CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218139Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 218139
Link to EDR	\\CDSESUB1\evsprod\NDA218139\0001
Submission Date	09/29/2023
Submission Type	Standard Review
Brand Name	TEZRULY
Generic Name	Terazosin
Dosage Form and Strength	Solution and 1 mg/mL
Route of Administration	Oral
Proposed Indication	The treatment of signs and symptoms of benign prostatic hyperplasia (BPH); The treatment of hypertension alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarction.
Applicant	Novitium Pharma, LLC
Associated IND	157262
OCP Review Team	Deepa A. Rao, PhD and Yanhui Lu, PhD
OCP Final Signatory	Yanhui Lu, PhD

Contents

1. Executive Summary

The Applicant submitted an original New Drug Application (NDA 218139/S-0001) to seek approval of terazosin oral solution 1 mg/mL per Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

The Applicant proposed to rely on the Agency's earlier findings of safety and effectiveness in the listed drug (LD) HYTRIN® capsules (NDA 020347; Abbott Laboratories). The dosing regimen and indication of the Applicant's proposed drug product are the same as that of the LD, i.e., HYTRIN® capsules.

To support the application, the Applicant conducted two studies, a pivotal, single dose, fasted comparative bioavailability (BA)/bioequivalence (BE), and food effect study (TERA-21-077) and a single dose fed comparative BA/BE study (TERA-23-003). Both studies were conducted in healthy male and female subjects and used the to-be marketed formulation of the proposed product, aiming to establish a scientific bridge to the LD. As the LD HYTRIN capsules have been discontinued, the Applicant used Terazosin 1 mg Capsules (ANDA 075317, manufactured by Jubilant Cadista Pharmaceutical Inc.), the designated Reference Standard (RS) in the Orange book, as the comparator in both studies.

Pharmacokinetics (PK) results of the two studies demonstrated that the 90% confidence intervals (CI) and the geometric mean ratio (GMR) of proposed Tezruly 1 mg/mL product to the RS product are within the pre-specified limit of 80% to 125% for primary PK endpoints (peak concentration (C_{max}), Area Under the Curve from time zero to time t (AUC_{0-t}), and Area Under the Curve from time zero to infinity ($AUC_{0-\infty}$)) for terazosin under both fasting and fed conditions. The results support the conclusion that the proposed product and RS product are bioequivalent and a scientific bridge to the LD is established.

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology has reviewed the information contained in NDA 218139/S-0001 and finds that the submitted PK data are acceptable to support approval from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

None.

2. Summary of Clinical Pharmacology Assessment

2.1 Findings of BE Studies

In the relative BA/BE studies, the Applicant's proposed product containing terazosin 1 mg/mL was found to be bioequivalent to the RS Jubilant Cadista Pharmaceutical 1 mg capsules.

Study TERA-21-077 (pivotal fasting relative BA/BE study)

Study TERA-21-077 is a single dose, open label, randomized, balanced, three-period, two-treatment, three-sequence, three-way crossover study in healthy human adult subjects to assess relative BA/BE and food effect (FE). The relative BA/BE of the proposed product (terazosin hydrochloride oral solution 1 mg/mL, Treatment B) compared to the RS (Jubilant Cadista Pharmaceutical 1 mg capsules, Treatment C) under fasted conditions was evaluated. The effect of food on the BA of proposed product was also evaluated (fed conditions Treatment A; fasted conditions, Treatment B).

In the BE study (Treatment B vs Treatment C), the 90% CI of GMRs for $C_{max,}$ AUC_{0-t}, and $AUC_{0-\infty}$ were 95.38% - 111.19%, 98.9% - 108.65%, and 98.87% - 108.61%, respectively. The 90% CI values are within the BE acceptance criteria of 80 – 125% and thus the proposed product is bioequivalent to the RS under fasting conditions.

In the FE BA study (Treatment A fed conditions vs Treatment B fasted conditions) yielded 90% CI of GMRs for $C_{max,}$ AUC_{0-t}, and $AUC_{0-\infty}$ of 66.13% - 76.23%, 92.47% - 104.8%, and 92.64% - 105.01%, respectively. Food decreased the C_{max} by 29% but did not affect AUC for terazosin.

Study TERA-23-003 (relative BA/BE study under fed conditions)

Study TERA-21-077 is an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover, oral BA study comparing the Applicant's proposed product with that of RS in healthy, adult human subjects under fed conditions. Terazosin 90% CI for GMRs for $C_{max,}$ AUC_{0-t}, and $AUC_{0-\infty}$ compared to RS were 82.26% - 97.33%, 96.03% - 102.86%, and 96.08% - 102.92%, respectively. The 90% CI values are within the BE acceptance criteria of 80 – 125% and thus the proposed product is bioequivalent to the RS under fed conditions.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The recommended dosing for BPH is:

- Initial Dose: 1 mg orally once daily at bedtime. This dose should not be exceeded as an initial dose. Patients should be closely followed during initial administration in order to minimize the risk of severe hypotensive response.
- Subsequent Doses: The dose should be increased in a stepwise fashion to 2 mg, 5 mg, or 10 mg once daily to achieve the desired improvement of symptoms and/or flow rates. Doses of 10 mg once daily are generally required for the clinical response. Therefore, treatment with 10 mg for a minimum of 4–6 weeks may be required to assess whether a beneficial response has been achieved. Some patients may not achieve a clinical response despite appropriate titration. Although some additional patients responded at a 20 mg daily dose, there was an insufficient number of patients studied to draw definitive conclusions about this dose. There are insufficient data to support the use of higher doses for those patients who show inadequate or no response to 20 mg daily. If Tezruly administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen.

The recommended dosing for hypertension is:

The dose of Tezruly and the dose interval (12 or 24 hours) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

- Initial Dose: 1 mg orally once daily at bedtime. Do not exceed the initial dosing regimen to minimize the potential for severe hypotensive effects, including syncope.
- Subsequent Doses: The dose may be slowly increased to achieve the desired blood pressure response. The usual recommended dose range is 1 mg to 5 mg administered once a day; however, some patients may benefit from doses as high as 20 mg per day. Doses over 20 mg do not appear to provide further blood pressure effect and doses over 40 mg have not been studied. Blood pressure should be monitored at the end of the dosing interval to be sure control is maintained throughout the interval. It may also be helpful to measure blood pressure 2-3 hours after dosing to see if the maximum and minimum responses are similar, and to evaluate symptoms such as dizziness or palpitations which can result from excessive hypotensive response. If response is substantially diminished at 24 hours, an increased dose or use of a twice daily regimen can be considered. If Tezruly administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen. In clinical trials, except for the initial dose, the dose was given in the morning.

2.2.2 Therapeutic Individualization

The therapeutic individualization of the proposed drug, Tezruly, is the same as that of the LD, HYTRIN.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The proposed Tezruly label was submitted in a Physician Labeling Rule (PLR) format while the HYTRIN label is not in a PLR format.

There are no significant content changes to the relevant clinical pharmacology sections in Tezruly label compared to the HYTRIN label. Formatting/editorial edits were recommended according to FDA guidance *Labeling for Human Prescription Drug and Biological Products*.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

On September 29, 2023, the Applicant submitted the original 505(b)(2) New Drug Application, seeking approval to market terazosin hydrochloride 1 mg/mL oral solution. Prior correspondence with the Agency under the associated IND is shown below.

Date	Communication from	Correspondence Details
Pre-NDA Meeting		
8/24/2021	Applicant	Request for Pre-NDA meeting (Type B) – Written Response Only (WRO) (IND 157262 eCTD Sequence # 0001)
9/1/2021	Agency	FDA granted Type B (Pre-NDA) Meeting Request as Written Responses Only.
9/23/2021	Applicant	Meeting Package for pre-NDA Meeting, Type B (WRO) submitted to Agency. (IND 157262 eCTD Sequence # 0002)
10/20/2021	Agency	Written Responses for Type B meeting received from the Agency.
10/11/2022	Applicant	Meeting Package for pre-NDA Meeting, Type B – to obtain Agency's guidance and consensus on key elements of its development program (IND 157262 eCTD Sequence # 0014)
10/20/2022	Agency	FDA denied Type B (Pre-NDA) Meeting Request
Pediatric Research Equity Act (PREA) Requirements		
12/30/2021	Applicant	Initial Pediatric Study Plan was submitted to Agency. (IND 157262 eCTD Sequence # 0006)
3/30/2022	Agency	Written Response for Initial Pediatric Study Plan received from the Agency.
6/22/2022	Applicant	Agreed Initial Pediatric Study Plan submitted to Agency. (IND 157262 eCTD Sequence # 0012)
7/18/2022	Agency	Agreed Initial Pediatric Study Plan – Agreement received from Agency.
Proprietary Name Review Request		
9/29/2023	Applicant	Request for Proprietary Names Review submitted to the Agency. (eCTD Sequence # 0006)
12/21/2023	Agency	Proprietary name granted

3.2 General Pharmacology and Pharmacokinetic Characteristics

Absorption

Following a single oral dose administration of TEZRULY in healthy subjects under fasted conditions, the median (range) time to reach peak plasma terazosin levels was 0.67 (0.50 - 1.75) hours. Mean (standard deviation) terazosin C_{max} and $AUC_{0-\infty}$ were 27.09 (7.85) ng/mL and 285.62 (74.77) h*ng/mL, respectively.

Effect of Food

No clinically significant differences in TEZRULY pharmacokinetics were observed following administration of a high-fat, high calorie meal [995.5 Kcalories; 38.31 g protein, 80.75 g carbohydrate, and 57.7 g fat]

Distribution

Terazosin is 90% to 94% bound to plasma proteins and binding is constant over the clinically observed concentration range.

Elimination

Terazosin has a half-life of approximately 13 hours.

Metabolism

Terazosin has been shown to undergo minimal hepatic first-pass metabolism and nearly all of the circulating dose is in the form of parent drug.

Excretion

Approximately 10% of an orally administered dose is excreted as parent drug in the urine and approximately 20% is excreted in the feces. The remainder is eliminated as metabolites. Overall, approximately 40% of the administered dose is excreted in the urine and approximately 60% in the feces.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The Applicant has based their 505(b)(2) submission on a single pivotal food effect and fasting BE study (TERA-21-077) and a relative BA/BE study under fed conditions (TERA-23-003). TERA-21-077 compared the oral BA of the proposed product terazosin 1 mg/mL oral solution (Treatment B) with that of RS, terazosin capsules 1 mg (Treatment C). TERA-21-077 also assessed the FE on the PK of proposed product (Treatment A vs. Treatment B). TERA-23-003 compared the oral BA of proposed product with that of RS under fed conditions.

Study TERA-21-077 Pivotal Single Dose FE and BE study

This is a single-dose, open label, randomized, balanced, three-period, two-treatment, three-sequence, three-way crossover study in healthy human adult subjects to assess oral BA and to assess 1) the FE on test formulation of terazosin hydrochloride oral solution 1 mg/mL under fed (Treatment A) and fasted (Treatment B) conditions, and 2) the relative BA/BE compared with a reference formulation of terazosin capsules 1 mg (Treatment C) under fasted conditions. The plasma concentration time profiles of terazosin (Figure 1) and statistical analyses (Tables 1 and 2) are shown below. The results demonstrate that the proposed product is bioequivalent to the RS under fasting conditions and that food decreased the C_{max} by 29% but did not affect AUC for terazosin. This study supports a scientific bridge to the LD HYTRIN in the fasted state.

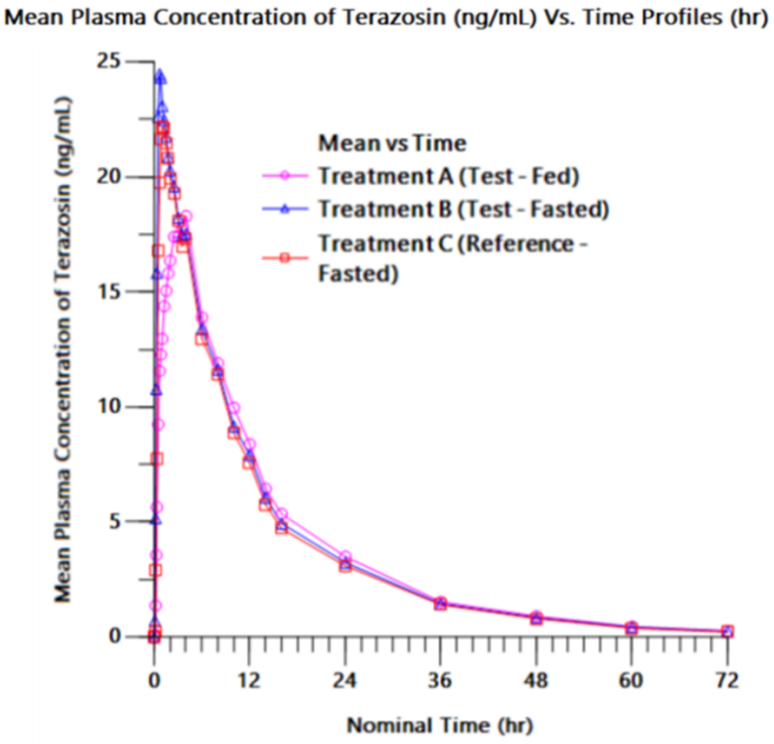

Figure 1: Linear Mean Concentration of terazosin in Applicant's proposed drug product Tezruly 1 mg/mL oral solution (Test) and RS Jubilant Cadista Pharmaceutical Inc., Terazosin 1 mg capsules (Reference) [Applicant Analysis; Clinical Study Report TERA-21-077 Figure 1]

Table 1: Results of Geometric Least Square mean, Power (%), Treatment (A)/Treatment (B) Ratios, ISCV (%), 90% Confidence Intervals of Test (Treatment B) versus Reference (Treatment C) based on Ln-transformed data for Terazosin Under Fasted Condition (N=28) [Applicant Analysis; Clinical Study Report TERA-21-077 Table 4]

Parameters (Units)	**Geometric mean**		**Power (%)**	**ISCV (%)**
	Test (Treatment B)	**Reference (Treatment C)**		
C_{max} (ng/mL)	25.9790	25.2264	99.45%	16.90%
AUC_{0-t} (hr*ng/mL)	270.5851	261.0275	100.0%	10.31%
$AUC_{0-\infty}$ (hr*ng/mL)	276.2671	266.6007	100.0%	10.30%
Parameters	**Ratio (%)**	**90% Confidence Intervals for B vs. C**	**Acceptance Criteria**	**Outcome of BE result**
	B/C			
C_{max}	102.98%	95.38% to 111.19%	80.00% - 125.00%	Bioequivalent
AUC_{0-t}	103.66%	98.9% to 108.65%	80.00% - 125.00%	
$AUC_{0-\infty}$	103.63%	98.87% to 108.61%	80.00% - 125.00%	

Test Product (Treatment B) – Terazosin Oral Solution 1 mg/mL under fasted conditions.
Reference Product (Treatment C) – Terazosin Capsules, USP 1 mg under fasted conditions

Table 2: : Results of Geometric Least Square mean, Power (%), Treatment (A)/Treatment (B) Ratios, ISCV (%), 90% Confidence Intervals of Test (Treatment A) versus Test (Treatment B) based on Ln-transformed data for Terazosin Under Fed/Fasted Condition (N=28) [Applicant Analysis; Clinical Study Report TERA-21-077 Table 14]

Parameters (Units)	**Geometric mean**		**Power (%)**	**ISCV (%)**
	Test (Treatment A)	**Test (Treatment B)**		
C_{max} (ng/mL)	18.4252	25.9519	99.77%	15.71%
AUC_{0-t} (hr*ng/mL)	266.1114	270.3188	99.96%	13.82%
$AUC_{0-\infty}$ (hr*ng/mL)	272.2054	275.9807	99.96%	13.84%
Parameters (Units)	**Ratio (%)**	**90% Confidence Intervals for A Vs. B**	**Acceptance Criteria**	**Outcome of BE result**
	A/B			
C_{max}	71.00%	66.13% to 76.23%	80.00% - 125.00%	Not Bioequivalent
AUC_{0-t}	98.44%	92.47% to 104.8%	80.00% - 125.00%	
$AUC_{0-\infty}$	98.63%	92.64% to 105.01%	80.00% - 125.00%	

Test Product (Treatment A) - Terazosin Oral Solution 1 mg/mL under fed conditions.
Test Product (Treatment B) - Terazosin Oral Solution 1 mg/mL under fasted conditions.

Study TERA-23-003 Relative BA/BE Study Under Fed Condition

This is an open label, randomized, single dose, two-treatment, two-sequence, two-period, two-way crossover oral BA study to compare terazosin hydrochloride oral solution 1 mg/mL (test; T) with terazosin 1 mg capsules (reference; R) in healthy, adult, human subjects under fed conditions. The plasma concentration time profiles of terazosin (Figure 2) and the Applicant's statistical analyses for BE assessment (Table 3) are shown below. The results demonstrate that the proposed product is bioequivalent to the RS under fed conditions.

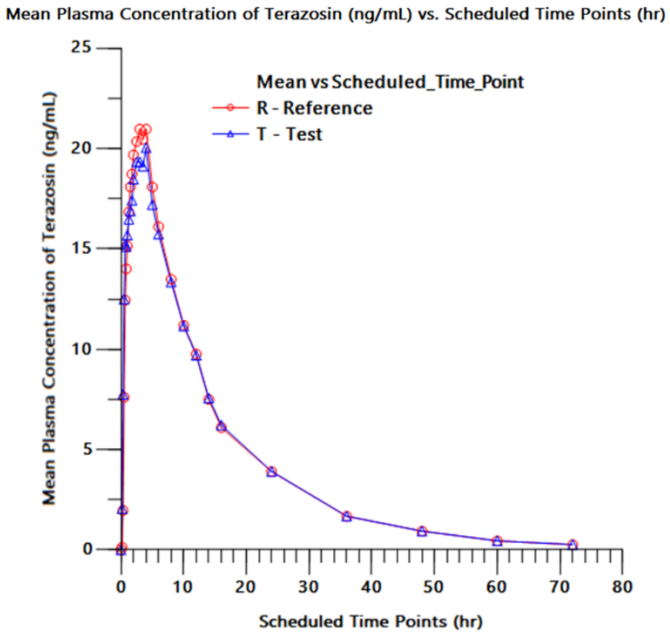

Figure 2: Linear Mean Concentration of terazosin in Applicant proposed drug product Tezruly 1mg/mL (test (T)) and RS Jubilant Cadista Pharmaceutical Inc., Terazosin 1 mg capsules (Reference (R)) [Applicant Analysis; Clinical Study Report TERA-23-003 Figure 1]

Table 3: Results of Geometric Least Square mean, Power (%), Test/Reference Ratios, ISCV (%), 90% Confidence Intervals of Test (Treatment A) versus Test (Treatment B) based on Ln-transformed data for Terazosin Under Fed Condition (N=29) [Applicant Analysis; Clinical Study Report TERA-23-003 Table 11]

Parameters (Units)	Geometric mean		Power (%)	ISCV (%)
	Test (T)	Reference (R)		
C_{max} (ng/mL)	20.557	22.974	98.67	18.96
AUC_{0-t} (hr*ng/mL)	289.949	291.741	100.0	7.69
$AUC_{0-\infty}$ (hr*ng/mL)	295.744	297.410	100.0	7.70
Parameters	**Ratio (%)**	**90% Confidence Intervals**	**Acceptance Criteria**	**Outcome of BE result**
C_{max}	89.48	82.26% to 97.33%	80.00% - 125.00%	Bioequivalent
AUC_{0-t}	99.39	96.03% to 102.86%	80.00% - 125.00%	
$AUC_{0-\infty}$	99.44	96.08% to 102.92%	80.00% - 125.00%	

Test Product - Terazosin Oral Solution 1 mg/mL.
Reference Product - Terazosin Capsules, USP 1 mg.

For both studies, an independent analysis was performed by the reviewer and the reviewer's analysis results are consistent with the Applicant's results.

Office of Study Integrity and Surveillance (OSIS) Inspection Assessment

OSIS has determined that inspections are not needed for both the analytical and clinical sites (Bioequivalence Establishment Inspection Report Review dated 1/26/2023 in DARRTS). OSIS conducted a Remote Regulatory Assessment for the analytical site in (b) (4) under the following submissions: NON-RESPONSIVE. The Office of Regulatory Affairs conducted an inspection for the clinical site in August 2023 for ANDA NON-RESPONSIVE

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought.

The proposed dosing regimen and indications for Tezruly are the same as those approved for the LD, HYTRIN. The Applicant demonstrated that the proposed product is bioequivalent to the LD under both fasted and fed conditions and thus established a scientific bridge for reliance on the Agency's previous findings of safety and efficacy of the LD.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. The Applicant established a scientific bridge to rely on the Agency's findings of Tezruly the LD, HYTRIN. No alternative dosing regimen is required for subpopulations based on intrinsic factors.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug Interaction:

No. Food decreased the C_{max} of terazosin by 29% but did not affect the AUC of terazosin (Table 2). The effect of food on C_{max} is not considered clinically relevant because 1) the proposed product was bioequivalent to the LD under both fasting and fed conditions and 2) food does not have a clinically meaningful effect on the PK of terazosin according to the approved label of the LD.

Drug-drug Interaction:

Yes. The Applicant established a scientific bridge to rely on the drug-drug interaction (DDI) information contained in the label of the LD. Below are clinically significant DDIs with management strategies.

- In a study (n=24) where terazosin and verapamil were co-administered, terazosin's mean AUC_{0-24} increased 11% after the first verapamil dose. After 3 weeks of verapamil treatment, terazosin's mean AUC_{0-24} increased by 24% with associated increases in C_{max} (25%) and C_{min} (32%) means. The systemic exposure increase of terazosin may increase the risk of hypotention. To reduce the risk of hypotension, dosage reduction and re-titration of either agent may be necessary.
- Concomitant use of Tezruly with other anti-hypertensive agents, especially the calcium channel blocker verapamil, can increase the risk of hypotension. To reduce the risk of hypotension, dosage reduction and re-titration of either agent may be necessary. Hypotension has been reported when terazosin has been used with phosphodiesterase-5 (PDE-5) inhibitors. Therefore, PDE-5 inhibitor therapy should be initiated at the lowest dose in patients taking Tezruly.

4. Appendices

4.1 Summary of Bioanalytical Method Validation and Performance

Terazosin concentration in plasma samples was assessed using a validated liquid-liquid extraction method with high performance liquid chromatography tandem mass spectrometry (LC-MS/MS). A summary of validation results is shown in Tables 5.

Incurred sample reanalysis (ISR) results and sample storage information from the pivotal food effect and relative BA/BE study under fasting conditions (Study TERA-21-077) and the relative BA/BE study under fed conditions (TERA-23-003) are included below:

Study TERA-21-077 (Bioanalytical Report \\CDSESUB1\EVSPROD\nda218139\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\tera-21-077\fast-fed-bioanalytical-report.pdf):

A total of 171 samples (7.27% of the total samples) were reanalyzed in two different assay runs (RUN32 and RUN33) for ISR. The results showed that 100% samples met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value).

Study TERA-23-003 (Bioanalytical Report \\CDSESUB1\EVSPROD\nda218139\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\tera23-003\fed-bioanalytical-report.pdf)

A total of 132 samples (8.43% of the total samples) were reanalyzed in two different assay runs (RUN17 and RUN18) for ISR. The results showed that 95.45% samples met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value).

In both studies, study samples were stored for up to 24 days before analysis. The storage stability of study samples is supported by the established long-term stability period of 99 days.

Overall, the results of bioanalytical method validation and performance are acceptable.

Table 4: Summary of LC-MS/MS method validation results

Analyte	**Terazosin**
Internal standard (IS)	Terazosin-D8
Method description	Liquid-Liquid Extraction Method using LC coupled with Tandem Mass Spectrometry detection
Limit of quantitation	0.201 ng/mL
Recovery of drug at each quality control (QC) (%)	Average: 79.18 ± 0.37% High QC (HQC) (36.420 ng/mL): 79.31% Medium QC (MQC) (17.110 ng/mL): 78.84% Low QC (LQC) (0.597 ng/mL): 79.38%
Average recovery of IS (%)	82.85 ± 0.62%
Standard curve concentrations (ng/mL)	0.201, 0.402, 2.506, 5.020, 10.040, 20.079, 29.969, 39.852, and 49.815
QC concentrations (ng/mL)	0.202 (lower limit of quantification; LLOQ), 0.597 (LQC), 3.764 (MQC1), 17.110 (MCQ), and 36.420 (HQC)
QC Intraday precision range (% CV)	0.42% to 6.92% (Intra-run)
QC Intraday accuracy range (% Deviation)	-12.48% to 5.84% (Intra-run)
QC Interday precision range (% CV)	2.04% to 9.33% (Inter-run)
QC Interday accuracy range (% Deviation)	-6.14% to 4.59% (Inter-run)
Bench-top stability (hrs)	22 hours at room temperature
Stock stability (days)	12 days for analyte internal standard at refrigerator temperature
Processed stability (hrs)	26 hours at room temperature and 128 hours at refrigerator temperature
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	99 days at -20°C and -70°C
Dilution integrity (%)	At 99.63 ng/mL concentration diluted 10 times
Selectivity	No significant interfering peak noted in blank plasma lots

4.2 Individual Study Review

4.2.1 Study TERA-21-077 Pivotal Single Dose FE and BE study

This is a single-dose, open label, randomized, balanced, three-period, two-treatment, three-sequence, three-way crossover study in healthy human adult subjects to assess oral BA and to assess 1) the FE on test formulation of terazosin hydrochloride oral solution 1 mg/ml under fed (Treatment A) and fasted (Treatment B) conditions, and 2) the relative BA/BE compared with a reference formulation of terazosin capsules 1 mg (Treatment C) under fasted conditions (Figure 3).

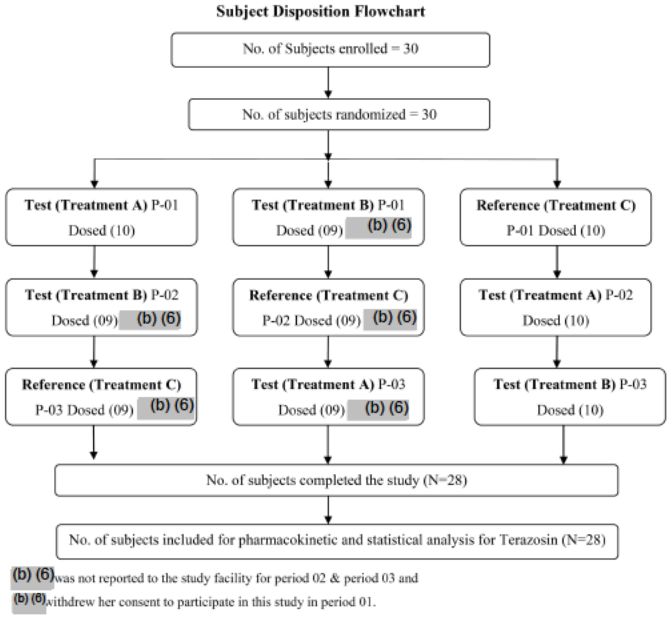

Figure 3 - TERA-21-077 Study Design [Applicant Analysis; Clinical Study Report TERA-21 -077]

A total of 30 healthy adults were planned and enrolled in the study. In period 1, 29 subjects were dosed and in periods 2 and 3, 28 subjects were dosed. In period 1, subject (b) (6) withdrew consent to participate in study and was not dosed in period 2 and 3. In periods 2 and 3, subject (b) (6) did not report to the study facility. The Applicant based their final PK and statistical analysis on the 28 subjects that completed the study.

Per the protocol a 7-day washout period was instituted between each period. This is adequate since the elimination $t_{1/2}$ of terazosin is ~ 12 hr.

Subjects received a single dose of the proposed drug or RS following a 10 hour overnight fast. For Treatment A, a high-fat high-calorie breakfast (995.5 kcal) was provided 30 min prior to administering test product with about 240 mL water at ambient temperature. The caloric content is in alignment with the recommended caloric content (800 –1000 kcal) for food-effect BA/BE studies as outline in the FDA Guidance *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations*.

For Treatment B, the test product was administered with about 240 mL of water at ambient temperature. For Treatment C, the reference product was administered with about 240 mL of water at ambient temperature.

In each period, total 28 venous blood samples were collected at pre-dose (0.0 hour) and at 0.08, 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00, 16.00, 24.00, 36.00, 48.00, 60.00, and 72.00 hours post dose after administration of each dose. The PK sampling time points were adequate to capture the full PK profile of terazosin. The PK concentration measurements of terazosin in plasma PK samples were measured using validated LC-MS/MS method as described in the Appendix 4.1.

The plasma concentration time profiles of terazosin (Figure 2) and statistical analyses (Tables 1 and 2) demonstrate that the proposed product is bioequivalent to the RS under fasting conditions and that food decreased the C_{max} by 29% but did not affect AUC for terazosin. This study supports a scientific bridge to the LD HYTRIN in the fasted state.

4.2.1 TERA-23-003 Relative BA/BE Study Under Fed Condition

This is an open label, randomized, single dose, two-treatment, two-sequence, two-period, two-way crossover oral BA study to compare terazosin hydrochloride oral solution 1 mg/mL (test; T) with terazosin 1 mg capsules (reference; R) in healthy, adult, human subjects under fed conditions.

A total of 30 healthy adults were planned and enrolled in the study with 29 subjects completing the study. Subject (b) (6) had inadequate or incomplete consumption of the high fat, high calories breakfast in period 1 was discontinued from the study. The Applicant based their final PK and statistical analysis on the 29 subjects that completed the study.

Per the protocol a 7-day washout period was instituted between each period. This is adequate since the elimination t1/2 of terazosin is ~ 12 hr.

Following a 10 hour overnight fast, subjects received a single dose of the proposed drug (T) or RS (R) 30 min after a high fat, high calorie breakfast (995.5 kcal) with about 240 mL water at ambient temperature. The caloric content is in alignment with the recommended caloric content (800 –1000 kcal) for food-effect BA/BE studies as outline in FDA Guidance.

In each period, total 27 venous blood samples were collected at pre-dose (0.0 hour) and at 0.17, 0.25, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00, 16.00, 24.00, 36.00, 48.00, 60.00, and 72.00 hours post dose after administration of each dose. The PK sampling time points were adequate to capture the full PK profile of terazosin. The PK concentration measurements of terazosin in plasma PK samples were measured using validated LC-MS/MS method as described in the Appendix 4.1.

The plasma concentration time profiles of terazosin (Figure 2) and the Applicant's statistical analyses for BE assessment (Table 3) demonstrate that the proposed product is bioequivalent to the RS under fed conditions.

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