# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 216190Orig1s000

# CLINICAL PHARMACOLOGY REVIEW(S)

# Office of Clinical Pharmacology

## Clinical Pharmacology Review

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| NDA/BLA Number | NDA 216190 |
| Associated IND | 156316 |
| Link to EDR | \\CDSESUB1\evsprod\NDA216190\0001 |
| Submission Date | May 31, 2023 |
| Submission Type | 505(b)(2) |
| Brand Name | Ontralfy |
| Generic Name | Tizanidine |
| Dosage form (Strength) | Oral Solution (2 mg/5 mL) |
| Proposed Indication | For the (b) (4) of spasticity |
| Applicant | Fidelity Biopharma, Inc. |
| OCP Review Team | Dawei Li, Ph.D., Bilal AbuAsal, Ph.D. |

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# Executive Summary

In this current New Drug Application (NDA) 216190 for Tizanidine Oral Solution (2 mg/5 mL), Ontralfy, the Applicant (Fidelity Biopharma) is seeking approval for the (b) (4) of spasticity. The applicant filed this application under the 505(b)(2) pathway and relied on previous findings from listed drugs (LD) Zanaflex® (Tizanidine Hydrochloride) 4 mg tablet (NDA 020397) for efficacy and safety.

The clinical pharmacology program includes 2 Phase 1 studies in healthy adult volunteers: Study TIZA-21-086, a pivotal relative bioavailability study between Ontralfy and the LD (Zanaflex® Tizanidine Hydrochloride tablet) under fasting and fed conditions; Study TIZA-22-046: a comparative PK study between Ontralfy and Zanaflex® (Tizanidine Hydrochloride capsule) under fed conditions. Considering study TIZA-22-046 (comparative PK study of Ontralfy with Zanaflex® capsule) is conducted under fed conditions and the food effect on the PK of Zanaflex® tablet and Zanaflex® capsule are different, the review team concludes that study TIZA-22-046 is not necessary to support this 505(b)(2) application. Study TIZA-21-086 is adequate to support scientific bridge between Ontralfy and the LD (Zanaflex® Tizanidine Hydrochloride tablet) and the food effect assessment of Ontralfy. The results from study TIZA-21-086 showed that the 90% confidence intervals of the geometric LSMs for Cmax and AUC0-inf were within the standard bioequivalence acceptance range (80 to 125%) under both fasting and fed conditions, indicating that Ontralfy and Zanaflex® Tizanidine Hydrochloride tablet are bioequivalent, and the food effect characteristics of Ontralfy and Zanaflex® Tizanidine Hydrochloride tablet are comparable.

The primary focus of this review is to evaluate the adequacy of scientific bridge between Ontralfy and the LD (Zanaflex® Tizanidine Hydrochloride tablet) based on the pivotal relative bioavailability study (Study TIZA-21-086).

## Recommendation

The Office of Clinical Pharmacology (OCP) team reviewed the information submitted under this NDA and recommends approval of Ontralfy provided an agreement is reached between the applicant and the Agency regarding the proposed labeling language. This recommendation is based on an adequate PK bridge demonstrated between Ontralfy and the LD (Zanaflex® Tizanidine Hydrochloride tablet), allowing the applicant to rely upon FDA's previous findings of LD for efficacy and safety.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study TIZA-21-086. OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4) under ANDAs NON-RESPONSIVE and NON-RESPONSIVE OSIS concluded that data from the reviewed study (study TIZA-21-086) were reliable. (Please refer to OSIS review in DARRTS dated 08/18/2023 for additional details).

### Overview of the Product

Ontralfy™ contains the active ingredient, Tizanidine Hydrochloride (2.29 mg equivalent to 2 mg Tizanidine base), and the inactive ingredients edetate disodium, dihydrate, sucralose, methylparaben sodium, propylparaben sodium, citric acid anhydrous (b) (4) sodium citrate anhydrous, flavor and purified water. It is a clear, colorless to pale yellow solution with a strawberry flavor.

### Summary of Key Clinical Pharmacology Findings

Scientific bridge between Ontralfy and the LD (Zanaflex® Tizanidine Hydrochloride tablet)

The applicant conducted an open label, single-dose, comparative bioavailability study (TIZA-21-086) in healthy subjects under fasting and fed conditions. The results from study TIZA-21-086 showed that Ontralfy was bioequivalent to the reference Zanaflex® Tizanidine Hydrochloride tablet with respect to the overall exposure (AUC0-inf and Cmax) under fasting and fed conditions. PK study conducted by the applicant provided an adequate scientific bridge for this application to rely on the relevant labeling information of LD.

Comparative PK study between Ontralfy and Zanaflex® Tizanidine Hydrochloride capsule

The applicant also conducted an open label, single-dose, comparative bioavailability study (TIZA-22-046) in healthy subjects under fed conditions. The results from study TIZA-22-046 showed that Ontralfy was bioequivalent to Zanaflex® Tizanidine Hydrochloride capsule with respect to the overall exposure (AUC0-inf and Cmax) under fed conditions. However, study TIZA-22-046 is not necessary to support the scientific bridging in this 505(b)(2) application.

## Summary of Relative Bioavailability Study

### Study TIZA-21-086 (pivotal BE study of Ontralfy with Zanaflex® Tizanidine Hydrochloride tablet)

Study Design: This was 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, compared with that of reference product, Zanaflex® (Tizanidine Hydrochloride), 4 mg tablet, in healthy adult human subjects under fasting and fed conditions.

Number of Subjects (Planned and Completed): 120 subjects were planned into the study. 115 subjects completed all study activities.

Treatments:

Administration of Test Product (T, Tizanidine Oral Solution) or Reference Product (R, Zanaflex® Tizanidine Hydrochloride, 4 mg tablet) under Fasting Conditions (Period 1 and 2)

After overnight fasting of at least 10.00 hours, a single dose of 10 mL (4 mg) of Tizanidine Oral Solution, 2 mg/5 mL, (Test Product) or one tablet of Zanaflex® (Tizanidine Hydrochloride), 4 mg tablet, (Reference Product) was administered to the subjects in a sitting posture with about 240 mL of water at ambient temperature in each period.

Administration of Test Product (T, Tizanidine Oral Solution) or Reference Product (R, Zanaflex® Tizanidine Hydrochloride, 4 mg tablet) under Fed Conditions (Period 3 and 4)

After overnight fasting of at least 10.00 hours, a high-fat high-calories breakfast was served 30 minutes prior to administration of the investigational product. Exactly 30 minutes after actual start time of a high-fat high-calories breakfast, a single dose of 10 mL (4 mg) of Tizanidine Oral Solution, 2 mg/5 mL, (Test Product) or a single dose of Zanaflex® (Tizanidine Hydrochloride), 4 mg tablet, (Reference Product) was administered to the subjects in a sitting posture with about 240 mL of water at ambient temperature in each period.

There was a washout period of 2 days between each single dose administration.

PK Sampling: A total of 21 blood samples (3 mL each) were obtained for PK measurement at the following times relative to each dose: Predose, 00.08, 00.17, 00.25, 00.33, 00.50, 00.67, 00.83, 01.00, 01.25, 01.50, 01.75, 02.00, 02.33, 02.67, 03.00, 04.00, 06.00, 08.00, 10.00 and 12.00 hours post-dose.

Bioequivalence Criteria: The PK parameters were estimated using non-compartmental model in Phoenix® WinNonlin® (version:8.3) for Tizanidine. The 90% CI of the relative mean (Geometric mean) of the test to reference products for Ln-transformed Cmax, AUC0-t and AUC0-inf was to be within 80.00% to 125.00% for Tizanidine to establish bioequivalence between Ontralfy and the reference Zanaflex® Tizanidine Hydrochloride tablet.

Results:

A total of 115 subjects completed all the periods of the study, and all 115 subjects' concentration data were used in pharmacokinetics and statistical evaluation for Tizanidine. All statistical evaluations of this four-period crossover study were performed by two-way crossover comparisons T1 vs R1 (fasting condition), T2 vs R2 (fed condition).

The relevant bioequivalence results between Tizanidine Oral Solution, 2 mg/5 mL (dosed as 4 mg/10 mL), and the Zanaflex® (Tizanidine Hydrochloride) 4 mg tablet under fasting and fed conditions are presented in Table 1 and Table 2, respectively.

**Table 1. Ratio of the Least Squares Geometric Means of PK parameters and 90% Confidence Intervals of Tizanidine (Fasting, n=115)**

| Parameters (Units) | Geometric Least Square mean | | Power (%) | Ratio (%) | ISCV (%) |
|---|---|---|---|---|---|
| | Test (T1) | Reference (R1) | | | |
| $C_{max}$ (ng/mL) | 5.0692 | 4.6893 | 100.00 | 108.10 | 24.69 |
| $AUC_{0-t}$ (hr*ng/mL) | 14.1082 | 12.7515 | 100.00 | 110.64 | 19.06 |
| $AUC_{0-\infty}$ (hr*ng/mL) | 14.6905 | 13.3195 | 100.00 | 110.29 | 18.46 |
| **Parameters (Units)** | **90% CI** | | **Acceptance Criteria (%)** | | **Outcome of BE result** |
| $C_{max}$ (ng/mL) | 102.49 to 114.02 | | 80.00 - 125.00 | | Bioequivalent |
| $AUC_{0-t}$ (hr*ng/mL) | 106.15 to 115.31 | | 80.00 - 125.00 | | |
| $AUC_{0-\infty}$ (hr*ng/mL) | 105.96 to 114.81 | | 80.00 - 125.00 | | |

*Source: Clinical Study Report-Protocol TIZA-21-086, Table 25 on page 102 of 149.*

**Table 2. Ratio of the Least Squares Geometric Means of PK parameters and 90% Confidence Intervals of Tizanidine (Fed, n=115)**

| Parameters (Units) | Geometric Least Square mean | | Power (%) | Ratio (%) | ISCV (%) |
|---|---|---|---|---|---|
| | Test (T2) | Reference (R2) | | | |
| $C_{max}$ (ng/mL) | 5.4733 | 5.1168 | 99.99 | 106.97 | 28.58 |
| $AUC_{0-t}$ (hr*ng/mL) | 19.2567 | 17.4795 | 100.00 | 110.17 | 11.47 |
| $AUC_{0-\infty}$ (hr*ng/mL) | 19.7596 | 17.9745 | 100.00 | 109.93 | 11.22 |
| **Parameters (Units)** | **90% CI** | | **Acceptance Criteria (%)** | | **Outcome of BE result** |
| $C_{max}$ (ng/mL) | 100.60 to 113.74 | | 80.00 - 125.00 | | Bioequivalent |
| $AUC_{0-t}$ (hr*ng/mL) | 107.44 to 112.96 | | 80.00 - 125.00 | | |
| $AUC_{0-\infty}$ (hr*ng/mL) | 107.26 to 112.67 | | 80.00 - 125.00 | | |

*Source: Clinical Study Report-Protocol TIZA-21-086, Table 26 on page 103 of 149.*

The relevant bioequivalence results indicated that Tizanidine Oral Solution (dosed as 4 mg/10 mL) and Zanaflex® Tizanidine Hydrochloride 4 mg tablet are bioequivalent in healthy adult human subjects under fasting and fed conditions, and the food effect characteristics with respect to the overall exposure of Tizanidine Oral Solution and the Zanaflex® Tizanidine Hydrochloride tablet are comparable.

***Reviewer's Comments:***

1. *The overall design of this pivotal BE study, including the dose selection, route of administration, study population, study sample size, PK sampling schedule, washout period and bioanalytical method validation data are appropriate.*
2. *The applicant conducted PK analysis and applied statistical testing criteria are acceptable.*
3. *The reviewer conducted independent analysis and verified that the Cmax, AUC0-t and AUC0-inf results were within the acceptable limits of 80.00% to 125.00% for concluding the bioequivalence of the test product to the LD under fasting and fed conditions.*

***Reviewer's Analysis***

Independent NCA analysis was conducted by the reviewer using the raw PK data from study TIZA-21-086. Table 3 summarized the reviewer calculated ratio of the Least Squares Geometric Means for PK parameters and confidence intervals (C.I.) under fasting and fed conditions, respectively.

**Table 3. Ratio of the Least Squares Geometric Means of PK parameters and 90% Confidence Intervals of Tizanidine (n=115, Reviewer's Analysis)**

| Comparison (Test vs Reference) | Parameter | Test Geometric LSM | Reference Geometric LSM | Test/ Reference (%) | 90% Confidence Interval |
|---|---|---|---|---|---|
| Tizanidine Oral Solution vs Zanaflex® Tablet (Fasting) | Cmax<br>AUC0-t<br>AUC0-inf | 5.21 ng/mL<br>14.56 hr*ng/mL<br>15.12 hr*ng/mL | 4.81 ng/mL<br>13.15 hr*ng/mL<br>13.70 hr*ng/mL | 108.17<br>110.70<br>110.31 | (102.34, 114.32)<br>(105.90, 115.71)<br>(105.66, 115.16) |
| Tizanidine Oral Solution vs Zanaflex® Tablet (Fed) | Cmax<br>AUC0-t<br>AUC0-inf | 5.57 ng/mL<br>19.59 hr*ng/mL<br>20.13 hr*ng/mL | 5.22 ng/mL<br>17.79 hr*ng/mL<br>18.29 hr*ng/mL | 106.69<br>110.11<br>110.07 | (100.07, 113.74)<br>(106.99, 113.32)<br>(107.00, 113.24) |

*Source: Reviewer's independent analysis*

### Study TIZA-22-046 (comparative PK study of Ontralfy with Zanaflex® Tizanidine Hydrochloride capsule)

Study Design: This was an open-label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, crossover oral relative bioavailability study comparing 10 mL (4 mg) of Test Product, Tizanidine Oral Solution, 2 mg/5 mL with Reference Product, Zanaflex® (Tizanidine Hydrochloride), 4 mg capsule, in healthy adult human subjects under fed conditions.

Number of Subjects (Planned and Completed): 64 subjects were planned into the study. 62 subjects completed all study activities.

Treatments:

After overnight fasting of at least 10.00 hours, a high-fat high-calories breakfast was served 30 minutes prior to administration of the investigational product. Exactly 30 minutes after actual start time of a high-fat high-calories breakfast, a single dose of 10 mL (4 mg) of Tizanidine Oral Solution, 2 mg/5 mL, (Test Product) or a single dose of Zanaflex® (Tizanidine Hydrochloride), 4 mg capsule, (Reference Product) was administered to the subjects in a sitting posture with about 240 mL of water.

There was a washout period of 2 days between each single dose administration.

PK Sampling: A total of 21 blood samples (3 mL each) were obtained for PK measurement at the following times relative to each dose: Predose, 00.08, 00.17, 00.25, 00.33, 00.50, 00.67, 00.83, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 03.00, 0.350, 04.00, 06.00, 08.00, 10.00 and 12.00 hours post-dose.

Bioequivalence Criteria: The PK parameters were estimated using non-compartmental model in Phoenix® WinNonlin® (version:8.3) for Tizanidine. The 90% CI of the relative mean (Geometric mean) of the test to reference products for Ln-transformed Cmax, AUC0-t and AUC0-inf was to be within 80.00% to 125.00% for Tizanidine to establish bioequivalence between Ontralfy and the reference Zanaflex® Tizanidine Hydrochloride capsule under fed conditions.

Results:

A total of 62 subjects completed the study, and all 62 subjects' concentration data were used in pharmacokinetics and statistical evaluation for Tizanidine.

The relevant bioequivalence results between Tizanidine Oral Solution, 2 mg/5 mL (dosed as 4 mg/10 mL), and the Zanaflex® (Tizanidine Hydrochloride) 4 mg capsule under fed conditions are presented in Table 4.

**Table 4. Ratio of the Least Squares Geometric Means of PK parameters and 90% Confidence Intervals of Tizanidine (Fed, n=62)**

| Parameters (Units) | Geometric Least Square mean | | Power (%) | Ratio (%) | ISCV (%) |
|---|---|---|---|---|---|
| | Test (T) | Reference (R) | | | |
| $C_{max}$ (ng/mL) | 4.805 | 5.136 | 92.22 | 93.55 | 36.63 |
| $AUC_{0-t}$ (hr*ng/mL) | 16.238 | 14.346 | 99.17 | 113.19 | 27.16 |
| $AUC_{0-\infty}$ (hr*ng/mL) | 16.684 | 14.950 | 99.28 | 111.59 | 26.40 |
| **Parameters** | **90% CI** | | **Acceptance Criteria (%)** | | **Outcome of BE result** |
| $C_{max}$ | 84.02 to 104.17 | | 80.00 - 125.00 | | Bioequivalent |
| $AUC_{0-t}$ | 104.4 to 122.72 | | 80.00 - 125.00 | | |
| $AUC_{0-\infty}$ | 103.04 to 120.85 | | 80.00 - 125.00 | | |

*Source: Clinical Study Report-Protocol TIZA-22-046, Table 14 on page 70 of 95.*

The relevant bioequivalence results indicated that Tizanidine Oral Solution (dosed as 4 mg/10 mL) and Zanaflex® Tizanidine Hydrochloride 4 mg capsule are bioequivalent in healthy adult human subjects under fed conditions.

***Reviewer's Comments:***

1. *The overall design of this comparative PK study, including the dose selection, route of administration, study population, study sample size, PK sampling schedule, washout period and bioanalytical method validation data are appropriate.*
2. *The applicant conducted PK analysis and applied statistical testing criteria are acceptable.*
3. *Considering study TIZA-22-046 is conducted under fed condition and the pivotal BE study with Zanaflex® Tizanidine Hydrochloride tablet is adequate to support the scientific bridging of the test product, the review team concludes that study TIZA-22-046 in not necessary to support this 505(b)(2) application.*

# Appendices

## Summary of Bioanalytical Method Validation and Performance

A validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method was used for determining the Tizanidine concentration in human plasma. The method met the acceptance criteria for bioanalytical methods according to the Bioanalytical Method Validation Guidance for Industry the FDA Guidance for the Industry. Description of method validation parameters for Tizanidine (validation report SPSTZMV01) are summarized in table below.

**Table 4. Summary of Bioanalytical Method and Validation Characteristics**

| | |
|---|---|
| Analyte | Tizanidine (TZ) |
| Internal standard (IS) | Tizanidine D4 (TZIS) |
| Lower Limit of Quantitation (LLOQ) (ng/mL) | 0.101 |
| Standard curve concentrations (ng/mL) | 0.100 – 10.000 |
| QC Concentrations (ng/mL) | LLOQQC: 0.101<br>LQC: 0.295<br>MQC1: 1.402<br>MQC: 3.506<br>HQC: 7.304 |
| Intra-run Accuracy and Precision | Biases: -8.91% to 6.63%<br>CV: 0.40% to 4.10% |
| Inter-run Accuracy and Precision | Biases: -1.58% to 4.09%<br>CV: 0.64% to 7.36% |
| Freeze and Thaw Stability | -70°C set point freezer/ thaw 5 cycles |
| Bench-top stability | 21.0 hours @ room temperature |
| Processed Sample stability | 25.5 hours @ room temperature<br>102.0 hours @ autosampler conditions (5 ± 5ºC) |
| Long-Term Stability of Analytes in Plasma: | 189 days @ -20°C set point freezer<br>189 days @ -70°C set point freezer |

*Source: Method validation report SPSTZMV01*

***Reviewer's Comments:*** *Method validation and sample analysis are acceptable.*

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