CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 137918

MEETING PRELIMINARY COMMENTS

Travere Therapeutics, Inc.
Attention: Lynley Thinnes
Executive Director, Regulatory Affairs
3611 Valley Centre Drive, Suite 300
San Diego, CA 92130

Dear Ms. Thinnes:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sparsentan.

We also refer to your August 19, 2021, correspondence, received August 19, 2021, requesting a Pre-NDA meeting to discuss the format and content of your New Drug Application (NDA) and to obtain concurrence that the cited analyses support the filing of an application for accelerated approval under Subpart H.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call Anna Park at (301) 796-1129.

Sincerely,
{See appended electronic signature page}

Christine (Tina) Sadr, MS
Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 20, 2021 (3:00 PM to 4:00 PM, EST)
Meeting Location: Teleconference

Application Number: 137918
Product Name: Sparsentan
Indication: Treatment of Immunoglobulin A Nephropathy (IgAN)
Sponsor Name: Travere Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **October 20, 2021 from 3:00 PM to 4:00 PM, EST between Travere Therapeutics, Inc. and the Division of Cardiology and Nephrology**. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Sparsentan (RE-021) is a dual endothelin receptor type A (ETA) and angiotensin II type 1 receptor (AT1) antagonist that is being developed by the Sponsor for the treatment of rare kidney diseases, including immunoglobulin A nephropathy (IgAN) under IND 137918 and focal segmental glomerulosclerosis (FSGS) under IND (b) (4).

The Sponsor has two ongoing pivotal studies, one for each indication.

- The DUPLEX study (protocol 021FSGS16010) is a randomized, double-blind, active control study comparing sparsentan with irbesartan in patients with FSGS. The trial is currently fully enrolled. A pre-specified interim analysis to support accelerated approval was conducted after the first 190 patients received 9 months of treatment and compared the proportion of patients in each treatment arm who achieved the FSGS partial response endpoint (FPRE).
- The PROTECT study (protocol 021IGAN17001) is a randomized, double-blind, active control study comparing sparsentan with irbesartan in patients with biopsy-proven IgAN, persistent proteinuria (UPCR ≥1 g/g) despite RAS inhibitor therapy, and eGFR ≥30 mL/min/1.73 m^2. The trial is currently fully enrolled. The Sponsor has completed a pre-specified interim analysis to support accelerated approval after the first 280 patients reached 36 weeks of treatment. The primary endpoint for this analysis was the change from baseline in UPCR at Week 36.

Both trials will continue to a final analysis based on eGFR slope to verify the benefit and support full approval.

The purpose of this meeting is to discuss the proposed format and content of an NDA for sparsentan for the treatment of IgAN and to obtain concurrence that the cited analyses support the filing of an application for accelerated approval under Subpart H.

2.0 DISCUSSION

2.1. Clinical

Question 1:

a. Does the Agency agree that the clinically meaningful and statistically significant effect on proteinuria and the promising preliminary eGFR data at the time of the interim analysis are supportive of filing for accelerated approval under Subpart H?

b. Based on the strength of the PROTECT data, including achievement of complete and partial remission of proteinuria, what consideration will be given for the potential for full approval of sparsentan for the treatment of IgAN?

FDA Response to Question 1: Based on the information provided, we agree that the analyses support filing of an application for accelerated approval under Subpart H. Whether the available data are sufficient to support full approval will be a review issue.

2.2. Administrative

Question 2: Does the Agency agree that there is a high unmet medical need with no approved pharmacologic therapies available for the treatment of IgAN in the US, and that the sparsentan NDA is eligible for Priority Review designation?

FDA Response to Question 2: Priority review designation is granted after NDA submission. While it may be possible to obtain such a designation for your program, it is premature for us to comment further at this time.

Question 3: Does the Agency confirm that an Advisory Committee will not be required for the sparsentan NDA?

FDA Response to Question 3: Based on the information provided thus far, we do not anticipate need for an Advisory Committee meeting.

Question 4: Does the Agency agree the proposed content and organization of the data package and NDA for the treatment of IgAN are acceptable for filing and registration?

FDA Response to Question 4: Yes, we agree.

2.3. Clinical Pharmacology

Question 5: Does the Agency agree with the proposed clinical pharmacology plan, including but not limited to, population pharmacokinetics (popPK) analysis and exposure-response analysis, to support the NDA for IgAN?

FDA Response to Question 5: Yes, we agree.

Additional Requests from the Agency

1. Please submit the following information at the time of NDA submission:

    a. Protocol and Statistical Analysis Plan (SAP)
        1) All versions of the protocol for the PROTECT study (021IGAN17001) and the dates when changes were implemented. Include a Summary of Changes for each version and the number of subjects enrolled in the trial at the time the change was made.

        2) All versions of the SAP for the PROTECT study. Include a summary of changes for each version and the number of subjects enrolled in the trial at the time the change was made.

b. Clinical Trial Materials

1) Case report forms (CRFs) and narratives for all subjects who died, dropped out, discontinued study drug for any reason, experienced a serious adverse event (SAE), or reached an efficacy endpoint. Please note that CRFs must include all clinical documents collected regardless of whether you label them as "CRFs" (MedWatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.).

2) Sample clinical trial kits, from both treatment arms, identical to those used during the PROTECT study. Ship them to Anna Park's desk address in the same packaging as used for shipping to investigative sites.

3) A description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in PROTECT.

4) All charters for committees involved in conducting PROTECT (e.g., Data Safety Monitoring Board [DSMB], Steering Committee, etc.).

5) All meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. Ensure that these packages include a table of contents and are bookmarked by date.

c. General Data and Analyses

1) All code and datasets used to create your analyses found in the main sections of your Summary of Clinical Efficacy, Summary of Clinical Safety, and Phase 3 trial clinical study report. If a script contains a macro, include the macro script.

2) Footnote the tables and figures featured in the main clinical efficacy and safety sections of the NDA with the name of the script used to create the table or figure.

3) List of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for an NDA review. Submit code that was used to create or clean up your analysis datasets.

4) Dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.

5) Dataset that contains a list of all subjects for whom you submitted a CRF or narrative. The dataset should contain an indicator for whether each item was submitted.

6) A table set up similarly to the dataset requested above, but with a hyperlink to the respective document. The table could be further organized by reason for narrative submission.

7) One table which includes the following information for PROTECT:
   - Dates of first patient and last patient visits
   - Date of data lock
   - Date of interim analysis
   - Dates of all versions of the SAP (with a hyperlink to each SAP)
   - Dates of the initial protocol and all revisions (with a hyperlink to the protocol and each revision)

d. Other

1) Statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC), please reference the waiver and include the date.

2) Rationale for assuring the applicability of foreign data to the U.S. population/practice of medicine. Your rationale should address whether patients in the rest of the world are similar to patients in the US and whether treatment practices (interventions and background therapies) are similar to those in the U.S.

3) An annotated version of the pre-NDA meeting minutes that includes a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable,

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[4] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[5]

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[6] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[7]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of

[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[6] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[7] http://www.regulations.gov

safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on

published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX “TRADENAME”	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY “TRADENAME”	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

[8] https://www.fda.gov/media/85061/download

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/

CHRISTINE M SADR
10/13/2021 03:43:29 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 137918

MEETING MINUTES

Retrophin, Inc.
Attention: Andrea Loewen-Rodriguez
Vice President, Regulatory Affairs and Quality
3721 Valley Centre Drive, Suite 200
San Diego, CA 92130

Dear Ms. Loewen-Rodriguez:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sparsentan (RE-021).

We also refer to the meeting between representatives of your firm and the FDA on April 24, 2018. The purpose of the meeting was to discuss your phase 3 trial for the treatment of primary IgA nephropathy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Anna Park, Regulatory Project Manager at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: April 24, 2018 10:00 AM – 11:00 AM
Meeting Location: White Oak Building 22 Room 1415

Application Number: 137918
Product Name: sparsentan (RE-021)

Indication: treatment of IgA nephropathy
Sponsor/Applicant Name: Retrophin, Inc.

Meeting Chair: Ellis Unger, M.D.
Meeting Recorder: Anna Park, M.S., R.Ph., RAC

FDA ATTENDEES

Dr. Ellis Unger	Director, Office of Drug Evaluation I
Dr. Naomi Lowy	Associate Director for Regulatory Science, Office of Drug Evaluation I

Division of Cardiovascular and Renal Products

Dr. Aliza Thompson	Medical Team Leader
Dr. Kimberly Smith	Medical Officer
Dr. William Link	Pharmacology Reviewer
Ms. Anna Park	Regulatory Project Manager

Office of Clinical Pharmacology

Dr. Martina Sahre	Clinical Pharmacology Reviewer

Office of Biostatistics

Dr. James Hung	Director, Division of Biometrics I, Office of Biostatistics (OB)
Dr. Ququan (Cherry) Liu	Statistician

SPONSOR ATTENDEES

(b) (4)	Statistical Consultant to Retrophin, (b) (4)
(b) (4)	Regulatory Affairs Consultant

	(b) (4)
Dr. Ulysses Diva	Executive Director, Biometrics, Retrophin, Inc., US
Ms. Michelle Greenman	Associate Director, Regulatory Affairs, Retrophin, Inc., US
(b) (4)	Medical Consultant to Retrophin, (b) (4)
Dr. Radko Komers	Medical Director, Nephrology, Retrophin, Inc., U
Ms. Andrea Loewen-Rodriguez	Vice President, Regulatory Affairs & Quality Retrophin, Inc., US
(b) (4)	Clinical Development Consultantm (b) (4)
Dr. William Rote	Sr. Vice President, Research and Developmentm Retrophin, Inc., US
(b) (4)	(b) (4)
(via telephone)	
Dr. Barbara Belli	Sr. Director, Non-Clinical Development Research, Retrophin Inc., US
(b) (4)	(b) (4)
(b) (4)	Clinical Pharmacology Consultant to Retrophin Inc.
Dr. Maeve McDonnell	Sr. Director, Regulatory Affairs, Retrophin, Inc., US

1.0 BACKGROUND

Sparsentan is a dual angiotensin II receptor type 1 (AT1) and endothelin receptor type A (ETA) antagonist that Retrophin plans to develop for the treatment of primary immunoglobulin A nephropathy (IgAN). The Sponsor requested this meeting to obtain Agency concurrence on the design of their phase 3 study and overall phase 3 development plan.

In brief, Retrophin has proposed a phase 3 clinical study (021IGAN17001) titled "A Randomized, Multicenter, Double-blind, Parallel-group, Active-control Study of the Efficacy and Safety of Sparsentan for the Treatment of Immunoglobulin A Nephropathy" (the PROTECT trial). The study will enroll approximately 280 adults with biopsy-proven IgAN on maximum tolerated ACE inhibitor or ARB therapy for at least 12 weeks, urine protein $\geq$ 1 g/day, and an eGFR $\geq$30 mL/min/1.73m^2. Patients will be randomized 1:1 to double-blind (over-encapsulated) sparsentan 400 mg daily or irbesartan 300 mg daily for 110 weeks. Half the target dose will be administered for the first two weeks to improve tolerability. Randomization will be stratified by eGFR (30 to <60 and $\geq$60 mL/min/1.73m^2) and urine protein ($\leq$1.75 g/day and >1.75 g/day). After randomization, patients will discontinue ACE inhibitor or ARB therapy and start study drug. Antihypertensive agents, other than RAS or endothelin inhibitors, are to be added or titrated during the study to achieve a target blood pressure of 125/75. Immunosuppressive therapy will be discouraged but may be started after consultation with the medical monitor. Proposed primary and key secondary efficacy endpoints are as follows:

Primary efficacy endpoint:

- The change from baseline in the urinary protein/creatinine ratio (Up/C), based on a 24-hour urine sample, at Week 36, assessed on the log scale.

Key secondary efficacy endpoints:

- The rate of change in eGFR over a 104-week (approximately 2-year) period following the initial acute effect of randomized therapy (6 weeks post randomization to 110 weeks post randomization)
- The rate of change in eGFR over a 52-week (approximately 1-year) period following the initial acute effect of randomized therapy (6 weeks post randomization to 58 weeks post randomization)
- (b) (4).

Retrophin proposes to use the Week 36 analysis of proteinuria to support an application for approval. After this analysis, patients will continue to be followed for the collection of longer-term eGFR data to examine rate of change over a 104-week period after the initial acute effect of randomized therapy (i.e., over the period from 6 weeks post randomization to 110 weeks post randomization).

Sparsentan is also being developed as a treatment for focal segmental glomerulosclerosis (FSGS) under IND (b) (4) and Retrophin is (b) (4).

Preliminary responses to the submitted questions were provided to the sponsor in advance of the meeting, and are copied below, followed by any additional discussions that took place during the meeting. The sponsor used the appended slide presentation to guide the discussion at the meeting.

2.0 DISCUSSION

2.1. Clinical

Question 1: *Does the Agency agree that the patient population selected for this study (i.e., patients with biopsy-proven primary IgAN who have a urine total protein value ≥1 g/day [despite receiving a maximum tolerated dose of RAS blockade therapy at ≥50% of a maximum labelled dose of an ACEI or ARB] and an eGFR value ≥30 mL/min/1.73 m^2 at screening) will support a sparsentan marketing application indicated for the treatment of primary IgAN?*

Preliminary FDA Response:
For the most part, the proposed patient population seems reasonable.

To provide confidence that the observed treatment effect on eGFR will, over time, translate into a meaningful effect on progression to ESRD, it will be important to show that the treatment effect continues to accrue across the various stages of disease. To address this issue, the protocol

should specify enrollment of minimum numbers of patients at the higher and lower ends of the proposed eGFR range.

We also recommend that you include patients with an eGFR < 30 mL/min/1.73 m^2 in your trial because the marketed product would likely be used in patients with lower levels of renal function and because efficacy data in later stages of disease would be important for modeling the likely impact of your treatment on time-to-progression to kidney failure. Given concerns about efficacy at lower eGFRs, you could prespecify that subjects with an eGFR < 30 mL/min/1.73 m^2 will be excluded from key efficacy analyses.

Additional discussion during the meeting: None.

Question 2: *Does the Agency agree that a positive treatment effect on proteinuria (Up/C) at Week 36 can be used as the basis for a new drug application (NDA) for sparsentan indicated for the treatment of primary IgAN?*

Preliminary FDA Response:
In brief, you propose to unblind the trial to assess the primary efficacy endpoint of change from baseline in the urine protein to creatinine ratio at Week 36 and the second key secondary endpoint of eGFR over 52 weeks (in a subset of ~222 subjects) to support submission of an application for accelerated approval. You note that the data will only be shared with regulatory agencies and no changes to trial conduct, data processing and procedures, the protocol, or the statistical analysis plan will be made after unblinding. All subjects will continue double-blind treatment through 110 weeks to allow evaluation of the rate of change in eGFR from Week 6 (post-baseline) to Week 110 to confirm the treatment benefit.

We have the following comments on your proposal:

1. Based on the meta-analysis by Inker et al, we agree that a substantial reduction in proteinuria would be reasonably likely to predict a clinical benefit in IgA nephropathy and that such a finding could be used as a basis for accelerated approval. To support accelerated approval, the magnitude of the treatment benefit on proteinuria would need to be sufficient to provide confidence that the anticipated benefit on loss of renal function could be verified with longer-term follow-up as you propose.

   Additional discussion during the meeting: None.

2. You hypothesize a treatment effect of spartsentan on proteinuria relative to irbesartan of 30% based on data with sparsentan in FSGS and ET_A receptor antagonism in addition to RAS blockade in IgA nephropathy. Based on the analysis by Inker et al, this magnitude of treatment effect is predicted to translate to a hazard ratio of 0.36 (95% CI 0.22, 0.61) on the first occurrence of doubling of serum creatinine, ESRD, or death. You also provide analyses of registry data showing associations between an early 30% reduction in proteinuria and decline in eGFR at later time points. If you wish to use an eGFR slope-based endpoint to verify the benefit of your product, you should provide data from intervention trials that speak

to the relationship between treatment effects on proteinuria and treatment effects on the rate of change in eGFR; the provided analyses of registry data are not sufficient. Alternatively, it may be feasible to use the Inker analyses to support a confirmatory endpoint based on a composite endpoint consisting of a 30% decline in eGFR, ESRD, or death.

Additional comments during the meeting: Referring to slide 15, the sponsor noted that sample size calculations suggest that it would not be feasible to conduct a confirmatory study using a composite endpoint of a 30% decline in eGFR or an eGFR of <15 mL/min/1.73m^2. To support use of an eGFR slope-based confirmatory endpoint, the sponsor referred to slides 4 to 8 including a new trial-level analysis conducted by Inker et al. showing an association between treatment effects on proteinuria at 12 months and chronic eGFR slope over 2 years in trials of IgA nephropathy. The Division noted that the analyses focused on treatment effects on proteinuria at 12 months, but the proposed primary endpoint is defined at 9 months. See also the discussion below regarding the use of chronic eGFR slope. The sponsor noted that the analyses presented were recently completed, and that they were awaiting additional analyses related to these issues.

The Division agreed in principle with the use of an eGFR slope-based endpoint, but noted that they would need additional time to review the new analyses and that there would need to be further discussions regarding the design of the post-marketing trial. The Division noted that there was substantial uncertainty around the estimates of eGFR slope and that the treatment effect on proteinuria would need to be sufficiently large to account for that uncertainty. The Division recommended a follow-up meeting to discuss these issues further before the protocol and SAP are finalized.

3. Because both sparsentan and irbesartan have acute effects on eGFR, you have proposed (b) (4) [redacted]. As discussed at the recent NKF workshop titled "Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of Chronic Kidney Disease," held on March 16, 2018 in Silver Spring, MD, (b) (4) [redacted] If there is concern with respect to the possibility of a large acute effect, you may want to consider comparing the change in renal function from a pre-treatment baseline to a post-treatment assessment. As a means to decrease variability and possibly improve trial efficiency, one could obtain multiple eGFR measurements pre- and post-treatment and use the average of these measurements in the analysis.

Additional discussion during the meeting: (b) (4) [redacted] **. The Division stated that further discussion of this issue was needed.**

4. It will be important to show that the treatment effect on the decline in renal function continues to accrue over time and across the various stages of disease. Such data provide confidence that the treatment effect on renal function observed in the trial (which may seem small in absolute terms) will, over time, translate into a meaningful effect on progression to ESRD. Unless your therapy essentially halts progression, demonstrating a statistically significant effect on (b) (4) is unlikely to provide the data needed to determine whether the treatment effect continues to accrue over time. See also our response to Question 1 regarding the importance of enrolling patients across the various stages of disease (as defined by level of renal function).

   Additional discussion during the meeting: **Referring to slides 17 and 23, the sponsor noted that their goal was to provide some supportive data regarding eGFR to support accelerated approval on the basis of proteinuria. The sponsor noted that there is a strong correlation between slope at 1, 2, and 3 years.**

2.2. Biostatistics

Question 3: *Does the Agency agree that the study, as designed, is suitable to support an NDA for sparsentan indicated for the treatment IgAN based upon*

a) The analysis of proteinuria as the primary endpoint at Week 36?
b) The longer-term analysis of eGFR slope over 104 weeks?
c) The associated sample size calculation and rationale?

Preliminary FDA Response:
See our response to Question 2. It is premature to comment on the specifics of your analytic plan; we should first reach agreement on the overall design of your study, including key efficacy endpoints.

Additional discussion during the meeting: **None.**

d) The proposed statistical methodology for overall Type I error control?

Preliminary FDA Response:
You propose to control the overall type I error rate by making the proteinuria endpoint a gate-keeper for the analyses of eGFR rate of change. The full alpha of 5% (2-sided) will be applied to the primary endpoint of Week 36 proteinuria. If statistical significance is met, then eGFR rate of change over time will be assessed at the 5% level with 1% alpha applied to the analysis at 52 weeks and 4% alpha applied to the analysis at 104 weeks. Type I error control for additional key secondary endpoints will be governed by the combination of a gate-keeper and the use of a closed test procedure such as Hochberg or Holm. The proposed approach is acceptable.

Additional discussion during the meeting: **None.**

Question 4: *The Sponsor recognizes that approval based on the primary endpoint of change from baseline in Up/C at Week 36 is dependent upon the magnitude of the treatment effect seen between sparsentan and irbesartan. If the primary endpoint delivers a statistically significant treatment effect with p≤0.05, the magnitude of the treatment effect on this endpoint may still be considered clinically modest. In this circumstance the Sponsor considers that a new drug application (NDA) could still be made for sparsentan in the treatment of IgAN in the following manner:*

Preliminary FDA Response:
See our response to Question 2.

Additional discussion during the meeting: **None.**

Question 5: *Does the Agency agree that data from a single pivotal phase 3 study in patients with IgAN together with supportive data from a phase 2 and a phase 3 clinical study in patients with FSGS is sufficient to support an NDA for sparsentan indicated for the treatment of patients with primary IgAN?*

Preliminary FDA Response:
FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. If you can make the argument that the pathophysiology of FSGS is sufficiently similar to IgA nephropathy and the mechanism of action of your drug is similar in both diseases, your phase 2 and 3 FSGS studies may be able to provide adequate support for an indication for the treatment of IgA nephropathy when combined with positive results of the PROTECT trial.

If your FSGS studies are not successful, it may be possible to rely on a single adequate and well-controlled multicenter study for approval without supporting information from other adequate and well-controlled studies. Reliance on a single study is generally limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome. Your proposed primary endpoint would not be sufficient to demonstrate such effects. Other characteristics of a single adequate and well-

controlled study that could make the study adequate support for an effectiveness claim include statistically persuasive findings (e.g., a very low p-value), and consistency of effects across primary and secondary endpoints, important patient subsets, and centers/investigators (see also our comments about secondary endpoints). The quality of trial execution and completeness of data collection are also critical. For further discussion of these issues, we refer you to the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078749.pdf).

Additional discussion during the meeting: The sponsor asked the Division to clarify whether a single pivotal trial with proteinuria as the primary endpoint could be sufficient to achieve accelerated approval in IgA nephropathy, regardless of the outcome or availability of the phase 3 FSGS study. The Division agreed that a single pivotal trial could be sufficient if the trial were well-conducted and the results were statistically persuasive.

Post-Meeting Comments and Requests:

1. **The proposed maximal dose in Protect-IgAN is 400 mg without dose adjustment for weight.** (b) (4) [redacted]
2. **Your summary of the meeting discussion, submitted on May 3, 2018, includes additional information intended to address issues that were not resolved at the meeting. We are reviewing this information and will provide a response in a separate advice letter.**

3.0 OTHER IMPORTANT MEETING LANGUAGE

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications (available at the following link https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm) be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes

3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ATTACHMENTS AND HANDOUTS

Please see below.

23 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANNA J PARK
05/24/2018

ELLIS F UNGER
05/24/2018