CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216354Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW (SAFETY)

Application Type	505(b)(2)
Application Number(s)	NDA 216354
Priority or Standard	Standard
Submit Date(s)	April 21, 2022
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Division/Office	DN1 / Office of Neuroscience / OND / CDER
Reviewer Name(s)	Kenneth Bergmann, MD
Review Completion Date	December 31, 2022
Established/Proper Name	TEV-50717 (deutetrabenazine extended release)
(Proposed) Trade Name	Austedo XR
Applicant	Teva Neuroscience, Inc
Dosage Form(s)	6, 12, and 24 mg osmotic tablets
Applicant Proposed Dosing Regimen(s)	Beginning at 12 mg q.d. by mouth, may be increased weekly in 6 mg/day increments to a maximum daily dosage of 48 mg.
Applicant Proposed Indication(s)/Population(s)	Adults: for the treatment of chorea associated with Huntington's disease and the treatment of Tardive Dyskinesia.
Recommendation on Regulatory Action	Approvable
Recommended Indication(s)/Population(s)	Adults: for the treatment of chorea associated with Huntington's disease and the treatment of Tardive Dyskinesia.

Table of Contents

Table of Tables

Table of Figures

Glossary

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

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Teva Pharmaceuticals Corporation has developed a novel, redesigned, once-a day extended-release formulation of the Austedo (deutetrabenazine) immediate release (IR) tablet which was first approved in 2017 under NDA 208082. Austedo XR (the proposed proprietary name for TEV-50717 tablets) employs an osmotic drug delivery system to provide drug delivery at a controlled rate for once daily oral administration.

The proposed registration formulation is designed to combine IR and extended release (ER) capabilities. The TEV-50717 tablet consists of a bilayer core manufactured with an osmotic push layer and an osmotic drug layer. The ER tablets are coated with a semipermeable coating system and are laser-drilled at the active drug layer to produce a precise hole for drug release.

Figure 1 Schematic of osmotic tablet design (Source: 2.5 Clinical Overview, p. 12)

Reviewer's note: *This review will refer to the approved deutetrabenazine product for BID administration as* ***Austedo****. The investigational product for QD use, the subject of this application, is referred to as* ***TEV-50717****.*

1.2. Benefit-Risk Integrated Assessment

As this application does not include efficacy data, the determination of benefit and risk depends significantly on the efficacy data from the listed drug (LD). The LD, Austedo (deutetrabenazine immediate release, NDA 208082), has been marketed in the United States for treatment of chorea associated with Huntington's disease (2017) and tardive dyskinesia (2018). The final Clinical Pharmacology assessment of this application is still pending at this time. No new or

unexpected adverse events were discovered in the course of the development program of TEV-50717 in healthy adults. There are no clinical safety issues impeding the approval of the proposed product.

2. Therapeutic Context

2.1. Analysis of Condition

Chorea is an involuntary movement resulting from disordered function of the basal ganglia, a region of the brain involved in the generation of the motor syndromes described below. While the motoric dysfunction seen in HD results from an autosomal dominant genetic disorder, the chorea of tardive dyskinesia likely results from chronic dopamine receptor blockade by neuroleptics used to treat the behavioral disorder of psychiatric illness.

Tetrabenazine and deutetrabenazine are vesicular monoamine transporter 2 (VMAT2) inhibitors, thought to act by depleting vesicles containing dopamine prior to their release from the neuron terminal into the synaptic cleft.

Huntington's Disease
Huntington's disease (HD) is a rare genetically inherited degenerative disorder of the brain. About 30,000 people in the US are affected and HD is considered an "orphan disease". It is inherited by receiving an abnormal gene that can come from either parent. The child of an affected parent has a 50-50 chance of inheriting the disease. While the classic sign of the disorder is chorea, involuntary and uncontrollable dance-like movements of the face and limbs, the illness is characterized by progressive motor, psychiatric disturbances, and dementia. The onset of the illness is generally between the ages of 30 and 50, progressing to death within 15 to 20 years. Definitive genetic testing is now available to diagnose the disorder in persons at risk before they become symptomatic.

Tardive Dyskinesia
First recognized in 1954, tardive dyskinesia (TD) is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as "involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles) developing in association with the use of a neuroleptic medication for at least a few months."

TD tends to occur months or years after initiation of a psychotropic, hence "tardive." The clinical course of TD is variable. It can be reversible in some, particularly younger, patients if identified early and the causative drug is withdrawn. However, TD is frequently persistent or may improve only partially, in conjunction with changing the neuroleptic medication type or

dose.

2.2. Analysis of Current Treatment Options

Huntington's Disease
No medication has been demonstrated to change the natural history of this genetic disorder which is inevitably fatal. Chorea, bradykinesia, irritability, apathy, depression, anxiety, and sleep disturbances have all been reported to be distressing symptoms of HD. A variety of medications can offer some palliation of the behavioral symptoms. However, only tetrabenazine (Xenazine, NDA 21894 and generic equivalents) and deutetrabenazine (Austedo, NDA 208082) are approved specifically for the treatment of the chorea associated with HD.

Tardive Dyskinesia
There are currently two FDA-approved products for the treatment of TD. Valbenazine (Ingrezza, NDA 209241) was approved on April 11, 2017, for the treatment of adults with TD. Immediate release deutetrabenazine (Austedo, NDA 208082) is also approved for the treatment of tardive dyskinesia.

Reviewer's comment: *The approved treatments above are administered at least twice a day in both conditions. Being able to administer a drug treatment just once a day can be a significant aid to the caregivers of HD and TD patients and makes compliance with therapy less onerous in these chronic illnesses. TEV-50717 would have this advantage over these currently marketed products.*

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Deutetrabenazine (Austedo), the listed drug in this 505(b)(2) application, was first approved in the United States for the treatment of chorea associated with Huntington's Disease (HD) on April 3, 2017, and for Tardive Dyskinesia (TD) on August 30, 2017. Since that time, Austedo has also been approved in China, Israel, South Korea, Australia, and Brazil.

3.2. Summary of Presubmission/Submission Regulatory Activity

There were three regulatory interactions with the applicant under IND 112975 regarding the development of this once daily formulation. These mostly pertained to the clinical pharmacology requirements and the outline below summarizes that discussion.

Type B EOP2 Teleconference (March 31, 2020)

This meeting discussed bridging to the approved Austedo product, the design for Phase 1 clinical studies, and study endpoints.

The Agency confirmed that in the single-dose bioequivalence (BE) study, the reference should be Austedo administered with food, as recommended in the current Austedo label. The QD formulation should be administered with and without food, as the test. The Agency emphasized that the food effect on the QD formulation should be addressed using a single-dose study.

Steady state exposure was acceptable as the primary analysis. C_{max} and AUC parameters following the single dose and C_{max}, AUC, and C_{min} following repeated dose will be evaluated during review. Any additional analyses performed by the applicant may be included in the NDA. The applicant was told to analyze the data for the parent compound using the confidence interval (CI) approach. They were also advised to report the geometric mean ratios and the CI for each active metabolite.

The applicant was advised that if the proposed once-daily formulation were not bioequivalent to Austedo (for Cmax and AUC), additional clinical efficacy studies would be needed.

Type C Guidance Written Response (December 17, 2020)

The applicant expressed concern regarding the contribution of the parent drug and its metabolites to bioequivalence and which of these should be considered most relevant. The Agency replied that review will be based on the totality of the data, and it will not be limited to a single measured analyte. The applicant was advised to adequately explain any significant differences in exposure. The Agency acknowledged the applicant's plan to further optimize the formulation to achieve bioequivalence based on C_{max} and AUC for all analytes.

The designs of the single dose comparative BA study (Study TV50717-BE-10165) and TV50717-PK-10175, the dose proportionality evaluation of the three dosage strengths (6, 12, and 24 mg), were acceptable.

Type B PreNDA Teleconference (February 17, 2022)

The applicant's application is based upon three bioequivalence studies and supplementary PK/PD modeling.

The applicant was advised to include justifications to show that any differences in the shape of the PK curves do not materially impact efficacy and safety. The Agency indicated that the sponsor could use metabolite data for exposure-response analysis as parent drug data was not available in the Phase 3 studies and commented that the sponsor should use available PK/PD data from different dosing regimens tested in previous studies. The applicant commented that the proposed product is titrated to effect and there is a wide therapeutic concentration range.

The Agency recommended the sponsor to include this rationale in their NDA submission. In addition, the Agency recommended that the sponsor confirm the bioanalysis for the parent and metabolite in the pivotal PK bridging.

3.3. Foreign Regulatory Actions and Marketing History

Austedo XR (TV50717 QD) has not been authorized for marketing by any regulatory authority worldwide.

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

Not applicable to this safety-only review.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Three completed registration studies of the TV50717 QD formulation intended for commercial development were submitted in support of this application for QD administration of the extended-release formulation in all indications for which Austedo is currently approved: TV50717-BE-10179, TV50717-PK-10175, and TV50717-BE-10165.

- Study TV50717-BE-10179 demonstrating BE between the BID and QD formulations at steady state for TEV-50717 (C_{max}, AUC) and metabolites (AUC, individually and as a sum).
- Study TV50717-PK-10175 demonstrating dose linearity across the dosage strengths as well as the clinical dose range for the QD formulation (TEV-50717 and metabolites individually and as a sum).
- Study TV50717-BE- 10165, a single dose relative BA of QD formulation vs. the commercial BID tablet and food effect characterization of the QD tablet formulation.

A table describing the studies in more detail may be found in Appendix 3.2

5.2. Review Strategy

This 505(b)(2) application is based upon bioequivalence studies to bridge the safety and efficacy of the new QD formulation to the approved tablet dosage form.
The safety population in this NDA consists of 443 healthy adult volunteers, aged 18-55 years, treated with at least one dose of TEV-50717 in the three registration studies: TV50717-BE-

10179 (n=243), TV50717-PK-10175 (n=116), and TV50717-BE-10165 (n=84). No more than a few doses were given to each subject, and these were within the dose range intended for commercialization.

The adequacy of these studies to support bioequivalence is not addressed in this review of safety; I defer to the assessment of my Clinical Pharmacology colleagues in this regard.

No other data in support of clinical efficacy or safety have been submitted. The review seeks to identify any potential safety signals in the submitted studies that could possibly change the current safety profile of immediate release deutetrabenazine.

6. Review of Individual Trials Used to Support Efficacy

Not applicable

7. Integrated Review of Effectiveness

Not applicable

8. Review of Safety

8.1. Safety Review Approach

The safety population in this NDA consists of 443 healthy adult volunteers who participated in the three registration studies: TV50717-BE-10179 (n=243), TV50717-PK-10175 (n=116), and TV50717-BE-10165 (n=84). (These will be referred to as Studies 10179, 10175, and 10165, below.) Because of the brevity of exposure to TEV-50717, the safety analysis is intended to ensure that no new or previously unidentified safety signal is present.

8.2. Description of Clinical Trials Used to Support Safety

8.2.1. Study TV50717-BE-10179

8.2.1.1. Study 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

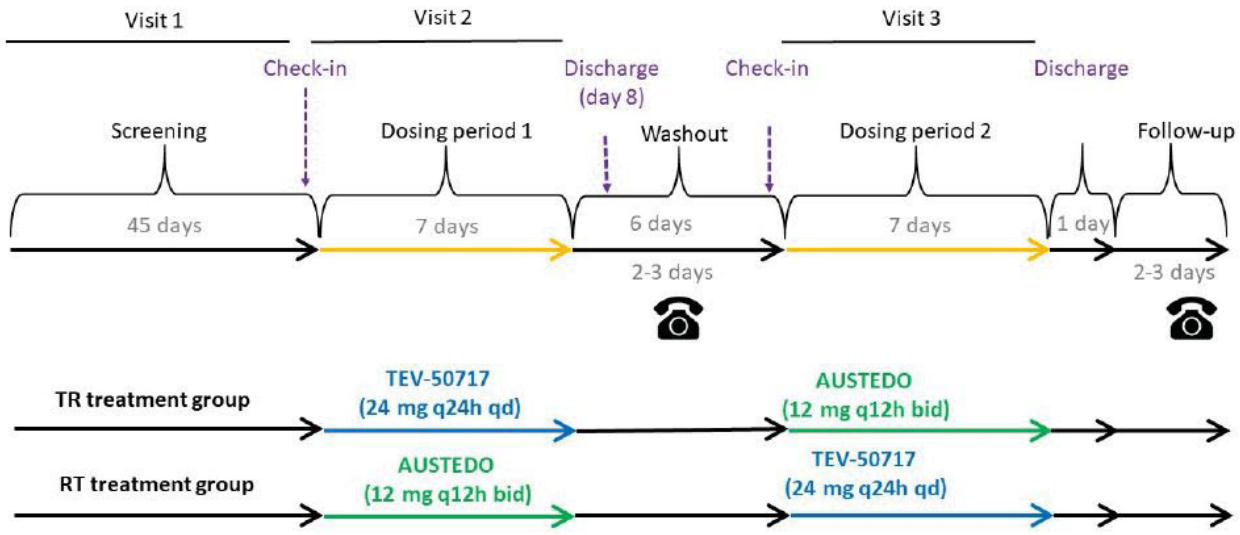
Bioavailability at Steady State Between Once Daily Administration of a 24-mg Extended-Release Tablet of TEV-50717 and Twice Daily Administration of a 12-mg Austedo Tablet

8.2.1.2. Study Design

This was a Phase 1, open-label, single-center, randomized, 2-period, 2-sequence, crossover repeated dose study using a full replicate design under fed conditions to assess BE and relative BA at steady state after repeated administration of TEV-50717 24 mg QD compared to repeated administration of Austedo 12 mg BID in healthy subjects who were extensive or intermediate CYP2D6 cytochrome P450 (CYP) 2D6 metabolizers.

While not blinded, subjects were randomly assigned in a 1:1 ratio to receive treatment sequences that began TEV-50717 (test) 24 mg, QD or Austedo (reference) 12 mg, BID, followed by the other treatment (Figure 2).

Figure 2 Study TV50717-BE-10179 Schema (Source: CSR, p. 25)

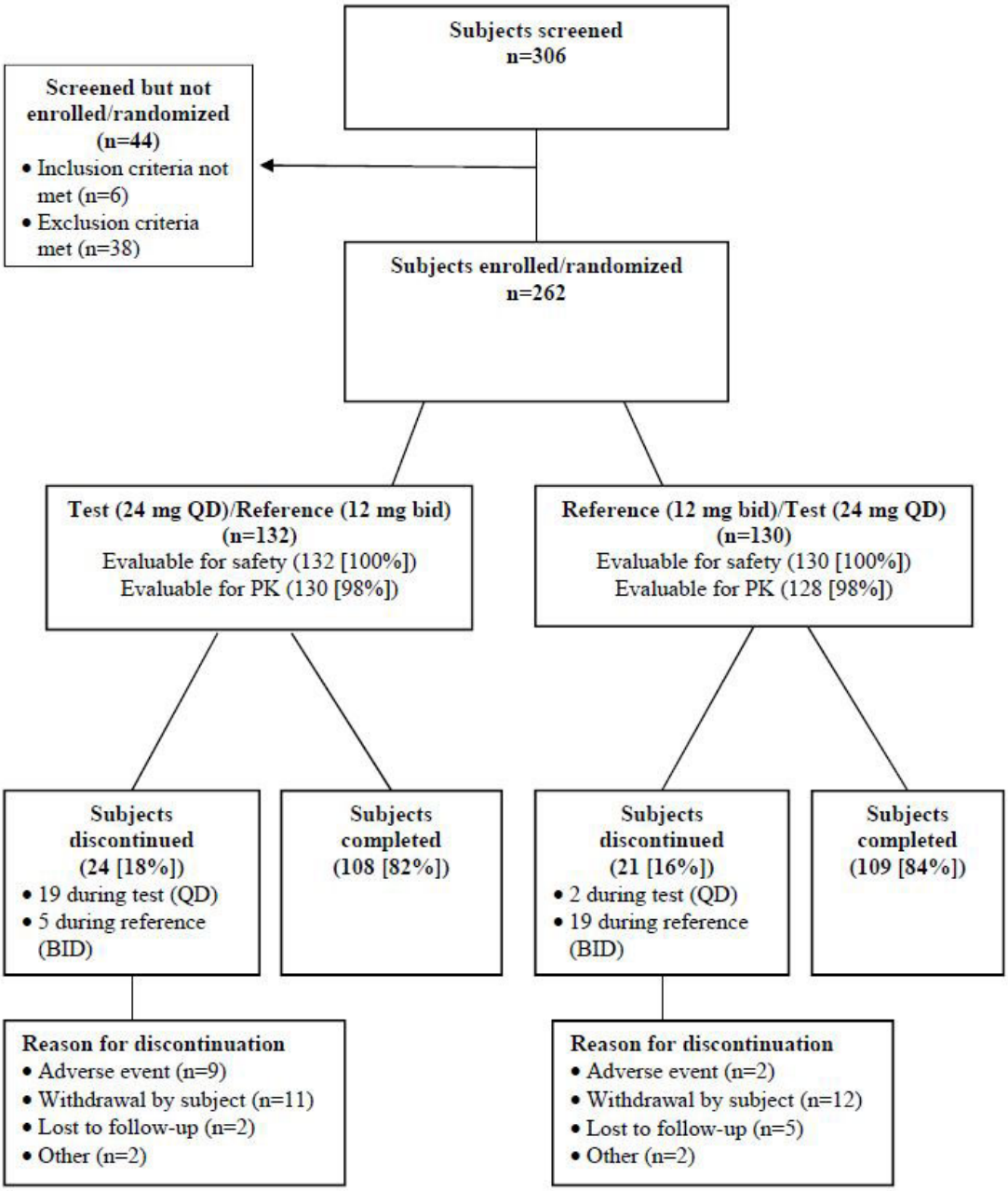


8.2.1.3. Safety Summary

In this study, 262 subjects were enrolled and randomized. Data from 258 subjects were analyzed for pharmacokinetics and data from 262 subjects were analyzed for safety. (Only 243 subjects received the investigational product.) The two arms (test → reference and reference → test) were well matched with regard to age (mean 38.8 and 38.3 years, respectively), sex (70% and 62% men, respectively), and race (87% and 87% white, respectively).

The disposition of the subjects is illustrated in Figure 3 below.

Figure 3 Study TV50717-BE-10179 Disposition of subjects (Source: CSR, p. 66)



There were no deaths, SAEs or severe AEs in this study. The adverse events are discussed further in Section 8.5, below.

8.2.2. Study TV50717-PK-10175

8.2.2.1. Study Title

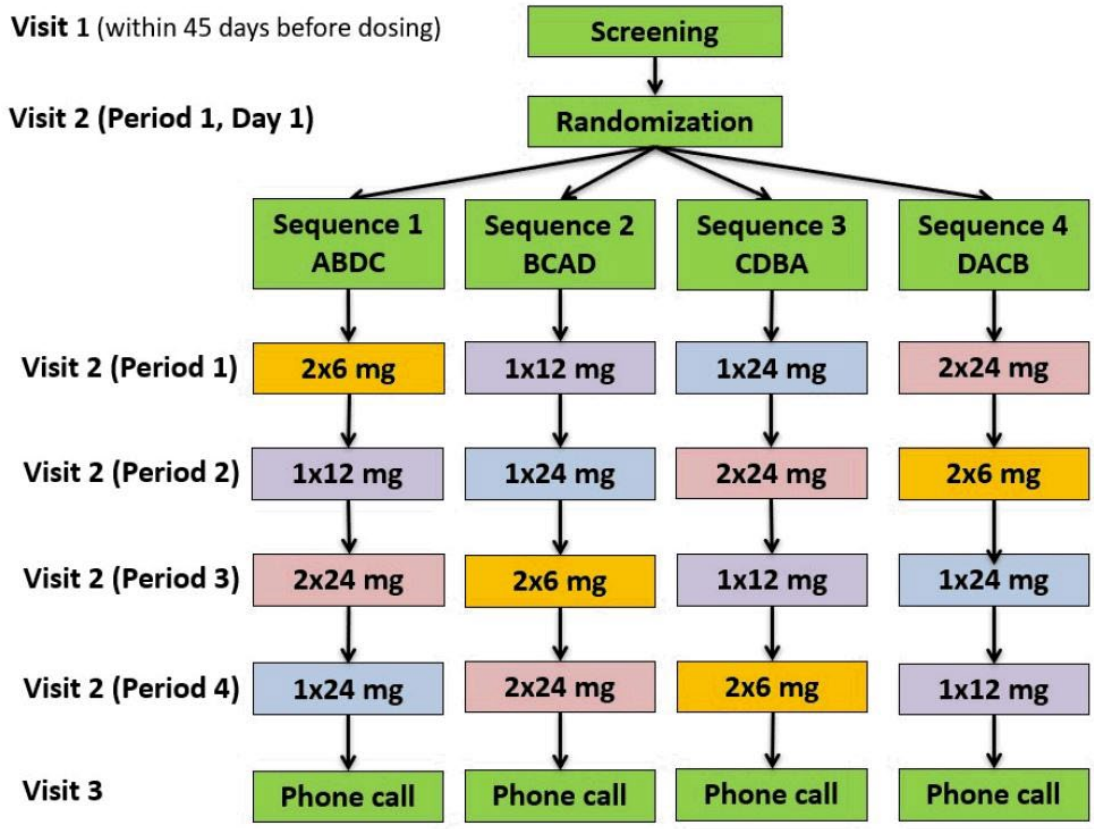
An Open-label, Randomized, Single Dose, 4-way, 4-sequence, Crossover Study in Healthy Subjects to Assess the Dose Proportionality of 6 mg, 12 mg, and 24 mg Extended-Release Tablets of TEV-50717 in the Fed State Over the Clinical Dose Range (6-48 mg)

8.2.2.2. Study Design

This was a Phase 1, open-label, single center, randomized, 4-period, 4-sequence crossover study to assess the dose proportionality of TEV-50717 (parent) and α-HTBZ and β-HTBZ metabolites (individually and as a sum) following the administration of a single dose of TEV-50717 osmotic tablets administered as 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg under fed conditions in healthy subjects, who were known extensive or intermediate CYP2D6 metabolizers (or a combination of the 2), to cover the recommended clinical dose range (6 to 48 mg).

Subjects were to be randomly assigned to receive 1 of the 4 treatment sequences presented in Figure 4 below in a 1:1:1:1 ratio. Subjects received each treatment once within each sequence:

Figure 4 Study TV50717-PK-10175 Schema with treatment sequence (Source: CSR, p. 25)



Note: TEV-50717 was administered under fed conditions.
A 6-day washout period was started after dosing on day 1 in periods 1, 2, and 3.

8.2.2.3. Safety Summary

The following number of healthy volunteers aged 18 to 55 received at least 1 dose of the respective TEV-50717 osmotic tablet dose strengths:

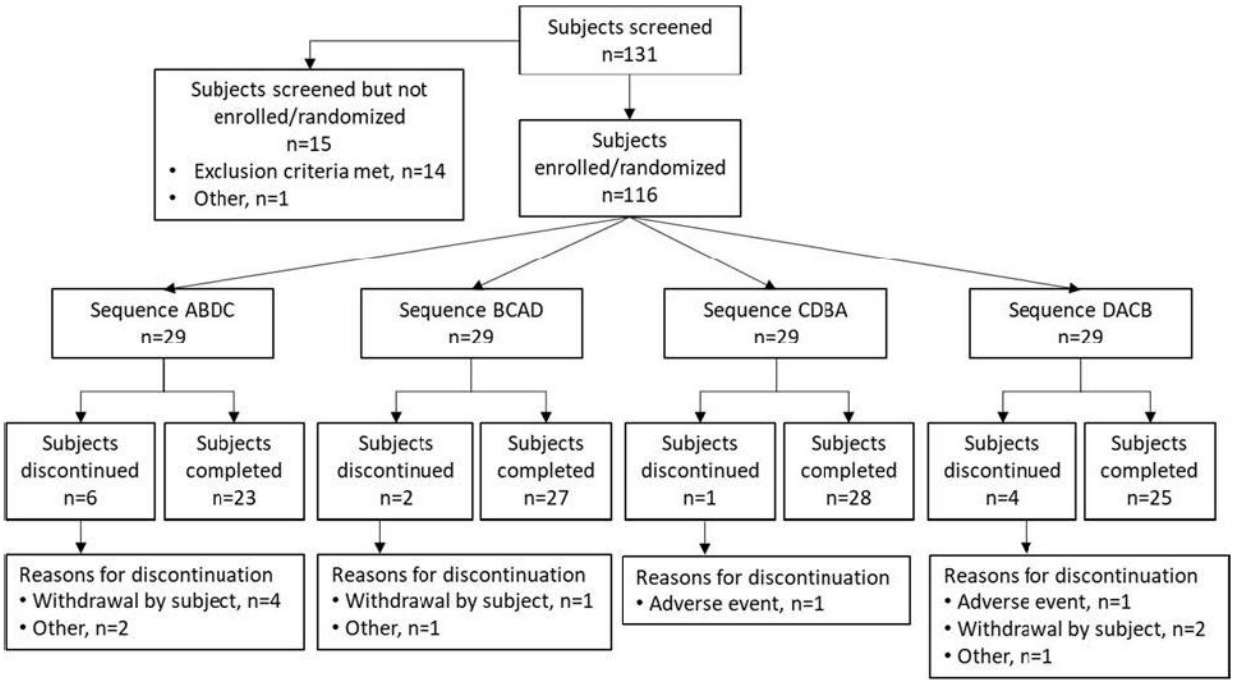
N=113 for the 2×6 mg dose level
N=110 for the 1×12 mg dose level
N=106 for the 1×24 mg dose level
N=111 for the 2×24 mg dose level

The 4 treatment groups (ABDC, BCAD, CDBA, and DACB, corresponding to sequence groups 1, 2, 3 and 4) were generally well matched with regard to age (mean 39.7, 41.9, 41.2, and 40.7 years, respectively), and weight (80.4, 73.3, 73.0, and 74.3 kg, respectively). The gender distribution was 69%, 48%, 59%, and 48% males in sequence groups 1, 2, 3, and 4, respectively.

All 116 subjects enrolled received at least 1 dose of the investigational drug and were evaluated

for safety in the study. Of those, a total of 103 completed the study, and 13 subjects discontinued the study. The disposition of study subjects is illustrated in Figure 5 below.

Figure 5 Study TV50717-PK-10175 Disposition of subjects (Source: CSR, p. 63)



There were no deaths, SAEs or severe AEs in this study. The adverse events are discussed further in Section 8.5, below.

8.2.3. Study TV50717-BE- 10165:

8.2.3.1. Study Title

An Open-label, Randomized, 3-Period, 3-Treatment, 6-Sequence Study in Healthy Subjects to Compare the Bioavailability of TEV-50717 and its Active Metabolites Between a Single Dose of a 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

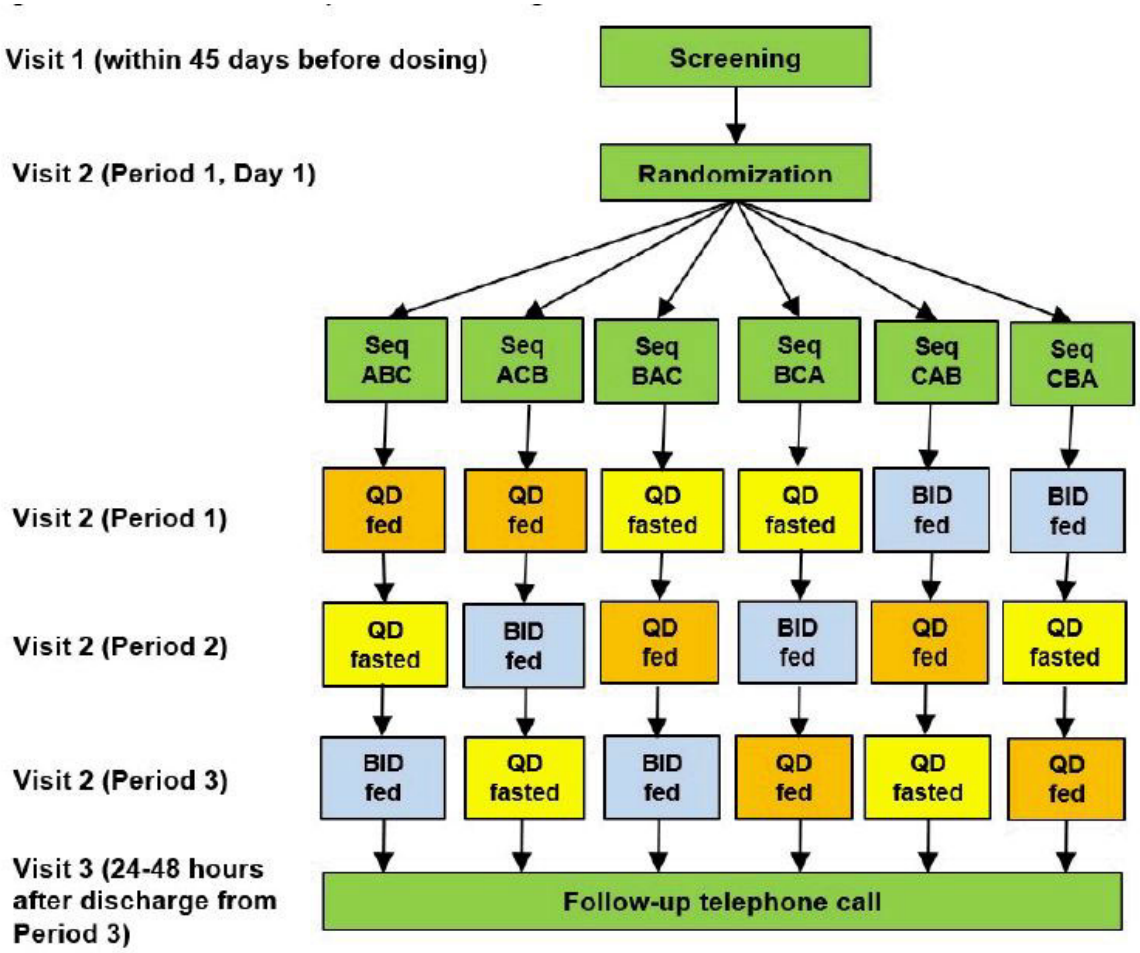
8.2.3.2. Study Design

This was a Phase 1, open-label, single center, randomized, 3-period, 3-treatment, 6-sequence, crossover study to assess the relative BA of TEV-50717 (parent), deuterated α-HTBZ and deuterated β-HTBZ metabolites (individually and as a sum), following oral administration of a single TEV-50717 24-mg QD osmotic tablet compared to a single Austedo 12-mg tablet

administered twice, 12 h apart under fed conditions in healthy subjects. The study also evaluated the effect of food on pharmacokinetics of TEV-50717, deuterated α-HTBZ and deuterated β-HTBZ (individually and as a sum), following a single oral dose of TEV-50717 osmotic tablet.

Subjects were randomly assigned to receive 1 of the 6 treatment sequences. The treatments and their sequence of administration are illustrated below.

Figure 6 Study TV50717-BE- 10165 Design schema and dosing sequence (Source: CSR, p. 23)



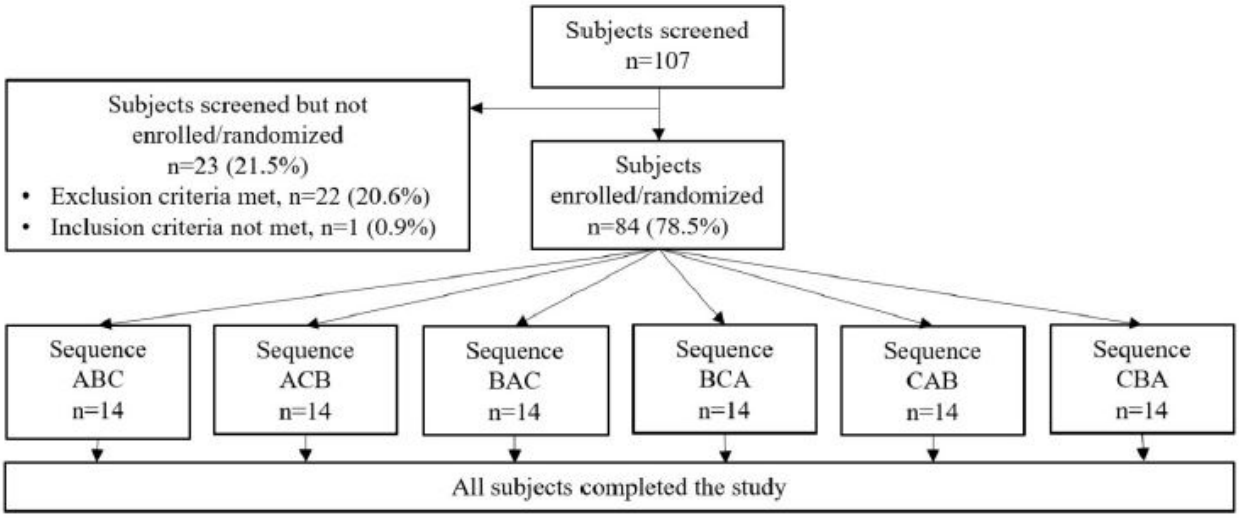
BID=twice daily; QD=once daily; Seq=Sequence
Notes: TEV-50717 was administered as a single dose in fed (QD fed) and fasted (QD fasted) conditions. AUSTEDO was administered as a 12-mg tablet, twice, 12 hours apart in fed condition (BID fed). There was at least a 6-day washout period between the first administration in a period and the first administration in the following period.

8.2.3.3. Safety Summary

All 84 subjects enrolled in the study successfully completed it. The six treatment groups (ABC,

ACB, BAC, BCA, CAB and CBA, corresponding to sequence groups 1, 2, 3, 4, 5 and 6) were matched regarding age (mean 35.6, 36.4, 41.7, 40.9, 36.6, and 39.0 years, respectively), and weight (76.4, 74.9, 73.8, 78.2, 75.1, and 79.4 kg, respectively). Overall, the gender distribution was balanced (56% male and 44 % female).

Figure 7 Study TV50717-BE- 10165 Disposition of subjects (Source: CSR, p. 60)



There were no deaths, SAEs or severe AEs in this study. The adverse events are discussed further in Section 8.5, below.

8.3. Review of the Safety Database

8.3.1. Overall Exposure

In these three biopharmaceutical registration studies, the safety population (n=443) received 851 individual doses of TEV-50717 ranging from 12 to 48 mg:

Table 1 Safety population dosing and exposure to TEV-50717. (Source: 2.7.4 SCS and individual study CSRs)

Study	Exposed to TEV50717QD	Administered dosing (# tabs x mg)	N receiving dose	AUSTEDO comparator dose
TV50717- BE-10179	243	1 x 24 mg	243	12 mg BID
TV50717-PK-10175	116	2 x 6 mg	113	N/A
		1 x 12 mg	110	
		1 x 24 mg	106	
		2 x 24 mg	111	
TV50717-BE-10165	84	1 x 24 mg, fed	84	12 mg BID, fed
		1 x 24 mg, fasted	84	

The disposition of subjects in each of these registrational studies is as follows:

Table 2 Disposition of subjects in TEV-50717 registrational studies. (Source: 2.7.4 SCS, p. 21 and individual study CSRs)

Study Disposition, n (%)	Total TV-50717-BE-10179 (N=262)	Total TV50717-PK-10175 (N=116)	Total TV50717-BE-10165 (N=84)
Screened	306	131	107
Screened but not enrolled/randomized	44	15	23
Randomized	262 (100)	116 (100)	84 (100)
Completed study	217 (83)	103 (89)	84 (100)
Discontinued study	45 (17)	13 (11)	0 (0)
Withdrawal by subject	23 (9)	7 (6)	0 (0)
Subjects discontinued due to AEs	11 (4)	2 (2)	0 (0)
Subjects lost to follow-up	7 (3)	0 (0)	0 (0)
Subjects discontinued due to other reasons	4 (2)	4 (3)	0 (0)

Reviewer's note: *The randomized population receiving TEV-50717 in Study 10179 is actually n=243 (not 262) due to dropout of randomized subjects after they received the Austedo immediate-release comparator but before receiving TEV-50717. In the other two studies, the randomized subjects all received the investigational drug product.*

8.3.2. Relevant characteristics of the safety population:

The population of healthy adult volunteers was suitable for these clinical pharmacology studies. The demographic characteristics of each study's population are listed in the table below. The

populations were equivalent across all three studies.

Table 3 Safety Population demographic characteristics in Studies 10179, 10175, and 10165. (Source: 2.7.4. SCS, p.24)

Demographic variables	TV50717-BE-10179	TV50717-PK-10175	TV50717-BE-10165
N	**262**	**116**	**84**
Age, years			
Mean (SD)	38.6 (9.27)	40.9 (10.43)	38.4 (9.56)
Median	38.0	42.5	40.0
Min, max	18, 55	19, 55	18, 55
Sex, n (%)			
Men	173 (66)	65 (56)	47 (56)
Women	89 (34)	51 (44)	37 (44)
Race, n (%)			
White	228 (87)	99 (85)	74 (88)
Black	34 (13)	17 (15)	10 (12)
Ethnicity, n (%)			
Hispanic or Latino	260 (>99)	115 (>99)	83 (99)

8.3.3. Adequacy of the safety database:

In the Phase 1 clinical studies, subjects were monitored for safety and tolerability and the methods were detailed in the Clinical Study Report for each study. The safety data included adverse events and their outcome, physical and neurological examination findings, vital signs and body weight, electrocardiogram (ECG) results, and clinical laboratory assessments. All studies evaluated the potential for suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS). The methods of assessment, evaluation, and reporting of adverse events are outlined in each study protocol and are considered adequate.

In Studies 10175 and 10179, all AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. Study 10165 employed MedDRA Version 24.0.

8.4. Adequacy of Applicant's Clinical Safety Assessments

8.4.1. Issues Regarding Data Integrity and Submission Quality

After review of the clinical data, there are no concerns regarding integrity of the data or quality of the submission.

8.4.2. Categorization of Adverse Events

The applicant's approach to recording, coding, and categorizing AEs was adequate, and adequately communicated in the study protocols. This includes assessment of severity and assignment of causality as well. Verbatim terms were accurately coded to their respective PTs.

8.4.3. Routine Clinical Tests

Routine clinical laboratory assessment was performed. These were adequate in scope and timing, considering the limited dosing of TEV-50717 in these studies, and their brevity.

8.5. Safety Results

8.5.1. Deaths, SAEs, and Severe AEs

There were no deaths, SAEs, or severe AEs in any of the three studies.

8.5.2. Dropouts and/or Discontinuations Due to Adverse Effects

Study 10179:
During the study, 243 subjects received one or more doses of TEV-50717 and at least 1 adverse event was reported for 28 subjects (12%) treated with TEV-50717 and 22 subjects (9%) treated with the reference product (Austedo BID).

Discontinuation occurred for with 6 in the TEV-507171 QD treatment arm (24 mg QD for 7 days) and 5 in the reference (Austedo 12 mg BID x 7 days) arm. It should be noted that the administered doses of deutetrabenazine are well above the labeled starting dose.

Table 4 Study 10179 AEs leading to discontinuation (Source: CSR and datasets)

Adverse Event Preferred Term	TEV-50717 (N=243)	Austedo BID (N=243)
N with 1 or more AE	**6**	**5**
Anxiety	2	0
Alanine aminotransferase increased	1	0
Aspartate aminotransferase increased	1	0
Asymptomatic COVID-19	1	0
COVID-19	1	1
Rhinorrhea	1	0
Back pain	0	1
Dizziness	0	1
Headache	0	2

Influenza-like illness	0	1

Following review of the narratives, the following events are notable and likely related to TEV-50717 treatment:

Subjects (b) (6) and (b) (6) Each person had anxiety with onset with drug and resolving after 2 days; these events were considered related to treatment.

Subject (b) (6) was a 45-year-old White, Hispanic male who had increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on Day 8 after completing 7 days of TEV-50717 24 mg QD) exposure. The increased ALT (349 IU/L, reference range 0 to 44 IU/L) and increased AST (133 IU/L, reference range 0 to 40 IU/L) resolved without treatment after 15 days. The subject had no history of liver disease, and his history of alcohol use is not reported.

Study 10175:
During the study, 116 subjects received at least one dose of TEV-50717 and 14 subjects (12 %) reported at least 1 AE. Adverse events leading to withdrawal were reported for 2 subjects including 1 subject while receiving 2x6 mg TEV-50717, and 1 subject while receiving 2×24 mg TEV-50717. The former was due to vomiting (considered related to TEV-50171) while the other was related to COVID-19 infection.

Study 10165:
During the treatment period, a total of 8 (10%) subjects reported at least 1 adverse event. All subjects completed the study.

8.5.3. Treatment Emergent Adverse Events and Adverse Reactions

This section includes treatment emergent adverse event occurring in all three studies and includes any that resulted in discontinuation as noted above. I have corroborated these events in each study's respective datasets. All of the events were considered mild or moderate, and all promptly resolved.

Study 10179:
During the study, 243 subjects received one or more doses of TEV-50717 and at least 1 adverse event was reported for 28 subjects (12%) treated with the TEV-50717 and 22 subjects (9%) treated with reference (Austedo BID) treatment. The following table lists the events that I consider reasonably likely to be due to the administered treatments.

Table 5 Study 10179 Treatment Emergent Adverse Events (Source: CSR and datasets)

Preferred Term (N, %)	TEV-50717 (N=243)	Austedo BID (N=243)
Subjects with at least 1 adverse event	**28 (12)**	**22 (9)**
Gastrointestinal disorders	**5 (2)**	**4 (2)**
Diarrhea	2 (<1)	1 (<1)
Constipation	1 (<1)	1 (<1)
Abdominal discomfort	1 (<1)	0
Dyspepsia	1 (<1)	0
Epigastric discomfort	0	1 (<1)
Nausea	1 (<1)	0
Vomiting	0	1 (<1)
Investigations	**2 (<1)**	**2 (<1)**
Alanine aminotransferase increased	1 (<1)	1 (<1)
Aspartate aminotransferase increased	1 (<1)	0
Blood creatine phosphokinase increased	0	1 (<1)
Blood creatinine increased	1 (<1)	0
Nervous system disorders	**8 (3)**	**9 (4)**
Headache	7 (3)	7 (3)
Dizziness	1 (<1)	2 (<1)
Psychiatric disorders	**3 (1)**	**0**
Anxiety	2 (<1)	0
Nightmare	1 (<1)	0

Study 10175:
During the study, 116 subjects received at least one dose of TEV-50717 and 14 subjects (12 %) reported at least 1 AE. The table below reflects the AEs that were considered treatment emergent.

Table 6 Study 10175 Treatment Emergent Adverse Events (Source: CSR and datasets)

Preferred Term	2x6 mg (N=113)	1x12 mg (N=110)	1x24 mg (N=106)	2x24 mg (N=111)	Total (N=116)
Subjects with at least 1 AE	5	3	2	4	14
Gastrointestinal disorders	**3**	**0**	**0**	**0**	**3**
Abdominal discomfort	1	0	0	0	1
Dyspepsia	1	0	0	0	1
Vomiting	1	0	0	0	1
Nervous system disorders	**2**	**0**	**0**	**0**	**2**
Dizziness	1	0	0	0	1
Headache	1	0	0	0	1

Study 10165:
In this study, 84 subjects in 6 different treatment schemas received three treatment conditions, either fed or fasted. During the treatment period, a total of 8 (10%) subjects reported at least 1 adverse event. In the safety population, the only adverse events that occurred in more than 1 subject were (PT) headache and presyncope, reported for 3 (4%) and 2 (2%) subjects, respectively.

Table 7 Study 10165 Treatment Emergent Adverse Events (Source: CSR and datasets)

Preferred Terms (N=84)	TEV-50717 24 mg fed	TEV-50717 24 mg fasted	Austedo 12 mg BID fed
Nervous system disorders (patients)	**1**	**3**	**1**
Headache	1	2	0
Presyncope	0	1	1
Dizziness	0	1	0
Other SOCs			
Toothache	0	0	1
Influenza like illness	0	1	0
Skin abrasion	0	1	0
Pain in extremity	1	0	0
Erythema	1	0	0

On review, it is unlikely that the AEs reported in SOCs other than Nervous System Disorders were related to medication.

8.5.4. Laboratory Findings

Abnormal hepatic function tests occurring in Study 10179 for subject (b) (6) were noted above: increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) on Day 8 after completing 7 days of TEV-50717 24 mg QD exposure. Another subject had a reported increase in creatinine, but no other details were submitted. No other laboratory abnormalities were reported.

8.5.5. Vital Signs

In all three studies the assessment of vital signs was standardized so that VS were taken at regular intervals following administration of the investigational medicinal product. No changes in VS were found using measures of central tendency and no AEs related to VS were reported.

While dizziness was reported as an AE in the safety population, orthostatic hypotension was not. No subject had clinically significant abnormal vital sign values in any of the three studies.

8.5.6. Electrocardiograms (ECGs)

The applicant found no clinically meaningful trends in mean changes from baseline at discharge for any ECG parameter and no clinically significant ECG findings were reported by the investigator at discharge. No subjects met discontinuation criteria based on QTcF. There were instances of lengthening of the QTc but not to the pre-specified criteria for additional concern or drug discontinuation.

8.6. Analysis of Submission-Specific Safety Issues

The prescribing information of the innovator product (Austedo, NDA 208082) lists a variety of adverse drug reactions that are relevant to this IMP. Because this information will be incorporated into the label for this product as well, I list them below. In this small development program, no such events occurred.

Increased risk of depression and suicidality in Huntington's disease
QT prolongation
Neuroleptic malignant syndrome
Akathisia, agitation, restlessness, and parkinsonism
Sedation/somnolence

In all three studies, none of the subjects reported suicidal behavior/ideation assessed using the C-SSRS.

8.7. Safety Analyses by Demographic Subgroups

Subgroup analysis for this application is neither informative nor valid due to the small number of subjects and limited exposure to TEV=50717.

8.8. Specific Safety Studies/Clinical Trials

No targeted clinical safety studies were performed.

8.9. Additional Safety Explorations

No additional safety explorations were performed.

8.10. Safety in the Postmarket Setting

8.10.1. Safety Concerns Identified Through Postmarket Experience

No postmarketing data is available for the TEV-50717 as the QD formulation is not currently commercially available in any country.

The sponsor did not provide a review of post-market experience for the innovator product but I reviewed the last Periodic Safety Update Report (PSUR) for Austedo (NDA 208082) covering the period 4/1/2021 to 3/31/2022. No new safety signal or concern was identified for deutetrabenazine.

8.10.2. Expectations on Safety in the Postmarket Setting

No new safety signals have been identified for deutetrabenzine in this application. None are expected in the postmarket setting.

8.10.3. Additional Safety Issues From Other Disciplines

None at the time of this review.

8.11. Integrated Assessment of Safety

No new safety concerns were identified for this extended-release formulation of deutetrabenazine. The proposed indications are the same as those of the immediate release-formulation: the treatment of chorea in Huntington's disease and tardive dyskinesia in adults.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee input was sought for this application. There is considerable safety and efficacy experience with the innovator listed drug for this QD formulation, deutetrabenazine, an approved VMAT2 inhibitor.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended at this time.

12. Postmarketing Requirements and Commitments

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

13. Appendices

13.1. Financial Disclosure

All three clinical pharmacology studies supporting the registration of TEV-50717 were performed in the same clinical trial site by the same investigator and subinvestigators. Separate (but identical) financial disclosure certification was provided for the three studies as summarized together in the form below. No financial conflict of interest was identified.

Covered Clinical Studies TV50717-BA-10165, TV50717-BE-10179 and TV50717-PK-10175.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 8		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **Not applicable** Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.2. Synopses of individual clinical pharmacology studies (Source: Module 2.7.6)

Study Identifier and study type	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, and route of administration	Number of subjects M/F: (enrolled) Age range (y) (enrolled)	Duration of treatment
TV50717-BE-10179 Phase 1: PK and safety 1 center United States	Repeated administration of TEV-50717 24 mg QD compared to repeated administration of Austedo 12 mg BID under fed conditions to assess: • BE with regard to AUC0- 24h,ss of TEV-50717 (parent), α- HTBZ and β-HTBZ (individually and as a sum) at a steady state • BE with regard to Cmax,ss for TEV-50717 (parent) • Relative BA with regard to Cmax,ss for α-HTBZ and β-HTBZ (individually and as a sum) • Relative BA with regard to Cmin,ss for TEV-50717 (parent), α-HTBZ and β-HTBZ (individually and as a sum) • PK parameters of TEV-50717 (parent) and α-HTBZ and β-HTBZ (individually and as a sum) at steady state • Safety and tolerability of TEV-50717 at steady state	Open-label, randomized, repeated dose, 2-treatment, 2-period, 2- sequence cross over study with full replicate design	Austedo tablets (reference); TEV-50717 QD osmotic tablets (test) 12 mg BID (reference); 24 mg QD (test) Oral administration	Entered: 262 Completed: 217 Analyzed for safety: 262 Analyzed for PK: 158 M/F: 173/89 18-55 (y)	21 days 7-day dosing period 1, 6- day washout, 7- day dosing period 2, 1- day discharge
TV50717-PK-10175 Phase 1: PK and safety 1 center United States	Single doses of TEV-50717 QD osmotic tablets administered as 2×6 mg, 1×12 mg, and 1×24 mg under fed conditions to assess: • Relative BA between 2×6 mg and 1×12 mg TEV-50717 QD osmotic tablets for all analytes (TEV-50717, α-HTBZ and β-HTBZ [individually and as a sum]) • Dose proportionality (6 mg-24 mg) of the PK of TEV-50717, α-HTBZ and β-HTBZ (individually and as a sum) • Dose proportionality (6 mg-24 mg) of Cmax of TEV-50717 Single doses of TEV-50717 QD osmotic tablets administered as 2×6 mg, 1×12 mg, 1×24 mg, and 2×24 mg under fed conditions to assess:	Open-label, randomized, single dose, 4-way, 4-sequence, cross over study	TEV-50717 QD osmotic tablet 2×6 mg, 1×12 mg, 1×24 mg, 2×24 mg Oral administration	Entered: 116 Completed: 103 Analyzed for safety: 113 Analyzed for PK: 112 M/F: 65/51 19-55 (y)	4-week treatment/ observation period where each single dose was followed by a 6-day wash-out period

Study Identifier and study type	Objective(s) of the study	Study design and type of control	Test product(s), dosage regimen, and route of administration	Number of subjects M/F: (enrolled) Age range (y) (enrolled)	Duration of treatment
	• Dose proportionality (6 mg – 48 mg) of the PK of TEV-50717, α-HTBZ and β-HTBZ (individually and as a sum) • PK parameters of TEV- 50717, α-HTBZ and β-HTBZ (individually and as a sum) after single doses of TEV-50717 QD tablets • Safety and tolerability of TEV-50717 after single doses of 6, 12, 24, and 48 mg				
TV50717-BE-10165 Phase 1: PK and safety 1 center United States	• Assess the relative BA with regard to extent of exposure of TEV-50717 (parent), α-HTBZ and β-HTBZ (individually and as a sum), after a single TEV-50717 24 mg QD dose compared to a single Austedo 12 mg tablet administered twice, 12 h apart under fed conditions • Assess the relative BA with regard to the peak of exposure of TEV 50717, α- HTBZ and β-HTBZ (individually and as a sum), after a single TEV-50717 24 mg QD dose compared to a single Austedo dose (12 mg administered twice, 12 h apart) under fed conditions • Assess the effect of food on TEV-50717, α- and β-HTBZ (individually and as a sum), after a single TEV-50717 24 mg QD dose under fed and fasted conditions • Assess additional PK parameters of TEV-50717, α- HTBZ and β-HTBZ (individually and as a sum), after a single TEV 50717 24 mg QD dose under fed and fasted conditions and after a single Austedo dose (12 mg administered twice, 12 h apart) under fed conditions • Evaluate the safety and tolerability of TEV-50717, after a single 24-mg QD tablet in fed and fasting conditions and a single Austedo dose (12 mg administered twice, 12 h apart) under fed conditions	Open-label, randomized, single dose, 3-period, 3-treatment, 6- sequence study	Austedo tablets (reference); TEV-50717 QD osmotic tablets (test) 2x12 mg where 12 mg was administered twice 12 h apart (reference); 1x24 mg QD Oral administration	Entered: 84 Completed: 84 Analyzed for safety: 84 Analyzed for PK: 84 M/F: 47/37 18-55 (y)	24-day treatment/ observation period where each single dose was followed by a 6-day washout period

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/s/

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