OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	218772
Link to EDR	\\CDSESUB1\evsprod\NDA218772\0001
Submission Date	10/19/2023
Submission Type	505(b)(2), Standard review
PDUFA Goal Date	8/19/2024
Brand Name	Arbli
Generic Name	Losartan Potassium
Dosage Form and Strength	Oral Suspension, 10 mg/mL
Route of Administration	Oral
Proposed Indications	• 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.
Proposed Dosage Regimen	Same as listed drug, Cozaar (see Section 2.1.5)
Applicant	Scienture Inc.
OCP Review Team	Po-Hung Hsieh, Ph.D., Brianna Cote, PharmD, Ph.D.

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1 EXECUTIVE SUMMARY

The Applicant, Scienture Inc., submitted this 505(b)(2) application for Arbli (losartan potassium oral suspension, 10 mg/mL), intending to seek approval for the same indications as the Listed Drug (LD) Cozaar (losartan potassium tablets). The Applicant proposes to rely on the safety and efficacy findings of Cozaar approved under NDA 020386 in 1995. Currently, there are no FDA-approved liquid formulations of losartan potassium, although an oral suspension can be prepared by adding Cozaar® tablets to purified water and later adding 50/50 Ora-Plus/Ora-Sweet SF mixture to the tablet and water slurry. Arbli is a new formulation which can provide an alternative to preparation of an oral suspension using losartan tablets. The proposed strength of Arbli oral suspension is 10 mg/mL.

The Applicant submitted two clinical studies: 1) the relative bioavailability study (study 14323) to assess the relative bioavailability of a single oral dose of losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) compared with Cozaar® (losartan potassium) 100 mg tablets under fasting conditions; and 2) the food effect study (study 14324) to assess the effect of food on the rate and extent of absorption of losartan and its major metabolite after a single oral dose of the proposed product administered immediately after a meal (fed condition) as compared to administration under fasting conditions (10 mL with a total dose of 100 mg).

The main objective of this review is to evaluate whether the relative bioavailability study and the food effect study conducted for losartan potassium oral suspension 10 mg/mL forms an adequate scientific bridge to the LD, Cozaar tablets, that allows relying on the efficacy and safety findings of the LD for all the proposed indications.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the NDA submission. The results of the relative bioavailability study support approval of losartan potassium oral suspension 10 mg/mL for the proposed indications at the doses approved for the listed drug Cozaar. The food effect results support administration of losartan potassium oral suspension 10 mg/mL with or without food. The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

1.2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

- The results of the relative bioavailability study (study 14323) demonstrated that the losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) under fasting conditions was not bioequivalent to Cozaar® (losartan potassium) 100 mg tablets under fasting conditions for losartan; however, the approximately 35% higher C_{max} is likely not clinically significant given the flat dose-response relationship, combined with the equivalent AUC for losartan.

    - In addition, the study results demonstrated similar pharmacokinetics between the two products under fasting conditions for losartan carboxylic acid, as the 90% CI for the geometric mean ratios were within the acceptance range of 80.00% to 125.00% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

- The results of the food effect study (study 14324) demonstrated that taking losartan potassium oral suspension with a high-fat, high-calorie meal slowed the absorption of losartan and decreased its C_{max}, but it had minor effects on its AUC or on the AUC of the active metabolite. As the effect of losartan appears to be driven more by AUC rather than C_{max}, dosing under either fed or fasted condition appears reasonable.

2 QUESTION BASED REVIEW

This review is specific to the evaluation of the clinical pharmacology studies conducted in support of the losartan potassium oral suspension (10 mg/mL) product from Scienture Inc. For details on the general clinical pharmacology properties of losartan, refer to the original New Drug Application (NDA) 020386 review for Cozaar.

2.1 GENERAL ATTRIBUTES

2.1.1 What are general features of the drug product?

The Applicant developed losartan potassium oral suspension (10 mg/mL). The proposed product is a white, translucent suspension with a peppermint odor.

The reference product, losartan potassium tablets, was approved by Food and Drug Administration (FDA) in 1995 under the brand name of Cozaar (NDA 020386). Cozaar is available in different strengths - 25 mg, 50 mg, and 100 mg.

2.1.2 What is the Applicant's rationale in developing this product?

Currently, there are no FDA-approved liquid formulations of losartan potassium; however, an oral suspension can be prepared by adding Cozaar® tablets to purified water and later adding 50/50 Ora-Plus/Ora-Sweet SF mixture to the tablet and water slurry. The suspension prepared from Cozaar tablets needs to be refrigerated at 2-8°C (36-46°F) and can be stored for up to 4 weeks after preparation. The Applicant developed losartan potassium oral suspension (10 mg/mL) to provide an alternative to preparation of an oral suspension using losartan tablets.

2.1.3 What are the proposed mechanism(s) of action of losartan?

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)] is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system, and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the angiotensin II type 1 (AT1) receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an angiotensin II type 2 (AT2) receptor found in many tissues, but it is not known to be associated with cardiovascular homeostasis.

Neither losartan nor its principal active metabolite exhibits any partial agonist activity at the AT1 receptor, and both have much greater affinity (about 1,000-fold) for the AT1 receptor than for the AT2 receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, noncompetitive inhibitor of the AT1 receptor.

Neither losartan nor its active metabolite inhibits ACE, nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

2.1.4 What are the proposed therapeutic indication(s)?

In this 505(b)(2) NDA for losartan potassium oral suspension, the Applicant is seeking approval for the same indications that are approved for Cozaar. The proposed indications are the following:

- 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.

2.1.5 What are the proposed dose(s)?

The proposed doses are the same as those for the reference listed drug (LD), Cozaar.

Hypertension

Adult Hypertension

The usual starting dose of the proposed product is 50 mg once daily. The dosage can be increased to a maximum dose of 100 mg once daily as needed to control blood pressure. A starting dose of 25 mg is recommended for patients with possible intravascular depletion (e.g., on diuretic therapy).

Pediatric Hypertension

The usual recommended starting dose is 0.7 mg per kg once daily (up to 50 mg total) administered as a suspension. Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg per kg (or in excess of 100 mg) daily have not been studied in pediatric patients. The proposed product is not recommended in pediatric patients less than 6 years of age or in pediatric patients with estimated glomerular filtration rate less than 30 mL/min/1.73 m^2.

Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of the proposed product once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of the proposed product should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response.

Nephropathy in Type 2 Diabetic Patients

The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response.

Dosage Modifications in Patients with Hepatic Impairment

In patients with mild-to-moderate hepatic impairment, the recommended starting dose of the proposed product is 25 mg once daily. The proposed product has not been studied in patients with severe hepatic impairment.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of clinical pharmacology studies used to support dosing or label claims?

The Applicant submitted two clinical studies that are listed in Table 1: 1) the relative bioavailability study (study 14323) to assess the single oral dose relative bioavailability of losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) (Test) compared with Cozaar® (losartan potassium) 100 mg tablets (Reference) in healthy adult study participants under fasting conditions; and 2) the food effect study (study 14324) to assess the effect of food on the rate and extent of absorption of losartan and its major metabolite after a single oral dose of test product administered immediately after a meal (fed condition) as compared to administration under fasting conditions (10 mL with a total dose of 100 mg) in healthy adult study participants.

Table 1: Listing of Clinical Studies

Study No.	Location of Study Report	Objectives of the Study	No. of Subjects	Study Design & Type of Control	Test Product (s); Dosage Regimen; Route of Administration
14323/21-22	Module 5.3.1.2	To assess the single oral dose relative bioavailability of Losartan Potassium Oral Liquid 10 mg/mL (10 mL with a total dose of 100 mg) (T) with COZAAR® (losartan potassium) tablets 100 mg (R) in healthy adult study participants under fasting conditions.	44	An open label, balanced, randomized, single oral dose, two-treatment, two-sequence, four-period, fully replicate, crossover study to assess the relative bioavailability with at least 07 days washout period between each study product administration under fasting conditions	**Test Product (T):** Losartan Potassium Oral Suspension 10 mg/mL (1 x 10mL, Suspension, Oral) [Batch No. S0083A0] **Reference Product (R):** Cozaar® (Losartan Potassium) Tablets 100 mg (1 x 100 mg, Tablets, Oral) [Lot No. U013033]
14324/21-22	Module 5.3.1.1	To assess the effects of food on the rate and extent of absorption of losartan and its major metabolite after a single oral dose of test product administered immediately after a meal (fed condition) as compared to administration under fasting conditions of Losartan Potassium 10 mg/mL oral liquid (10 mL with a total dose of 100 mg) in healthy adult study participants.	35	An open label, randomized, single oral dose, two-treatment, two-sequence, two-period, two-way crossover study to assess the effects of food on the bioavailability of the test product under fasting verses fed conditions	**Test Product (T):** Losartan Potassium Oral Suspension 10 mg/mL (1 x 10mL, Suspension, Oral) [Batch No. S0083A0

Source: Module 5.2 TABULAR LISTING OF ALL CLINICAL STUDIES

2.2.2 Is the active moiety in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Losartan and its metabolite, losartan carboxylic acid, in human dipotassium ethylenediaminetetraacetic acid (K2EDTA) plasma were determined by using a validated LC-MS/MS analytical method. The internal standards were losartan-D4 and losartan carboxylic acid-D4.

The bioanalytical validation summary is provided in **Table 2**.

Table 2: Bioanalytical Method Validation Summary for Losartan and Losartan Carboxylic Acid Plasma Concentration Quantification

Validation Parameters	**Results Summary**
Linearity	r > 0.99 in all cases
Validated assay range (ng/mL)	Losartan: 5.006 ng/mL to 3003.357 ng/mL Losartan carboxylic acid: 5.009 ng/mL to 3005.498
Standard curve concentrations (ng/mL)	Losartan: 5.006, 10.011, 25.028, 100.112, 400.448, 1201.343, 2502.797 & 3003.357 Losartan carboxylic acid: 5.009, 10.018, 25.046, 100.183, 400.733, 1202.199, 2504.582 & 3005.498
Quality control (QC) concentrations (ng/mL)	Losartan: Lower limit of Quantitation Quality Control (LLOQ-QC) = 5.007 Low Quality Control (LQC) = 14.819 Medium Quality Control (MQC) = 1501.953 High Quality Control (HQC) = 2403.125 Losartan carboxylic acid: LLOQ-QC = 5.021 LQC = 14.862 MQC = 1506.275 HQC = 2410.040
QC Inter-batch accuracy range (%)	Losartan: LLOQ-QC = 98.82 LQC = 98.83 MQC = 96.73 HQC = 95.91

	Losartan carboxylic acid: LLOQ-QC = 105.21 LQC = 101.21 MQC = 97.47 HQC = 96.92
QC Inter-batch precision range (%)	Losartan: LLOQ-QC = 3.63 LQC = 2.84 MQC = 1.22 HQC = 2.31 Losartan carboxylic acid: LLOQ-QC = 3.72 LQC = 2.41 MQC = 1.49 HQC = 2.14
QC Intra-batch accuracy range (%)	Losartan: LLOQ-QC = 94.58 % to 100.75 % LQC = 97.80 % to 100.98 % MQC = 95.91 % to 97.28 % HQC = 94.41 % to 97.23 % Losartan carboxylic acid: LLOQ-QC = 102.66 % to 107.84 % LQC = 99.80 % to 103.52 % MQC = 96.34 % to 98.22 % HQC = 95.54 % to 98.31 %
QC Intra-batch precision range (%)	Losartan: LLOQ-QC = 1.75 % to 4.11 %

	LQC = 2.16 % to 3.57 % MQC = 0.56 % to 1.57 % HQC = 1.18 % to 3.00% Losartan carboxylic acid: LLOQ-QC = 1.38 % to 4.83 % LQC = 1.25 % to 2.62 % MQC = 1.17 % to 1.57 % HQC = 1.25 % to 2.35%
Average recovery of drug (%) Average recovery of internal standard (IS) (%)	Losartan: 78.93 % Losartan carboxylic acid: 78.82 % Losartan D4: 82.08 % Losartan carboxylic acid D4: 83.05 %
Freeze-thaw stability (cycles)	After five cycles at -20 ºC ± 4 ºC Losartan: % Stability at LQC = 102.88 % & HQC = 99.43 % Losartan carboxylic acid: % Stability at LQC = 103.30 % & HQC = 97.34 %
Bench-top stability (hr)	After 22.23 hours at room temperature Losartan: % Stability at LQC = 99.70 % & HQC = 100.18 % Losartan carboxylic acid: Stability at LQC = 102.55 % & HQC 100.29 %
Long-term storage stability (days)	In aqueous media: 119 Days at 2 - 8 °C In matrix K2EDTA human plasma: 117 Days at -20 °C ± 4 °C
Selectivity	No significant interfering peaks were noted in blank plasma samples
Specificity, Carryover Effect (COE), Matrix Effect, Matrix Factor, Geometric Mean Quality Control (GMQC) samples, Re-Injection Reproducibility (RIR),	Specificity, COE, Matrix Effect, Matrix Factor, GMQC samples, RIR, Low & High Hemolytic Effect, Lipemic Effect, Whole Blood Stability, Ruggedness & Concomitant Medication parameters were performed, and results were

Hemolytic (Low & High), Lipemic Effect, Whole Blood Stability (WBS), Ruggedness & Concomitant Medication	within the acceptance criteria.
Dilution Integrity	3 times of calibration curve concentration 8 (CC8) (8961.652 ng/mL) diluted in 1:4 Losartan: % Accuracy = 98.52 % & % CV = 4.10 % 3 times of CC8 concentration (8987.441 ng/mL) diluted in 1:4 Losartan carboxylic acid: % Accuracy = 99.35 % & % CV = 3.60%

Source: Method Validation Report (23/MVR/LS & LCA/350) and Supplementary Method Validation Report (23/SMVR/LS & LCA/350/01)

- OSIS clinical and analytical sites inspection:

  - Clinical site inspection: Decline to conduct an on-site inspection. The Office of Regulatory Affairs (ORA) conducted an inspection of the site in January 2023 under the submission of (b) (4). After review of the discussion items and the site's response, OSIS concluded that the data from the reviewed studies were reliable.

  - Analytical site inspection: OSIS conducted a remote regulatory assessment (RRA) of the analytical site of study 14323/21-22 (NDA 218772, losartan potassium), conducted at (b) (4) No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. There were no items discussed at the inspection close-out. Based on the inspection findings, there are no identified concerns for (b) (4) regarding the reliability of the data for inspected study 14323/21-22 (NDA 218772).

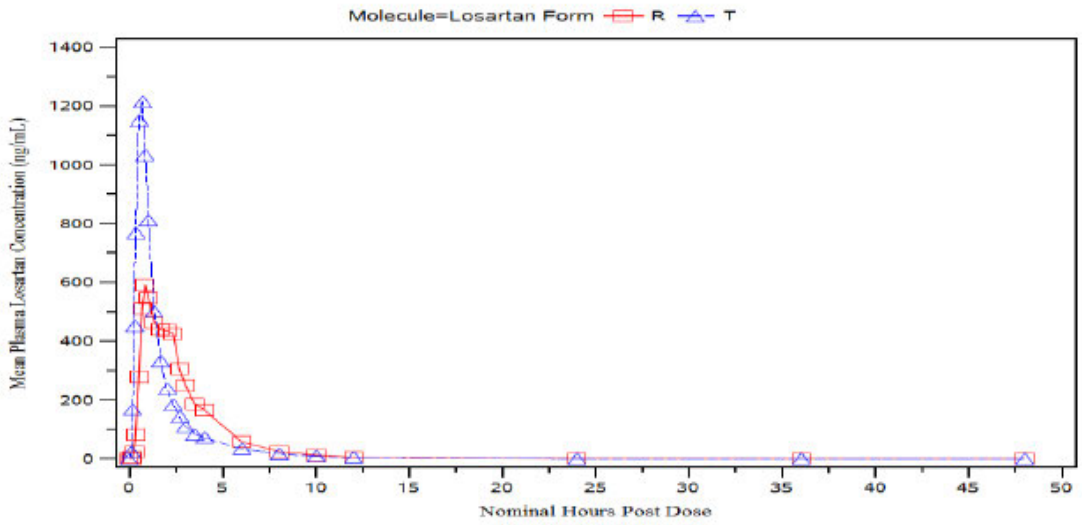
In summary, the bioanalytical method, as reported, appears to be validated and robust in supporting the results and conclusions from both the relative bioavailability and food effect studies.

2.2.3 What is the relative bioavailability of losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) compared to Cozaar 100 mg tablets?

The relative bioavailability study (study 14323) was an open label, randomized, single oral dose, two-treatment, two-sequence, four-period, fully replicate, crossover study to assess the relative bioavailability of losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) (T) compared with Cozaar® (losartan potassium) 100 mg tablets (R) in healthy adult participants under fasting conditions.

For losartan plasma concentration time profiles and pharmacokinetics (PK) parameters, see **Figure 1** and Table 3.

Figure 1: Mean Losartan Plasma Concentration Vs. Time Plots-Linear Scale



Source: Clinical Study Report Study 14323, Figure 1a

Table 3: Summary of Pharmacokinetic Parameters of Losartan

PK Parameter (Units)	N	Treatment T1	Treatment T2	Treatment R1	Treatment R2
C_{max} (ng /mL)	42	1355.023 (419.9176)	1455.464 (596.4127)	1002.659 (485.7758)	1187.435 (663.5368)
AUC_{0-t} (ng.hr/mL)	42	1627.674 (667.665)	1751.950 (710.969)	1595.818 (604.310)	1759.309 (731.373)
$AUC_{0-\infty}$ (ng.hr/mL)	42	1652.33 (677.61)	1778.65 (720.93)	1621.15 (616.77)	1785.81 (744.04)
*T_{max} (hr)	42	0.67 (0.33, 1.33)	0.67 (0.27, 1.67)	1.67 (0.50, 4.00)	1.33 (0.50, 4.00)
$t_{1/2}$ (hr)	42	2.240 (1.2142)	2.358 (1.4391)	2.031 (1.2087)	2.061 (1.2278)
Kel (1/h)	42	0.348 (0.0985)	0.336 (0.0931)	0.399 (0.1284)	0.390 (0.1192)
AUCRatio#	42	98.433 (0.8400)	98.442 (0.7301)	98.449 (0.8302)	98.481 (0.7976)
AUC_%extrap_obs#	42	1.567 (0.8400)	1.558 (0.7301)	1.551 (0.8302)	1.519 (0.7976)

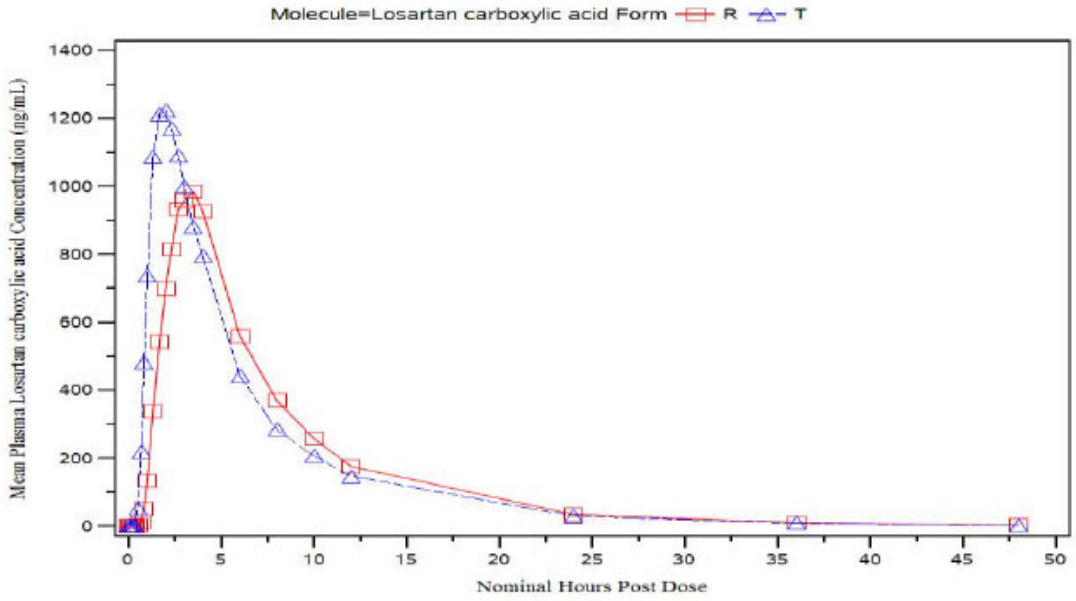
*For T_{max}, Median (Min, Max) are presented.

NOTE: The above data is excerpted from **Table14.2.2-1a** & **14.2.2-2a** Section 14.2

Source: Clinical Study Report Study 14323, Table 1a

For losartan carboxylic acid plasma concentration time profiles and PK parameters, see **Figure 1** and **Table 4**.

Figure 2: Mean Losartan Carboxylic Acid Plasma Concentration Vs. Time Plots-Linear Scale



Source: Clinical Study Report Study 14323, Figure 1b

Table 4: Summary of Pharmacokinetic Parameters of Losartan Carboxylic Acid

PK Parameter (Units)	N	Treatment T1	Treatment T2	Treatment R1	Treatment R2
C_{max} (ng /mL)	42	1323.500 (526.7642)	1334.737 (599.1675)	1160.183 (553.7189)	1221.286 (523.0448)
AUC_{0-t} (ng.hr/mL)	42	7184.458 (2215.847)	7566.706 (2646.560)	7042.013 (2380.101)	7523.710 (2557.562)
$AUC_{0-\infty}$ (ng.hr/mL)	42	7260.88 (2219.95)	7641.26 (2644.67)	7118.19 (2378.06)	7594.02 (2558.15)
*T_{max} (hr)	42	2.00 (1.33, 4.00)	1.84 (1.33, 4.03)	3.00 (1.67, 6.00)	2.84 (1.67, 10.00)
$t_{1/2}$ (hr)	42	5.732 (1.1681)	6.018 (1.1509)	5.733 (1.2622)	6.039 (1.3365)
Kel (1/h)	42	0.125 (0.0209)	0.119 (0.0198)	0.126 (0.0245)	0.119 (0.0225)
AUCRatio#	42	98.611 (1.9597)	98.613 (2.0512)	98.563 (2.0048)	98.609 (2.6932)
AUC_%extrap_obs#	42	1.389 (1.9597)	1.387 (2.0512)	1.437 (2.0048)	1.391 (2.6932)

*For T_{max}, Median (Min, Max) are presented.

NOTE: The above data is excerpted from **Table14.2.2-1b** & **14.2.2-2b** Section 14.2.

Source: Clinical Study Report Study 14323, Table 1b

In **Table 5**, the within-subject standard deviation of the reference product (SWR) was found to be < 0.294 for the ln-transformed primary pharmacokinetic parameters of AUC_{0-t} and $AUC_{0-\infty}$. Hence, the statistical analysis for the relative bioavailability assessment was carried out using the average bioequivalence (ABE) approach for the ln-transformed AUC_{0-t} and $AUC_{0-\infty}$ for losartan. The within-subject standard deviation of the reference product (SWR) was found to be > 0.294 for the ln-transformed primary pharmacokinetic parameter of C_{max}. Hence, the statistical analysis for the relative bioavailability assessment was carried out using the scaled average bioequivalence (SABE) approach for the ln-transformed C_{max} for losartan.

Table 5: Within-Subject Standard Deviation (SWR) and Intra-Subject Variability of the Reference Product for Losartan (N = 44)

Parameter	S_{WR}	ISCVR%
C_{max}	0.3361	34.58
AUC_{0-t}	0.1576	15.86
$AUC_{0-\infty}$	0.1549	15.59

Source: Clinical Study Report Study 14323, Table 11.4-3a; ISCVR: intra-subject coefficient of variation

The geometric mean (GM) ratios along with the 90% confidence interval (CI) of losartan C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) (T) compared to Cozaar® (losartan potassium) 100 mg tablets (R) are summarized in **Table 6**.

Table 6: Summary of the Relative Bioavailability Results for Losartan (Test Versus Reference)

PK Parameter	N	Geometric Means of Treatment:		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
		Test (T)	Reference (R)				
Log C_{max} (ng/mL)	44	1317.6955	974.6741	T vs R	135.19	39.6	122.19 - 149.58
LogAUC_{0-t} (ng.hr/mL)	44	1590.6271	1581.0602	T vs R	100.61	13.2	97.25 - 104.08
LogAUC_{0-inf} (ng.hr/mL)	44	1615.4717	1605.3052	T vs R	100.63	13.0	97.34 - 104.03

NOTE: The above results are excerpted from **Table 14.2.3-1a, Section 14.2.**

Source: Clinical Study Report Study 14323, Table 11.4-6a

The geometric mean (GM) ratios along with the 90% CI of losartan carboxylic acid C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) (T) compared to Cozaar® (losartan potassium) 100 mg tablets (R) are summarized in **Table 7**.

Table 7: Summary of the Relative Bioavailability Results for Losartan Carboxylic Acid (Test Versus Reference)

PK Parameter	N	Geometric Means of Treatment:		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
		Test (T)	Reference (R)				
Log C_{max} (ng/mL)	44	1160.0978	1056.3253	T vs R	109.82	25.5	102.91 - 117.20
LogAUC_{0-t} (ng.hr/mL)	44	6775.8841	6726.8952	T vs R	100.73	10.3	98.11 - 103.42
LogAUC_{0-inf} (ng.hr/mL)	44	6872.6739	6823.3736	T vs R	100.72	10.2	98.13 - 103.39

NOTE: The above results are excerpted from **Table 14.2.3-1b, Section 14.2.**

Source: Clinical Study Report Study 14323, Table 11.4-4b

The independent relative bioavailability analysis generated internally showed the geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values for losartan were 133%, 101% (90% CI 97% - 104%), and 101% (90% CI 97% - 104%), respectively, and the geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values for losartan carboxylic acid were 110% (90% CI 103% - 117%), 101% (90% CI 98% - 103%), and 101% (90% CI 98% - 103%), respectively, for test versus reference. The internal relative bioavailability analyses were similar with those produced by the Applicant.

Based on these results, it was concluded that the test losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) under fasting conditions was not

bioequivalent to the reference treatment Cozaar® (losartan potassium) tablets 100 mg under fasting conditions for losartan. The geometric mean ratio with 90% CI for C_{max} was not within 80.00% to 125.00% for losartan (approximately 35% higher for the suspension when compared to the LD Cozaar tablets [90% CI 1.222, 1.496]); however, the 90% CIs for AUC_{0-t} and $AUC_{0-\infty}$ were within the 80.00-125.00% range for losartan. In addition, the study results demonstrated similar pharmacokinetics between the two products under fasting conditions for losartan carboxylic acid, as the 90% CI for the geometric mean ratios were within the acceptance range of 80.00% to 125.00% for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$.

2.2.4 Are the PK differences noted with losartan potassium oral suspension compared to Cozaar® tablets under fasting conditions clinically relevant?

In a randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension ([1]Gradman et al., Hypertension. 1995;25(6):1345-1350), losartan potassium 10, 25, 50, 100, and 150 mg, enalapril maleate 20 mg, or placebo was administered to 576 patients with essential hypertension once daily (QD) for 8 weeks. This study indicated that there were no dose-related trends for losartan potassium (up to 150 mg) with respect to the percentage of patients with any adverse events, serious adverse events, drug-related adverse events, or patients who withdrew because of an adverse event. Additionally, the study by Gradman et al. showed that there appeared to be a flat dose response for changes in supine diastolic blood pressure (SuDBP) versus losartan dose at doses above approximately 50 mg (**Figure 3**). Considering the flat dose-response relationship of losartan tablets and that the higher doses of losartan (and thus higher C_{max}) appear not to increase the risk of adverse events, combined with the equivalent AUC for losartan (and equivalent AUC and C_{max} for the active metabolite), the PK differences noted with losartan potassium oral suspension compared to Cozaar tablets do not appear to be clinically relevant.

Figure 3: Changes in Supine Diastolic Blood Pressure (SuDBP) in mmHg Versus Losartan Dose

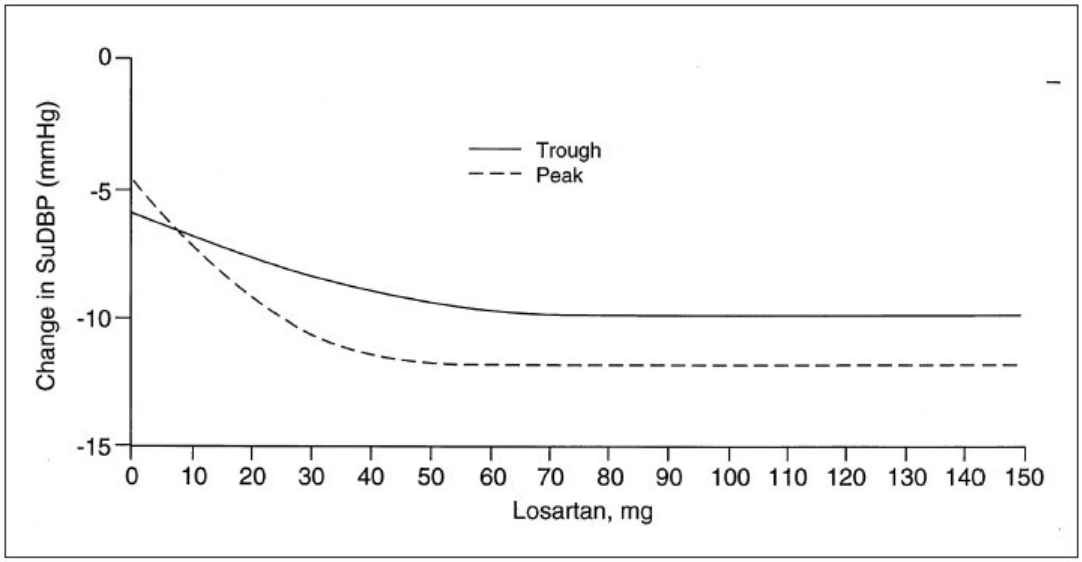


Figure generated by [1]Gradman et al. Changes in SuDBP at peak effect measured at 6 hours post dose and trough effect measured at 24 hours post dose are plotted for the different losartan doses.

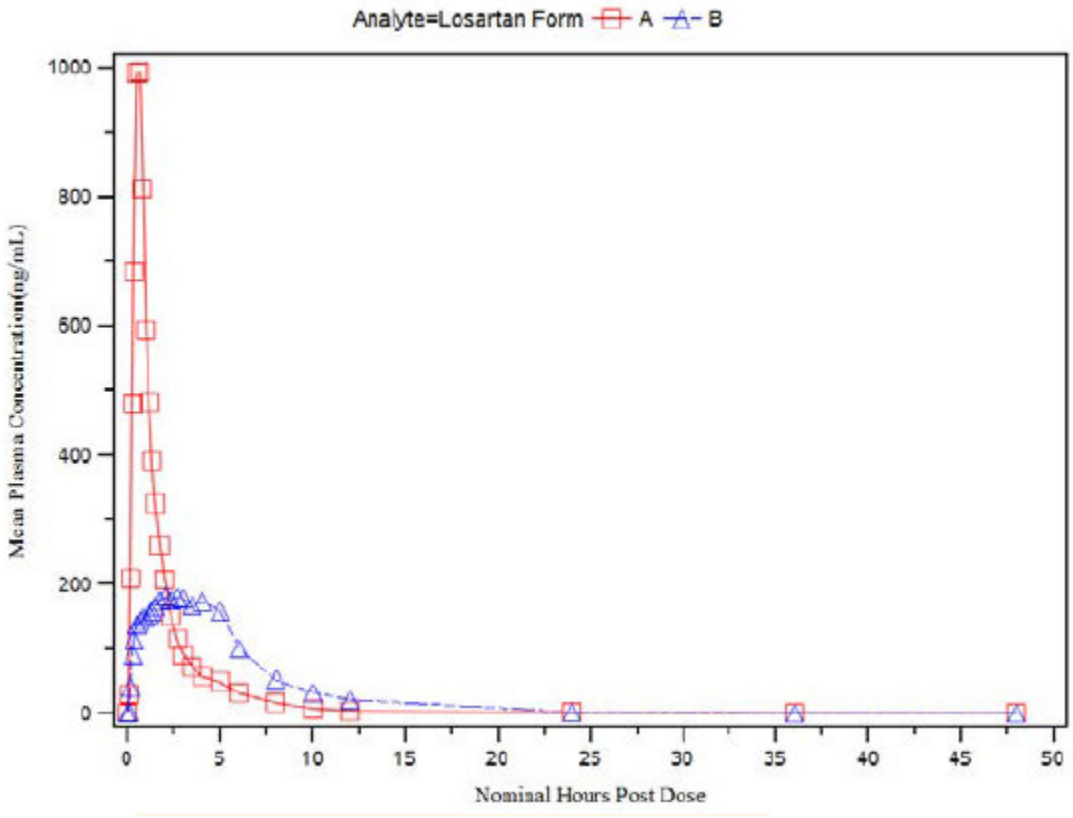
[1] Gradman AH, Arcuri KE, Goldberg AI, et al. A randomized, placebo-controlled, double-blind, parallel study of various doses of losartan potassium compared with enalapril maleate in patients with essential hypertension. Hypertension. 1995;25(6):1345-1350.

2.2.5 What is the effect of food on the bioavailability of losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) under fed condition compared to administration under fasting condition?

The food effect study (study 14324) was an open label, randomized, single oral dose, two-treatment (Treatment A: fasting vs. Treatment B: fed), two-sequence, two-period, two-way crossover study to assess the effects of food on the bioavailability of losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) in healthy adult participants.

For losartan plasma concentration time profiles and PK parameters, see **Figure 4** and **Table 8**.

Figure 4: Mean Losartan Plasma Concentrations Vs. Time Plots-Linear Scale



Source: Clinical Study Report Study 14324, Figure 1a

Table 8: Summary of Pharmacokinetic Parameters of Losartan

Losartan				
PK Parameter (Units)	**N**	**Treatment (A)**	**N**	**Treatment (B)**
C_{max} (ng /mL)	35	1109.585 (455.5514)	35	268.729 (110.6006)
AUC_{0-t} (ng.hr/mL)	35	1411.953 (683.4699)	35	1268.174 (619.9297)
$AUC_{0-\infty}$ (ng.hr/mL)	35	1436.591 (696.1065)	35	1324.855 (637.1567)
*T_{max} (hr)	35	0.50 (0.33, 1.50)	35	3.00 (0.25, 6.00)
$t_{1/2}$ (hr)	35	2.165 (1.5751)	35	2.526 (1.3547)
Kel (1/h)	35	0.382 (0.1027)	35	0.326 (0.1116)
AUCRatio#	35	98.262 (1.1507)	35	95.820 (4.0360)
AUC_%extrap_obs#	35	1.738 (1.1507)	35	4.180 (4.0360)

*For T_{max}, Median (Min, Max) are presented.

Treatment (A) = Single oral dose of Losartan Potassium Oral Liquid 10mg/mL under Fasting Condition.

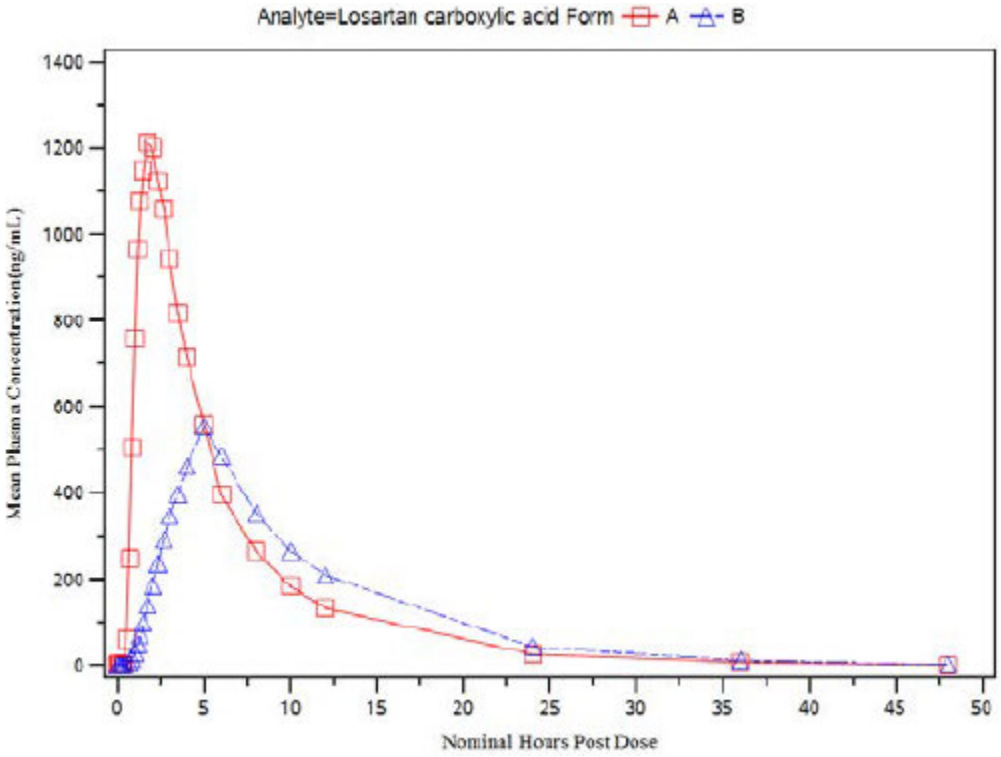
Treatment (B) = Single oral dose of Losartan Potassium Oral Liquid 10mg/mL under Fed Condition.

NOTE: The above data is excerpted from **Table14.2.2-1a** and **14.2.2-2a** Section 14.2.

Source: Clinical Study Report Study 14324, Table 1a

For losartan carboxylic acid plasma concentration time profiles and PK parameters, see **Figure 5** and **Table 9**.

Figure 5: Mean Losartan Carboxylic Acid Plasma Concentration Vs. Time Plots-Linear Scale



Source: Clinical Study Report Study 14324, Figure 1b

Table 9: Summary of Pharmacokinetic Parameters of Losartan Carboxylic Acid

Losartan				
PK Parameter (Units)	**N**	**Treatment (A)**	**N**	**Treatment (B)**
C_{max} (ng /mL)	35	1301.645 (613.6161)	35	602.133 (279.7392)
AUC_{0-t} (ng.hr/mL)	35	6884.400 (2703.6307)	35	5581.454 (2113.7871)
$AUC_{0-\infty}$ (ng.hr/mL)	35	6961.585 (2702.5325)	32	5942.040 (1940.0507)
*T_{max} (hr)	35	2.00 (1.17, 5.00)	35	5.00 (1.50, 12.03)
$t_{1/2}$ (hr)	35	5.800 (1.3759)	32	5.937 (2.3753)
Kel (1/h)	35	0.124 (0.0220)	32	0.126 (0.0262)
AUCRatio#	35	97.965 (4.1629)	32	97.150 (7.4967)
AUC_%extrap_obs#	35	2.035 (4.1629)	32	2.850 (7.4967)

*For T_{max}, Median (Min, Max) are presented.

Treatment (A) = Single oral dose of Losartan Potassium Oral Liquid 10mg/mL under Fasting Condition.

Treatment (B) = Single oral dose of Losartan Potassium Oral Liquid 10mg/mL under Fed Condition.

NOTE: The above data is excerpted from **Table14.2.2-1b** and **14.2.2-2b** Section 14.2.

Source: Clinical Study Report Study 14324, Table 1b

The losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) geometric mean ratios along with the 90% CI of the losartan C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ under fed condition (B) compared to administration under fasting condition (A) are summarized in **Table 10** below.

Table 10: Summary of Food Effect Results for Losartan

PK Parameter	N	Least Squares Geometric Means of Treatment		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
		Test (A)	Test (B)				
Log C_{max} (ng/mL)	35	1019.3785	250.5876	A vs B	24.58	33.56	(21.54, 28.06)
$LogAUC_{0-t}$ (ng.hr/mL)	35	1293.9006	1176.8313	A vs B	90.95	11.82	(86.72, 95.39)
$LogAUC_{0-\infty}$ (ng.hr/mL)	35	1316.7986	1229.4545	A vs B	93.37	11.40	(89.17, 97.76)

NOTE: The above results are excerpted from **Table 14.2.3-1a, Section 14.2.**

Note: Ratio (%) was calculated by B over A (B/A). Source: Clinical Study Report Study 14324, Table 11.4-2a

The losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) geometric mean ratios along with the 90% CI of the losartan carboxylic acid C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ under fed conditions (B) compared to administration under fasting conditions (A) are summarized in **Table 11** below.

Table 11: Summary of Food Effect Results for Losartan Carboxylic Acid

PK Parameter	N	Least Squares Geometric Means of Treatment		Comparison	Ratio (%)	Intra-subject %CV	90% CI of Ratio
		Test (A)	Test (B)				
Log C_{max} (ng/mL)	35	1037.6733	494.5857	A vs B	47.66	24.52	(43.22, 52.56)
$LogAUC_{0-t}$ (ng.hr/mL)	35	5970.4038	4863.6964	A vs B	81.46	8.69	(78.65, 84.38)
$LogAUC_{0-\infty}$ (ng.hr/mL)	35	6099.1566	5008.4379	A vs B	82.12	9.50	(78.87, 85.49)

NOTE: The above results are excerpted from **Table 14.2.3-1a, Section 14.2.**

Note: Ratio (%) was calculated by B over A (B/A). Source: Clinical Study Report Study 14324, Table 11.4-2b

The independent analyses generated internally showed the geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ under fed versus fasted condition for losartan were 24% (90% CI 22% - 28%), 91% (90% CI 86% - 95%), and 94% (90% CI 90% - 98%), respectively, and the geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values for the losartan carboxylic acid metabolite were 47% (90% CI 43% - 52%), 80% (90% CI 76% - 84%), and 85% (90% CI 80% - 91%), respectively. The results from internal analyses were similar with those produced by the Applicant.

Based on these results, administration of losartan potassium oral suspension 10 mg/mL with a high-fat high-calorie meal decreased losartan C_{max} and $AUC_{0-\infty}$ by 75% and 7%, respectively, and decreased losartan carboxylic acid C_{max} and $AUC_{0-\infty}$ by 52% and 18%, respectively. Taking with a meal slowed the absorption of losartan and decreased its Cmax, but food had minor effects on the AUC or on the AUC of the active metabolite.

2.2.6 Are the PK differences noted with losartan potassium oral suspension under fed condition compared to losartan potassium oral suspension under fasting condition clinically relevant?

In Section 12.3 of the Cozaar label, it is noted that "A meal slows absorption of losartan and decreases its Cmax but has only minor effects on losartan AUC or on the AUC of the metabolite (~10% decrease)." Therefore, there appears to be a food effect on the Cmax of the reference product, though the magnitude was not specified; however, no dose adjustment or food restriction is required per Cozaar labeling, suggesting that a decrease in Cmax is not a concern.

Additionally, the Cozaar labeling text in Section 12 states: "Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours"; on the other hand, "a dose of 100 mg inhibits the pressor effect by about 85% at peak (6 hours after dosing) with 25-40% inhibition persisting for 24 hours." It appears the effect of losartan is not mainly driven by C_{max}, as plasma concentrations decrease within a few hours, and the persisting effect is more likely driven by AUC. Further, as shown in **Figure 3**, there appears to be only slight reduction in blood pressure lowering effect between peak effect and trough effect measured at 6 hours post dose and 24 hours post dose, respectively, while there is a significant drop in drug concentration between Cmax and Ctrough, which also indicates that AUC is more important than Cmax for efficacy. Therefore, as the effect of losartan appears to be driven more by AUC rather than C_{max}, dosing under either the fed or fasted condition appears reasonable for the Applicant's losartan potassium oral suspension 10 mg/mL formulation.

3 APPENDIX INDIVIDUAL STUDY REVIEW

3.1 RELATIVE BIOAVAILABILITY STUDY 14323/21-22

Study No: 14323/21-22	EDR link: \\CDSESUB1\EVSPROD\nda218772\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\14323\fast-study-report-body.pdf
First subject first dose: 23 Nov 2022 Last subject last visit: 13 Jan 2023	
Title of study: An open label, balanced, randomized, single oral dose, two-treatment, two-sequence, four period, fully replicate, crossover study to assess the relative bioavailability of Losartan Potassium	

10 mg/mL oral Liquid (10 mL with a total dose of 100 mg) (T) with Cozaar® (losartan potassium) tablets 100 mg (R) in healthy adult study participants under fasting conditions.

Investigational product:
Test product: Losartan Potassium Oral Liquid 10 mg/mL (10 mL with a total dose of 100 mg)
Reference: Cozaar® (losartan potassium) 100 mg tablets

Study:
Objectives:
To assess the single oral dose relative bioavailability of losartan potassium oral liquid 10 mg/mL (10 mL with a total dose of 100 mg) (T) with Cozaar® (losartan potassium) 100 mg tablets (R) in healthy adult study participants under fasting conditions.

Study design: open-label, single oral dose, two-treatment, two-sequence, four-period, fully replicate, crossover relative bioavailability study

- Test Treatment (T): Losartan Potassium Oral Liquid 10 mg/mL (10 mL with a total dose of 100 mg) in healthy adult study participants under fasting conditions; Manufactured for: Scienture Inc, 150 Motor Pkwy, Suite 401, Hauppauge, NY 11788, USA. Manufactured by: (b) (4) .
- Reference Treatment (R): Cozaar® (losartan potassium) 100 mg tablets in healthy adult study participants under fasting conditions; Manufactured for: Organon LLC, a subsidiary of ORGANON & CO., Jersey City, NJ 07302, USA; manufactured by: Organon Pharma (UK) Limited Cramlington, Northumberland, UK NE23 3JU.

- Washout: *7* days
- Study participants: 44 healthy adults
- Sampling times (hr): blood samples were collected prior to drug administration and at 0.08, 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 24.00, 36.00 and 48.00 hours post dose.
- Pharmacokinetic parameters calculated: C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, residual area, Tmax, $t_{½}$, and K_{el}.

Analytical methods:
- Plasma samples were analyzed for losartan and the carboxylic acid metabolite using a validated LC-MS/MS analytical method developed at (b) (4) as described in Section 2.2.2.
- Reviewer comment: the performance of the analytical method is acceptable per the specifications in the Bioanalytical Method Validation Guidance.

Statistical methods:
- The descriptive statistics (such as count (N), mean, median, minimum, maximum, standard deviation (SD) and coefficient of variation (%CV) for the relevant pharmacokinetic parameters were estimated for both the Test and Reference formulations. The geometric mean and %CV were estimated for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
- Using Mixed Scaling approach, the 95% upper confidence bound of the reference-scaled criterion was computed. The selection of the reference-scaled approach depends on the study estimate of SWR of the reference product for ln-transformed pharmacokinetic C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
  - If SWR was < 0.294, then two one-sided test procedures were used to determine bioequivalence.
  - A linear mixed effects model that includes fixed effects terms for treatment, and a random effects term for subject was used. Within the framework of this model and consistent with the two one-sided tests for bioequivalence, 90% confidence intervals for the difference between test and reference treatment least-squares means for the comparisons Test Treatment T vs Reference Treatment R were calculated for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of losartan and the active metabolite, losartan carboxylic acid. The differences and the confidence intervals were exponentiated to obtain point estimates of the ratio of the test over reference geometric means and the 90% CI for the ratio, respectively. If the 90% CI of the ratio estimates

of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are all within the 80.00 to 125.00% range for losartan and the metabolite, then Test Treatment T would be concluded as bioequivalent to Reference Treatment R.

- If SWR was ≥ 0.294, the reference scale procedure was used to determine bioequivalence of Test Product T vs Reference Product R.

Results:
A total of 44 subjects were dosed. Reasons for absence or withdrawal of the participants in this study are shown in **Table 12**.

Table 12: Reasons for Absence or Withdrawal of the Participants in Study 14323

Period	Participant Nos.	Reason
II	02	Absent for period-II participation due to personal reasons.
	05	Absent for period-II participation due to personal reasons.
	10	Absent for period-II participation due to personal reasons.
	19	Withdrawn from period-II participation due to period-I washout AEs.
III	03	Withdrawn from period-III participation due to period-II washout AE.
IV	03	Withdrawn from period- IV participation due to usage of OTC drugs.
	13	Withdrawn from study due to SAE.
	34	Absent for period-IV participation due to not willing to participate in the study.

Source: Clinical Study Report Study 14323, page 52

Number of subjects included in the data set for pharmacokinetic (PK) analysis: Overall N=44; Number of participants dosed in period I: 44; Number of participants dosed in period II: 40; Number of participants dosed in period III: 43; Number of participants dosed in period IV: 41.
For demographics information, see **Table 13**.

Table 13: Summary of Subject Demographics

Demographic	Category	Statistic	---Treatment Sequence---- TRTR	RTRT	Overall
SEX	Female	N	10	10	20
	Male	N	12	12	24
AGE(yrs)		N	22	22	44
		Mean	32.7	31.6	32.2
		SD	6.31	5.56	5.90
		Min	21.0	22.0	21.0
		Median	33.0	32.0	32.5
		Max	45.0	44.0	45.0
		CV	19.3	17.6	18.3
WEIGHT(Kgs)		N	22	22	44
		Mean	67.2	63.8	65.5
		SD	10.79	7.02	9.16
		Min	53.7	52.7	52.7
		Median	64.2	63.6	63.9
		Max	91.0	74.5	91.0
		CV	16.1	11.0	14.0
HEIGHT(cms)		N	22	22	44
		Mean	162.2	158.0	160.1
		SD	11.06	6.75	9.30
HEIGHT(cms)		Min	143.5	144.5	143.5
		Median	159.6	158.6	158.8
		Max	176.5	172.0	176.5
		CV	6.8	4.3	5.8
BMI(Kg/m2)		N	22	22	44
		Mean	25.5	25.7	25.6
		SD	2.87	3.16	2.98

Source: Clinical Study Report Study 14323, Table 14.1.2

For plasma concentration time profiles, PK parameters, and relative bioavailability analysis results for losartan and losartan carboxylic acid, see **Figure 1**, **Figure 2**, **Table 3**, **Table 4**, **Table 6**, and **Table 7**.

Conclusion:
The GM T/R Ratio with 90% CI of the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values for losartan were 135.19% (CI 122.19%- 149.58%), 100.61% (CI 97.25% - 104.08%) and 100.63% (CI 97.34% - 104.03%), respectively. The 90% CI for C_{max} was not within the 80.00% to 125.00% range for losartan; however, the 90% CIs for AUC_{0-t} and $AUC_{0-\infty}$ were within the 80.00-125.00% range for losartan.

The GM T/R Ratio with 90% CI of the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values for the losartan carboxylic acid metabolite were 109.82% (CI 102.91% - 117.20%), 100.73% (CI 98.11% - 103.42%) and 100.72% (CI 98.13% - 103.39%), respectively. The 90% CI of losartan carboxylic acid for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the 80.00-125.00% range.

Based on these results, it was concluded that the test treatment losartan potassium oral suspension 10 mg/mL (10 mL with a total dose of 100 mg) under fasting conditions was not bioequivalent to the reference treatment Cozaar® (losartan potassium) 100 mg tablets under fasting conditions for losartan; however, the approximately 35% higher C_{max} is likely not clinically significant given the flat dose-response relationship.

3.2 FOOD EFFECT STUDY 14324/21-22

Study No: 200221	EDR link: \\CDSESUB1\EVSPROD\nda218772\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\14324\food-effect-study-report-body.pdf
First subject first visit: 08 Mar 2023 Last subject last visit: 13 Apr 2023	
Title of study: An open label, randomized, single oral dose, two-treatment (fasting versus fed) two-sequence, two-period, two-way crossover study to assess the effects of food on the bioavailability of Losartan Potassium 10 mg/mL Oral Liquid (10 mL with a total dose of 100 mg) in healthy adult study participants.	
Investigational product: Test product: Losartan Potassium Oral Liquid 10 mg/mL (10 mL with a total dose of 100 mg)	

Study:
Objectives:
To assess the effects of food on the rate and extent of absorption of losartan and the losartan carboxylic acid metabolite after a single oral dose of test product administered immediately after a high-fat meal (fed condition) as compared to administration under fasting conditions of losartan potassium 10 mg/mL oral liquid (10 mL with a total dose of 100 mg) in healthy adult study participants.

Study design: single oral dose, two-treatment (fasting versus fed), two-sequence, two-period, two-way crossover study.

- Treatments A and B: losartan potassium oral liquid 10 mg/mL (10 mL with a total dose of 100 mg) in healthy adult study participants under fasting conditions; Manufactured for: Scienture Inc, 150 Motor Pkwy, Suite 401, Hauppauge, NY 11788, USA. Manufactured by: (b) (4)

- Washout: 7 days
- Study participants: 38 healthy adults
- Sampling times (hr): blood samples were collected prior to drug administration and at 0.08, 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 24.00, 36.00 and 48.00 hours post dose.
- Pharmacokinetic parameters calculated: C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, residual area, T_{max}, $t_{½}$, and K_{el}.

Analytical methods:

- Plasma samples were analyzed for losartan and the losartan carboxylic acid metabolite using a validated LC-MS/MS analytical method developed at [redacted] (b) (4) as described in Section 2.2.2.
- Reviewer comment: the performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical methods:

- The descriptive statistics (such as count (N), mean, median, minimum, maximum, standard deviation (SD) and coefficient of variation (%CV) for the relevant pharmacokinetic parameters were estimated for the losartan potassium oral suspension under fasting and fed conditions. The geometric mean and coefficient of variation were estimated for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.
- The 90% confidence interval was determined for the ratio of geometric least square means between losartan potassium oral suspension administered in the fasting and fed conditions, obtained from the log-transformed primary and secondary pharmacokinetic parameters.
- T_{max} was measured using a non-parametric method.
- Comparative bioavailability of the food effect on exposure was assessed based on: No food effect is considered when the 90% CI of the geometric mean ratio of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ between the fasting versus fed products fall within the range of 80.00% to 125.00% for both losartan and the losartan carboxylic acid metabolite.

Results:

A total of 38 subjects were dosed. Reasons for withdrawal of the participants in this study are shown in **Table 14**.

Table 14: Reasons for Withdrawal of the Participants in Study 14324

Period	Participant Nos.	Reason
I	22	Withdrawn from study due to AE (Giddiness and Hypotension)
I	28	Withdrawn from study due to AE (Vomiting)
II	31	Withdrawn from study due to AE (Vomiting)

Source: Clinical Study Report Study 14324, page 47

Number of subjects included in the data set for pharmacokinetic (PK) analysis: Overall N=35; Number of participants dosed in period I: 38; Number of participants dosed in period II: 36.

For demographics information, see **Table 15**.

Table 15: Summary of Subject Demographics

Demographic	Category	Statistic	Treatment Sequence AB	Treatment Sequence BA	Overall
SEX	Female	N	6	6	12
	Male	N	13	13	26
AGE (yrs)		N	19	19	38
		Mean	32.6	32.1	32.3
		SD	5.77	7.15	6.41

Source: Clinical Study Report Study 14324, Table 14.1.2

For plasma concentration time profiles, PK parameters, and food effect analysis results, see **Figure 4**, **Figure 5**, **Table 8**, **Table 9**, **Table 10**, and **Table 11**.

Conclusion:
The GM B/A (fed/fasting) ratio (90% CI) of the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values of the losartan potassium oral suspension 10 mg/mL were 24.58% (CI 21.54% - 28.06%), 90.95% (CI 86.72 % - 95.39%), and 93.37% (CI 89.17% - 97.76%), respectively, for losartan.

The GM B/A (fed/fasting) ratio (90% CI) of the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values of the losartan potassium oral suspension 10 mg/mL were 47.66% (43.22% - 52.56%), 81.46% (78.65% - 84.38%), and 82.12% (78.87% - 85.49%), respectively, for losartan carboxylic acid.

The 90% CI for the C_{max} for both losartan and losartan carboxylic acid were not within the 80.00-125.00% range. AUC_{0-t} and $AUC_{0-\infty}$ were within the 80.00-125.00% range for losartan, but not for the losartan carboxylic acid metabolite (slightly lower than the 80.00-125.00% range). Overall, a high-fat, high-calorie meal slowed absorption of losartan, decreased its C_{max}, and had minor effects on its AUC and the AUC of the active metabolite. As the effect of losartan appears to be driven more by AUC rather than C_{max}, dosing under either fed or fasted condition appears reasonable.

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