1000 risk of a Hy's Law case. Therefore, we are concerned that severe liver injury could arise in the larger post-market population, particularly if SPTN is not withheld as quickly as it was in the clinical trials. Our full assessment and recommendations are in Section 5.0. We provide line-item recommendations for both approval and non-approval scenarios.

Full Consultation Sections:

Section 1.0 – 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.

Abbreviations:
ACEi: angiotensin-converting enzyme inhibitor
ALP: alkaline phosphatase
ALT: alanine aminotransferase
ARBs: angiotensin receptor blockers
AST: aspartate aminotransferase
AT1: angiotensin II receptor type 1
CKD: chronic kidney disease
DB: double blind
DILI: drug-induced liver injury
eGFR: estimated glomerular filtration rate
ET_AR: endothelin type A receptor
GGT: gamma-glutamyl transferase
HDS: herbal/dietary supplements
IgAN: immunoglobulin A nephropathy
OLE: open-label extension
OTC: over the counter
DEARA: dual endothelin angiotensin receptor antagonist
SOC: standard of care
SPTN: sparsentan
TA: transaminase (ALT and/or AST)
TB: total bilirubin
ULN: upper limit normal

1.0 Disease and Rationale:

1.1 Disease: IgA nephropathy (IgAN), also known as Berger's disease, is the most common cause of primary glomerulonephritis worldwide. It affects all ages with a peak incidence in the second and third decades of life. The prevalence is the greatest in East Asians (around 45% in a study from China) and Whites, and relatively rare in Blacks[1]. Males are affected twice as frequently in Whites, but the sex ratio is even in East Asians. Peak incidence is in the 2nd to 3rd decades of life, but children can also be affected. Clinical presentation is wide from asymptomatic hematuria to nephrotic syndrome and progressive GN. Of note, chronic liver disease, particularly alcoholic liver

[1] https://www.uptodate.com/contents/iga-nephropathy-clinical-features-and-diagnosis, accessed on July 29, 2022

disease, is a well-described disease association. Celiac disease, which is in turn associated with chronic liver disease, is also associated with IgAN.

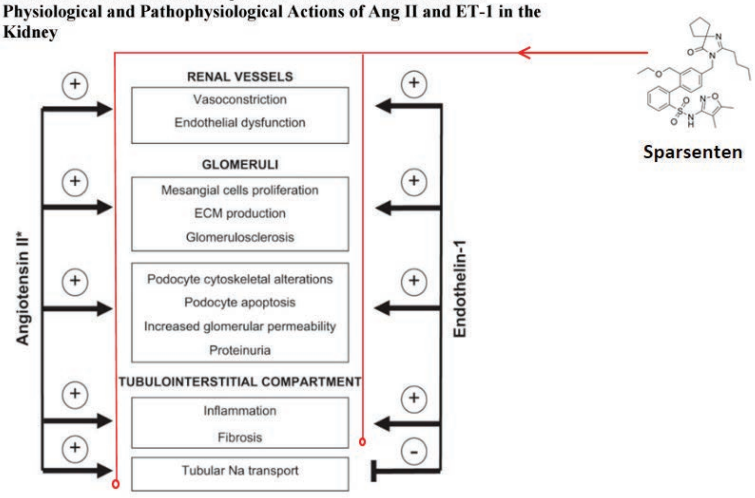
IgAN is a chronic autoimmune disease in which up to 40% of patients progress to end-stage renal disease within 20 years of diagnosis[2,3,4]. Overt proteinuria or elevated serum creatinine occur progression to end-stage renal disease is up to 25% at 10 years. The diagnosis requires a kidney biopsy with the presence of mesangial deposits of IgA. About 30-40% of IgAN patients are detected on routine urine screening because their only clinical manifestation is asymptomatic hematuria and proteinuria. Patients with nephrotic syndrome are the target population of sparsentan.

Standard of care (SOC) treatment includes anti-hypertensive agents, particularly those acting on the renin-angiotensin-aldosterone system (RAAS) such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs). These agents slow disease progression. Short-term glucocorticoids are used for patients at high risk of progressive disease. FDA approved budesonide in December 2021 as the first agent to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression. A variety of other immunosuppressive medications are used as well, including mycophenolate mofetil, calcineurin inhibitors, rituximab, cyclophosphamide, azathioprine, leflunomide and hydroxychloroquine.

1.2 Rationale (mechanism of action): Sparsentan is an orally active, single molecule, highly selective, dual endothelin and angiotensin receptor antagonist (DEARA) for ET_AR and AT1. The sponsor expects a positive effect of sparsentan on the pathophysiological changes in the glomeruli and tubulointerstitial compartment that occurs in IgAN, given the role of endothelin-1 (ET-1) and Ang II in glomerulonephropathies. (Figure 1)

[2] Manno et. al. Am J Kidney Dis 2007
[3] Berthoux et. al. J Am Soc Nephrol 2011
[4] Moriyama et. al. PLoS One 2014

Figure 1: **Schematic Presentation of Major Similarities and Differences in Physiological and Pathophysiological Actions of Ang II and ET-1 in the Kidney**

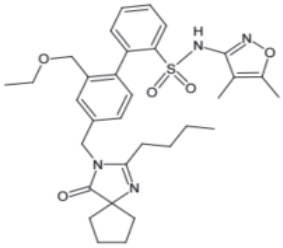


Ang II = angiotensin II; ECM = extracellular matrix; ET-1 = endothelin-1.
Notes: Schematic presentation of major similarities and differences in physiological and pathophysiological actions of Ang II and ET-1 in the kidney. Both peptides have similar impact on processes implicated in renal pathophysiology (impact, indicated by "+" sign). In contrast, they differ in their role in the control of tubular transport (lacking evidence of impact, indicated by "-" sign).
* Applies also to aldosterone.

2.0 ADME pertinent to DILI:

2.1 Chemical structure

Figure 2: Skeletal structure of sparsentan



2.2 Absorption: Following an oral administration, sparsanten showed good absorption (>50%) in humans. Studies using Caco-2 cells (human colon carcinoma cells resembling small intestine cells after differentiation) suggest absorption in humans is via the transcellular route. Bioavailability in rats is 56% with rapid absorption (T_{max} of 0.65 hours). Bioavailability was 32% in male cynomolgus monkeys following an oral dose of 10 mg/kg. The sponsor suggests incomplete absorption or the influence of first pass metabolism may result in lower bioavailability in monkeys.

Oral administration of 10 mg/kg of SPTN as an aqueous solution in dogs resulted in an AUC of 49,458 ng.h/mL, Cmax 11125 ng/mL and half-life of 1.47 hour. In three male dogs, the oral bioavailability of an aqueous solution and (b) (4) solution at 10 mg/kg were similar at 67.5% and 77.1% respectively. (Table 1)

Thus, sparsentan is well absorbed in humans and is expected to have reasonable bioavailability.

Table 1: Absorption parameters for different forms of sparsentan.

Form	Cmax (ng/mL)	Tmax* (h)	AUC(INF) (ng•h/mL)	MRT(INF) (h)	T-HALF (h)	Relative F (%)
PEG solution	17563 (3027)	0.25 (0.25, 0.25)	69840 (20543)	2.90 (0.59)	1.20 (0.57)	--
Aqueous suspension	11125 (4758)	1.00 (0.75, 2.00)	49458 (28414)	3.33 (0.39)	1.47 (0.30)	67.5 (18.5)
(b) (4) aqueous suspension	13194 (5631)	0.75 (0.25, 2.00)	57474 (41656)	3.16 (0.98)	1.52 (0.75)	77.1 (34.7)

* median (minimum, maximum)

2.3 Distribution: Sparsentan is highly protein bound (>90% bound). In vitro protein binding to human serum albumin and human a1-Acid Glycoprotein (AAG) was concentration dependent. Accordingly, volume of distribution is expected to be high in humans, but on target levels comparatively low.

2.4 Metabolism: Studies done on several species showed the metabolism of sparsentan to be moderate to extensive after four hours of incubation. The relative percentages of parent drug in human, monkey, dog, rat, and mouse hepatocytes were 84.0%, 46.3%, 83.8%, 61.1%, and 66.9% respectively. Seventeen metabolites were detected in human hepatocytes. The biotransformation of these metabolites was primarily due to oxidation. All metabolites in human hepatocytes incubation were detected in one or more animal species. Sixty-five metabolites were identified in the bile of rats with the major biotransformation pathway being mono-oxygenation.

Using expressed recombinant human enzymes CYPs incubated with 10 µM sparsentan, CYP3A4 was the major metabolizing CYP isoform and CYP2C8 played a minor role. In a six-month toxicity study in rats, the NOAEL was 80 mg/kg/day. A thirteen-week study in rats, NOAEL was 320 mg/kg/day, and in a nine-month monkey study at the PO dose of 0, 50, 125, and 200 mg/kg, the NOAEL was 50 mg/kg. We found no glutathione trapping data in this application.

Thus, the biotransformation of this drug was predominantly in the liver with many metabolites. However, the percent of parent drug in human serum is relatively high at 84%.

2.5 Elimination: Biliary clearance of sparsentan is high. Following 12-hour oral administration of 25 mg/kg in four male rats, an average of 72% and 2% of the dose was excreted in bile and urine respectively. During toxicokinetic analysis in a 13-week oral toxicity study in mice, half-life estimates were <1 hr (0.66 to 0.85) with t_{last}=8 hrs.

Therefore, bile was found to be the primary route of excretion.

2.6 Transporter inhibition: In vitro studies suggest sparsentan inhibited OATP1B3, OATP1B1, OATP2B1, and NTCP. Using Caco-2 cells, sparsentan was a weak inhibitor of the efflux transporter P-glycoprotein. SPTN is likely a substrate for BSEP and further investigation of BSEP. SPTN at 300 µM fully inhibited the vesicular transport of E2β17G in MRP2 containing membrane vesicles and Estrone-3-sulfate in BCRP containing vesicles. Additionally, it strongly inhibited BSEP in the vesicular transport assay with the IC50<10 µM. The sponsor mentioned drew no direct conclusions on whether SPTN is an inhibitor of BSEP. Nevertheless, sparsentan may inhibit MRP_2 and BSEP which may be pertinent to DILI risk.

3.0 Non-clinical data related to DILI

3.1 In vitro data: Based on studies using cultured immortalized human hepatocytes with defined CYP3A4 activity, sparsentan is a CYP3A4 inhibitor (IC50:6 µM at 65 minutes) with a kinetic profile similar to aminobenzotriazole which is a reference CYP3A4 inhibitor. In human hepatic microsomal studies, sparsentan showed direct inhibition of hepatic CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 and metabolism dependent inhibition of CY2B6, CYP2D6, and CYP3A4/5. (b) (4) Sparsentan significantly inhibited CYP2C8 and CYP3A4 in a concentration dependent manner following co-incubation with specific substrates and pooled human liver microsomes. (Table 2) It significantly inhibited CYP3A4 only when midazolam was used as a substrate.

Table 2. IC_{50} values* (µM) for CYP3A4 inhibition.

Test Article	Time of Exposure (min)			
	5	20	50	65
BMS-346567	33.81 ± 2.41	15.75 ± 2.09	8.56 ± 0.96	5.74 ± 0.45
Aminobenzotriazole	10.94 ± 1.85	3.96 ± 0.30	4.05 ± 0.24	0.90 ± 0.01
Ketoconazole	0.35 ± 0.02	0.19 ± 0.01	0.05 ± 0.01	0.05 ± 0.002
Mibefradil	2.82 ± 0.39	1.40 ± 0.22	1.50 ± 0.07	1.19 ± 0.07
Troleandomycin	3.64 ± 0.39	0.47 ± 0.09	1.22 ± 0.04	0.79 ± 0.34

* Mean (n = 3) ± SE

Thus, the study drug may have accumulation and toxicity potential since it is metabolized by CYP3A4 and inhibits this same CYP. It is unclear to us whether time dependent inhibition (TDI) occurs. Study RE-021-007 makes one reference to TDI, and the summary wording is vague (page 60).[5] Upon review of the primary data, the DILI Team believes there may be TDI of

[5] Study RE-021-007: Inhibitory Potential of Sparsentan towards Human Hepatic Microsomal Cytochrome P450 Enzymes. NDA216403 (216403 - 0035 - (35) - 2022-07-29 - ORIG-1 /Quality/Response To Information Request) - RE-021-0007 (#60)

CYP3A4. Besides concerns for intra-hepatic dug accumulation, CYP3A4 metabolizes many other drugs including acetaminophen which may have implications for DILI.

3.2 Animal data:

3.2.1 Liver injury marker data: Following a 13-weeks oral toxicity study in mice, mild non-statistically significant dose dependent increases in ALT was observed at 750 mg/kg/day. There was also an elevation in ALP in males at this same dose. A statistically significant increase in liver weight was observed in mice at both the 200 and 750 mg/kg/day doses which was associated with hepatocellular hypertrophy.

3.2.2 Liver histopathology: Thirteen-week oral toxicity study in mice of SPTN at 50, 200, and 750 mg/kg/day showed minimal to moderate single cell necrosis of hepatocytes in some animals. All male and female mice receiving SPTN at 750 mg/kg/day had hepatocellular hypertrophy. Several mice had hepatocellular hypertrophy at 50 and 200 mg/kg/day doses. Mice and rats receiving sparsentan single oral 2000 mg/kg did not show any gross-pathologic lesions at 2 weeks post dose observations, so no histopathologic evaluation was conducted. Microscopic changes correlated with mild increase in ALT.

Following a 26-week toxicity study in rats with 8-week recovery, there was an increase in liver weight in correlation with gross liver enlargement in some females receiving SPTN at 320 mg/kg/day. Changes resolved by day 239 of the study. These findings were related to SPTN. On day 183 of the study, there was hepatocellular hypertrophy in males at 15, 80, and 320 mg/kg/day and in females at 80 and 320 mg/kg/day.

Thus, SPTN was associated with liver histopathology in animals, including mild to moderate necrosis that correlated with mild increase in ALT.

4.0 Clinical data

4.1 In class or near class DILI data: Sparsentan is the first-in-class dual endothelin and angiotensin receptor antagonist (DEARA) for ETAR and AT1, but there are three marketed ETAR antagonists that are pertinent.

LiverTox® reports ETAR antagonists 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.[6] Rare instances of severe liver injury are

[6] LiverTox: https://www.ncbi.nlm.nih.gov/books/NBK548723/ accessed on July 29, 2022

reported. Three endothelin receptor antagonists (bosentan, ambrisentan, macitentan) are approved for pulmonary hypertension. (Table 3)

Table 3: Labeling and LiverTox® comments for approved ETAR antagonists

ETAR antagonist	Liver injury labeling	LiverTox®[6]
Bosentan	Box warning Check baseline and monthly monitoring	7-8% TA elevation; 3-4% drug stop; rare jaundice; Latency 1-6 mo. Likelihood score: C
Ambrisentan	None	0-3% TA elevation; rare severe injury Latency 1-6 mo. Likelihood score: E
Macitentan	Warning and precaution Check baseline and monitor as indicated.	0-4% TA elevation; rare clinically significant elevation Latency 1-6 mo. Likelihood score: E*

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 angiotensin II receptor antagonists, also known as ARBs (including the active comparator irbesatan used in sparsentan studies), are considered rare causes of clinically apparent liver injury. LiverTox reported Irbesartan associated transient serum aminotransferase elevations (<2%) within one to eight weeks of starting therapy, that rarely required dose modification. Rare instances of clinically apparent acute liver injury have been reported in associated with irbesartan. The serum enzyme pattern is typically hepatocellular with an acute hepatitis-like clinical syndrome. In some instances, cholestasis has developed which can be prolonged and relapsing, but irbesartan therapy has not been associated with vanishing bile duct syndrome or chronic liver injury. Immunoallergic manifestations (rash, fever, eosinophilia) are not common, nor is autoantibody formation. Serum aminotransferase levels may also be raised during ARB therapy due to fatty liver and steatohepatitis in patients who develop the severe ARB-related enteropathy[7].

4.2 Summary of Studies:

The sparsentan program includes various studies in healthy volunteers and multiple indications including IgAN and FSGS. This IgAN application included only one clinical study report (CSR) based on interim results from the pivotal phase 3 study 021IGAN17001 (PROTECT), *A Randomized, Multicenter, Double-blind, Parallel-Group, Active-Control Study of the Efficacy and Safety of Sparsentan for the Treatment of Immunoglobulin A Nephropathy*. (Table 4)

[7] LiverTox: https://www.ncbi.nlm.nih.gov/books/NBK548450/ accessed on July 29, 2022

There is a brief summary of two ongoing FSGS studies (DUET and DUPLEX) in the ISS and PROTECT CSR. After discussion with DCN, we decided to focus on PROTECT for study level DILI evaluation. However, case level assessment includes subjects from non-IgAN indications with liver biochemistry abnormalities.

Table 4 Clinical Study in IgAN Patients

Study	Phase	Design and Duration	Participants and Number	Placebo or SOC
021IGAN17001 (PROTECT)	3	114-wk study: Period 1: 110-week R (1:1), DB, SOC Period 2: OLE	404	Yes

DB = double blind; SOC = standard of care; OLE = open label extension; R = randomized

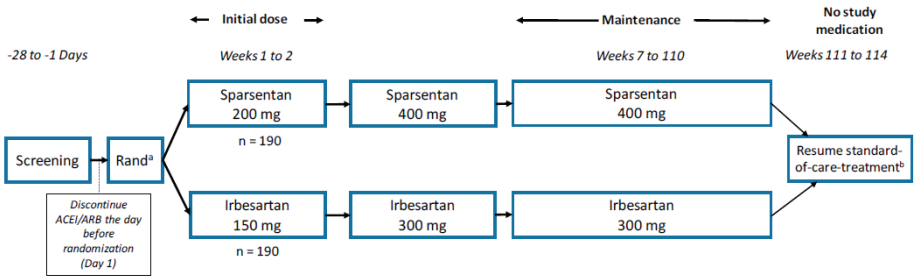
Source: DILI team

4.2.1 Phase 3 study design features related to DILI evaluation:

Study population: PROTECT included adult patients with biopsy-proven IgAN on a stable dose of RAS inhibitor therapy, proteinuria ≥ 1 g/day and eGFR ≥30 mL/min/1.73 m^2.

Study periods: (Figure 3). Note that there was an open label extension opportunity at the Week 110 visit. Patients with an eGFR value of <30 (but >20) mL/min/1.73 m2 were eligible for participation.

Figure 3: Study PROTECT Schematic



Source: PROTECT Protocol Amendment 5, Page 35

Exclusion criteria: Subjects with jaundice, hepatitis, or known hepatobiliary disease (excluding asymptomatic cholelithiasis), or ALT and/or AST >2 x ULN at screening.

Pre-specified Liver Related Adverse Event of Interest (AESI): If a subject with normal baseline patient has post-baseline ALT or AST > 3x ULN, or a subject with elevated baseline ALT or AST has post-

baseline ALT or AST > 2x baseline value, treatment is held with repeat liver biochemistries within 48-72 hours. If the abnormality persisted, liver enzymes and bilirubin were monitored two to three times a week, and INR was measured as needed until the abnormality stabilized and the subject became asymptomatic.

Treatment was stopped for any of the following:

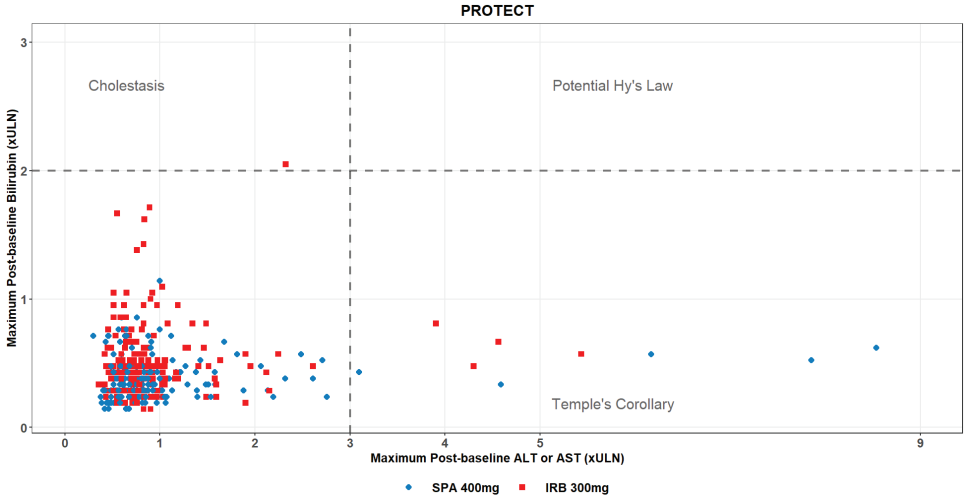
- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and total bilirubin >2 x ULN or INR >1.5
- ALT or AST >3 x ULN, with symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5% eosinophils)

4.2.2 Study Level Findings relevant to DILI

4.2.2.1 Study PROTECT (Phase 3, R, DB, SOC with OLE; n = 404)

No subject met the criteria for Hy's Law. There were no subjects with jaundice. Some cases fell into Temple's Corollary (Figure 4). More sparsentan subjects fell into ALT or AST > 5 x ULN region of Temple's Corollary quadrant. This imbalance would be consistent with potential increased hepatocellular injury risk. (Table 5)

Figure 4: PROTECT eDISH



Source: FDA CDS output

Table 5: PROTECT Post-baseline Liver Biochemistry

Laboratory Abnormality	SPA 400mg N=202 n (%)	IRB 300mg N=202 n (%)	SPA 400mg vs IRB 300mg Risk Difference (%) (95% CI)
ALT			
≥3X ULN	5/202 (2.5)	4/201 (2.0)	0.5 (-2.4, 3.4)
≥5X ULN	3/202 (1.5)	0/201 (0)	1.5 (-0.2, 3.2)
≥10X ULN	0/202 (0)	0/201 (0)	0 (0, 0)
AST			
≥3X ULN	2/202 (1.0)	2/201 (1.0)	-0.0 (-1.9, 1.9)
≥5X ULN	0/202 (0)	1/201 (0.5)	-0.5 (-1.5, 0.5)
≥10X ULN	0/202 (0)	0/201 (0)	0 (0, 0)
ALP			
≥2X ULN	1/202 (0.5)	0/201 (0)	0.5 (-0.5, 1.5)
Total Bilirubin			
≥2X ULN	0/202 (0)	1/201 (0.5)	-0.5 (-1.5, 0.5)
Direct Bilirubin			
≥2X ULN	0/202 (0)	0/201 (0)	0 (0, 0)
GGT			
≥2X ULN	16/202 (7.9)	8/201 (4.0)	3.9 (-0.7, 8.5)
INR			
≥1.5X ULN	1/198 (0.5)	2/197 (1.0)	-0.5 (-2.2, 1.2)

Source: DILI team adapted from CDS report

4.3 Integrated Safety Summary (ISS): While the ISS included other studies, the information on these in progress studies was limited and/or had no CSRs submitted with this IgAN NDA. Therefore, we limited our study level analysis to the largest phase 3 study (PROTECT) as outlined above.

4.4 Estimation of subjects exposed for this NDA: Based on the ISS document, the number of subjects with chronic kidney disease (CKD) exposed to SPTN in an RCT is 504. (Table 6)

Table 6: ISS subject counts by study arms.

Sparsentan ISS for IgAN

Table 1.1.1
Number of Subjects in Each Study by Study Pool and ISS Treatment Group
All Studies
Safety Analysis Set

	Double-blind				
	Placebo n (%) (N=95)	Irbesartan n (%) (N=483)	Sparsentan n (%) (N=680)	All Sparsentan n (%) (N=1249)	All Subjects n (%) (N=1813)
IgAN Study Pool	NA	202 (41.8)	202 (29.7)	212 (17.0)	405 (22.3)
PROTECT	NA	202 (41.8)	202 (29.7)	211 (16.9)	404 (22.3)
SPARTAN001	NA	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
FSGS Study Pool	NA	223 (46.2)	257 (37.8)	293 (23.5)	480 (26.5)
DUPLEX	NA	187 (38.7)	184 (27.1)	185 (14.8)	371 (20.5)
DUET	NA	36 (7.5)	73 (10.7)	108 (8.6)	109 (6.0)
CKD RCT Study Pool [a]	NA	425 (88.0)	459 (67.5)	504 (40.4)	884 (48.8)
Hypertension Study Pool	95 (100.0)	58 (12.0)	221 (32.5)	221 (17.7)	374 (20.6)
PCO-C-006	59 (62.1)	58 (12.0)	144 (21.2)	144 (11.5)	261 (14.4)
PCO-C-008	36 (37.9)	NA	77 (11.3)	77 (6.2)	113 (6.2)
Healthy Volunteers Study Pool	NP	NP	NP	523 (41.9)	554 (30.6)
Hepatic Impaired Cohort	NA	NA	NA	16 (1.3)	16 (0.9)
Healthy Subjects [b]	NP	NP	NP	507 (40.6)	538 (29.7)

Abbreviations: CKD=chronic kidney disease, FSGS=focal segmental glomerulosclerosis, IgAN=immunoglobulin A nephropathy, NA=not applicable, NP=not presented, RCT=randomized controlled trial.
Note 1: Data cutoff dates were 22Jan2021 for DUPLEX, 05Feb2021 for DUET, 01Aug2021 for PROTECT, and 14Sep2021 for SPARTAN001.
2: All Sparsentan column includes subjects who received at least one dose of sparsentan during any treatment period. Subjects are counted only once regardless of different sparsentan doses received.
3: All Subjects column includes subjects who received at least one dose of study drug during any treatment period. Subjects are counted only once regardless of different treatments received.
[a] CKD RCT Study Pool includes PROTECT, DUPLEX and DUET.
[b] Includes the normal hepatic function cohort in Study 021IHFX16009 who received sparsentan.

4.5 Case level analysis:

4.5.1 We reviewed 9 cases of potential DILI from PROTECT and DUET and one case from DUPLEX based on liver tests and/or liver related SAEs. These cases fell in Temple's Corollary quadrant and/or were identified as having significant liver related SAEs. No subjects had serum liver test elevations that would meet Hy's Law.

Of these ten, we considered five as probable DILI due to SPTN, three as possible, and two as unlikely. Both the unlikely DILI subjects (b) (6) & (b) (6); RET-D-001 DUET) had only modest ALT elevations (3-5 x ULN) and resolution of injury while still on SPTN. The sources of these elevations were unknown, but DILI with tolerance could not be ruled out. We show the data for the remaining possible and probable cases in Table 7.

Table 7: Summary demographics and serum liver tests for cases with probable or possible DILI due to SPTN.

#	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)	R value peak (AST)
1	(b) (6)	3	NA	021IGAN17001 PROTECT	47	M	White	No	168	-85	805	480	104	1.6	23.7	14.1
2		3	NA	021IGAN17001 PROTECT	27	M	White	No	257	-118	277	89	104	0.6	8.1	2.6
3		3	NA	021IGAN17001 PROTECT	55	M	White	No	166	-2	350	144	113	0.8	9.5	3.9
4		3	NA	021IGAN17001 PROTECT	54	M	Latinx	No	406	-6	188	76	104	0.3	5.5	2.2
5		3	NA	021FSGS16010	42	M	Latinx	No	82	-22	759	504	104	0.6	22.3	14.8
6		4	Gallstone disease	021IGAN17001 PROTECT	72	M	White	No	174	-3	322	177	104	0.6	9.5	5.2
7		4	Unknown	RET-D-001 DUET	65	F	White	No	28	0	179	103	191	0.5	2.9	1.6
8		4	Acute hepatitis C	RET-D-001 DUET	38	M	White	No	319	-30	1288	420	155	0.6	25.4	8.3
				Mean	*50*				*200*	*-33*	*521*	*249*	*122*	*0.7*	*13.4*	*6.6*
				Std dev	*13.7*				*115*	*41*	*368*	*173*	*31*	*0.4*	*8.4*	*4.9*
				Median	*50.5*				*171*	*-14*	*336*	*161*	*104*	*0.6*	*9.5*	*4.6*
				Min	*27*				*28*	*-118*	*179*	*76*	*104*	*0.3*	*2.9*	*1.6*
				Max	*72*				*406*	*0*	*1288*	*504*	*191*	*1.6*	*25.4*	*14.8*

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate
^For R-value calculations, ULN of 104 U/L for ALP imputed when peak ALP remained normal
NA = not applicable

We show just the probable cases in Table 8.

Table 8: Summary demographics and serum liver tests for cases with probable DILI due to SPTN.

#	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)	R value peak (AST)
1	(b) (6)	3	NA	021IGAN17001 PROTECT	47	M	White	No	168	-85	805	480	104	1.6	23.7	14.1
2		3	NA	021IGAN17001 PROTECT	27	M	White	No	257	-118	277	89	104	0.6	8.1	2.6
3		3	NA	021IGAN17001 PROTECT	55	M	White	No	166	-2	350	144	113	0.8	9.5	3.9
4		3	NA	021IGAN17001 PROTECT	54	M	Latinx	No	406	-6	188	76	104	0.3	5.5	2.2
5		3	NA	021FSGS16010 DUPLEX	42	M	Latinx	No	82	-22	759	504	104	0.6	22.3	14.8
				Mean	*45*				*216*	*-47*	*476*	*259*	*106*	*0.8*	*13.8*	*7.5*
				Std dev	*10.18*				*110*	*47*	*256*	*192*	*4*	*0.4*	*7.6*	*5.7*
				Median	*47*				*168*	*-22*	*350*	*144*	*104*	*0.6*	*9.5*	*3.9*
				Min	*27*				*82*	*-118*	*188*	*76*	*104*	*0.3*	*5.5*	*2.2*
				Max	*55*				*406*	*-2*	*805*	*504*	*113*	*1.6*	*23.7*	*14.8*

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate
^For R-value calculations, ULN of 104 U/L for ALP imputed when peak ALP remained normal
NA = not applicable

The pattern of injury was largely hepatocellular (R values $\geq$ 5) with only two cases with mixed or cholestatic injuries. Both were

possible DILI due to SPTN. Latencies were unusually long for the possible and probable cases. The means are skewed by one probable case with latency of 406 days. Nevertheless, limiting latency data to probable cases lengthened the median to 213 days (7 months). While not typical, long latency DILI is well-documented for other drugs. Moreover, the probable DILI due to SPTN cases had positive rechallenges supporting this long latency finding (see case level analyses below).

4.5.2 We discuss the four probable DILI cases and one possible case in more detail below:

4.5.2.1 Subject (b) (6) (Study 021IGAN17001 PROTECT):

Summary: This is a 47-year-old white man with IgAN.

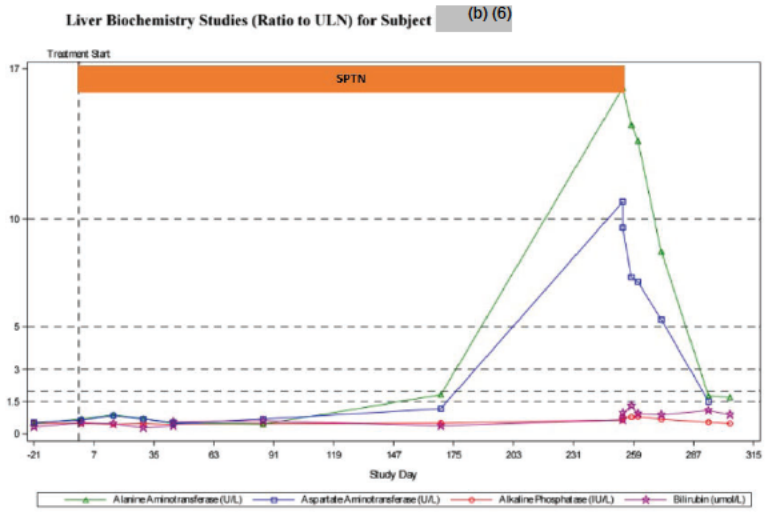
At baseline, he had a history of appendectomy, left inguinal hernioplasty and allergic asthma. The subject's medication history included irbesartan, beclomethasone-formoterolo (inhaler), ramipril, and urodeoxycholic acid. He had received Pfizer COVID-19 vaccination. His ALT was 29 U/L, AST 24 U/L, AP 64 U/L, and TB 0.64 mg/dL (direct <0.018 mg/dL, normal range 0-0.3)

He started SPTN on (b) (6). On (b) (6), his ALT increased to 75 (from 29), AST 44. AP and TB still normal. He had no symptoms and SPTN continued.

At the next check, (b) (6), ALT was 661. It went up to 806 on recheck later that day. AST was 480 while AP was normal. TB was 0.82 mg/dL. SPTN was held, TB would later peak at 1.58 mg/dL with direct bilirubin of 0.40 mg/dL, both just over ULN. Thereafter, enzymes fell by 50% within 40 days but had not returned to normal at last follow-up. (Figure 5)

HAV IgM, HBsAg, anti-HBc IgM, anti-HCV antibody and anti-EBV IgM were negative. Ultrasound (US) was normal. No other evaluation tests done or available.

Figure 5: Serum liver test line graph for subject (b) (6)



Assessment: This is probable DILI due to SPTN based on latency and dechallenge. Evaluation testing was fair. No autoimmune markers were done, but resolution without immunosuppression makes autoimmune hepatitis less likely. There was no HCV RNA done leaving acute hepatitis C as a possibility, but the anti-HCV antibody was negative and no risk factors were mentioned. Onset is probably when ALT rose to 75 U/L from subject baseline of 29 U/L. This was the only case to have a TB rise to >ULN, but it did not reach >2x ULN (i.e., no jaundice). DB also rose to just over ULN.

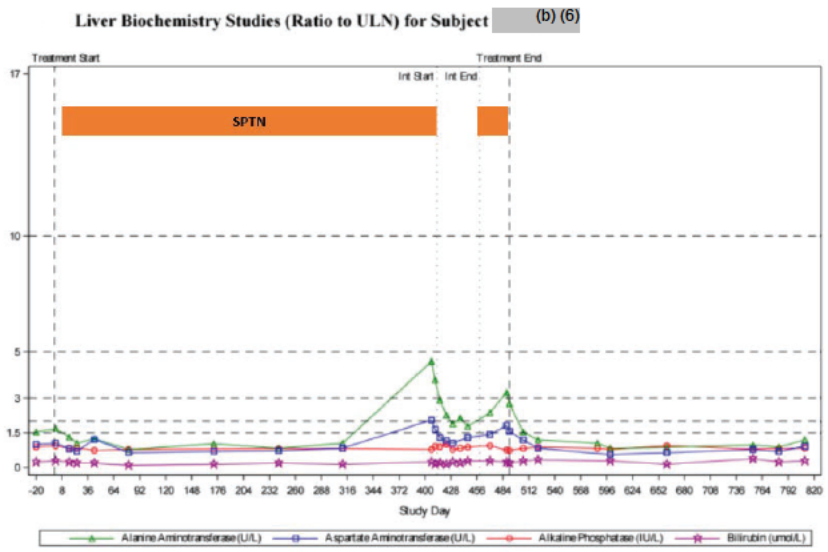
4.5.2.2 Subject (b) (6) (Study 021IGAN17001 PROTECT)

Summary: This is a 54-year-old Hispanic man with IgAN.

At baseline, this subject had a history of hepatitis A infection over 40 years prior, seasonal allergies, proteinuria, deviated septum repair, hypophosphatemia, and metabolic acidosis. He took only fish oil. At baseline, his ALT was 69 U/L, AST 39 U/L, AP 121 U/L, TB 0.3 mg/dL. His BMI was 30.7 kg/m^2.

The subjected started SPTN (b) (6). ALT fell from the modestly elevated screening level shortly thereafter. On (b) (6), elevation in TA's was noted without symptoms. SPTN was held on (b) (6). TA's fell and SPTN was restarted on (b) (6), which was followed by a quick repeat rise in ALT and AST (133, 67). (Figure 6) The SPTN was permanently stopped on (b) (6). US showed steatosis only, but no other evaluation testing noted.

Figure 6: Serum liver test line graph for subject (b) (6)



Assessment: The latency is long, and evaluation testing is lacking. However, we assessed the case as probable DILI due to SPTN because of the positive rechallenge injury pattern. To suggest otherwise would mean the rises and de-challenges with the two SPTN exposures were purely coincidental.

4.5.2.3 Subject (b) (6) (Study 021IGAN17001 PROTECT)

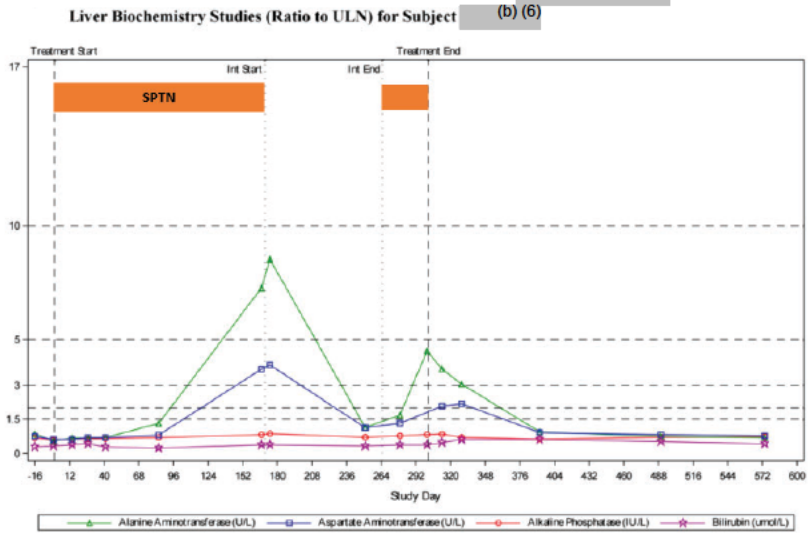
Summary: This is a 55-year-old white man with IgAN.

At baseline, he had hypertension, chronic kidney disease (stage 3), diabetes mellitus (steroid induced), venous thrombosis of the left leg, intermittent hypercalcemia, intermittent hyperparathyroidism, supraventricular tachycardia, hyperuricemia, and hyperlipoproteinemia. Medications included cholecalciferol, magnesium, clobetasol, enoxaparin, heparin, torsemide, and metoprolol. Liver chemistries were ALT 23 U/L, AST 23 U/L, AP 77 U/L, and TB normal.

He started SPTN on (b) (6). On (b) (6) (week 12) ALT rose from 29 to 54 U/L. SPTN continued. On (b) (6), TA's were noted to be elevated without symptoms. SPTN was held on (b) (6), and enzymes fell. US imaging was normal. HAV IgM, anti-HBc IgM and anti-HCV antibody negative. No other evaluation tests were noted.

SPTN was restarted on (b) (6), and enzymes rose again. SPTN was stopped permanently on (b) (6), with fall in enzymes to normal. (Figure 7)

Figure 7: Serum liver test line graph for [redacted] (b) (6)



Assessment: This is probable DILI due to SPTN because of the positive rechallenge. The latency is relatively long, but in retrospect, injury onset might be traced to [redacted] (b) (6) (week 12) when ALT rose from 29 to 54 U/L.

4.5.2.4 Subject [redacted] (b) (6) (021IGAN17001 PROTECT)

Summary: This is 27-year-old white man with IgAN.

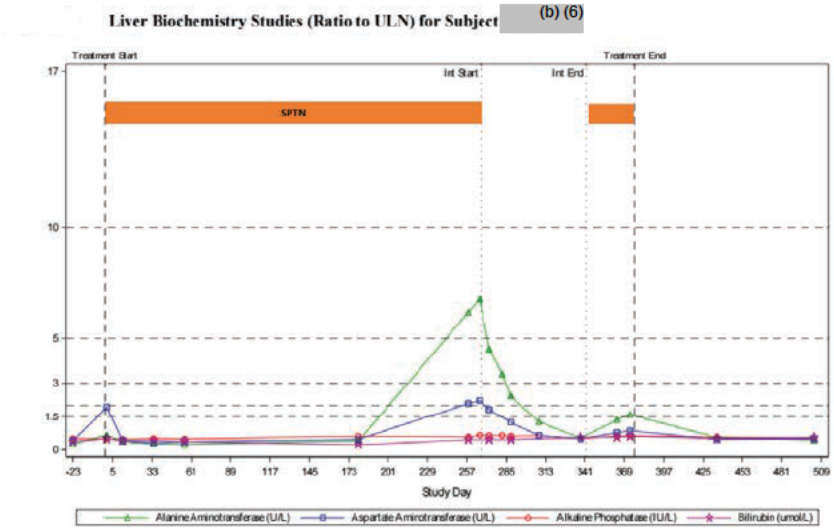
At baseline, he had hypertension but was on no medications. His ALT was 28 U/L, AST 71 U/L, AP 65 U/L, and TB normal.

On [redacted] (b) (6), he started SPTN. On [redacted] (b) (6), ALT was up to 253 U/L, AST 77 U/L, AP 104, and TB 0.6 mg/dL. SPTN continued, but on [redacted] (b) (6), the enzymes peaked at 277 U/L and 89 U/L respectively. SPTN was held.

Thereafter, enzymes fell back to normal and SPTN was restarted on [redacted] (b) (6). Enzyme began to rise again, and SPTN was stopped on [redacted] (b) (6). (Figure 8)

No evaluation testing was done.

Figure 8: Serum liver test line graph for [redacted] (b) (6)



Assessment: This is probable DILI due to SPTN because of the positive rechallenge. The latency is long at over 250 days. No evaluation testing is unfortunate, but the rises and de-challenges with the two SPTN exposures are compelling.

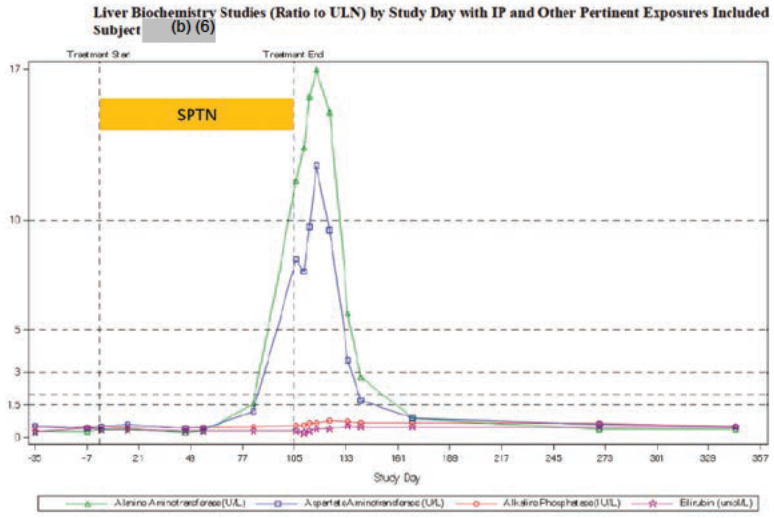
4.5.2.5 Subject (b) (6) (021FSGS16010 DUPLEX):

Summary: This is a 42-year-old white man with FSGS and enrolled in the United States.

At baseline, he had chronic kidney disease stage 3, hypertension, hyperuricemia, microscopic hematuria, proteinuria, and gout. Concomitant medications included Uloric (febuxostat) 40mg daily which started 2 years prior to initiating study treatment. At baseline, his ALT was 11 U/L, AST 20; AP and TB were normal as well.

He started SPTN 400 bid on (b) (6). He did well until (b) (6), when ALT rose to 64 and AST 45 U/L. AP and TB remained normal. Local investigator decided to hold the SPTN over the phone, so last dose was (b) (6). However, his liver tests continued to rise, peaking on (b) (6), before falling back to baseline. Evaluation testing including negative ultrasound imaging, negative acute hepatitis A, B and C serologies. No new medications, over-the-counter (OTC) agents, or herbal/dietary supplements (HDS) taken. Alcohol was not mentioned. ANA was negative. No CMV, EBV, or HEV testing. He remained asymptomatic throughout.

Figure 9: Serum liver tests for subject (b) (6)



Assessment: This is probable DILI due to SPTN. Latency and dechallenge are consistent with DILI. Evaluation testing was fairly complete. HCV RNA was not checked, but HCV antibody was negative. Acute hepatitis C caught prior to seroconversion is possible but less likely unless obvious risk factors were present. HEV could compete but is less common and on the decline in the US. AIH is unlikely due to resolution without immunosuppression. CMV and EBV are less likely without symptoms of a viral infection.

4.5.2.6 Subject (b) (6) (021IGAN17001 PROTECT)

Summary: This is a 72-year-old white man with IgAN.

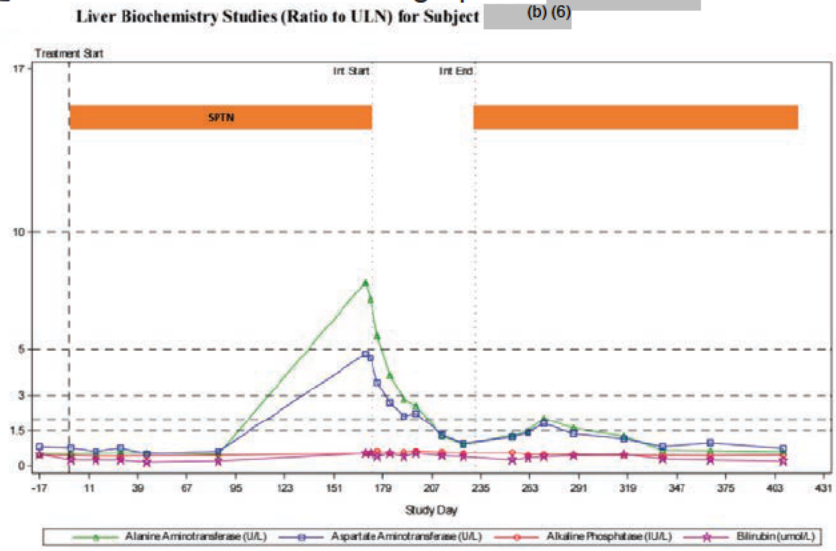
At baseline, his history included hypertension, benign renal cysts, peripheral vascular calcification, left hydronephrosis, left hydroureter, gallbladder sludge, hyperlipidemia, hepatitis A 20 years prior. Concomitant medications included fish oil, atorvastatin (no start or stop dates given), sildenafil, fluticasone, and Norvasc (amlodipine). Liver tests were all normal.

He started SPTN on (b) (6). On (b) (6), ALT and AST were up to 322 and 177 without symptoms. SPTN continued until (b) (6). By then enzymes have fallen slightly, but with confirmation of elevation, SPTN was held.

Thereafter liver enzymes fell to normal ranges by (b) (6), and SPTN was restarted on (b) (6). Liver enzyme climbed mildly but then resettled despite continued exposure to SPTN. (Figure 10)

No evaluation testing done.

Figure 10: Serum liver test line graph for (b) (6)



Assessment: We assessed this case as possible DILI due to SPTN, but probable is arguable. The pattern of enzyme elevations would be consistent with a positive rechallenge followed by the development of tolerance. In fact, the enzymes fell modestly even before stopping the SPTN on first exposure. Thus, this case is notable for the possible development of tolerance.

5.0 Assessment and Recommendations

5.1 Assessment: Sparsentan (SPTN) is an orally delivered, small molecule, and dual endothelin and angiotensin receptor antagonist (DEARA), blocking endothelin type A receptor (ET_AT) and angiotensin II receptor type 1 (AT1). Activation of these two receptors has a key role in glomerulonephropathies including IgA nephropathy (IgAN), the targeted disease for this NDA.

Non-clinical data suggest hepatic metabolism with excretion via bile and feces. Renal excretion is minimal. Up to 17 metabolites may be present in hepatocytes, but the dominant form in serum is parent drug. We found no glutathione trapping studies, but SPTN did inhibit BSEP and MRP2 in vesicular transport assays. These two transporters are important in bile acid and bilirubin secretion from hepatocyte to bile canaliculus. MRP2 is also important in drug elimination. Thus, inhibition of these transporters can have implications for DILI due to potential intra- and extra hepatic accumulation of bile acids, bilirubin and drugs.

SPTN also directly inhibits its primary metabolizing cytochrome, CYP3A4. It is unclear to us whether time dependent inhibition (TDI) occurs. The

cytochrome inhibition study makes one reference to TDI, but the wording is vague without definitive statement on TDI presence or absence. Nevertheless, the DILI Team assessed the primary data and feels TDI may occur. Such CYP3A4 inhibition could increase intra-hepatic SPTN accumulation. Mice given SPTN for 13-weeks had minimal to moderate single cell hepatocyte necrosis which correlated with ALT elevation. Rats given SPTN for 26 weeks showed liver hypertrophy only. In totality, non-clinical data suggest hepatotoxicity potential.

In a phase 2 study for focal segmental glomerulosclerosis, a case of significant liver injury occurred, and hepatotoxicity became an AE of special interest for the Phase 3 PROTECT study treating IgAN. The ISS is dominated by PROTECT without significant concerning liver injury data from other smaller or ongoing ISS studies. Thus, we limited our study level analysis to PROTECT. eDISH did not have subjects in Hy's Law quadrant, but there was an imbalance in Temple's Corollary at AT >5x ULN cut-off. On case level analyses, we assessed five subjects, four from study 021IGAN17001 (PROTECT) and one from study 021FSGS16010 (DUPLEX) as having probable DILI from SPTN. Three of the five had positive rechallenges. The injuries were hepatocellular, but mostly modest without jaundice and resolution prompt on holding SPTN. Therefore, we see a hepatocellular DILI in this NDA, but no Hy's Law cases.

There are two major difficulties in assessing DILI risk and risk mitigation should SPTN be approved.

1. Small number of CKD subjects exposed to SPTN: The total CKD subjects exposed to SPTN is about 500 subjects, which is well below the threshold to have 95% confidence in observing a Hy's Law case at a rate of 1 in 1000. By Rule of 3, around 3000 exposed are needed to reach 95% chance of such detection. Therefore, the resolution of DILI with holding SPTN does not rule out more severe injury that may occur post-market. One subject had total bilirubin rise above ULN suggesting a potential for more severe injury. On the other hand, another case may have developed tolerance with continued SPTN dosing.
2. Long DILI latency: The latencies from drug start to DILI onset for the possible and probable cases of DILI were long (mean 200 days +/- 115; median 171 days, range 28 - 406). Limiting the latencies to just probable cases does not change the mean or median much (216 and 168 days respectively). The positive rechallenges are compelling and suggest the long latency is true. These latencies create challenges for monitoring. Monthly liver tests for 6-8 months may cover the median but not the maximum that goes beyond twelve months. If the total number of exposed subjects was much larger, then more leniency for monitoring might be given because we would have more confidence that SPTN does not lead to Hy's Law cases. Latencies of several months exist with other drugs, including a marketed ETAR antagonist. The mechanism of delay

in injury is unknown. SPTN is a direct inhibitor of its primary cytochrome, CYP3A4, and inhibits MRP2, so intra-hepatic accumulation of drug may be explanatory. However, this idea is speculative without more non-clinical data.

Overall, we can support approval if the efficacy and need for this drug are compelling because there are no cases of jaundice documented, and the TA elevations consistently resolved with SPTN discontinuance. However, the risk of severe DILI in a larger post-market population remains unclear, and monitoring will need careful consideration should SPTN be approved.

5.2 Recommendations:

1. If DCN approves SPTN, then consider the following:
   a. Monthly monitoring of serum liver tests for 12-14 months.
   b. Post-market research aimed at detecting DILI and liver related adverse events.
      i. Issue consults to OSE requesting advice on optimal study and surveillance strategies for post-market hepatotoxic risk assessment as well as risk management.
      ii. Consider issuing a request to the sponsor to perform a post-market observational study and an enhance pharmacovigilance to further characterize the hepatotoxic risk associated with SPTN.
2. If DCN does not approve SPTN, the sponsor should consider the following:
   a. Larger clinical trial experience with IgAN and other glomerulonephropathies
   b. Animal and quantitative systems toxicology modeling to assess for intra-hepatic drug and drug metabolite accumulation
   c. Glutathione trapping studies to look for reactive metabolites
   d. Clarify current data or do more in vitro studies to determine time dependent CYP inhibition, particularly of CYP3A4.

Ling Lan -S
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Date: 2022.09.19 08:28:51 -04'00'

Ling Lan, MD, PhD
Clinical Analyst, DILI Team, Division of Hepatology and Nutrition
CDER/OND

Paul H. Hayashi -S

Digitally signed by Paul H. Hayashi -S
Date: 2022.09.19 11:04:38 -04'00'

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

Frank A. Anania -S

Digitally signed by Frank A. Anania -S
Date: 2022.09.19 12:59:41 -04'00'

Frank Anania, MD
Acting Director, Division of Hepatology and Nutrition
CDER/OND

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/s/

PAUL H HAYASHI
09/20/2022 12:02:33 PM

MEMORANDUM

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

Date of This Memorandum:	September 19, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 216403
Product Name and Strength:	Filspari (sparsentan) tablets, 200 mg and 400 mg
Applicant/Sponsor Name:	Travere Therapeutics
OSE RCM #:	2022-566-2
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on September 12, 2022 for Filspari. We reviewed the revised carton labeling for Filspari (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling is acceptable from a medication error perspective, and we do not have further recommendations at this time.

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

[a] Vee, S. Label and Labeling Review for Filspari (NDA 216403). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 AUG 19. RCM No.: 2022-566-1.

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

/s/

SARAH K VEE
09/19/2022 02:52:22 PM

HINA S MEHTA
09/19/2022 03:15:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric 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
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 8/24/2022 **Date consulted:** 7/22/2022

From: Katherine Kratz, M.D., Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, Division Director, DPMH

To: Division of Cardiology and Nephrology (DCN)

Drug: Filspari (sparsentan)

NDA: 216403

Applicant: Travere Therapeutics

Subject: Pregnancy and Lactation Labeling

Indication: To reduce proteinuria in adults aged 18 years and older with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ X[1]g/g.

Materials Reviewed:

- DPMH consult request dated July 22, 2022. DARRTS Reference ID 5017935
- Applicant's submitted background package and proposed labeling for NDA 216403
- DPMH review of Tracleer (bosentan) NDA 209279 by Jane Liedtka, M.D., dated March 30, 2017. DARRTS Reference ID: 4075715

[1] Proposed by the sponsor (NDA 216403, Sparsentan background package, SN0001, Annotated Draft Labeling, Module 1.14.1.2.) and under review by the DCN Review Team.

- DPMH review of Prexxartan (valsartan) NDA 209139 by Carrie Ceresa, PharmD., MPH, dated June 6, 2017. DARRTS Reference ID: 4107871
- United States Prescribing Information (USPI) for bosentan (NDA 209279), ambrisentan (NDA 022081), and macitentan (NDA 204410)

Consult Question: "Please assist with reviewing the pregnancy section of the label. In addition to section 8.1, we would also appreciate your help with section 8.2."

I. INTRODUCTION AND BACKGROUND

On March 17, 2022, the applicant, Travere Therapeutics, submitted a 505(b)(1) New Drug Application (NDA) for priority review for Filspari (sparsentan) to treat IgAN in adults aged 18 years and older with primary IgAN. DCN consulted DPMH on July 22, 20222 to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- Sparsentan is a new molecular entity (NME) and is an endothelin (ERA) and angiotensin receptor (ARB) antagonist.
- ERA-class drugs, including ambrisentan, bosentan, and macitentan, have a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of embryo-fetal toxicity.
- ARBs pose teratogenic risks, including reduced fetal renal function leading to fetal renal failure, anuria, hypotension and death, and serious adverse events during pregnancy, such as oligohydramnios causing fetal lung and skull hypoplasia. These risks are mitigated via product labeling.

Drug Characteristics[2]

Drug class	endothelin and angiotensin II receptor antagonist.
Mechanism of action	Sparsentan has high-affinity for both the endothelin type A receptor (ET_AR) and the angiotensin II receptor type 1 (AT1) and greater than 500-fold selectivity for these receptors over the endothelin type B and angiotensin II subtype 2 receptors.
Dosage forms	200 mg and 400 mg tablets
Molecular weight	592.8 Daltons
Half-life	9.6 hours
% protein bound	≥ 99%
Bioavailability	Not yet determined

Proposed Labeling[3]

(b) (4)

[2] Proposed by the sponsor and verified by the DCN Review Team.
[3] Proposed by the sponsor (NDA 216403, Sparsentan background package, SN0001, Annotated Draft Labeling, Module 1.14.1.2.) and updated by the DCN Review Team.

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II. REVIEW

PREGNANCY

IgAN and Pregnancy[4,5,6,7]

- The worldwide incidence rate of IgAN is 2.5 per 100,000 per year in adults.
- The incidence rate in females of reproductive potential and pregnant females is not known.
- IgA nephropathy can occur at any age, but it usually occurs in the teens to late thirties, which are the prime reproductive years.
- IgAN is the most common primary glomerulonephritis worldwide.
- Pregnancy is generally well tolerated in patients with IgAN and a normal or near-normal glomerular filtration rate (GFR).
- The risk of worsening kidney disease with pregnancy is increased in women with an initial GFR below 70 mL/min, uncontrolled hypertension, or severe arteriolar and tubulointerstitial disease on kidney biopsy.
- Treatment involves angiotensin inhibitors and immunosuppressive medications such as cyclophosphamide and mycophenolate mofetil, which should be discontinued at the earliest indication of pregnancy or prior to attempted conception due to risks to the fetus with these medications.

Nonclinical experience with sparsentan

In nonclinical studies with sparsentan, there was no evidence of genotoxicity, clastogenicity, carcinogenicity, or mutagenicity.[8]

Developmental toxicities occurred in rats and rabbits, which were consistent with class effects for approved ERAs and ARBs. In rats, teratogenic effects and other forms of developmental toxicity including craniofacial malformations, skeletal abnormalities, increased post-implantation loss, and reduced fetal weights, were observed at all doses tested. In a pre- and postnatal development study in rats, there were reductions in pup survival and in preweaning pup weights.[3] The presumptive no-observed-adverse-effect-level (NOAEL) for developmental toxicity was considered to be below the lowest dose (<80 mg/kg/d).[9]

The reader is referred to the labeling except above (Animal Data) and the full Pharmacology/Toxicology review by Srinivasa Raju Datla, Ph.D. in DARRTS.

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[4] Cattran, D et al. IgA nephropathy: Treatment and prognosis. UptoDate. July 2022. Topic 3039. Version 54.0

[5] Chen H, Li X, Wu Y, Fan L, Tian G. Pregnancy-induced complications in IgA nephropathy: A case report. Medicine (Baltimore). 2018 Apr;97(15):e0470. doi: 10.1097/MD.0000000000010470. PMID: 29642221; PMCID: PMC5908630.

[6] McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011 Feb;26(2):414-30. doi: 10.1093/ndt/gfq665. Epub 2010 Nov 10. PMID: 21068142.

[7] National Organization for Rare Disorders (NORD), Rare Disease Database, https://rarediseases.org/rare-diseases/iga-nephropathy/ Accessed 8/10/22.

[8] NDA 216403, Sparsentan background package, SN0001, Module 2.5, Clinical Overview, pages 41 and 48.

[9] NDA 216403, Sparsentan background package, SN0001, Module 2.4, Nonclinical Overview, page 29.

Pharmacovigilance data (based on clinical trials conducted to support this NDA)[10]

- Twelve pregnancies have been reported in subjects receiving sparsentan or enrolled in a sparsentan study to date.
    - PROTECT study (phase 3 study in subjects with IgAN)
        - 4 pregnancies
            - 2 pregnancies in the sparsentan group: 1 spontaneous abortion (SAB) and 1 ongoing pregnancy with unknown outcome.
            - 2 pregnancies in the irbesartan group: 1 SAB and 1 elective abortion
        - 1 pregnancy in a partner of a study subject with a normal live birth.
    - DUPLEX study (Phase 3 study in subjects with focal segmental glomerulosclerosis)
        - 1 pregnancy in the irbesartan group: preterm delivery 3.5 months early with fatal congenital defect. No exposure to sparsentan.
    - DUET study (Phase 2 study evaluating the efficacy and safety of sparsentan in patients with focal segmental glomerulosclerosis)
        - 2 elective abortions
        - 1 SAB
        - 2 live births:1 infant was born premature, and 1 was born full term. Both infants were healthy.
    - Compassionate Use
        - 1 pregnancy: ongoing. Outcome is unknown.
- No congenital anomalies have been reported following any pregnancy in a sparsentan-treated subject during the development program.

Review of Literature

Applicant's review:

The applicant cites two publications related to ARB and ERA use in pregnancy. These publications are shown in the table below.

Publication; Author date country	**Type of study**	**Population**	**Exposure/drug**	**Results**	**Strengths (S)/ Limitations (L)**
Bullo et al.[11] 2012 Multinational	Review of case reports and case series 72 reports included in review 37 related to	118 cases of intrauterine exposure to ACE-I 68 cases of intrauterine exposure to ARBs	During pregnancy ACE-I or ARB	52% of newborns exposed to ACE-I did not exhibit complications 13% of newborns exposed to ARB did not exhibit complications Neonatal complications following ARB exposure included: renal failure, oligohydramnios, death, arterial hypertension, intrauterine growth restriction, respiratory distress	S: Large, multinational study population L: Data are based on case reports and small case series

[10] NDA 216403, Sparsentan background package, SN0001, Module 2.7.4, Summary of Clinical Safety, page 139.

[11] Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension. 2012 Aug;60(2):444-50. doi: 10.1161/HYPERTENSIONAHA.112.196352. Epub 2012 Jul2. PMID: 22753220.

	angiotensin-converting enzymes inhibitors (ACE-I) 35 related to ARBs			syndrome, pulmonary hypoplasia, hypocalvaria, limb defects, persistent patent ductus arteriosus, or cerebral complications	
Hitzerd et al.[12] 2019 Multinational	Review of 18 articles related to ERA exposure in pregnancy	39 cases of ERA exposure during pregnancy	During pregnancy 26 exposed to bosentan (20 in 1st trimester; 4 until delivery; 1 through 2nd trimester; 1 unknown time of exposure) 1 exposed to ambrisentan until 15 weeks gestation 1 exposed to sitaxentan in 1st trimester 11 ERA exposure – unknown drug	12 (31%) of the ERA-exposed pregnancies were electively terminated 2 (5%) ended in spontaneous abortion In the remaining 25 cases, no fetal congenital anomalies were described	S: Multinational study L: Small sample size; missing data with regards to dosage and outcomes; data are based on case reports and small case series

DPMH review:
As sparsentan is an NME, there are no published reports of human pregnancies exposed to sparsentan.

In 2017, DPMH completed a consult to update the labeling for bosentan to the Pregnancy and Lactation Rule (PLLR) format. Like sparsentan, bosentan is an ERA. DPMH conducted a literature search for bosentan exposure in pregnancy for the 2017 consult, and the results of this search can be found in Appendix A. In 2017, DPMH also completed a consult to update the labeling for an ARB, valsartan, to the PLLR format. The literature search for valsartan exposure in pregnancy can be found in Appendix B.

[12] Hitzerd E, Neuman RI, Mirabito Colafella KM, Reiss IKM, van den Meiracker AH, Danser AHJ, Visser W, Versmissen J, Saleh L. Endothelin receptor antagonism during preeclampsia: a matter of timing? Clin Sci (Lond). 2019 Jun 20;133(12):1341-1352. doi: 10.1042/CS20190464. PMID: 31221823.

Given that DPMH conducted a literature review for pregnancy outcomes and ERAs in 2017, DPMH conducted a search of published human studies related to ERAs and pregnancy in PubMed and Embase from 2017 to the present for this consult. The following search terms were used: "endothelin receptor antagonists" or "bosentan" or "ambrisentan" or "macitentan" or and "pregnancy," "pregnancy outcomes," "birth defects," "stillbirth," and "spontaneous abortion." The results of the literature search are as follows:

Publication; Author date country	**Type of study**	**Population**	**Exposure/drug**	**Results**	**Strengths (S)/ Limitations (L)**
Hitzerd, et al.[13] 2020 Netherlands	Perfusion model study using ex vivo human placentas	23 postpartum placentas 5 perfused with sitaxenten 5 perfused with ambrisentan 5 perfused with macitentan 8 controls		There was placental transfer of sitaxentan, ambrisentan, and macitentan. Macitentan was transferred across the placenta more slowly than ambrisentan and sitaxentan	S: First study to evaluate placental transfer of ERAs L: Ex vivo model
Tokgöz et al.[14] 2017 Turkey	Case report	22-year-old female with Eisenmenger syndrome, class IV	Bosentan 125 mg BID throughout pregnancy and postpartum	Infant born via cesarean section at 27 weeks gestation due to maternal status Infant did not have any congenital malformations	S: Contributes to the literature L: Single case report

Given that pregnancy outcomes associated with ARBs are well-characterized, additional literature and database searches related to ARBs and pregnancy were not conducted.

[13] 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. doi: 10.1161/HYPERTENSIONAHA.119.14183. Epub 2019 Dec 30. PMID: 31884859.

[14] Tokgöz HC, Kaymaz C, Poci N, Akbal ÖY, Öztürk S. A successful cesarean delivery without fetal or maternal morbidity in an Eisenmenger patient with cor triatriatum sinistrum, double-orifice mitral valve, large ventricular septal defect, and single ventricle who was under long-term bosentan treatment. Turk Kardiyol Dern Ars. 2017 Mar;45(2):184-188. doi: 10.5543/tkda.2016.17747. PMID: 28424444.

DPMH also searched Micromedex,[15] Reprotox,[16] TERIS,[17] and Shepard's[18] for endothelin receptor antagonists, including ambrisentan, bosentan, and macitentan, with the following results:

Micromedex:

- Pregnancy Rating: Contraindicated
- Avoid use of this drug during pregnancy and prescribe an alternative. Evidence has demonstrated fetal abnormalities or risks when used during pregnancy. Advise women of childbearing potential of fetal risk.
- Crosses Placenta: Unknown

Reprotox:

- ERAs increase the risk for congenital anomalies in humans based on rodent studies and on the mechanism of action of the drug products.
- It is not known whether therapeutic use in humans would produce effects similar to those seen in rodents.
- Successful human pregnancy outcomes with bosentan exposure have been reported. We did not locate human data on malformations.

TERIS and Shepard's did not provide additional information.

Reviewer comment:
DCN met with the Risk Evaluation and Mitigation Strategy (REMS) Oversight Committee (ROC) on August 1, 2022, to obtain ROC concurrence on a new REMS with elements to assure safe use (ETASU) to mitigate the risk of embryo-fetal toxicity with sparsentan. Similar to other drugs in the ERA and ARB drugs classes, there is a concern that sparsentan has the potential to cause embryo-fetal toxicity. For ARBs, a REMS was not needed because the risks could be reasonably communicated through labeling since the risk occurs with second and third trimester exposure. Drugs in the ERA class have been approved with a REMS to mitigate the risk of embryo-fetal toxicity. The ROC concurred that a REMS is necessary for sparsentan to ensure that the benefits of sparsentan use outweigh the risk of embryo-fetal toxicity.[19] DPMH agrees with this plan.

Animal studies with sparsentan demonstrate teratogenic effects including craniofacial malformations and skeletal abnormalities and poor pregnancy outcomes including increased post-implantation loss and reduced fetal weights. With regards to human data, the Hitzerd at al. article suggests that there is placental transfer of ERAs through human placentas in the ex vivo setting. Despite evidence of placental transfer, animal study data, and the known mechanism of action of ERAs, no congenital anomalies have been reported in infants exposed to another ERA, bosentan, during pregnancy in the published case reports and case series (as shown above and in Appendix A). Additionally, no congenital anomalies have been reported following two completed human pregnancies in

[15] Truven Health Analytics information, http://www.micromedexsolutions.com. Accessed 8/3/22.
[16] Reprotox Website: www.Reprotox.org. Accessed 8/3/22.
[17] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 8/4/22.
[18] Shepard's database, Truven Health Analytics, Micromedex Solutions. Accessed 8/3/22.
[19] REMS ROC Meeting Minutes for Sparsentan. August 1, 2022.

sparsentan-treated subjects during the development program. Given the limited nature of these human pregnancy data, the plan to mitigate the risk of embryo-fetal toxicity through a REMS is critical.

LACTATION

Nonclinical Experience

In a pre- and post-natal development study in rats, a reduction in pup survival occurred at the high dose of sparsentan at 80 mg/kg/d, and significant reductions in pre-weaning pup weights occurred at the mid dose (20 mg/kg/d) and the high dose. Reduced pup survival was associated with reduced nursing or nesting in litters and reduced evidence of nursing (reduced milk bands) in pups. Therefore, the no observed effect level (NOEL) for postnatal development was the low dose of 5 mg/kg/d. No studies were conducted to assess secretion of sparsentan in animal milk.[20] The reader is referred to the full Pharmacology/Toxicology review by Srinivasa Raju Datla, Ph.D. in DARRTS.

Pharmacovigilance Data

No pharmacovigilance data are available for this NME.

Review of Literature

Applicant's review:

There is no information about the presence of sparsentan in human milk, the effects on the breastfed infant, or the effects on milk production. As sparsentan is highly protein bound, it is reasonable to assume it would be present in breast milk. Therefore, breastfeeding is not advised while being treated with sparsentan.[1]

DPMH review:

In the 2017 DPMH consult for bosentan, no reports of adequate and well-controlled studies of bosentan use in lactating women were found.

The 2017 DPMH consult for valsartan stated,

> "It is unknown whether valsartan is present in human milk and serious adverse events have been observed in pediatric patients under the age of six. In a pediatric study (n=90) in subjects 1-5 years, two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. A causal relationship to valsartan was not established. In a second study of 75 pediatric subjects there were no deaths however one case of marked liver transaminase elevations.[21] Therefore breastfeeding is not recommended."

For this consult, DPMH conducted a search for published human studies from 2017 to present in PubMed and Embase, using the search terms: "endothelin receptor antagonists" or "bosentan" or "ambrisentan" or "macitentan" or "angiotensin II receptor antagonists" and "lactation" and "breastfeeding." The following publications were found:

[20] NDA 216403, Sparsentan background package, SN0001, Module 2.4, Nonclinical Overview, pages 29-30.
[21] Diovan (valsartan). FDA approved labeling. Drugs@FDA. Accessed 2/3/17 for 2017 DPMH consult for NDA 209139.

Publication; Author date country	Type of study	Population	Exposure/drug	Results	Strengths (S)/ Limitations (L)
Nauwelaerts et al.[22] 2022 Netherlands/ Belgium	Case report Pharmacokinetic (PK) study	43-year-old female with PAH	Bosentan 125 mg PO BID Sildenafil 20 mg PO TID	The Daily Infant Dosage ingested by the nursing infant through human milk of bosentan was 0.28 µg/kg/day at day 637. The Relative Infant Dose calculated for an exclusively breastfed infant with an estimated milk intake of 150 ml/kg/day, was 0.24% for bosentan. This dosage would also be far below the infant therapeutic dosage of 4 mg/kg. General health outcome of the infant, reported by the mother, was uneventful.	S: Contributes to the literature L: reports on a single mother-infant pair; results may not be applied to younger infants as infant in this study was 21 months, was not exclusively breastfed, and has different pharmacodynamics than a younger infant
Coberger, et al.[23] 2019 New Zealand	Case series PK study	3 breastfeeding mothers	Candesartan 1 subject: 32 mg daily 2 subjects: 8 mg daily	The amount of candesartan the infants ingested (i.e., the relative infant dose) was estimated to be 0.09% (95% CI 0.07–0.11) of the maternal dose (weight-adjusted). Candesartan was undetectable (less than 0.2 micrograms/L) in infant plasma samples.	S: Contributes to the literature L: Small sample size

In addition, DPMH conducted a search for endothelin receptor antagonists, including ambrisentan, bosentan, and macitentan, in Micromedex,[8] Hale's *Medications and Mothers' Milk*,[24] Reprotox,[9] the Drugs and Lactation Database (LactMed),[25] and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*.[26] The results are as follows:

[22] 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.

[23] Coberger ED, Jensen BP, Dalrymple JM. Transfer of Candesartan Into Human Breast Milk. Obstet Gynecol. 2019 Sep;134(3):481-484. doi: 10.1097/AOG.0000000000003446. PMID: 31403599.

[24] Hale, Thomas W. Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www halesmeds.com

[25] Drugs and Lactation Database (LactMed). Accessed 7/26/22.

[26] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.

Micromedex:

- Lactation Rating: Infant risk cannot be ruled out.
- Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.
- It is unknown whether bosentan/ambrisentan/macitentan is present in human milk, affects milk production, or impacts the breastfed infant.
- Advise women that breastfeeding is not recommended during bosentan/ambrisentan/macitentan therapy due to the risk of serious adverse effects, including fluid retention and hepatotoxicity, to the infant.

Hale's:

- L4 – No data- Possibly Hazardous

Reprotox and LactMed did not provide additional information.

Briggs:

- "One report described the use of bosentan during breastfeeding,[27] but milk concentrations were not determined…no adverse effects were mentioned in the above case, but there is a potential for toxicity."

With regards to database searches for ARBs, the reader is referred to the 2017 DPMH review of valsartan in which the reviewer wrote, "In Medications and Mother's Milk, Dr. Thomas Hale, a breastfeeding expert notes that there are no data on the use of valsartan and lactating women and ARBs are contraindicated in pregnancy and there are other medications more suitable for maternal medical conditions."

> ***Reviewer comment:***
> *There are no data on the presence of sparsentan in human or animal milk. There is one case report[13] that indicates that another ERA, bosentan, is present in human milk with an acceptable relative infant dose (RID) and no adverse effects on the exposed infant. There is also a case series related to an ARB, candesartan, that suggests that the maternal benefit from candesartan at the standard dose may outweigh the risk in breastfeeding healthy, term infants. From the single case report and case series, it is not possible to draw conclusions that can be generalized to all breastfed infants. Given that the human data are limited related to the effects of ERAs and ARBs on the breastfed infant and the potential serious adverse events of fluid retention, hypotension, impaired kidney function, and hyperkalemia, in infants exposed to ERAs, DMPH recommends that patients be advised not to breastfeed while taking sparsentan. This recommendation follows the labeling language that is currently in the USPI for approved ERA and ARB class drugs.*

[27] Molelekwa V, Akhter P, McKenna P, Bowen M, Walsh K. Eisenmenger's syndrome in a 27 week pregnancy—management with bosentan and sildenafil. Ir Med J 2005;98:87-8.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No adverse effects on fertility (estrous cycles, mating, fertility, sperm evaluation, or pregnancy incidence at any dose level) and no sparsentan-related effects on male or female reproductive organs were observed in rat embryo-fetal development studies.[28] There were no sparsentan-related effects on male reproductive organs and no sparsentan-related necropsy observations in females at any dose level up to 320 mg/kg/day. Therefore, the NOEL for male and female fertility was 320 mg/kg/day.[12] The reader is referred to the full Pharmacology/Toxicology review by Srinivasa Raju Datla, Ph.D. in DARRTS.

Pharmacovigilance Data

No pharmacovigilance data are available for this NME.

Review of Literature

Applicant's review:

The applicant did not provide a review of the literature related to reproductive potential.

DPMH review:

The 2017 DPMH consult for another ERA, bosentan, stated, "Based on human and animal fertility studies, bosentan may impair fertility in male patients."

The 2017 DPMH consult for another ARB, valsartan, stated, "there are no infertility issues in humans or animals."

DPMH conducted a literature search for studies in humans using PubMed and Embase, using the search terms "endothelin receptor antagonists" or "bosentan" or "ambrisentan" or "macitentan" or "angiotensin II receptor antagnosists" and "fertility," "contraception," "oral contraceptives," and "infertility." DPMH also conducted a search in Micromedex,[8] Reprotox,[9] and TERIS.[10] The results are shown below:

Publication; Author date country	**Type of study**	**Population**	**Exposure/drug**	**Results**	**Strengths (S)/ Limitations (L)**
Hurst, et al.[29] 2016 Germany	Open-label, crossover, phase 1 PK study	26 subjects	Macitentan 10 mg + oral contraceptive (ethinyl estradiol + norethindrone or norethisterone)	Macitentan does not affect the PK of oral contraceptives	S: Provides data where there are little available L: Related to macitentan and not sparsentan, small sample size

[28] NDA 216403, Sparsentan background package, SN0001, Clinical Overview, page 41.

[29] Hurst N, Pellek M, Dingemanse J, Sidharta PN. Lack of Pharmacokinetic Interactions Between Macitentan and a Combined Oral Contraceptive in Healthy Female Subjects. J Clin Pharmacol. 2016 Jun;56(6):669-74. doi: 10.1002/jcph.639. Epub 2015 Dec 29. PMID: 26381054.

Spence et al.[30] 2010	Open-label, single-sequence, PK study	28 subjects	Ambrisentan 10 mg + Ortho-Novum 1/35	No dose adjustment of the oral contraceptive NT 1 mg/EE 35 microg is warranted with the coadministration of ambrisentan.	S: Provides data where there are little available L: short duration, small sample size, included healthy subjects not those with PAH

Micromedex:

- Bosentan:
  - In a 6-month study of 25 male patients, a decline in sperm count of at least 50% was observed in 25% of patients after 3 or 6 months of bosentan treatment. One patient experienced marked oligospermia at 3 months during the program, and his sperm count remained low over the following 6 weeks. The patient's sperm count returned to baseline 2 months after the discontinuation of bosentan. In the 22 patients who completed 6 months of bosentan treatment, no changes in sperm count, sperm morphology, sperm motility, or hormone levels were seen. Based on these findings and animal data, fertility impairment may occur in males of reproductive potential; it is unclear if fertility impairment is reversible.
  - During animal studies, no effects on sperm count, sperm motility, mating performance, or fertility were reported in animals administered oral bosentan at doses up to 50 times the maximum recommended human dose (MRHD); however, an increased incidence of testicular tubular atrophy was reported with oral bosentan doses as low as 4 times the MRHD.

- Ambrisentan:
  - In animal studies, testicular tubular degeneration occurred in rats treated with ambrisentan for 2 years at doses 8 times the maximum recommended human dose (MRHD), and increased incidences of testicular findings were observed in mice treated for 2 years at ambrisentan doses 28 times the MRHD. In separate fertility studies, effects on sperm count, sperm morphology, mating performance and fertility were noted in male rats treated with ambrisentan at oral doses 236 times the MRHD. Testicular histopathology observations in the absence of fertility and sperm effects were present at doses of 10 mg/kg/day or higher.

- Macitentan:
  - Based on animal studies, fertility impairment may occur in men of reproductive potential with macitentan use, although it is unknown whether the effects are reversible. In animal studies, reduced body weight gain and testicular tubular atrophy were observed in rats treated with macitentan from postnatal day 4 to day 114 at exposures 7 times the human exposure, although fertility was not affected. In separate chronic toxicity studies, reversible testicular tubular dilatation occurred in rats and dogs at macitentan exposures greater than 7 times and 23 times the human exposure, respectively. Tubular atrophy was observed in rats

[30] Spence R, Mandagere A, Walker G, Dufton C, Boinpally R. Effect of steady-state ambrisentan on the pharmacokinetics of a single dose of the oral contraceptive norethindrone (norethisterone) 1 mg/ethinylestradiol 35 microg in healthy subjects: an open-label, single-sequence, single-centre study. Clin Drug Investig. 2010;30(5):313-24. doi: 10.2165/11534940-000000000-00000. PMID: 20384387.

following 2 years of treatment at exposures 4 times the human exposure. However, male and female fertility were not affected and there were no effects on sperm count, motility, and morphology in male rats at exposures up to 44 times the human exposure. There were also no testicular findings in mice administered macitentan up to 2 years

Reprotox:

- Bosentan:
  - Because some individuals on oral contraceptives experienced a large decrease in serum progestin concentrations when bosentan is administered, the product labeling recommends not relying on hormonal contraceptive methods for pregnancy prevention. According to the product labeling, bosentan did not interfere with fertility in rats, although at about 50 times the human dose, adverse effects on testicular histology were noted. Also in product labeling, decreased sperm counts were noted in 25% of 25 men receiving bosentan at 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily for 5 months. Sperm counts returned to normal after treatment.

- Ambrisentan: No additional information found.

- Macitentan:
  - Untreated females mated to treated males had a decrease in embryo viability.

No additional information was found in TERIS related to ERAs.

No information was found in the database search related to ARBs and reproductive potential.

Reviewer comment:
Animal studies with sparsentan showed no adverse effects on estrous cycles, mating, fertility, sperm evaluation, pregnancy incidence, and male or female reproductive organs at necropsy. There are no human data available related to the effects of sparsentan on fertility. DPMH recommends including the animal fertility data in subsection 13 of labeling.

Due to concerns for embryo-fetal toxicity with sparsentan, pregnancy testing prior to initiation of treatment, monthly during treatment, and one month after stopping treatment is required. To prevent pregnancy during treatment with sparsentan, DPMH recommends that females of reproductive potential use effective contraception during treatment and for one month after the last dose. The DCN Clinical Pharmacology team agrees with the Applicant's proposed one-month duration for effective contraception after cessation of sparsentan treatment. DPMH also agrees with the contraception duration.

Little is known about the effects of sparsentan on hormonal contraceptives. Per the DCN Clinical Pharmacology team's review, sparsentan is an inducer of CYP3A4 and CYP2C9; however, sparsentan is also an inhibitor of CYP3A4 and experiments have demonstrated that CYP3A4 substrates can be used concomitantly with sparsentan. Based on these data, the DCN Clinical Pharmacology team does not recommend including

information in the labeling that sparsentan may reduce the efficacy of hormonal contraceptives. DPMH agrees with the DCN Clinical Pharmacology team.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

Given the embryo-fetal risks observed in animal studies with sparsentan, sparsentan's mechanism of action, and since other ERA class drugs have a Risk Evaluation and Mitigation Strategy (REMS) for embryo-fetal toxicity, DPMH agrees with DCN that there is a REMS for embryo-fetal toxicity for sparsentan.

Animal data demonstrate that sparsentan increases the risk of malformations. Human pregnancy data related to sparsentan and other ERA class drugs are limited. Human data show that ARBs result in increased fetal and neonatal morbidity and death. As sparsentan contains both an ERA and an ARB, which pose embryo-fetal risks, the labeling will include a boxed warning. Section 4, Contraindications, will include a pregnancy contraindication. Section 5, Warnings and Precautions, will include an "Embryo-fetal Toxicity" subsection. Subsection 8.1, Pregnancy, will include the "Risk Summary," and "Data" subheadings.

Sparsentan is proposed to treat adult patients with IgA nephropathy. Since pregnancy is not recommended and there will be a REMS, a pregnancy contraindication and a Warning and Precautions for embryo-fetal toxicity, a pregnancy safety study is unlikely to be able to recruit sufficient numbers of participants to provide interpretable data. Therefore, DPMH will not issue any pregnancy safety study postmarketing requirements.

Lactation

The presence of sparsentan in human milk, the effects of sparsentan on the breastfed infant, and the effects of sparsentan on milk production are unknown. As sparsentan 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 sparsentan will be used in females of reproductive potential, there will be a recommendation to avoid breastfeeding while on sparsentan 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 sparsentan in human milk, it would not provide information about the extent to which sparsentan 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, sparsentan 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

Animal fertility studies involving administration of sparsentan did not show any effects on fertility. There are no human data available related to the effects of sparsentan on fertility. Although other drugs in the ERA class have demonstrated effects on male fertility, the DCN

Clinical Team is reassured by the lack of findings in the nonclinical studies for sparsentan and does not believe that an ERA class effect on male fertility should be labeled

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

IV. LABELING RECOMMENDATIONS

DPMH revised sections 4, 5, and 17 and subsections 8.1, 8.2, 8.3 of labeling. DPMH shared our labeling recommendations with DCN on 8/15/2022. DPMH recommendations are below and reflect the discussions with DCN. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling:

(b) (4)

[redacted]

FULL PRESCRIBING INFORMATION

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A – Literature Search from Tracleer Consult

No reports of adequate and well-controlled studies of bosentan use in pregnant women were found. The details of relevant articles are in Table 1 below.

Table 1: Pregnancies Exposed to Bosentan Reported in the Published Literature

Pregnancy # Author/Year	Maternal Age	Diagnosis	Timing of Exposure	Outcome
#1 Doherty S *et al*[12] 2003	21	Primary Pulmonary Hypertension (PAH)	Started at 35 weeks gestation	-Delivered vaginally at 39 weeks -Healthy 8 lb baby girl-was "doing well" at 3 months
#2 Elliot *et al*[13] 2005	23	Idiopathic Pulmonary Arterial Hypertension (IPAH)	Conception to gestation week 6	-Maternal cardiopulmonary arrest at 25 weeks, -Cesarean section (C-section) delivery at 26 weeks, 0.65 kg male infant with APGARS of 8+9 at 1 and 5 minutes who required ventilation and neonatal intensive care unit (NICU), 16 months later- infant is "progressing well"
#3 Molelekwa V *et al*[14] *2005*	23	Eisenmenger's Syndrome*	Exposed throughout pregnancy	Scan at 30 weeks revealed intrauterine growth restriction (IUGR) and reduced fetal movement, planned cesarean section delivery of a 1.41 kg "healthy baby girl" who was in the NICU for 11 weeks with "good outcome" but succumbed to respiratory syncytial virus (RSV) at 26 weeks postpartum". No congenital malformations (CM) were noted
#4, #5 Kiely DG *et al*[15] 2010	23 23	IPAH IPAH	Conception to week 6 Conception to week 9	Delivery via C-section at 26 weeks of a 0.65 kg infant with APGARs of 8 + 9 at 1 and 5 minutes, No CM noted Delivery via C-section at 34 weeks of a 1.58 kg infant with APGARs of 9 + 9 at 1 and 5 minutes, No CM noted, Maternal death at 4 weeks post-partum after patient discontinued her medications
#6 Streit M *et al*[16] 2009	29	Systemic Lupus Erythematosus (SLE), PAH	Conception to gestation week 5	Delivery via C-section at 37 weeks of a 2760 gm female infant with APGARs of 8 + 9 at 1 and 5 minutes. No CM noted.

#7 Cotrim C *et al*[17] 2010	**36**	PAH-Not otherwise specified (NOS)	Started at 28 weeks	Emergency C-section at 29 weeks for severe worsening of maternal status and premature rupture of membranes, infant in NICU- no other infant information reported.
#8 Alvarez PA *et al*[18]	28	Leflunomide-Induced PAH	Conception to gestation week 12	None reported
#9 Smith JS *et al*[19] 2012	37	IPAH	Conception to gestation week 4	Delivery via C-section at 36 weeks, No infant information reported.
#10 Sahni S et al[20]	23	Eisenmenger's Syndrome*	At diagnosis of pregnancy NOS	Delivery via C-section at unknown estimated gesational age (EGA), No infant information reported.
#1 Picard et al.[21] 2015	22	SLE-PAH	Conception to gestation week 5	Delivery via C-section at 32 weeks, reported that the baby grows No infant information reported.

*Eisenmenger's Syndrome: pulmonary hypertension at systemic level due to high pulmonary vascular resistance with reversed or bi-directional shunt through any large systemic to pulmonary communications [Ventricular-septal defect (VSD) was present in the case originally described]
Source: Reviewer's Table

[12] Doherty S *et al*. Severe Primary Pulmonary Hypertension in Late Pregnancy Successfully Managed with the Endothelin Antagonist, Bosentan. Presented at the World health Organization Pulmonary Hypertension Meeting, Venice Italy. 2003.
[13] Elliot *et al*. The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. Eur Respir J, 2005. 26 (1): p. 168-73.
[14] Molelekwa V *et al*. Eisenmenger's Syndrome in a 27 Week Pregnancy - Management with Bosentan and Sildenafil. Ir Med J. 2005 March; 98 (3): 87-88.
[15] Kiely DG *et al*. Improved survival in pregnancy and pulmonary hypertension using a multi-professional approach. BJOG 2010;117:565–574.
[16] Streit M *et al*. Successful pregnancy in pulmonary arterial hypertension associated with systemic lupus erythematosus: a case report. Journal of Medical Case Reports 2009, 3:7255.
[17] Cotrim C et al. Three cases of pregnancy in patients with severe pulmonary arterial hypertension: experience of a single unit. Rev Port Cardiol 2010; 29 (01): 95-103.
[18] Alvarez PA et al. Leflunomide-Induced Pulmonary Hypertension in a Young Woman with Rheumatoid Arthritis: A Case Report. Cardiovasc Toxicol (2012) 12:180–183.
[19] Smith JS et al. Pulmonary Arterial Hypertension in the Setting of Pregnancy: A Case Series and Standard Treatment Approach. Lung (2012) 190:155–160.
[20] Sahni S et al. Pregnancy and pulmonary arterial hypertension: A clinical conundrum. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 5 (2015) 157–164.
[21] Picard et al. A complicated pregnancy (in French) La Lettre du Pneumologue Volume XVII, September- October 2015. Translation provided by the applicant.

Appendix B. Review of Published Literature – ARB Exposure During Pregnancy

Table 1. Review Articles – ARB Exposure During Pregnancy

Publication	Country	Prospective or Retrospective Data – study type	Outcomes Measured	Maternal Exposure (dose/duration)	Total Pregnancies	Miscarriages	Congenital Abnormality/Complication	Conclusion
Bullo (2012)[8]	Various: English, German, French, Portugues e, Spanish or Italian publications	Retrospective – systematic review of published case reports and case series of prenatal exposure to ACE-Is and ARBs; data collected from years 1981 to 2011	Neonatal and long-term (present after 6 months of life) complications following medications inhibiting Renin Angiotensin System (RAS)	Captopril n=59; enalopril n=42; Lisinopril n=11; Ramipril n=3; benazepril n=2; quinapril n=1; losartan n=20; candesartan n=17; valsartan n=17; irbesartan n=7; olmesartan n=6; telmisartan n=1;	186	Not reported	Overall, Oligohydraminios (63%); renal failure or need for dialysis (51%); anuria (40%); respiratory distress (37%); hypocalvaria (32%); limb defects (32%); intrauterine growth retardation (16%); pulmonary hypoplasia (16%); arterial hypotension (15%); cerebral complication (10%); persistent patent ductus arteriosus (9%)	Poorer outcomes reported in those taking ARBs than ACE Is. In 18 cases, ARBs were taken exclusively during first trimester or during first and second; ARB was rarely taken exclusively during second trimester or only during third; only in 2 cases were ARBs taken only during second and third trimester
Walfisch (2011)[9]	Various	Metanalysis reviewing 5 cohort studies comparing 1st trimester exposure to ACE/ARBs to no exposure or to exposure to other antihypertensives	Comparing 1st trimester exposure to no exposure or to exposure to other antihypertensives	First trimester/various medications	424	Not reported overall	First trimester exposure to antihypertensives in general may be associated with an elevated risk of major malformations but no increased risk with ACE/ARBs compared to other antihypertensives	Authors concluded that the hypertension caused the fetal adverse effects and not the medication

Table 2. Studies/Trials – ARBs Exposure During Pregnancy

Publication	Country	Prospective or Retrospective Data – study type	Maternal Exposure (dose/duration)	Total Pregnancies	Miscarriages	Congenital Abnormality/ Complication	Conclusion
Moretti (2012)[10]	Canada	Prospective, observational, controlled cohort; identified women who were callers to the Motherisk Program at the Hospital for Sick Children in Toronto; any patient reporting use of ACE/ARB during pregnancy was eligible; women compared to females exposed to any other type of hypertensive med and healthy group without hypertension	Ramipril n=8; lisinopril n=25; enalapril n=15; monopril n=8; valsartan n=8; perindopril n=7; candesartan n=6; irbesartan n=6; losartan n=5; quinapril n=5; cilazapril n=3; fosinopril n=3; telmisartan n-3; captopril n=2; prinivil n=1; trandolapril n=1; polytherapy n=2	138 exposed to ACE or ARB; 112 to any other antihypertensive and 138 healthy pregnancies	25 (18%) overall in ACE/ARB group; 16 (11.8%) in healthy nonexposed group; 4 (8.9%) in other antihypertension group	No difference between groups	No difference in rates of congenital malformations between the two groups; rates of miscarriage were higher in the ACE/ARB group
Diav-Citrin (2011)[11]	Israel & Italy	Prospective observational cohort observing first trimester ACE/ARBs exposure during pregnancy at two teratology information services in Israel and Italy; compared to other antihypertensive	252 ACE/ARB exposure, 256 other antihypertensive exposure (OAH), 495 non teratogenic exposure (NTE)	252 ACE/ARB	Higher rate in ACE/ARB group compared to NTE group however more women in ACE/ARB group reported having two or more previous miscarriages	Comparable between the groups (8/190, 4.2%, ACEI, ARB; 9/212, 4.2% OAH; 18/427, 3.8%; p-0.954	Rate of preterm deliveries two fold higher and median birth weight 200 g lower in the ACE/ARB and OAH groups compared to the NTE group

Table 3. Case Report – Valsartan Exposure During Pregnancy

Publication	Subject Demographics	Maternal Exposure (dose/duration)	Estimated Fetal Exposure	Other meds	Mother's OB history	Pregnancy/Lactation Outcome
Berkane (2004)[12]	43 year old pregnant female	Treated with valsartan until gestation week 20; dose not reported	0-20 weeks gestation	Not reported	Chronic hypertension	Complete anhydramnios; six day after treatment stopped amniotic fluid reappeared; delivered at 38 weeks gestation; healthy baby
Bos-Thompson (2004)[13]	Pregnant female; unknown age	Valsartan 80 mg/day	0-25 weeks gestation	HCTZ 12.5 mg/day, prazosin 10 mg/day; lysine acetylsalicylate 100 mg/day levothyroxine 240 mcg/day	Hypertension	Anhydramnios diagnosed at 24 weeks gestation and valsartan/hctz stopped; at 31 weeks gestation amniotic fluid returned to normal; delivered at 38 weeks gestation due to deep fetal decelerations; wide cranial suture suggested mild skull bone hypoplasia; limb deformation with mild varus of right foot; renal ultrasound showed abnormally enlarged kidneys with diffuse hyperechogenicity of the parenchyma and whole blood perfusion; poor vascularization at 30 months, normal growth parameters, mild chronic renal insufficiency
Briggs (2001)[14]	40 year old pregnant female	Valsartan 80 mg/day	0-24 weeks gestation	Atenolol 75 mg/day	Chronic hypertension and type 2 diabetes	Normal fetal growth with anhydramnios fluid index 0 at 24 weeks gestation; valsartan discontinued and normal fetal volume resumed two weeks later; intrauterine fetal death documented at 33 weeks gestation; stillbirth
Chung (2001)[15]	3 pregnant females ages 36 (asian), 34 (white) and 31 (black)	Valsartan 80 mg/day	0-7 weeks; 0-10 weeks; 0-18 weeks	Not reported	hypertension	Delivery of 3 healthy babies at 38, 38 and 32 weeks gestation; one with growth retardation contributed to the mothers hypertension

Martinovic (2001)[16]	Pregnant female age 41 years	Valsartan 80 mg/day	0-24 weeks	HCTZ 12.5 mg/day, metformin and potassium	Hypertension and type 2 diabetes	Presented at 24 weeks gestation with severe oligohydramnios; substituted methyldopa and nicardipine for valsartan and hctz and 2 weeks later anamnios was complete; elective termination at 27 weeks gestation
	Pregnant female 39 years	Valsartan dose not reported	Not reported	HCTZ	Hypertension	Presented at 28 weeks complete absence of amniotic fluid; 2 weeks after substitution of drugs by trandate, amniotic fluid was normal but with fetal abnormalities including renal hyperchogenicity, dilation of cerebral ventricles and narrow chest; elective termination 32 weeks
	Pregnant female 35 years	Losartan 50 mg/day	Not reported	Not reported	Not reported	At 34 weeks gestation presented with severe oligohydramnios; after amnio infusion developed fever with fetal tachycardia; delivery of hypotonic male at 34 weeks by cesarean; infant died day 4
Saar (2016)[17]	39 year old pregnant female	Valsartan 160 mg	30 weeks gestation	HCTZ 12.5 mg	Hypertension diagnosed 8 years prior	Anhydramnios observed at 30 weeks gestation; delivery induced at 34 weeks gestation following premature rupture of membranes and maternal fever; during two-year follow up no signs of renal insufficiency were noted
Tsepkentzi (2016)[18]	Pregnant female age not reported	Valsartan 160 mg/day	24 to 32 weeks gestation	Not reported	Gestational hypertension	Delivered healthy baby; no congenital anomalies

	Pregnant female age not reported	Valsartan dose not reported	Not reported	HCTZ dose not reported	Chronic hypertension	Ultrasound at 29 weeks revealed small for gestational age fetus and severe oligohydramnios; cesarean performed at 31 weeks; ultrasound showed hyperechoic kidneys and loss of corticomedullary differentiation
Schaefer (2003)[19]	Pregnant female unknown age	Valsartan unknown dose	0-13 weeks gestation	Not reported	Not reported	Cleft palate, patent ductus arteriosus, coarctation of the aorta and growth retardation
Schimada (2015)[20]	Pregnant female unknown age	Valsartan unknown dose	0-24 weeks gestation	Amlodipine	Not reported	Anhydramnios detected during ultrasound at 24 weeks gestation; at that time valsartan was switched to nifedpine and amlodipine; amniotic fluid returned; unremarkable pregnancy after drug switch except for fetal growth restriction; healthy baby; small for gestational age
Hunseler (2011)	Pregnant female unknown age	Valsartan unknown dose	0-31 weeks gestation	Not reported	Not reported	Ultrasound detected oligohydramnios and polycystic kidney; after birth infant had impaired diuresis, enlarged kidneys and required dialysis for 7 months; child diagnosed with renal insufficiency stage IV, deafness and ulnar deviation of hands and reduced muscular strength
	Pregnant female unknown age	Valsartan unknown dose	0-42 weeks gestation	Not reported	Not reported	At birth child with normal kidneys but anuria; child died day 2 cardiorespiratory failure

Schindera (2012)[22]	Pregnant women unknown age	Valsartan unknown dose	0-35 weeks gestation	Not reported	Not reported	Presented at 35 weeks gestation with preterm labor and complete anhydramnios; spontaneous delivery and eutrophic male infant showed typical signs of fetotoxicity from valsartan including neonatal anuria, enlarged hyperechogenic kidneys, initial arterial hypotension, limb contractures, skull bone hypoplasia and narrow chest;
Vendemmia (2005)[23]	Pregnant female unknown age	Valsartan unknown dose	0-24 weeks gestation	HCTZ	Not reported	Ultrasound at 36 weeks showed oligohydramnios and after birth severe pulmonary artery hypertension; infant needed mechanical ventilation; echography showed hyperechogenic kidneys; limb deformations consisted of bilateral talus valgus and fixed internal rotation of right hand; Potter's syndrome facies, cranial sutures widely open and skull bones hypoplastic

Source: Reviewer's Table

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[11] Diav-Citrin, O, 2011, Pregnancy outcome after in utero exposure to angiotensin converting enzyme inhibitors or angiotensin receptor blockers, Reproductive Toxicology, 31:540-545.
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[22] Schindera C, et al, 2012, Journal of Neonatal Biology, 1:1-2.[23] Vendemmia M, et al, 2005, Fetal and neonatal consequences of antenatal exposure to type 1 angiotensin receptor antagonists, The Journal of Maternal-Fetal and Neonatal Medicine, 18(2):137-140.

[23] Vendemmia M, et al, 2005, Fetal and neonatal consequences of antenatal exposure to type 1 angiotensin receptor antagonists, The Journal of Maternal-Fetal and Neonatal Medicine, 18(2):137-140.

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Clinical Inspection Summary

Date	August 24, 2022
From	Tina Chang, M.D. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Anna Park, M.S., R.Ph., RAC, Regulatory Project Manager Rekha Kambhampati, M.D., Clinical Reviewer Aliza Thompson, M.D., Deputy Director Norman Stockbridge, M.D., Ph.D., Division Director Division of Cardiology and Nephrology (DCN)
NDA#	216403
Applicant	Travere Therapeutics AB
Drug	Filspari (sparsentan)
NME	Yes
Proposed Indication	Treatment of IgA nephropathy
Consultation Request Date	April 26, 2022
Summary Goal Date	October 17, 2022
Action Goal Date	November 17, 2022
PDUFA Date	November 17, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 021IGAN17001 was submitted to the Agency in support of a New Drug Application (NDA) 216403 for sparsentan to treat IgA nephropathy. The review division requested a clinical inspection of the sponsor, Travere Therapeutics Inc., in order to evaluate whether blinding procedures and firewalls (according to the Data Access and Dissemination Plan) had been implemented appropriately at the time of the interim analysis to support accelerated approval.

Based on the clinical inspection of Travere Therapeutics, no significant concerns regarding the conduct or oversight of study 021IGAN17001 were identified, and the blinding appeared appropriately maintained during the study.

II. BACKGROUND

Sparsentan is a dual endothelin angiotensin receptor antagonist developed for the treatment of immunoglobulin A nephropathy (IgAN) in adults 18 years and older. A sponsor inspection was requested for one study:

- **Protocol 021IGAN17001 (PROTECT)**, "A randomized, multicenter, double-blind, parallel group, active control study of the efficacy and safety of sparsentan for the treatment of immunoglobulin A nephropathy (IgAN)."

Protocol 021IGAN17001 was a Phase 3, randomized, multicenter, double-blind, parallel-group, active-control study to determine the effect of sparsentan on proteinuria and preservation of renal function as compared to an angiotensin receptor blocker (irbesartan) in subjects with IgAN.

- ***Sites:*** Subjects were enrolled in 3 regions (North America, Europe, and Asia-Pacific), in 18 countries, and in 156 sites.

- ***Subjects:*** A total of 406 subjects were randomized (i.e., 202 subjects received sparesentan and 202 received active control irbesartan). Two subjects were randomized and not dosed.

- ***Study Initiation Date:*** 11 Dec 2018 (first patient, first visit)

- ***Interim Database Lock Date:*** 30 July 2021

- ***Study Unblinding Date:*** 6 August 2021

The study consisted of a 114-week, randomized, double-blind period and an open-label extension (OLE) period of up to 156 weeks. Subjects were randomized in a 1:1 fashion to sparsentan or an active control (irbesartan). Subjects who completed the double-blind period and met all inclusion criteria and none of the exclusion criteria were eligible to enroll in the 156-week open-label extension (OLE) period to assess the long-term efficacy, safety, and tolerability of open-label treatment with sparsentan.

The main inclusion criteria were male and female subjects ≥18 years of age; biopsy proven IgAN; a urine protein excretion value ≥1.0 g/day and an eGFR ≥30 mL/min/1.73 m^2 at screening; and remain at high risk of disease progression despite being on a stable dose (or doses) of an angiotensin converting enzyme inhibitor and/or ARB that is (are) a maximum tolerated dose that is at least one half of the maximum labeled dose. Please see protocol for the full inclusion and exclusion criteria.

Sparsentan was to be administered as 200-mg tablets and irbesartan was to be administered as 150 mg tablets. Subjects were to receive the initial 200 mg dose of sparsentan or 150 mg of irbesartan for the first 2 weeks after randomization. The goal was to titrate to the target dose which was 400 mg of sparsentan or 300 mg or irbesartan at Week 2 after the CI evaluated the dose tolerance in a blinded manner. Subjects who tolerated the initial dose after 2 weeks but displayed asymptomatic blood pressure values ≤100/60 mm Hg or presented with clinical symptoms of orthostatic hypotension were to continue the initial dose after the Week 2 visit without titrating up to the target dose. At the Week 2 visit, subjects who did not tolerate the initial dose for any reason were to discontinue the study drug.

The ***primary efficacy endpoint*** was the change from baseline (Day 1) in the urine

protein/creatinine ratio (UP/C; based on a 24-hour urine sample) to Week 36.

Key secondary endpoints included:

- The mean change from baseline in eGFR and selected proteinuria variables based on a 24-hour urine sample (e.g., urine protein excretion, urine albumin excretion, urine albumin/creatinine ratio [UA/C] and UP/C) through Week 110
- The proportion of subjects reaching a confirmed 40% reduction in eGFR or end stage renal disease or who died.

According to the protocol, the subjects' treatment allocation for the double-blind period was to remain blinded to all parties involved with study conduct throughout its course with the exception of the:

- Data Monitoring Committee (DMC)
- Study drug supply
- SAE reporting contact
- Independent statistical team responsible for producing outputs for the DMC
- Team of individuals prespecified in the "data analysis and dissemination plan" who were supporting the primary analysis and regulatory submission.

An unblinded interim analysis was performed 36 weeks following randomization of 280 subjects was performed for the primary endpoint and key secondary efficacy endpoints. After the interim analysis, subjects remained in the study and are eligible to receive treatment until the end of the double-blind period for the final analysis at Week 114.

III. RESULTS:

1. **Travere Therapeutics Inc.**
   Sponsor
   3611 Valley Centre Drive, Suite 300
   San Diego, CA 92130
   PDUFA Inspection dates: June 13-20, 2022

   For Protocol 021IGAN17001 (PROTECT), this inspection reviewed the organizational charts, protocol versions, financial disclosures, Form FDA 1572s, blinding plan (Data Access and Dissemination Plan) and supporting records to demonstrate adherence to the plan, oversight meeting minutes and records, contracts/transfer agreements, standard operating procedures, monitoring reports, investigator CVs, investigator and monitor selection records, training records, investigational new drug (IND) safety reports, data collection and management records, and test article accountability records.

   Monitoring visit reports for the top 20 sites with the highest number of randomized subjects were reviewed and appeared adequate. No clinical investigator sites were terminated during this study.

   For the interim analysis, there was a shared folder containing the unblinded data. The

inspection reviewed forms that documented the person and level of unblinding and crosschecked this information with the access audit trail to the shared folder and the handoff of randomization codes to vendors and the biostats teams for report writing. There was no evidence of unintentional blinding. The blinding procedures appear to have been implemented appropriately during the interim analysis and throughout the study in accordance with the blinding plan.

No significant concerns regarding the conduct or oversight of study Protocol 021IGAN17001 were identified.

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

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.,
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D., signing for:
Jenn Sellers, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

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OSI/Database PM/Dana Walters

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MEMORANDUM

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

Date of This Memorandum:	August 19, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 216403
Product Name and Strength:	Filspari (sparsentan) tablets, 200 mg and 400 mg
Applicant/Sponsor Name:	Travere Therapeutics
OSE RCM #:	2022-566-1
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 12, 2022 for Filspari. Division of Cardiology and Nephrology (DCN) requested that we review the revised container label and carton labeling for Filspari (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels are acceptable from a medication error perspective. We note the location of the strength statement on the carton labeling is at the top of the principal display panel which in not the typical location of the strength on labels and labeling and could be overlooked. In addition, the location of the NDC at the bottom of the carton labeling is not typical and may be overlooked. We provide recommendations for the Applicant to revise the location of the strength statement and NDC.

3 RECOMMENDATIONS

1. Carton Labeling

[a] Vee, S. Label and Labeling Review for Filspari (NDA 216403). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 JUN 29. RCM No.: 2022-566.

a. Typically, US labeling consists of the proprietary name followed by the established name, dosage form, and then the strength statement. As currently presented on the carton labeling the strength (e.g., 200 mg) is located at the top of the principal display panel and may be overlooked. Consider relocating the strength statement in a colored box below the proprietary name, established name, and dosage form similar to the depiction on the container label.
b. Typically, the NDC number is located at the top of the carton labeling. As currently presented, it is located at the bottom of the principal display panel and it may be overlooked. Consider relocating the NDC number to the top of the carton labeling.

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

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

Date of This Review:	June 29, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 216403
Product Name, Dosage Form, and Strength:	Filspari (sparsentan) tablets, 200 mg and 400 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Travere Therapeutics
FDA Received Date:	March 17, 2022
OSE RCM #:	2022-566
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Filspari (sparsentan) tablets NDA 216403, we reviewed the proposed Filspari prescribing information (PI), medication guide (MG), 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 – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, MG, container label, and carton labeling for Filspari (sparsentan) tablets to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We find the proposed PI and MG acceptable from a medication error perspective. We identified areas of the proposed container labels and carton labeling that could be revised to improve clarity and readability of important information. We note the statement on the container labels and carton labeling directs pharmacists to dispense the MG to (b) (4). After discussion with the Division, it was determined that the MG should be dispensed to all patients. In addition, we note prominence of the quantity statement and lack of expiration and lot number designations. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Applicant in Section 4.1 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed PI and MG acceptable from a medication error perspective. We identified areas in the proposed container label and carton labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product.

We provide recommendations in Section 4.1 for Travere Therapeutics to address our concerns.

4.1 RECOMMENDATIONS FOR TRAVERE THERAPEUTICS

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

A. General Comments (Container labels & Carton Labeling)

1. The proposed proprietary name "Filspari" was found conditionally acceptable. Replace the "Tradename" placeholder with the conditionally acceptable proprietary name "Filspari".
2. We recommend using the term "patients" instead of "(b) (4)" in the statement "Dispense the accompanying medication guide to (b) (4) patients" to be consistent with the prescribing information.
3. To ensure consistency with the Prescribing Information, revise the statement, "Dosage: See prescribing information" to read "Recommended Dosage: See prescribing information."
4. As currently presented, the format and placement for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

B. Container Labels

1. Use of same color scheme for the quantity statement and the strength may draw attention away from the strength statement. We recommend revising the quantity statement to use different colors from the strength statements.
2. The drug barcode is often used as an additional verification before drug administration; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to the container bottle as required per 21CFR 201.25(c)(2).

C. Carton Labeling

1. Revise and relocate the quantity statements away from the established name and strength since it is more prominent than the strength statement that immediately follows the established name. This may lead to medication errors if the quantity is mistaken for the strength.

2. As currently presented the strength statement lacks prominence. Revise the strength statement that is immediately after the established name (i.e., use the same color scheme) to be consistent with the container label and increase its prominence.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Filspari received on March 17, 2022 from Travere Therapeutics.

Table 2. Relevant Product Information for Filspari	
Initial Approval Date	N/A
Active Ingredient	sparsentan
Indication	for treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older.
Route of Administration	oral
Dosage Form	tablets
Strength	200 mg and 400 mg
Dose and Frequency	Initiate treatment at 200 mg once daily by mouth. After 14 days, increase to the recommended dose of 400 mg once daily, as tolerated.
How Supplied	bottles of 30 tablets with child-resistant caps
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store in its original container.

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 Filspari labels and labeling submitted by Travere Therapeutics.

- Container label received on March 17, 2022
- Carton labeling received on March 17, 2022
- Prescribing Information (Image not shown) received on March 17, 2022, available from \\CDSESUB1\evsprod\NDA216403\0001
- Medication Guide received on March 17, 2022, available from \\CDSESUB1\evsprod\NDA216403\000

G.2 Label and Labeling Images

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

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA216403
Submission Number	001
Submission Date	4/12/2022
Date Consult Received	4/12/2022
Drug Name	Sparsentan
Indication	Immunoglobin A nephropathy
Therapeutic Dose	200 mg QD for 14 days followed by 400 mg QD
Clinical Division	DCN
Protocol Review	Link (extracted from SP)

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 4/12/2022 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Cardiac Safety Report (NDA 216403 / SDN1; link);
- Concentration-QTc Report (NDA 216403 / SDN1; link)
- Previous IRT review dated 12/29/2015, 06/22/2016, and 03/22/2021 in DARRTS;
- Draft labelling text (NDA 216403 / SDN1; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 216403 / SDN1; link).

1 SUMMARY

In this thorough QT study, sparsentan prolonged the QTc interval; however, the increase was not dose-dependent and there was a time-delay between peak effects on QTc interval and maximal sparsentan concentrations. The underlying mechanism behind the observed QTc prolongation is unknown but is unlikely to be mediated via direct inhibition of hERG channels by sparsentan (see section 3.1.2). Sparsentan did not inhibit the hERG channel (hERG safety margin *>2912x*) and no QTc prolongation was detected in the *in vivo* QT study in monkeys at 6x the high clinical exposure.

Study 021HVOL16002 was a randomized, positive-, and placebo-controlled, single-dose, 4-arm, 4-period crossover study to assess QTc effects of sparsentan at therapeutic and supratherapeutic exposures in healthy subjects. Therapeutic exposures were covered by the 800 mg dose which provided a mean Cmax of 8.2 µg/mL and is similar to the mean steady state Cmax values for 400 mg QD (7.1 µg/mL). The highest dose that was evaluated was a single dose of 1600 mg which provided a mean Cmax of 11.6 µg/mL and therefore covers 1.2-fold the high clinical exposure scenario (CYP3A inhibition, section 3.1).

Data were analyzed using by-time analysis as the primary analysis, which showed that sparsentan failed to exclude a 10-ms increase in ΔΔQTcF interval for dose levels – evaluated see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall results. No subjects had QTcF >500 ms or ΔQTcF >60 ms. Moxifloxacin demonstrated assay sensitivity.

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

ECG parameter	Treatment	Time (h)	ΔΔ QTCF (msec)	90% CI
QTc	Sparsentan 800 mg	5	9.0	(6.0 to 11.9)
QTc	Sparsentan 1600 mg	5	8.2	(5.3 to 11.1)

For further details of the FDA analysis, please see section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

The sponsor submitted QT evaluation reports with no specific questions to be addressed by IRT.

1.2 COMMENTS TO THE REVIEW DIVISION

- Sparsentan caused PR shortening at 5 hours post-dosing on both doses of sparsentan, -4.9 msec and -5.1 msec on 800 mg and 1600 mg, respectively (see Figure 3).
- The mean ΔΔHR values for sparsentan did not exceed 5 bpm at any postdose timepoint (the largest values of 3.5 bpm at 6 hours for 800 mg and 4.7 bpm at 8 hours for 1600 mg).

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

No additional studies are recommended.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 1 (link) from the CSS-IRT. *Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Additionally, we are omitting section x, as we do not have any edits to that section. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.*

(b) (4)

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Sparsentan (MW = 592.8) is a dual endothelin angiotensin receptor antagonist (DEARA) indicated for treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older. This indication is approved under accelerated approval. Dosing is increased from 200 mg once daily to 400 mg once daily after 14 days. Sparsentan is administered with water (b) (4).

We have reviewed this application under IND (b) (4) and agreed with the sponsor's TQT study protocol (see previous review). Study 021HVOL16002 (CSR) was a double-blind, randomized, single-dose, placebo and moxifloxacin controlled, 4-arm, 4-period crossover study evaluating 800 mg SD and 1600 mg SD in 60 healthy adults. Moxifloxacin was not blinded to patients and investigators. The geometric mean of the maximum Cmax was ~11.6 µg/mL in the 1600 mg SD dose group, which provided 1.2-fold coverage over the high clinical exposure scenario.

3.1.1 Clinical Pharmacology

An overview of sparsentan clinical pharmacology is provided in the highlights of clinical pharmacology table. In brief, the geometric mean (CV%) of the expected clinical exposure following 400 mg once daily is 7.1 µg/mL (54.6%), as measured on day 57 in focal segmental glomerulosclerosis (FSGS) patients in active-controlled (irbensaten), dose-escalation (200, 400, 800, 1600 mg once daily) study DUET (protocol). Patients were instructed to take medication prior to the first meal of the day, (b) (4). Food effect had the highest impact on Cmax: a high fat meal increases Cmax for 800 mg SD by 108% compared with fasting condition. However, since the clinical exposure of 7.1 µg/mL in DUET study has taken proper food effect into consideration (b) (4), the high clinical exposure is expected at 9.9 µg/mL when sparsentan is co-administered with moderate CYP3A4 inhibitors (x1.4).

3.1.2 Nonclinical Safety Pharmacology Assessments

An exploratory hERG assay tested 0 µM, 10 µM, and 30 µM concentrations of sparsentan in HEK293 cells stably transfected with the hERG and identified minimal inhibition of the hERG channel: 1.7% and 8.1% at 10 µM and 30 µM, respectively. In a definitive in vitro hERG assay (RE-021-Report050-2015-SPHARM), 500 µM sparsentan produced 7% inhibition of hERG-mediated IKr. Consistent with the initial non-GLP study, no meaningful inhibition (<5%) was observed at 150 µM. The concentration of sparsentan associated with 20% of maximum inhibition and half-maximal inhibitory concentration values could not be determined from the concentrations tested and are estimated to be greater than 500 µM.

Within the nonclinical studies, a safety pharmacology study was conducted in telemetered cynomolgous monkeys receiving a single oral dose of sparsentan at 32 mg/kg, 500 mg/kg, and 1000 mg/kg (PCO-NC-010). Under the conditions of the study, none of the doses adversely altered the electrocardiographic intervals (PR, QRS, QT, and QTc) or core body temperature, and the ECGs appeared quantitatively normal. The Cmax and AUC at the NOAEL were 64.5 µg/mL and 1103.3µg·h/mL, respectively.

***Reviewer's comments**: The sponsor evaluated the effects of sparsentan on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The hERG study report (021-050-2015-spharm;link) describes the potential effects of sparsentan on the hERG current in HEK293 cells. The hERG current was assessed at near-physiological temperature (34.6 - 36 o^C), using a step-step voltage protocol(from a holding potential of -80 mv to a depolarizing pulse of 40 mV for 2 seconds, followed by a repolarizing pulse to -50 mV for 1.5 seconds) that is different from the recommended hERG current protocol by the FDA (link). The reviewer does not expect protocol differences to impact hERG current pharmacology. The positive control (100 nM cisapride) inhibited hERG potassium current by 80.03%. Samples of the test article solutions collected from the containers were analyzed for concentration verification. The results from the sample analysis indicated that measured concentrations for the 150 µM and 500 samples were within the acceptance criteria, thereby the measured concentrations were used to describe drug effects.*

Sparsentan inhibited the hERG currents by 2.7% and 7.1% at 150 and 500 µM, respectively. The estimated IC50 for the inhibitory effect of sparsentan on hERG current was greater than 500 µM.

The hERG safety margin of sparsentan on hERG current is summarized below:

Table 2 Safety Margin of SPARSENTAN on hERG Current

	Cmax (ng/mL)	*Protein Binding*	*Free Cmax (ng/mL)*	*hERG IC50 (µM)*	*Mol Weight (g/mol)*	*Safety Margin (Ratio)*
Sparsentan	*9900*	*99%*	*99*	*>500*	*576.76*	*>2912x*

High clinical exposure (Cmax):9900 ng/mL.

The in vivo monkey study (PCO-NC-010) assessed the potential effects of sparsentan on ECG parameters following a single oral administration in conscious, unrestrained, telemetry monkeys. Doses selected for this study were 32, 500, and 1000 mg/kg on Days 1, 4, 9, and 14, respectively. Blood samples were collected before treatment and at 1, 2, 4, 8, and 24 hours after treatment on Days 1, 4, 9, and 14 for toxicokinetic analyses. The mean plasma concentrations of sparsentan were 1.8, 60.7 and 61.3 µg/mL for the 32,500 and 1000 mg/kg doses, respectively. The exposure exceeded (6.2x) the anticipated high clinical exposure in humans (9900 ng/mL). There were no sparsentan -related QTc, QRS changes at dose up to 1000 mg/kg. No positive drugs were used in the study.

In summary, the hERG assay met most of the best practice recommendations for an in vitro assay according to the new ICH S7B Q&A 2.1. The estimated hERG safety margin was greater than 2912x (7% inhibition at 500 µM), suggesting sparsentan has a low risk

for QT prolongation by direct inhibition of the hERG current at therapeutic exposure. The deviations from best practice recommendations (e.g., solution samples were collected from container and only one concentration for positive control) will not impact the interpretation of the large safety margin.

No QTc prolongations were observed at exposure exceeded (6.2x) the anticipated high clinical exposure in the in vivo monkey study.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis, the largest upper bound of 90% CI of ΔΔQTcF for Sparsentan were larger than 10 msec for both 800mg and 1600mg for ΔΔQTcF.

Reviewer's comment: *Results from FDA reviewer's analysis are similar to those of the sponsor. The largest upper bound of the 90% CI for ΔΔQTcF is greater than 10 msec for both 800 mg and 1600 mg.*

Please see Section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm using a by-time point analysis. Plasma concentrations of moxifloxacin were not determined to enable exposure-response analyses.

Reviewer's comment: *Results from FDA reviewer's analysis are like those of the sponsor. The adjusted lower bound of CI for moxifloxacin exceeds 5 msec. Please see Section 4.3 for additional details.*

3.2.1.1.1 QT Bias Assessment

Not applicable

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

There was one subject with HR > 100 bpm and ΔHR > 25% in the sparsentan 800mg and 2 subjects with the same change in the sparsentan 1600 mg.

Reviewer's comment: *Results from FDA reviewer's analysis are similar to sponsor's results. We used different cut-off for PR categorical table though. Please see Section 4.3 for additional details.*

3.2.3 Exposure-Response Analysis

The sponsor's linear mixed effects model included placebo-corrected change from baseline QTcF (ΔΔQTcF) as a dependent variable and sparsentan concentration as the independent variable. The model also included an intercept term, and random effects parameters for the intercept and the slope. The results of the sponsor's analysis show a

statistically significant positive concentration-QTc relationship, with intercept significantly different from zero (Intercept = 2.69 msec, slope = 0.00037 msec per ng/mL). Based on the model, predicted mean (90% CI) ΔΔQTcF at geometric mean Cmax of 800 mg (8169 ng/mL) and 1600 mg doses (11638 ng/mL) were 5.74 (4.79 – 6.68) msec and 7.03 (5.97 – 8.05) msec, respectively. The sponsor also conducted a nonlinear CQT modeling to test for violation of linearity assumption due greater than 0 intercept. The sponsor's Emax model provided a better fit to the data with intercept that was not significantly different from 0. The Emax model predicted mean (90% CI) ΔΔQTcF of 5.99 (6.02 – 6.96) msec and 6.60 (5.52 – 7.68) msec at the geometric mean Cmax of 800 mg (8169 ng/mL) and 1600 mg doses (11638 ng/mL) respectively.

Reviewer's comment: *Due to violation of the linearity assumptions and since the by-time point analysis was the primary analysis for this TQT study, the reviewer did not evaluate the C-QT relationships for sparsentan.*

3.2.4 Cardiac Safety Analysis

A total of 58 of the 60 subjects in Part 2 each received at least 1 oral dose of sparsentan; 2 subjects (Subjects (b) (6) and (b) (6)) who withdrew early received placebo only.

There were no SAEs following administration of sparsentan. One subject reported an SAE of appendicitis following administration of placebo that led to discontinuation from the study, and one other subject was discontinued because of an AE of neutropenia following administration of placebo.

No cardiac AEs were reported. One subject taking sparsentan 1600 mg experienced syncope.

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

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 0).

4.2 ECG ASSESSMENTS

4.2.1 Quality

Overall, ECG acquisition and interpretation in this study appear 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 3.

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

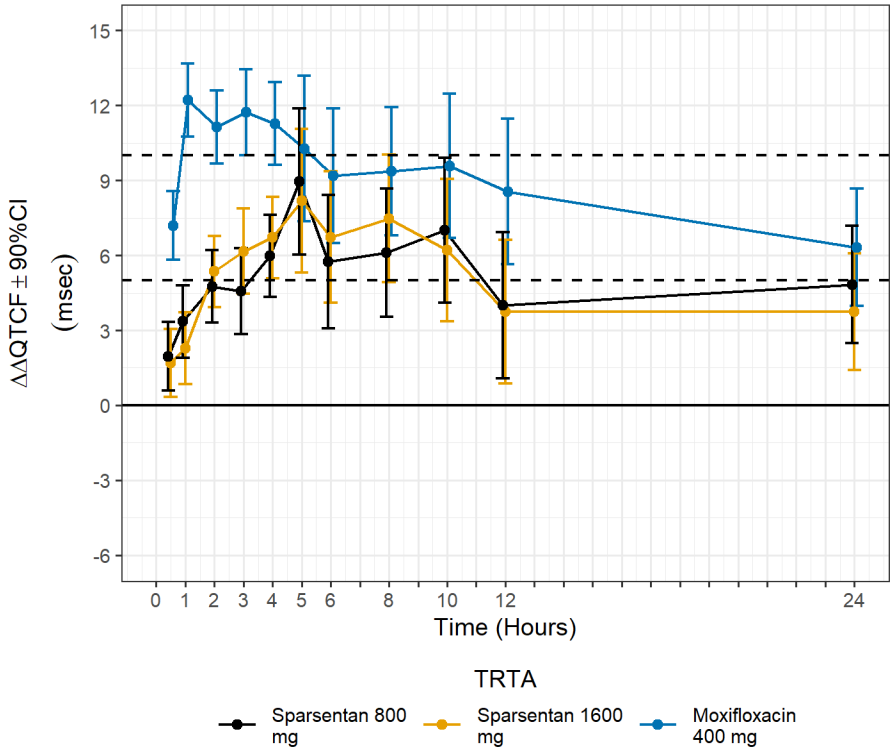


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Sparsentan 800 mg	55 / 58	5.0	9.0	(6.0 to 11.9)
Sparsentan 1600 mg	58 / 58	5.0	8.2	(5.3 to 11.1)

4.3.1.1 Assay Sensitivity

The model used for assay sensitivity is the same as the primary model. 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 4 time points (Table 4).

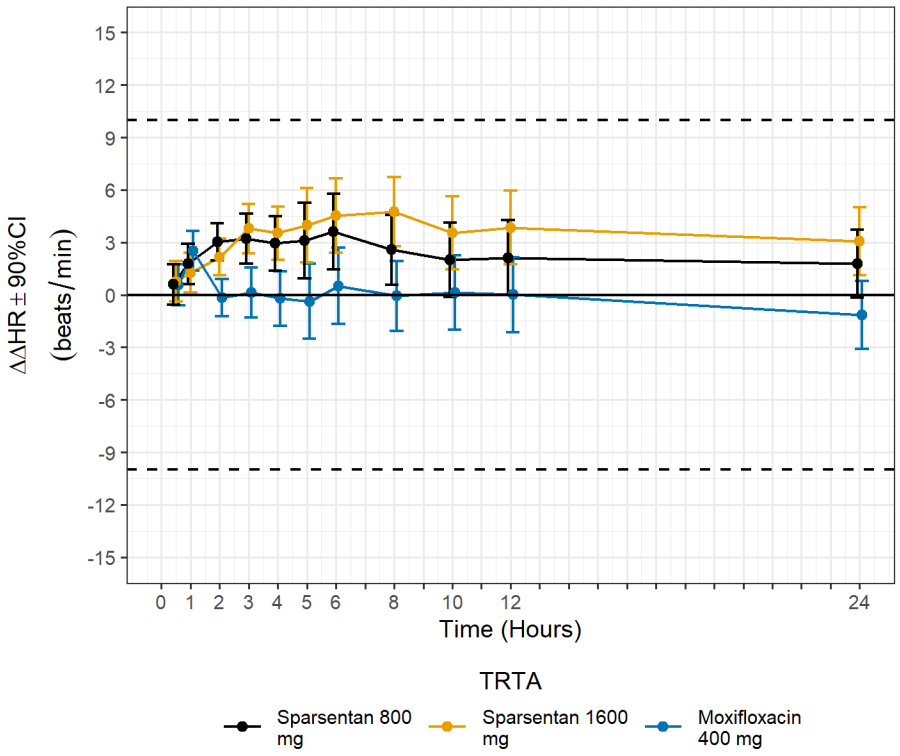
Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	54 / 58	1.0	12.2	(10.8 to 13.7)	(10.2 to 14.2)

4.3.2 HR

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

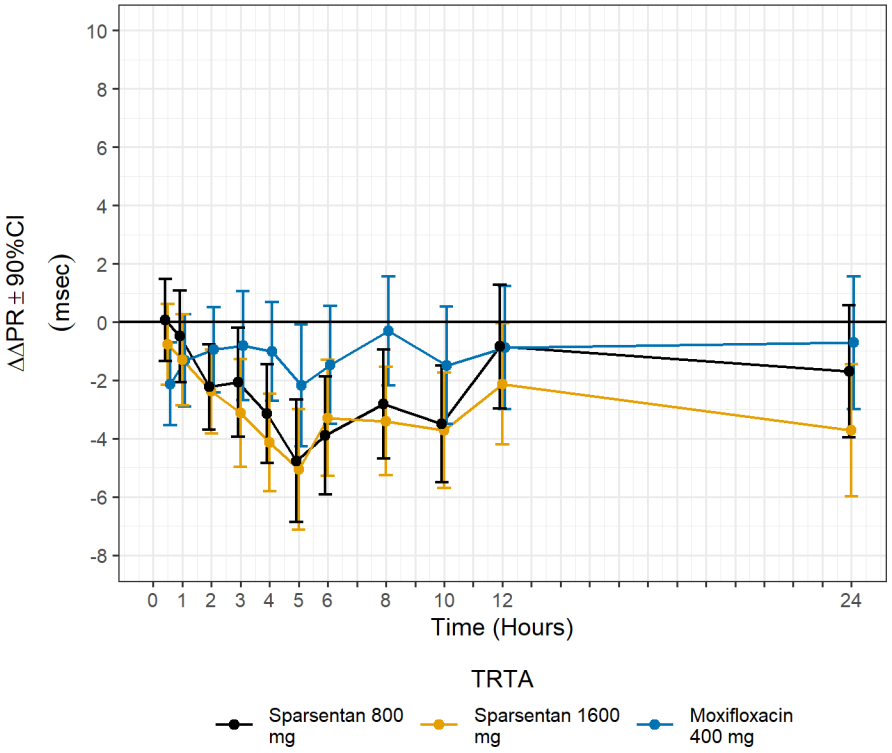
Figure 2: Mean and 90% CI of ΔΔHR Time-course



4.3.3 PR

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

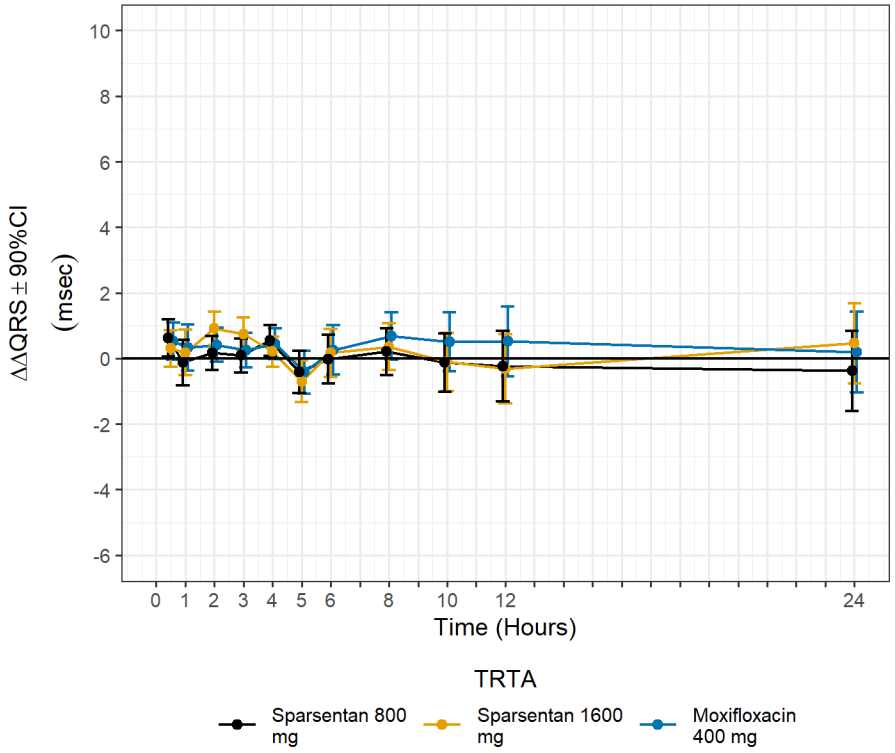
Figure 3: Mean and 90% CI of ΔΔPR Time-course



4.3.4 ΔΔQRS

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. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects had QTcF value >500 msec. None of the subjects had ΔQTcF value >60 msec.

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min), and Table 6 lists the categorical analysis results for minimum HR (>45 beats/min and <45 beats/min).

Table 5: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Sparsentan 800 mg	56	605	55 (98.2%)	603 (99.7%)	1 (1.8%)	2 (0.3%)
Sparsentan 1600 mg	58	626	56 (96.6%)	623 (99.5%)	2 (3.4%)	3 (0.5%)
Placebo	58	629	57 (98.3%)	628 (99.8%)	1 (1.7%)	1 (0.2%)

Table 6: Categorical analysis for HR (minimum)

Actual Treatment	Total (N)		Value <=45 beats/min		Value >45 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Sparsentan 800 mg	56	605	1 (1.8%)	6 (1.0%)	55 (98.2%)	599 (99.0%)
Sparsentan 1600 mg	58	626	3 (5.2%)	6 (1.0%)	55 (94.8%)	620 (99.0%)
Placebo	58	629	4 (6.9%)	10 (1.6%)	54 (93.1%)	619 (98.4%)

4.4.3 PR

None of the subjects had PR value >220 msec and 25% over baseline.

4.4.4 QRS

None of the subjects had QRS value >120 msec and 25% over baseline.

4.5 EXPOSURE-RESPONSE ANALYSIS

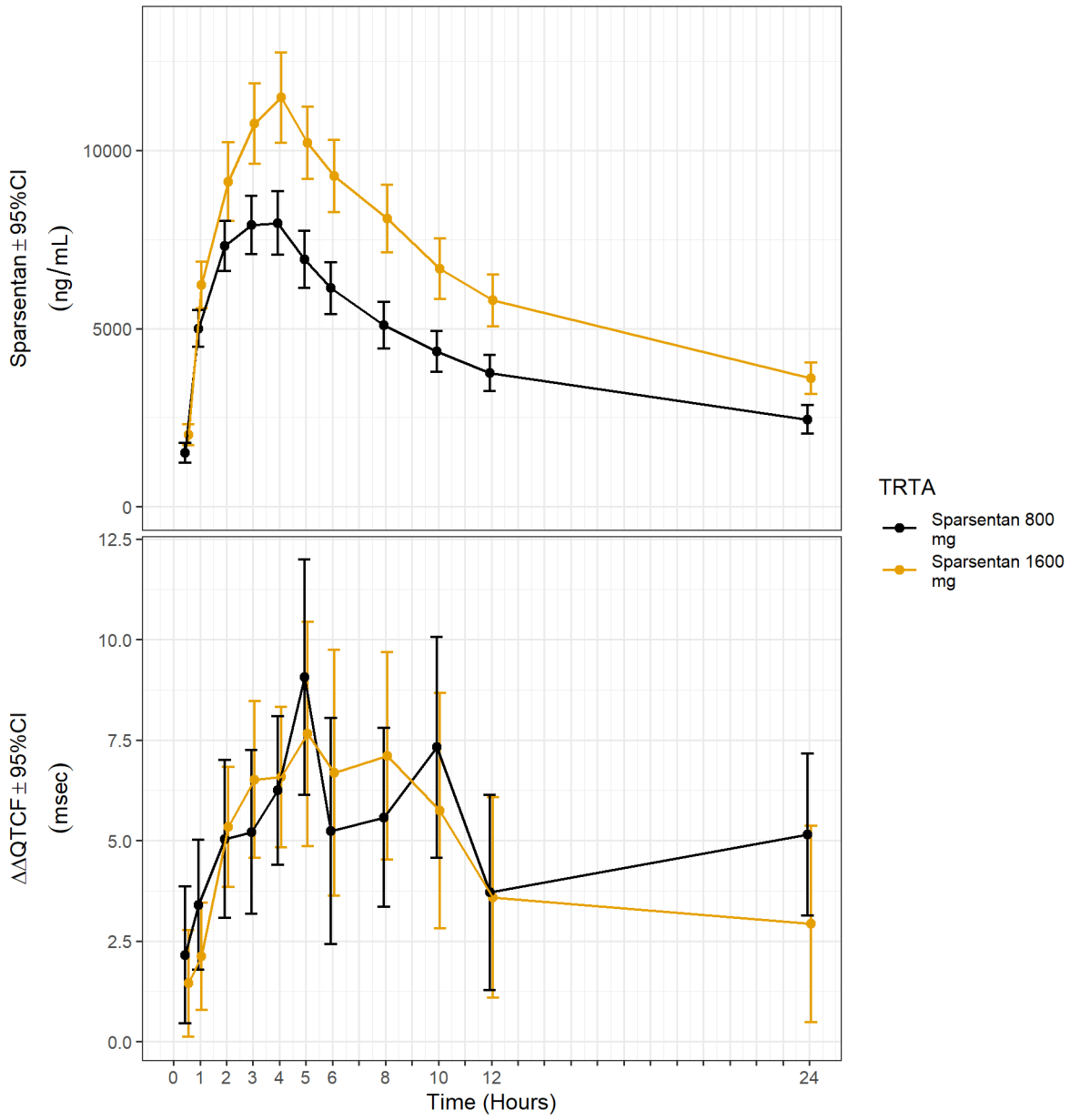
Exploratory exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK (n=60).

4.5.1 QTc

Exploratory analyses were conducted to evaluate assumptions for linear concentration-QTc (CQT) model. The first assumption for linear model is absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR). Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. The second assumption is absence of delay between plasma concentration and ΔΔQTcF. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF. The figure shows a 1-hour delay between mean sparsentan Cmax and maximum of mean ΔΔQTcF. The mechanism for delayed QTcF response is not yet known. Moreover, there is no dose-response, i.e., despite the 1600mg dose resulting on larger concentrations than the 800mg dose (top panel), the QT effects are similar between both dosing regimens (bottom panel). The third assumption is absence of

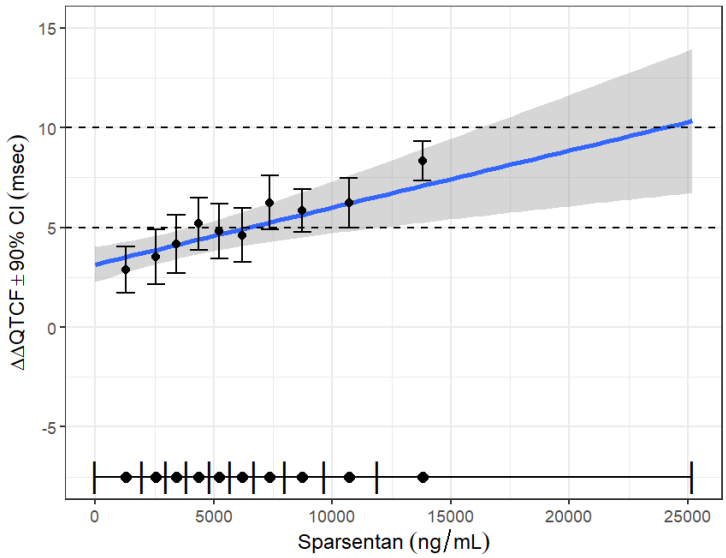
nonlinear relationship. Figure 6 shows that a linear concentration-ΔΔQTcF relationship would have intercept that deviates from 0. This would not be plausible since no QTc prolongation is expected in absence of drug exposure. Figure 6 therefore does not support the linearity assumption. Due to the violation of the hysteresis and linearity assumptions and since by-time point analysis is the primary analysis for this TQT study, the reviewer did not evaluate CQT relationships for sparsentan.

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



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

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



4.5.1.1 Assay Sensitivity

Assay sensitivity was established using by-time analysis. Please see section 0 for additional details.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

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/s/

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YANYAN JI
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DEVI KOZELI on behalf of CHRISTINE E GARNETT
06/27/2022 03:16:41 PM
Signing on behalf of Christine as she is OOO