CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218772Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 157056

MEETING REQUEST-
WRITTEN RESPONSES

Scienture Inc.
Attention: Shreena Patel
Senior Director, Regulatory Affairs and Project Management
150 Motor Parkway, Suite 401
Hauppauge, NY 11788

Dear Ms. Patel:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SCN-102 (losartan potassium) oral suspension.

We also refer to your submission dated May 12, 2023, containing a meeting request. The purpose of the requested meeting was to discuss your overall plan to submit a 505(b)(2) new drug application.

Further reference is made to our Meeting Granted letter dated May 23, 2023, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 9, 2023 background package.

If you have any questions, call Quynh Nguyen, PharmD, RAC-US, Regulatory Project Manager, at 301-796-0510.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD, MS
Deputy Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-NDA
Application Number:	IND 157056
Product Name:	SCN-102 (losartan potassium) oral suspension
Indication:	Treatment of hypertension, to lower blood pressure in adults and children greater than 6 years old; Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy; Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension.
Sponsor Name:	Scienture Inc.
Regulatory Pathway:	505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Scienture Inc. is developing SCN-102 (losartan potassium) oral suspension, 10 mg/mL. Losartan is an angiotensin II receptor blocker (ARB) acting on the AT_1 receptor subtype. The Sponsor plans to submit a New Drug Application (NDA) for SCN-102 via the 505(b)(2) pathway and to rely in part on the Agency's previous finding of safety and efficacy for Cozaar® (losartan potassium) tablets, approved under NDA 020386 on April 14, 1995. The Sponsor intends to seek approval for the same indications, doses, and dosing regimen as the planned listed drug (LD), Cozaar tablets.

The proposed indications are:

- Treatment of hypertension, to lower blood pressure in adults and children greater than 6 years old.
- Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy.
- Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension.

Currently, there are no FDA-approved liquid formulations of losartan potassium. An oral suspension can be prepared by adding Cozaar (losartan potassium) tablets to purified water and later adding the 50/50 Ora-Plus/Ora-Sweet SF mixture to the tablet and water slurry. This suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 4 weeks. The Sponsor believes that their proposed product, SCN-102, will provide a convenient alternative for patients and healthcare providers with a longer product shelf-life compared to the Cozaar suspension.

On July 29, 2021, the Sponsor submitted a Pre-IND meeting request under PIND 157056 to discuss their development plans for SCN-102; the Division issued Written Responses on September 24, 2021.

On September 23, 2022, the Sponsor submitted the original IND. A Study May Proceed letter was issued by the Division on October 20, 2022. The Sponsor's IND submission outlined their intent to conduct the following two clinical pharmacokinetic (PK) studies:

- **Study LOS/CR/046/21-22:** An open-label, balanced, randomized, single oral dose, two-treatment, two-sequence, four-period, fully replicate, crossover study to evaluate the relative bioavailability (BA) of SCN-102 (oral liquid formulation) as compared to Cozaar (immediate-release tablet) under fasting conditions. This relative BA study was completed on December 21, 2022.

- **Study LOS/CR/047/21-22:** An open-label, balanced, randomized, single oral dose, two-treatment, two-sequence, two-period, two-way crossover study to assess the effect of food on the bioavailability of SCN-102 oral suspension. This food-effect study was completed on March 23, 2023.

Upon availability of the 12-month stability data for the NDA exhibit batches, the Sponsor plans to submit a 505(b)(2) NDA in the third quarter of 2023. On May 12, 2023, Scienture Inc. submitted this Pre-NDA meeting request to obtain the Agency's feedback on their overall plan for the planned NDA submission for SCN-102 (losartan potassium) oral suspension.

2.0 QUESTIONS AND RESPONSES

2.1 Chemistry, Manufacturing and Controls (CMC)

(b) (4)

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2.2 Clinical Pharmacology

Question 5:
Based on the summarized fasting PK LOS/CR/046/21-22 (Study # 14323/21-22) study data, does the Agency agree that SCN-102 would be considered therapeutically equivalent to the listed drug, Cozaar tablets?

FDA Response to Question 5:
As a preliminary matter, FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book) contains therapeutic equivalence evaluations for approved multisource prescription drug products. FDA previously has published therapeutic equivalence evaluations for certain drug products approved through the 505(b)(2) pathway that have been demonstrated to be pharmaceutically equivalent and bioequivalent to a listed drug, and that have met the definition of therapeutic equivalent as defined in 21 CFR 314.3(b). When the Agency assigns therapeutic equivalence ratings for 505(b)(2) NDAs, such ratings are assigned after approval. It is also worth noting that pharmaceutical equivalents are defined in 21 CFR 314.3(b) as "drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient…"

2.3 Additional FDA Comments

Regulatory
As a regulatory matter, FDA agrees that the Summary Basis of Approval (SBA)/FDA publicly available reviews may be used in support of drug development at the IND stage if scientifically persuasive. However, you may not rely on the SBA/FDA publicly available reviews for support of safety and/or effectiveness in a future NDA application. Both 505(b)(1) and 505(b)(2) NDAs require "full reports of investigations" of safety and effectiveness and the SBA/FDA publicly available reviews are considered a summary.

Clinical Pharmacology
Based on your meeting package, the C_{max} for losartan is higher with your product than with the reference listed drug and failed to meet the general bioequivalence criteria. In your NDA submission, you will need to address why the approximate 35% increase in the C_{max} of losartan that was observed with your product does not pose a safety concern. As part of your justification, we encourage you to provide data, if available, on losartan's exposure-response relationships. The acceptability of your rationale and the approvability of SCN-102 suspension will be a review issue.

Product Quality Microbiology:
At the time of NDA submission, provide the results of an antimicrobial effectiveness test (AET) according to USP <51> or equivalent methodology with the lowest labeled preservative content. Additionally, the stability protocol should include an AET on at least one primary stability batch at the end of the proposed shelf life (reference

Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products).

3.0 OTHER IMPORTANT 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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, 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.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing

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

facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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).[7] 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.[8]

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

[7] 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.
[8] http://www.regulations.gov

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.

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to identify uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[9] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

[9] https://www.fda.gov/media/124795/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/

ALIZA M THOMPSON
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