Clinical Study Protocol

Real-World Effectiveness and Safety of Deutetrabenazine in Chinese Patients with Chorea Associated with Huntington's Disease

Study Number TV50717-NDG-40182

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TITLE PAGE

Phase 4 Study protocol with Amendment 01

Study Number TV50717-NDG-40182

Real-World Effectiveness and Safety of Deutetrabenazine in Chinese Patients with Chorea Associated with Huntington's Disease

Phase 4

Protocol Approval Date: 14 May 2024

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This study will be conducted in accordance with current applicable national legislation, regulation, health authority guidance and Teva (or designated CRO's) SOP.

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AMENDMENTS AND UPDATES

Table: Major Amendments and updates

Number	Date	Original text	New wording	Reason
1	14 May 2024	5.1 Overall Study Design and Plan This is a multi-centre, prospective, longitudinal, observational study of deutetrabenazine for the treatment of chorea associated with HD in the real-world setting in China. Patient demographics, comorbidities, concomitant medications, disease and clinical characteristics of the chorea associated with HD (including severity, impact, and treatment), and effectiveness and safety outcomes will be collected at baseline and follow-up visits and contacts. Data will be collected using comprehensive case report forms (CRFs) at enrolment and follow-up contacts, separately, by treating physicians and/or research delegates from participating centres.	5.1 Overall Study Design and Plan This is an open-label, single arm, multi-centre, prospective, interventional study of deutetrabenazine for the treatment of chorea associated with HD in the real-world setting in China. With the exception of drug provision, other clinical procedures shall follow the current clinical practice, to maintain the minimal level of intervention on disease management, so that the effectiveness and safety outcomes of deutetrabenazine in this study could best indicate product's performance in the real world. The investigational medicinal product (IMP) is provided by the sponsor once the patients are enrolled and throughout the study treatment period. The total duration of individual participation in the study is planned to be 16 weeks. Patients are expected to participate in this study for its entire duration. The IMP has been launched on the Chinese market and was officially included in NRDL of China. After completing the protocol-defined treatment period, it is up to patients to choose the follow-up treatment based on the physician's recommendation and personal preference.	Investigational products will be provided to enrolled patients, the study design is changed from an observational study to an interventional study, relevant descriptions of IMP are added to the amendment.

Number	Date	Original text	New wording	Reason
2	14 May 2024	5.1 Overall Study Design and Plan The visit window of all scheduled visits during follow-up is ± 3 days. Detailed summary of the schedule and data collection scope for each visit/contact is presented in Table 2.	5.1 Overall Study Design and Plan The visit window of all scheduled visits during follow-up is ± 3 days. If the patient discontinues deutetrabenazine treatment early, on-site follow-up to assess the TMC score will be required within 3 days of the investigator's becoming aware of discontinuation. Detailed summary of the schedule and data collection scope for each visit/contact is presented in Table 4	The description of efficacy data collection for patients who discontinue treatment early is further clarified
3	14 May 2024	Table 1. Schedule of visits 7. Chorea control will be collected per the physician's practice.	Table 2. Schedule of visits 7. Chorea control will be collected per the physician's practice. 8. Drug can be dispensed on unscheduled visit if drug available is not enough until next visit. 9. If the patient discontinues deutetrabenazine treatment early, on-site follow-up to assess the TMC score will be required within 3 days of the investigator's becoming aware of discontinuation.	Corresponding to the update of main text, new descriptions of IMP dispensing and early treatment discontinuation are added to the table remarks.
4	14 May 2024	**5.2.1** Patient Population Follow-up will be examined independently for each of the study outcomes. Study participants will be followed-up from the date of deutetrabenazine initiation until the earliest of the following dates: • End of study period • Loss to follow-up Death	**5.2.1** Patient Population Study participants will be followed-up from the date of deutetrabenazine initiation until the earliest of the following dates: • End of study period • Withdrawal of consent • Loss to follow-up Death	Patient withdrawal of consent could be considered a condition of study termination.

5	14 May 2024	• **NA**	New Section: 6. Study treatment 6.1 Investigational Medicinal Products Used in the Study As the IMP, this study uses AUSTEDO® (deutetrabenazine) tablets, which received marketing authorization from CDE and is on the Chinese market. One dose strength of AUSTEDO® will be available for use: 6 mg tablets. IMP is coated with a colored polymer coating. The colored polymer coating is applied to the tablets according to dose strength; 6 mg - purple. The dose strength will have a black marking of SD 6, corresponding to the dose strength. AUSTEDO® (deutetrabenazine) tablets have been manufactured according to current Good Manufacturing Practices regulations. During titration/dose adjustment, AUSTEDO® (deutetrabenazine) tablets will be supplied in bottles of 28 tablets as 6 mg tablets and will be labeled according to applicable regulatory guidelines. Patients will be provided sufficient supply of drug according to physicians' prescription until the next specified visit or the end of study, plus coverage to account for potential delays in study visits or evaluations or receipt of their supplies. After completing the protocol-defined treatment period, patients can choose the follow-up treatment based on the physician's recommendation and the patient's preference. AUSTEDO® (deutetrabenazine) tablets must be stored according to the specifications listed in Table 2. The investigator must confirm appropriate temperature conditions have been maintained for all IMP received and any discrepancies are reported and resolved before use of the IMP. 6.2 Dosing and Administration	Because the study design is changed to an interventional study, relevant descriptions of IMP are added to the amendment.

The titration and the maintenance dose for each patient will be based on the physician's clinical judgments in the real-world setting. Thus, the titration and maintenance dose can vary due to the heterogeneity across patients.

The Chinese product insert (PI) is provided as general reference to help physicians determine treatment regimens. Per the Chinese PI15, the initiation dose of AUSTEDO for the treatment of chorea associated with HD is 12 mg daily, with weekly intervals of dose increase in 6 mg increments. Deutetrabenazine dose will be titrated to a level in which adequate chorea control has been achieved and the patient is tolerating the treatment regimen, or until the maximum permitted dose is reached. Per the PI15,17, the maximum recommended daily dose of deutetrabenazine is 48 mg (24 mg twice daily), unless the patient is a poor cytochrome P450 2D6 (CYP2D6) metabolizer or with concomitant use of strong CYP2D6 inhibitor(s), in which case the maximum total daily dose is 36 mg. At the end of the titration period, the patient's dose will be established for the maintenance period. Patients will be recommended to receive treatment with deutetrabenazine ≥24 mg/day for at least 4 weeks in the maintenance period if the patient is tolerating the treatment.

Administer IMP with food. Swallow IMP whole. Do not chew, crush, or break tablets.

Table 3. Investigational Medicinal Products Used in Study

IMP name	AUSTEDO®
Trade name and INN, if applicable, or company-assigned number	TEV-50717 (deutetrabenazine)
Formulation	Solid oral dosage form (tablet with nonfunctional film coating)

Unit dose strength(s)/Dosage level(s)	6 mg
Route of Administration	Oral
Packaging	IMP will be provided in bottles
Manufacturer	Anesta LLC 4745 Wiley Post Way Salt Lake City, UT 84116, USA
Storage Conditions	Protect from light; store sealed below 25°C in a dry place

INN=international nonproprietary name.

6.3 Accountability

The IMP must be used in accordance with the Chinese PI and the protocol. All materials supplied are for use only in this study and should not be used for any other purpose.

The IMP shipment will include a packing slip listing the contents of the shipment and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMP from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the local regulations, and used in accordance with this protocol.

A record of IMP accountability (i.e., IMP and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Unused bottles of IMP and partially used IMP due to early treatment discontinuation will be returned to the sponsor or its designee according to local and national regulations and the site's SOPs, following written authorization from the

Number	Date	Original text	New wording	Reason
			sponsor. These activities will be performed after the study close out to allow the monitor to conduct a reconciliation of the IMP.	
6	14 May 2024	NA	New Section: 11. Study monitoring. The Sponsor (or designated CRO) is responsible for assuring the proper conduct of the study regarding protocol adherence and validity of the data recorded on the eCRFs. Subject confidentiality will be maintained. In accordance with applicable regulations18, and Sponsor (or designated CRO) procedures, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrolment rate. The visits will be conducted in accordance with the Sponsor's (or designated CRO's) SOP and study monitoring plan. In general, the Investigator agrees to fully cooperate with the monitor, allow the monitor direct access to all relevant documents, to allocate his/her time and the time of his/her staff to the monitor to discuss any findings and any relevant issues as needed.	Study monitoring is very important for data quality control, and this part of the original protocol is missing, it is added in the amendment.

RESPONSIBLE PARTIES

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Investigators

Principal Investigator

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For Adverse Events and Special Situations Reporting:

Send by e-mail to local safety officer (LSO) at: safety.china@tevachina.com

General reports describing all adverse events and special situations will be provided to Teva upon study completion.

SYNOPSIS

Protocol Title	Real-World Effectiveness and Safety of Deutetrabenazine in Chinese Patients with Chorea Associated with Huntington's Disease (HD)
Protocol ID	Amendment 01
Phase	IV
Name of IMP	Deutetrabenazine
Study Objectives	Primary objective: to evaluate the real-world effectiveness of deutetrabenazine in adult patients with chorea associated with HD in China Secondary objectives: to evaluate the real-world safety of deutetrabenazine in adult patients with chorea associated with HD in China
Study Sites	Leading site: Huaxi Hospital
Study Design	An open-label, single arm, multi-centre, prospective, interventional study
Number of Study Patients	Eighteen patients receiving treatment with deutetrabenazine ≥24 mg/day, and total fifty patients regardless of dosage.
Study Population	Adult patients with chorea associated with HD who are eligible for deutetrabenazine in China and meet the study inclusion/exclusion criteria
Inclusion Criteria	• Patients aged 18 years or older with clinically confirmed diagnosis of chorea associated with HD • Patients whose baseline total maximal chorea (TMC) score ≥ 8 • Patients who are deutetrabenazine-naïve before study entry or who did not receive deutetrabenazine within 30 days of study entry, and who are about to be treated with deutetrabenazine for chorea associated with HD • Patients who have provided written consent for the use of personal and medical information for study purposes
Exclusion Criteria	• Patients who have an unstable or serious medical or psychiatric illness at baseline • Patients with any history of suicidality, untreated or inadequately treated depression • Patients with certain comorbidities, including hepatic impairment, congenital long QT syndrome, and clinically significant cardiac arrhythmias. • Patients who received reserpine within 20 days of deutetrabenazine treatment initiation • Patients who received monoamine oxidase inhibitors within 14 days of deutetrabenazine treatment initiation • Patients who received vesicular monoamine transporter 2 (VMAT2) inhibitors, e.g., tetrabenazine or valbenazine, within 30 days of deutetrabenazine treatment initiation • Patients unable to provide a written consent for the study. • Patients who are participating in another study that includes treatment with an investigational drug and/or intervention at the same time as enrolment in the current study

Study Procedures/Frequency	Patients will be followed up on a biweekly (every two weeks) basis, and the primary endpoint, i.e., the effectiveness of deutetrabenazine, will be assessed at week 16 after study baseline. The study follow-up will be ended after 16 weeks from study baseline.
Study arm	Single arm: Deutetrabenazine
IMP dosing and administration	The titration and the maintenance dose for each patient will be based on the physician's clinical judgments in the real-world setting.
Study Endpoints	Primary endpoint: the effectiveness of deutetrabenazine assessed as the change of TMC score from baseline to week 16 after study baseline in patients receiving deutetrabenazine treatment ≥24 mg/day. Secondary endpoints: 1) the occurrence of adverse events for all patients (regardless of dosage); 2) the effectiveness of deutetrabenazine assessed as the change of TMC score from baseline to week 16 after study baseline in all patients (regardless of dosage) Exploratory endpoint: [redacted]
Statistical Analysis	Descriptive statistics will be provided for patient demographics, disease and clinical characteristics, treatment information, effectiveness, and safety outcomes. The primary analysis of the TMC scores will be conducted using an adjusted linear mixed effects regression model. Variables such as age at baseline, sex, comorbidities, and concomitant medications will be adjusted in the model if feasible/applicable.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CCI	Charlson Comorbidity Index
CDE	Center for Drug Evaluation
CDISC	Clinical Data Interchange Standards Consortium
CDMS	Clinical data management system
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRO	Contract research organisation
CSR	Clinical Study Report
CYP2D6	Cytochrome P450 2D6
DMP	Data Management Plan
EC	European Commission
eCRF	Electronic case report form
eDC	Electronic data capture
EMR	Electronic medical records
HCP	Health care professional
HD	Huntington's disease
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LoE	Lack of Efficacy
LSO	Local safety officer
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
PI	Product insert
PV	Pharmacovigilance

Abbreviation	Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDTM-CT	Study Data Tabulation Model-Controlled Terminology
SOP	Standard operating procedures
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
TD	Tardive dyskinesia
TFC	Total functional capacity
TMC	Total maximal chorea
UHDRS	Unified Huntington's Disease Rating Scale
ULN	Upper limit of the normal range
VMAT2	Vesicular monoamine transporter 2

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1. RATIONALE AND BACKGROUND

Huntington's disease (HD) is a hereditary, progressive, neurodegenerative disorder characterized by involuntary movements, cognitive dysfunction, and psychiatric symptoms[1]. The estimated prevalence of HD is 0.42 per 100,000 in the Asian population[2]. Huntington's disease causes significant disability with declining cognitive function and increasing movement disorders, and leads eventually to death[3]. Along the course of the disease, HD is associated with substantial impact on the quality of life and imposes economic burden on both patients and caregivers[4]. Specifically, chorea is one of the prominent symptoms of HD and can interfere with daily activities and increase the risk of injury[1,5,6]. Studies have shown that chorea is the first clinical feature in more than 50% of patients with late-onset (≥60 years) HD and is a presenting feature in over 90% of this population[7].

HD is currently incurable. The treatment of HD is presently focused on symptomatic management, including chorea control[8]. Deutetrabenazine, a highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor, was approved by the United States Food and Drug Administration for the treatment of chorea associated with HD and tardive dyskinesia (TD) in adults in 2017[9]. The approval for the indication of chorea associated with HD was based on evidence from a phase 3 clinical trial, First-HD[1]. This randomised, double-blind, placebo-controlled study demonstrated that treatment with deutetrabenazine improved chorea control at 12 weeks. Specifically, mean Unified Huntington's Disease Rating Scale (UHDRS) total maximal chorea (TMC) score decreased from baseline to maintenance therapy by 4.4 points in the deutetrabenazine group (N=45) vs. 1.9 points in the placebo group (N=45), with a statistically significant difference of 2.5 points ($p<0.001$)[1]. The study also demonstrated a promising safety profile of deutetrabenazine in adults[1]. The safety profile was further confirmed with the long-term open-label extension study, ARC-HD[10,11].

2. INTRODUCTION

In 2018, Center for Drug Evaluation (CDE) of China's National Medical Products Administration (NMPA) placed deutetrabenazine on the List of Overseas New Drugs Urgently Needed in Clinical Settings (the First Batch)[12]. After the approval for a priority review by CDE in 2019[13], deutetrabenazine was approved by NMPA for the treatment of chorea associated with HD and TD in adults in China in May 2020[14,15]. Deutetrabenazine was launched in China on 17 January 2021. At present, deutetrabenazine has passed the national medical insurance negotiation and was officially included in the National Reimbursement Drug List（NRDL） of China[16].

[redacted]

Currently, real-world evidence on the use of deutetrabenazine among Chinese patients with chorea associated with HD is limited. Although the need for a pre-approval clinical trial in China for the purpose of registration was waived under the Urgent Clinical Need Medicines Policy promulgated by NMPA, a post-marketing study of deutetrabenazine for Chinese patients with chorea associated with HD is required.

A multi-centre, prospective, longitudinal study of deutetrabenazine for the treatment of chorea associated with HD in the real-world setting in China will be conducted. Patient demographics, comorbidities, concomitant medications, disease and clinical characteristics of the chorea associated with HD (including severity, impact, and treatment), and effectiveness and safety outcomes will be collected throughout the study. Treatment with deutetrabenazine will start with a titration period, followed by a maintenance period. The duration of titration and the maintenance dose for each patient will be based on physicians' clinical judgments in the real-world setting and other non-clinical factors such as affordability. Patients will be followed up on a biweekly (every two weeks) basis, and the primary endpoint, i.e., the effectiveness of deutetrabenazine, will be assessed at week 16 after study baseline. The study follow-up will be ended after 16 weeks from study baseline. The study will be conducted in compliance with the protocol.

3. COMPLIANCE STATEMENT

The study is a real-world effectiveness and safety study. This study will be conducted in accordance with applicable laws, regulations, guidelines, and the Sponsor's Standard Operating Procedures (SOPs) that have been made available to the data vendor from time to time and as applicable to the study.

The investigator is responsible for performing the study in accordance with this protocol and the applicable guidelines for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the applicable study staff must be familiar with the background and requirements of the study.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Institutional Review Board (IRB), and with local authorities.

4. STUDY OBJECTIVES

4.1. Primary Objective

To evaluate the real-world effectiveness of deutetrabenazine in adult patients with chorea associated with HD in China, as assessed by the change in TMC score.

4.2. Secondary Objective

To evaluate the real-world safety of deutetrabenazine in adult patients with chorea associated with HD in China, as assessed by the proportion of adverse events (AEs) and AEs leading to discontinuation of treatment.

5. STUDY DESIGN

5.1. Overall Study Design and Plan

This is an open-label, single arm, multi-centre, prospective, interventional study of deutetrabenazine for the treatment of chorea associated with HD in the real-world setting in China. With the exception of drug provision, other clinical procedures shall follow the current clinical practice, to maintain the minimal level of intervention on disease management, so that the effectiveness and safety outcomes of deutetrabenazine in this study could best indicate product's performance in the real world.

The investigational medicinal product (IMP) is provided by the sponsor to the patients who are enrolled after amendment 01 become effective and throughout the study treatment period. The total duration of individual participation in the study is planned to be 16 weeks. Patients are expected to participate in this study for its entire duration. The IMP has been launched on the Chinese market and was officially included in NRDL of China[16]. After completing the protocol-defined treatment period, it is up to patients to choose the follow-up treatment based on the physician's recommendation and personal preference.

Adult patients with confirmed diagnosis of chorea associated with HD will be enrolled. Detailed inclusion/exclusion criteria are described in **Section 5.2**. This study aims to recruit fifty adult patients. The sample size estimation is described in detail in **Section 8.1**.

An overview of the study design is shown in **Figure 1.**

At study baseline, information on patients' demographics, comorbidities, concomitant medications, disease and clinical characteristics of the chorea associated with HD (including severity, impact, and treatment) will be collected, and the baseline TMC score (described in detail in **Section 5.3.2**) will be assessed by trained physicians and/or research delegates. After the baseline assessment, deutetrabenazine treatment will be initiated and its detailed treatment information (including treatment phase, duration, dose and dosing schedule, and dose modification) for chorea associated with HD will be collected at baseline and during each follow-up visit/contact.

Treatment with deutetrabenazine will start with a titration period, followed by a maintenance period, the whole treatment period will last for 16 weeks. Per the Chinese product insert (PI)[15], the initiation dose for the treatment of chorea associated with HD is 12 mg daily, with weekly intervals of dose increase in 6 mg increments. Deutetrabenazine dose will be titrated to a level in which adequate chorea control has been achieved and the patient is tolerating the treatment regimen, or until the maximum permitted dose is reached. Per the Deutetrabenazine PI[15,17], the maximum recommended daily dose of deutetrabenazine is 48 mg/day (24 mg twice daily), unless the patient is poor cytochrome P450 2D6 (CYP2D6) metabolizer or with concomitant use of strong CYP2D6 inhibitor(s), in which case the maximum total daily dose is 36 mg/day. At the end of the titration period, the patient's dose will be established for the maintenance period. Patients will be recommended to receive treatment with deutetrabenazine ≥24 mg/day for at least 4 weeks in the maintenance period if the patient is tolerating the treatment with deutetrabenazine.

However, in the real-world setting, the titration and maintenance dose can vary due to the heterogeneity in treatment effectiveness and tolerance across different patients. Therefore, the duration of titration and the maintenance dose for each patient will be based on physicians' clinical judgments in the real-world setting. Patient treatment information, including maintenance dose and the initiation date of maintenance, will be collected and reviewed on a rolling basis, and a data-driven approach to define initiation of maintenance based on time on dose might be considered as applicable.

During the study period, the primary endpoint of TMC score change from baseline will be assessed at week 16 after study baseline. In addition, effectiveness outcomes assessed at other timepoints throughout the study, e.g., weeks 4, 8, 12 and other unscheduled visits, will also be collected (**Table 4)**. Each assessment will be conducted by trained physicians and/or research delegates.

Patients and/or caregivers will be contacted by telephone or during the scheduled hospital visits on a biweekly (every two weeks, i.e., weeks 2, 6, 10, and 14 by telephone, weeks 4, 8, 12, and 16 during hospital visits) basis by trained physicians and/or research delegates to collect and document information including chorea control, deutetrabenazine treatment dosing, and concomitant medication use. On-site follow-up at the end of treatment will be required for all patients for the assessment of TMC score if the patient discontinues deutetrabenazine treatment early. If the patient cannot do the on-site visits at weeks 4, 8, and 12, the patients and/or caregivers will be contacted by telephone. These data will also be collected at any follow-up visit/contact, if available, throughout the study.

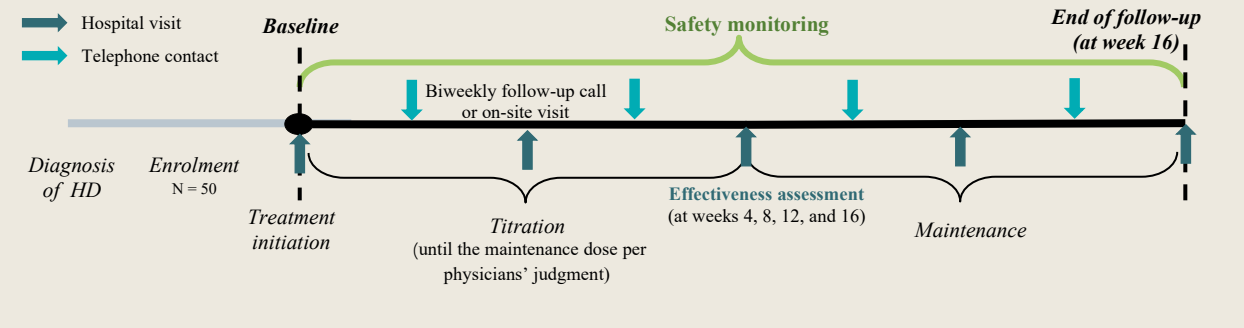
The visit window of all scheduled visits during follow-up is ± 3 days. If the patient discontinues deutetrabenazine treatment early, on-site follow-up to assess the TMC score will be required within 3 days of the investigator's becoming aware of discontinuation. Detailed summary of the schedule and data collection scope for each visit/contact is presented in **Table 4**.

For safety outcomes (secondary endpoint), in addition to scheduled or unscheduled follow-up visits/contacts (**Table 4**), real-time safety monitoring will be conducted from study baseline to the end of study period to collect any AEs. Only AEs recorded in the electronic medical records (EMR) system and documented by the health care professional (HCP) will be collected. The study follow-up will be ended after 16 weeks from study baseline.

Data will be collected using comprehensive case report forms (CRFs) at enrolment and follow-up contacts, separately, by treating physicians and/or research delegates from participating centres.

Detailed description of endpoints is provided in **Section 5.3.2**.

Figure 1. Overview of study design



Abbreviation: HD, Huntington's disease.

Table 4. Schedule of visits

	Screening	**Scheduled visits[1]**																**Uns[2]**
Week	Baseline[3]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Visit windows (in days)	0	± 3																n/a[9]
Visit/Contact / **Data collection**	V1		R1[4]		V2[5]		R2[4]		V3[5]		R3[4]		V4[5]		R4[4]		V5[5]	U#
Treatment information of deutetrabenazine	X		X		X		X		X		X		X		X		X	X[6]
Informed consent/Assent	X																	
Selection criteria	X																	
Medical history/demographics	X																	
Time-independent disease and clinical characteristics	X																	
Height	X																	
Weight	X		X		X		X		X		X		X		X		X	X[6]
Lab test and other procedures	X[6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]	X[6]
Concomitant medications	X		X		X		X		X		X		X		X		X	X[6]
Medical conditions and comorbidities	X		X		X		X		X		X		X		X		X	X[6]
UHDRS – TFC	X																	X[6]
UHDRS – TMC	X		X[6]		X		X[6]		X		X[6]		X		X[6]		X	X[6]
Disease management – control of involuntary movements[7]	X		X		X		X		X		X		X		X		X	X[6]
Drug dispense	X				X				X				X					X[8]
Adverse events			X		X		X		X		X		X		X		X	X[6]
Drop-out survey			X		X		X		X		X		X		X		X	X[6]

Abbreviations: n/a, not applicable; TFC, total functional capacity score; TMC, total maximal chorea score; UHDRS, Unified Huntington's Disease Rating Scale.

Notes:

1. Physician will adjust the duration of the titration period based on clinical judgments in the real-world setting.
2. Unscheduled visit/contact can occur by telephone or onsite if feasible throughout the study period.
3. Baseline visit will occur on the day of the first prescription of deutetrabenazine in this study and before the initiation of deutetrabenazine.
4. Visits can occur by telephone or onsite if feasible.
5. Effectiveness outcomes will be assessed at weeks 0, 4, 8, 12 and 16.
6. Data will be collected as occurred, to the extent of data availability.
7. Chorea control will be collected per the physician's practice.
8. Drug can be dispensed on unscheduled visit if drug available is not enough until next visit.
9. If the patient discontinues deutetrabenazine treatment early, on-site follow-up to assess the TMC score will be required within 3 days of the investigator's becoming aware of discontinuation.

[Uns] Unscheduled visit/contact
[V#] Clinic visit number
[R#] Remote contact number
[U#] Unscheduled visit/contact number

5.2. Study Population

5.2.1. Patient Population

The study population will comprise adult patients with chorea associated with HD who are eligible for deutetrabenazine in China.

This study aims to recruit fifty adult patients from multiple centres in China, including Huaxi Hospital. Other potential sites will be confirmed based on the feasibility assessment.

Patients will be considered for enrolment in the study after the participating physician has determined the appropriateness of deutetrabenazine use. The participating physician will first decide on the treatment regimen for his/her patient. Then, after the treatment is agreed upon, the physician will assess patient eligibility by going through a checklist to verify if the patient meets the inclusion/exclusion criteria (details in **Sections 5.2.2** and **5.2.3**). All eligible patients are to be asked by their physician if they are willing to participate in the study. Therefore, the decision of the physician to treat the patient with one treatment regimen or another is separated from the decision of the patient to participate in the study. Participation in the study will be discussed between the physician and potential participant only after the treatment has been agreed upon. The physician will explain the nature of the study, its purpose and associated procedures, and the expected duration of follow-up for each patient prior to his/her entry into the study. Each patient is to have opportunity to ask questions and is to be informed that he/she is entitled to withdraw from the study for any reason at any time. Information about the study and the participant's rights will be provided on an informed consent and data privacy form and must be signed by all study participants.

Study participants will be followed-up from the date of deutetrabenazine initiation until the earliest of the following dates:

- End of study period
- Withdrawal of consent
- Loss to follow-up
- Death

To minimize loss to follow-up and drop-out from the study, reminder calls to patients and caregivers will be made in between scheduled follow-up visits. Loss to follow-up is defined as no response to 3 reminder attempts. If a patient decided to withdraw from the present study, a drop-out survey will be conducted to collect the reason of withdrawal, use of deutetrabenazine at the withdrawal, chorea control at the withdrawal, and self-reported clinical outcomes at the withdrawal (details described in **Section 5.3.3**). Patients who withdraw from the study will also be invited for a final on-site effectiveness assessment, to the extent of patients' willingness.

5.2.2. Inclusion Criteria

Patients will be included in the study only if they meet all of the following criteria:

- Patients 18 years of age or older with clinically confirmed diagnosis of chorea associated with HD
- Patients whose baseline TMC score ≥ 8
- Patients who are deutetrabenazine-naïve before study entry or who did not receive deutetrabenazine within 30 days of study entry, and who are about to be treated with deutetrabenazine for chorea associated with HD
- Patients who have provided written consent for the use of personal and medical information for study purposes

5.2.3. Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

- Patients who have an unstable or serious medical or psychiatric illness at baseline
- Patients with any history of suicidality, untreated or inadequately treated depression
- Patients with certain comorbidities, including hepatic impairment, congenital long QT syndrome, and clinically significant cardiac arrhythmias
- Patients who received reserpine within 20 days of deutetrabenazine treatment initiation
- Patients who received monoamine oxidase inhibitors within 14 days of deutetrabenazine treatment initiation
- Patients who received VMAT2 inhibitors, e.g., tetrabenazine or valbenazine, within 30 days of deutetrabenazine treatment initiation
- Patients unable to provide a written consent for the study
- Patients who are participating in another study that includes treatment with an investigational drug and/or intervention at the same time as enrolment in the current study

5.3. Data Elements:

Exposures, endpoints, and other variables of interest listed in the sections below will be collected by physicians and/or research delegates at baseline and during follow-up. Detailed summary of the schedule and data collection scope for each visit/contact is presented in **Table 4**.

5.3.1. Exposure

The exposure variable is administration of deutetrabenazine. Treatment information of deutetrabenazine will be collected at each follow-up telephone contact and hospital visit

throughout the study period. Detailed deutetrabenazine treatment information to be collected include the following:

- Treatment phase (i.e., titration or maintenance)
- Treatment initiation date
- Initiation date of maintenance
- Treatment duration (by treatment phase)
- Dose and dosing schedule
- Dose reduction and modification, including dates and reasons
- Treatment adherence, treatment cessation, and subsequent re-initiation of treatment (if any)

5.3.2. Endpoints

Primary endpoint

The primary endpoint is the effectiveness of deutetrabenazine assessed as the change of TMC score from baseline to week 16 after study baseline in patients receiving deutetrabenazine treatment ≥24 mg/day. For each patient, effectiveness assessments will be conducted at hospital visits and will be performed by the same treating physician who is trained to use UHDRS. Furthermore, effectiveness outcomes assessed at other timepoints throughout the study, e.g., weeks 4, 8,12 and other unscheduled visits, will also be collected. On-site assessments of TMC score at week 16 are highly recommended.

Specifically, the TMC score is determined from Item 12 of the motor assessment (Part 1) of the UHDRS and quantifies chorea (range, 0-28, lower score indicates less chorea). It is the sum of maximal chorea scores for seven body regions (face, buccal-oral-lingual, trunk, and four extremities), each of which is scored on a scale from 0 to 4 (0, absent; 1, slight or intermittent; 2, mild and common or moderate and intermittent; 3, moderate and common; and 4, marked and prolonged)[1]. A validated Chinese version of TMC scale will be used.

Secondary endpoints

The secondary endpoints are:

1) The occurrence of AEs in all patients (regardless of dosage), including proportions of AEs of the following:
    - Any AEs with severity grade
    - Serious Adverse Events (SAEs)
    - Drug-related AEs
    - AEs leading to treatment reduction, suspension, discontinuation, and/or withdrawal
    - AEs by treatment phase (i.e., titration and maintenance)

- AEs of special interest, including suicidality, depression, somnolence, QTc prolongation, akathisia, and parkinsonism

All AEs will be collected in a real-time manner as they occur, in addition to at each follow-up telephone contact and hospital visit. Detailed definitions of these safety outcomes are provided in **Section 10.1**.

2) The effectiveness of deutetrabenazine assessed as the change of TMC score from baseline to week 16 after study baseline in all patients (regardless of dosage)

On-site assessment of TMC score at week 16 is highly recommended. For each patient, effectiveness assessments will be conducted at hospital visits and will be performed by the same treating physician who is trained to use TMC. Furthermore, effectiveness outcomes assessed at other timepoints throughout the study, e.g., weeks 4, 8,12 and other unscheduled visits, will also be collected.

Exploratory endpoint

[redacted]

5.3.3. Other Variables

Other variables, including potential risk factors and effect modifiers to be collected include:

- Baseline patient demographics
  - Age at baseline
  - Sex
  - Geographic information (i.e., province of residence)
  - Healthcare insurance type (i.e., Urban Employee Basic Medical Insurance, Urban and Rural Resident Basic Medical Insurance, commercial insurance, and no insurance)
  - Socioeconomic status (e.g., years of education, employment status)
- Baseline disease and clinical characteristics
  - Date of initial diagnosis of HD
  - Duration of HD
  - Duration of chorea associated with HD

- CAG repeat length, if available
- Weight
- Height
- Treatment history for HD/chorea associated with HD (e.g., prior VMAT2 inhibitors and reasons for discontinuation), if available.
- Baseline TMC score
- Baseline total functional capacity (TFC) score
- Baseline medical conditions and comorbidities
    - Charlson Comorbidity Index (CCI)
        - Myocardial infarction
        - Congestive heart failure
        - Peripheral vascular disease
        - Cerebrovascular disease
        - Dementia
        - Chronic pulmonary disease
        - Connective tissue disease
        - Ulcer disease
        - Mild liver disease
        - Diabetes
        - Hemiplegia
        - Moderate or severe renal disease
        - Diabetes with end organ damage
        - Any tumour without metastasis
        - Leukaemia
        - Lymphoma
        - Moderate or severe liver disease
        - Metastatic solid tumour
        - Acquired immunodeficiency syndrome
    - Depression
    - Suicidality
    - Others

  - Concomitant medications
    - Name
    - Dose
    - Initiation date
    - Treatment duration
    - Indication
  - Other baseline variables of interest
- Other time-varying variables to be collected during follow-up, including
  - Any clinical events, such as complications and comorbidities, that occurred between visits
  - Changes in treatment usage (e.g., discontinuation, dose change) for concomitant medications
  - Chorea control
  - Drop-out survey
    - Date of drop-out
    - Reasons of withdrawal
    - Use of deutetrabenazine at the withdrawal
      - Dose of deutetrabenazine (if on treatment)
      - Reasons of treatment discontinuation (if not on treatment)
    - Chorea control at the withdrawal
    - Self-reported clinical outcomes at the withdrawal

6. STUDY TREATMENT

6.1. Investigational Medicinal Products Used in the Study

As the IMP, this study uses AUSTEDO® (deutetrabenazine) tablets, which received marketing authorization from CDE and is on the Chinese market. One dose strength of AUSTEDO® will be available for use: 6 mg tablets.

IMP is coated with a colored polymer coating. The colored polymer coating is applied to the tablets according to dose strength; 6 mg - purple. The dose strength will have a black marking of SD 6, corresponding to the dose strength. AUSTEDO® (deutetrabenazine) tablets have been manufactured according to current Good Manufacturing Practices regulations. During titration/dose adjustment, AUSTEDO® (deutetrabenazine) tablets will be supplied in bottles of 28 tablets as 6 mg tablets and will be labeled according to applicable regulatory guidelines. Patients will be provided sufficient supply of drug according to physicians' prescription until the next specified visit or the end of study, plus coverage to account for potential delays in study visits or evaluations or receipt of their supplies.

After completing the protocol-defined treatment period, patients can choose the follow-up treatment based on the physician's recommendation and the patient's preference.

AUSTEDO® (deutetrabenazine) tablets must be stored according to the specifications listed in **Table 2**.

The investigator must confirm appropriate temperature conditions have been maintained for all IMP received and any discrepancies are reported and resolved before use of the IMP.

6.2. Dosing and Administration

The titration and the maintenance dose for each patient will be based on the physician's clinical judgments in the real-world setting. Thus, the titration and maintenance dose can vary due to the heterogeneity across patients.

The Chinese product insert (PI) is provided as general reference to help physicians determine treatment regimens. Per the Chinese PI[15], the initiation dose of AUSTEDO for the treatment of chorea associated with HD is 12 mg daily, with weekly intervals of dose increase in 6 mg increments. Deutetrabenazine dose will be titrated to a level in which adequate chorea control has been achieved and the patient is tolerating the treatment regimen, or until the maximum permitted dose is reached. Per the PI[15,17], the maximum recommended daily dose of deutetrabenazine is 48 mg (24 mg twice daily), unless the patient is a poor cytochrome P450 2D6 (CYP2D6) metabolizer or with concomitant use of strong CYP2D6 inhibitor(s), in which case the maximum total daily dose is 36 mg. At the end of the titration period, the patient's dose will be established for the maintenance period. Patients will be recommended to receive treatment with deutetrabenazine ≥24 mg/day for at least 4 weeks in the maintenance period if the patient is tolerating the treatment.

Administer IMP with food. Swallow IMP whole. Do not chew, crush, or break tablets.

Table 5. Investigational Medicinal Products Used in Study

IMP name	AUSTEDO®
Trade name and INN, if applicable, or company-assigned number	TEV-50717 (deutetrabenazine)
Formulation	Solid oral dosage form (tablet with nonfunctional film coating)
Unit dose strength(s)/Dosage level(s)	6 mg
Route of Administration	Oral
Packaging	IMP will be provided in bottles
Manufacturer	Anesta LLC 4745 Wiley Post Way Salt Lake City, UT 84116, USA
Storage Conditions	Protect from light; store sealed below 25°C in a dry place

INN=international nonproprietary name.

6.3. Accountability

The IMP must be used in accordance with the Chinese PI and the protocol. All materials supplied are for use only in this study and should not be used for any other purpose.

The IMP shipment will include a packing slip listing the contents of the shipment and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMP from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the local regulations, and used in accordance with this protocol.

A record of IMP accountability (i.e., IMP and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Unused bottles of IMP and partially used IMP due to early treatment discontinuation will be returned to the sponsor or its designee according to local and national regulations and the site's SOPs, following written authorization from the sponsor. These activities will be performed after the study close out to allow the monitor to conduct a reconciliation of the IMP.

7. DATA HANDLING, DATA QUALITY CONTROL, AND DATA RECORD KEEPING

7.1. Data Source

Data for this study will obtained from the participating sites including Huaxi Hospital. Various sources will be used, including treating physicians and source documentation such as medical records, as applicable.

Exposure to deutetrabenazine, primary and secondary outcomes, and other variables listed in **Section 5.3** will be documented by the treating physicians and/or research delegates. Data will be recorded and summarised using study-specific enrolment and follow-up CRFs, as detailed in **Section 5.1**.

7.2. Data Collection

7.2.1. Data Collection/Handling

Data relevant for this study will be collected from the patient's treating physicians and summarised in CRFs specifically designed for this study, as described in **Section 5.1**. CRFs must be completed for each patient who provided informed consent. All data recorded will be anonymised. The data collected on the CRFs will be captured in a clinical data management system (CDMS)/electronic data capture (eDC). The CDMS/eDC will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS/eDC, all users will receive training on the system and study-specific training.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screen failure reason, and demography from the time of informed consent will be entered into the CRF. All AE and special situation collected in the study, including CRF data, will be included in the final report provided to Teva upon study completion, if applicable.

All medical and health related terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Medical and health related terms include AEs, medical procedures, clinical characteristics, clinical diagnosis including primary diagnosis, comorbidities, and complications, names and qualitative results of laboratory tests, etc. All prior and ongoing therapy and medications will be coded according to Anatomical Therapeutic Chemical (ATC) Classification System based on generic names. Other social-economic characteristics and geospatial information are compilated according to dictionaries published by the government.

The processes for database management differ by the data source. Data extraction and analysis will be performed according to the applicable practices of data vendor's and Teva's.

Data extraction and analysis will be performed by dedicated personnel trained to work for this study. These personnel will be responsible for data management, accuracy, quality, completeness, and internal consistency. Data handling, including data quality assurance, will comply with regulatory guidelines. The secure storage of data, study programmes, log files, output files and back up will be ensured as required by regulatory guidelines. Logical checks of data consistency and validity will be implemented during data extraction and entry.

7.2.2. Data Quality Assurance

The accuracy, quality, completeness, and internal consistency of the data from this study will be verified. Data handling, including data quality assurance, will comply with applicable regulatory guidelines.

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with applicable international regulatory guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a data-management plan.

CRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS/eDC. Discrepancies found will be queried.

Checks will be in place to ensure that patients have signed the informed consent form.

Data will be transcribed directly from the patient's medical records into CRFs that are specifically designed for this study.

All records related to the study (i.e., medical records, CRFs, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must be retained until the sponsor notifies the center, in writing, that records may be destroyed.

The sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the sponsor's SOPs for clinical studies.

If data management and filing of documents for this study are delegated to a contract research organization (CRO), these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management and filing activities. The original CRFs will be archived by the sponsor.

7.2.3. Quality Control/Data Validation

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits of the data, accuracy and consistency of collected data, validation of coding, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Data collection at each site will be monitored both remotely and in an on-site manner. Written programming will be reviewed independently. The secure storage of data, study programmes, log files, output files and back up will be ensured as required by regulatory guidelines. All key study documents, such as the statistical analysis plan and study reports, will undergo quality control and review.

7.2.4. Archiving of Case Report Forms and Source Documents

Study records (including data and relevant documents) are created, maintained, and archived according to relevant standard operating procedures (SOPs) and local laws regulations.

CRFs will be transferred to Teva at the completion of the study for archive. The site source documents will remain at the investigation sites.

At the conclusion of the study the following information will be archived by the Sponsor.

- Protocol and Protocol Amendments as applicable
- Blank CRF or questionnaires
- Electronic CRFs and CRF instructions
- Statistical Analysis Plan (SAP) and SAP amendments as applicable
- Data Management Plan (DMP)
- Relevant SOPs
- Final SAS/R datasets including:
  - External Raw data and analysis data
  - All variables in the SAS/R files including labels
  - SAS/R programs
  - Tables, listings, and graphs
- For all patients enrolled:
  - eDC - electronic completed CRFs with discrepancy and audit history
  - Paper – scanned report forms and Data Clarification Forms
  - Clinical Study Report (CSR) and its appendices
  - AE and SAE reports
  - Special situations

Study sites are required to maintain appropriate files for the agreed upon time frame.

8. STATISTICS

8.1. Sample Size and Power Considerations

The target sample size was determined based on power calculation with the comparison of the baseline and post-treatment difference in effectiveness assessment scores. A mean decrease of 4.4 points (standard deviation [SD] of 3.0) of TMC score was observed in the First-HD double-blind placebo-controlled trial[1] and served as the basis of sample size estimation. Considering patients will be less adherent in their medication in real-world setting than they would be in a clinical trial, assuming the expected mean change in TMC score from baseline to week 16 after study baseline is 2.5 points with a SD of 3.0, a sample size of 18 is needed to provide 90% power to detect a statistically significant difference from a mean change of zero, at a two-sided significance level of 5%. Therefore, this study aims to recruit 18 adult patients receiving treatment with deutetrabenazine ≥24 mg/day. More scenarios varying the mean change in TMC score, SD, power, and significance level are presented in **Table 6**. Considering the real-world features of this study including the heterogeneity across patients, variations in treatment dosing schedules, patient adherence, potential drop-outs and loss to follow-up, and the need to collect as much AEs data as possible from the patient, this study aims to recruit fifty adult patients receiving treatment with deutetrabenazine regardless of dosage, so the desired sample size for the primary end-point can be achieved. This study will continue enrolment until both the number of total patients reaches the targeted sample size of fifty and the number of patients receiving treatment with deutetrabenazine ≥24 mg/day reaches the targeted sample size of eighteen.

Table 6. Sample size calculation

Change in TMC	Power	SD=2.5		SD=2.75		SD=3		SD=3.25		SD=3.5	
		p=0.05	p=0.01	p=0.05	p=0.01	p=0.05	p=0.01	p=0.05	p=0.01	p=0.05	p=0.01
-2	**0.8**	15	22	17	26	20	30	23	35	27	40
	0.9	19	27	22	32	26	37	30	43	35	49
	0.99	31	41	37	49	44	58	51	67	59	77
-2.5	**0.8**	10	16	12	18	14	21	16	24	18	27
	0.9	13	19	15	22	**18**	25	20	29	23	33
	0.99	21	28	25	33	29	39	34	45	39	51
-3	**0.8**	8	12	9	14	10	16	12	18	13	20
	0.9	10	14	11	16	13	19	15	21	17	24
	0.99	15	21	18	24	21	28	24	32	28	37
-3.5	**0.8**	7	10	7	11	8	12	9	14	10	16
	0.9	8	12	9	13	10	15	12	17	13	19
	0.99	12	16	14	19	16	22	18	25	21	28
-4	**0.8**	6	8	6	9	7	10	8	12	9	13
	0.9	7	10	8	11	9	12	10	14	11	15
	0.99	10	13	11	15	13	18	15	20	17	22
-4.5	**0.8**	5	8	6	8	6	9	7	10	7	11
	0.9	6	9	7	10	7	11	8	12	9	13
	0.99	8	11	10	13	11	15	12	17	14	19
-5	**0.8**	5	7	5	7	6	8	6	9	7	10
	0.9	5	8	6	8	7	9	7	10	8	11
	0.99	7	10	8	11	9	13	10	14	12	16
-5.5	**0.8**	4	6	5	7	5	7	5	8	6	9

	0.9	5	7	5	8	6	8	6	9	7	10
	0.99	7	9	7	10	8	11	9	12	10	14
-6	**0.8**	4	6	4	6	5	7	5	7	5	8
	0.9	5	7	5	7	5	8	6	8	6	9
	0.99	6	8	7	9	7	10	8	11	9	12

Abbreviations:
TMC, total maximal chorea; SD, standard deviation.

8.2. Data Analysis

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the SAP. After finalization of the SAP, any additional analyses or changes to analyses that may be required will be fully disclosed in the CSR.

8.2.1. General Considerations

Descriptive statistics will be provided for baseline patient demographics as well as disease and clinical characteristics of enrolled patients. Continuous variables will be summarised using means and SDs and/or medians with interquartile ranges. Categorical variables will be summarised using counts and proportions.

For the primary endpoint, the change in TMC score from baseline to week 16 after study baseline in patients receiving deutetrabenazine treatment ≥24 mg/day, will be presented in mean, SD, and 95% confidence interval. More details are provided **Section** 错误!未找到引用源。.

For the secondary endpoint, AEs will be summarised using counts and proportions; the change in TMC score from baseline to week 16 after study baseline in all patients (regardless of dosage), will be presented in mean, SD, and 95% confidence interval. More details are provided **Section** 错误!未找到引用源。**.**

For the exploratory endpoint, [redacted]

8.2.2. Analysis of Endpoints

The primary endpoint, i.e., the change in TMC score from baseline to week 16 after study baseline in patients receiving deutetrabenazine treatment ≥24 mg/day, will be summarised using mean, SD, and 95% confidence intervals. The primary analysis TMC scores will be conducted using an adjusted linear mixed effects regression model. Variables such as age at baseline, sex, comorbidities, concomitant medications will be adjusted in the model if feasible/applicable. With available repeated measurements of TMC score, the longitudinal mixed effects model will consider all measurements, while accounting for the correlation of the measurements obtained

from the same patient. Details of the primary endpoint measurements and variables are provided in **Section 5.3.2**.

The secondary endpoint 1), i.e., the proportion of AEs, will be summarised by counts and proportions. Details of the secondary endpoint measurements and variables are provided in **Section 5.3.2**.

The secondary endpoint 2), i.e., the change in TMC score from baseline to week 16 after study baseline in all patients (regardless of dosage), will be summarised using mean, SD, and 95% confidence intervals. The primary analysis of the TMC score will be conducted using an adjusted linear mixed effects regression model. Variables such as age at baseline, sex, comorbidities, concomitant medications, etc. will be adjusted in the model if feasible/applicable. With available repeated measurements of TMC score, the longitudinal mixed effects model will consider all measurements, while accounting for the correlation of the measurements obtained from the same patient. Details of the secondary endpoint measurements and variables are provided in **Section 5.3.2**.

The exploratory endpoint, [redacted]

8.3. Limitations of the Research Methods

This study follows up patients treated with deutetrabenazine in routine clinical practice to estimate the effectiveness and safety in patients with chorea associated with HD in China. The study has several limitations:

- The study may be subject to selection bias as it mainly depends on the selection of participating study centres or physician and patient recruitment, including the initial contact of patients or health care providers, as well as their consent to participate and their compliance. Nonparticipation bias may be expected and may influence the representativeness of the sample selected. This selection bias may affect the generalisability of the findings. To address this limitation, all efforts will be made to recruit a representative set of study sites. Specifically, based on the availability and accessibility of deutetrabenazine, sites that represent the clinical practice of deutetrabenazine in the real-world setting in China will be recruited. The observation will also start 2 years after the product launch to allow physicians to adopt the use of the deutetrabenazine. To minimize selection bias/informative censoring due to loss to follow-up, once medical sites have been selected, several strategies will be used to increase participation in the study, including telephone reminders to non-responding patients. In order to assess the representativeness of the sample and the size and direction of the

potential selection bias (due to nonparticipation), a list of eligible patients (both enrolled and not enrolled) treated with deutetrabenazine will be established and the characteristics of enrolled and not enrolled patients will be compared. This list will provide an insight on enrolment rates and potential selection bias.

- In this study, clinical decisions of physicians, prior treatment, medical history, and presence of comorbidities may result in differences between patients. These differences could potentially introduce bias and confound the association between treatment and the outcomes. The collection of the baseline information will help to identify potential confounding factors. During the data analysis stage, every effort will be undertaken to control for potential confounding factors and reduce biases in the statistical models used. This can be attempted by use of stratified analysis (up to 4 subgroups) and/or the implementation of multivariate statistical models.
- As an inherent limitation of an open label study, the lack of blinding may introduce detection bias and reporting bias in effectiveness and safety assessments. To minimize bias and increase robustness of effectiveness assessment results, experienced physicians with expertise in the treatment of chorea associated with HD will be enrolled to conduct effectiveness assessments. Comprehensive training will be provided to these physicians to ensure consistent standards of rating will be applied across different study sites. In addition, change of the rater will be avoided to minimize differential measurement error in rating before and post treatment, and scores at baseline and after treatment for one patient will be assessed using a consistent approach by the same physician throughout the study.
- As a single-arm study, the lack of control arm limits the demonstration of the treatment effect as it is difficult to accurately infer the benefit of treatment without knowing what it would have been in the absence of the treatment. However, external controls can be used to address evidence gaps in single-arm studies, while accounting for potential bias using analytical methods. Therefore, the single-arm study can still provide important evidence on the real-world effectiveness and safety of deutetrabenazine. If deemed necessary, external controls using historical data or real-world data can be considered for further analysis.

9. ETHICS

The study is a real-world effectiveness and safety study. This study will be conducted in accordance with applicable laws, regulations, guidelines and the Sponsor's SOPs that have been made available to the data vendor from time to time and as applicable to the study.

The study will be conducted in a manner that is consistent with all relevant national guidelines and regulations where the study is being conducted. The legislation on data protection will be followed in accordance with national regulations on the protection of individuals with regard to the processing of personal data.

The marketing authorisation holder will ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and will ensure that the confidentiality of the records of the study subjects remains protected.

All data used in the study will be anonymised and analysis will be performed on an anonymised patient-level dataset. The data system will be maintained and secured as requested by the local patient privacy regulations. Processes assuring data security will be employed during data extraction, storage, and back up. The data and all study documents will be kept until MAH's written notification that records may be destroyed.

9.1. Health Authorities and Independent Ethics Committees/Institutional Review Boards

Review and approval of the study protocol will be obtained at the Institutional Review Board (IRB) in China as required by local law. Regulatory review and approval by the Ministry of Science and Technology of China will be obtained as required by national regulations.

9.2. Informed Consent

This study is in real-world setting, no additional procedures will be performed on the patient in addition to the normal clinical practice of the treating physician. Informed consent will be obtained from all patients for their clinical data to be recorded anonymously. Patients will also be informed of their right to withdraw their consent at any time during the study.

The physician, or a qualified person designated by the physician, should fully inform the patient of all pertinent aspects of the study. All written and/or oral information about the study will be provided in a language (i.e., Chinese) as nontechnical as practical and understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study.

Written informed consent will be obtained from each patient participating in the study. The patient's willingness to participate in the study will be documented on a consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The physician will keep the original consent forms, and a copy will be given to the patient. It will also be explained to the patients that the patient is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

9.3. Patient Confidentiality

The investigator must ensure the privacy of patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (eg, initials and identification number). All data will be collected, maintained, and analyzed on an anonymised patient-level dataset.

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Definitions

10.1.1. Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

An adverse event can, therefore, be any unfavourable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or a significant worsening of the disease under study or of any concurrent disease, whether considered related or not related to the study drug.

The following will not be considered as adverse events and will not be reported to pharmacovigilance (PV) but will be collected as part of the study database:

- Stable chronic conditions that are present before study entry and do not worsen during this study

10.1.1.1. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

10.1.2. Serious Adverse Event

The physician should assess the seriousness of all adverse events.

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- Death
- A life-threatening adverse event (i.e., the patient was at an immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalisation or prolongation of existing hospitalisation, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalisations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in this study will not be considered serious adverse events.
- Persistent or significant disability or incapacity (refers to a substantial disruption of one’s ability to conduct normal life functions)
- A congenital anomaly/birth defect

- An important medical event that may not result in death, be life-threatening, or require hospitalisation, but may jeopardise the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

In addition, all occurrences of possible drug-induced liver injury that meet Hy's Law criteria, defined as all the below, must be reported by the investigator to the sponsor as a serious adverse event:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 times the upper limit of the normal range (ULN)
- Total bilirubin ≥ 2 times the ULN
- The absence of initial findings of cholestasis (i.e., no substantial increase of alkaline phosphatase)

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

10.1.3. Special Situations

The following are considered special situations:

- **Breastfeeding (drug exposure via parent):** Reports, where the infant may have been exposed to medicinal products from breast milk.
- **Exposure during pregnancy:** Reports, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or through transmission of a medicinal product via semen following paternal exposure).
- **Lack of efficacy (LoE)**: Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.
- **Transmission or suspected transmission of an infectious agent via a medicinal product:** Suspected transmission of infectious agents, any organism, virus or "infectious particle". Relevant for biological products including vaccines (e.g., live attenuated vaccines) or blood products.
- **Unexpected beneficial effect:** When a product improves a condition different from that for which it has been prescribed.
- **Overdose**: Administration of a quantity of the medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.
- **Abuse of a medicinal product:** Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

- **Off-label use**: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.
- **Misuse**: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.
- **Occupational exposure**: Exposure to the medicinal product, as a result of one's professional or non-professional occupation.
- **Medication error:** This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

10.1.4. Protocol-Defined Adverse Events of Special Interest

For purposes of this protocol, the AEs of special interest include suicidality, depression, somnolence, QTc prolongation, akathisia, and parkinsonism.

10.2. Recording Adverse Events (Including Special Situations)

For adverse event recording, the study period is defined for each patient as the time period from signing the informed consent form through the end of the study period (including the follow-up period).

All adverse events, including special situations (see **Section 10.1.3**), that occur during the defined study period must be recorded in the study database, regardless of the severity of the event or the relationship to the study drug. AE identified and reported by physicians through abnormal lab results will also be collected and data will enter safety analysis.

10.2.1. Relationship of an Adverse Event to the Medicinal Product

The physician should provide relationship assessment to all adverse events.

The causal relationship of an adverse event to the medicinal product is characterised as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the medicinal product.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the medicinal product. • It could readily have been produced by the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the medicinal product. • It does not reappear or worsen when the medicinal product is re-administered.

Term	Definition	Clarification
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the medicinal product administration cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the medicinal product. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the medicinal product, yet a drug relationship clearly exists. • It follows a known pattern of response to the medicinal product.

10.3. Reporting Requirements for Adverse Events (Including Special Situations)

The treating physician should report the following to Teva:

- All collected adverse events (regardless of the seriousness, severity, or relatedness to the medicinal product)
- Pregnancies and all other special situations listed in **Section 10.1.3**.

For serious adverse events, related non-serious adverse events, special situations leading to either a serious adverse event or a related non-serious adverse event and protocol defined adverse events of special interest as listed in **Section 10.1.4**, the Adverse Event Report Form must be completed, and the adverse event and special situation (if applicable) must be reported to by the investigator to Teva within 24 hours of becoming aware of its occurrence.

For not related non-serious adverse events and other special situations (i.e., not leading to a serious adverse event or a non-serious related adverse event), whenever possible, the data should be extracted from the study database and sent to Teva on a weekly basis. If these data cannot be extracted, the adverse event/special situation must be reported by the investigator to Teva using the Adverse Event Report Form within 7 days of awareness.

10.3.1. Adverse Event Reporting

Adverse events, including special situations shall be sent by the physician to the Teva local safety officer (LSO) according to the details provided in **Section 10.3** and shall contain the following details: study name/number, name of medicinal product, physician contact details (including name, phone number, fax number, and e-mail address), patient number (if applicable), patient initials, patient demographics, and a description of the adverse event/special situation

(including date of onset, and treatment [drug, dose, and dosage form]), AE relationship to study drug, and the action taken regarding study drug in direct relationship to the adverse event. In fatal cases, the report shall also include the cause of death (whether or not the death was related to the study drug) and autopsy findings (if available). For serious adverse events, related non-serious adverse events, and special situations leading to either a serious adverse event or a related non-serious adverse event and protocol defined adverse events of special interest as listed in **Section 10.1.4**, all additional information required in the Adverse Event Report Form should be added as applicable. Relevant documents (such as medical records and hospital discharge, etc) should be summarised in the narrative section of the Adverse Event Report Form and should not be added as appendices.
The LSO will forward the report to the relevant pharmacovigilance data processing unit. For serious adverse events, related non-serious adverse events, and special situations leading to either a serious adverse event or a related non-serious adverse event, the physician should forward additional information (follow-up) unavailable at the initial reporting of an adverse event within 24 hours to the LSO once he or she becomes aware of this information.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline or until a determination of a cause unrelated to the medicinal product or study procedure is made.

The sponsor's relevant pharmacovigilance data processing unit will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities and IRBs according to local regulations.

For adverse events that are not systematically collected as part of the study settings, health care professionals and consumers may report adverse reactions to the marketing authorisation holder of the suspected medicinal product (for which they suspect a causal association, whether studied or not) or to the concerned competent authority via the national spontaneous reporting system.

10.3.2. Pregnancy

All pregnancies of women participating in the study that occur during the study or within 45 days of the completion of the study are to be reported within 7 days of awareness to the Teva LSO by completing the Pregnancy Form. The process for reporting a pregnancy is the same as that for reporting serious adverse events, related non-serious adverse events, and special situations leading to either a serious adverse event or a related non-serious adverse event (as described in Section 10.3.1 Adverse Event Reporting). This also includes pregnancies without an adverse event. The pregnancy should be followed up to determine outcome, including spontaneous, elective, or voluntary abortion.

If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and the presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications will be reported to Teva. Any complication of a pregnancy during the study and any complication of a pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, the following has to be provided to Teva:

- for a spontaneous abortion: an updated Pregnancy Form and an Adverse Event Report Form including the spontaneous abortion as a serious adverse event
- for an elective abortion due to developmental anomalies: an updated Pregnancy Form and an Adverse Event Report Form including the developmental anomalies as a serious adverse event
- for an elective abortion not due to developmental anomalies: an updated Pregnancy Form

11. STUDY MONITORING

The Sponsor (or designated CRO) is responsible for assuring the proper conduct of the study regarding protocol adherence and validity of the data recorded on the eCRFs. Subject confidentiality will be maintained.

In accordance with applicable regulations[18], and Sponsor (or designated CRO) procedures, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrolment rate. The visits will be conducted in accordance with the Sponsor's (or designated CRO's) SOP and study monitoring plan.

In general, the Investigator agrees to fully cooperate with the monitor, allow the monitor direct access to all relevant documents, to allocate his/her time and the time of his/her staff to the monitor to discuss any findings and any relevant issues as needed.

12. PRODUCT COMPLAINTS

A product complaint is defined as any report indicating a possible deviation from the product specification. These reports may concern packaging, labeling, medical devices or drug products. Product complaints may include but are not limited to:

- suspected contamination
- questionable stability (e.g., color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (e.g., primary container is received with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

If a product compliant is identified for a Teva product or device, during the course of the study, the investigator should contact Teva, within 48 hours of becoming aware of the issue at:

Email: GC_QualityComplaint@teva.cn

Contact number: +86 21 6091 9500

Product complaints for non-Teva products should be directed to the appropriate manufacture.

Product complaints accompanied by an AE should be reported to both QAS department and PV.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements and regulations for registration and posting of results.

The sponsor is responsible for the preparation of a CSR, in cooperation with the principal investigator. The final report is signed by the sponsor and, if applicable, by the principal investigator.

Common study protocol, study status, and report(s) will be included in regulatory communications and other regulatory milestones and requirements, as applicable.

Study results will be considered for publication and will follow the International Committee of Medical Journal Editors (ICMJE, December, 2021) guidelines. In addition, communication in appropriate scientific meetings will be considered.

If applicable, when reporting results of this study, the appropriate STROBE checklist or equivalent shall be followed.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor. The primary publication from this study will report the results of the study in accordance with the current "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. Authorship will be based on meeting all the following 4 criteria:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorisation of the sponsor.

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SIGNATURE PAGE

Document Type:	Phase 4 Study protocol with Amendment01
Study No.:	TV50717-NDG-40182
Study Title:	Real-World Effectiveness and Safety of Deutetrabenazine in Chinese Patients with Chorea Associated with Huntington's Disease
Sponsor:	Teva Pharmaceutical Information Consulting (Shanghai) Co., Ltd.

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Approved by: Date

[redacted]

[redacted]

Teva Pharmaceutical Information Consulting (Shanghai) Co., Ltd.

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SIGNATURE PAGE

Document Type:	Phase 4 Study protocol with Amendment01
Study No.:	TV50717-NDG-40182
Study Title:	Real-World Effectiveness and Safety of Deutetrabenazine in Chinese Patients with Chorea Associated with Huntington's Disease
Monitor:	Beijing Analysis International Consulting Co., Ltd.

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Reviewed by: Date

[redacted]

[redacted]

Beijing Analysis International Consulting Co., Ltd.

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Study No.:	TV50717-NDG-40182
Study Title:	Real-World Effectiveness and Safety of Deutetrabenazine in Chinese Patients with Chorea Associated with Huntington's Disease
Contract Research Organization:	Beijing B&R PharmaStudies Co., Ltd.

_____ _____

Reviewed by: Date

[redacted]

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Beijing B&R PharmaStudies Co., Ltd.

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Document Type:	Phase 4 Study protocol with Amendment01
Study No.:	TV50717-NDG-40182
Study Title:	Real-World Effectiveness and Safety of Deutetrabenazine in Chinese Patients with Chorea Associated with Huntington's Disease
Data solution partner:	Beijing Huashu Yihui Technology Co., Ltd.

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Reviewed by: Date

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Beijing Huashu Yihui Technology Co., Ltd.

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Study sites:	

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