# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 216354Orig1s000

# CLINICAL PHARMACOLOGY REVIEW(S)

# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | NDA 216354 |
| **Link to EDR** | \\CDSESUB1\evsprod\nda216354 |
| **Submission Date** | 04/21/22 |
| **Submission Type** | NDA – 505(b)(2) |
| **Brand Name** | AUSTEDO XR |
| **Generic Name** | Deutetrabenazine |
| **Dosage Form and Strength** | Extended-Release Tablets, 6 mg,12 mg and 24 mg |
| **Route of Administration** | Oral |
| **Proposed Indication** | For treatment of chorea associated with Huntington's disease (HD) and tardive dyskinesia (TD) in adults |
| **Applicant** | Teva |
| **Associated IND** | IND 112975 |
| **OCP Review Team** | Min Li, Vishnu Sharma, Atul Bhattaram, and Bilal AbuAsal |
| **OCP Final Signatory** | Mehul Mehta, Division Director |

## Table of Contents

# 1. Executive Summary

In this NDA, Teva Pharmaceutical Industries, ltd is seeking approval for AUSTEDO XR (deutetrabenazine) tablets, for the treatment of chorea associated with Huntington's disease (HD) and tardive dyskinesia (TD) in adults under the 505(b)(2) pathway. AUSTEDO XR is a once daily (QD) extended-release formulation of deutetrabenazine developed as 6, 12 and 24 mg tablets. The approval is based on pharmacokinetic (PK) bridging to the immediate release AUSTEDO tablets as the reference drug which is also owned by Teva. AUSTEDO was approved for the same indications as 6, 9, and 12 mg tablets for twice daily (BID) administration through the 505(b)(2) pathway under NDA 208082 for HD and NDA 209885 for TD using XENAZINE as the Listed Drug (LD).

The dosage of AUSTEDO XR is determined individually for each patient based on reduction of chorea or tardive dyskinesia and tolerability. The initial starting dose for AUSTEDO XR is 12 mg QD. The dose of AUSTEDO XR may be increased at weekly intervals in increments of 6 mg per day up to a maximum recommended daily dosage of 48 mg.

To support the approval of AUSTEDO XR (referred as the QD product), a pivotal multi-dose relative bioavailability (BA) study (Study TV50717-BE-10179) was conducted to demonstrate the PK comparability at steady state (SS) between the QD product (Test) and the AUSTEDO BID tablets (Reference) under fed conditions. In general, the QD product resulted in more controlled drug release for a prolonged period and a relatively flatter PK curve compared to the AUSTEDO BID product. Based on the steady state PK results, the $C_{trough,ss}$ of the parent drug from the QD product was higher than that of the reference product (as shown by the GMR of $C_{trough,ss}$ 144 % with 90%CI 135.3%-155.5%), indicating the QD product is non-inferior in term of the parent drug's $C_{trough,ss}$ compared to the BID product. The geometric mean ratios (GMR, specifically T/R) and 90% confidence intervals (90%CI) of area under the plasma concentration-time curve over a 24-hour interval at a steady state ($AUC_{0-24h,ss}$) and maximum observed plasma concentration ($C_{max,ss}$) of the parent drug were 115.2% (90%CI: 110.4%-120.3%) and 95.0% (90%CI: 90.5%-99.7%), respectively, meeting the bioequivalence (BE) criteria (90%CI limit within 80-125%). For the two active metabolites, α-dihydrotetrabenazine (α-HTBZ) and β-dihydrotetrabenazine (β-HTBZ), the 90%CI of the GMR for $AUC_{0-24h,ss}$ and $C_{trough,ss}$ were within the BE criteria (80-125%), while the GMR of the $C_{max}$ were slightly below 80%, in a range of 74%-79%.

The impact of PK exposure difference particularly $C_{max,ss}$ of active metabolites on the efficacy was evaluated using exposure-response (E-R) analyses. Under the conservative assumption that $C_{max,ss}$ is a major driver of the efficacy, E-R analyses suggested that the mean decrease in the efficacy endpoints, namely the changes from baseline in the total motor AIMS score in TD patients, and in the UHDRS-TMC score in HD patients, was predicted to be 13% in TD and 11% in HD subjects for the QD product, due to the $C_{max}$

difference between the QD and the BID products. Additionally, the clinical relevance of PK shape was assessed in an open label extension long-term safety study (Study SD-809-C-16) consisting of a switch cohort. In that study, the switch from TBZ (XENAZINE) in stable dose with a wide range of dose and dosing frequency in HD patients to AUSTEDO tablets administered BID with matching total active metabolites' AUC demonstrated no significant change in the efficacy after the switch, indicating the difference in the PK shape and $C_{max}$ is unlikely to significantly impact efficacy as long as total active metabolites' AUC is similar. In addition, AUSTEDO is dosed using a titration dosing scheme which implies that the range of effective PK exposures derived from AUSTEDO would bracket the exposures resulted from the QD product.

The Clinical pharmacology program also includes:1) a single dose relative BA Study TV50717-BE-10165 to evaluate food effect for the QD product and also compare the PK between the QD product and the BID product under fed condition; 2) a dose proportionality study TV50717-BE-10175 to assess PK linearity for a single dose of 6 mg, 12 mg, and 24 mg of the proposed QD product. With the proposed dose strengths of the QD product, dose proportionality results support dose conversions for all the approved dosing regimens of AUSTEDO. Further, results from the food effect study suggested that AUSTEDO XR can be taken with or without food.

The focus of this review is to evaluate the adequacy of the PK bridging strategy used to support the registration of AUSTEDO XR and to evaluate the adequacy of the supportive dose proportionality and food effect assessment for supporting the labeling recommendations.

## 1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA (#216354) and recommends approval based on the adequate scientific bridge established between this proposed QD product and the reference drug, AUSTEDO tablets, for the treatment of chorea associated with Huntington's disease (HD) and tardive dyskinesia (TD) in adults. No post-market commitment or post-market requirement is needed.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study TV50717-BE-10179. OSIS arranged a clinical inspection of Study TV50717-BE-10179 and concluded that the audited study data was reliable (please refer to OSIS review in DARRTS dated 12-06-22 for additional details).

Key review issues with specific recommendations and comments are summarized below:

| Review Issue | Recommendations and Comments |
|---|---|
| **Pivotal or supportive evidence of effectiveness** | The evidence of effectiveness was based on results from the pivotal relative BA study TV50717-BE-10179 comparing the proposed QD product and the reference BID product. The differences seen in the PK shape and $C_{max,ss}$ for the metabolite was justified by the E-R analyses as well as the switch cohort study and considered not clinically meaningful. |
| **General dosing instructions** | The recommended starting dosage is 12 mg once daily. Titrate at weekly intervals by 6 mg per day based on reduction of chorea or tardive dyskinesia, and tolerability, up to a maximum recommended daily dosage of 48 mg. Administer AUSTEDO XR with or without food. |
| **Switching Between AUSTEDO XR and AUSTEDO** | As the scientific bridge is established adequately between the proposed QD product and AUSTEDO, patients who are currently being treated with once-daily doses of AUSTEDO XR tablets, may be switched to AUSTEDO tablets at the same total daily dose, taken in two divided doses (twice daily), and vice versa. |
| **Dosing in patient subgroups (intrinsic and extrinsic factors)** | Same as AUSTEDO. |
| **Labeling** | The proposed labeling edits related to the dosing instruction and food effect recommendations are generally acceptable. |
| **Bridge between the to-be-marketed and clinical trial formulations** | The to-be-marketed formulation is same as the formulation used in the pivotal studies. |

## 2. Background and Regulatory History

AUSTEDO® (Deutetrabenazine) received the original approval for the treatment of chorea associated with Huntington's disease (HD) on Apr 03, 2017 (NDA 208082) and for the treatment of chorea associated with tardive dyskinesia (TD) on Aug 30, 2017 (NDA 209885). Deutetrabenazine is a selectively deuterated form of tetrabenazine (TBZ). XENAZINE (TBZ) was approved in NDA 21894 for the same indications and also referred as the listed drug (LD) for AUSTEDO approval. TBZ and deutetrabenazine act as prodrugs undergoing extensive and almost complete hepatic metabolism by carbonyl reductase, yielding the active dihydro metabolites α-dihydrotetrabenazine (α-HTBZ) and β-dihydrotetrabenazine (α-HTBZ), which primarily contributes to the efficacy. The approved dosage for AUSTEDO tablets (**Table 1**) recommends drug administration with food and initiating at a low dose followed by titration to achieve optimal efficacy and tolerability for individual patients (see USPI section 2). The maintenance dose ranges from 6 to 48 mg per day for HD and from12 to 48 mg per day for TD, and daily doses of 12 mg or above should be administered in 2 divided doses.

**Table 1**: Dosage comparison between AUSTEDO XR and AUSTEDO

| | **AUSTEDO XR extended-release tablet (proposed)** | **AUSTEDO tablet (approved)** |
|---|---|---|
| **Recommended Starting Dosage** | 12 mg once daily (12 mg per day) for both TD and HD | 6 mg twice daily (12 mg per day) for HD and TD |
| **Recommended Dose Titration** | The dosage of AUSTEDO XR/AUSTEDO may be increased at weekly intervals in increments of 6 mg per day based on reduction of chorea or tardive dyskinesia, and tolerability, up to a maximum recommended daily dosage of 48 mg | |
| **Important Administration Instructions** | • Administer AUSTEDO XR with or without food.<br>• Swallow AUSTEDO XR whole. Do not chew, crush, or break tablets.<br>• Administer AUSTEDO XR once daily. | • Administer AUSTEDO with food.<br>• Swallow AUSTEDO whole. Do not chew, crush, or break tablets.<br>• Administer AUSTEDO total daily dosages of 12 mg or above in two divided doses. |

The deuteration of TBZ attenuates metabolic breakdown of the active metabolites mediated by cytochrome P450 2D6 (CYP2D6) enzyme and confers important PK advantages (e.g., longer half-life of the active metabolites and less PK variability) relative to TBZ. The mechanism by which TBZ and deutetrabenazine (mainly their active metabolites) exert their pharmacological effects is attributed to their function as a reversible vesicular monoamine transporter type 2 (VMAT2) inhibitor depleting monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. More details about the general clinical pharmacology properties of AUSTEDO please refer to the Clinical Pharmacology review conducted by Hristina Dimova documented in DARRTS on 04/13/2016.

This current submission is a 505(b)(2) application for an extended-release tablet in a bilayer osmotic drug delivery system (AUSTEDO XR), with reliance on the FDA's previous finding of the safety and effectiveness of AUSTEDO (NDA 208082 and NDA 209885) as the reference. The proposed dosage of AUSTEDO XR is same as that of AUSTEDO in term of total daily dose and maximum daily dose (48mg). The formulation allows once daily administration (QD) and is expected to improve patient and caregiver compliance.

In the End-of-Phase 2 (EOP2) meeting (submitted in IND 112975) held on Mar 31, 2020, the Agency recommended that the relative BA between the proposed QD product and the reference product might use the steady state exposure for both parent and active metabolites as the primary analysis to support the bridge. In addition, for multi-strength product development, a single dose dosage strength equivalence/proportionality study was recommended. In the type C meeting held in Nov 2020, the selection of the analytes (i.e., active metabolites vs parent drug) for PK comparisons and the shape difference in PK profiles (QD vs BID) for comparative bioavailability analysis were further discussed and the Agency stated that the PK bridge would be evaluated based on the totality of the data. In the pre-NDA meeting occurred in Feb 2022, the Agency agreed with the overall clinical pharmacology package to support the NDA submission and indicated that adequacy of submission would be a matter of review of NDA.

In this NDA submission, the to-be-marketed formulation of the proposed QD product was evaluated in a relative BA study at steady state (QD 24 mg vs 2*12 mg BID) (Study TV50717-BE-10179) and after single dose (Study TV50717-BE-10165). The food effect was also evaluated in Study TV50717-BE-10165 to assess the effect of a high fat meal on the PK of the parent and the active metabolites. The dose proportionality was evaluated in a single dose BA study (TV50717-BE-10175) under fed condition. In addition, the development history of the formulations included 7 Phase 1 clinical studies in which several pilot formulations were evaluated. The clinical pharmacology studies to support this NDA approval are summarized in **Table 2**.

**Table 2** Clinical pharmacology studies included in the NDA submission

| Study # | Study Title | Brief Description |
|---|---|---|
| TV50717-BE-10179 * | An Open-label, Randomized, Repeated Dose, 2-Treatment, 2-Period, 2-Sequence Crossover Study with Full Replicate Design in Healthy Subjects to Assess the Bioequivalence and Relative Bioavailability at Steady State Between Once Daily Administration of a 24-mg | To assess steady state relative BA between the proposed QD product and the reference BID product |
| TV50717-BE-10165 * | An Open-label, Randomized, 3-Period, 3-Treatment, 6-Sequence Study in Healthy Subjects to Compare the BA of TEV-50717 and its Active Metabolites between a Single Dose of TEV-50717 24-mg Tablet and a Single AUSTEDO 12-mg Tablet Administered Twice 12 Hours Apart and to Evaluate the Effect of Food on the Pharmacokinetics Following a Single TEV-50717 24-mg Osmotic Tablet. | To assess single dose relative BA between the proposed QD product and the BID product and the food effect for the QD product |

| | | |
|---|---|---|
| **TV50717-PK-10175 *** | **An Open-label, Randomized, Single Dose, 4-way, 4-sequence, Crossover Study in Healthy Subjects to Assess the Dose Proportionality of 6 mg, 12 mg, and 24 mg Extended-Release Tablets of TEV-50717 in the Fed State Over the Clinical Dose Range (6-48 mg) Administration of a 12-mg AUSTEDO Tablet Volunteers** | **To assess dose proportionality under fed condition** |
| TV50717-BE-10150 | An Open-label, Randomized, 2-Part, 3-Period, 6-Sequence, Crossover Study to Assess the Comparative Bioavailability of Four Different 24 mg TEV-50717 Once Daily Formulations Following Single Dose Administration Compared to a Single 12 mg AUSTEDO®1 Tablet Administered Twice 12 Hours Apart in Healthy Subjects | To assess relative BA between the pilot QD formulations of 24 mg and the BID product |
| TV50717-BE-10158 | An Open-label, Randomized, 2-Part, 3-Period, 6-Sequence, Crossover Study to Assess the Comparative Bioavailability of Four Different TEV-50717, either 18 or 24 mg, Once Daily Formulations Following Single Dose Administration Compared to a Single 12 mg AUSTEDO®[1] Tablet Administered Twice 12 Hours Apart in Healthy Subjects. | To assess rBA between the pilot QD formulations of 18 and 24 mg and the BID product |
| TV50717-FE-10163 | An open label, randomized, two-way crossover study to evaluate the effect of food on pharmacokinetics of TEV-50717 (deutetrabenazine) ER tablet, 24 mg in healthy human, adult male and female subjects an osmotic tablet pilot formulation in the fasting and fed conditions. | To assess food effect for the pilot QD formulations of 24 mg |
| TV50717-BE-10166 | An Open-label, Randomized, Repeated Dose, 2-Treatment, 2-Period, 2-Sequence Crossover Study with Full Replicate Design in Healthy Subjects to Assess the Bioequivalence and Relative Bioavailability of Once Daily Administration of a 24 mg Osmotic Tablet of TEV 50717 Compared to Twice Daily Administration of a 12 mg AUSTEDO® | To assess rBA at steady state for a pilot QD formulations of 24 mg compared to the BID product |
| TV50717-BA-10171 | An open label, randomized, two-way crossover study in the fed state to assess the pharmacokinetics of TEV-50717 and its active metabolites after single and repeated oral doses and to assess the relative bioavailability between an extended release once-daily pilot formulation (osmotic tablet) and AUSTEDO tablet administered twice daily in healthy volunteers. | To assess rBA at single dose and steady state for a pilot QD formulations of 24 mg compared to the BID product |
| TV50717-BA-10172 | An open-label, randomized, two-way crossover study in the fed state to assess the pharmacokinetics of TEV-50717 and its active metabolites after single and repeated oral doses and to assess the relative bioavailability between a second extended release once-daily pilot formulation (osmotic tablet) and AUSTEDO tablet administered twice daily in healthy volunteers (Pilot 2). | To assess rBA at single dose and steady state for a pilot QD formulations (Pilot 2) of 24 mg compared to the BID product |
| TV50717-BA-10176 | An open-label, randomized, 2-way crossover study in the fed state to assess the pharmacokinetics of TEV-50717 and its active metabolites after single and repeated oral doses and to assess the relative bioavailability at steady state between a third extended release once-daily pilot formulation (osmotic tablet) and AUSTEDO tablet administered twice daily in healthy volunteers (Pilot 3). | To assess rBA at single dose and steady state for a pilot QD formulation (Pilot 3) of 24 mg compared to the BID product |
| TV50717-BA-10176 | A Phase 1 Study to Evaluate the Pharmacokinetics of Two Extended Release (ER) Formulations of SD-809 with and without Food, compared to Tetrabenazine Tablets and the pharmacokinetics and Dose Proportionality of the Selected Formulation Following Single and Multiple Doses | To assess PK of two candidate ER formulation of deutetrabenazine and food effect compared to the BID product |

Note: *, the studies in bold were conducted with the to-be-marketed formulation of the QD product.
Source: Reviewer's summary

# 3. Summary of Pivotal Evidence of Effectiveness

## 3.1 Overview of the Information to Support Evidence of Effectiveness

To support the reliance on the FDA's previous finding of the safety and effectiveness of AUSTEDO® (NDA 208082 for HD and NDA 209885 for TD as the reference drug), the scientific bridge between the proposed AUSTEDO® XR (QD product) and the approved AUSTEDO® (BID product) was established primarily through the pivotal relative BA study conducted at steady state. The exposure-response (E-R) analyses was used to demonstrate that the differences in the exposure (i.e., the $C_{max}$ difference for the two active metabolites), along with the efficacy results from a switch cohort (TBZ to AUSTEDO) to justify that PK curve shapes are unlikely clinically relevant.

The pivotal relative BA study (TV50717-BE-10179) was designed as an open-label, randomized, 2-period, 2-sequence, crossover repeated dose study in healthy subjects under fed condition (as the reference drug is labeled to be administered under fed condition), to compare the PK of deutetrabenazine (parent) and the active metabolites at steady state between the test formulation (AUSTEDO® XR, 24 mg QD) and the approved AUSTEDO® 12 mg administered BID. As the QD product releases the drug in a controlled manner, the PK curves resulted from the QD product are generally flatter (or smoother) than those from the BID product. Based on the BE analysis, the geometric ratio (GMR: T/R) and the 90%CI for $AUC_{0\text{-}24h,ss}$ ,and $C_{max,ss}$ of the parent drug at steady state met the standard BE criteria. The $C_{trough,ss}$ of the parent drug from the QD product was higher than that of the reference product (as shown by the GMR of $C_{trough,ss}$ 144 % with 90%CI 135.3%-155.5%), indicating the QD product is non-inferior in term of the parent drug's $C_{trough,ss}$ compared to the BID product. For the two active metabolites (individually and as a sum), the 90% CI of the GMR for $AUC_{0\text{-}24h,ss}$ and $C_{trough,ss}$ were within the BE criteria (80-125%), while the GMR of the $C_{max}$ were slightly below 80%, in a range of 74%-79% as shown in **Table 3**.

The differences in the $C_{max,ss}$ of the active metabolites were further evaluated by previously developed E-R models using total (α+β)-HTBZ concentrations as the predictor of efficacy for both TD and HD indications under the conservative assumption that $C_{max}$ is the main driver of the efficacy. Simulation results suggested that the $C_{max,ss}$ difference of the active metabolite would lead to an average of 13% decrease in change of AIMS score from baseline in TD subjects and 11% decrease in change of the UHDRS-TMC score from the baseline in HD subjects, when compared to the BID product. Such a small decrease in the efficacy endpoints is considered not clinically meaningful. Moreover, the small difference in $C_{max}$ may not impact the efficacy considerably in the clinical use, as AUSTEDO XR (and also AUSTEDO) dosage is individually titrated in each patient based on clinical efficacy and tolerability. The titration strategy results in a wide range of doses

and exposure levels which proved to be efficacy and safe. The effective exposure range resulted from AUSTEDO brackets the PK exposures from the AUSTEDO XR product.

The clinical relevance of the PK shape difference (as well as the $C_{max}$ difference of active metabolites) was further assessed in an open label extension long-term safety study (Study SD-809-C-16) which used to support the AUSTEDO approval in NDA 208082 for the HD indication. Study SD-809-C-16 included a switch cohort consisting of 37 patients with chorea associated with HD who were switched from TBZ to AUSTEDO overnight. Prior to the switch to AUSTEDO BID, the patients were treated with stable dosing regimens of TBZ which varied in total daily dose (ranging from 12.5 mg to 100 mg) and doing frequency (TID, BID and QD) across patients. After the switch, the patients received AUSTEDO in approximately half the dose (in mg) compared to TBZ, administered 6 mg once daily or a total daily dose ≥ 12 mg twice daily to provide comparable exposure to total (α+β)-HTBZ metabolites relative to the prior TBZ dose.

Although the switch in the drug and dosing regimens would result in a wide range of PK profiles in HD subjects, a comparable $AUC_{0\text{-}24h}$ of total (α+β)-HTBZ metabolites relative to the prior TBZ dose was expected after the switch. The efficacy measures in this switch cohort showed that efficacy was maintained at one week after the switch, indicating the difference in PK shape (as well as $C_{max}$ change) might not be clinically meaningful as long as similar PK exposures were achieved. For more details please refer to 5.3 Pharmacometric Review.

Furthermore, the Applicant demonstrated dose proportionality for all the strengths of the proposed QD product (6 mg, 12 mg and 24 mg) as well as dosage strength equivalence between 2*6 mg and 1*12 mg, supporting the dosing recommendations for the QD tablets follow the same titration schedule as the commercially available AUSTEDO BID tablets. Hence, the proposed dose strengths of the QD product allows appropriate dose conversions from the BID product. More details about dose proportionality assessment please refer to Section 4.2 Dose Proportionality Assessment.

Overall, an adequate scientific bridge was established for the proposed QD product (AUSTEDO XR, 6 mg, 12 mg and 24 mg) to rely on the labeling information, including the safety and efficacy, of the reference product, AUSTEDO tablets, 6 mg, 9 mg and 12 mg.

## 3.2 Summary of Relative Bioavailability at Steady State

***Overall Study Design and Methodology:***

The relative BA between AUSTEDO XR and AUSTEDO at steady state under fed condition was evaluated in an open-label, randomized, 2-period crossover study (Study TV50717-BE-10179) with 2 treatment periods either 7-day treatment of AUSTEDO 12 mg BID as the reference (R) or 7-day treatment of AUSTEDO XR 24 mg QD as the Test (T) separated by a 6-day washout period. The study was conducted under fed condition to

match the dosing recommendations for the reference product. The study was conducted in healthy subjects with functional CYP2D6 metabolizer genotype to reduce the PK variability, since the two active metabolites are primarily eliminated by hepatic metabolism mediated by CYP2D6. Frequent blood samples were collected on both Days 6 and 7 of each treatment period to determine the plasma concentrations of TEV-50717 (parent) and the two active HTBZ metabolites for PK comparisons. On both sampling days, the treatment was given after a standardized high-calorie, high-fat breakfast.

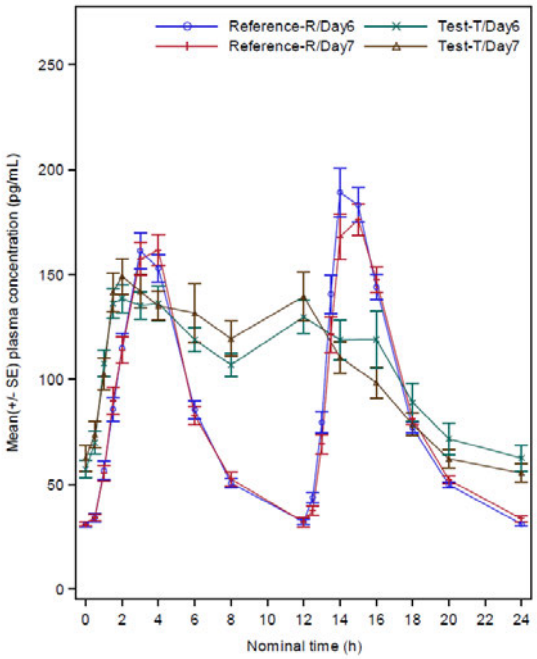
To assess the relative BA and BE at steady state between the test and the reference products, plasma exposure of TEV-50717 (parent), α-HTBZ, β-HTBZ, and total (α+β)-HTBZ metabolites in both sampling days, as characterized by $AUC_{0\text{-}24h,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ was determined and compared utilizing BE criteria. More details about the study design and method please refer to 5.2 Summary for Pivotal Relative BA study at Steady State**.**

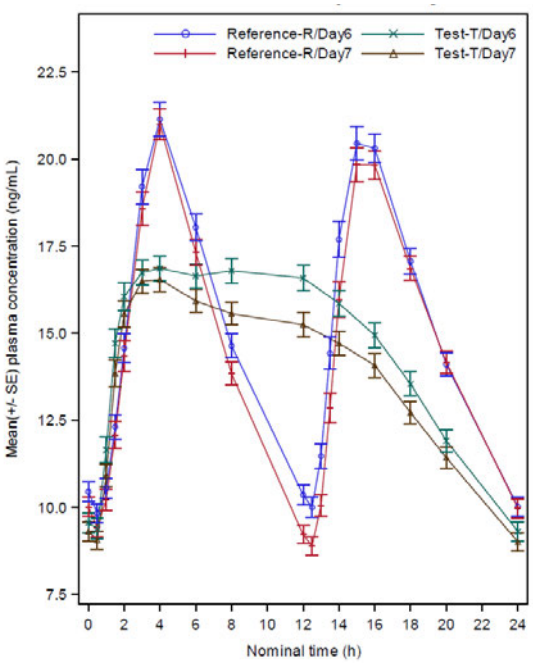
***Summary of PK Results***

A total of 262 subjects were enrolled and randomized, and 258 subjects were included for PK analysis in which PK data of 241 subjects were available for the test (QD) treatment and for the reference (BID) treatment. Mean plasma concentration-time profiles of TEV-50717 (parent) and total (α+β)-HTBZ for the test (QD) and reference (BID) formulations measured at steady state (Days 6 and 7) after administration of TEV-50717 are presented in **Figure 1**. The attainment of steady state was confirmed by comparing trough levels ($C_{trough}$) on Days 4, 5, and 6 for all the analytes using a simple linear regression method (based on the significance of the slope). Based on the results, steady state for all the analytes was reached by Day 6 in more than 90% of the subjects. The steady state also reflects in the overlap of the PK profiles of Day 6 and Day 7 as shown in **Figure 1**.

**Figure 1** Mean Plasma Concentrations (±SD) vs Time of the Parent and Active Metabolites (as Individual and Total) at Steady State

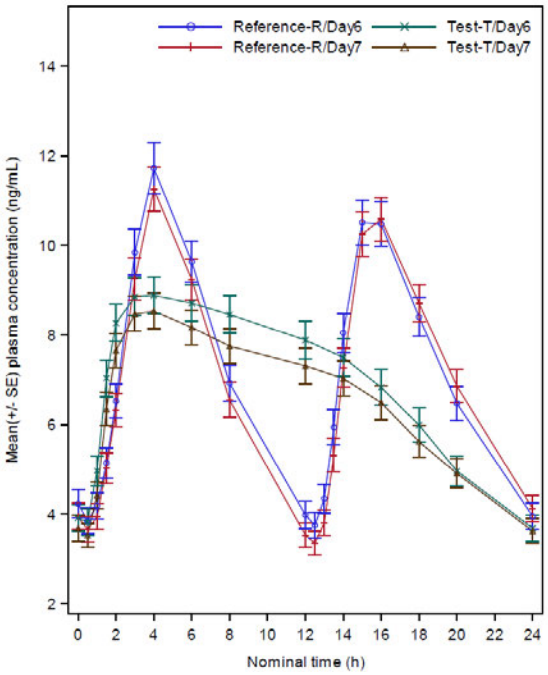
A: Parent (TEV-50717) B: α-HTBZ

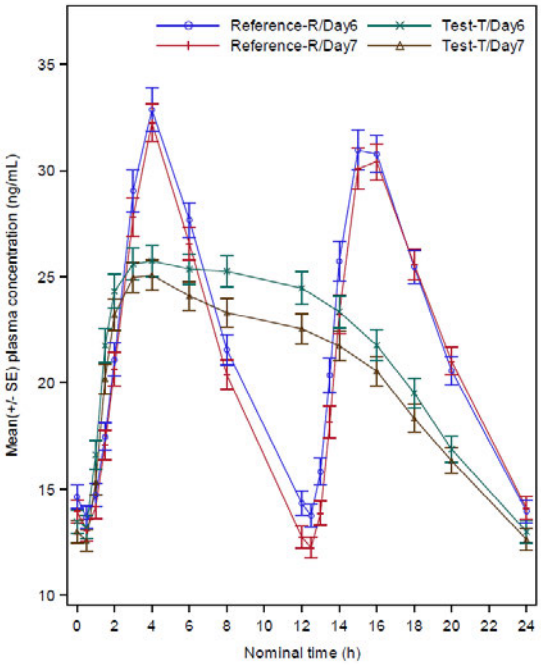



C: β-HTBZ

D: total (α+β)-HTBZ




Source: Clinical Study Report for Study TV50717-BE-10179, Figure 15.1.1 Page 72 \\CDSESUB1\EVSPROD\nda216354\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\tv50717-be-10179\report-body.pdf

In general, the shape of the PK profiles was smoother over the 24 hours for the test (QD) formulation as compared to the reference (BID). It reflected in a relatively flat plateau of plasma concentrations of the parent and the active metabolites for several hours in the

curves of the QD formulation after reaching $C_{max}$. The QD product resulted in a slightly lower geometric mean $C_{max,ss}$ for the active metabolites and a higher geometric mean $C_{trough,ss}$ for the parent drug, compared to the exposure of the BID product. The $T_{max}$ of the test product was similar as that of the reference, probably because the $T_{max}$ was contributed mainly by the absorption of TEV-50717 (parent) released by the immediate release portion of the osmotic bilayer tablets.

***Bioequivalence Assessment***

The Applicant claimed this study was a fully replicate design since PK samples were collected on two consecutive days (Day 6 and Day 7) for each treatment period (Test and Reference). However, in principle, this is not a typical fully replicated design in which each subject should be studied in four periods and receives each formulation (T:Test and R:Reference) twice over the course of the study (e.g., TRTR and RTRT). Since the PK within-subject standard deviation of the reference product (SWR) was <0.294 (in the range of 0.060-0.286 for $AUC_{0-24h,ss}$, $C_{max,ss}$, and $C_{trough,ss}$ of both the parent and metabolites), the classical 2 one-sided tests procedure was used to determine bioequivalence. The analyses were performed on ln-transformed parameters using a linear mixed effects model with fixed effects for treatment, sequence, period and day, and subject as a random effect. The results of the statistical analysis of $AUC_{0-24h,ss}$ and $C_{max,ss}$ assessing the BE of the TEV-50717 24 mg QD (test) and the AUSTEDO 12 mg BID (reference) are presented in **Table 3**.

Based on the results of the parent drug's PK, $C_{max,ss}$ and $AUC_{0-24h,ss}$ are similar between the test and reference products, meeting the BE criteria as shown in 90%CI range of GMR between 80-125%. For the two major active metabolites (individually and as a sum), the $C_{max,ss}$ for the test product is slightly smaller than those of the reference, although $AUC_{0-24h,ss}$ met the BE criteria. The GMRs of $C_{max,ss}$ T/R for active metabolites were smaller than 80% (in the range of 74.8%-77.7%), not meeting the BE criteria (**Table 3**). The clinical relevance of $C_{max,ss}$ difference of the active HTBZ metabolites as well as the PK shape difference was further evaluated by the E-R analyses which presented in section **3.3** .

Very similar BE results were obtained by the reviewer's independent BE analysis using the same statistical analysis method as the Applicant (treatment days treated as a fixed effect) or using the data of Day 7 (data are not shown).

***Conclusion***

The PK results indicated that the PK parameters' within-subject standard deviation of the reference product (SWR) was less than the limit of 0.294; therefore, the average BE approach was used for the BE analysis. Overall, the PK comparisons between the QD product and the BID product indicate that the standard BE criteria (GMR 90% CI within 80-125%) is met for $AUC_{0-24h,ss}$ for all the analytes. The $C_{trough,ss}$ of the active metabolites

meets BE criteria and the $C_{trough,ss}$ of parent drug is non-inferior compared to AUSTEDO. Although the $C_{max}$ met the standard BE criteria for the parent drug, the GMR of $C_{max}$ for the active metabolites (individually and as a sum) are slightly outside of the BE lower bound limit (i.e., 80%).

**Table 3**: Bioequivalence assessment of PK parameters at steady state between the test QD formulation (24 mg) and the reference BID formulation (2*12 mg) in Study TV50717-BE-10179 (Reviewer's analysis)

| Analyte | Treatment | n | GeoMean | Comparison | GeoMean Ratio (%) | 90% CI lower | 90% CI upper |
|---|---|---|---|---|---|---|---|
| Parent | $AUC_{0-24h,ss}$ (pg*hr/mL) | | | | | | |
| | A: Test (QD) | 239 | 2087.5 | T/R | 115.2 | 110.4 | 120.3 |
| | B: Reference (BID) | 235 | 1811.5 | | | | |
| | $C_{max,ss}$ (pg/mL) | | | | | | |
| | A: Test (QD) | 239 | 183.4 | T/R | 95.0 | 90.5 | 99.7 |
| | B: Reference (BID) | 236 | 193.1 | | | | |
| | $C_{trough,ss}$ (pg/mL) | | | | | | |
| | A: Test (QD) | 239 | 42.2 | T/R | 144.1 | 135.3 | 155.5 |
| | B: Reference (BID) | 235 | 29.3 | | | | |
| α-HTBZ | $AUC_{0-24h,ss}$ (ng*hr/mL) | | | | | | |
| | A: Test (QD) | 239 | 320.3 | T/R | 95.4 | 94.2 | 96.7 |
| | B: Reference (BID) | 235 | 335.7 | | | | |
| | $C_{max,ss}$ (ng/mL) | | | | | | |
| | A: Test (QD) | 239 | 18.16 | T/R | 79.5 | 78.2 | 80.9 |
| | B: Reference (BID) | 236 | 22.82 | | | | |
| | $C_{trough,ss}$ (ng/mL) | | | | | | |
| | A: Test (QD) | 239 | 8.3 | T/R | 90.1 | 89.1 | 92.6 |
| | B: Reference (BID) | 235 | 9.1 | | | | |
| β-HTBZ | $AUC_{0-24h,ss}$ (ng*hr/mL) | | | | | | |
| | A: Test (QD) | 239 | 320.3 | T/R | 94.1 | 92.4 | 96.0 |
| | B: Reference (BID) | 235 | 335.7 | | | | |
| | $C_{max,ss}$ (ng/mL) | | | | | | |
| | A: Test (QD) | 239 | 8.6 | T/R | 74.8 | 73.1 | 76.6 |
| | B: Reference (BID) | 236 | 11.6 | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | $C_{trough,ss}$ (ng/mL) | | | | | | |
| | A: Test (QD) | 239 | 2.4 | T/R | 88.3 | 85.6 | 91.1 |
| | B: Reference (BID) | 235 | 2.7 | | | | |
| **Total (α+β)-HTBZ** | $AUC_{0-24h,ss}$ (ng*hr/mL) | | | | | | |
| | A: Test (QD) | 239 | 453.5 | T/R | 95.1 | 93.7 | 96.5 |
| | B: Reference (BID) | 235 | 477.1 | | | | |
| | $C_{max,ss}$ (ng/mL) | | | | | | |
| | A: Test (QD) | 239 | 26.9 | T/R | 77.7 | 76.3 | 79.1 |
| | B: Reference (BID) | 236 | 34.6 | | | | |
| | $C_{trough,ss}$ (ng/mL) | | | | | | |
| | A: Test (QD) | 239 | 10.9 | T/R | 90.2 | 88.3 | 92.2 |
| | B: Reference (BID) | 235 | 12.1 | | | | |

Source: Reviewer's analysis based on PK parameter data submitted in \\CDSESUB1\evsprod\nda212304\0028\m5\datasets\cl-p-20003\analysis\adam\datasets\adpp.xpt

## 3.3 Clinical Relevance of the PK Differences Between QD and BID

AUSTEDO QD product have shown lower $C_{max,ss}$ (~22% lower for total active metabolite) and different PK profile shapes when compared to the BID product (**Figure 1** and **Table 3**). The clinical relevance of these PK differences was evaluated as follows:

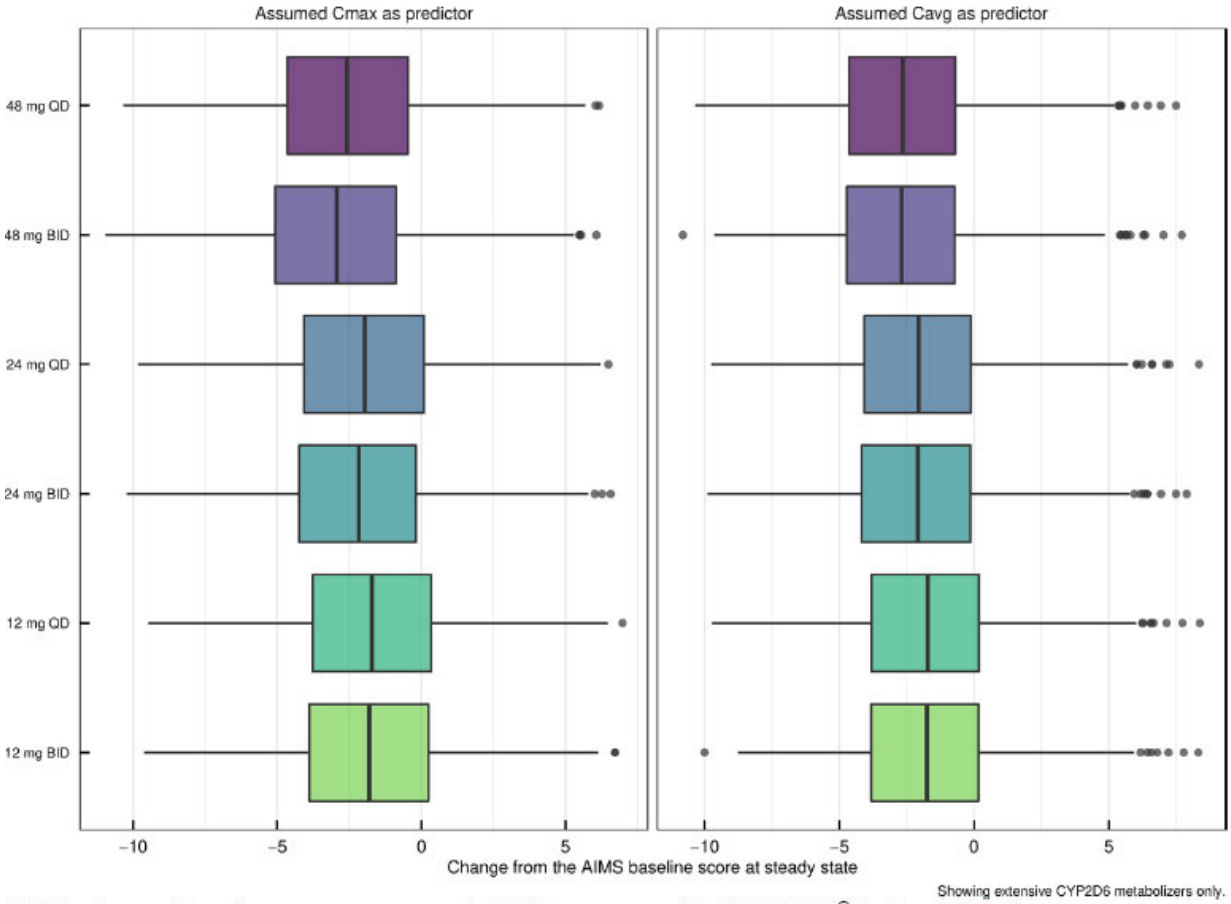
***Impact of lower $C_{max,ss}$ on efficacy***

The clinical relevance of the differences in $C_{max,ss}$ observed between the AUSTEDO BID and to-be-marketed QD product in TD and HD subjects was evaluated using population PK and E-R analysis. The population PK analysis was used to characterize the PK data from Study TV50717-BE-10175 (dose proportionality study) and Study TV50717-BE-10179 (steady state rBA study). The developed PK model was then used to predict and compare PK exposures at steady state between the QD and BID products. For the total daily dose of 48 mg, the QD product resulted in 9% lower $C_{min,ss}$ (BID: 23.52 ng/mL vs. QD: 21.39 ng/mL), 9% lower $C_{avg,ss}$ (BID: 41.37 ng/mL vs. QD: 37.63 ng/mL), and 26% lower $C_{max,ss}$ (BID: 66.83 ng/mL vs. QD: 49.49 ng/mL) of total (α+ β)-HTBZ concentrations at the mean level when compared to the BID product.

The $C_{max,ss}$ of total (α+ β)-HTBZ concentrations was used to predict change from baseline (CFB) in AIMS score in TD subjects and CFB in UHDRS-TMC in HD subjects using the E-R model. Briefly, linear E-R models were developed previously to characterize the E-R relationships in both TD and HD subjects based on AUSTEDO dosing. The Emax models

did not lead to any meaningful improvement of the fit as compared to the linear model, and suggested over-parameterization, especially for the model with Cmax as predictor. Thus, the most parsimonious (linear model) was used. Of note, high correlation in the different exposure parameters (i.e., $C_{min}$, $C_{max}$, $C_{avg}$ and $C_{avg,all}$) from the BID product at Week 12 did not allow the confirmation of the main driver of efficacy. As lower $C_{max,ss}$ of the QD product as compared to the BID product was a key concern, $C_{max.ss}$ was used as the predictor of efficacy endpoints. Assuming $C_{max,ss}$ as a main driver of efficacy, for a total daily dose of 48 mg, the QD product would lead to an average of 13.4% lower CFB in AIMS scores (**Figure 2**) in TD and 11% lower CFB in UHDRS scores (**Figure 3**) in HD subjects when compared to the BID product. Please refer to Appendix 5.3 Pharmacometrics Review for more details on PK and E-R models.

**Figure 2*:*** Overview of the change from baseline in AIMS score at steady state in extensive CYP2D6 metabolizers between the BID and QD formulations




AIMS: abnormal involuntary movement scale, BID: treatment with AUSTEDO® (twice daily), $C_{avg}$: average total (α+β)-HTBZ concentration at steady-state, $C_{max}$: maximum total (α+β)-HTBZ concentration at steady-state, QD: treatment with once daily tablet formulation.

**A. Cmax,ss as predictor**

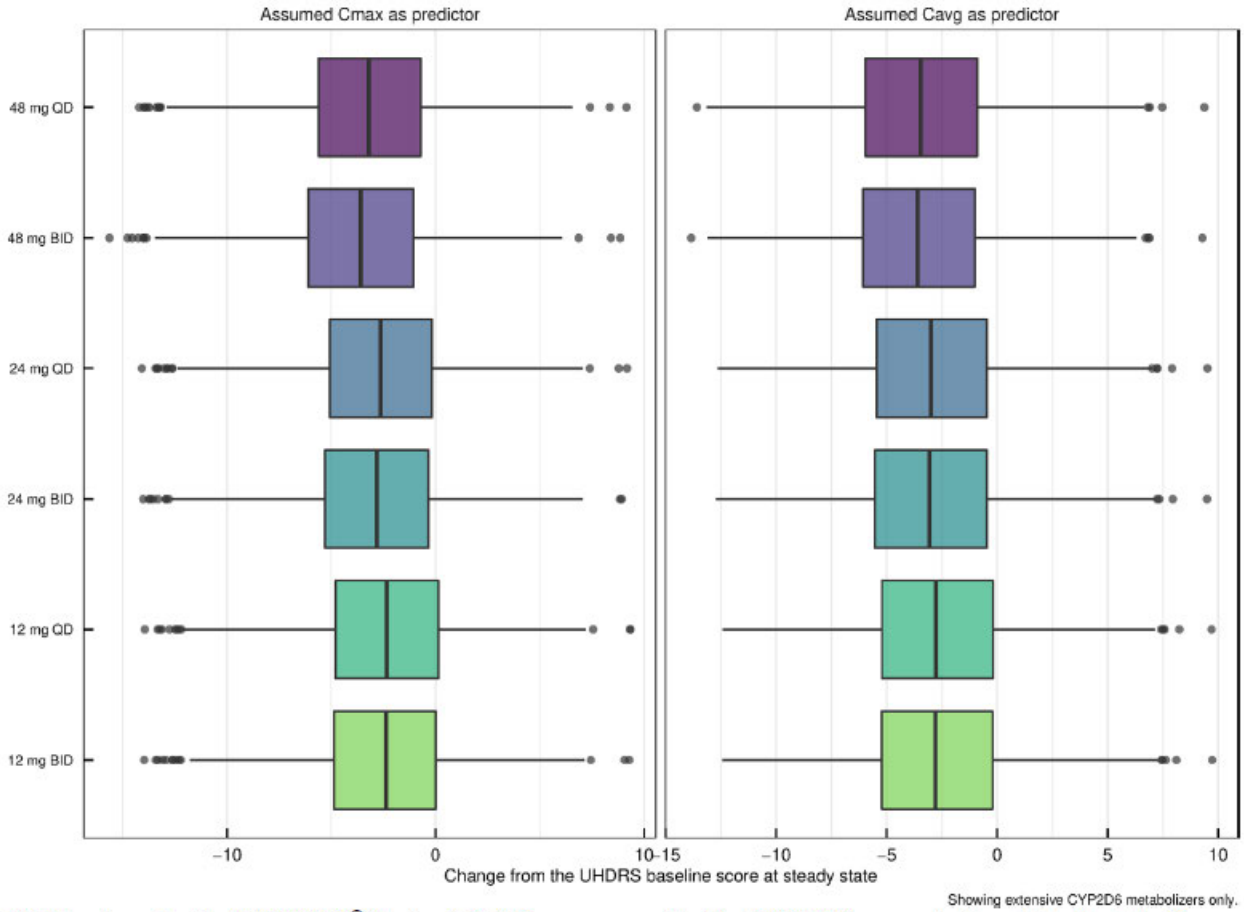
| Total daily dose | CHGBL AIMS [BID Cmax,ss] | CHGBL AIMS [QD Cmax,ss] | QD-vs-BID CHGBL AIMS [%BID] |
|---|---|---|---|
| 12 mg | -1.8 [-6.93, 3.34] | -1.71 [-6.84, 3.42] | -5.12% |
| 24 mg | -2.17 [-7.31, 3.01] | -1.98 [-7.2, 3.22] | -8.69% |
| 48 mg | -2.94 [-8.02, 2.21] | -2.54 [-7.74, 2.67] | -13.4% |

### B. Cavg,ss as predictor

| Total daily dose | CHGBL AIMS [BID Cavg,ss] | CHGBL AIMS [QD Cavg,ss] | QD-vs-BID CHGBL AIMS [%BID] |
|---|---|---|---|
| 12 mg | -1.75 [-6.6, 3.1] | -1.72 [-6.5, 3.21] | -1.55% |
| 24 mg | -2.06 [-6.85, 2.96] | -2 [-6.8, 2.87] | -2.72% |
| 48 mg | -2.68 [-7.42, 2.27] | -2.57 [-7.35, 2.45] | -4.21% |

Simulated values are reported as mean [5% quantile, 95% quantile].
**Source:** PMX-21-14-Ver-01, Page 80-81

**Figure 3:** Overview of the change from baseline in UHDRS Score at steady state in extensive CYP2D6 metabolizers between the BID and QD formulations




BID: treatment with AUSTEDO® (twice daily), $C_{avg}$: average total (α+β)-HTBZ concentration at steady-state, $C_{max}$: maximum total (α+β)-HTBZ concentration at steady-state, QD: treatment with once daily tablet formulation, UHDRS: Unified Huntington's Disease Rating Scale.

### C. Cmax,ss as predictor

| Total daily dose | CHGBL UHDRS [BID Cmax,ss] | CHGBL UHDRS [QD Cmax,ss] | QD-vs-BID CHGBL UHDRS [%BID] |
|---|---|---|---|
| 12 mg | -2.42 [-8.5, 3.69] | -2.33 [-8.46, 3.71] | -3.8% |
| 24 mg | -2.8 [-8.89, 3.33] | -2.61 [-8.74, 3.35] | -6.75% |
| 48 mg | -3.56 [-9.72, 2.61] | -3.17 [-9.29, 2.94] | -11% |

**D. Cavg,ss as predictor**

| Total daily dose | CHGBL UHDRS [BID Cavg,ss] | CHGBL UHDRS [QD Cavg,ss] | QD-vs-BID CHGBL UHDRS [%BID] |
|---|---|---|---|
| 12 mg | -2.67 [-8.66, 3.46] | -2.65 [-8.57, 3.48] | -0.891% |
| 24 mg | -2.95 [-8.85, 3.16] | -2.9 [-8.8, 3.23] | -1.68% |
| 48 mg | -3.5 [-9.37, 2.68] | -3.4 [-9.24, 2.8] | -2.85% |

Simulated values are reported as mean [5% quantile, 95% quantile].
**Source:** PMX-21-14-Ver-01, Page 82-83

***Impact of different PK shapes on efficacy***

The QD product is expected to have a different PK profile shape when compared to BID formulations. The impact of PK shape on efficacy was evaluated based on efficacy results from a switch cohort of an open label extension long-term safety study (Study SD-809-C-16).Briefly, the SD-809-C-16 open-label long-term extension study in HD comprised of two cohorts, a rollover from the SD-809-C-15 efficacy study to long-term safety and tolerability, and a switch from a stable dose of XENAZINE to AUSTEDO BID for evaluating efficacy, long-term safety, and tolerability. Focusing on the switch cohort, 37 HD subjects with chorea switched overnight from XENAZINE to a dosing regimen of AUSTEDO predicted to provide comparable exposures to total (α+β)-HTBZ metabolites (**Table 4**). No dose adjustment was allowed during the first week after the switch.

The purpose of this analysis was to simulate and compare the active metabolite concentration profiles following the actually used dosing regimens in the study SD-809-C-16 and compare with AUSTEDO BID concentration profile using previously developed PK model of tetrabenazine. As XENAZINE dosage were initiated by titration, the PK profiles of the active metabolites from the XENAZINE dose regimens (prior to the switch) in Switch cohort of the study SD-809-C-16 showed a wide range of distribution. Simulated PK profiles of total (α+β)-HTBZ from XENAZINE (12.5 mg QID) comparing to the AUSTEDO product for 50 mg/day (25 mg BID) are shown in **Figure 4**, which suggested comparable daily AUC but lower $C_{max}$ after switching to AUSTEDO BID.

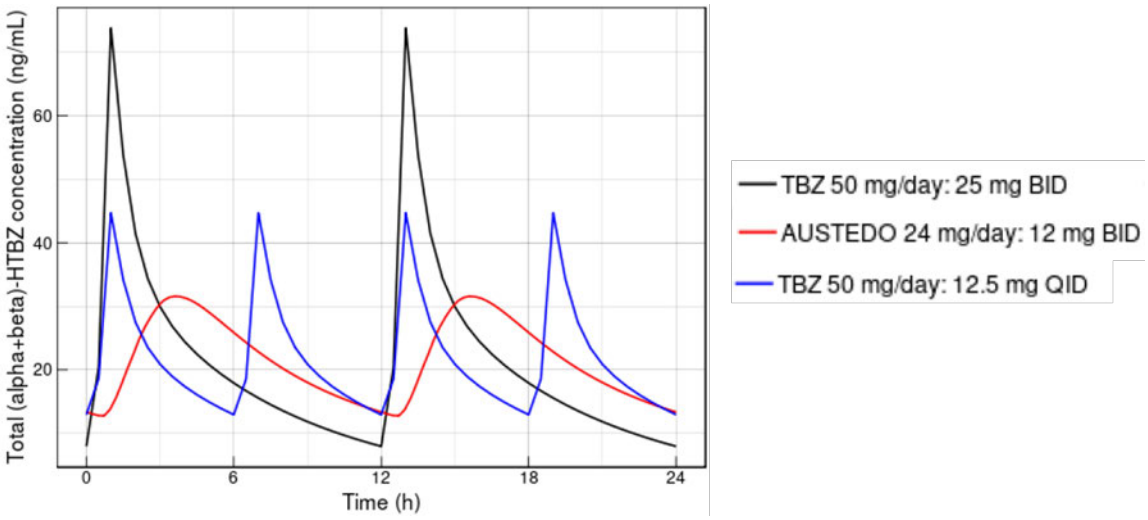
However, the efficacy was maintained post-one week of switch in these HD subjects (**Figure 5**): the mean (SD) TMC score at baseline and at Week 1 post-switch was 12.46 (5.22) and 11.76 (5.11), respectively. This suggested that chorea control was maintained as long as concentrations are in the range of previously approved dosing regimens, and differences in PK profile shapes and $C_{max}$ may have no impact on efficacy.

**Table 4**: Tetrabenazine Doses (Pre-Switch) and AUSTEDO Doses (Post-Switch) in Huntington Disease (SD-809-C-16) Switch Cohort

| Total daily dose (mg) | XENAZINE (Pre-Switch) | AUSTEDO (Post-Switch) | |
|---|---|---|---|
| | Regimen | Total daily dose (mg) | Regimen |
| 12.5 (N=3) | 12.5mg QD (N=3) | 6 | QD |
| 18.75 (N=1) | 6.25mg TID (N=1) | 6 | QD |
| 25 (N=7) | 12.5mg BID (N=7) | 12 | BID |
| 37.5 (N=10) | 37.5mg QD (N=1), 12.5mg TID (N=7), 12.5mg QD and 25mg QD (N=2) | 18 | BID |
| 50 (N=11) | 25mg BID (N=8), 12.5mg QID (N=2), 25mg QD and 12.5mg BID (N=1) | 24 | BID |
| 75 (N=4) | 37.5mg BID (N=1), 25mg TID (N=3) | 36 | BID |
| 100 (N=1) | 37.5mg BID and 25mg QD (N=1) | 48 | BID |

**Source:** PMX-22-09, Page 9, Table 1

**Figure 4**: Concentration-time profiles of simulated total (α+β)-HTBZ from tetrabenazine comparing to the Switched AUSTEDO BID Formulation for 50 mg/day Tetrabenazine (12.5 mg QID and 25 mg BID)




| Regimen | Exposure | | | |
|---|---|---|---|---|
| | $C_{min}$ (ng/mL) | $C_{av}$ (ng/mL) | $C_{max}$ (ng/mL) | $AUC_{0-24h}$ (ng·h/mL) |
| Tetrabenazine 25 mg BID | 7.933 | 21.901 | 73.841 | 525.615 |
| Tetrabenazine 12.5 mg QID | 12.922 | 21.906 | 44.693 | 525.742 |
| AUSTEDO BID 12 mg BID | 12.741 | 21.596 | 31.570 | 518.305 |

**Source:** PMX-22-09, Page 9, Table 1

**Figure 5**: Open-label Huntington Disease (SD-809-C-16) Switch Cohort- total maximal Chorea Scores at Baseline and Week 1 in 37 subjects who switched from tetrabenazine

to a dosing regimen of AUSTEDO predicted to provide comparable exposures to total (α+β)-HTBZ metabolites


**Source:** Summary of Clinical Efficacy, Page 40, Figure 6

# 4. Summary of Food Effect and Dose Proportionality Assessments

## 4.1 Food Effect Assessment

Study TV50717-BE-10165 was conducted to assess the food effect for the proposed QD product (TEV-50717 24 mg ER osmotic tablet) in healthy volunteers after a single dose under fasted and fed condition, along with the single-dose relative BA assessment between the QD and the BID products. For the fasted condition assessment, subjects began fasting at least 10 hours prior to dosing, and continued to fast for a minimum of 4 hours after dose intake (fasted condition). For the fed assessment, TEV-50717 (24 mg ER osmotic tablet) was administered after a standardized high-calorie, high-fat breakfast in the morning of each administration day.

A total of 87 subjects were enrolled into the study with 84 subjects' data available for food effect assessment. The key findings on the food effect part were summarized below:

- $T_{max}$ occurred more rapidly for all analytes (TEV-50717 [parent], α-HTBZ, β-HTBZ and total [α+β]-HTBZ) in the fasted state (median $T_{max}$ 1 hour) compared to that in the fed state (median $T_{max}$ 4 hours) after administration of the 24-mg QD osmotic tablet.

- The terminal $t_{1/2}$ was similar for all analytes after administration of the 24-mg QD formulation under fasted or fed conditions.
- The $C_{max}$ and AUC (see **Table 5**) met the BE criteria, indicating no clinically meaningful food effect for the QD product.

**Table 5** Analysis of Relative Bioavailability for Effect of Food (TEV-50717 QD Osmotic Tablet [QD Fasted vs QD Fed])

| PK Parameter | | TEV-50717 (Parent) | | α-HTBZ | | β-HTBZ | | Total (α+β)-HTBZ | |
|---|---|---|---|---|---|---|---|---|---|
| | | 24 mg QD fasted (N=84) | 24 mg QD fed (N=84) | 24 mg QD fasted (N=84) | 24 mg QD fed (N=84) | 24 mg QD fasted (N=84) | 24 mg QD fed (N=84) | 24 mg QD fasted (N=84) | 24 mg QD fed (N=84) |
| $C_{max}$[a] (pg/mL)[b] (ng/mL)[c] | N | 84 | 84 | 84 | 84 | 84 | 84 | 84 | 84 |
| | LS Mean | 141.21 | 143.47 | 12.20 | 10.75 | 6.46 | 6.01 | 18.66 | 16.66 |
| | Geom mean ratio (90% CIs) | 101.60 (86.90, 118.78) | | 88.10 (85.10, 91.19) | | 93.04 (87.90, 98.47) | | 89.31 (85.69, 93.09) | |
| $AUC_{0-t}$ (pg x h/mL)[b] (ng x h/mL)[c] | N | 84 | 84 | 84 | 84 | 84 | 84 | 84 | 84 |
| | LS Mean | 1729.13 | 1664.54 | 310.40 | 282.41 | 115.27 | 105.36 | 434.60 | 397.92 |
| | Geom mean ratio (90% CIs) | 96.26 (85.26, 108.69) | | 90.98 (86.53, 95.65) | | 91.40 (85.27, 97.97) | | 91.56 (86.58, 96.83) | |
| $AUC_{0-\infty}$ (pg x h/mL)[b] (ng x h/mL)[c] | N | 78 | 80 | 84 | 84 | 82 | 80 | 84 | 84 |
| | LS Mean | 1871.41 | 1807.25 | 317.89 | 291.08 | 122.22 | 114.41 | 442.22 | 406.82 |
| | Geom mean ratio (90% CIs) | 96.57 (85.05, 109.65) | | 91.57 (87.25, 96.09) | | 93.61 (87.31, 100.36) | | 92.00 (87.11, 97.15) | |

Source: Summary 15.2.4

[a] $C_{max}$ from 0 to 96 h is used

[b] Unit for TEV-50717 (parent)

[c] Unit for metabolites (α-HTBZ, β-HTBZ and total [α+β]-HTBZ)

Source: Study Report TV50717-BE-10165 Table 18

## 4.2 Dose Proportionality Assessment

Study TV50717-BE-10175 was conducted to assess the dose proportionality of TEV-50717 (parent) and α-HTBZ and β-HTBZ metabolites (individually and as a sum) for the proposed QD product in AUSTEDO XR. This was a Phase 1, open-label, single center, randomized, 4-period, 4-sequence crossover study to assess the dose proportionality following the administration of a single dose of TEV-50717 QD osmotic tablets administered as 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg under fed condition in healthy subjects, who were known extensive or intermediate CYP2D6 metabolizers. A total of 116 subjects enrolled and received a dose (safety population) and data from 114 subjects were used for dose proportionality assessment. The objectives were to assess the dosage strength proportionality (6, 12, and 24 mg) using the power model based on the PK parameters, Cmax, $AUC_{0-\infty}$, and $AUC_{0-36h}$ of TEV-50717 and the α-HTBZ and β-HTBZ metabolites. Specifically, the slope of the doses to each of the PK parameters, and 90% CI, calculated by the power model, was estimated using a mixed effect analysis with log-transformed variables to determine if they are within the confidence limits for establishing dose proportionality. In addition, the relative BA between 2×6 mg and 1×12 mg TEV-50717 QD tablets administered as single doses in the fed state for all analytes were also assessed to support dosage strength equivalence.

Based on the results (**Table 6**), dose proportionality was demonstrated for both $C_{max}$ and AUC using all the analytes' data after single doses of the QD tablet across the clinical dose range (6, 12, 24, and 48 mg). The relative BA with regard to $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$ of all the analytes demonstrated BE between 2×6 mg and 1×12 mg QD osmotic tablets (see **Table 7**). Overall, a linear PK was demonstrated across the dosage strengths and the full clinical range (6-48 mg), which allows the dosing recommendations for the QD tablets can follow the same titration schedule as the commercially available AUSTEDO product.

**Table 6**: Analysis of dose proportionality for clinical dose range (6 mg, 12 mg, 24 mg and 48 mg QD osmotic tablets)

| PK parameter (Unit) | Estimate Slope (90% Confidence Interval[a]) | | | |
|---|---|---|---|---|
| | TEV-50717 (Parent) [N] | α-HTBZ [N] | β-HTBZ [N] | (α+β)-HTBZ [N] |
| $C_{max}$ (pg/mL)[b] (ng/mL)[c] | 0.9343 (0.8969, 0.9716) [114] | 0.9993 (0.9869, 1.0116) [114] | 1.0730 (1.0554, 1.0907) [114] | 1.0215 (1.0081, 1.0349) [114] |
| $AUC_{0-36h}$ (pg x h/mL) [b] (ng x h/mL) [c] | 0.9463 (0.9159, 0.9767) [114] | 1.0198 (1.0082, 1.0313) [114] | 1.0736 (1.0555, 1.0916) [114] | 1.0350 (1.0219, 1.0482) [114] |
| $AUC_{0-\infty}$ (pg x h/mL) [b] (ng x h/mL) [c] | 0.9623 (0.9319, 0.9927) [114] | 1.0212 (1.0088, 1.0336) [114] | 1.0476 (1.0302, 1.0650) [114] | 1.0310 (1.0172, 1.0447) [114] |

Source: Summary 15.2.3.2

[a] Confidence limits for establishing dose proportionality were 0.839 to 1.107

[b] Unit for TEV-50717 (parent)

[c] Unit for metabolites (α-HTBZ, β-HTBZ and total [α+β]-HTBZ)

Source: Study Report TV50717-PK-10175 Table 17

**Table 7**: Analysis of Relative BA (2×6 mg vs 1×12 mg) QD osmotic tablets

| PK parameter | | TEV-50717 (Parent) | | α-HTBZ | | β-HTBZ | | (α+β)-HTBZ | |
|---|---|---|---|---|---|---|---|---|---|
| | | 2x6 mg | 1x12 mg | 2x6 mg | 1x12 mg | 2x6 mg | 1x12 mg | 2x6 mg | 1x12 mg |
| $C_{max}$ (pg/mL)[a] (ng/mL)[b] | N | 111 | 109 | 110 | 110 | 111 | 110 | 111 | 110 |
| | LS Mean | 77.76 | 77.06 | 6.43 | 6.27 | 2.68 | 2.63 | 9.10 | 8.88 |
| | Geo mean ratio (90% CIs) | 100.91 (93.19, 109.26) | | 102.55 (99.84, 105.34) | | 102.00 (98.05, 106.10) | | 102.43 (99.39, 105.56) | |

| PK parameter | | TEV-50717 (Parent) | | α-HTBZ | | β-HTBZ | | (α+β)-HTBZ | |
|---|---|---|---|---|---|---|---|---|---|
| | | 2x6 mg | 1x12 mg | 2x6 mg | 1x12 mg | 2x6 mg | 1x12 mg | 2x6 mg | 1x12 mg |
| $AUC_{0-t}$ (pg x h/mL)[a] (ng x h/mL)[b] | N | 110 | 109 | 109 | 110 | 110 | 110 | 110 | 110 |
| | LS Mean | 1045.54 | 984.35 | 163.91 | 163.52 | 52.91 | 53.15 | 219.25 | 219.77 |
| | Geo mean ratio (90% CIs) | 106.22 (99.12, 113.82) | | 100.24 (97.42, 103.13) | | 99.54 (95.53, 103.72) | | 99.76 (96.68, 102.95) | |
| $AUC_{0-\infty}$ (pg x h/mL)[a] (ng x h/mL)[b] | N | 108 | 107 | 109 | 110 | 109 | 110 | 110 | 110 |
| | LS Mean | 1093.05 | 1038.12 | 166.42 | 166.37 | 54.62 | 54.76 | 222.49 | 224.08 |
| | Geo mean ratio (90% CIs) | 105.29 (98.26, 112.83) | | 100.03 (97.20, 102.94) | | 99.74 (95.88, 103.76) | | 99.29 (96.19, 102.49) | |

Source: Summary 15.2.4

[a] Unit for TEV-50717 (parent)

[b] Unit for metabolites (α-HTBZ, β-HTBZ and total [α+β]-HTBZ)

Source: Study Report TV50717-PK-10175 Table 16

# 5. Appendix

## 5.1 Summary of Bioanalytical Method Validation and Performance

The validated LC/MS/MS method (# BM-425-03) for the determination of deutetrabenazine and the metabolites, α-HTBZ and β-HTBZ, in human plasma was used for the pivotal relative BA study at steady state (Study TV50717-BE-10179). The method was validated (included in Report VR-425-18-01) and met the acceptance criteria for bioanalytical methods according to the Bioanalytical Method Validation Guidance for Industry the FDA Guidance for the Industry. Performance characteristics and validation attributes the bioanalytical method are summarized in **Table 8**.

**Table 8**: Validation Summary for Method BM-425-03

| Analyte | Deutetrabenazine | α-Dihydrodeutetrabenazine | β- Dihydrodeutetrabenazine |
|---|---|---|---|
| Internal Standard (IS) | Tetrabenazine | α-Dihydrotetrabenazine | β- Dihydrotetrabenazine |
| Lower Limit of Quantitation (LLOQ) | 2.925 pg/mL | 256.514 pg/mL | 258.424 pg/mL |
| Mean recovery of analyte (%) | 89.84% | 95.49% | 84.18% |

| | | | |
|---|---|---|---|
| Mean recovery of IS (%) | 86.56% | 98.72 | 86.38% |
| Standard curve concentrations (pg/mL) and linearity ($r^2$) | 2.905 to 751.061 pg/mL; Linearity: $r^2 \geq 0.99$ | 0.256 to 1000.09 ng/mL; Linearity: $r^2 \geq 0.99$ | 0.258 to 1001.2ng/mL; Linearity: $r^2 \geq 0.99$ |
| Between-run accuracy and precision | Biases: -0.58 to 3.74%; CV: 3.96-10.78 % | Biases: -3.26 to 2.06%; CV: 8.34 % | Biases: -5.95 to 8.58%; CV: 2.69-3.90 % |
| Within-run accuracy and precision | Biases: -8.04 to 10.88%; CV: 2.04 to 11.32% | Biases: -5.87 to 7.72%; CV: 0.54 to 7.22% | Biases: -8.63 to 10.41%; CV: 0.87 to 4.85% |
| Bench-top stability (hrs) (equivalent to short-term stability of analytes in matrix) | 72 h at room temperature | 45 h at room temperature | 19 h at room temperature |
| Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix) | 14 days at 5°C | 14 days at 5°C | 14 days at 5°C |
| Freeze-thaw stability in matrix | 5 cycles (-70°C to ambient temperature) | | |
| Stock stability (days) (equivalent to long-term stability of analyte or IS in solution) | 14 days at 5°C | | |
| Matrix selectivity | No significant interference in 6 plasma lots tested matrices; No effect on the quantitation of analytes | | |
| Incurred sample re-analysis | >96% of reanalysis within ±20% of the mean | | |

Source: Watson Validation Study VR-425-18-01 and Bioanalytical Report for Study TV50717-BE-10179

## 5.2 Pivotal Relative BA study at Steady State (#TV50717-BE-10179)

Title: An Open-label, Randomized, Repeated Dose, 2-Treatment, 2-Period, 2-Sequence Crossover Study with Full Replicate Design in Healthy Subjects to Assess the Bioequivalence and Relative Bioavailability at Steady State Between Once Daily Administration of a 24-mg

***Primary Objective*:** To assess the bioequivalence with regard to $AUC_{0\text{-}24,ss}$ of deutetrabenazine (TEV-50717, parent) and α-HTBZ and β-HTBZ metabolites (individually and as a sum) at steady state, following repeated QD administration of a TEV-50717 24-mg osmotic tablet compared to repeated BID administration of an AUSTEDO 12-mg tablet under fed conditions.

***Key Second Objectives:***

- To assess BE with regard to maximum observed plasma concentration at steady state ($C_{max,ss}$) for TEV-50717 (parent).
- To assess the relative BA with regards to the $C_{max,ss}$ for the α-HTBZ and β-HTBZ metabolites (individually and as a sum) following repeated QD administration of TEV-50717 24-mg osmotic tablet compared to repeated BID administration of an AUSTEDO 12-mg tablet under fed conditions

***Study Design and Methodology:***

This is a Phase 1, open-label, randomized, 2-period, 2-sequence, crossover repeated dose study. Healthy subjects were enrolled and randomized to 1 of 2 sequences: 1. AUSTEDO 12 mg BID then TEV-50717 24-mg osmotic tablet QD; 2. TEV-50717 24-mg osmotic tablet QD then AUSTEDO 12 mg BID. Within each sequence, a washout period of 6 days separated the two administration periods. QD administration of TEV-50717 24-mg osmotic tablet or BID administration of the AUSTEDO 12-mg tablet was carried out for 7 consecutive days. Within each treatment period, there were 2 full PK sampling days (Days 6 and 7; 0 to 24 h).

***Drug administration:***

Test (T) was a once daily administration in the morning (24 mg QD) of TEV-50717 for 7 consecutive days and reference (R) was a twice daily administration in the morning and evening, 12 hours apart, (12 mg tablet BID) of AUSTEDO for 7 consecutive days. On Days 6 and 7, morning dosing was administered after a standardized high-calorie, high-fat breakfast was served.

***Study Population:***

Healthy male and female subjects between 18 and 55 years of age, body mass index (BMI) within the range of 18.0 to 30.0 $kg/m^2$, with CYP2D6 extensive or intermediate metabolizer genotype.

***PK Sampling:***

The blood samples were collected for PK analysis, prior to morning dosing on Days 4 to 6, with frequent blood sample collection during Days 6 and 7 in both treatment periods to determine the plasma concentrations of TEV-50717 (parent) and the active HTBZ metabolites. The time points for blood collection are provided below.

Test (the QD product): within 15 minutes pre-dose on Days 4, 5, and 6, then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 14, 16, 18, 20, and 24 hours after each dose on Days 6 and 7.

Reference (AUSTEDO BID): within 15 minutes pre-dose of the morning dose on Days 4, 5, and 6, and then 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after each morning and evening dose on Days 6 and 7.

***PK Analysis Method:***

The plasma concentration data of the parent drug and the two active metabolites (individually and as a sum) from Day 6 and 7 were used to compare the steady-state PK of AUSTEDO 12 mg BID and TEV-50717 24-mg osmotic tablet QD. For BE analysis, plasma exposure of TEV-50717 (parent), α-HTBZ, β-HTBZ, and total (α+β)-HTBZ metabolites, as characterized by $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$, was assessed and compared utilizing bioequivalence criteria.

***Number of Subjects (Planned and Analyzed):***

Up to 272 healthy, adult male and female subjects were planned to be enrolled in this study, in order to attain data from at least 204 subjects. A total of 262 subjects were enrolled and randomized. A total of 258 subjects were evaluable for PK analysis, with 241 subjects having PK data for the test (QD) treatment and 241 subjects having data for the reference (BID) treatment.

***PK Results:***

The key results are summarized in Section 3.2.

## 5.3 Pharmacometrics Review

***Executive Summary***

This document is a review of the sponsor's modeling and simulation report (PMX-21-14-Ver-01 and PMX-22-09), which assess the clinical relevance of the differences in Cmax observed between the commercially available twice daily (BID) and to-be-marketed QD formulations of AUSTEDO in Tardive Dyskinesia (TD) and Huntington's Disease (HD) subjects.

***Sponsor's Analysis***

**Population Modeling Report (PMX-21-14-Ver-01)**
*Objectives:*

- To qualify the previously developed BID population PK models for parent, α-HTBZ, and β-HTBZ based on new clinical data for the BID formulation
- To develop QD population PK models for parent, α-HTBZ, and β-HTBZ based on the new QD formulation data
- To bridge E-R between the BID and QD formulations by statistical comparison of the steady state PK markers of exposure

*Data:* The PK data of 378 subjects from studies TV50717-PK-10175 and TV50717-BE-10179 who received the BID or QD formulation were used for the analysis. The covariate characteristics of the data is provided in **Table I**.

*Method:* Nonlinear mixed effect PK modeling was conducted using NONMEM v7.4.3. Previously developed PK BID model for parent, α-HTBZ, and β-HTBZ was qualified using

visual predictive check (VPC). The PK QD models were developed on top of their qualified BID counterparts. Covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was used. The final PK models were evaluated using goodness-of-fit plots and visual predictive checks. Stochastic simulations were conducted for both QD and BID formulations to compare steady-state PK exposure using PK models, and to compare change from baseline in TD and HD subjects using previously developed E-R model. Previously, linear models were developed to characterize the E-R relationships in both TD and HD subjects (5). High correlation in the different exposure parameters (i.e. $C_{min}$, $C_{max}$, $C_{avg}$ and $C_{avg,all}$) under the BID formulation at Week 12 did not allow the confirmation of the main driver of efficacy. As a result, all exposure parameters were similarly predictive of the response.

*Results:*

The PK of parent, α-HTBZ, and β-HTBZ population was described by two-compartment model with linear elimination. Previously developed α-HTBZ, and β-HTBZ population PK models were predictive of the new BID data in TV50717-BE-10179. The QD data was modeled by adding a parallel first- and zero-order absorption model with lag times to the previous BID model and only estimating QD-related absorption parameters. The population PK parameter estimates of the final model are presented in **Table II**. In addition, VPCs of the final model for 24 mg QD stratified by studies are presented in **Figure I**. Overall, the PK models well described the PK data of Study TV50717-PK-10175 and TV50717-BE-10179.

The PK model was used to simulate steady-state PK exposures for QD and BID formulation of AUSTEDO. Previously developed E-R model was then used to simulate change from baseline (CFB) in AIMS score in TD subjects and CFB in UHDRS-TMC in HD subjects using either $C_{max}$ or $C_{avg}$ as predictors in the model (**Figure II** and **Figure III**). As lower $C_{max}$ of QD formulation as compared to BID formulation was a key concern, $C_{max}$ was most relevant in the current situation. Assuming $C_{max}$ as a main driver of efficacy, the QD formulation would lead to small decrease in efficacy i.e., 13.4% in TD and 11% in HD subjects when compared to the BID formulation.

**Table I: Summary Statistics of the *378* Subjects Included in the PK dataset**

**A. Continuous information**

| Characteristic | TV50717-BE-10179 [N=262] | TV50717-PK-10175 [N=116] | TOTAL [N=378] |
|---|---|---|---|
| Age (years) | 38.6 (9.27) [18-55] | 40.9 (10.4) [19-55] | 39.3 (9.69) [18-55] |
| Body mass index (kg/m2) | 26.7 (2.74) [18.8-30] | 26.7 (2.71) [19.8-29.9] | 26.7 (2.72) [18.8-30] |
| Body weight (kg) | 76.4 (11.4) [50-100] | 75.2 (10.8) [50.2-99] | 76.1 (11.2) [50-100] |

N: Number of subjects
Entries represent: Mean (Standard deviation) [Minimum-Maximum]

**B. Categorical information**

| Characteristic | Category | TV50717-BE-10179 [N=262] | TV50717-PK-10175 [N=116] | TOTAL [N=378] |
|---|---|---|---|---|
| Indication | HV | 262 (100%) | 116 (100%) | 378 (100%) |
| Female Gender | No | 173 (66%) | 65 (56%) | 238 (63%) |
| | Yes | 89 (34%) | 51 (44%) | 140 (37%) |
| Race | White | 228 (87%) | 99 (85.3%) | 327 (86.5%) |
| | Black or African American | 34 (13%) | 17 (14.7%) | 51 (13.5%) |
| Ethnicity | Not Hispanic or Latino | 2 (0.763%) | 1 (0.862%) | 3 (0.794%) |
| | Hispanic or Latino | 260 (99.2%) | 115 (99.1%) | 375 (99.2%) |
| CYP2D6 metabolizer status | UM | 0 (0%) | 0 (0%) | 0 (0%) |
| | EM | 248 (94.7%) | 110 (94.8%) | 358 (94.7%) |
| | IM | 14 (5.34%) | 6 (5.17%) | 20 (5.29%) |
| | PM | 0 (0%) | 0 (0%) | 0 (0%) |

N: Number of subjects, EM: extensive metabolizers, HV: healthy volunteer, IM: intermediate metabolizers, PM: poor metabolizers, UM: ultra-metabolizers. Values represent the number of subjects in each category and percentage within this category.

**Source:** PMX-21-14-Ver-01, Page 142

## Table II: Population Parameter Estimates of QD and BID formulation of AUSTEDO

### A. Parent

| PARAMETER | VALUE | RSE |
|---|---|---|
| **Typical parameters** | | |
| CL | 282000 | 1.77% |
| Vc | 13700 | 4.01% |
| Vp | 123000 | 2.8% |
| Q | 130000 | 3.33% |
| FrelQD | 0.247 | 3.89% |
| Tlag4 | 0.385 | 2.72% |
| FabsBID | 1 (FIX) | - |
| FrelBID | 0.624 | 2.59% |
| Tlag1 | 0.0241 | 3.44% |
| ka1 | 11.4 | 1.39% |
| Tlag2 | 0.0602 | 2.64% |
| ka2 | 16 | 2.16% |
| FabsQD | 1 (FIX) | - |
| Tlag3 | 0.0196 | 2.47% |
| ka3 | 3.03 | 2.13% |
| Tk4 | 0.341 | 3.86% |
| **Inter-individual variability** | | |
| omega(CL) | 0.526 | 2.89% |
| omega(Vc) | 1.01 | 3.16% |
| omega(Vp) | 0.678 | 3.74% |
| omega(Q) | 0.809 | 3.5% |
| omega(FrelQD) | 0.993 | 4.91% |
| omega(Tlag4) | 0.438 | 6.52% |
| omega(FabsBID) | 0 (FIX) | - |
| omega(FrelBID) | 0.683 | 8.61% |
| omega(Tlag1) | 0.389 | 6.91% |
| omega(ka1) | 0.0642 | 31.6% |
| omega(Tlag2) | 0.336 | 7.45% |
| omega(ka2) | 0.11 | 43.7% |
| omega(FabsQD) | 0 (FIX) | - |
| omega(Tlag3) | 0.511 | 4.39% |
| omega(ka3) | 0.247 | 8.98% |
| omega(Tk4) | 0.733 | 4.94% |

### B. α-HTBZ

| PARAMETER | VALUE | RSE |
|---|---|---|
| **Typical parameters** | | |
| CL | 1670 (FIX) | - |
| Vc | 583 (FIX) | - |
| Q | 2510 (FIX) | - |
| Vp | 483 (FIX) | - |
| ka1 | 26.8 (FIX) | - |
| ka2 | 10.7 (FIX) | - |
| Tlag1 | 0.023 (FIX) | - |
| Tlag2 | 0.0219 (FIX) | - |
| FrelQD | 0.741 | 0.757% |
| ka3 | 27.7 | 4.83% |
| Tk4 | 0.697 | 0.653% |
| Tlag3 | 0.0427 | 2.06% |
| Tlag4 | 0.0249 | 3.57% |
| FabsBID | 1 (FIX) | - |
| FrelBID | 0.576 (FIX) | - |
| FabsQD | 1.19 | 0.825% |
| **Inter-individual variability** | | |
| omega(CL) | 0.306 (FIX) | - |
| omega(Vc) | 0.306 (FIX) | - |
| omega(Q) | 0.245 (FIX) | - |
| omega(Vp) | 0.208 (FIX) | - |
| omega(ka1) | 0.963 (FIX) | - |
| omega(ka2) | 0.832 (FIX) | - |
| omega(Tlag1) | 0.661 (FIX) | - |
| omega(Tlag2) | 0.615 (FIX) | - |
| omega(FrelQD) | 0.657 | 4.86% |
| omega(ka3) | 1.04 | 4.11% |
| omega(Tk4) | 0.136 | 4.21% |
| omega(Tlag3) | 0.498 | 3.37% |
| omega(Tlag4) | 0.685 | 3.31% |
| omega(FabsBID) | 0 (FIX) | - |
| omega(FrelBID) | 0 (FIX) | - |
| omega(FabsQD) | 0.1 (FIX) | - |

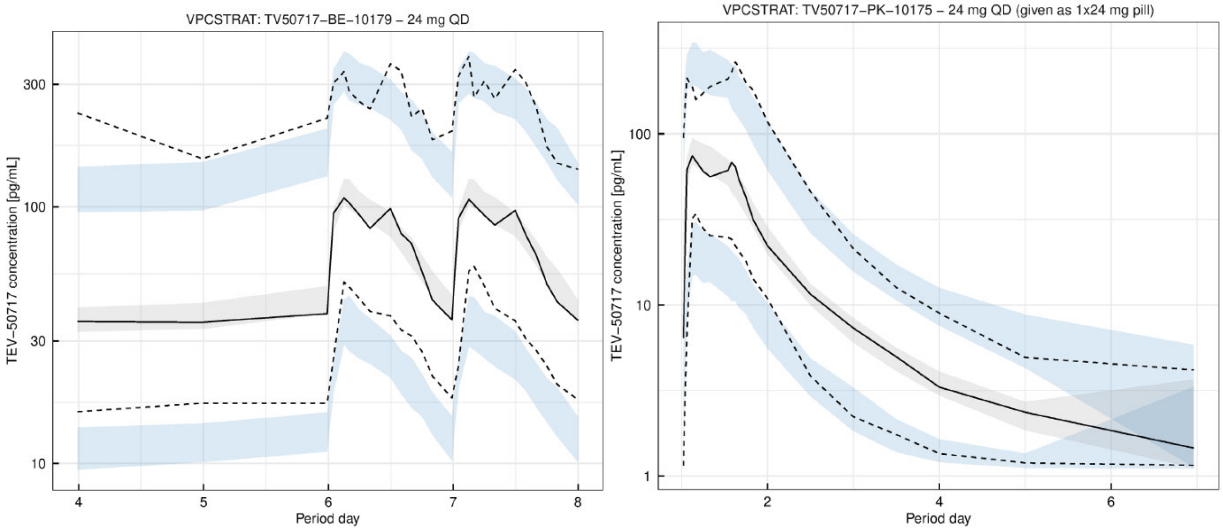
### C. β-HTBZ

| PARAMETER | VALUE | RSE |
|---|---|---|
| **Typical parameters** | | |
| CL | 4170 (FIX) | - |
| Vc | 878 (FIX) | - |
| Q | 3460 (FIX) | - |
| Vp | 1140 (FIX) | - |
| ka1 | 14.6 (FIX) | - |
| Tlag1 | 0.0407 (FIX) | - |
| ka2 | 12.6 (FIX) | - |
| Tlag2 | 0.0208 (FIX) | - |
| ka3 | 17.7 | 4.8% |
| Tlag3 | 0.0457 | 1.96% |
| Tlag4 | 0.0323 | 2.95% |
| FabsBID | 1 (FIX) | - |
| FrelBID | 0.378 (FIX) | - |
| FabsQD | 1.03 | 1.42% |
| FrelQD | 0.736 | 0.938% |
| Tk4 | 0.657 | 0.839% |
| factorCLnew | 0.769 (FIX) | - |
| **Inter-individual variability** | | |
| omega(CL) | 0.568 (FIX) | - |
| omega(Vc) | 0.452 (FIX) | - |
| omega(Q) | 0.635 (FIX) | - |
| omega(Vp) | 0.648 (FIX) | - |
| omega(ka1) | 0.553 (FIX) | - |
| omega(Tlag1) | 0.443 (FIX) | - |
| omega(ka2) | 1 (FIX) | - |
| omega(Tlag2) | 0.418 (FIX) | - |
| omega(ka3) | 1.01 | 4% |
| omega(Tlag3) | 0.451 | 3.68% |
| omega(Tlag4) | 0.592 | 4.15% |
| omega(FabsBID) | 0 (FIX) | - |
| omega(FrelBID) | 0 (FIX) | - |
| omega(FabsQD) | 0.1 (FIX) | - |
| omega(FrelQD) | 0.675 | 5.23% |
| omega(Tk4) | 0.174 | 8.41% |
| omega(factorCLnew) | 0 (FIX) | - |

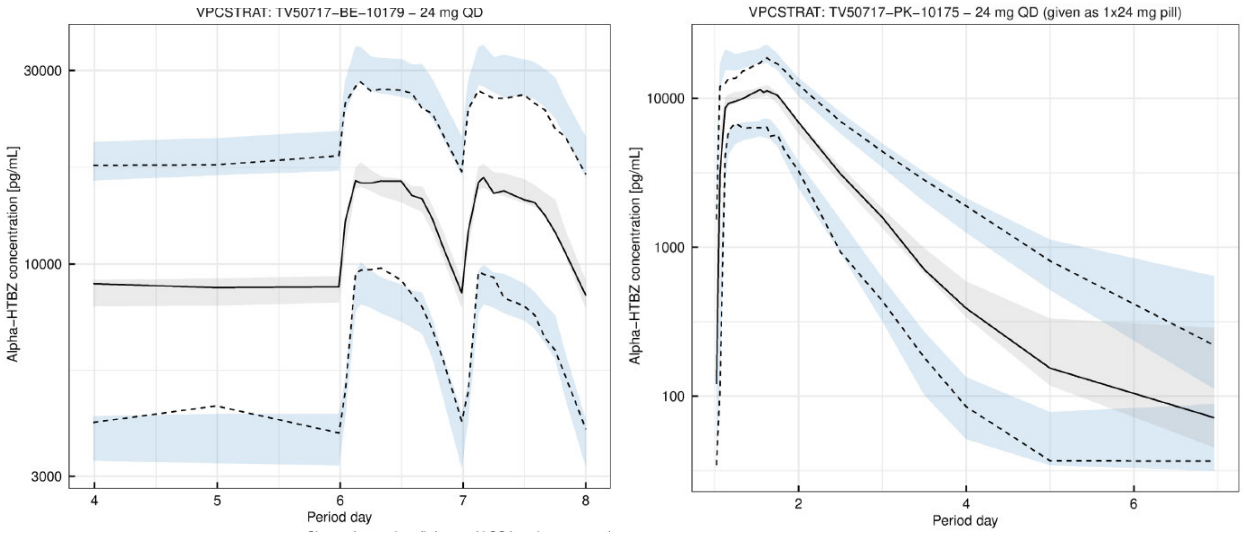
**Source:** PMX-21-14-Ver-01, Page 40, 53, 64

## Figure I: Visual Predictive Checks of the 24 mg QD Formulation of AUSTEDO

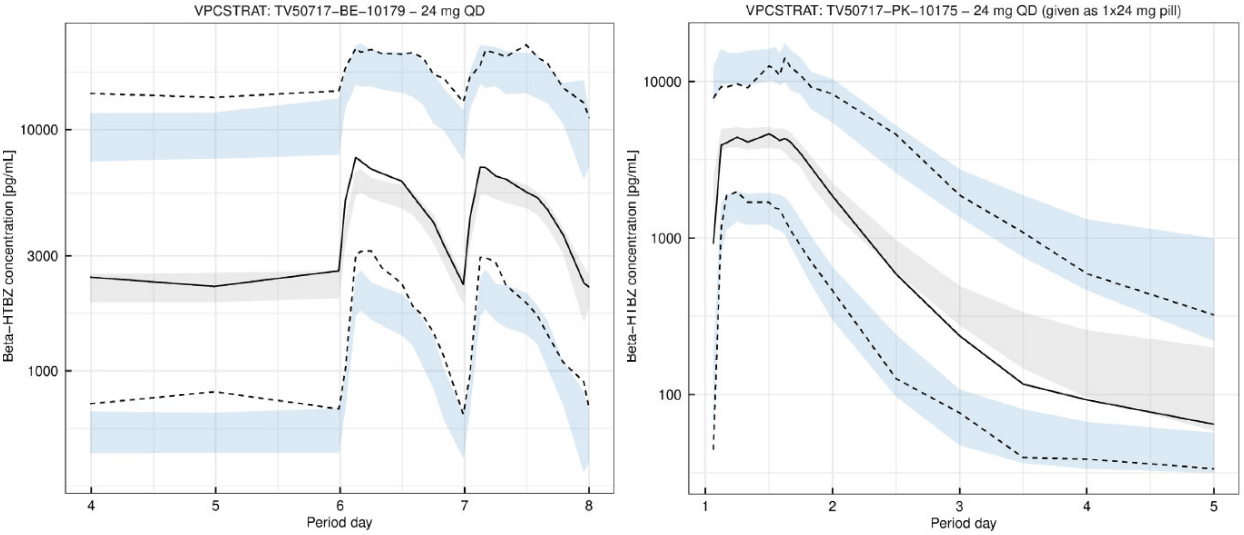
### A. Parent




### B. α-HTBZ



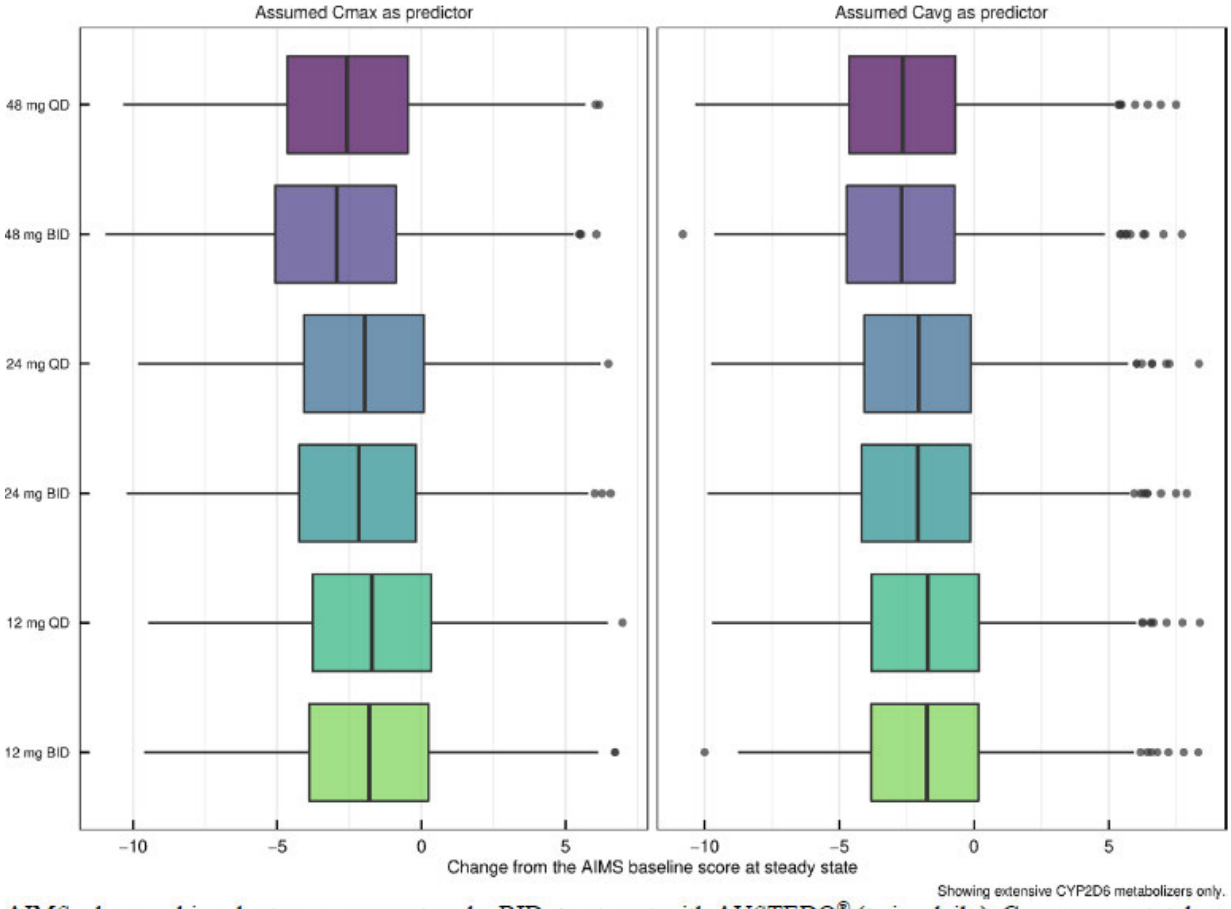

**C. β-HTBZ**




The median (bold line), 5th and 95th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the median (light gray), 5th and 95th percentiles (blue) of the simulated data.

**Source:** PMX-21-14-Ver-01, Page 43, 46, 56, 59, 66,69

**Figure II: Overview of the Change from Baseline in AIMS Score at Steady-state in Extensive CYP2D6 Metabolizers Between the BID and QD Formulations**




AIMS: abnormal involuntary movement scale, BID: treatment with AUSTEDO® (twice daily), $C_{avg}$: average total (α+β)-HTBZ concentration at steady-state, $C_{max}$: maximum total (α+β)-HTBZ concentration at steady-state, QD: treatment with once daily tablet formulation.

### E. $C_{max,ss}$ as predictor

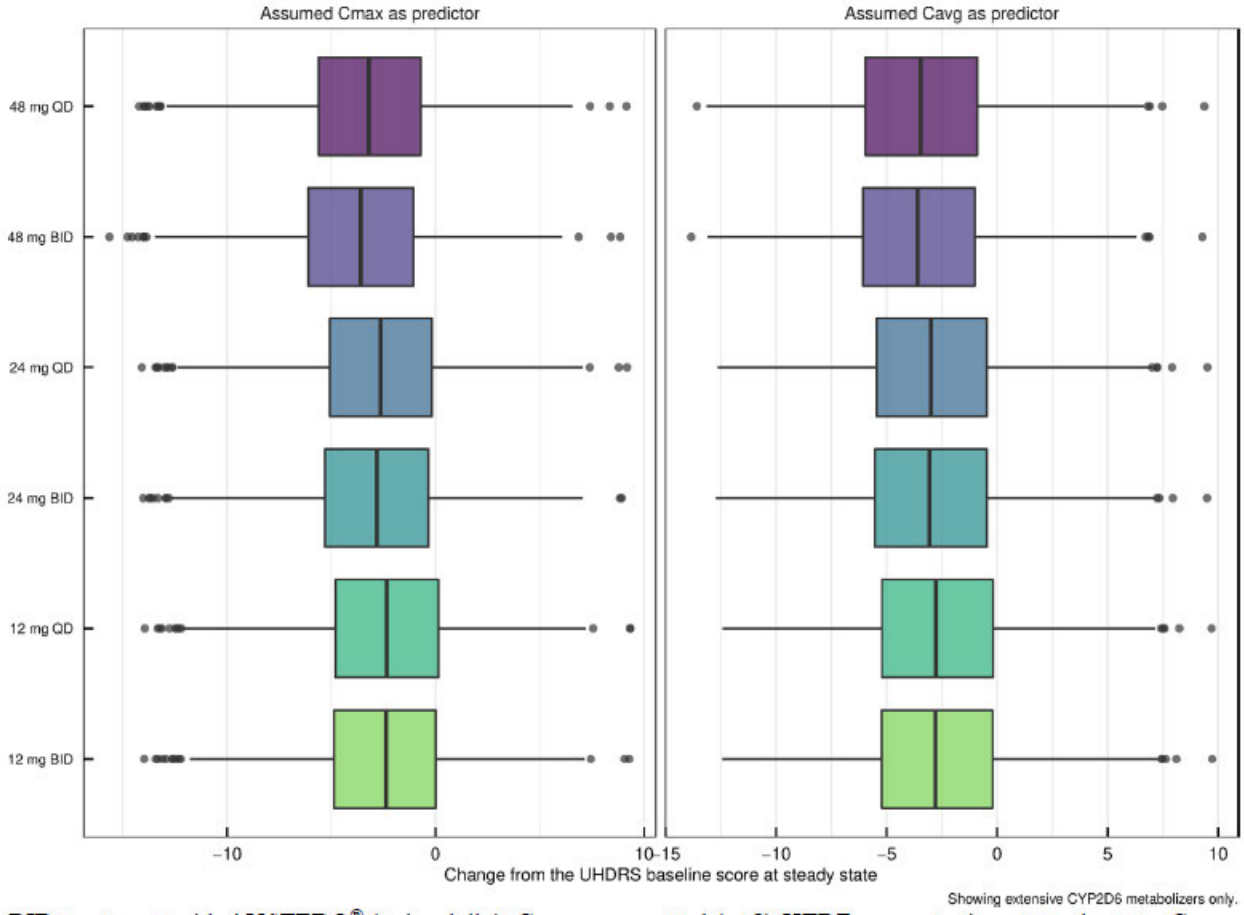
| Total daily dose | CHGBL AIMS [BID Cmax,ss] | CHGBL AIMS [QD Cmax,ss] | QD-vs-BID CHGBL AIMS [%BID] |
|---|---|---|---|
| 12 mg | -1.8 [-6.93, 3.34] | -1.71 [-6.84, 3.42] | -5.12% |
| 24 mg | -2.17 [-7.31, 3.01] | -1.98 [-7.2, 3.22] | -8.69% |
| 48 mg | -2.94 [-8.02, 2.21] | -2.54 [-7.74, 2.67] | -13.4% |

### F. $C_{avg,ss}$ as predictor

| Total daily dose | CHGBL AIMS [BID Cavg,ss] | CHGBL AIMS [QD Cavg,ss] | QD-vs-BID CHGBL AIMS [%BID] |
|---|---|---|---|
| 12 mg | -1.75 [-6.6, 3.1] | -1.72 [-6.5, 3.21] | -1.55% |
| 24 mg | -2.06 [-6.85, 2.96] | -2 [-6.8, 2.87] | -2.72% |
| 48 mg | -2.68 [-7.42, 2.27] | -2.57 [-7.35, 2.45] | -4.21% |

Simulated values are reported as mean [5% quantile, 95% quantile].
**Source:** PMX-21-14-Ver-01, Page 80-81

**Figure III: Overview of the Change from Baseline in UHDRS Score at Steady-state in Extensive CYP2D6 Metabolizers Between the BID and QD Formulations**




BID: treatment with AUSTEDO® (twice daily), $C_{avg}$: average total (α+β)-HTBZ concentration at steady-state, $C_{max}$: maximum total (α+β)-HTBZ concentration at steady-state, QD: treatment with once daily tablet formulation, UHDRS: Unified Huntington's Disease Rating Scale.

## G. Cmax,ss as predictor

| Total daily dose | CHGBL UHDRS [BID Cmax,ss] | CHGBL UHDRS [QD Cmax,ss] | QD-vs-BID CHGBL UHDRS [%BID] |
|---|---|---|---|
| 12 mg | -2.42 [-8.5, 3.69] | -2.33 [-8.46, 3.71] | -3.8% |
| 24 mg | -2.8 [-8.89, 3.33] | -2.61 [-8.74, 3.35] | -6.75% |
| 48 mg | -3.56 [-9.72, 2.61] | -3.17 [-9.29, 2.94] | -11% |

## H. Cavg,ss as predictor

| Total daily dose | CHGBL UHDRS [BID Cavg,ss] | CHGBL UHDRS [QD Cavg,ss] | QD-vs-BID CHGBL UHDRS [%BID] |
|---|---|---|---|
| 12 mg | -2.67 [-8.66, 3.46] | -2.65 [-8.57, 3.48] | -0.891% |
| 24 mg | -2.95 [-8.85, 3.16] | -2.9 [-8.8, 3.23] | -1.68% |
| 48 mg | -3.5 [-9.37, 2.68] | -3.4 [-9.24, 2.8] | -2.85% |

Simulated values are reported as mean [5% quantile, 95% quantile].
**Source:** PMX-21-14-Ver-01, Page 82-83

***PMX-22-09: Simulations of Tetrabenazine and AUSTEDO PK Profiles for the SD-809-C-16 Switch Cohort***

The SD-809-C-16 open-label long-term extension study in HD comprised of two cohorts, a rollover from the SD-809-C-15 efficacy study to long-term safety and tolerability, and a switch from a stable dose of XENAZINE to AUSTEDO BID for efficacy, long-term safety, and tolerability. Focusing on the Switch cohort, 37 HD subjects with chorea switched overnight from XENAZINE to a dosing regimen of AUSTEDO predicted to provide comparable exposures to total (α+β)-HTBZ metabolites (**Table IV**). No dose adjustment was allowed during the first week after the switch.

The purpose of this analysis was to simulate and compare tetrabenazine concentration profiles following the actually used dosing regimens in the study SD-809-C-16 and compare with AUSTEDO BID concentration profile using previously developed PK model of tetrabenazine (3,4). The concentration profiles from the tetrabenazine dose regimens in Switch cohort of the study SD-809-C-16 showed wide range of distribution. Concentration-time profiles of simulated total (α+β)-HTBZ from tetrabenazine comparing to the switched AUSTEDO BID formulation for 50 mg/day tetrabenazine (12.5 mg QID and 25 mg BID) are shown in **Figure V**, which suggested comparable daily AUC but lower $C_{max}$ for subjects switching from tetrabenazine to AUSTEDO BID.

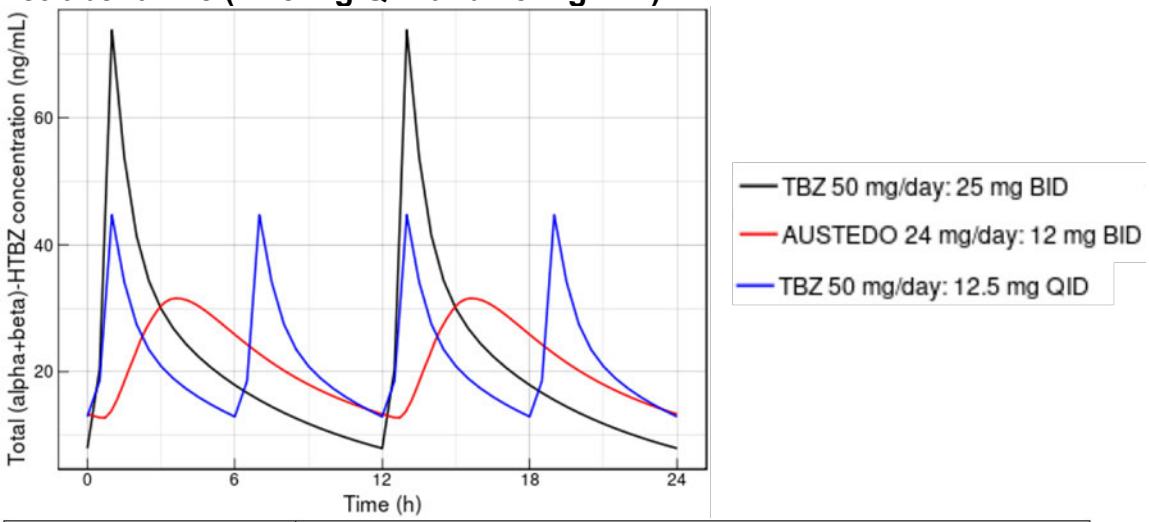
*Reviewer's comment: The QD formulations of AUSTEDO is expected to have different PK profile shape when compared to BID formulations i.e., similar AUC and lower $C_{max}$. Impact of shape of PK curve on efficacy was one of the key review issues. Study SD-809-C-16 Switch Cohort has provided dosing and efficacy data for 37 HD subjects who switched from tetrabenazine to AUSTEDO BID. As shown in the above analysis, such switching resulted in a range of PK profiles in HD subjects. Specifically, comparable AUC and lower $C_{max}$ were obtained in subjects switching from tetrabenazine to AUSTEDO BID. However, the efficacy was maintained post-one week of switch in these HD subjects (Figure VI): the mean (SD) TMC score at baseline and at Week 1 post-switch was 12.46 (5.22) and 11.76 (5.11) respectively. This suggested that chorea control was maintained as long as concentrations are in the range of previously approved dosing regimens, and differences in PK profile shapes and $C_{max}$ may have no impact on efficacy.*

**Table IV: Tetrabenazine Doses (Pre-Switch) and AUSTEDO Doses (Post-Switch) in Huntington Disease (SD-809-C-16) Switch Cohort**

| Total daily dose (mg) | XENAZINE (Pre-Switch) | AUSTEDO (Post-Switch) | |
|---|---|---|---|
| | Regimen | Total daily dose (mg) | Regimen |
| 12.5 (N=3) | 12.5mg QD (N=3) | 6 | QD |
| 18.75 (N=1) | 6.25mg TID (N=1) | 6 | QD |
| 25 (N=7) | 12.5mg BID (N=7) | 12 | BID |
| 37.5 (N=10) | 37.5mg QD (N=1), 12.5mg TID (N=7), 12.5mg QD and 25mg QD (N=2) | 18 | BID |
| 50 (N=11) | 25mg BID (N=8), 12.5mg QID (N=2), 25mg QD and 12.5mg BID (N=1) | 24 | BID |
| 75 (N=4) | 37.5mg BID (N=1), 25mg TID (N=3) | 36 | BID |
| 100 (N=1) | 37.5mg BID and 25mg QD (N=1) | 48 | BID |

**Source:** PMX-22-09, Page 9, Table 1

**Figure V: Concentration-time profiles of simulated total (α+β)-HTBZ from tetrabenazine comparing to the Switched AUSTEDO BID Formulation for 50 mg/day Tetrabenazine (12.5 mg QID and 25 mg BID)**

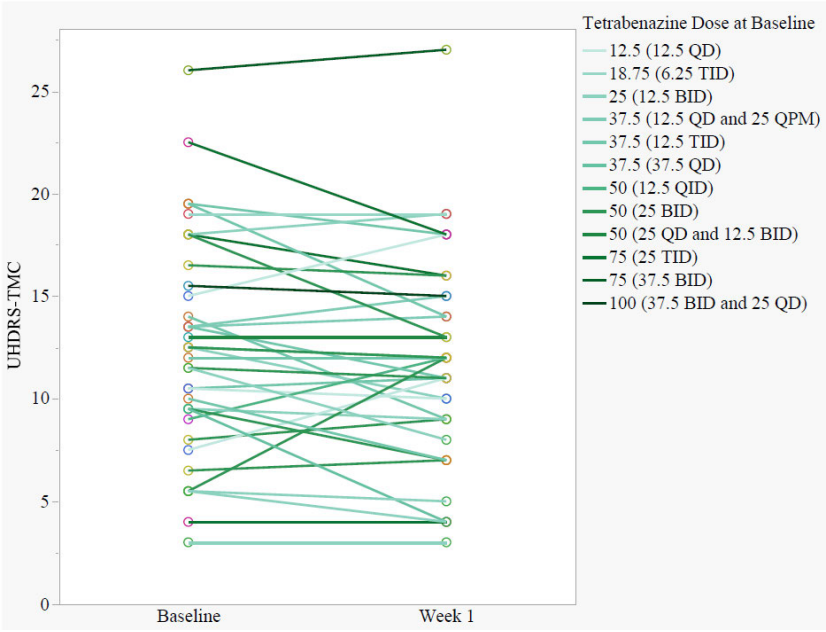



| Regimen | Exposure | | | |
|---|---|---|---|---|
| | $C_{min}$ (ng/mL) | $C_{av}$ (ng/mL) | $C_{max}$ (ng/mL) | $AUC_{0-24h}$ (ng·h/mL) |
| Tetrabenazine 25 mg BID | 7.933 | 21.901 | 73.841 | 525.615 |
| Tetrabenazine 12.5 mg QID | 12.922 | 21.906 | 44.693 | 525.742 |
| AUSTEDO BID 12 mg BID | 12.741 | 21.596 | 31.570 | 518.305 |

**Source:** PMX-22-09, Page 9, Table 1

**Figure VI: Open-label in Huntington Disease (SD-809-C-16) Switch Cohort- Total Maximal Chorea Scores at Baseline and Week 1 in 37 subjects who switched from**

**tetrabenazine to a dosing regimen of AUSTEDO predicted to provide comparable exposures to total (α+β)-HTBZ metabolites**




**Source:** Summary of Clinical Efficacy, Page 40, Figure 6

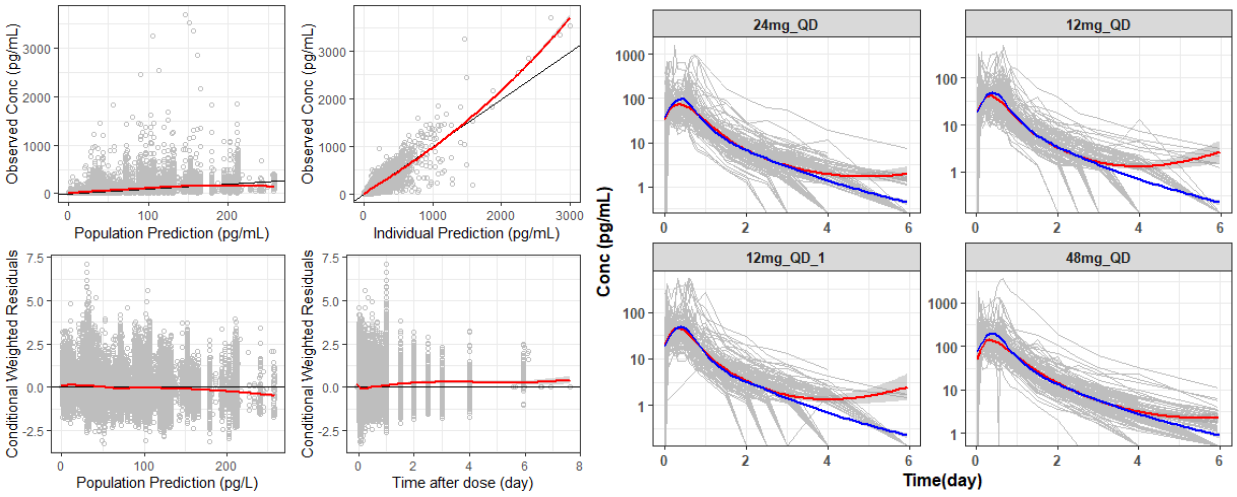
## ***Reviewer's Analysis***

### Applicant's population PK and E-R model evaluation

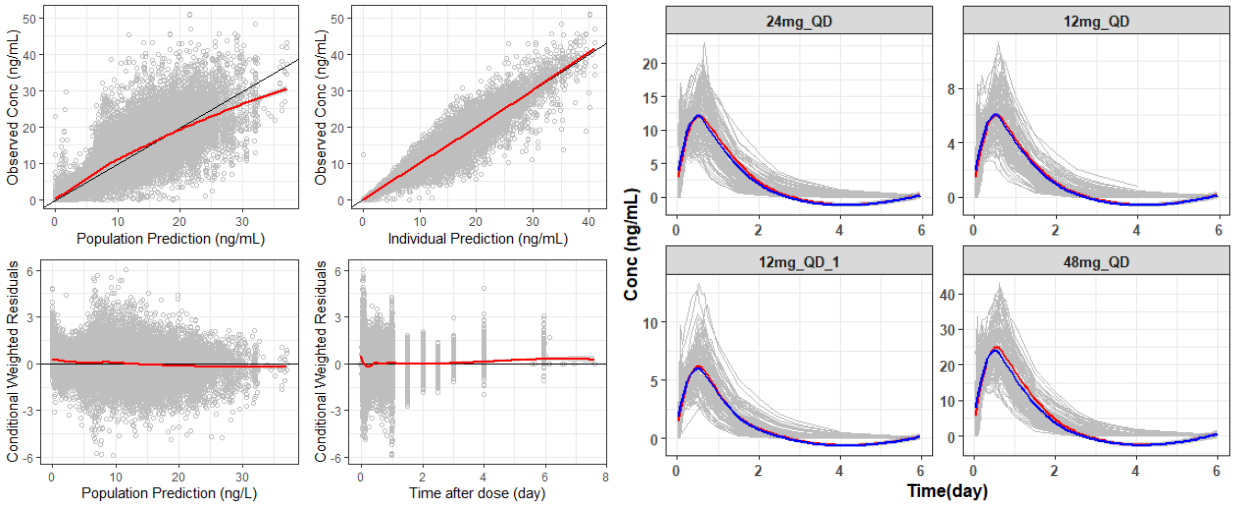
The reviewer was able to run the applicant's final PK models and obtained similar results. Model diagnostics for parent, α-HTBZ, and β-HTBZ are shown in **Figure VII**. Overall, the PK models well described the PK data of AUSTEDO BID and QD formulation. The final PK models were used to generate individual PK metrics ($C_{max}$, $C_{min}$, and $C_{avg}$ on Day 1 and/or Day 7) of parent, α-HTBZ, and β-HTBZ for subjects enrolled in Study TV50717-PK-10175 and TV50717-BE-10179, and then to provide support for E-R analysis.

**Figure VII: Goodness-of-Fit plots (Left Side) and Sphagetti Plots (Right) Using Applicant's Final PK model for Parent, α-HTBZ, and β-HTBZ**

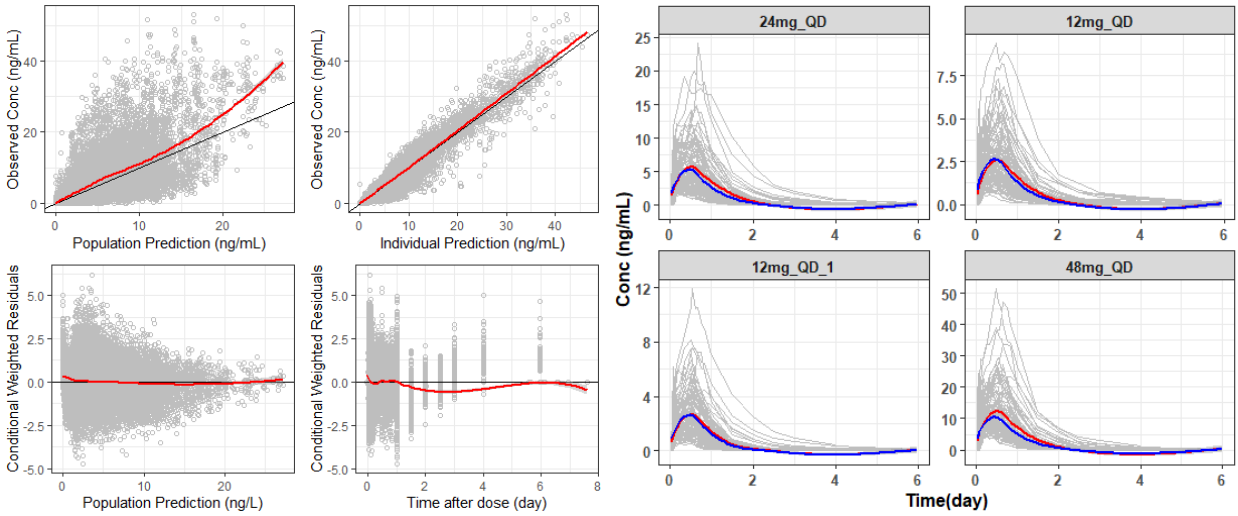
**A. Parent**




## B. α-HTBZ



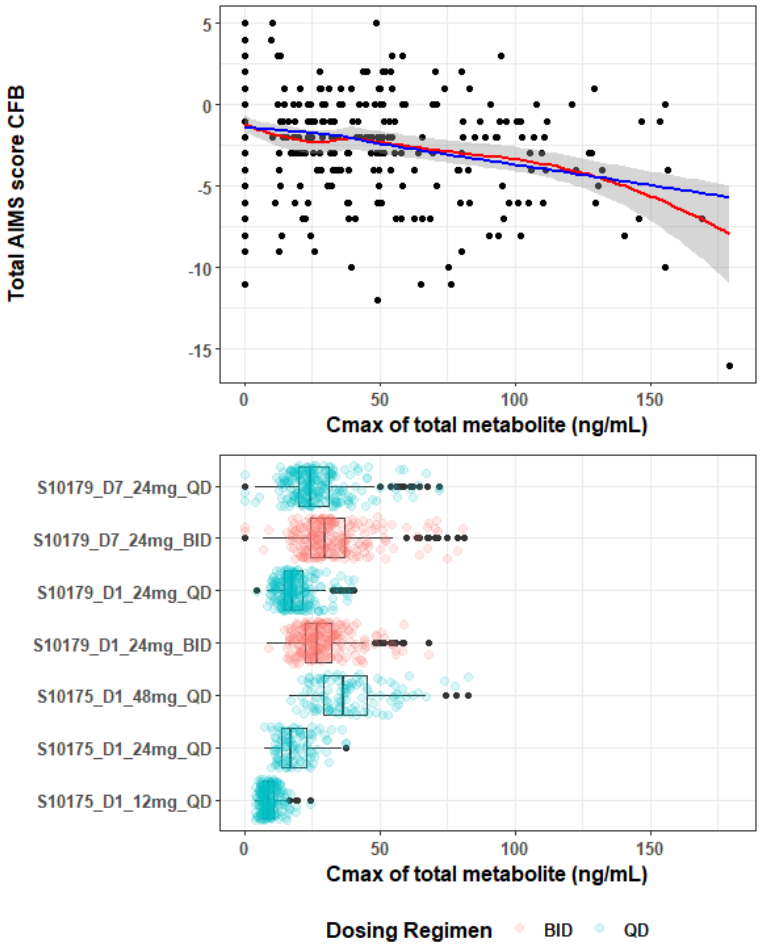

## C. β-HTBZ



Goodness-of-fit plots: red line represents loess curve; Sphagetti plots: blue and red line represents loess curve for model-predictions and observed data respectively
**Source**: Reviewer's analysis

AUSTEDO QD formulation has shown lower $C_{max}$ as compared to BID formulation (mean $C_{max,total\ metabolite,\ day\text{-}7}$ = 32 ng/mL for 12 mg BID vs. 27 ng/mL for 24 mg QD in Study-10179). Impact of lower $C_{max}$ on efficacy was evaluated using previously developed E-R models for HD and TD subjects. Briefly, the linear E-R models were developed using data from BID formulation and utilized $C_{avg}$ or $C_{max}$ of total (α + β)-HTBZ as a driver for efficacy (5). Of note, high correlation in the different exposure parameters (i.e. $C_{min}$, $C_{max}$, $C_{avg}$ and $C_{avg,all}$) under the BID formulation at Week 12 did not allow the confirmation of the main driver of efficacy. The objective of the analysis was to evaluate the adequacy of the E-R models in predicting the efficacy of QD formulation in HD and TD subjects. The final PK models were used to generate individual $C_{max}$ of total (α + β)-HTBZ at Day 1 and/or Day 7 for subjects enrolled in Study TV50717-PK-10175 and TV50717-BE-10179. These individual $C_{max}$ of total (α + β)-HTBZ were compared to the $C_{max}$ of total (α + β)-HTBZ used in the E-R model of AUSTEDO BID formulation (**Figure VIII** and **Figure IX**). It was observed that the $C_{max}$ range of the total (α + β)-HTBZ from QD formulation overlapped with the $C_{max}$ range utilized in the E-R model, and thus the E-R model should be able to predict efficacy response of AUSTEDO QD formulation in HD and TD subjects. For efficacy comparison between QD and BID formulation, please refer to the Result Section of the Applicant's Analysis.

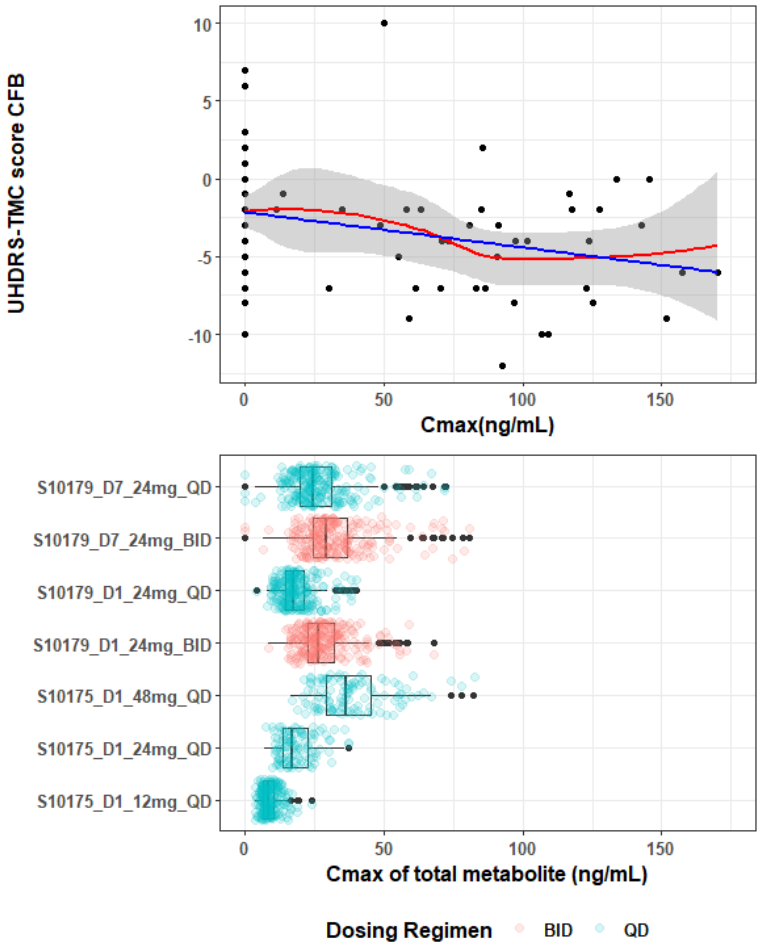
**Figure VIII: Relationship Between the Change From Baseline in AIMS Score and Cmax of Total (α + β)-HTBZ in TD Subjects**




Top figure: blue and red line represents linear-regressed line and loess curve respectively; Bottom figure: y-label represents Study number, Day number, Dose, and Dosing regimen separated by dashed sign.

**Source**: Reviewer's analysis

**Figure IX: Relationship Between the Change From Baseline in UHDRS-TMC Score and $C_{max}$ of Total (α + β)-HTBZ in HD Subjects**




Top figure: blue and red line represents linear-regressed line and loess curve respectively; Bottom figure: y-label represents Study number, Day number, Dose, and Dosing regimen separated by dashed sign.
**Source**: Reviewer's analysis

## ***Conclusions:***

1. The previously developed E-R model was adequate to predict the efficacy of AUSTEDO QD formulation in HD and TD subjects.
2. Assuming Cmax as a main driver of efficacy, the QD formulation would lead to small decrease in efficacy i.e., 13.4% in TD and 11% in HD subjects when compared to the BID formulation.
3. Efficacy data from Study SD-809-C-16 Switch Cohort showed that efficacy in HD subjects was maintained as long as concentrations are in the range of previously approved dosing regimens, and differences in PK profile shapes and Cmax may have no impact on efficacy.

***References:***


1. PMX-21-14-Ver-01: Modeling & Simulation Analysis to Evaluate Daily Dosing Regimen for AUSTEDO, March 2022
2. PMX-22-09: Simulations of Tetrabenazine and AUSTEDO PK Profiles for the SD-809-C-16 Switch Cohort, September 2022.
3. SD-809-CLN-076 (Pharsight Project No. AUSP-PCS-100) Pharsight Report. Population PK Modeling and Simulations to Support Dosing Switching Scheme from Tetrabenazine to SD-809 in Patients with Huntington's Chorea, January 2015.
4. PMX-21-14. (b) (4) Report. Model & Simulation Analysis to Evaluate Daily Dosing Regimen for AUSTEDO®, January 2022.
5. PMX-20-14-Ver-01: Modeling & Simulation Support for TEV-50717 QD Formulation, 30 November 2020

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