Statistical Analysis Plan

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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Sponsor

Teva Pharmaceutical Information Consulting

(Shanghai) Co., Ltd

Unit 03, 57F, No.1717 West Nanjing Road,

Jing'an District, Shanghai, P.R China

Prepared by: Beijing Analysis International Consulting Co., Ltd.

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: Number [TV50717-NDG-40182]

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Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

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[redacted]

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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
CRF	Case report form
CYP2D6	Cytochrome P450 2D6
ECG	Electrocardiogram
eCRF	Electronic case report form
EMR	Electronic medical records
HCP	Health care professional
HD	Huntington's Disease
IQR	Interquartile range
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
PI	Product insert
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TD	Tardive dyskinesia
TFC	Total functional capacity
TMC	Total maximal chorea
UHDRS	Unified Huntington's Disease Rating Scale
ULN	Standard operating procedures
VMAT2	Vesicular monoamine transporter 2

INTRODUCTION

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].

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 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 clinical study of deutetrabenazine for Chinese patients with chorea associated with HD is required.

A multi-centre, prospective, longitudinal, observational 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.

This Statistical Analysis Plan describes the planned analysis and reporting for Teva Pharmaceutical Information Consulting (Shanghai) Co., Ltd. study number [TV50717-NDG-40182] (Real-World Effectiveness and Safety of Deutetrabenazine in Chinese Patients with Chorea Associated with Huntington's Disease) and was written in accordance with GSD-SOP-702_V1: Statistical Analysis Plan (SAP).

The reader of this Statistical Analysis Plan is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (e.g., other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this Statistical Analysis Plan, the Statistical Analysis Plan prevails; the differences will be explained in the Clinical Study Report.

1. STUDY OBJECTIVES

1.1. Primary and Secondary Study Objectives

To understand the real-world effectiveness and safety of deutetrabenazine in adult patients with chorea associated with HD in China, a multi-centre, prospective, longitudinal, observational study is initiated in the real-world clinical setting in China.

The primary objective is 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 from baseline to week 16 after study baseline.

The secondary objective is 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 from study baseline to the end of study period.

1.2. Exploratory/Other Objectives

Not applicable.

2. STUDY DESIGN

2.1. General Design

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 chorea associated with HD (including severity, 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.

Adult patients with confirmed diagnosis of chorea associated with HD and who are about to receive deutetrabenazine will be enrolled. Detailed inclusion/exclusion criteria are described in **Section 5.1**. 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 $\geqslant$24 mg/day. 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 50 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 to recruit patients and monitor the treatment of deutetrabenazine for them until both reaching the sample size of total 50 patients and reaching the sample size of 18 patients who received treatment with deutetrabenazine ≥24 mg/day for at least 4 weeks. The sample size estimation is described in detail in **Section 2.3**.

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 chorea associated with HD (including severity, impact, and treatment) will be collected, and the baseline TMC score (described in detail in **Section 10**) 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 each follow-up visit/contact.

Treatment with deutetrabenazine will start with a titration period, followed by a maintenance period. Per the Chinese product insert (PI)[15], the initiation dose for the treatment of chorea associated with HD is 6 mg daily for oral administration, 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 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 with deutetrabenazine.

However, in the real-world setting, the maintenance dose can vary due to the heterogeneity in treatment effectiveness, tolerance, and affordability among 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 and other non-clinical factors such as affordability. 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, i.e., 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 at least 4 weeks (**Section 10.2**), will be assessed. The secondary endpoint, i.e., 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), and the exploratory endpoint, [redacted] 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 1**). Each assessment will be conducted by trained physicians and/or research delegates.

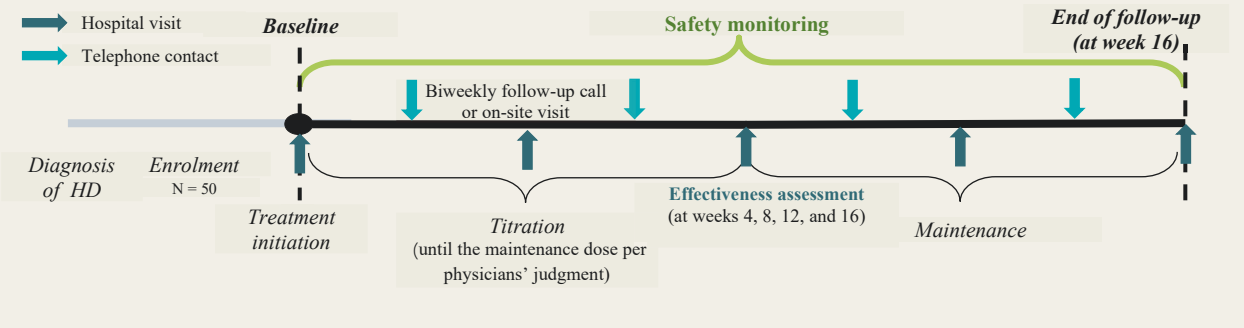
Patients and/or caregivers will be contacted by telephone or during the scheduled hospital visits on a biweekly (every two weeks, i.e., weeks 2, 6, 10, and 14 by telephone, weeks 4, 8, 12, and 16 during hospital visits) basis by trained physicians and/or research delegates to collect and document information including chorea control, deutetrabenazine treatment dosing, and concomitant medication use. On-site follow-up at week 16 will be highly recommended for all patients for the assessment of TMC score. 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. Detailed summary of the schedule and data collection scope for each visit/contact is presented in **Table 1**.

For safety outcomes (secondary endpoint), in addition to scheduled or unscheduled follow-up visits/contacts (**Table 1**), 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.

Detailed description of endpoints is provided in **Sections 10** and **12**.

Figure 1. Overview of study design



Abbreviation: HD, Huntington's disease.

Table 1. 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
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 – chorea control[7]	X		X		X		X		X		X		X		X		X	X[6]
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.

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

2.2. Data Monitoring Committee

Not applicable.

2.3. 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%. More scenarios varying the mean change in TMC score, SD, power, and significance level are presented in **Table 2**. 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 50 adult patients. This study will continue to recruit until reaching the sample size of 18 patients who received treatment with deutetrabenazine ≥24 mg/day for at least 4 weeks.

Table 2. 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.

2.4. Sequence of Planned Analyses

2.4.1. Planned Interim Analyses

There will be no formal interim analysis for this study.

2.4.2. Final Analyses and Reporting

All analyses identified in this Statistical Analysis Plan will be performed after the end of data collection, as defined in the study protocol.

This Statistical Analysis Plan and any corresponding amendments will be approved before database lock, in accordance with GSD-SOP-702_V1: Statistical Analysis Plan.

3. ANALYSIS SETS

The effectiveness analysis set will include all patients who are enrolled, receive deutetrabenazine, and have at least one post-baseline assessment of the TMC score. Patients who withdraw informed consent form from the study will not be included in the effectiveness analysis set. Specifically, the effectiveness analysis set for the primary endpoint, i.e., 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 at least 4 weeks (detailed in **Section 10.2**), will include patients who meet such criteria (at least 18 patients); the effectiveness analysis set for the secondary endpoint, i.e., 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) (detailed in **Section 10.2**), will include all patients in the effective analysis set; [redacted]

The safety analysis set will include all patients who are enrolled and receive at least one dose of deutetrabenazine. Patients who withdraw informed consent form from the study will not be included in the safety population.

All patients who are enrolled and receive at least one dose of deutetrabenazine and who do not withdraw informed consent form from the study will be included for the baseline characteristics summary.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

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 with SDs and/or medians with interquartile ranges. Categorical variables will be summarised using counts and proportions.

For the effectiveness analysis, the primary analysis of the change in TMC score will be conducted using an adjusted linear mixed effects model. In addition, the change in TMC score will be evaluated using a paired t-test. 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. The change in TMC score from baseline to week 16 will be presented in mean, SD, and 95% confidence interval. Details of the definition of effectiveness endpoints are provided in **Section 10.2.** Details of the effectiveness analysis are provided in **Section 10.3.**

For the safety analysis, AEs will be summarized using counts and proportions.

All analyses will be performed using SAS (9.4) and/or R statistical software (3.6.3).

4.2. Specification of Baseline Values

Baseline period is defined as the time between enrolment and the initiation of deutetrabenazine. At the baseline hospital visit, patients' demographics, comorbidities, concomitant medications, disease and clinical characteristics of chorea associated with HD (including severity, impact, and treatment) will be collected, and the baseline TMC score (described in detail in **Section 10.2**) will be assessed by trained physicians and/or research delegates. Descriptive statistics will be provided for baseline characteristics of enrolled patients. More details are provided in **Sections 7** to **9**.

4.3. Handling Withdrawals and Missing Data

Data from enrolled patients who withdraw informed consent form from the study will be collected but not included in any analysis. The number of patients with withdrawal will be summarized using counts and proportions. Details are provided in **Section 5.2** and **Section 13**.

Data on effectiveness, safety, and other variables, such as patient demographics, disease and clinical characteristics, and treatments information, will be prospectively collected using eCRFs through the electronic data capture platform which will be maintained and monitored throughout the study. The eCRF and the platform will be thoroughly tested and reviewed to ensure clarity, accuracy, and completeness during data collection. Real-time logic control will be applied to the data collection process to minimize data entry error and to ensure all applicable fields are completed in a timely manner. The use of the linear mixed effects models provides a powerful tool to handle missing data using maximum likelihood estimation.

The pattern of missingness and the underlying reason(s) will be investigated. The missingness of patient demographics, disease and clinical characteristics, and treatment information at baseline and during follow-up can be reported using counts and proportions of missingness.

4.4. Study Days and Visits

Study weeks are numbered relative to the baseline, as detailed in **Section 2.1**. Activities by visit are summarized in **Table 1**. Specifically, after baseline visit and the initiation of deutetrabenazine, 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. Besides the baseline visit, 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 treating physicians and/or research delegates. The study follow-up will be ended after 16 weeks from study baseline.

5. STUDY POPULATION

5.1. General

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

This study aims to recruit at least 50 adult patients from multiple participating centres in China. This study will continue to recruit until reaching the sample size of 18 patients who received treatment with deutetrabenazine ≥24 mg/day for at least 4 weeks in the maintenance period. Patients who received 4 weeks of 24 mg/day for most of the days with occasional dose interruption or reduction will also be included in the primary endpoint analyses. Patients will be considered for enrolment in the study after the treating physician has determined the appropriateness of deutetrabenazine use. The treating 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 below.

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

- Patients aged 18 years or older with clinically confirmed chorea associated with HD diagnosis
- Patients whose baseline TMC score ≥ 8
- Patients who are deutetrabenazine-naïve before study entry or didn't 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

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

- Patients who have an unstable or serious medical or psychiatric illness at baseline
- Patients with a 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 receive reserpine within 20 days of deutetrabenazine treatment initiation
- Patients who receive monoamine oxidase inhibitors within 14 days of deutetrabenazine treatment initiation
- Patients who receive 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

Since the representativeness of the enrolled sample is unknown, a list documenting eligible patients (both enrolled and not enrolled) treated with deutetrabenazine will be established. The register will include information such as the proposed enrolment date, age, disease characteristics, previous treatments, and reason for not participating (a list will be provided in the study report). This register will provide some insight on participation rates and potential selection bias.

The study period for each patient will be from baseline to week 16 after study baseline, during June 2023 to May 2025. 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, i.e., week 16 after study baseline
- Loss to follow-up
- Death

5.2. Patient Disposition

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 drop out from the present study, a drop-out survey will be conducted to collect the reason of drop out, use of deutetrabenazine at drop out, chorea control at drop out, and self-reported clinical outcomes at drop out (details described in **Section 13**). Patients who decided to drop out from the study will also be invited for a final on-site effectiveness assessment, to the extent of patients' willingness.

The numbers and proportions of patients who are screened for study eligibility, enroll, complete, and discontinue the study will be summarized. Corresponding reasons of study discontinuation will also be summarized using counts and proportions to the extent of data availability.

6. 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 (by treatment phase)
- Dose reduction and modification, including dates and reasons (by treatment phase)
- Physician-reported non-adherence to treatment, treatment cessation, subsequent re-initiation of treatment, including dates and reasons (if any) (by treatment phase)

Exposure information will be summarized in descriptive statistics. Specifically, treatment duration will be summarized using mean (SD) and/or median (IQR) by treatment phase as the number of days that a patient receives deutetrabenazine (last day of exposure – first day of exposure + 1). Treatment dose will be summarized by treatment phase using mean (SD) and/or median (IQR). The numbers and proportions of patients who experience dose reduction and modification and the corresponding reason(s) will be summarized by phase. Treatment adherence, including the numbers and proportions of patients experienced treatment cessation, and subsequent re-initiation of treatment (if any) will be summarized by phase.

7. DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

At study baseline, information on patients' demographics and disease and clinical characteristics will be collected. In addition, information on weight, height, pregnancy status, and chorea control will be collected at study baseline and follow-up visits. Specifically, clinical diagnosis will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

- 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)
    - Pregnancy status
- Disease and clinical characteristics
    - Weight
    - Height
    - Date of initial diagnosis of HD
    - Date of initial diagnosis of chorea associated with HD
    - Duration of HD
    - Duration of chorea associated with HD
    - CAG repeat length, if available
    - Baseline TMC score
    - Baseline total functional capacity (TFC) score
    - Chorea control

Descriptive statistics will be summarized for each data element. Continuous variables will be summarized using mean (SD) and/or median (IQR), and categorical variables will be summarized using counts and proportions.

8. COMORBIDITIES AND COMPLICATIONS

At study baseline, comorbidities and complications will be collected. Clinical diagnosis of comorbidities and complications will be coded using MedDRA.

- 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
  - Other comorbidities
- Complications

Descriptive statistics will be summarized for each data element. Continuous variables will be summarized using mean (SD) and/or median (IQR), and categorical variables will be summarized using counts and proportions.

9. PRIOR THERAPY AND CONCOMITANT MEDICATION

Prior therapy will be collected at baseline and concomitant medication will be collected at both baseline and throughout the follow-up period. All prior and ongoing therapy and medications will be coded according to Anatomical Therapeutic Chemical (ATC) Classification System based on generic names.

- Prior therapy for HD
    - Drug name
    - Treatment initiation date
    - Dose and dosing schedule
    - Treatment duration (if applicable)
    - Date of treatment discontinuation (if applicable)
    - Reasons for discontinuation (if applicable)
- Prior therapy for other conditions, including dopamine receptor antagonists (typical and atypical antipsychotics)
    - Drug name
    - Indication/Reason for treatment
    - Treatment initiation date
    - Treatment duration (if applicable)
    - Date of treatment cessation (if applicable)
- Concomitant medication
    - Drug name
    - Reason for concomitant medication
    - Treatment initiation date
    - Dose and dosing schedule
    - Treatment duration (if applicable)
    - Date of treatment discontinuation (if applicable)

Descriptive statistics will be summarized for each data element. Continuous variables will be summarized using mean (SD) and/or median (IQR), and categorical variables will be summarized using counts and proportions.

10. ENDPOINT - EFFECTIVENESS ANALYSIS

10.1. General

The effectiveness population, i.e., patients receiving treatment with deutetrabenazine ⩾24 mg/day for at least 4 weeks will be used for the analysis of the primary endpoint. All patients who are enrolled, receive deutetrabenazine, and have at least one post-baseline assessment of the TMC score will be used for the analysis of secondary endpoint and [redacted]

The analysis sets are defined in **Section 3**.

10.2. Effectiveness Endpoint

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 at least 4 weeks. For each patient, effectiveness assessments will be conducted at hospital visits and will be performed by the same treating physician who received training to administer 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.

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]. Other items in the UHDRS will not be rated and included in the calculation of TMC score. A validated Chinese version of TMC scale will be used.

Secondary endpoint

The secondary endpoint includes 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). 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]

10.3. Effectiveness Analysis

The effectiveness endpoint, i.e., the change in TMC score from baseline to week 16 after study baseline, will be summarized using mean, SD, and 95% confidence intervals. The primary analysis of change in TMC score will be conducted using an adjusted linear mixed effects model for repeated measurements. Treatment status, time point, baseline TMC score, and other covariates such as age at baseline, sex, comorbidities, concomitant medications will be included 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. The linear mixed effects model will be fitted as:

$$Y_{ij} = \beta_0 + \beta_1 \times treatment_{ij} + \beta_2 \times time_{ij} + \beta_3 \times baselineTMC_i + \beta_4 \times X_{4ij} \ldots + \beta_p \times X_{pij} + \beta_{ij} + \varepsilon_{ij}$$

where

- Y_{ij} is the change in TMC from baseline to visit j for patient i;
- β_0 is the overall intercept;
- β_4 to β_p are the coefficients for the covariates;
- $treatment_{ij}$ is the treatment status (1 = with treatment; 0 = without treatment) for patient i at visit j; at baseline, treatment status is 0;
- $time_{ij}$ is the number of weeks for patient i at visit j;
- $baselineTMC_i$ is the TMC score for patient i at baseline;
- X_{4ij} to X_{pij} are the covariates for patient i at visit j;
- β_{ij} is the separate random intercept for patient i at visit j;
- ε_{ij} *is the residual error*

The primary endpoint estimated change in TMC from baseline to week 16 will be predicted with $time_{ij}$ = 16 weeks for each patient.

The population level least squared means of the change at week 4, 8, 12, 16 will be reported.

In addition, the statistically significant difference of the mean change in TMC score comparing to a mean change of zero will also be evaluated using a paired t-test at a two-sided significance level of 5%.

Such linear mixed effects models and paired t-tests will be fitted for primary, secondary, and [redacted] among patients receiving deutetrabenazine treatment ≥24 mg/day, all patients in the effectiveness analysis set (defined in **Section 3**), and [redacted]

10.3.1. Sub-Group Analyses

No sub-group analyses will be conducted.

11. MULTIPLE COMPARISONS AND MULTIPLICITY

Not applicable.

12. ENDPOINT - SAFETY ANALYSIS

12.1. General

The safety analysis set, i.e., all patients who are enrolled and receive at least one dose of deutetrabenazine (defined in **Section 3**) will be used for all safety analyses.

12.2. Safety Endpoint

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. AEs will be reported by the physicians and collected throughout the study period.

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

All physician-reported AEs, including special situations (defined below in this section), 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. All AEs (including special situations) will be reported by physicians and collected in a real-time manner as they occur, at each follow-up telephone contact and hospital visit. Adverse events are coded using MedDRA.

The safety endpoint is the occurrence of AEs concluded based on clinical inputs (including clinical events and abnormal laboratory test results), including proportions of AEs of the following by treatment phase:

- Any AEs with severity grade
- Serious adverse events (SAEs)
- Drug-related AEs
- AEs leading to treatment reduction, suspension, discontinuation, and/or withdrawal
- AEs of special interest, including suicidality, depression, somnolence, QTc prolongation, akathisia, and parkinsonism

An SAE 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 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 SAEs.
- 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, the occurrences of possible drug-induced liver injury events that meet Hy's Law criteria, defined as all the below, will be reported by physicians as an SAE:

- 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 in 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.

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.

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 and summarized.

12.3. Safety Analysis

The safety outcome, i.e., the proportion of patients with any physician-reported AEs and subtypes of AEs defined in **Section 12.2**, will be summarized by counts and proportions in all patients in the safety analysis set (defined in **Section 3**) for the overall study period, and by treatment phase. AE identified and reported by physicians through abnormal lab results will also be collected and data will enter safety analysis.

13. DROP-OUT SURVEY

A drop-out survey will be attempted/administered at the end of follow-up when the patient is identified as death, loss to follow-up, or decide to withdraw from the present study to the extent feasible (details in **Section 5.1**). The following information will be collected and recorded in the eCRF.

- Date of drop-out
- Reasons of drop-out (including death, loss to follow-up, or consent withdrawal)
- Reasons of consent withdrawal
- Last dose and timing of deutetrabenazine
- Reasons of treatment discontinuation (if applicable)
- Chorea control at the drop-out
- Self-reported clinical outcomes at the drop-out
- Date of death and cause of death (if applicable)

Descriptive statistics will be summarized for each data element. Continuous variables will be summarized using mean (SD) and/or median (IQR), and categorical variables will be summarized using counts and proportions.

14. STATISTICAL SOFTWARE

Consistency checks, distributional analytics, and data completeness checks will be performed to ensure the quality of the analytical dataset. Data analysis will follow this SAP. All analyses will be conducted using SAS for Windows Version 9.4 and/or R 3.6.3. All SAS and R programs for the analyses will be written by one programmer from AG and independently audited by a second AG programmer. AG's programmers have proficiency in SAS and R programming and will be involved in all discussions of the analysis to ensure their knowledge of the study background and objectives. Programming will involve commented source codes for analysis and annotated output. Prior to analysis and auditing, all raw data will be checked for internal consistency. In the audit process, SAS and R programs will be rerun and program files, log files, and output files will be reviewed. AG's auditors will read the entire code to understand the purpose and logic of the code and to ensure that the code (including datasets, variables, and macros) is appropriate for the analysis and that data is being read correctly. SAS log files will be searched for text indicating errors (e.g., "error", "uninitialized", "invalid", "more than one" or "warning"). The number of observations after each data step will also be checked in the log file to ensure that observations were correctly added or subtracted from the data. Comments from the audit will be addressed in a revised program.

All final tables in Excel will also be audited to ensure accurate presentation of analysis results. All results tables will be evaluated by the project team and principal investigator to evaluate internal consistency of counts and totals and comparability with the literature where similar studies will be conducted. Written materials, such as the study report, will also be audited for accuracy and consistency.

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Specifically, these electronic systems must comply with Title 21 of the Code of Federal Regulations (21CFR Part 11) relating to electronic records and electronic signatures. This affidavit is required for each employee using an electronic signature and must be signed prior to his/her use of electronic signatures.

Please read this affidavit and sign below to signify that you have read and understood this affidavit.

Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, the undersigned hereby certifies that his/her electronic signature is the legally binding equivalent of his/her traditional handwritten signature.

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Updated: May 2021