CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216190Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	216190
Priority or Standard	Standard
Submit Date(s)	May 31, 2023
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Division/Office	Division of Neurology 1, Office of New Drugs
Reviewer Name(s)	Michael A. Dimyan, MD
Review Completion Date	March 1, 2024
Established/Proper Name	Tizanidine oral solution 2 mg/ 5mL
(Proposed) Trade Name	Ontralfy
Applicant	Fidelity BioPharma Co.
Dosage Form(s)	Oral solution 2 mg/5 mL
Applicant Proposed Dosing Regimen(s)	• Recommended starting dose: 2 mg; dose can be repeated at 6- to 8-hour intervals, up to a maximum of 3 doses in 24 hours • Dosage can be increased by 2 mg to 4 mg per dose, with 1 to 4 days between increases; total daily dose should not exceed 36 mg • Ontralfy may be prescribed with or without food. Once the decision to take with or without food has been made, this regimen should not be altered. • To discontinue Ontralfy, decrease dose slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia
Applicant Proposed Indication(s)/Population(s)	Indicated for the management of spasticity
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
R	Reference Treatment – tizanidine hydrochloride tablets, 4 mg
RLD	Reference Listed Drug
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
T	Test treatment – tizanidine oral solution, 2 mg/5 mL, 4 mg dose
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Fidelity BioPharma Co. has developed tizanidine oral solution 2 mg/5 mL, an oral solution formulation of tizanidine. The Applicant claims that the main advantages of this formulation are:

a. To improve compliance and ease of use for adult patients with swallowing difficulties,
b. To provide an alternative dosage form to alleviate swallowing difficulties with tablets and capsules for patients experiencing dysphagia, and
c. To provide flexibility in oral dose titration.

This application was submitted under the 505(b)(2) regulatory pathway with the Applicant relying on the Reference Listed Drug (RLD) Zanaflex (tizanidine hydrochloride) tablets (NDA 020397) approved in 1996. The Sponsor claimed reliance on Zanaflex capsules (NDA 021447), approved 2002; however, the agency determined that the bridge to the tizanidine tablets was sufficient to establish efficacy and safety. The Applicant relies on the RLD for nonclinical, safety, and effectiveness, with a scientific pharmacokinetic bridge to the RLD. The pharmacokinetic bridge is based on the bioequivalence results of two pharmacokinetic clinical trials, TIZA-21-086 and TIZA-22-046.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The two studies, TIZA-21-086 and TIZA-22-046 evaluated the bioequivalence of the tizanidine oral solution (test) against tizanidine tablets and tizanidine capsules, respectively. The test drug was found to be bioequivalent and hence, effective as compared to the RLD. See the Clinical Pharmacology Review of this application for details.

However, due to deficiencies found by the OPQ review, the recommended action for this application is Complete Response.

1.3. Benefit-Risk Assessment

This is a 505(b)(2) application relying on evidence of efficacy and safety from the RLD, tizanidine hydrochloride. Tizanidine hydrochloride was approved in tablet formulation in 1996 and in capsule formulation in 2002. There has been no change in the benefit-risk assessment of the RLDs since their approvals.

However, due to deficiencies found by the OPQ review, the recommended action for this application is Complete Response.

1.4. Patient Experience Data

Not applicable for this 505(b)(2) application.

2. Therapeutic Context[1][2]

2.1. Analysis of Condition

The most commonly accepted definition of spasticity is a motor disorder marked by a velocity-dependent increase in muscle tone or tonic stretch reflexes caused by and part of the syndrome of upper motor neuron injury or maldevelopment. Spasticity presentation is quite variable with the most minimal of subtle neurological examination findings to the most severe muscle tone leading to joint immobility. Within a single patient, spasticity severity can vary modestly even minute to minute depending on activity, temperature, to triggering stimuli such as noxious, infectious, or systemic abnormalities such as bowel or bladder retention.

The effects of the presence of spasticity can alter motor and sensory function beyond the primary motor deficits caused by the upper motor neuron abnormality. Spasticity can also lead to complications including pain, interference with hygiene, which can lead to skin maceration, soft-tissue contractures, subluxation/dislocation, and heterotopic ossification. On the other side of the spectrum, mild to moderate amounts of spasticity may actually be beneficial for a joint as it can potentially allow for joint stabilization or use in alternative but functionally relevant mobility patterns.

There are no large epidemiological studies of spasticity across all the various etiologies. However, estimates for the prevalence of spasticity in specific disorders are 70% in spinal cord injury, 25% in stroke, 80% in multiple sclerosis, and >90% in cerebral palsy.

Spasticity is diagnosed by clinical exam and can be rated by clinician-administered scales that assess passive stretch of a muscle in its slow-velocity range of motion compared to a fast-velocity stretch. The clinician judges increases in tone, catches, or changes in range of motion due to high-speed passive movement. These findings along with other upper motor neuron syndrome findings lead to the diagnosis. There are no confirmatory or diagnostic laboratory tests available.

2.2. Analysis of Current Treatment Options

[1] Rivelis, Y., N. Zafar and K. Morice (2024). Spasticity. StatPearls. Treasure Island (FL).
[2] Kheder, A. and K. P. Nair (2012). "Spasticity: pathophysiology, evaluation and management." Pract Neurol 12(5): 289-298.

FDA approved therapies for spasticity, some with indications more specifically targeted to particular etiologies, include oral formulations of baclofen, tizanidine hydrochloride, cyclobenzaprine, dantrolene sodium, diazepam, intrathecal formulations of baclofen, and various serotypes of botulinumtoxin for intramuscular administration. All of the oral treatments are dosed multiple times per day, and most carry the risks of excessive adverse effects if not titrated correctly or withdrawal if not tapered correctly. All of the oral treatments have an elevated risk of causing fatigue or somnolence amongst other adverse reactions. The injected botulinumtoxin treatments work by reducing the release of acetylcholine at the neuromuscular junction, thereby causing a temporary chemodenervation of the muscle. Intramuscular injection is painful for most patients. Patients require re-treatment every 3 months. When spasticity affects multiple muscles, requiring multiple injections, there may be a higher risk of potential distal spread of toxin effect or outright botulism.

Unapproved therapies for spasticity include chemoneurolysis with phenol or ethyl alcohol delivered by perineural injection, and surgical therapies such as neurectomy, rhizotomy, neuroablation, or orthopedic surgeries such as tendon lengthening or tendon transfer.

The Applicant indicates that since most patients with spasticity suffer from central nervous system disorders, they often are dealing with dysphagia that may make swallowing tablets or capsules difficult. Therefore, the Applicant has formulated tizanidine oral solution to allow for easier oral administration of tizanidine. The Applicant also indicates that titration and tapering of doses may be easier with a liquid formulation since there is more precision in delivering various dosages of drug.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The RLDs for this 505(b)(2) application are Zanaflex (tizanidine hydrochloride) tablets (NDA 020397) and capsules (NDA 021447), approved in 1996 and 2002 respectively. The original formulation did not have any post-marketing requirements or commitments (PMR/PMC). The capsule formulation was approved August 29, 2002, with Postmarketing Requirement 1739-1 to conduct a study in pediatric patients aged 2 to 17. (b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

On August 31, 2021, the Agency provided written responses to a pre-IND meeting request by the Applicant under IND 156316. The Agency advised that the application, proposing a new dosage form of tizanidine, would trigger the Pediatric Research Equity Act (PREA) and that an Initial Pediatric Study Plan (iPSP) should be submitted. The Applicant was advised regarding the design of their clinical pharmacology and chemistry, manufacturing, and controls plans.
On January 28, 2022, IND 156316 was opened for the study of tizanidine oral solution 2 mg/5 mL for the treatment of spasticity. An iPSP was submitted by the Sponsor on May 18, 2022, and after advice from the Agency, an Agreed iPSP was accepted on June 28, 2023.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Pharmaceutical Quality (OPQ)

The OPQ review noted multiple deficiencies in drug substance and manufacturing process noting that the "*applicant has not provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product… the outstanding issues are related deficiencies in the drug substance supplier's drug master file (DMF), the potential presence of* (b) (4) *and inadequate information for the manufacturing process."*

The final results from other disciplines were not available at the time of completion of this review. Based on discussion at the internal Wrap-Up meeting on February 28, 2024, and the OPQ review deficiencies, it was concluded that this application should be recommended for Complete Response.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant conducted two bioequivalence BE studies to compare the pharmacokinetics of tizanidine oral solution 2 mg/5 mL with the RLDs, tizanidine tablets in study TIZA-21-086 and tizanidine capsules in TIZA-22-048. Two separate BE studies were conducted since there is a known pharmacokinetic difference between tizanidine tablets and capsules in the fed state compared to the fasting state.

Sample Table. Listing of Clinical Trials Relevant to this NDA/BLA [Replace this title with a Table Caption using the *Insert Caption* button in the References Tab.]

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Biopharmaceutic Studies to Evaluate Bioequivalence for the 505(b)(2) Pathway							
TIZA-21-086-	An Open-Label, Balanced, Randomized, Single Dose, Two-Treatment, Two-Sequence, Four-Period, Crossover Study to Assess the Effect of Food on the Absorption and Comparing Oral Relative Bioavailability of 10 mL (4 mg) of test product, Tizanidine Oral Solution, 2 mg/5 mL, with that of reference Product, Zanaflex® (Tizanidine Hydrochloride), 4 mg Tablet, in Healthy Adult Human Subjects Under Fasting and Fed Conditions.	1 dose of either TEST or REFERENCE Drug given followed by 24hr observation, 24hr washout, and then crossover to other drug. 1 period fasted and 2nd period fed.	Pharmacokinetics	9 days from Period 1 check-in to last blood sample collection of Period 4 with two day interval between drug dosing.	115	Healthy Adults	1, India
TIZA-22-046	Open-Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Two-Period, Two-Way Crossover, Oral Relative Bioavailability Study Comparing 10 mL (4 mg) of test Product, Tizanidine Oral Solution, 2 mg/5 mL with that of reference Product, Zanaflex® (Tizanidine	1 dose of either TEST or REFERENCE drug followed by 48 hrs of observation and washout followed by	Pharmacokinetics	5 days from Period 1 check-in to last blood sample of Period 2. Two day interval between doses of drug.	64	Healthy Adults	1, India

	Hydrochloride) 4 mg Capsule, in Healthy, Adult, Human Subjects Under Fed Conditions.	crossover during only fed condition					

5.2. Review Strategy

This is a review of safety for this 505(b)(2) application which relies on the data of the RLD, Zanaflex (tizanidine hydrochloride) tablets and capsules, for demonstration of efficacy and safety based on a scientific bridge to the RLD through two bioequivalence studies. Therefore, there is no efficacy data for review. The brief safety data is obtained from single dose studies of tizanidine oral solution in 179 healthy adults who participated in the pharmacokinetic bioequivalence studies.

The adequacy of the bioequivalence studies is deferred to the Clinical Pharmacology Review.

This review seeks to identify any potential safety signals in the submitted data that could possibly change the current safety profile of tizanidine.

6. Review of Relevant Individual Trials Used to Support Efficacy

This section is not applicable because this application is a 505 (b)(2) application based on a bioequivalence study to bridge the safety and efficacy of the new oral solution formulation to the approved tablet dosage form. The applicant is relying on efficacy data from the already approved RLD Zanaflex tablets (NDA 020397) and capsules (NDA 021447). The applicant has not conducted any studies of efficacy.

7. Integrated Review of Effectiveness

This section is not applicable because this application is a 505 (b)(2) application based on a bioequivalence study to bridge the safety and efficacy of the new oral solution formulation to the approved tablet dosage form. The applicant is relying on efficacy data from the already approved RLD Zanaflex tablets (NDA 020397) and capsules (NDA 021447). The applicant has not conducted any studies of efficacy.

8. Review of Safety

8.1. Safety Review Approach

This is a 505(b)(2) application for a new oral solution formulation of tizanidine. The RLD is Zanaflex tablets (NDA 020397), which was approved on November 27, 1996. Therefore, the risks and safety signals of tizanidine drug substance are well established.

This application is supported by two bioequivalence studies. TIZA-21-086 was a 4-period crossover trial of the new tizanidine oral solution 2mg/5mL compared to the tablet formulation of the RLD and was conducted in 115 completing subjects who received two doses total of the oral solution. The study's two periods were conducted in order to test fasted and fed states given that the RLD, tizanidine tablets, are known to have different pharmacokinetics in the two states, with 30% higher Cmax in the fed compared to the fasted state. TIZA-22-046 was 2-period cross over trial, this time comparing the oral solution against the capsule formulation of the RLD, since the capsule formulation has altered PK with reduced and delayed Cmax compared to the fasted state. TIZA-22-046 completed 62 subjects.

Given the low sample size and infrequent intermittent dosing of, at most, 4 doses of the novel formulation, it was not expected that reliable safety data could be obtained from these studies. However, the two bioequivalence trials were reviewed for any and all adverse events that were not previously identified.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Healthy adult subjects were exposed to tizanidine oral solution 2 mg/5 mL in two bioequivalence studies, TIZA-21-086 and TIZA-22-046. In TIZA-21-086, 120 subjects were enrolled and 115 subjects completed all 4 periods. Two periods were cross-over under fasted and the second two periods were a cross-over trial under fed conditions. Therefore, 115 subjects were exposed to two doses of tizanidine oral solution 2 mg/5 mL at the 4 mg dose.

In TIZA-22-046 64 subjects were enrolled and 62 completed both periods of the study, so 62 subjects were exposed to 4 mg of tizanidine oral solution for at least 1 dose due to the crossover design. In both studies, dosing and pharmacokinetics were completed over two days for each period, and two days later the next period started. The total duration in TIZA-21-086 was 9 study days with exposures to IMP or RLD occurring on days 1, 3, 5, and 7.

8.2.2. Relevant characteristics of the safety population:

As this is a 505(b)(2) application with only bioequivalence studies, the population tested was healthy volunteers, the age and race demographics demonstrated in Table 1 and Table 2. Subjects are categorized in the tables by the sequence of treatments they received over the four periods of the crossover studies. Subject treatment is labeled as either reference (R), meaning they had received the RLD, 4mg tizanidine tablet, or test (T), meaning they received 4 mg of tizanidine oral solution 2 mg/5 mL. Also of note, as the studies were conducted in India, the sample populations were not racially diverse. However, there is no reason to believe that the population targeted for treatment, patients with spasticity, would be at greater risk for the known adverse effects of tizanidine based on any racial or ethnic difference in central catecholaminergic receptor physiology. As will be reviewed, the adverse events captured in the

small samples of TIZA-21-086 and TIZA-22-046 were comparable to those already reported in the RLD label.

Table 1 TIZA-21-086 DEMOGRAPHICS

	Actual Sequence of Treatments				
	R	RTRT	T	TRTR	Total
	(N = 1)	(N = 58)	(N = 3)	(N = 57)	(N = 119)
Age Groups	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
0<=Age<=35	0 (0.0%)	45 (77.6%)	2 (66.7%)	44 (77.2%)	91 (76.5%)
35<Age<=64	1 (100.0%)	13 (22.4%)	1 (33.3%)	13 (22.8%)	28 (23.5%)
Sex (SEX)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
F	1 (100.0%)	27 (46.6%)	3 (100.0%)	28 (49.1%)	59 (49.6%)
M	0 (0.0%)	31 (53.4%)	0 (0.0%)	29 (50.9%)	60 (50.4%)
Race	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
ASIAN	1 (100.0%)	58 (100.0%)	3 (100.0%)	57 (100.0%)	119 (100.0%)

		Actual Sequence of Treatments				
		R	RTRT	T	TRTR	Total
		(N = 1)	(N = 58)	(N = 3)	(N = 57)	(N = 119)
Age	N	1.0	58.0	3.0	57.0	119.0
	Mean	36.0	30.1	36.7	30.4	30.5
	Std Dev	.	6.6	6.4	6.6	6.6
	Max	36.0	44.0	44.0	43.0	44.0

SOURCE: Reviewer analysis of submitted datasets using JMP Clinical 8.1; R = Reference Listed Drug; T = tizanidine oral solution 2 mg/5 mL; those subjects not in the RTRT or TRTR groups were withdrawn or discontinued prior to completion of all four periods of the crossover trial; Std Dev = Standard Deviation; Min = minimum; Max = maximum

Table 2 TIZA-22-046 DEMOGRAPHICS

	Actual Sequence of Treatments				
	R	RT	T	TR	Total
	(N = 1)	(N = 31)	(N = 1)	(N = 31)	(N = 64)
Age Groups	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
0<=Age<=35	1 (100.0%)	25 (80.6%)	0 (0.0%)	25 (80.6%)	51 (79.7%)
35<Age<=64	0 (0.0%)	6 (19.4%)	1 (100.0%)	6 (19.4%)	13 (20.3%)
Sex (SEX)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
F	1 (100.0%)	16 (51.6%)	1 (100.0%)	14 (45.2%)	32 (50.0%)
M	0 (0.0%)	15 (48.4%)	0 (0.0%)	17 (54.8%)	32 (50.0%)
Race	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
ASIAN	1 (100.0%)	31 (100.0%)	1 (100.0%)	31 (100.0%)	64 (100.0%)

		Actual Sequence of Treatments				
		R	RT	T	TR	Total
		(N = 1)	(N = 31)	(N = 1)	(N = 31)	(N = 64)
Age	N	1.0	31.0	1.0	31.0	64.0
	Mean	28.0	31.4	36.0	30.2	30.8
	Std Dev	.	5.3	.	6.0	5.6
	Min	28.0	20.0	36.0	21.0	20.0
	Max	28.0	41.0	36.0	43.0	43.0

SOURCE: Reviewer analysis of submitted datasets using JMP Clinical 8.1; R = Reference Listed Drug; T = tizanidine oral solution 2 mg/5 mL; those subjects not in the RTRT or TRTR groups were withdrawn or discontinued prior to completion of all four periods of the crossover trial; Std Dev = Standard Deviation; Min = minimum; Max = maximum

8.2.3. Adequacy of the safety database:

For a 505(b)(2) application, this small sample size of healthy volunteers in two foreign bioequivalence crossover trials is adequate as the primary safety analysis is dependent on the established history of the RLD.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

On initial submission, it was noted that variables LBSTNRHI and LBSTNRHLO were missing for numerous cases. An information request (IR) was sent to the Applicant on July 7, 2023, that

pointed this out and also stated:

> *"We also note that in your Data Conformance Summaries you have recorded a large number of nonconformance issues with inadequate explanations. Please resubmit your datasets to include the missing values and with correction for these nonconformance errors…"*

Another IR was sent on July 13, 2023 further clarifying the deficiencies requiring correction:

> *"Please resubmit complete datasets for both studies TIZA-21-086 and TIZA-24-046 with accurate continuous numerical values in variables LBSTNRLO and LBSTNRHI for the following values of LBTESTCD which should be in continuous numerical format. For the following labs, you have set the variable category incorrectly to character when they should be numerical:*
> *GLUC*
> *CHOL*
> *BILIDIR*
> *AST*
> *ALT*
> *Also, please change the variable category for VSSTRESN to numerical; character is incorrect."*

The Applicant responded on July 17, 2023, with new datasets correcting the deficiencies. Other than these issues, no other issues with data integrity or submission were identified during the review process.

During TIZA-21-086, subjects were confined to the clinical research unit for convenience and frequency of testing, which also contributed to monitoring for safety. Meal plans were all identical to reduce risk of altered pharmacokinetics based on dietary intake. Subjects refrained from caffeine and alcohol. Subjects were asked to lie down and remain supine for at least four hours after drug administration. Blood samples were collected 84 times not to exceed a total of 316 mL, with 21 samples being collected pre- and post-dose of investigational medical product. Safety assessments included examination, vital sign measurement, 12-lead electrocardiogram (ECG), a Well-being assessment, and basic laboratory assessments.

REVIEWER COMMENT: The supine positioning of subjects for 4 hours of administration of the drug is not consistent with likely real world use, and hence limits the generalizability of the safety conclusions that can be made from these studies, because that is not their purpose, this is only a minor deficiency.

8.3.2. Categorization of Adverse Events

The two protocols used standard definitions of adverse events, periodic assessment directly from the subjects for adverse events, classified those events from mild to severe, and classified

them on a relatedness to treatment protocol.

8.3.3. Routine Clinical Tests

Pregnancy testing was conducted as part of screening to exclude pregnant subjects. As the primary purpose of TIZA-21-086 and TIZA-22-046 were as bioequivalence studies, frequent blood samples were taken after dosing of drug including every 8 minutes for the first half-hour, every 16 minutes until 1 hour, every 25 minutes until hour three, then every 2 hours until 12 hours post-dose. However, safety labs (hematology, chemistry) were only evaluated at screening and end of study unless the investigator deemed it necessary to obtain safety labs as part of evaluation during the study.

REVIEWER COMMENT: Given that both studies were crossover studies, evaluating safety labs only at the beginning and end of the studies is not really useful for evaluating the safety of tizanidine oral solution. However, again, this was not the purpose of the studies as it is expected that, if bioequivalence is demonstrated, that the systemic effects of tizanidine on any serum biomarkers would be equivalent to those that occur with the RLD.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in TIZA-21-086 or TIZA-22-046.

8.4.2. Serious Adverse Events

There were no serious adverse events in TIZA-21-086 or TIZA-22-046.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In TIZA-21-086, 115 subjects are counted as completing the study from an enrollment of 120. Subject (b) (6) is reported to have been discontinued prior to any treatment due to a Day 1 prolonged QTc. The Applicant reported that no treatment emergent adverse events led to study withdrawal or discontinuation. However, four withdrawals of consent were noted.

On further evaluation, this reviewer determined that subject (b) (6) had actually experienced TEAE of vomiting after Period 1 dosing that led to their withdrawal of consent. Subject (b) (6) is listed as withdrawing consent on (b) (6) at 2:10a.m. However, it is also recorded that the subject had blood collected on (b) (6) at 2:33a.m. which was reported on (b) (6) (b) (6) at 5:49p.m. with an eosinophil percentage on CBC of 18% (adult norm 1-6%) and was documented as having eosinophilia as a post-study adverse event.

In TIZA-22-046, two subjects were withdrawn during the trial, subjects (b) (6) and (b) (6) Both were withdrawn due to QTc prolongation >440 ms at the period 02 pre-dose evaluation. The specifics

of each case were reconstructed from the CRFs provided by the Applicant:

Subject (b) (6)
On (b) (6) Subject (b) (6) had received test drug, and QTc/HR had been at pre-dose, 1.5 hours post, 3.5 hours post. and 12 hours post 428/65, 430/69, 435/68, and 434/73 ms/bpm. On Study Day 3, (b) (6) the subject was being evaluated for their next dose of study drug, which would have been the reference drug, when the pre-dose ECG returned with a QTc/HR of 463/80 ms/bpm. A repeat ECG approximately 30 minutes later returned a QTc/HR of 455/89 ms/bpm and the subject was withdrawn. The ECG was rechecked two-hours later and the QTc/HR had normalized to 439/83 ms/bpm. The QTc prolongation was not considered related to the previous dose of reference tizanidine given the duration of close to 48 hours since dosing.

Subject (b) (6)
On (b) (6) Subject (b) (6) received a dose of reference drug. The subject's pre-dose ECG and 3 post-dose ECGs recorded QTc/HR of 426/67, 439/77, 407/67, and 433/68 ms/bpm. The subject progressed through the procedures for Day 1 dosing and Day 2 follow-up without complaints. On Day 3, (b) 6) the prior to receiving test drug pre-dose ECG had a QTc of 450/77 ms/bpm at 8:32 a.m., leading to subject withdrawal from the study. Repeat ECGs at 9 a.m. and 12:21 p.m. had QTc/HR measurements of 472/94 and 424/76 ms/bpm, respectively, the latter leading to resolution of the AE and dismissal of the subject. This AE was considered unrelated due to the latency between last dose and the QTc prolongation.

REVIEWER COMMENT: The withdrawal of subjects being marked in "Withdrawal by Subject" when in close proximity to a TEAE raises some concern regarding the methods used to monitor subject disposition.

Given the latency between the last drug dose and QTc prolongation, the individual variation in QTc over short periods of time, consistent with the known variability of both manual and automated QTc measurement,[3] and the rapid resolution of QTc prolongation in these two subjects, it is reasonable to consider these two cases as being unrelated to study drug administration.

8.4.4. Significant Adverse Events

According to the Applicant, there were no significant adverse events in either TIZA-21-086 or TIZA-22-046. All reported adverse events were reported as "mild" in intensity.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

[3] Hnatkova, K. and M. Malik (2020). "Sources of QTc variability: Implications for effective ECG monitoring in clinical practice." Annals of Noninvasive Electrocardiology 25(2).

The Applicant reported adverse events for each trial separately. In TIZA-21-086, 120 subjects were enrolled, 118 of whom were exposed to test product at some point, and 116 were exposed to reference product. The total TEAEs reported were 110. They report 75 TEAEs in 50 subjects during the in-house stay of the 4 crossover periods and 35 TEAEs in 26 subjects during the post-study safety assessment at checkout. The further reporting of TEAEs by the Applicant was only done by relatedness, in which the Applicant categorized 26 TEAEs after test product administration as possibly related including dizziness, sedation, orthostatic hypotension, QTc interval prolongation, vomiting, and nausea. The Applicant categorized 46 TEAEs as possibly-related after reference product administration, including dizziness, sedation, orthostatic hypotension, QTc interval prolongation, vomiting, and nausea. The 35 TEAEs occurring in the post-study safety assessment were all mild laboratory abnormalities and were not judged by the Applicant to be related or non-related (Table 3).

In TIZA-22-046, 64 subjects were enrolled, with 63 being exposed to both test and reference product at some point during the crossover trial. A total of 28 TEAEs were reported, 20 during the inpatient portion of the study. The Applicant reports 20 TEAEs in 19 subjects, and then only reports on those TEAEs categorized as possibly related or greater. Of possibly related TEAE, 7 occurred after exposure to test product (sedation, dizziness, orthostatic hypotension) and 11 after administration of reference product (dizziness, sedation, headache, and orthostatic hypotension).

See section 8.4.9 regarding the occurrences of QTc prolongation.

Tables from the Applicant:
Table 3 Applicant Table of Adverse Events for TIZA-21-086

Body System / Adverse Event	**Pre-dose adverse event N=120 N (%)**	**Test (T) N=118 n (%)**	**Reference (R) N=116 n (%)**	**Post-Study Safety Assessment Adverse Events (N=119)**
Central Nervous System				
Dizziness	0	10 (8.47)	19 (16.38)	0
Sedation	0	09 (7.63)	22 (18.97)	0
Headache	0	01 (0.85)	0	0
Cardiovascular System				
Orthostatic Hypotension	0	01 (0.85)	01 (0.86)	0
QTc Interval Prolongation	03 (2.50)	04 (3.39)	02 (1.72)	0
Gastrointestinal System				
Vomiting	0	01 (0.85)	01 (0.86)	0

Nausea	0	0	01 (0.86)	0
Hepatic system				
Elevated SGPT	0	0	0	15 (12.61)
Elevated SGOT	0	0	0	06 (5.04)
Elevated Bilirubin Direct	0	0	0	01 (0.84)
Blood and Lymphatic System				
Elevated Eosinophil	0	0	0	05 (4.20)
Decreased Hemoglobin	0	0	0	05 (4.20)
Endocrinology System				
Elevated Random Glucose	0	0	0	03 (2.52)
Total	03 (2.50)	26 (22.03)	46 (39.66)	35 (29.41)

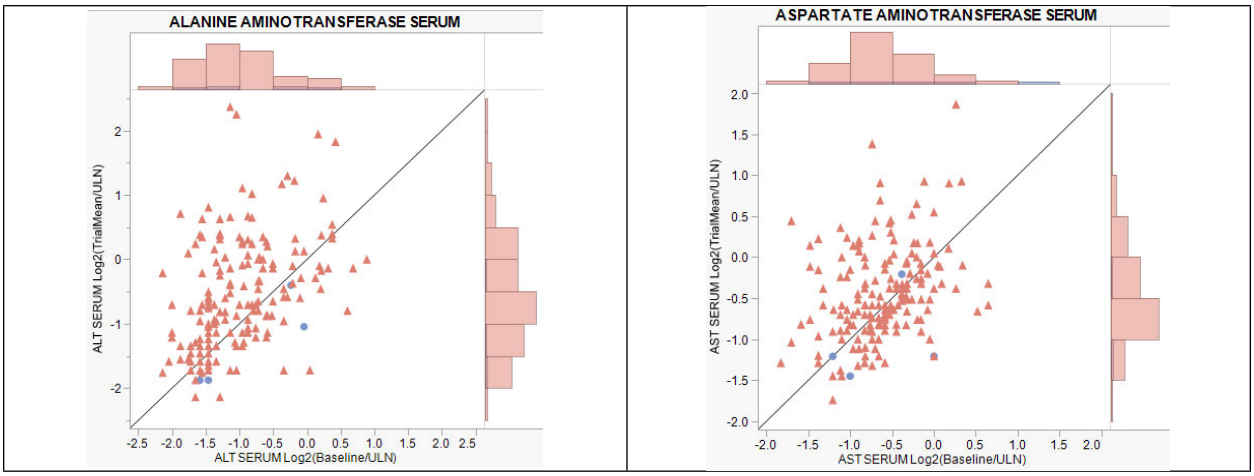
8.4.6. Laboratory Findings

Laboratory safety monitoring in both studies TIZA-21-086 and TIZA-22-046 consisted of hematology and chemistry evaluations that occurred twice, at baseline and at the end of all study periods.

The Applicant reported 35 laboratory changes associated with TEAEs in TIZA-21-086 including 15 ALT increased, 6 AST increased, 5 elevated eosinophil, 5 decreased hemoglobin, 3 elevated random glucose, and 1 elevated bilirubin direct. The Applicant reported 8 TEAEs related to laboratory changes in TIZA-22-046 including 4 ALT increased, 2 AST increased, and 2 eosinophil increased.

Using shift plot analysis on pooled data from TIZA-21-086 and TIZA-22-046, this reviewer confirmed that values of ALT and AST demonstrated trends toward increasing after completion of the trial (Table 4).

Table 4 Notable Laboratory Shift Plot from Pooled Data of TIZA-21-086 and TIZA-22-046, Reviewer Analysis, JMP Clinical



REVIEWER COMMENT: The RLD, Zanaflex, label carries a warning regarding the risk of liver injury and precaution to monitor ALT and discontinue the medication if liver injury occurs. Therefore, these findings are consistent with known risks of the RLD.

8.4.7. Vital Signs

As noted in section 8.4.5 on TEAE, orthostatic hypotension was a common TEAE reported during both studies.

REVIEWER COMMENT: Hypotension is the top Warning and Precaution in the RLD label and hence the episodes of orthostatic hypotension seen in these studies is common.

8.4.8. Electrocardiograms (ECGs)

See the following section regarding QTc Prolongation. No other ECG findings were notable.

8.4.9. QT

In the Tables of Adverse Events presented by the Applicant, QTc prolongation appears as the 5th most common TEAE in both studies, with 9 reports in TIZA-21-046 and 2 in TIZA-22-046. Of these 11 reports, 3 occurred immediately prior to dosing and far enough from any prior doses to be considered related.

In this reviewer's analysis, only 10 reports total (rather than 11) of QTc prolonged were found in the pooled data of TIZA-21-086 and TIZA-22-046. Four of those reports occurred at the pre-

dose ECG check and can be considered unrelated to dosing. The remaining 6 events occurred in 5 subjects and are detailed in Table 5.

Table 5 Narratives of Episodes of Post-Dose QTc Prolongation Pooled Across TIZA-21-086 and TIZA-22-046

TIZA-21-(b) (6) During Period 3, having received a dose of test drug (tizanidine hydrochloride oral solution) at 09:00 a.m on (b) (6) the subject experience AE#1 at 09:55 a. m., where the 1.5 hr post-dose ECG had a QTc of 443 ms. Subsequent ECG at 11:50 a.m. (3.5h post-dose) QTc was 420 ms.
TIZA-21-(b) (6) in Period 2 on (b) (6) had received a dose of test drug at 09:18 a.m. At 8:55 p.m. during what was considered their 12 hr post-dose ECG QTc=442 ms with heart rate of 85 bpm. A subsequent ECG performed at 9:46 a.m. on (b) (6) (b) (6) had a QTc of 428 ms with a heart rate of 91 bpm.
TIZA-21-(b) (6) in Period 3 had received test product on (b) (6) 09:18 a.m. and on (b) (6) at 08:48 p.m. during the 12 hr post-dose ECG had a QTc of 442 ms and heart rate of 88 bpm. Subsequent ECG on (b) (6) 09:48 a.m. QTc had resolved to 414 ms with heart rate of 70 bpm.
TIZA-21 (b) (6) in Period 2 received reference drug at 09:28 a.m. on (b) (6) and then on (b) (6) at 10:46 a.m. at the 1.5 hr post-dose ECG had a QTc of 443 ms with a heart rate of 48 bpm. At the 3.5 hr post-dose ECG (12:20 p.m.) QTc was still prolonged at 442 ms with heart rate of 51 bpm and a repeat ECG added at 3:55 p.m. the QTc had resolved to 427 ms with a heart rate of 70 bpm.
TIZA-21-(b) (6) in Period 1 on (b) (6) at 10:15 a.m. after receiving test drug had QTc of 449 ms and heart rate of 78 bpm on the 1.5 hr post-dose ECG. ECG at the 3.5 hr and 12 hr post-dose evaluations at 12:07 p.m. and 4:02 p.m. had QTc of 474 ms and 442 ms with heart rates of 83 and 85 bpm. A repeat ECG at 8:52 p.m. had resolved with QTc of 423 ms and heart rate of 73 bpm.
The same subject in Period 2 received reference drug on (b) (6) at 09:20 a.m. and at the 1.5 hr post-dose ECG at at 10:15 a.m. had QTc of 449 ms and heart rate of 78 bpm. Subsequent ECG at 3.5 hr post-dose 12:07 p.m. QTc was 474 ms with heart rate of 83 bpm. A repeat ECG was done at 04:02 p.m. to follow this QTc prolongation and was still mildly prolonged at 442 ms with heart rate of 85 bpm. The 12 hr post-dose ECG performed at 08:52 p.m. was normalized with QTc of 423 ms and heart rate of 73 bpm and the AE was considered resolved.

QTc Prolonged Pre-Dose

The following is a listing of 4 cases where QTc prolongation was noted at the pre-dose ECG, and can be considered unrelated to study drug:

TIZA-21 (b) (6) Had prolonged QT on the pre-dose ECG during Period 2 prior to receiving reference drug in Part A of the study but was not withdrawn from the study but rather did not receive study drug in Period 2 but continued to be followed and completed Periods 3 and 4.

TIZA-21 (b) (6) in Period 1 on (b) (6) at 08:09 a.m. had a pre-dose ECG with QTc of 450ms with heart rate of 77 bpm. The ECG was repeated at 08:53 a.m. with a QTc of 406 ms and heart rate of 89 bpm. After this normalization, the subject was dosed at 09:04 a.m. with test drug. No further QTc prolongations were recorded for this subject throughout the remaining 3 periods.

As previously reviewed, subjects TIZA-22-(b) (6) and TIZA-22 (b) (6) both had pre-dose ECG with QTc prolongation that led to withdrawal from the entire study.

Because of the frequency of QTc prolongation with both reference and test drugs, this reviewer referred to the Interdisciplinary Review Team for QT Studies (IRT) consultation on the thorough QT study (TQT) performed under NDA 021447 for tizanidine oral tablets (Zanaflex), the RLD. The TQT was reviewed under submission 181 through a Post-Marketing Requirement (PMR) mechanism. The review is dated January 28, 2015 (Reference ID: 3693559). The conclusions of that review were as follows:

"No significant QTc prolongation effect of tizanidine (8 mg and 24 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between tizanidine (8 mg and 24 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established."

To ensure that there were no differences between what was found under NDA 021447 and this NDA 216190, a consult request was placed to the IRT and the consult response (December 13, 2023, Reference ID: 5292880) concluded:

"We do not consider the 6 episodes of QTc prolongation with the test drug to be of clinical concerns and therefore do not warrant further QT risk assessment for the following reasons:
1) The study's baseline QTc inclusion criteria of ≤ 440 msec and the cutoff used to identify subjects with QTc prolongation as those with QTcF > 440 msec are considered to be within normal QT limits of < 450 msec for males and < 470 msec for female.
2) Only one of the identified cases of mild QTc prolongation exceeded 470 msec and was < 480 msec.
3) The largest change from baseline in QTc were > 30 msec but < 60 msec.
4) Other treatment periods did not indicate higher frequency of mild QT prolongation for test compared to the Reference drug.

5) Test drug met the bioequivalence (BE) criteria after 4 mg/day dose and no significant QTc prolongation effect of tizanidine was observed at higher dose of 8 mg and 24 mg in the previous TQT study."

8.4.10. Immunogenicity

There was no concern for immunogenicity with tizanidine and no special assessments were conducted.

8.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety concerns were identified.

8.6. Safety Analyses by Demographic Subgroups

Subgroup analysis for this application would be neither informative nor valid due to the small number of healthy volunteer subjects and limited exposure.

8.7. Specific Safety Studies/Clinical Trials

No targeted clinical safety studies were performed.

8.8. Additional Safety Explorations

No additional safety explorations were performed.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Tizanidine oral solution is not yet approved and hence no postmarket safety experience has been collected.

Fidelity Biopharma Co. submitted a 120-day safety update on September 28, 2023, where the Applicant reported results of their review of literature and FDA Adverse Event Reporting System from May 31, 2023 to September 26, 2023. The line listing provided did not reveal any new safety signals.

This reviewer accessed the Annual Reports for NDA 020397, Zanaflex Tablets, one of the RLD for this application. Annual Report #26, covering the period of November 27, 2021, to November 26, 2022, was submitted January 26, 2023. The Applicant conducted literature reviews which they concluded did not lead to any new safety findings.

REVIEWER COMMENT: This reviewer concurs with the findings of the current and RLD Applicants' analyses.

8.9.2. Expectations on Safety in the Postmarket Setting

The only concern with the addition of tizanidine oral solution to the two currently available formulations, tizanidine tablets and capsules, is the differing pharmacokinetic profiles, specifically between tablet/solution and capsules in the fed condition. However, this risk already existed prior to the new oral solution formulation currently being evaluated in this NDA. This risk was managed via labeling with instructions to providers to not substitute one formulation for another. Similar labeling instructions will reduce the safety risks for tizanidine oral solution in the postmarket setting.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues from other disciplines were identified at the time of this review.

8.10. Integrated Assessment of Safety

Tizanidine oral solution is being developed as a 505(b)(2) application with reference to the RLDs of tizanidine tablets which were approved in 1996 and tizanidine capsules, approved in 2002. The oral solution has demonstrated bioequivalence to the tablets under both fed and fasted conditions and to the capsules under fasted conditions. The proposed indication for tizanidine oral solution is the same as the approved formulations, "for the management of spasticity."

9. Advisory Committee Meeting and Other External Consultations

No advisory committee input was sought for this application. There is considerable safety and efficacy experience with the reference listed drug.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The drug labeling for this NDA is pending at the time of completion of this review.

10.2. Nonprescription Drug Labeling

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended at this time.

12. Postmarketing Requirements and Commitments

The necessity of post-marketing requirements or commitments has not been determined at the time of this review.

13. Appendices

13.1. References

N/A

13.2. Financial Disclosure

The two bioequivalence studies conducted under this NDA were done so by Scitus Pharma Services Private Limited, of Tamilnadu, India. The three clinical investigators listed in the clinical study reports, Drs. Senthilkumar, Shanmugarajan, and Viswanath provided signed financial disclosure forms which identified no conflicts of interest.

Covered Clinical Study (Name and/or Number): TIZA-22-046

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ NA	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ NA	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ NA	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): TIZA-21-086

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S		

Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ NA	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ NA	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ NA	No ☐ (Request explanation from Applicant)

Hnatkova, K. and M. Malik (2020). "Sources of QTc variability: Implications for effective ECG monitoring in clinical practice." Annals of Noninvasive Electrocardiology 25(2).
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