Report on the Deliberation Results

March 2, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Dysval Capsules 40 mg
Non-proprietary Name	Valbenazine Tosilate (JAN*)
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	April 22, 2021

Results of Deliberation

In its meeting held on February 25, 2022, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

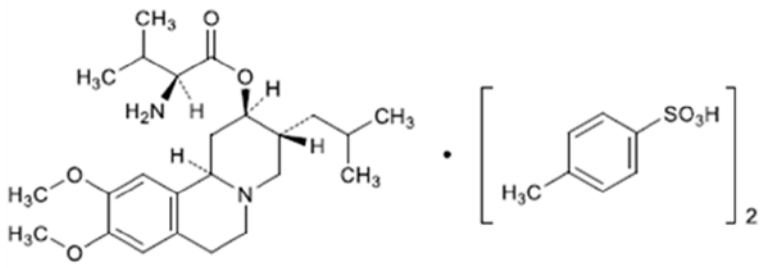
Review Report

February 7, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Dysval Capsules 40 mg
Non-proprietary Name	Valbenazine Tosilate
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	April 22, 2021
Dosage Form/Strength	Capsules: Each capsule contains 73 mg of Valbenazine Tosilate (equivalent to 40 mg of valbenazine).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{24}H_{38}N_2O_4 \cdot 2C_7H_8O_3S$
Molecular weight: 762.97
Chemical name:
(2*R*,3*R*,11b*R*)-9,10-Dimethoxy-3-(2-methylpropyl)-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-yl L-valinate bis(4-methylbenzenesulfonate)

Items Warranting Special Mention None
Reviewing Office Office of New Drug III

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of tardive dyskinesia, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition.

Indication	Tardive dyskinesia
Dosage and Administration	The usual adult dosage is 40 mg of valbenazine administered orally once daily. The dose may be adjusted according to the patient's symptoms. The maximum dosage is 80 mg once daily.
Approval Condition	The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

December 24, 2021

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Dysval Capsules 40 mg
Non-proprietary Name	Valbenazine Tosilate
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	April 22, 2021
Dosage Form/Strength	Capsules: Each capsule contains 73 mg of Valbenazine Tosilate (equivalent to 40 mg of valbena zine).
Proposed Indication	Tardive dyskinesia
Proposed Dosage and Administration	The usual adult dosage is 40 mg of valbenazine administered orally once daily. If response is inadequate, the dose may be increased to 80 mg once daily.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Tardive dyskinesia is a neurologic disorder characterized by involuntary movements of the orofacial region (the tongue, lips, jaw, and face), extremities, and torso. It is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as "involuntary athetoid or choreiform movements (lasting at least a few weeks) developing in association with the use of a neuroleptic medication for at least a few months." Although tardive dyskinesia is considered to be caused by hypersensitivity of nigrostriatal postsynaptic dopamine receptors after long-term treatment with drugs that block the dopamine receptor (*Can J Psychiatry*. 2005; 50: 541-7), its pathogenesis is not fully understood. Tardive dyskinesia may be persistent even if a potential causative drug is discontinued or changed. In psychotic patients who require stable maintenance antipsychotic treatment, dose reduction or discontinuation of the causative drug for the management of tardive dyskinesia has been reported to lead to increased risks of psychotic exacerbation and relapse even through it might improve tardive dyskinesia (*BMC Psychiatry*. 2018; 18: 330-40). Initial symptoms of tardive dyskinesia are generally mild involuntary movements. However, as the severity of physical impairment increases, speech disturbance, joint inflammation, gait disturbance, falls, and other abnormalities may occur (*Psychosomatics.* 1985; 26: 305-13, *CNS Spectrums*. 2018; 23: 370-7). The risk factors for tardive dyskinesia include older age, schizophrenia, and cognitive impairment, in addition to the duration of use and dosage of causative agents (*Can J Psychiatry*. 2005; 50: 541-7).

In Japan, no drugs have been approved for tardive dyskinesia.

Valbenazine Tosilate (hereinafter referred to as valbenazine [VBZ]) is a vesicular monoamine transporter 2 (VMAT2) inhibitor, licensed in by Mitsubishi Tanabe Pharma Corporation from Neurocrine Biosciences, Inc. Valbenazine is expected to improve involuntary movements in patients with tardive dyskinesia by selectively inhibiting VMAT2 in presynaptic vesicles, thereby preventing the uptake of monoamines and reducing the amount of dopamine released into the synaptic cleft.

In Japan, a clinical study was initiated in [redacted] 20[redacted]. Claiming that a Japanese phase II/III study etc. have demonstrated the efficacy and safety of valbenazine in the treatment of tardive dyskinesia, the applicant has now filed a marketing application for valbenazine.

Outside Japan, valbenazine was approved for the indication of tardive dyskinesia in April 2017 in the US.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white solid, and its description, solubility, hygroscopicity, pH, melting point and thermal analysis, dissociation constant, partition coefficient, optical rotation, and [redacted] have been determined. Although 6 polymorphic forms of the drug substance exist (2 [redacted], 3 [redacted], and 1 [redacted]), the commercial synthesis has been demonstrated to yield stable [redacted] (Form I).

Its chemical structure has been elucidated by elemental analysis, ultraviolet-visible spectroscopy (UV-VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H- and ^{13}C-NMR), mass spectrometry (MS), and single-crystal X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], and [redacted] as starting materials.

A quality by design (QbD) approach was used. Critical quality attributes (CQAs) were identified, and material attributes and process parameters that impact CQAs were characterized, etc. Then, a quality control strategy was developed (Table 1).

Table 1. Overview of drug substance control strategy

CQA	Method of control
[redacted]	[redacted]

[redacted],[1] [redacted],[2] [redacted],[3] and a step to obtain the drug substance have been defined as critical steps. [redacted],[4] [redacted], [redacted], and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (IR), purity [related substances (high performance liquid chromatography [HPLC]), [redacted] (HPLC), residual solvents (gas chromatography [GC])], [redacted], [redacted], [redacted], [redacted], and assay (HPLC).

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2. The stability results indicated that the drug substance is stable. Photostability data showed that the drug substance is photostable.

Table 2. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 [redacted] batches	25 ± 2℃	60 ± 5%RH	double polyethylene bags + silica gel + high-density polyethylene drum	60 months (2 batches) 48 months (1 batch)
		30 ± 2℃	65 ± 5%RH		
Accelerated		40 ± 2℃	75 ± 5%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a re-test period of [redacted] months has been

1) [redacted]
2) [redacted]
3) [redacted]
4) [redacted]

proposed for the drug substance when stored [redacted] in double polyethylene bags in a high-density polyethylene drum with silica gel. The long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release hard capsule containing 73 mg of valbenazine tosilate (equivalent to 40 mg of valbenazine) and the following excipients: D-mannitol, pregelatinized starch, colloidal silicon dioxide, and magnesium stearate.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of [redacted], blending, [redacted], [redacted], capsule filling, and packaging. Process control items and values have been established for [redacted] step and [redacted] step.

CQAs of the drug product were identified, and material attributes and process parameters that impact CQAs were characterized, etc. Then, a quality control strategy was developed (Table 3).

Table 3. Overview of drug product control strategy

CQA	Method of control
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (IR), purity [related substances (HPLC)], uniformity of dosage units [content uniformity testing (HPLC)], dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

The primary stability studies on the drug product (the proposed commercial drug product in Japan or [redacted] drug product) are shown in Table 4. The stability results indicated that the drug product is stable. Photostability data showed that the drug product is photostable.

Table 4. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	6 commercial-scale batches[a, b)]	25 ± 2℃	60 ± 5%RH	polyvinyl chloride/ polychlorotrifluoroethylene film/ aluminum foil	[redacted] months[a)] [redacted] months[b)]
Accelerated	3 commercial-scale batches[a)]	40 ± 2℃	75 ± 5%RH		6 months

a) 3 batches of the proposed commercial drug product in Japan
b) 3 batches of [redacted] drug product

The difference between the proposed commercial drug product in Japan and [redacted] drug product is [redacted] (the proposed commercial drug product in Japan [redacted], [redacted] drug product [redacted]) only. Because the results of stability studies on the proposed commercial drug product in Japan and [redacted] drug product [redacted], a shelf-life of 60 months has been proposed for the drug product

when packaged in blister packs (polyvinyl chloride/polychlorotrifluoroethylene film/aluminum foil) and stored at room temperature. The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted the results from the following non-clinical pharmacology studies of valbenazine: primary pharmacodynamic, secondary pharmacodynamic, and safety pharmacology studies. In some studies, the metabolites of valbenazine, i.e., NBI-98782 (a metabolite of valbenazine formed via ester hydrolysis), NBI-136110 (mono-oxidized valbenazine), NBI-679006 (mono-oxidized NBI-98782), and NBI-124976 (desmethyl NBI-98782) were also tested. Doses are expressed in terms of valbenazine. The main study results are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity for VMAT2

Valbenazine and its metabolites (NBI-98782, NBI-136110, NBI-679006, NBI-124976)[5)] were tested for their ability to inhibit the binding of ^{3}H-dihydrotetrabenazine to VMAT2 in rat striatal and human platelet homogenates to determine their binding affinities for rat and human VMAT2. The results are shown in Table 5. NBI-98782 and NBI-679006 displayed a higher binding affinity for VMAT2 than valbenazine (CTD 4.2.1.1-2, 4.2.1.1-3).

Table 5. Binding affinities of valbenazine and its metabolites for VMAT2

VMAT2	Ki value (nmol/L)				
	Valbenazine	NBI-98782	NBI-136110	NBI-679006	NBI-124976
Rat striatal	110 [a)]	1.0,[b)] 2.8 [a)]	160 [a)]	28 [b)]	3100 [b)]
Human platelet	150 [a)]	2.6,[b)] 3.3 [a)]	220 [a)]	74 [b)]	5500 [b)]

Mean
a) CTD 4.2.1.1-2, b) CTD 4.2.1.1-3

NBI-98782 is one of 4 dihydrotetrabenazine stereoisomers (NBI-98782, NBI-98795, NBI-98771, NBI-98772), which are the metabolites of tetrabenazine, and it is the common metabolite of valbenazine and tetrabenazine. Valbenazine, NBI-98782, NBI-98795, NBI-98771, and NBI-98772 were tested for their ability to inhibit the binding of ^{3}H-dihydrotetrabenazine to VMAT2 in rat forebrain homogenates to determine their binding affinities for rat VMAT2. The results are shown in Table 6. NBI-98782 displayed the highest binding affinity for VMAT2 (CTD 4.2.1.1-1).

5) NBI-98782, NBI-136110, NBI-679006, and NBI-124976 were assessed because NBI-98782 is the active metabolite of valbenazine, NBI-136110 is the most abundant metabolite in human plasma, and NBI-679006 and NBI-124976 were detected as primary metabolites in *in vivo* metabolism studies in rats, dogs, and humans (CTD 4.2.2.4-1). Valbenazine, NBI-98782, NBI-136110, and NBI-679006 represented 42.4%, 9.9%, 12.7%, and 8.2% of the total exposure in human plasma, respectively, and NBI-124976 was detectable, but unquantifiable (Reference data CTD 5.3.1.1-1).

Table 6. Binding affinities of valbenazine, NBI-98782, NBI-98795, NBI-98771, and NBI-98772 for VMAT2

VMAT2	Ki value (nmol/L)				
	Valbenazine	NBI-98782	NBI-98795	NBI-98771	NBI-98772
Rat forebrain	190	4.2	9.7	250	690

Mean

3.1.2 *In vivo* studies

3.1.2.1 VMAT2 inhibition

VMAT2 inhibition results in decreased uptake of monoamines into synaptic vesicles and depletion of brain monoamines, which induces palpebral ptosis, decreased locomotor activity, and increased serum prolactin. Thus, VMAT2 inhibition was determined by measuring these effects in rats.

Rats were given a single oral dose of valbenazine (1, 3, 10, and 30 mg/kg), NBI-98782 (0.3, 1, and 3 mg/kg), or tetrabenazine (1, 3, and 10 mg/kg) and evaluated for their ability to induce palpebral ptosis[6)] at 2 hours post-dose. Valbenazine, NBI-98782, and tetrabenazine all induced palpebral ptosis in a dose-dependent manner.

Rats were given a single oral dose of vehicle,[7)] valbenazine, NBI-98782, or tetrabenazine (all 3 mg/kg) and evaluated for their ability to induce palpebral ptosis at 1, 3, 6, and 9 hours post-dose. Compared with vehicle, NBI-98782 induced significant palpebral ptosis at 1, 3, 6, and 9 hours post-dose, valbenazine induced significant palpebral ptosis at 3, 6, and 9 hours post-dose, and tetrabenazine induced significant palpebral ptosis at 3 hours post-dose. The onset of palpebral ptosis was more rapid with NBI-98782 (CTD 4.2.1.1-4).

Rats were given a single oral dose of valbenazine (0.1, 0.3, 1, 3, and 10 mg/kg) or NBI-98782 (0.01, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg) and evaluated for their ability to induce palpebral ptosis at 1 hour post-dose. NBI-98782 was more potent than valbenazine (palpebral ptosis score [mean ± standard deviation (SD)], 1.2 ± 0.3 in the valbenazine 10 mg/kg group, 1.7 ± 0.3 in the NBI-98782 10 mg/kg group). The relationship between the mean plasma concentration of NBI-98782 and palpebral ptosis was assessed in the valbenazine vs. NBI-98782 groups. A similar degree of palpebral ptosis was observed according to the mean plasma concentration of NBI-98782, suggesting that NBI-98782 primarily contributes to VMAT2 inhibition following oral administration of valbenazine in rats (CTD 4.2.1.1-5).

Vehicle[8)] or NBI-98782 (0.27, 0.81, and 2.7 μg/min/kg) was intravenously infused for 12 hours in rats, and the minimum effective plasma concentration of NBI-98782 at steady state to induce palpebral ptosis was determined. Compared with vehicle, NBI-98782 at 0.81 μg/min/kg induced significant palpebral ptosis at 9 hours (palpebral ptosis score [mean ± SD], 1.1 ± 0.8 in the vehicle group, 1.8 ± 0.3 in the NBI-98782 0.81 μg/min/kg group), and the corresponding plasma concentration of NBI-98782 (mean ± SD) was 27.4 ± 17.9 ng/mL (CTD 4.2.1.1-5).

6) Palpebral ptosis score was measured on a 3-point scale (0 = no eyelid drooping; 1 = some drooping to half-closed eyelids; 2 = half-closed to completely closed eyelids).
7) 10% Cremophor EL
8) 5% dextrose

Rats were given a single oral dose of valbenazine, NBI-98782, or tetrabenazine (0.3, 1, 3, and 10 mg/kg for all) and evaluated for locomotor activity[9] at 1 hour post-dose. Valbenazine, NBI-98782, and tetrabenazine all produced a decrease in locomotor activity in a dose-dependent manner, and the minimum effective doses of valbenazine and tetrabenazine were 3 mg/kg, and the minimum effective dose of NBI-98782 was ≤0.3 mg/kg. NBI-98782 was more potent at decreasing locomotor activity (CTD 4.2.1.1-4).

Vehicle[10] or valbenazine (3, 10, and 15 mg/kg) was administered orally once daily for 14 days to rats, and serum prolactin levels at pre-dose and 0.5, 1, 3, 8, and 24 hours post-dose on Days 1 and 14 were determined. On both Days 1 and 14, valbenazine dose-dependently increased serum prolactin, and there was a trend towards a greater maximal effect in female rats compared with male rats (CTD 4.2.1.1-6).

3.2 Secondary pharmacodynamics

3.2.1 Effects on other receptors etc.

Valbenazine (10 μmol/L), NBI-98782 (1 μmol/L), and NBI-136110 (1 μmol/L) were screened for their inhibition of radioligand binding or activity of a panel of 80 receptors, transporters, ion channels, etc. Valbenazine showed 68% inhibition of ligand binding to the sigma receptor, but did not inhibit ligand binding to other receptors etc. by ≥50%. NBI-98782 or NBI-136110 did not inhibit ligand binding to any of the receptors etc. by ≥50% (CTD 4.2.1.2-1, 4.2.1.2-2).

The binding affinities of NBI-98782, NBI-98795, NBI-98771, and NBI-98772 for the serotonin receptor, the adrenergic receptor, the dopamine receptor, the transporters for serotonin, norepinephrine, and dopamine, and VMAT2 were determined. NBI-98771 exhibited a higher binding affinity for the 5-HT_7 and dopaminergic D_2 receptors relative to VMAT2.[11] NBI-98772 exhibited a higher binding affinity for the 5-HT_{2B}, 5-HT_7, adrenergic $_{\alpha 2A}$, and dopaminergic D_2 receptors relative to VMAT2.[12] NBI-98782 or NBI-98795 did not show a higher binding affinity for any of the receptors etc. relative to VMAT2 (CTD 4.2.1.2-1).

3.2.2 Effect on VMAT1 (CTD 4.2.1.2-3)

Using Chinese hamster ovary (CHO) cells expressing human VMAT1, the abilities of valbenazine and its metabolites (NBI-98782, NBI-136110, NBI-679006) (all 10 μmol/L) to inhibit VMAT1 were determined. Valbenazine or its metabolites did not inhibit uptake through VMAT1.

3.3 Safety pharmacology

Table 7 shows an overview of main safety pharmacology studies.

9) Locomotor activity was assessed based on the number of sensor breaks in the cage during a 30-minute period.
10) 0.25% methylcellulose
11) The mean Ki values for VMAT2 and the 5-HT_7 and dopaminergic D_2 receptors were 250, 71, and 180 nmol/L, respectively.
12) The mean Ki values for VMAT2 and the 5-HT_{2B}, 5-HT_7, adrenergic $_{\alpha 2A}$, and dopaminergic D_2 receptors were 690, 460, 5.9, 220, and 53 nmol/L, respectively.

Table 7. Overview of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Doses or concentrations	Route of administration	Findings	CTD
Cardiovascular	HEK293 cells	hERG channel current	Valbenazine: 0.3, 1.2, 3.6, 12.5 µmol/L NBI-98782: 3, 10, 30, 100 µmol/L	*In vitro*	Valbenazine IC_{50} = 2.0 µmol/L NBI-98782 IC_{50} = 36.1 µmol/L	4.2.1.3-2
	Dog (6/sex/group)	Telemetry (systemic blood pressure, heart rate, ECG)	Valbenazine: 5, 15, 30 mg/kg (single dose) NBI-98782: 7.5, 15 mg/kg (single dose)	Oral	Valbenazine ≥15 mg/kg, NBI-98782 ≥7.5 mg/kg: a transient increase in heart rate, QTc prolongation Valbenazine 30 mg/kg: a transient increase in mean blood pressure	4.2.1.3-6
CNS	Rat (8/sex/group)	FOB, motor activity	Valbenazine 15, 25, 50 mg/kg (single dose)	Oral gavage	Valbenazine 50 mg/kg: death Valbenazine ≥15 mg/kg: decreased neuromuscular function, decreased sensorimotor function, decreased behavior, effects on autonomic function	4.2.1.3-7
Respiratory	Dog (4-6/sex/group)	Respiratory rate, tidal volume, minute volume	Valbenazine: 5, 15, 35/30[a)] mg/kg (once daily for 14 days) NBI-98782: 7.5, 15 mg/kg (once daily for 14 days)	Oral	Valbenazine ≥15 mg/kg, NBI-98782 ≥7.5 mg/kg: decreases in respiratory rate and minute volume, increases in tidal volume	4.2.1.3-8

HEK293 cells: human embryonic kidney cells
FOB: a functional observation battery
a) The dose was reduced from 35 mg/kg to 30 mg/kg on Day 10.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of valbenazine

PMDA asked the applicant to explain the mechanism of action of valbenazine, taking account of the pathogenesis of tardive dyskinesia.

The applicant's explanation:

- Although the pathogenesis of tardive dyskinesia is not fully understood, long-term treatment with dopamine receptor blocking agents etc. has been reported to lead to compensatory dopamine D_2 receptor upregulation in the striatum (*Psychopharmacology*. 2000; 152: 174-80, *Eur J Pharmacol.* 1991; 207: 165-8), and tardive dyskinesia is considered to be caused by an increased dopamine D_2 receptor-mediated response to dopamine released in the striatum (*Can J Psychiatry.* 2005; 50: 541-7). A transporter protein that is located in presynaptic vesicles, VMAT, is involved in the transport, storage, and release of monoamines including dopamine, and VMAT2 regulates monoamine uptake from the cytoplasm to the synaptic vesicle in the CNS (*Microbiol Rev.* 1996; 60: 575-608).
- Valbenazine and its metabolite NBI-98782 demonstrated binding affinity for VMAT2 in *in vitro* studies [see Section 3.1.1.1] and induced palpebral ptosis, decreased locomotor activity, and increased serum prolactin through depletion of brain monoamines in *in vivo* studies [see Section 3.1.2.1]. Thus, valbenazine is considered to reduce involuntary movements in tardive dyskinesia by inhibiting VMAT2, thereby preventing monoamine uptake from the cytoplasm to the synaptic vesicle and reducing the amount of dopamine released into the synaptic cleft.

PMDA asked the applicant to describe differences in the pharmacological profile between another VMAT2 inhibitor, tetrabenazine, and valbenazine, including their metabolites, and then explain the possibility that adverse events similar to those associated with tetrabenazine occur with valbenazine, from a pharmacological point of view.

The applicant's explanation:

- Upon administration, tetrabenazine is rapidly metabolized into 4 dihydrotetrabenazine stereoisomers (NBI-98782, NBI-98795, NBI-98771, NBI-98772). Of which, NBI-98782 binds with the highest affinity to VMAT2 and is also a metabolite of valbenazine. The binding affinity of NBI-98782 to human VMAT2 is approximately 45 times higher than that of valbenazine [see Section 3.1.1.1].
- Other metabolites of tetrabenazine, i.e., NBI-98771 and NBI-98772, exhibited a higher binding affinity for the dopaminergic D_2 and 5-HT_7 receptors relative to VMAT2, whereas valbenazine, NBI-98782, and another metabolite of valbenazine, NBI-136110, had no binding affinity for the dopaminergic D_2 and 5-HT_7 receptors [see Section 3.2.1].
- Valbenazine (10 μmol/L) showed 68% inhibition of ligand binding to the sigma receptor [see Section 3.2.1]. Since this valbenazine concentration was approximately 7500-fold the human exposure[13)] at the maximum recommended human dose (MRHD) of 80 mg, there is no possibility that inhibition of the sigma receptor will become a clinically relevant problem.
- Valbenazine, NBI-98782, or another metabolite of valbenazine, NBI-136110, did not inhibit ligand binding to other receptors etc., including uptake through VMAT1, 1 of 2 isoforms of VMAT, which is not expressed in the CNS, but is primarily expressed in endocrine tissues [see Sections 3.2.1 and 3.2.2].
- VMAT2 is primarily expressed in the synaptic vesicles of monoamine nerve endings in the CNS. Following VMAT 2 inhibition in the CNS, depression- and suicide-related adverse events, hostility/aggression-related adverse events, sedation-related adverse events, extrapyramidal symptom-related adverse events, neuroleptic malignant syndrome-related adverse events, and prolactin elevation-related adverse events are anticipated as adverse events associated with reduction of monoamine release. Thus, similar adverse events are expected to occur also with valbenazine from a pharmacological point of view.
- VMAT2 has been demonstrated to be expressed also in small intensely fluorescent (SIF) cells in the sympathetic ganglion, mast cells, platelets, enteric neurons, and enterochromaffin-like cells of the stomach. Adverse events expected to occur with VMAT2 inhibition in these peripheral tissues and cells are unknown.
- Based on the above, valbenazine has no dopaminergic D_2 or 5-HT_7 receptor inhibitory activity, which is considered a major difference from the pharmacological profile of tetrabenazine. However, [redacted], adverse events similar to those associated with tetrabenazine may occur with valbenazine from a pharmacological point of view.

13) Using the steady state C_{max} of valbenazine following once daily administration of valbenazine 80 mg obtained from simulations using the PPK model (Reference data CTD 5.3.3.5-1) (556.0 ng/mL) and protein binding (99.9%), the unbound plasma concentration of valbenazine (0.556 ng/mL) was calculated.

PMDA's view:

The mechanism of action of valbenazine and its metabolites has been explained from the pharmacological point of view, based on the currently available findings. However, the safety of valbenazine will be further discussed in Section 7.R.3.

3.R.2 Safety pharmacology studies

PMDA asked the applicant to explain the possibility that the findings noted in the safety pharmacology studies will be observed also in humans and become a clinically relevant problem.

The applicant's explanation:

- Effects on the cardiovascular system

  The IC_{50} values of valbenazine and NBI-98782 for the inhibition of hERG channel current[14)] were approximately 1500-fold and approximately 790-fold the human exposures after multiple-dose administration at the MRHD of 80 mg,[15)] respectively. The no-observed-effect-levels (NOELs) of valbenazine and NBI-98782 for increased mean blood pressure following oral administration of valbenazine or NBI-98782 in dogs were both 15 mg/kg. Valbenazine and NBI-98782 exposures[16)] at the NOEL of valbenazine were 123- and 6.4-fold the human exposures after multiple-dose administration at the MRHD of 80 mg, respectively. NBI-98782 exposure[17)] at the NOEL of NBI-98782 was 29-fold the human exposure after multiple-dose administration at the MRHD of 80 mg. The NOEL of valbenazine for increased heart rate and QTc prolongation in dogs was 5 mg/kg, and these effects were noted after administration of NBI-98782 at ≥7.5 mg/kg, the lowest dose tested. Valbenazine and NBI-98782 exposures[18)] at the NOEL of valbenazine were 27- and 1.9-fold the human exposures after multiple-dose administration at the MRHD of 80 mg, respectively. NBI-98782 exposure[19)] at 7.5 mg/kg of NBI-98782 was 15-fold the human exposure after multiple-dose administration at the MRHD of 80 mg. Since there were no clinically relevant changes in vital signs (blood pressure and heart rate) during the double-blind period of a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) [see Section 7.2.1], increases in the mean blood pressure and heart rate are unlikely to become a problem in clinical use. On the other hand, in a clinical pharmacology study that evaluated the effect of valbenazine on the QT/QTc interval (CTD 5.3.4.1-1, Study 1401), QT prolongation was observed at 160 mg of valbenazine. A pooled concentration-QT analysis suggested that NBI-98782 causes plasma concentration-dependent increases in the QTc interval [see Section 6.R.5]. Thus, the package insert will include precautionary statements about patients in whom an increased plasma concentration of NBI-98782 is anticipated.

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14) The IC_{50} values (valbenazine, 837 ng/mL; NBI-98782, 11500 ng/mL) were calculated based on the molecular weight of the free base (valbenazine, 418.57; NBI-98782, 319.44).

15) Using the steady state C_{max} following once daily administration of valbenazine 80 mg obtained from simulations using the PPK model (Reference data CTD 5.3.3.5-1) (valbenazine, 556.0 ng/mL; NBI-98782, 39.0 ng/mL) and protein binding (valbenazine, 99.9%; NBI-98782, 62.9%), the unbound plasma concentrations (valbenazine, 0.556 ng/mL; NBI-98782, 14.5 ng/mL) were calculated.

16) The unbound plasma concentrations based on the C_{max} at 15 mg of valbenazine on Day 1 in a 14-day repeated dose toxicity study in dogs (CTD 4.2.1.3-8) (the mean of males and females) (valbenazine, 68.3 ng/mL; NBI-98782, 93.1 ng/mL) were used.

17) The unbound plasma concentration based on the C_{max} at 15 mg of NBI-98782 on Day 1 in a 14-day repeated dose toxicity study in dogs (CTD 4.2.1.3-8) (the mean of males and females) (NBI-98782, 419 ng/mL) was used.

18) The unbound plasma concentrations based on the C_{max} at 5 mg of valbenazine on Day 1 in a 14-day repeated dose toxicity study in dogs (CTD 4.2.1.3-8) (the mean of males and females) (valbenazine, 15.2 ng/mL; NBI-98782, 27.7 ng/mL) were used.

19) The unbound plasma concentration based on the C_{max} at 7.5 mg of NBI-98782 on Day 1 in a 14-day repeated dose toxicity study in dogs (CTD 4.2.1.3-8) (the mean of males and females) (NBI-98782, 211 ng/mL) was used.

- CNS effects

  Decreased neuromuscular function, decreased sensorimotor function, decreased behavior, and effects on autonomic function were observed following oral administration of valbenazine at ≥15 mg/kg, the lowest dose tested, in rats. Since the incidences of CNS adverse events (sedation-related adverse events and extrapyramidal symptom-related adverse events) tended to be higher in the valbenazine group than in the placebo group during the double-blind period of Japanese Study J02 [see Sections 7.R.3.3 and 7.R.3.4], the package insert will include a precaution about CNS adverse events.

- Effects on the respiratory system

  Decreases in respiratory rate and minute volume were observed following oral administration of valbenazine or NBI-98782 in dogs. The NOEL of valbenazine was 5 mg/kg, and these effects were noted following administration of NBI-98782 at ≥7.5 mg/kg, the lowest dose tested. Valbenazine and NBI-98782 exposures at the NOEL of valbenazine were 27- and 1.9-fold the human exposures after multiple-dose administration at the MRHD of 80 mg, respectively, and NBI-98782 exposure at 7.5 mg/kg of NBI-98782 was 15-fold the human exposure after multiple-dose administration at the MRHD of 80 mg. The incidences of respiratory adverse events[20)] during the double-blind period of Japanese Study J02 were 1.2% (1 of 84 subjects) in the placebo group, 1.2% (1 of 85 subjects) in the valbenazine 40 mg group, and 4.8% (4 of 84 subjects) in the valbenazine 80 mg group, showing no clear differences in the incidence of adverse events between the placebo and valbenazine groups. Thus, decreases in respiratory rate and minute volume are unlikely to become a problem in clinical use.

PMDA's view:

The above explanation by the applicant is acceptable. However, the safety of valbenazine will be further discussed in Sections 6.R.5 and 7.R.3.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted the results from absorption, distribution, metabolism, and excretion studies in mice, rats, rabbits, dogs, and monkeys as non-clinical pharmacokinetic studies of valbenazine. Concentrations of unchanged valbenazine and its major metabolites, NBI-98782 and NBI-136110, in biological samples were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation [LLOQ], 5.00 ng/mL for unchanged valbenazine, 1.00 ng/mL for NBI-98782, 2.00 ng/mL for NBI-136110). In studies using ^{14}C-valbenazine, radioactivity levels in biological samples were determined by liquid scintillation counter (LLOQ, 2 times the response of blank samples). Tissue radioactivity levels were determined using quantitative whole-body autoradiography (LLOQ, 0.0342 μg eq/g). Doses are expressed in terms of valbenazine. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD. The main study results are described below.

20) Events in the MedDRA SOC "respiratory, thoracic and mediastinal disorders"

4.1 Absorption

4.1.1 Single-dose studies

Table 8, Table 9, and Table 10 show the pharmacokinetic parameters of unchanged valbenazine and its major metabolites, NBI-98782 and NBI-136110, in plasma following a single intravenous or oral dose of valbenazine in male mice, male rats, male and female dogs, and male and female monkeys (CTD 4.2.2.2-2, 4.2.2.2-13, 4.2.2.2-28, 4.2.2.2-29, 4.2.2.2-35).

Table 8. Pharmacokinetic parameters of unchanged valbenazine in plasma following a single intravenous or oral dose of valbenazine

Species	Route of administration	Dose (mg/kg)	Sex (No. of animals/group)	Feeding condition	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	V_d or V_d/F (L/kg)	CL or CL/F (mL/min/kg)	CTD
Mouse[b)]	Oral gavage	8.5	3M/time point	Fasted	1570	0.5	3680	1.3	13.3	116	4.2.2.2-2
		25.5	3M/time point	Fasted	6080	0.5	18200	1.5	1.04	7.77	
Rat	IV	2.5	3M	Non-fasted	2600 ± 83.9	—	1820 ± 265	1.3 ± 0.11	2.68 ± 0.344	23.2 ± 3.19	4.2.2.2-13
	Oral gavage[c)]	10	4M	Non-fasted	1910 ± 688	0.75 [0.5, 1.0]	4990 ± 1660	1.6 ± 0.15	5.19 ± 1.80	36.8 ± 14.2	
Dog	IV	2.5	4 (2M2F)	Fasted	9120 ± 3450	—	5870 ± 1760	5.9 ± 1.7	3.85 ± 1.36	7.72 ± 2.83	4.2.2.2-28
	Oral gavage[c)]	10	4 (2M2F)	Fasted	9170 ± 2850	0.38 [0.25, 0.50]	27400 ± 5450	6.0 ± 1.3	3.34 ± 1.33	6.26 ± 1.21	
		10	3M	Fasted	6560 ± 3210	0.5 [0.5, 4.0]	31000 ± 11200	5.7 ± 0.91	—	—	4.2.2.2-29
		10	3M	Fed	3110 ± 1300	0.5 [0.5, 1.0]	17200 ± 4730	5.6 ± 1.16	—	—	
Monkey	IV	2.5	4 (2M2F)	Fasted	1820 ± 343	—	2270 ± 310	6.8 ± 2.2	11.1 ± 4.44	18.6 ± 2.61	4.2.2.2-35
	Oral gavage[c)]	10	4 (2M2F)	Fasted	1790 ± 1420	1.5 [0.5, 2.0]	7770 ± 3930	4.4 ± 0.17	10.3 ± 5.90	27.3 ± 16.4	

Mean or Mean ± SD; —, Not applicable or not calculated

a) Median or Median [Min., Max.]

b) Parameters were calculated based on the mean plasma concentration at each time point.

c) The absolute oral bioavailability of valbenazine was 68.5% in rats, 123% in dogs, and 91.0% in monkeys.

Table 9. Pharmacokinetic parameters of NBI-98782 in plasma following a single intravenous or oral dose of valbenazine

Species	Route of administration	Dose (mg/kg)	Sex (No. of animals/group)	Feeding condition	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CTD
Mouse[b)]	Oral gavage	8.5	3M/time point	Fasted	55.4	1.0	242	2.1	4.2.2.2-2
		25.5	3M/time point	Fasted	167	0.5	849	2.9	
Rat	IV	2.5	3M	Non-fasted	126 ± 18.6	2.0 [1.0, 2.0]	717 ± 166	2.5 ± 0.35	4.2.2.2-13
	Oral gavage	10	4M	Non-fasted	475 ± 94.6	2.0 [0.5, 2.0]	2640 ± 603	2.9 ± 0.31	
Dog	IV	2.5	4 (2M2F)	Fasted	55.5 ± 3.94	2.1 [2.1, 2.1]	462 ± 52	4.4 ± 0.51	4.2.2.2-28
	Oral gavage	10	4 (2M2F)	Fasted	164 ± 45.3	2.0 [2.0, 4.0]	1370 ± 239	5.0 ± 0.49	
		10	3M	Fasted	182 ± 67.1	4.0 [2.0, 4.0]	1750 ± 590	6.3 ± 0.71	4.2.2.2-29
		10	3M	Fed	92.9 ± 27.4	4.0 [2.0, 4.0]	1230 ± 481	6.1 ± 1.1	
Monkey	IV	2.5	4 (2M2F)	Fasted	45.2 ± 8.73	1.1 [0.13, 1.1]	244 ± 95	3.9 ± 1.0	4.2.2.2-35
	Oral gavage	10	4 (2M2F)	Fasted	66.1 ± 20.6	2.0 [2.0, 2.0]	558 ± 188	5.0 ± 1.0	

Mean or Mean ± SD

a) Median or Median [Min., Max.]

b) Parameters were calculated based on the mean plasma concentration at each time point.

Table 10. Pharmacokinetic parameters of NBI-136110 in plasma following a single intravenous or oral dose of valbenazine

Species	Route of administration	Dose (mg/kg)	Sex (No. of animals/group)	Feeding condition	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CTD
Mouse[b)]	Oral gavage	8.5	3M/time point	Fasted	699	1.0	2880	2.8	4.2.2.2-2
		25.5	3M/time point	Fasted	2270	0.5	11100	2.6	
Dog	Oral gavage	10	3M	Fasted	593 ± 99.8	4.0 [4.0, 4.0]	6740 ± 935	9.6 ± 1.9	4.2.2.2-29
		10	3M	Fed	282 ± 35.4	4.0 [2.0, 4.0]	5220 ± 1310	10 ± 2.5	

Mean or Mean ± SD
a) Median or Median [Min., Max.]
b) Parameters were calculated based on the mean plasma concentration at each time point.

4.1.2 Repeated-dose studies

Toxicokinetics were evaluated in repeated oral dose toxicity studies in mice, rats, and dogs. Table 11, Table 12, and Table 13 show the pharmacokinetic parameters of unchanged valbenazine and its major metabolites, NBI-98782 and NBI-136110, in plasma in these studies (CTD 4.2.2.2-11, 4.2.2.2-23, 4.2.2.2-34)

Table 11. Pharmacokinetic parameters of unchanged valbenazine in plasma following repeated oral dosing of valbenazine

Species	Time point	Dose (mg/kg)	Sex (No. of animals/group)	C_{max} (ng/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (ng·h/mL)	$t_{1/2}$ (h)	CTD
Mouse[b)]	Day 1	10	M (3/time point)	697	0.5	2793	2.02	4.2.2.2-11
			F (3/time point)	870	0.5	2969	1.65	
		30	M (3/time point)	4061	0.5	21126	2.17	
			F (3/time point)	3348	1.0	18575	2.30	
		60	M (3/time point)	8177	1.0	81234	2.04	
			F (3/time point)	9025	1.0	67530	—	
		100	M (3/time point)	16389	1.0	120754	2.65	
			F (3/time point)	12135	2.0	133142	3.87	
		300	M (3/time point)	34164	6.0	737400	—	
			F (3/time point)	32856	1.0	548423	—	
	Day 91	10	M (3/time point)	914	0.5	3112	1.92	
			F (3/time point)	500	0.5	1414	1.61	
		30	M (3/time point)	2462	0.5	11504	2.35	
			F (3/time point)	3269	0.5	8372	2.59	
		60	M (3/time point)	5229	0.5	29396	2.60	
			F (3/time point)	7012	0.5	21161	—	
		100	M (3/time point)	4290	2.0	42580	2.66	
			F (3/time point)	6026	0.5	28507	2.29	
Rat[b)]	Day 1	3	M (3/time point)	37.7	1.0	215	2.20	4.2.2.2-23
			F (3/time point)	52.2	1.0	289	2.66	
		10	M (3/time point)	287	1.0	1570	2.67	
			F (3/time point)	258	1.0	2050	—	
		15	M (3/time point)	690	1.0	3850	—	
			F (3/time point)	869	1.0	5300	—	
	Day 180	3	M (3/time point)	311	1.0	954	2.19	
			F (3/time point)	472	1.0	1650	2.40	
		10	M (3/time point)	822	1.0	3940	2.99	
			F (3/time point)	1180	1.0	4840	—	
		15	M (3/time point)	1570	1.0	7270	3.25	
			F (3/time point)	971	0.5	5430	3.66	
Dog	Day 1	3	M (7)	1280 ± 124	0.5 [0.5, 1.0]	4280 ± 811	4.90 ± 0.515	4.2.2.2-34
			F (7)	1340 ± 206	0.5 [0.5, 1.0]	4160 ± 452	4.61 ± 0.718	
		10	M (7)	4310 ± 621	1.0 [0.5, 1.0]	14600 ± 2890	4.71 ± 0.338	
			F (6)	4110 ± 2060	1.0 [0.5, 1.0]	15000 ± 3110	4.73 ± 1.16	
		15	M (7)	8120 ± 1210	1.0 [0.5, 1.0]	30900 ± 11500	4.95 ± 0.362	
			F (7)	6510 ± 1020	1.0 [0.5, 1.0]	25900 ± 5500	4.92 ± 0.438	
	Day 273	3	M (7)	1780 ± 597	1.0 [0.5, 3.0]	10200 ± 3210	5.79 ± 0.650	
			F (7)	1670 ± 911	1.0 [0.5, 3.0]	7450 ± 1980	5.51 ± 1.18	
		10	M (7)	6620 ± 2250	0.5 [0.5, 3.0]	36700 ± 9270	5.91 ± 0.481	
			F (7)	6360 ± 2910	0.5 [0.5, 1.0]	28700 ± 7910	5.98 ± 1.02	
		15	M (7)	10900 ± 3310	0.5 [0.5, 1.0]	73000 ± 19200	5.97 ± 0.458	
			F (7)	9730 ± 3600	0.5 [0.5, 1.0]	52200 ± 18700	6.67 ± 1.38	

Mean or Mean ± SD

a) Median or Median [Min., Max.]

b) Parameters were calculated based on the mean plasma concentration at each time point.

Table 12. Pharmacokinetic parameters of NBI-98782 in plasma following repeated oral dosing of valbenazine

Species	Time point	Dose (mg/kg)	Sex (No. of animals/group)	C_{max} (ng/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (ng·h/mL)	$t_{1/2}$ (h)	CTD
Mouse[b)]	Day 1	10	M (3/time point)	45.1	1.0	361	—	4.2.2.2-11
			F (3/time point)	92.1	0.5	333	2.36	
		30	M (3/time point)	172	0.5	1203	3.59	
			F (3/time point)	273	0.5	1365	2.50	
		60	M (3/time point)	217	0.5	2827	3.36	
			F (3/time point)	382	0.5	3343	3.11	
		100	M (3/time point)	307	0.5	3162	5.31	
			F (3/time point)	639	0.5	6015	6.99	
		300	M (3/time point)	361	1.0	6695	—	
			F (3/time point)	1359	0.5	9800	—	
	Day 91	10	M (3/time point)	44.8	0.5	316	—	
			F (3/time point)	75.2	0.5	257	1.84	
		30	M (3/time point)	119	0.5	980	4.07	
			F (3/time point)	186	0.5	856	2.84	
		60	M (3/time point)	196	0.5	1903	4.08	
			F (3/time point)	227	0.5	1360	3.30	
		100	M (3/time point)	248	0.5	2736	4.65	
			F (3/time point)	207	0.5	1810	3.66	
Rat[b)]	Day 1	3	M (3/time point)	68.1	3.0	626	—	4.2.2.2-23
			F (3/time point)	68.1	3.0	773	2.74	
		10	M (3/time point)	262	3.0	2270	2.98	
			F (3/time point)	281	3.0	3070	3.02	
		15	M (3/time point)	461	3.0	4050	2.94	
			F (3/time point)	595	3.0	5530	2.97	
	Day 180	3	M (3/time point)	110	1.0	897	3.37	
			F (3/time point)	125	1.0	1150	3.83	
		10	M (3/time point)	326	1.0	3050	3.68	
			F (3/time point)	383	1.0	3350	3.50	
		15	M (3/time point)	412	1.0	4720	3.79	
			F (3/time point)	476	1.0	4310	3.67	
Dog	Day 1	3	M (7)	41.3 ± 8.27	1.0 [1.0, 3.0]	336 ± 81.8	5.09 ± 0.710	4.2.2.2-34
			F (7)	45.4 ± 13.4	1.0 [1.0, 3.0]	329 ± 64.3	4.85 ± 0.752	
		10	M (7)	124 ± 25.0	1.0 [1.0, 3.0]	1130 ± 198	5.50 ± 0.618	
			F (6)	98.4 ± 23.9	3.0 [1.0, 3.0]	994 ± 262	5.41 ± 1.30	
		15	M (7)	176 ± 66.2	3.0 [1.0, 3.0]	2000 ± 960	6.08 ± 0.784	
			F (7)	167 ± 55.1	3.0 [1.0, 3.0]	1850 ± 693	5.95 ± 0.970	
	Day 273	3	M (7)	42.9 ± 14.8	3.0 [1.0, 3.0]	445 ± 102	7.75 ± 0.687	
			F (7)	39.4 ± 15.3	3.0 [1.0, 3.0]	369 ± 69.0	6.10 ± 0.722[c)]	
		10	M (7)	175 ± 67.0	3.0 [3.0, 3.0]	2100 ± 800	7.66 ± 1.11	
			F (7)	128 ± 28.4	3.0 [1.0, 3.0]	1350 ± 344	6.86 ± 1.02	
		15	M (7)	290 ± 80.4	3.0 [3.0, 3.0]	3890 ± 1540	8.62 ± 0.994[c)]	
			F (7)	238 ± 87.4	3.0 [3.0, 3.0]	2880 ± 1290	8.23 ± 0.891	

Mean or Mean ± SD; —, Not calculated

a) Median [Min., Max.]

b) Parameters were calculated based on the mean plasma concentration at each time point.

c) N = 6

Table 13. Pharmacokinetic parameters of NBI-136110 in plasma following repeated oral dosing of valbenazine

Species	Time point	Dose (mg/kg)	Sex (No. of animals/group)	C_{max} (ng/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (ng·h/mL)	$t_{1/2}$ (h)	CTD
Mouse[b)]	Day 1	10	M (3/time point)	218	1.0	1878	4.05	4.2.2.2-11
			F (3/time point)	340	0.5	2267	2.95	
		30	M (3/time point)	1007	0.5	9210	3.52	
			F (3/time point)	1129	1.0	9721	2.95	
		60	M (3/time point)	2275	6.0	31584	—	
			F (3/time point)	1831	6.0	26434	—	
		100	M (3/time point)	2201	2.0	30030	4.27	
			F (3/time point)	2626	2.0	36661	7.69	
		300	M (3/time point)	4916	24	96792	—	
			F (3/time point)	3247	6.0	62324	—	
	Day 91	10	M (3/time point)	270	0.5	1870	4.76	
			F (3/time point)	199	1.0	1179	4.35	
		30	M (3/time point)	764	0.5	7207	4.40	
			F (3/time point)	585	0.5	4530	3.77	
		60	M (3/time point)	1603	1.0	16972	3.75	
			F (3/time point)	1076	1.0	10489	3.75	
		100	M (3/time point)	2,089	1.0	24131	4.02	
			F (3/time point)	925	6.0	13553	—	
Rat[b)]	Day 1	3	M (3/time point)	21.8	3.0	240	—	4.2.2.2-23
			F (3/time point)	15.5	3.0	210	5.14	
		10	M (3/time point)	85.1	3.0	1050	4.29	
			F (3/time point)	59.5	8.0	864	—	
		15	M (3/time point)	165	8.0	2340	—	
			F (3/time point)	104	8.0	1540	—	
	Day 180	3	M (3/time point)	66.4	1.0	472	5.77	
			F (3/time point)	64.2	1.0	599	6.53	
		10	M (3/time point)	134	3.0	1560	6.52	
			F (3/time point)	121	1.0	1350	6.75	
		15	M (3/time point)	208	1.0	2680	6.75	
			F (3/time point)	109	1.0	1590	9.55	
Dog	Day 1	3	M (7)	75.6 ± 26.6	1.0 [0.5, 3.0]	866 ± 144	10.3, 10.7[c)]	4.2.2.2-34
			F (7)	126 ± 34.4	1.0 [0.5, 1.0]	1040 ± 181	8.15 ± 1.83[d)]	
		10	M (7)	339 ± 69.5	1.0 [1.0, 1.0]	3460 ± 768	9.42 ± 1.13[d)]	
			F (6)	238 ± 34.0	1.0 [1.0, 8.0]	3170 ± 702	8.58 ± 1.56[e)]	
		15	M (7)	482 ± 141	1.0 [1.0, 3.0]	5140 ± 952	9.68 ± 0.639[f)]	
			F (7)	390 ± 102	1.0 [1.0, 8.0]	5190 ± 1480	8.97, 10.6[c)]	
	Day 273	3	M (7)	135 ± 39.6	1.0 [0.5, 3.0]	1890 ± 489	—	
			F (7)	136 ± 78.5	3.0 [1.0, 3.0]	1450 ± 454	9.03 ± 0.248[f)]	
		10	M (7)	423 ± 87.4	1.0 [0.5, 3.0]	6260 ± 1550	—	
			F (7)	433 ± 129	1.0 [0.5, 3.0]	5200 ± 1170	9.30[g)]	
		15	M (7)	677 ± 212	3.0 [0.5, 3.0]	10800 ± 2390	—	
			F (7)	539 ± 121	3.0 [0.5, 8.0]	8350 ± 2540	—	

Mean or Mean ± SD; —, Not calculated
a) Median [Min., Max.]
b) Parameters were calculated based on the mean plasma concentration at each time point.
c) N = 2 (individual values), d) N = 5, e) N = 4, f) N = 3, g) N = 1 (individual value)

4.2 Distribution

4.2.1 Tissue distribution

Following a single oral dose of ^{14}C-valbenazine 15 mg/kg in male albino rats and male pigmented rats, tissue radioactivity concentrations (1 animal/time point) were determined at 1, 8, 24, 72, and 168 hours post-dose (at 4, 48, 504, and 840 hours post-dose in pigmented rats only). Among the tissues examined,[21)] peak radioactivity concentrations were reached at 1 hour post-dose in most tissues except for the testis, Harderian gland, eye (pigmented rats only), and uveal tract (pigmented rats only) and by 8 hours post-dose in all tissues examined.

21) plasma, blood, brain, lung, liver, kidney, testis, muscle, pancreas, spleen, skin, pigmented skin (pigmented rats only), eye, lens, uveal tract, adrenal gland, Harderian gland, pituitary gland, salivary gland, thyroid gland, thymus

In pigmented rats, plasma radioactivity was below the LLOQ at 168 hours post-dose, whereas radioactivity was quantifiable in the uveal tract, eye, thyroid gland, lens, adrenal gland, Harderian gland, and spleen even at 840 hours post-dose (The tissue radioactivity concentrations at 840 hours post-dose were 96.4, 15.3, 0.564, 0.189, 0.167, 0.0638, and 0.0378 μg eq/g, respectively). In pigmented rats, the ratio of tissue to plasma radioactivity $AUC_{0\text{-last}}$ was ≥1 for all tissues, and valbenazine-related radioactivity was highly distributed to particularly the uveal tract and eye (The ratios of tissue to plasma radioactivity $AUC_{0\text{-last}}$ of 4190 and 735, respectively). The ratio of tissue to plasma radioactivity $AUC_{0\text{-last}}$ was ≥10 for the Harderian gland, thyroid gland, liver, pituitary gland, spleen, salivary gland, kidney, and lens (The ratios of tissue to plasma radioactivity $AUC_{0\text{-last}}$ were 94.0, 53.8, 28.8, 21.3, 11.2, 10.7, 10.3, and 10.2, respectively). There were no clear differences in the tissue distribution of radioactivity between pigmented and albino rats, except for the uveal tract and eye (CTD 4.2.2.2-15).

The distribution of unchanged valbenazine and its active metabolite, NBI-98782, to the brain was evaluated following a single oral dose of valbenazine 13.1 mg/kg in male rats (3/time point). Peak concentrations of unchanged valbenazine and NBI-98782 in the brain were reached at 1 hour post-dose, and the brain concentrations were higher than the plasma concentrations at all time points (at 1, 4, 8, and 24 hours post-dose) (The brain to plasma ratios were 1.4-5.8 for unchanged valbenazine and 2.3-5.0 for NBI-98782). Unchanged valbenazine and NBI-98782 were shown to cross the blood-brain barrier (CTD 4.2.2.3-4).

4.2.2 Protein binding

The plasma from mouse, rat, rabbit, and dog was spiked with valbenazine (1-10 μg/mL for mouse and dog plasma, 0.5-5 μg/mL for rat and rabbit plasma), and the plasma protein binding of valbenazine was determined using an ultrafiltration method. The percentages of unchanged valbenazine bound to plasma proteins were 95.4% to 96.6%, 98.3%, 99.3% to 99.4%, and 98.8% to 99.0%, respectively (CTD 4.2.2.3-1).

The plasma from mouse, rat, rabbit, and dog was spiked with NBI-98782 (10-100 ng/mL), and the plasma protein binding of NBI-98782 was determined using an equilibrium dialysis method. The percentages of NBI-98782 bound to plasma proteins were 74.7% to 76.0%, 71.7% to 73.8%, 47.0% to 48.0%, and 58.9%, respectively (CTD 4.2.2.3-2).

4.2.3 Placental transfer

Female rats received a single oral dose of valbenazine 15 mg/kg on gestation day 11 or 13. In rats on gestation day 11, the concentrations of unchanged valbenazine and its major metabolites, NBI-98782 and NBI-136110, were higher in fetal tissue relative to maternal plasma (The fetal tissue to maternal plasma ratios at 1, 4, and 24 hours post-dose were 8.1, 14.6, and 61.9, respectively, for unchanged valbenazine, 2.7, 2.7, and 5.3, respectively, for NBI-98782, and 4.6, 7.4, and 16.7, respectively, for NBI-136110). In rats on gestation day 13, the concentrations of unchanged valbenazine at 1 and 4 hours post-dose were higher in fetal tissue relative to maternal plasma (The fetal tissue to maternal plasma ratios were 1.7 and 2.8, respectively), but the fetal tissue concentration at 24 hours post-dose was below the LLOQ (The fetal tissue to maternal plasma ratios of NBI-98782 were 0.6 and 0.7 at 1 and 4 hours post-dose, respectively, and the fetal tissue concentration was

below the LLOQ at 24 hours post-dose. The fetal tissue to maternal plasma ratios of NBI-136110 were 0.7, 0.9, and 1.1 at 1, 4, and 24 hours post-dose, respectively [CTD 4.2.2.3-5]). Based on the above, the applicant explained that unchanged valbenazine and its metabolites cross the placenta into the fetus.

4.3 Metabolism

4.3.1 *In vitro* metabolism

Valbenazine 10 μmol/L was incubated with rat and dog hepatocytes for 120 minutes. NBI-98782 (a metabolite of valbenazine formed via ester hydrolysis), NBI-136110/M14 (mono-oxidized valbenazine), NBI-679006 (mono-oxidized NBI-98782), M3a (mono-oxidized valbenazine), M4 (*O*-desmethyl valbenazine), NBI-124976/M8b [22)] (*O*-desmethyl NBI-98782), M11 (sulfate conjugate of *O*-desmethyl valbenazine), M17 (glucuronide conjugate of mono-oxidized valbenazine), M27 (carbamate glucuronide of valbenazine), M28 (glucuronide conjugate of *O*-desmethyl valbenazine), and M44 (glucuronide conjugate of *O*-desmethyl NBI-98782) were identified (CTD 4.2.2.4-2).

4.3.2 *In vivo* metabolism

Following a single oral dose of ^{14}C-valbenazine 15 mg/kg in rats (16/sex), unchanged valbenazine (8.8% of the total radioactivity in plasma) and NBI-679006 (mono-oxidized NBI-98782), NBI-98782, NBI-136110, NBI-124976 (*O*-desmethyl NBI-98782), and M10a/M57 (mono-oxidized NBI-98782) (32.3%, 18.2%, 7.3%, 6.2%, and 5.9% of the total radioactivity in plasma, respectively) as primary metabolites were detected in the plasma collected up to 48 hours post-dose. In rats (3/sex), NBI-136110/NBI-679006, M10a/M57, and NBI-98782 (12.8%, 5.3%, and 1.3% of the administered radioactivity, respectively) were mainly detected in the urine collected up to 48 hours post-dose, and M49 (didesmethyl NBI-98782), M54b (didesmethyl/mono-oxidized NBI-98782), and M58[23)] (9.0%, 7.6%, and 5.6% of the administered radioactivity, respectively) were mainly detected in feces.

In bile duct cannulated rats (3 males), M44b (glucuronide conjugate of desmethyl NBI-98782), NBI-124976, and M9a (desmethyl mono-oxidized NBI-98782) (7.6%, 3.0%, and 1.0% of the administered radioactivity, respectively) were detected as primary metabolites in the bile collected up to 24 hours post-dose (CTD 4.2.2.4-1).

Following a single oral dose of ^{14}C-valbenazine (10 mg/kg) in dogs (3/sex), unchanged valbenazine was the main component (47.0% of the total radioactivity in plasma) in the plasma collected up to 48 hours post-dose, and NBI-679006, NBI-136110, NBI-98782, M9b (desmethyl mono-oxidized NBI-98782), and NBI-124976 (8.7%, 8.1%, 5.2%, 5.0%, and 4.9% of the total radioactivity in plasma, respectively) were detected as metabolites. In the urine collected up to 72 hours post-dose, unchanged valbenazine (1.8% of the administered radioactivity) and M9b, NBI-136110/NBI-679006, and NBI-98782 (4.9%, 4.7%, and 2.0% of the administered radioactivity, respectively) as metabolites were mainly detected. In the feces collected up to 72 hours post-dose, unchanged valbenazine (13.2% of the administered radioactivity) and M9b, M49, M54b,

22) NBI-124976 and M8b were not completely separated by chromatography.
23) Its structure is unknown.

and NBI-98782 (3.3%, 2.9%, 2.3%, and 2.2% of the administered radioactivity, respectively) as metabolites were mainly detected.

In bile duct cannulated dogs (3 females), trace amounts of unchanged valbenazine, NBI-98782, NBI-679006, and M38 (glucuronide conjugate of NBI-98782) were detected in the bile collected up to 72 hours post-dose (CTD 4.2.2.4-1).

4.4 Excretion

4.4.1 Urinary and fecal excretion

Following a single oral dose of ^{14}C-valbenazine 15 mg/kg in bile duct cannulated rats (3 males) and intact rats (3/sex), 36.2%, 8.68%, and 49.9% of the total radioactivity administered were excreted in urine, feces, and bile, respectively, over 72 hours in bile duct cannulated rats, and 36.2% and 57.8% of the total radioactivity administered were excreted in urine and feces, respectively, over 168 hours in intact rats (CTD 4.2.2.5-1).

Following a single oral dose of ^{14}C-valbenazine 10 mg/kg in dogs (3/sex), 35.0% and 56.4% of the total radioactivity administered were excreted in urine and feces, respectively, over 168 hours (CTD 4.2.2.5-2).

4.4.2 Excretion into milk

Valbenazine 1, 3, or 10 mg/kg was administered orally to lactating rats (3/group) from gestation day 7 through lactation day 14. On lactation day 14, unchanged valbenazine, NBI-98782, and NBI-136110 were detected in milk, and the milk concentrations of unchanged valbenazine, NBI-98782, and NBI-136110 at 3 hours post-dose (53.6-314, 106-797, and 23.5-125 ng/mL, respectively) increased dose-dependently, which were higher than the plasma concentrations (12.5-130 ng/mL for unchanged valbenazine, 23.1-278 ng/mL for NBI-98782, 10.8-89.1 ng/mL for NBI-136110) (CTD 4.2.2.5-3).

4.R Outline of the review conducted by PMDA

PMDA's view on the submitted non-clinical pharmacokinetic studies:

- In pigmented rats, valbenazine was highly distributed to the uveal tract and eye and remained for long hours [see Section 4.2.1], suggesting the possibility of valbenazine accumulation in melanin-containing tissues in clinical use. Thus, the possibility that the distribution of valbenazine to melanin-containing tissues will cause safety issues in the clinical use of valbenazine will be discussed also in Section 5.R.1.
- Since the placental transfer of unchanged valbenazine and its metabolites into the fetus was suggested [see Section 4.2.3], and their excretion into milk was shown [see Section 4.4.2], the effects of valbenazine on fetuses and pups will be discussed also in Section 5.R.2.
- There is no particular problem with other results from the non-clinical pharmacokinetic studies.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from the following toxicity studies of valbenazine: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other

toxicity studies. Doses are expressed in terms of valbenazine. Unless otherwise specified, 0.25% (w/v) methylcellulose solution was used as vehicle in *in vivo* studies.

5.1 Single-dose toxicity

Single oral dose toxicity studies were conducted in rats and dogs (Table 14). The approximate lethal doses following oral dosing were determined to be 150 mg/kg in male rats, 100 mg/kg in female rats, and 80 mg/kg in dogs.

Table 14. Overview of single oral dose toxicity studies

Test system	Route of administration	Doses (mg/kg)	Noteworthy findings	Approximate lethal dose (mg/kg)	CTD
Male and female rats (SD)	Oral gavage	0, 60, 80, 100, 150	Moribund sacrifices[a)]: 100 (1 of 3 females), 150 (3 of 3 females, 1 of 3 males) ≥60: decreased activity, lethargy, eyes partially closed, piloerection, hunched posture, decreased fecal volume, decreased body weight	Males: 150 Females: 100	Reference data 4.2.3.1-2
Male and female dogs (Beagle)	Oral gavage or capsule	50, 80	Moribund sacrifices[b)]: 80 (1 of 2 females, 2 of 2 males) ≥50: ataxia, trembling, decreased activity, lethargy, recumbency, excessive salivation, emesis	80	Reference data 4.2.3.1-3

a) Sacrificed in moribund condition on Day 2.
b) Sacrificed due to convulsions or in moribund condition at approximately 1 hour post-dose (1 male and 1 female) and at 32 hours post-dose (1 male).

5.2 Repeated-dose toxicity

A repeated oral dose toxicity study in mice (91 days), repeated oral dose toxicity studies in rats (2 weeks, 3 months, 6 months), and repeated oral dose toxicity studies in dogs (2 weeks, 3 months, 9 months) were conducted (Table 15 and Table 16). The noteworthy findings were effects on female reproductive organs (mice and rats), CNS effects (mice, rats, dogs), and retinal degeneration (rats). The applicant explained that effects on female reproductive organs are considered related to increased blood prolactin resulting from a pharmacological action of valbenazine and that CNS effects are considered associated with a pharmacological action of valbenazine.

Valbenazine exposure ($AUC_{0\text{-}24h}$ [the mean of males and females], 1300 ng·h/mL) at the no-observed-adverse-effect-level (NOAEL) (3 mg/kg/day) in the 6-month repeated oral dose toxicity study in rats (CTD 4.2.3.2-8) and valbenazine exposure ($AUC_{0\text{-}24h}$ [the mean of males and females], 62600 ng·h/mL) at the NOAEL (15 mg/kg/day) in the 9-month repeated oral dose toxicity study in dogs (CTD 4.2.3.2-12) were 0.2- and 12-fold the human exposure[24)] at the MRHD of 80 mg.

24) The steady-state $AUC_{0\text{-}tau}$ (5350 ng·h/mL) following once daily administration of valbenazine 80 mg obtained from simulations using the PPK model (Reference data CTD 5.3.3.5-1) was used.

Table 15. Outline of repeated oral dose toxicity studies in rodents

Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg)	CTD
Male and female mice (CD-1)	Oral gavage	91 days (once daily) + 28-day recovery period	0, 10, 30, 60, 100, 300	Died or sacrificed moribund: 100 (1 of 10 males, 1 of 10 females), 300 [a] (9 of 10 males, 4 of 10 females) ≥10: lobular hyperplasia of the mammary gland (female) ≥30: decreased activity, decreased body weight (male), decreased thymus weight (male) 100: increased activity These findings were reversible.	60	4.2.3.2-2
Male and female rats (SD)	Oral gavage	14 days (once daily) + 10-day recovery period	0, 15, 25, 50	Mortality: 25 (1 of 10 females), 50 (2 of 10 females) ≥15: eyes partially closed, decreased activity, piloerection, hunched posture, increased activity (predose), labored breathing, decreased body weight, acinar hyperplasia/increased secretion of the mammary gland (female) ≥25: trembling, decreases in uterine/cervix/thymus weights, increased incidence of feminization of the mammary gland (male), decreased bone marrow cellularity in the sternum/femur 50: cold to touch, thin, decreased fecal volume, staining of snout/extremities/anogenital staining, decreased pituitary gland weight These findings were reversible.	15	4.2.3.2-6
Male and female rats (SD)	Oral gavage	91 days (once daily) + 6-week recovery period	0, 1, 3, 10, 15	Mortality [b]: 3 (1 of 10 females), 10 (1 of 10 males) ≥1: increased adrenal weight (female) ≥3: eyelids partially closed, decreased activity, increased activity (predose), decreases in food consumption/body weight gain/body weight (female), increased bone marrow cellularity in the sternum/femur (female) ≥10: decreased body weight (male), increased adrenal weight (male), increased ovary weight, lobuloalveolar hyperplasia of the mammary gland (female) 15: decreases in food consumption/body weight gain (male), feminization of the mammary gland (male), increased bone marrow cellularity in the sternum/femur (male) These findings were reversible.	15	4.2.3.2-7
Male and female rats (SD)	Oral gavage	6 months (once daily) + 6-week recovery period	0, 3, 10, 15	Died or sacrificed moribund: 10 (2 of 10 males),[c] 15 (2 of 10 males) ≥3: decreased activity, increased activity (predose), eyelids partially closed, decreases in food consumption/body weight gain/body weight, lobular hyperplasia of the mammary gland, mucification/atrophy in the vagina (female), angiectasis of the adrenal cortex (female), decreased adipocytes in sternal/femoral bone marrow, retinal degeneration ≥10: clonic convulsions (male), myoclonic jerking (male), twitching (male), increased eosinophilic nondegenerate corpora lutea in the ovary (female), decreased cell size in the uterine myometrium (female), lobular hyperplasia of the mammary gland (male), alveolar macrophage infiltrates in the lung (male)[d] 15: clonic convulsions (female), myoclonic jerking (female), twitching (female), decidual reaction of the uterus (female), alveolar macrophage infiltrates in the lung (female)[d] These findings were reversible (except for retinal degeneration; and decreased adipocytes in sternal/femoral bone marrow in males).	3	4.2.3.2-8

a) Two males were found dead, and 7 males and 4 females were sacrificed in moribund condition following a single administration of valbenazine.
b) The deaths were attributed to esophageal perforation and considered unrelated to valbenazine.
c) One male was sacrificed on Day 100 due to repeated clonic convulsions, and another male was sacrificed on Day 26 due to proptosis and right eye rupture related to trauma suffered in the cage resulting from increased activity.
d) Considered associated with incidental aspiration.

Table 16. Overview of repeated oral dose toxicity studies in non-rodents

Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg)	CTD
Male and female dogs (Beagle)	Oral (capsule)	14 days (once daily) + 11- to 12-day recovery period	Valbenazine: 0,[a] 5, 15, 35/30[b] NBI-98782: 7.5, 15	Valbenazine Moribund sacrifice: 35 (1 of 4 males) ≥5: decreased activity, lethargy, recumbency, decreased thymus weight/decreased thymus cellularity [c] ≥15: ataxia, trembling, unsteady head, excessive salivation, rigidity, ptosis, aggressive, vocalizing, circling 35/30: seizure-like activity, jerky/uncoordinated movement, weak pulse, pale/grey gums, difficulty standing, head bobbing, vomiting, decreased body weight (female) NBI-98782 ≥7.5: ataxia, trembling, decreased activity, lethargy, recumbency, decreased thymus weight/decreased thymus cellularity[c] 15: decreased body weight (female) These findings were reversible.	Valbenazine: 15[d] NBI-98782: 15[d]	4.2.3.2-10
Male and female dogs (Beagle)	Oral (capsule)	91 days (once daily) + 28-day recovery period	0,[a] 2, 5, 12.5, 20	≥2: a trend towards decreased thymus weight (male),[c] lymphoid depletion in the thymus,[c] perivascular inflammation in the cervix (female)[e] ≥5: decreased activity, tremors, wobbly gait ≥12.5: decreases in food consumption/body weight gain/body weight, a trend towards decreased thymus weight (female),[c] small thymus (male),[c] perivascular inflammation in the heart (female)[e] 20: QT interval/QTc prolongation[f] (female), granulocytic infiltration/Kupffer cell hyperplasia/pericholangial inflammation in the liver,[g] perivascular inflammation in the oviducts (female)[e] These findings were reversible (except for decreased body weight).	20	4.2.3.2-11

Male and female dogs[h)] (Beagle)	Oral (capsule)	9 months (once daily) + 1-month recovery period	0,[a)] 3, 10, 15	≥3: decreased activity, intermittent tremors, decreases in body weight gain/body weight (female) ≥10: eyelids partially closed, irregular surface of the renal capsule/loss of tubules/interstitial fibrosis/foci of mononuclear cell infiltrates in the unilateral kidney[i)] (male) 15: QTc prolongation (male),[j)] decreased prostate weight[k)] (male), pale areas/irregular surface coincident with pale areas/loss of tubules/interstitial fibrosis/foci of mononuclear cell infiltrates in the bilateral kidneys (female)[l)] These findings were reversible (except for decreased body weight).	15	4.2.3.2-12

a) Empty capsule
b) Based on the observation of convulsions at 35 mg/kg/day, the dose was lowered to 30 mg/kg/day on Day 10/11.
c) The applicant explained that the findings were likely secondary to stress associated with clinical signs resulting from a pharmacological action.
d) Although decreased activity, lethargy, and recumbency associated with a pharmacological action were observed at all dose levels of valbenazine and NBI-98782, as the findings were transient and were not associated with organic changes in the brain, the site of pharmacological action, the applicant considered that these findings were of no toxicological significance.
e) The applicant considered that the findings were unrelated to valbenazine because the incidences of the findings were low and were not dose-dependent, and these findings were absent in a 9-month repeated oral dose toxicity study in dogs.
f) The applicant considered that the findings were of no toxicological significance because 20 mg females at baseline had longer QT interval and QTc compared with the controls, and prolongation of QT interval or QTc was not noted in 20 mg males.
g) The applicant considered that the toxicological significance of these findings was unknown because these changes occurred in only 1 male, no similar findings were noted in other animals, and there were no abnormalities in clinical chemistry or hematology parameters.
h) To rule out a link between tremors and abnormal EEG patterns of seizure or increased risk of convulsions, EEG and EMG were performed, and no abnormal EEG patterns were observed. Although convulsions were observed at ≥35 mg/kg/day in single-dose and 2-week repeated oral dose toxicity studies in dogs, convulsions or signs of seizure were not noted at up to the highest dose of 15 mg/kg/day in a 9-month repeated oral dose toxicity study in dogs. Thus, the applicant considered that valbenazine induces convulsions in dogs only at very high exposure levels.
i) The applicant considered that the changes were not related to valbenazine and were possibly idiosyncratic, incidental findings because the unilateral changes were noted in only 1 animal at the end of a recovery period.
j) The applicant considered that the finding was of no toxicological significance because the finding was attributed to shorter QTc on Day 137 compared with other days in male controls, the QTc change was small, and there were no changes in QTc in males on Day 270 and females on Days 137 and 270.
k) The applicant considered that the finding was of no toxicological significance because dilation of acini in the prostate was observed in all groups including the control group, the acinar change was not dose-dependent, and mononuclear cell infiltrates did not correlate with changes in prostate weights.
l) The applicant considered that the changes were not related to valbenazine and were possibly idiosyncratic, incidental findings because these findings were noted in only 1 animal, and BUN and Cre levels were high at baseline, suggesting that the animal may have had compromised renal function prior to valbenazine exposure.

5.3 Genotoxicity

The following studies were conducted, and valbenazine was considered negative for genotoxicity (Table 17).

Table 17. Overview of genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment)	Concentrations or doses	Test result	CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A	S9−/+	0,[a)] 11.6, 41.6, 100, 403, 1000, 2000, 5000 (μg/plate)	Negative	4.2.3.3.1-2
	Chromosomal aberration assay in cultured mammalian cells	Human peripheral blood lymphocytes	S9−/+ (3 hours)	0,[a)] 42.6, 57.8, 78.4, 108, 154, 207, 280, 402, 558, 672, 960, 1370, 1960, 2800, 3580 (μg/mL)	Negative	4.2.3.3.1-4
			S9− (22 hours)	0,[a)] 7.0, 13.0, 24.2, 46.8, 59.8, 75.0, 134, 150, 200, 300, 400 (μg/mL)		
			S9+ (3 hours)	0,[a)] 75.0, 150, 200, 250, 300, 350, 400, 475, 550, 650 (μg/mL)		
In vivo	Rodent micronucleus assay	Male rat (SD) bone marrow		0, 15, 30, 60 (mg/kg) (oral gavage, single dose)	Negative	4.2.3.3.2-1

a) dimethyl sulfoxide

5.4 Carcinogenicity

Carcinogenicity studies were conducted in rats and rasH2 Tg mice (Table 18). In the rat carcinogenicity study, an increase in the incidence of total mammary gland neoplasms (fibroadenoma, adenoma, carcinoma), which was considered related to increased blood prolactin, was observed in females at 2 mg/kg, but there was no statistically significant difference. The applicant explained that as no valbenazine-related neoplastic changes were observed, the carcinogenic risk to humans is not suggested.

Table 18. Overview of carcinogenicity studies

Test system	Route of administration	Duration of dosing	Major lesions	Sex	Doses (mg/kg/day)				NOEL for carcinogenicity (mg/kg/day)	CTD
					0	0.5	1	2		
Male and female rats (SD)	Oral gavage	104 weeks (once daily)		N	60	60	60	60	2	4.2.3.4.1-1
			Mammary gland: Fibroadenoma	M	1	0	1	0		
				F	21	23	23	29		
			Mammary gland: Adenoma	M	0	0	0	0		
				F	1	0	0	4		
			Mammary gland: Carcinoma	M	3	0	2	0		
				F	17	23	19	24		
			Total mammary gland neoplasms	M	4	0	3	0		
				F	32	37	31	42		
Male and female mice (Tg)	Oral gavage	26 weeks (once daily)	Major lesions	Sex	Doses (mg/kg/day)				75	4.2.3.4.2-2
					0	10	30	75		
				N	25	25	25	25		
			Lung: Single adenoma	M	1	1	3	1		
				F	3	0	1	1		
			Lung: Multiple adenomas	M	0	0	0	1		
				F	0	0	0	0		
			Spleen: Hemangiosarcoma	M	1	2	0	1		
				F	1	0	2	0		

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, a rat study for effects on pre- and postnatal development, including maternal function, and a repeated oral dose toxicity study in juvenile mice were conducted (Table 19 and Table 20).

As effects on fertility and early embryonic development to implantation, prolonged estrous cycles, delayed mating, and decreased conception and fertility indices were observed in female rats at 10 mg/kg of valbenazine. The applicant explained that these changes were associated with valbenazine-related hyperprolactinemia or were the effects of decreased activity on mating behavior. As to hyperprolactinemia, the applicant explained that increased blood prolactin levels may cause reproductive dysfunction also in humans.

As embryo-fetal effects, decreased fetal body weights and delayed ossification were observed in rabbits at 100 mg/kg of valbenazine, but there were no teratogenic effects. Valbenazine exposures (the $AUC_{0\text{-}24h}$ of 4230 ng·h/mL in rats, the $AUC_{0\text{-}24h}$ of 6030 ng·h/mL in rabbits) at the NOAELs for embryo-fetal development in rats and rabbits (15 mg/kg/day in rats, 50 mg/kg/day in rabbits) were 0.8- and 1.1-fold the human exposure[24)] at the MRHD of 80 mg, respectively.

As effects on pre- and postnatal development, including maternal function, an increase in the number of stillborn pups and decreases in pup survival and pup body weight were observed in rats.

In a juvenile mouse study compared with toxicity studies in adult mice, no specific or increased toxicity in juvenile mice was noted.

Table 19. Overview of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	CTD
Fertility and early embryonic development to implantation	Male rat (SD)	Oral gavage	28 days prior to mating through scheduled sacrifice (once daily)	0, 1, 3, 10	Parental animals Mortality: 3 mg/kg/day[a)] (1 of 22 animals) 10: squinted eyes, increased activity, decreases in food consumption/body weight gain, decreased absolute prostate weights,[b)] decreased fertility index	Parental animals (Reproductive toxicity): 3	4.2.3.5.1-1
	Female rat (SD)		14 days prior to mating through gestation day 7 (once daily)		Parental animals ≥3: squinted eyes 10: decreased activity, decreases in food consumption/body weight gain, prolonged estrous cycles, persistent diestrus, delayed mating, decreased conception index, decreased fertility index		
Embryo-fetal development	Female rat (SD)	Oral gavage	Gestation days 6-17 (once daily)	0, 1, 5, 15	Parental animals ≥5: decreases in food consumption/body weight gain 15: decreased activity, squinted eyes Fetuses 1: absence of lobus intermedius in the lung/interrupted aortic arch/a right aortic arch[c)] 5: diaphragmatic hernia in the liver[c)] 15: polydactyly/fusion of sternebrae 1-3,[c)] increased incidence of rudimentary 13 rib[d)]	Maternal general toxicity: 1 Embryo-fetal development: 15	4.2.3.5.2-3

	Female rabbit (NZW)	Oral gavage	Gestation days 7-20 (once daily)	0, 20, 50, 100	Parental animals Mortality: 100 mg/kg/day (1 of 20 animals) ≥50: decreased activity, squinted eyes, closed eyes, rapid respiration, ataxia, recumbency, constricted pupils, audible respiration, soft feces, few feces, no feces, decreases in food consumption/body weight gain Fetuses ≥20: ventricular septal defect[e)] ≥50: increased incidence of extra presacral vertebras [e)] 100: decreased body weight,[f)] absent gallbladder,[e)] incomplete ossification/unossification of sternebrae,[f)] skeletal abnormalities (anomalies in nasal bone/premaxilla associated with fused skull bones, vertebral anomaly, fused sternebrae),[e)] increased incidence of 13th rib [e)]	Maternal general toxicity: 20 Embryo-fetal development: 50	4.2.3.5.2-4
Pre- and postnatal development, including maternal function	Female rat (SD)	Oral gavage	Gestation day 7 to lactation day 20 (once daily)	0, 1, 3, 10	Parental animals ≥3: ptosis, whole body tremors, piloerection, mild dehydration, hunched posture, decreases in food consumption/body weight/body weight gain, an increase in the number of dams with stillborn pups, increases in the mean number/percentage of stillborn pups, decreases in the mean number/percentage of liveborn pups, a decrease in mean live litter size 10: hyperpnea, red perivaginal substance, decreased motor activity, an increase in the duration of gestation F1 pups Mortality: 1 (7 of 265 pups), 3 (17 of 206 pups), 10 (96 of 169 pups) ≥3: decreased survival rate, cold to touch, no milk band present, dehydration, purple/gray/pale head or whole body 10[g)]: decreased lactation index, decreased body weight, absence of nursing, lack of nesting, decreased motor activity, labored breathing	Maternal general toxicity: 1 F1 pup development: 1	4.2.3.5.3-1

a) The applicant considered that the death was incidental because no clinical signs or macroscopic findings at necropsy were observed, and mortality was not dose-dependent.
b) The applicant explained that the changes were associated with decreased body weights because there were no differences in the relative weight compared to the control group.
c) The applicant considered that the findings were of no toxicological significance because these findings were observed in only 1 fetus at the low or mid dose level, the incidence fell within the historical control range, or no signs of similar developmental toxicity were observed in other fetuses or the litter.
d) The applicant explained that the change was not related to valbenazine because the incidence fell within the historical control range, and the change was a variation commonly observed in rats.
e) The applicant explained that the changes were not related to valbenazine because the incidences fell within the historical control range.
f) The applicant considered that the findings were associated with delayed fetal development secondary to decreases in body weight and food consumption in parental animals.
g) Due to the high pup mortality, post-weaning evaluations were not performed.

Table 20. Overview of repeated-dose toxicity study in juvenile mice

Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg)	CTD
Male and female mice (CD-1)	Oral gavage	10 weeks, postnatal days 21-91 (once daily) + 8-day recovery period	0, 30, 60, 90	Mortality[a)]: 30 (3 of 40 females), 60 (4 of 40 females), 90 (1 of 40 males, 6 of 40 females) ≥30: decreased activity, tremors, eyelids half-closed, decreased body weight gain, increased liver weight/centrilobular hepatocellular hypertrophy and vacuolation, increased motor activity (mean total count and ambulatory count) ≥60: decreased body weight (male), decreased food consumption 90: decreased body weight (female)	60	4.2.3.5.4-5

a) Although the cause was not identified for some deaths, the applicant discussed that many of the deaths were caused by gavage error.

5.6 Other toxicity studies

5.6.1 Phototoxicity

A phototoxicity study in mouse fibroblasts was conducted, and valbenazine was considered to have no phototoxic potential (Table 21).

Table 21. Overview of phototoxicity study

Type of study	Test system	Test method	Noteworthy findings	CTD
In vitro	Mouse fibroblasts BalB/c 3T3	1.78, 3.16, 5.62, 10.0, 17.8, 31.6, 56.2, 100 µg/mL Irradiation with UV-A and UV-B	No phototoxicity	4.2.3.7.7-1

5.6.2 Metabolite safety evaluation

Among the primary metabolites in humans, NBI-136110 was observed at exposures >10% of total drug-related exposure in human plasma. Thus, in accordance with the ICH M3 guideline, the general toxicity, carcinogenicity, and reproductive and developmental toxicity of NBI-136110 were assessed.

The general toxicity of NBI-136110 was assessed based on mouse 3-month repeated-dose toxicity (CTD 4.2.3.2-2) and dog 9-month repeated-dose toxicity (CTD 4.2.3.2-12) studies of valbenazine. NBI-136110 exposure ($AUC_{0\text{-}24h}$ [the mean of males and females], 13700 ng·h/mL) at the NOAEL (60 mg/kg/day) in the 3-month repeated-dose toxicity study in mice and NBI-136110 exposure ($AUC_{0\text{-}24h}$ [the mean of males and females], 9580 ng·h/mL) at the NOAEL (15 mg/kg/day) in the 9-month repeated-dose toxicity study in dogs were 5.2- and 3.6-fold the human exposure[25)] at the MRHD of 80 mg, respectively.

The carcinogenicity of NBI-136110 was assessed based on a 26-week repeated oral dose carcinogenicity study of valbenazine in rasH2 Tg mice (CTD 4.2.3.4.2-2). NBI-136110 exposure ($AUC_{0\text{-}24h}$ [the mean of males and females], 12700 ng·h/mL) at the highest dose (75 mg/kg/day) used in the 26-week repeated oral dose carcinogenicity study in rasH2 Tg mice was 4.8-fold the human exposure at the MRHD of 80 mg.

The reproductive and developmental toxicity of NBI-136110 was assessed based on an embryo-fetal development study of valbenazine in rats (CTD 4.2.3.5.2-3). NBI-136110 exposure ($AUC_{0\text{-}24h}$ [the mean of males and females], 2140 ng·h/mL) at the NOAEL (15 mg/kg/day) in the embryo-fetal development study in rats was 0.81-fold the human exposure ($AUC_{0\text{-}24h}$, 2640 ng·h/mL) at the MRHD of 80 mg.

Based on the above, the applicant explained that the general toxicity, carcinogenicity, and reproductive and developmental toxicity of NBI-136110 were assessed appropriately and that NBI-136110 was qualified.

5.6.3 Toxicity studies on impurities and degradants

Among the impurities and degradants present at levels above the qualification threshold based on the ICH Q3A and ICH Q3B guidelines, NBI-123670 and NBI-123673 were evaluated based on a 14-day repeated oral dose toxicity study in dogs (CTD 4.2.3.2-10), and NBI-724208 was evaluated based on a 9-month repeated-dose

25) A value of 2 times the $AUC_{0\text{-}24h}$ (2640 ng·h/mL) following once daily administration of valbenazine 40 mg in a Japanese phase I study (CTD 5.3.3.1-1, Study J01) was used.

toxicity study in dogs (CTD 4.2.3.2-12) (Table 16). Furthermore, NBI-123670, NBI-123673, and NBI-724208 were assessed by *in silico* (Q)SAR analysis based on the ICH M7 guideline. The doses of NBI-123670, NBI-123673, and NBI-724208[26)] at the NOAEL of valbenazine in dogs were 23-, 11-, and 4.9-fold the human doses[27)] at the MRHD of valbenazine of 80 mg, respectively, and the *in silico* (Q)SAR analysis showed no structural alerts. Thus, the applicant explained that no safety concerns were suggested for NBI-123670, NBI-123673, and NBI-724208 at the upper specification limits for the drug substance and the drug product.

Among the impurities and degradants present at levels above the qualification threshold, NBI-139326 was tested in a 14-day repeated oral dose toxicity study in rats (CTD 4.2.3.7.6-1) and *in vitro* genotoxicity studies (Table 22). Since there were no NBI-139326-related findings, and NBI-139326 tested negative for genotoxicity, the applicant explained that no safety concerns were suggested. Potential degradants, NBI-638091 and NBI-743407, tested negative for mutagenicity in bacterial reverse mutation assays.

Table 22. Overview of repeated-dose toxicity and genotoxicity studies with impurity (NBI-139326)

Type of study		Test system	Concentrations or doses	Test result	CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A	1.5-5000 μg/plate	Negative	4.2.3.7.6-8
	Chromosomal aberration assay in cultured mammalian cells	Human peripheral blood lymphocytes	80-1100 μg/mL	Negative	4.2.3.7.6-9
In vivo	14-day repeated oral dose toxicity study in rats	Male and female rats (SD)	0, 0.5 mg/kg/day	No findings	4.2.3.7.6-1

5.6.4 Dependence assessment

No independent dependence studies with valbenazine or its metabolites were conducted. Valbenazine and its metabolites have a low abuse potential based on the pharmacological action of reducing dopamine release with no appreciable binding affinity for the receptors known to be associated with drug abuse (dopamine, serotonin, γ-aminobutyric acid, opioid, cannabinoid, ion channels, transporters). No evident withdrawal syndrome was observed during the recovery period in a 9-month repeated oral dose toxicity study in dogs (CTD 4.2.3.2-12) or a 6-month repeated oral dose toxicity study in rats (CTD 4.2.3.2.-8). Furthermore, no adverse events indicative of abuse/dependence were reported in foreign phase II clinical studies of valbenazine (Reference data CTD 5.3.5.2-1, Study 1001; Reference data CTD 5.3.5.1-2, Study 1101; Reference data CTD 5.3.5.1-3, Study 1201; Reference data CTD 5.3.5.1-4, Study 1202). Based on the above, the applicant explained that the risk of physical or psychological dependence in humans treated with valbenazine has not been suggested.

5.R Outline of the review conducted by PMDA

5.R.1 Retinal degeneration

Valbenazine was shown to be highly distributed to and remain for long hours in the uveal tract and eye in pigmented rats [see Section 4.2.1]. In a 6-month repeated oral dose toxicity study in rats (CTD 4.2.3.2-8), retinal degeneration was observed, and valbenazine exposure at a dose associated with retinal degeneration

26) Based on the percentages of impurities or degradants present in the drug substance batch used in toxicity studies, the doses (NBI-123670, 0.09 mg/kg; NBI-123673, 0.08 mg/kg; NBI-724208, 0.02 mg/kg) were calculated.
27) Based on the percentages based on the upper specification limits for the drug substance and the drug product, the doses (NBI-123670, 0.004 mg/kg; NBI-123673, 0.007 mg/kg; NBI-724208, 0.004 mg/kg) at the MRHD of valbenazine of 80 mg in humans weighing 60 kg were calculated.

(3 mg/kg/day) was 0.2-fold the human exposure [24)] after multiple dosing at the MRHD of 80 mg [see Section 5.2]. PMDA asked the applicant to explain the human relevance of these findings and safety.

The applicant's explanation:

- For the following reasons, retinal degeneration observed in rats is considered light-induced retinopathy caused by increased exposure to light source in the animal house due to the location of the cage during the study.
  - ➢ It is inferred that all animals with retinal degeneration were placed in the top row of the cage rack with a perforated top throughout the dosing period. The observed retinal degeneration was characterized by bilaterally symmetric degeneration of the photoreceptors and outer nuclear layer, and these morphological characteristics were consistent with light-induced retinopathy.
  - ➢ SD rats used in the 6-month repeated oral dose toxicity study are albino animals, and albino animals are known to be more susceptible to light-induced retinopathy (*Invest Ophthalmol*. 1966; 5: 450-73).
- Then, based on the following results of non-clinical studies, retinal degeneration is not a direct effect of valbenazine, but is considered secondary to longer exposure to light source in the animal house throughout the dosing period in the valbenazine treatment groups compared to the control group because hyperactivity associated with a pharmacological action of valbenazine was noted in rats prior to dosing each day (22-23 hours after dosing of valbenazine on the previous day), and this hyperactivity occurred during the period when room lights were on (the eyes were exposed to light for longer hours).
  - ➢ Although the distribution of valbenazine into the eyes and uveal tract of pigmented animals, dogs, has not been evaluated, retinal degeneration was not observed in a 9-month repeated oral dose toxicity study (CTD 4.2.3.2-12).
  - ➢ Although the pharmacological effect of valbenazine on the retina is unknown, there were no retinal changes with tetrabenazine, another VMAT2 inhibitor, in a 26-week repeated-dose toxicity study in rats or a 9-month repeated-dose toxicity study in dogs (Review Report on Choreazine Tablets 12.5 mg as of November 12, 2012).
  - ➢ The ratio of tissue to plasma radioactivity derived from valbenazine was high for the eye and uveal tract in pigmented animals, Long-Evans rats, and high melanin affinity of valbenazine was inferred. Meanwhile, the ratios of tissue to plasma radioactivity derived from valbenazine for the eye and uveal tract were both <10 in albino animals, SD rats, which were 1/1114 and 1/1190 of those in pigmented rats, respectively. Thus, valbenazine is not highly accumulated in the eye or uveal tract in SD rats [see Section 4.2.1].
- Since retinal degeneration was observed in a non-clinical study, ophthalmologic examinations (eyesight test/color-vision test) were conducted at screening, Day 5, and follow-up or study withdrawal in the single-dose cohort and at screening, Day 13, the end of treatment, and follow-up or study withdrawal in the multiple-dose cohort (study drug administered for 8 days) in a Japanese phase I study (CTD 5.3.3.1-1, Study J01). There were no abnormal changes or findings assessed as clinically significant changes from baseline by the investigator (sub-investigator), and no adverse events possibly related to retinal degeneration were reported.

- In a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02), the incidences of eye disorder-related adverse events[28)] were 2.4% (2 of 84 subjects) (blepharitis; and allergic conjunctivitis [1 subject each]) in the placebo group, 1.2% (1 of 85 subjects) (keratitis [1 subject]) in the valbenazine 40 mg group, and 2.4% (2 of 84 subjects) (blepharitis; and eyelid ptosis [1 subject each]) in the valbenazine 80 mg group during the double-blind phase and 2.4% (3 of 126 subjects) (blepharitis; cataract; and keratitis [1 subject each]) in the valbenazine 40 mg group and 4.1% (5 of 123 subjects) (blepharitis; conjunctival oedema; eye discharge; eye pain; and eyelid ptosis [1 subject each]) in the valbenazine 80 mg group during the long-term treatment phase. No adverse events possibly related to retinal degeneration were reported.
- Based on the above, retinal degeneration is unlikely to occur following administration of valbenazine in humans.

PMDA accepted the applicant's explanation that retinal degeneration observed in rats is unlikely to occur in humans, given the following findings: While valbenazine was highly distributed to the uveal tract and eye in pigmented rats [see Section 4.2.1], and retinal degeneration was observed in a 6-month repeated oral dose toxicity study in rats [see Section 5.2], retinal degeneration was not observed in dogs, pigmented animals, and a direct effect of valbenazine on the eyes due to its high melanin affinity and pharmacological action was not suggested. No events possibly related to retinal degeneration were reported based on the occurrence of eye disorder-related adverse events in Japanese clinical studies.

5.R.2 Effects on fetuses and pups

Valbenazine crosses the placenta and is excreted into milk [see Sections 4.2.3 and 4.4.2], and an increase in the number of stillborn pups and a decrease in pup survival were observed in a rat study for effects on pre- and postnatal development, including maternal function (CTD 4.2.3.5.3-1) [see Section 5.5]. PMDA asked the applicant to explain the effects of valbenazine on human fetuses and infants.

The applicant's explanation about fetal effects:

- As to fetal effects, an increase in the number of stillborn pups observed in rats is unlikely to be a direct effect of valbenazine on the fetuses, but is considered secondary to maternal toxicity, for the following reasons.
  - ➢ In the rat study for effects on pre- and postnatal development, including maternal function, an increase in the number of stillborn pups was observed at doses associated with maternal toxicity (decreases in body weight gain and food consumption).
  - ➢ Although valbenazine was administered at higher doses in an embryo-fetal development study in rats (CTD 4.2.3.5.2-3) than in the rat study for effects on pre- and postnatal development, including maternal function, no embryo-fetal toxicity was observed. Thus, toxicity leading to fetal death is unlikely to have occurred in the rat study for effects on pre- and postnatal development, including maternal function.

28) Events in the MedDRA SOC "eye disorders"

- ➢ In an embryo-fetal development study in rabbits (CTD 4.2.3.5.2-4), delayed fetal ossification and decreased fetal body weights were observed, which are considered secondary to maternal toxicity (decreases in body weight gain and food consumption).
- ➢ Also in a study for effects on pre- and postnatal development, including maternal function, with tetrabenazine, another VMAT2 inhibitor, tetrabenazine increased stillborn pups at doses associated with maternal toxicity (Review Report on Choreazine Tablets 12.5 mg as of November 12, 2012).

- In a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02), there were no particular differences between the incidences of weight decreased (4.8% [6 of 126 subjects] in the valbenazine 40 mg group, 4.1% [5 of 123 subjects] in the valbenazine 80 mg group) and weight increased (4.8% [6 of 126 subjects], 2.4% [3 of 123 subjects]) in the valbenazine groups during the long-term treatment phase, and valbenazine did not increase the risk of decreased body weight in humans. Thus, valbenazine is unlikely to increase the risk of stillbirth in humans.

The applicant's explanation about pup effects:

- As to pup effects, decreased pup survival observed in rats is unlikely to be a direct effect of valbenazine on the pups, but is considered a pharmacological effect of valbenazine on maternal care, for the following reasons.
  - ➢ Although valbenazine crosses the placenta into the fetus, as no embryo-fetal toxicity was observed in an embryo-fetal development study in rats, pup death is unlikely associated with exposure to valbenazine during the fetal period.
  - ➢ Dopamine receptor antagonists have been reported to affect maternal care, e.g., reduce nest building, retrieval (a maternal behavior: pups scattered throughout the cage are brought into the nest), and licking of pups in lactating rats (*Behav Neurosci*. 2005; 119: 1072-83, *Pharmacol Biochem Behav*. 2001; 68: 461-8).
  - ➢ Tetrabenazine, another VMAT2 inhibitor, reduced pup retrieval, and a decreased number of surviving pups, decreased pup body temperature, and an increased proportion of pups with no milk band, which are considered associated with poor maternal care, were observed in a study for effects on pre- and postnatal development, including maternal function (Review Report on Choreazine Tablets 12.5 mg as of November 12, 2012).
  - ➢ As the maintenance of pup's body temperature by contact with the dam is important for post-natal pup development (*Developmental Toxicology*. CRC; 1994: p203), cold to touch, no milk band present, and dehydration observed in pups in the valbenazine groups are considered to have resulted from inadequate maintenance of pup's body temperature, suckling, and maternal care due to reduced maternal contact with pups.
  - ➢ Although valbenazine and its metabolites were shown to be excreted into milk [see Section 4.4.2], pup plasma concentrations of valbenazine and its metabolites via milk were low, and few pups in the valbenazine groups died on post-natal day 5 or later. Thus, pup death is unlikely to be a direct effect of valbenazine on the pups via milk.
- As to a pharmacological effect of valbenazine on maternal caregiving behavior in humans, dopamine is involved in human maternal instinct, but oxytocin, infant cues, and the environment surrounding the mother

and the infant are also considered to impact a mother-child relationship (*J Neuroendocrinol*. 2011; 23: 1054-65). Thus, decreased dopamine only is unlikely to lead to a reduced human maternal instinct, resulting in an infant death.

Based on the above, the applicant explained that the following precaution information should be included in the package insert.

- Valbenazine and its metabolites have been suggested to cross the placenta into the fetus [see Section 4.2.3], but are unlikely to affect the fetuses and infants. Thus, valbenazine may be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks.
- Although valbenazine and its metabolites have been shown to be excreted into milk [see Section 4.4.2], given the pharmacological effects of valbenazine and the levels of pup exposure via milk, an infant death is unlikely to occur in humans, and the effects on suckling human infants are unknown. Thus, a decision to continue or discontinue breastfeeding should be made, taking account of the therapeutic benefits of valbenazine and the benefits of breastfeeding nutrition.
- In rats, decreases in maternal body weight gain and food consumption and a decrease in the number of liveborn pups were observed at doses resulting in exposures that were less than the human exposure based on the AUC. In rabbits, delayed fetal ossification and decreased fetal body weights associated with decreases in maternal body weight gain and food consumption were observed at doses resulting in exposures that were less than the human exposure based on the AUC.

PMDA's view:

- Valbenazine and its metabolites cross the placenta [see Section 4.2.3] and are excreted into milk [see Section 4.4.2], indicating a certain level of fetal and pup exposure to valbenazine and its metabolites in animals.
- However, given that fetal death due to a direct effect of valbenazine on the fetuses is not anticipated, and that there were findings indicating poor maternal care in dead pups, valbenazine or its metabolites are unlikely to have had a direct effect on the fetuses or pups. Thus, an increase in the number of stillborn pups is considered secondary to maternal toxicity, and decreased pup survival is considered a pharmacological effect of valbenazine on maternal care. There is no problem with the above explanation by the applicant.
- As to human relevance, there is no concern about maternal toxicity affecting the fetuses in humans. Although decreased dopamine results in poor maternal care in rats, this is not anticipated in humans. Given these explanations, there is no problem with the applicant's explanation that the changes observed in animals are unlikely to occur in humans.
- Based on the above, there is no problem with the applicant's explanation regarding the precaution information in the package insert.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted the results from a bioequivalence and food effect study (Reference data CTD 5.3.1.1-2, Study 1504), a relative bioavailability and food effect study (Reference data CTD 5.3.3.3-1, Study 1102), and

a bioequivalence study (Reference data CTD 5.3.1.2-1, Study 1602) in non-Japanese healthy adult subjects as reference data.

Concentrations of unchanged valbenazine and its metabolites in biological samples were determined by LC-MS/MS (LLOQ, 1 ng/mL in plasma and 1 or 100 ng/mL in urine for unchanged valbenazine; 0.1 ng/mL in plasma and 0.1 or 100 ng/mL in urine for NBI-98782, 0.2 ng/mL in plasma and 0.2 or 100 ng/mL in urine for NBI-136110). Unless otherwise specified, doses are expressed in terms of valbenazine.

The formulations used in clinical studies of valbenazine were [redacted] capsules ([redacted] 40 [redacted] mg) and the gelatin capsules (40 and 80 mg). In the main clinical studies of valbenazine, [redacted] capsules ([redacted] mg) were used in a Japanese phase I study (CTD 5.3.3.1-1, Study J01), and the gelatin capsules (40 mg) were used in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) and a food effect study. The proposed commercial formulation in Japan is a gelatin capsule (40 mg), which differs in [redacted] from the formulation used in Japanese Study J02, and dissolution testing demonstrated comparable dissolution profiles between the proposed commercial formulation and the formulation used in Japanese Study J02.

6.1.1 Bioequivalence (Reference data CTD 5.3.1.1-2, Study 1504; Reference data CTD 5.3.1.2-1, Study 1602)

Non-Japanese healthy adult subjects (24 subjects included in pharmacokinetic assessment) received a single oral dose of the valbenazine 40-mg gelatin capsule (the clinical trial formulation) or 40-mg [redacted] capsule under fasting conditions, and the bioequivalence between the two formulations was assessed in a crossover study. The valbenazine C_{max} and $AUC_{0\text{-last}}$ geometric mean ratios for the gelatin capsule vs. [redacted] capsule [90% confidence interval (CI)] were 1.09 [1.02, 1.17] and 1.04 [1.00, 1.07], respectively, demonstrating the bioequivalence between the two formulations (Reference data CTD 5.3.1.1-2, Study 1504).

Non-Japanese healthy adult subjects (31 subjects included in pharmacokinetic assessment) received a single oral dose of 2 × the 40-mg gelatin capsule (the clinical trial formulation) or 1 × the 80-mg gelatin capsule ([redacted] formulation) under fasting conditions, and the bioequivalence between the two formulations was assessed in a crossover study. The valbenazine C_{max} and $AUC_{0\text{-last}}$ geometric mean ratios for the 80-mg gelatin capsule vs. 2 × the 40-mg gelatin capsule [90% CI] were 0.97 [0.89, 1.05] and 1.04 [1.01, 1.07], respectively, demonstrating the bioequivalence between the two formulations (Reference data CTD 5.3.1.2-1, Study 1602).

6.1.2 Relative bioavailability (Reference data CTD 5.3.3.3-1, Study 1102)

Non-Japanese healthy adult subjects (12 subjects included in pharmacokinetic assessment) received a single oral dose of the valbenazine [redacted]-mg [redacted] formulation or [redacted]-mg [redacted] capsule under fasting conditions, and the relative bioavailability was assessed. The unchanged valbenazine C_{max} and $AUC_{0\text{-}\infty}$ geometric mean ratios for [redacted] capsule vs. [redacted] formulation [90% CI] were 1.06 [0.95, 1.17] and 1.02 [0.95, 1.10], respectively, and the geometric mean ratios of the C_{max} and $AUC_{0\text{-}\infty}$ of its active metabolite,

NBI-98782 [90% CI] were 1.00 [0.91, 1.09] and 1.02 [0.97, 1.08], respectively.

6.1.3 Food effect (Reference data CTD 5.3.1.1-2, Study 1504)

Non-Japanese healthy adult subjects (24 subjects included in pharmacokinetic assessment) received a single oral dose of 2 × the 40-mg gelatin capsule (the clinical trial formulation) under fasting conditions or after ingestion of high-fat and high-calorie meal (800-1000 kcal, approximately 50% fat), and the effect of food on the pharmacokinetics of unchanged valbenazine and NBI-98782 was assessed in a crossover study. Table 23 shows the pharmacokinetic parameters of unchanged valbenazine and NBI-98782 under fasting conditions or after ingestion of high-fat and high-calorie meal. While the AUC of unchanged valbenazine and the C_{max} and AUC of NBI-98782 were largely unchanged in the presence of food, ingestion of high-fat and high-calorie meal delayed the t_{max} of unchanged valbenazine and decreased the C_{max} compared with fasting conditions.

Table 23. Pharmacokinetic parameters of unchanged valbenazine and NBI-98782 under fasting conditions or after high-fat meal

Analyte	Dosing condition	N	C_{max} (ng/mL)	t_{max} [a)] (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng·h/mL)	Geometric mean ratio [95% CI] (High-fat meal/Fasted)	
							C_{max}	$AUC_{0-\infty}$
Unchanged valbenazine	Fasted	24	769 ± 230	0.63 [0.50, 2.0]	16 ± 1.6	6010 ± 1530	0.54 [0.50, 0.58]	0.87 [0.85, 0.90]
	High-fat meal	22	409 ± 112	3.0 [1.3, 4.0]	16 ± 1.9	5200 ± 1270		
NBI-98782	Fasted	24	25.1 ± 6.55	4.0 [3.0, 8.0]	17 ± 2.0	711 ± 181	—	—
	High-fat meal	22	20.5 ± 5.35	8.0 [4.0, 10]	17 ± 1.8	666 ± 165	—	—

Mean ± SD; —, Not calculated
a) Median [Min., Max.]

6.2 Clinical pharmacology

The applicant submitted evaluation data, in the form of the results from a phase I study in Japanese healthy adult subjects (CTD 5.3.3.1-1, Study J01), a phase I study in non-Japanese healthy adult subjects (CTD 5.3.4.1-3, Study 0901), and QT/QTc evaluation studies in non-Japanese healthy adult subjects (CTD 5.3.4.1-1, Study 1401; CTD 5.3.4.1-2, Study 1301). The applicant submitted the results from a mass balance and absolute bioavailability study in non-Japanese healthy adult subjects (Reference data CTD 5.3.1.1-1, Study 1204), studies in special populations, and drug interaction studies as reference data. The applicant also submitted the results of *in vitro* studies using human biomaterials.[29)] Unless otherwise specified, doses are expressed in terms of valbenazine, and pharmacokinetic parameters are expressed as the mean ± SD. The main pharmacokinetic studies are described below.

6.2.1 Studies using human biomaterials

Human plasma was spiked with valbenazine (0.1 and 1 μg/mL), and the plasma protein binding of valbenazine was determined using an ultrafiltration method. The percentage of valbenazine bound to plasma proteins was 99.9% at 1 μg/mL. For plasma at 0.1 μg/mL, the concentration in ultrafiltrate samples was below the LLOQ (0.5 ng/mL), and the percent unbound was not calculated (CTD 5.3.2.1-1, Study [redacted]-[redacted]02)

29) CTD 5.3.2.1-1, CTD 5.3.2.1-2, CTD 5.3.2.3-1, CTD 5.3.2.3-2, CTD 5.3.2.3-3, CTD 5.3.2.3-4, CTD 5.3.2.3-5, CTD 5.3.2.3-6, CTD 5.3.2.3-7, CTD 5.3.2.3-8, CTD 5.3.2.3-9

Human plasma was spiked with NBI-98782 (10 and 100 ng/mL), and the plasma protein binding of NBI-98782 was determined using an equilibrium dialysis method. The percentage of NBI-98782 bound to plasma proteins was 62.9% and 65.2%, respectively (CTD 5.3.2.1-2, Study [redacted]-[redacted]01).

Human blood was spiked with valbenazine (10 and 100 ng/mL), and the blood to plasma concentration ratio of valbenazine was determined. The blood to plasma concentration ratios were 0.75 and 0.72, respectively (CTD 5.3.2.1-1, Study [redacted]-[redacted]02).

Human hepatocytes were incubated with valbenazine (10 μmol/L) for 120 minutes. Unchanged valbenazine (51%) was mainly detected, and NBI-136110 (mono-oxidized valbenazine, 18%), M17 (glucuronide conjugate of mono-oxidized valbenazine, 8%), M3a (mono-oxidized valbenazine, 7%), NBI-98782 (a metabolite of valbenazine formed via ester hydrolysis, 5%), and M11a/b (sulfate conjugate of *O*-desmethyl valbenazine, 3%) were detected as primary metabolites (CTD 5.3.2.3-2, Study [redacted]-98854-002-MT).

Human hepatocytes were incubated with NBI-98782 (50 μmol/L) for 120 minutes. NBI-98782 was mainly detected (86%), and NBI-124976/M8b[22)] (*O*-desmethyl NBI-98782, 7.0%), NBI-679006 (mono-oxidized NBI-98782, 3.3%), and M38 (glucuronide conjugate of NBI-98782, 1.4%) were detected as primary metabolites (CTD 5.3.2.3-3, Study [redacted]-98854-002-MT).

In the presence of a CYP2D6 inhibitor (quinidine) or a CYP3A inhibitor (azamulin), valbenazine was incubated with human liver microsomes for 120 minutes, and the relative contribution of CYP2D6 and CYP3A in the clearance of valbenazine was evaluated. The percent contribution of CYP2D6 and CYP3A to the CL_{int} of valbenazine was estimated at 12.5% and 82.4%, respectively (CTD 5.3.2.3-2, Study [redacted]-98854-002-MT).

In the presence of a CYP3A inhibitor (azamulin), valbenazine was incubated with human hepatocytes for 120 minutes, and the role of CYP3A in the metabolism of valbenazine was investigated. The CYP3A inhibitor produced 47%, 97%, 98%, and 100% reductions in the formation of NBI-98782, NBI-136110, M3a, and M14, respectively (CTD 5.3.2.3-2, Study [redacted]-98854-002-MT).

The expression systems of recombinant human P450 isoforms [30)] or recombinant flavin-containing monooxygenase 3 (FMO3) were incubated with NBI-98782 (5 μmol/L) for 120 minutes, and the role of P450 isoforms or FMO isoform in the metabolism of NBI-98782 was investigated. NBI-124976/M8b (*O*-desmethyl NBI-98782) was formed in the CYP1B1 and CYP2D6 expression systems, and NBI-679006 (mono-oxidized NBI-98782) was formed in the CYP1A1, CYP3A4, and CYP3A5 expression systems. Also in the expression systems of other P450 isoforms and FMO3, trace amounts of NBI-124976/M8b and NBI-679006 were detected, suggesting little contribution to the metabolism of NBI-98782 (CTD 5.3.2.3-3, Study [redacted]-98854-002-MT).

30) CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9*1, CYP2C18, CYP2C19, CYP2D6*1, CYP2E1, CYP3A4, CYP3A5, CYP4A11

In the presence of inhibitory monoclonal antibodies to specific human P450 isoforms,[31] NBI-98782 (5 μmol/L) was incubated with human liver microsomes for 60 minutes to investigate the role of P450 isoforms in the metabolism of NBI-98782. The CYP2D6 inhibitory monoclonal antibody produced 74% and 66% reductions in the formation of NBI-124976/M8b (*O*-desmethyl NBI-98782), respectively, and the CYP3A4/5 inhibitory monoclonal antibody produced a 51% reduction in the formation of NBI-679006 (mono-oxidized NBI-98782) (CTD 5.3.2.3-3, Study [redacted]-98854-002-MT).

In the presence of a CYP2D6 inhibitor (quinidine), NBI-98782 (1 μmol/L) was incubated with human liver microsomes or human hepatocytes for 120 minutes to investigate the relative contribution of CYP2D6 in the clearance of NBI-98782. The percent contribution of CYP2D6 to the CL_{int} of NBI-98782 in human liver microsomes and human hepatocytes was estimated at 62.6% and 54.3%, respectively (CTD 5.3.2.3-3, Study [redacted]-98854-002-MT).

The expression systems of recombinant human P450 isoforms[32] or recombinant FMO isoforms[33] were incubated with valbenazine (10 μmol/L) for 120 minutes, and the role of P450 isoforms or FMO isoforms in the formation of NBI-136110 was investigated. Trace amounts of NBI-136110 were formed also in the CYP2C8 and CYP2C9 expression systems etc., but the highest amount of NBI-136110 was formed in the CYP3A4 and CYP3A5 expression systems. Little contribution of other P450 isoforms and FMO isoforms to the formation of NBI-136110 was suggested (CTD 5.3.2.3-2, Study [redacted]-98854-002-MT).

Using the specific substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A,[34] the potential of valbenazine (0.08-50 μmol/L), NBI-98782 (0.08-50 μmol/L), or NBI-136110 (0.1-10 μmol/L) to inhibit these isoforms in human liver microsomes was assessed. Valbenazine and NBI-98782 inhibited the metabolism of CYP2D6 substrate, with IC_{50} values of 9.0 and 14.2 μmol/L, respectively. NBI-136110 did not cause evident inhibition of any of the CYP isoforms at the concentrations tested (CTD 5.3.2.3-3, Study [redacted]-98854-002-MT; CTD 5.3.2.3-4, Study [redacted]-98854-001-MT).

Using the specific substrates of CYP2B6, CYP2C8, and CYP2E1,[35] the potential of valbenazine, NBI-98782, or NBI-136110 (all 0.03-30 μmol/mL) to inhibit these isoforms in human liver microsomes was assessed. Valbenazine, NBI-98782, or NBI-136110 did not cause evident inhibition of any of the isoforms at the concentrations tested (CTD 5.3.2.3-5, Study [redacted]5100).

Human hepatocytes were treated with valbenazine or NBI-98782 (both 0.1-10 μmol/L), and the potential of valbenazine or NBI-98782 to induce CYP1A2, CYP2B6, and CYP3A was assessed. Valbenazine or NBI-98782 did not induce any of the isoforms at the concentrations tested (CTD 5.3.2.3-7, Study [redacted]3088).

31) CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5
32) CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A6b5, CYP2B6, CYP2C8b5, CYP2C9*1, CYP2C9b5, CYP2C18, CYP2C19, CYP2D6*1, CYP2E1, CYP3A4, CYP3A5, CYP3A5b5, CYP3A7b5, CYP4A11, CYP4F2b5, CYP4F3Ab5, CYP4F3Bb5, CYP4F12b5
33) FMOs 1, 3, and 5
34) phenacetin for CYP1A2, diclofenac for CYP2C9, *S*-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, midazolam for CYP3A
35) efavirenz for CYP2B6, amodiaquine for CYP2C8, chiorzoxazone for CYP2E1

The *in vitro* cell permeability of valbenazine and NBI-98782 was evaluated using human colon carcinoma-derived Caco-2 cell line and Madin-Darby canine kidney (MDCK) cells expressing P-glycoprotein (P-gp). The ratios of the apparent permeability coefficient in the basolateral to apical direction (Papp B→A) to the apparent permeability coefficient in the apical to basolateral direction (Papp A→B) of valbenazine (20 μmol/L) across Caco-2 cells and MDCK cells expressing P-gp were 0.4 and 0.6, respectively. The ratio of Papp B→A to Papp A→B of NBI-98782 (20 μmol/L) across MDCK cells expressing P-gp was 0.6. The above results suggested that valbenazine or NBI-98782 is not a substrate of P-gp (CTD 5.3.2.3-1, Study [redacted]-98854-001-MT).

Using the human embryonic kidney HEK293 cell line expressing organic anion transporting polypeptide (OATP) 1B1 or OATP1B3, OATP-mediated transport of valbenazine and NBI-98782 (both 0.1 or 1 μmol/L) was evaluated. There were no clear differences in the uptake activity for valbenazine or NBI-98782 between the OATP1B1 or OATP1B3-expressing HEK293 cell line and the control cell line, suggesting that valbenazine or NBI-98782 is not a substrate of OATP1B1 or OATP1B3 (CTD 5.3.2.3-8, Study [redacted]-1813-[redacted]).

Using the MDCK-II cell line expressing organic anion transporter 1 (OAT1), OAT3, organic cation transporter 2 (OCT2), OATP1B1, or OATP1B3, the potential of valbenazine (25 μmol/L), NBI-98782 (5 μmol/L), or NBI-136110 (5 μmol/L) to inhibit transport of substrates of these transporters[36] was assessed. Valbenazine, NBI-98782, or NBI-136110 did not cause evident inhibition of transport of any transporter substrate (CTD 5.3.2.3-6, Studies [redacted]-011 and [redacted]-034).

Using Caco-2 cell monolayers, the potential of valbenazine (100 μmol/L), NBI-98782 (5 μmol/L), or NBI-136110 (5 μmol/L) to inhibit the transport of a BCRP substrate (^{3}H-genistein 25 nmol/L) was assessed. Valbenazine, NBI-98782, or NBI-136110 did not show evident inhibition (CTD 5.3.2.3-6, Studies [redacted]-011 and [redacted]-034).

Using MDCK cell monolayers expressing human P-gp, the potential of valbenazine (100 μmol/L), NBI-98782 (5 μmol/L), or NBI-136110 (5 μmol/L) to inhibit the transport of a P-gp substrate (^{3}H-digoxin 100 nmol/L) was assessed. Valbenazine inhibited the transport of digoxin with an IC_{50} value of 23.8 μmol/L, whereas NBI-98782 or NBI-136110 did not show evident inhibition (CTD 5.3.2.3-6, Studies [redacted]-011 and [redacted]-034).

Using the HEK293 cell line expressing multidrug and toxin extrusion 1 (MATE1) or MATE2-K, the potential of valbenazine, NBI-98782, or NBI-136110 (all 0.1-100 μmol/L) to inhibit the transport of a substrate of MATE1 and MATE2-K (^{14}C-metformin 10 μmol/L) was assessed. Valbenazine, NBI-98782, and NBI-136110 inhibited the transport of metformin. The IC_{50} values for MATE1 were 5.38, 44.0, and 25.9 μmol/L, respectively, and the IC_{50} values for MATE2-K were 17.6, 69.8, and 58.2 μmol/L, respectively (CTD 5.3.2.3-9, Study [redacted]-1775-[redacted]).

36) *p*-aminohippuric acid for OAT1 and OAT3, metformin for OCT2, estradiol-17β-D-glucuronide for OATP1B1, cholecystokinin-8 for OATP1B3

Using the DPX2 cell line[37] and the 1A2-DRE cells,[38] the effects of valbenazine (1-10 μmol/L), NBI-98782 (1-10 μmol/L), or NBI-136110 (0.1-30 μmol/L) on the pregnane X receptor (PXR) and the aryl hydrocarbon receptor (AhR) were investigated. The results suggested that valbenazine, NBI-98782, and NBI-136110 are weak PXR agonists (CTD 5.3.2.3-3, Study [redacted]-98854-002-MT; CTD 5.3.2.3-4, Study [redacted]-98854-001-MT).

6.2.2 Studies in healthy adult subjects

6.2.2.1 Japanese phase I study in Japanese healthy adult subjects (CTD 5.3.3.1-1, Study J01)

A placebo-controlled, randomized, double-blind study was conducted to evaluate the safety and pharmacokinetics of valbenazine following single or multiple oral dosing in Japanese healthy adult subjects (59 subjects included in pharmacokinetic assessment) [for the study design and safety, see Section 7.1.1].

Subjects who were classified as intermediate metabolizers (IMs) or extensive metabolizers (EMs) based on their CYP2D6 genotype were to receive a single oral dose of placebo or valbenazine 40, 80, or 160 mg under fasting conditions, or multiple oral doses of placebo or valbenazine 40 or 80 mg under fasting conditions for 8 days. Subjects who were classified as ultra-rapid metabolizers (UMs) or poor metabolizers (PMs) based on their CYP2D6 genotype were to receive a single oral dose of open-label valbenazine 40 mg under fasting conditions.

Table 24 shows the plasma pharmacokinetic parameters of unchanged valbenazine and its major metabolites, NBI-98782 and NBI-136110, in CYP2D6 IMs or EMs following a single oral dose of valbenazine 40 or 80 mg under fasting conditions. The $AUC_{0-\infty}$ values of NBI-98782 and NBI-136110 were 12.2% to 13.3% and 27.1% to 30.2%, respectively, of that of unchanged valbenazine. Following administration of valbenazine 80 mg, 1.2%, 1.5%, and 2.0% of the dose were excreted as unchanged valbenazine, NBI-98782, and NBI-136110, respectively, in urine.

Table 24. Pharmacokinetic parameters following a single oral dose of valbenazine [a] (fasted) in Japanese healthy adult subjects (CYP2D6 IMs or EMs)

Analyte	Dose (mg)	N	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-24h} (ng·h/mL)	AUC_{0-last} (ng·h/mL)
Unchanged valbenazine	40	8	542 ± 164	0.75 [0.50, 2.00]	15.88 ± 2.60	3624.5 ± 846.4	2795.5 ± 704.2	3584.7 ± 847.6
	80	8	1260 ± 344	0.50 [0.50, 1.00]	15.68 ± 3.89	8535.0 ± 1796.9	6788.1 ± 1497.9	8496.9 ± 1798.0
	160	8	3010 ± 837	0.75 [0.50, 1.00]	15.15 ± 2.82	18051.3 ± 4224.9	14602.6 ± 3585.1	17938.8 ± 4227.9
NBI-98782	40	8	9.89 ± 2.94	6.00 [4.00, 12.00]	16.64 ± 2.04	349.3 ± 99.6	185.9 ± 54.2	341.3 ± 97.4
	80	8	24.6 ± 5.88	4.00 [4.00, 8.00]	18.66 ± 2.09	773.1 ± 217.0	437.4 ± 117.0	765.0 ± 214.3
	160	8	55.4 ± 15.8	4.00 [4.00, 8.00]	16.18 ± 2.38	1674.8 ± 371.8	961.4 ± 250.8	1642.0 ± 368.2
NBI-136110	40	8	31.0 ± 5.83	1.75 [1.50, 8.00]	28.59 ± 6.39	1118.7 ± 172.6	499.5 ± 100.5	1012.9 ± 181.0
	80	8	71.3 ± 16.8	2.50 [1.00, 4.00]	27.64 ± 3.87	2547.5 ± 539.9	1168.5 ± 264.8	2429.2 ± 526.5
	160	8	164 ± 44.2	1.75 [1.00, 3.00]	26.03 ± 4.27	5066.5 ± 1172.1	2431.0 ± 608.3	4712.9 ± 1124.3

Mean ± SD
a) Median [Min., Max.]

Table 25 shows the plasma pharmacokinetic parameters of unchanged valbenazine, NBI-98782, and NBI-136110 following a single oral dose of valbenazine 40 mg under fasting conditions by CYP2D6 genotype.

37) A cell line stably transfected with both a PXR expression vector as well as a luciferase reporter gene under the control of human CYP3A4 promoters
38) A cell line stably transfected with a luciferase gene under the control of the human CYP1A2 promoter and dioxin response element

Table 25. Pharmacokinetic parameters following a single oral dose of valbenazine 40 mg in Japanese healthy adult subjects by CYP2D6 genotype

Analyte	CYP2D6 genotype	Day	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-24h} (ng·h/mL)	Metabolite to unchanged drug $AUC_{0-\infty}$ ratio (%)
Unchanged valbenazine	PM	1	817 [b]	0.50 [b]	20.08 [b]	4073.8 [b]	3095.9 [b]	—
	IM	4	552 ± 141	0.75 [0.50, 0.75]	14.76 ± 2.76	3271.5 ± 645.4	2581.7 ± 545.6	—
	EM	4	533 ± 207	0.88 [0.75, 2.00]	16.99 ± 2.19	3977.6 ± 960.5	3009.3 ± 858.8	—
	UM	2	351, 473 [b]	0.75, 1.00 [b]	10.81, 11.18 [b]	2829.2, 3799.2 [b]	2317.8, 3015.7 [b]	—
NBI-98782	PM	1	17.7 [b]	4.00 [b]	19.83 [b]	802.3 [b]	363.8 [b]	25.80
	IM	4	10.8 ± 2.23	6.00 [4.00, 12.00]	16.35 ± 1.38	389.1 ± 95.9	206.3 ± 44.7	16.03
	EM	4	8.98 ± 3.61	6.00 [4.00, 8.00]	16.93 ± 2.74	309.5 ± 98.8	165.5 ± 61.3	10.46
	UM	2	6.81, 10.9 [b]	4.00, 4.00 [b]	12.68, 14.24 [b]	154.4, 294.2 [b]	97.4, 179.9 [b]	8.65
NBI-136110	PM	1	34.5 [b]	1.50 [b]	35.85 [b]	1380.8 [b]	574.7 [b]	32.65
	IM	4	31.6 ± 6.86	1.50 [1.50, 2.00]	27.03 ± 5.85	1012.8 ± 121.5	482.8 ± 105.4	30.17
	EM	4	30.3 ± 5.59	2.50 [1.50, 8.00]	30.16 ± 7.38	1224.5 ± 157.7	516.1 ± 108.4	30.27
	UM	2	32.7, 35.3 [b]	1.50, 4.00 [b]	21.09, 24.17 [b]	955.0, 1280.2 [b]	507.2, 603.4 [b]	32.48

Mean ± SD; —, Not applicable
a) Median [Min., Max.], b) Individual values

Table 26 shows the plasma pharmacokinetic parameters of unchanged valbenazine, NBI-98782, and NBI-136110 in CYP2D6 IMs or EMs following multiple oral dosing of valbenazine 40 or 80 mg for 8 days under fasting conditions. Since all subjects in the valbenazine 80 mg group discontinued treatment on Day 6, the plasma pharmacokinetic parameters on Day 8 could not be assessed [see Section 7.1.1]. In the valbenazine 40 mg group, while there were no major differences in the C_{max} of unchanged valbenazine between Days 1 and 8, the C_{max} values of NBI-98782 and NBI-136110 increased by 2.1- and 2.3-fold, respectively. The Day 8 to Day 1 AUC_{0-24h} ratios for unchanged valbenazine, NBI-98782, and NBI-136110 were 1.3, 2.1, and 2.4, respectively.

Table 26. Pharmacokinetic parameters following multiple oral dosing of valbenazine in Japanese healthy adult subjects (CYP2D6 IMs or EMs)

Analyte	Dose (mg)	Day	N	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	AUC_{0-24h} (ng·h/mL)	AUC_{0-last} (ng·h/mL)
Unchanged valbenazine	40	1	10	504 ± 143	0.75 [0.50, 2.00]	9.76 ± 1.90	2920.9 ± 731.3	2920.9 ± 731.3
		8	10	465 ± 120	0.75 [0.50, 3.00]	18.01 ± 1.27	3832.1 ± 807.3	5551.5 ± 1072.1
	80	1	10	1380 ± 355	0.63 [0.50, 1.00]	11.28 ± 3.76	6705.8 ± 1743.8	6705.8 ± 1743.8
NBI-98782	40	1	10	13.8 ± 4.23	8.00 [4.00, 8.00]	29.57 ± 7.59	252.1 ± 87.6	252.1 ± 87.6
		8	10	29.0 ± 10.9	4.00 [3.00, 4.00]	19.91 ± 1.28	520.6 ± 216.2	995.0 ± 466.8
	80	1	10	23.1 ± 6.30	4.00 [4.00, 8.00]	32.24 ± 14.10	405.0 ± 120.2	405.0 ± 120.2
NBI-136110	40	1	10	35.5 ± 11.3	3.00 [1.50, 8.00]	26.64 ± 8.81	569.4 ± 172.2	569.4 ± 172.2
		8	10	80.9 ± 16.6	4.00 [3.00, 4.00]	30.67 ± 4.14	1318.2 ± 288.0	3036.8 ± 597.7
	80	1	10	73.8 ± 23.6	2.00 [1.00, 4.00]	44.05 ± 41.46	1139.5 ± 285.1	1139.5 ± 285.1

Mean ± SD; —, Not applicable
a) Median [Min., Max.]

6.2.2.2 Single-dose study in non-Japanese healthy adult subjects (CTD 5.3.4.1-2, Study 1301)

A placebo-controlled, randomized, double-blind study was conducted to evaluate the safety and pharmacokinetics of valbenazine following a single dose of valbenazine in non-Japanese healthy adult subjects (12 subjects included in pharmacokinetic assessment).

A single oral dose of placebo or valbenazine 150 or 300 mg was to be administered after a meal. Table 27 shows the plasma pharmacokinetic parameters of unchanged valbenazine and NBI-98782. While the C_{max} and $AUC_{0-\infty}$ of unchanged valbenazine increased more than dose-proportionally, the C_{max} and $AUC_{0-\infty}$ of NBI-98782 increased dose-proportionally at the doses tested.

Table 27. Plasma pharmacokinetic parameters of unchanged valbenazine and its metabolites following a single oral dose of valbenazine in non-Japanese healthy adult subjects

Analyte	Dose (mg)	N	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL/F (L/h)	V/F (L)
Unchanged valbenazine	150	6	817 ± 168	2.1 [0.55, 3.1]	15 ± 1.4	9830 ± 1510	15.6 ± 2.29	340 ± 76
	300	6	2430 ± 450	2.1 [1.1, 4.1]	18 ± 3.7	28600 ± 5350	10.8 ± 2.10	270 ± 39
NBI-98782	150	6	42.6 ± 9.70	8.1 [4.1, 8.1]	19 ± 2.5	1500 ± 448	—	—
	300	6	97.3 ± 30.0	8.1 [4.1, 12]	20 ± 2.2	3580 ± 1130	—	—
NBI-136110	150	6	80.5 ± 20.3	4.1 [4.1, 8.1]	29 ± 3.8	3300 ± 807	—	—
	300	6	205 ± 66.9	4.1 [3.1, 4.1]	29 ± 4.8	8810 ± 1710	—	—

Mean ± SD; —, Not applicable
a) Median [Min., Max.]

6.2.2.3 Single- and multiple-dose study in non-Japanese healthy adult subjects (CTD 5.3.4.1-3, Study 0901)

A placebo-controlled, randomized, double-blind study was conducted to evaluate the safety and pharmacokinetics of valbenazine following single or multiple oral dosing in non-Japanese healthy adult subjects (target sample size, 40 subjects).

A single oral dose of placebo or valbenazine 75, 100, 125, or 150 mg was to be administered under fasting conditions, or placebo or valbenazine 50 or 100 mg was to be administered orally under fasting conditions for 8 days.[39)]

Table 28 shows the plasma pharmacokinetic parameters of unchanged valbenazine and NBI-98782 following a single oral dose of valbenazine 75 to 150 mg under fasting conditions. The C_{max} and $AUC_{0-\infty}$ values of unchanged valbenazine and NBI-98782 were shown to increase dose-proportionally over the dose range tested.

Table 28. Plasma pharmacokinetic parameters of unchanged valbenazine and its metabolite following a single oral dose of valbenazine in non-Japanese healthy adult subjects

Analyte	Dose (mg)	N	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL/F (L/h)	V/F (L)
Unchanged valbenazine	75	2	527, 817[b)]	0.5, 1.5[b)]	18, 25[b)]	5770, 7850[b)]	9.6, 13[b)]	250, 480[b)]
	100	6	779 ± 293	0.5 [0.3, 0.8]	19 ± 3.9	6590 ± 1560	15.9 ± 3.70	420 ± 77
	125	4	1030 ± 293	0.7 [0.5, 1.3]	17 ± 3.3	9130 ± 1660	14.1 ± 2.81	330 ± 40
	150	6	1230 ± 281	0.6 [0.5, 2.0]	20 ± 3.6	12200 ± 2940	13.0 ± 3.17	370 ± 99
NBI-98782	75	2	29.6, 52.5[b)]	6.0, 10[b)]	19, 22[b)]	905, 2400[b)]	—	—
	100	6	31.9 ± 11.0	5.0 [4.0, 8.0]	20 ± 2.4	872 ± 284	—	—
	125	4	45.2 ± 13.9	6.0 [4.0, 8.0]	18 ± 2.1	1310 ± 260	—	—
	150	6	56.2 ± 25.4	7.0 [4.0, 12]	19 ± 1.5	1840 ± 1290	—	—

Mean ± SD; —, Not applicable
a) Median [Min., Max.], b) Individual values (1 subject was a CYP2D6 PM.)

Table 29 shows the plasma pharmacokinetic parameters of unchanged valbenazine and NBI-98782 following multiple oral dosing of valbenazine 50 or 100 mg under fasting conditions for 8 days. The Day 8 to Day 1 ratios of the AUC_{0-24h} of unchanged valbenazine and NBI-98782 were 1.4 to 1.5 and 2.3 to 2.6, respectively.

39) [redacted] was administered as [redacted] in the valbenazine groups.

Table 29. Plasma pharmacokinetic parameters of unchanged valbenazine and its metabolite following multiple oral dosing of valbenazine in non-Japanese healthy adult subjects

Analyte	Dose (mg)	Day	N	C_{max} (ng/mL)	t_{max} [a)] (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
Unchanged valbenazine	50	1	14	393 ± 157	0.5 [0.2, 3.0]	—	2580 ± 709
		8	13	400 ± 132	0.8 [0.5, 1.5]	21 ± 3.7	3590 ± 1050
	100	1	8	813 ± 392	0.5 [0.3, 1.3]	—	5390 ± 1710
		8	4	878 ± 638	0.5 [0.5, 1.3]	20 ± 1.7	6730 ± 3100
NBI-98782	50	1	14	18.1 ± 7.58	8.0 [4.0, 10]	—	314 ± 151
		8	13	35.1 ± 11.1	4.1 [3.0, 6.0]	21 ± 2.1	630 ± 218
	100	1	8	31.8 ± 6.75	6.0 [4.0, 10]	—	557 ± 159
		8	4	64.0 ± 13.2	4.0 [4.0, 4.0]	19 ± 1.6	1110 ± 243

Mean ± SD; —, Not calculated
a) Median [Min., Max.]

6.2.2.4 Mass balance and absolute bioavailability study in non-Japanese healthy adult subjects (Reference data CTD 5.3.1.1-1, Study 1204)

An open-label study was conducted to assess the mass balance and absolute bioavailability of valbenazine in non-Japanese healthy adult subjects (6 subjects per cohort).

In the mass balance cohort, a single oral dose of ^{14}C-valbenazine 50 mg was administered under fasting conditions. Unchanged valbenazine was mainly detected in plasma, and unchanged valbenazine accounted for 42.4% of the total radioactivity in plasma up to 168 hours post-dose. NBI-136110, NBI-98782, and NBI-679006 were detected as primary metabolites, which accounted for 12.7%, 9.9%, and 8.2% of the total radioactivity in plasma up to 168 hours post-dose, respectively. As other metabolites of valbenazine, NBI-124976 (*O*-desmethyl NBI-98782), M3a/c (mono-oxidized valbenazine), M9a/b/c (mono-oxidized desmethyl NBI-98782), M17 (glucuronide conjugate of mono-oxidized valbenazine), M21a/b (glucuronide conjugate of di-oxidized valbenazine), M27 (carbamate glucuronide of valbenazine), M38 (glucuronide conjugate of NBI-98782), M44a (glucuronide conjugate of *O*-desmethyl NBI-98782), M50a/b (sulfate conjugate of desmethyl NBI-98782), and M51 (sulfate conjugate of didesmethyl NBI-98782) were detected.

The cumulative recoveries of the administered radioactivity in urine and feces over 168 hours were 55.7% and 13.3%, respectively, with 1.8% excreted as unchanged valbenazine in either urine or feces, and 1.6% and <1% excreted as NBI-98782 in urine and feces, respectively.

In the absolute bioavailability cohort, a single oral dose of valbenazine 50 mg was administered under fasting conditions, and 45 minutes later, ^{14}C-valbenazine 15 μg was administered intravenously. The absolute oral bioavailability of valbenazine was calculated to be 48.6%.

6.2.3 Study in patients

6.2.3.1 Japanese phase II/III study (CTD 5.3.5.1-1, Study J02)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of valbenazine in Japanese patients with tardive dyskinesia and underlying schizophrenia,

schizoaffective disorder, bipolar disorder, or depressive disorder (248 subjects included in pharmacokinetic assessment[40)]) [for the study design and efficacy and safety results, see Section 7.2.1].

Table 30 shows the plasma concentrations of unchanged valbenazine and NBI-98782 by treatment group at different time points (Weeks 2, 4, 6, 16, 32, and 48).

Table 30. Plasma concentrations of unchanged valbenazine and NBI-98782 following administration of valbenazine 40 or 80 mg in patients with tardive dyskinesia

	Valbenazine 40 mg			Valbenazine 80 mg[a)]		
Time point	N	Unchanged valbenazine	NBI-98782	N	Unchanged valbenazine	NBI-98782
Week 2	81	157 ± 97.2	25.2 ± 17.7	79	416 ± 337	58.8 ± 33.3
Week 4	76	170 ± 117	26.5 ± 17.1	70	425 ± 339	60.7 ± 40.5
Week 6	70	156 ± 106	24.1 ± 13.2	61	436 ± 279	60.1 ± 34.9
Week 16	93	166 ± 100	26.2 ± 17.0	73	383 ± 284	51.5 ± 29.4
Week 32	81	174 ± 112	24.8 ± 16.2	58	315 ± 301	42.3 ± 34.4
Week 48	67	165 ± 110	27.1 ± 16.8	50	305 ± 263	42.5 ± 34.7

Mean ± SD (ng/mL)
a) Including subjects who had their dose reduced at Week ≥16.

6.2.4 Intrinsic factor pharmacokinetic studies

6.2.4.1 Pharmacokinetic study in subjects with hepatic impairment (Reference data CTD 5.3.3.3-2, Study 1303)

An open-label, parallel-group study was conducted to evaluate the safety and pharmacokinetics of a single oral dose of valbenazine in non-Japanese healthy adult subjects (normal hepatic function) and subjects with hepatic impairment (target sample size, 24 subjects [normal hepatic function, Child-Pugh class A (mild hepatic impairment), Child-Pugh class B (moderate hepatic impairment), Child-Pugh class C (severe hepatic impairment) (6 subjects each)]).

A single oral dose of valbenazine 50 mg was to be administered under non-fasting conditions.

Table 31 shows the plasma pharmacokinetic parameters of unchanged valbenazine and its major metabolites, NBI-98782 and NBI-136110, following a single oral dose of valbenazine 50 mg. The C_{max} and $AUC_{0-\infty}$ of unchanged valbenazine, NBI-98782, and NBI-136110 increased with increasing severity of hepatic impairment.

40) Including 79 subjects who were assigned to the placebo group during the double-blind period and received valbenazine during the extension period. Plasma concentration data from these subjects are included in Week ≥16 data.

Table 31. Plasma pharmacokinetic parameters of unchanged valbenazine and its metabolites following a single oral dose of valbenazine in subjects with normal hepatic function or hepatic impairment

Analyte	Hepatic function	N	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	Geometric mean ratio [90% CI] [b]	
							C_{max}	$AUC_{0-\infty}$
Unchanged valbenazine	Normal	6	233 ± 52.0	1.1 [0.75, 3.0]	22 ± 3.3	2680 ± 246	—	—
	Mild	6	384 ± 285	1.4 [0.50, 3.0]	21 ± 1.8	3510 ± 1530	1.4 [0.86, 2.4]	1.2 [0.88, 1.7]
	Moderate	6	556 ± 448	1.8 [0.50, 3.0]	22 ± 4.7	5550 ± 2840	2.0 [1.2, 3.3]	1.9 [1.3, 2.6]
	Severe	6	631 ± 302	1.5 [0.50, 4.0]	28 ± 4.3	6430 ± 1390	2.5 [1.5, 4.2]	2.4 [1.7, 3.3]
NBI-98782	Normal	6	8.61 ± 0.95	6.0 [4.0, 16]	23 ± 4.0	335 ± 26.8	—	—
	Mild	6	10.6 ± 2.76	6.0 [6.0, 10]	23 ± 1.1	430 ± 145	1.2 [0.89, 1.7]	1.2 [0.83, 1.8]
	Moderate	6	20.0 ± 10.7	16 [6.0, 24]	24 ± 4.0	1110 ± 697	2.1 [1.5, 2.9]	2.8 [1.9, 4.1]
	Severe	6	19.2 ± 5.58	14 [12, 16]	32 ± 8.6	1180 ± 358	2.2 [1.6, 3.0]	3.4 [2.3, 5.1]
NBI-136110	Normal	6	23.1 ± 4.55	4.0 [1.5, 4.0]	36 ± 8.3	1030 ± 79.3	—	—
	Mild	6	25.0 ± 6.82	3.0 [1.3, 10]	36 ± 6.4	1140 ± 276	1.1 [0.80, 1.4]	1.1 [0.81, 1.5]
	Moderate	6	32.5 ± 14.3	2.5 [1.5, 6.0]	33 ± 10	1610 ± 802	1.3 [0.99, 1.8]	1.4 [1.1, 1.9]
	Severe	6	36.5 ± 6.91	2.6 [0.8, 8.0]	57 ± 15	1970 ± 434	1.6 [1.2, 2.1]	1.9 [1.4, 2.5]

Mean ± SD; —, Not applicable
a) Median [Min., Max.]
b) Ratio of C_{max} or $AUC_{0-\infty}$ for hepatic impairment vs. normal hepatic function estimated using an analysis of variance model

6.2.4.2 Pharmacokinetic study in subjects with renal impairment (Reference data CTD 5.3.3.3-3, Study NBI-98854-1701)

An open-label, parallel-group study was conducted to evaluate the safety and pharmacokinetics of a single oral dose of valbenazine in non-Japanese healthy adult subjects (normal renal function with eGFR ≥90 mL/min/1.73 m^2) and subjects with severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) (target sample size, 16 subjects [8 subjects with normal renal function and 8 subjects with severe renal impairment]).

A single oral dose of valbenazine 40 mg was to be administered under fasting conditions.

Table 32 shows the plasma pharmacokinetic parameters of unchanged valbenazine and its major metabolites, NBI-98782 and NBI-136110, following a single oral dose of valbenazine 40 mg. The fractions of unchanged valbenazine and NBI-98782 unbound to plasma proteins in subjects with severe renal impairment were 0.75% to 1.80% and 47.5% to 48.1%, respectively, which were similar to those in subjects with normal renal function (0.5%-0.8% and 38.3%-49.8%, respectively).

Table 32. Plasma pharmacokinetic parameters of unchanged valbenazine and its metabolites following a single oral dose of valbenazine in subjects with normal renal function or severe renal impairment

Analyte	Renal function	N	C_{max} (ng/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	Geometric mean ratio [90% CI] [b]	
							C_{max}	$AUC_{0-\infty}$
Unchanged valbenazine	Normal	8	300 ± 79.2	0.50 [0.50, 1.0]	21 ± 4.5	2350 ± 472	—	—
	Severe	8	271 ± 101	0.75 [0.50, 1.0]	22 ± 5.5	2300 ± 482	0.87 [0.64, 1.2]	0.98 [0.81, 1.2]
NBI-98782	Normal	8	8.17 ± 2.84	6.0 [4.0, 8.0]	25 ± 6.0	355 ± 126	—	—
	Severe	8	9.90 ± 2.17	6.0 [4.0, 12.0]	28 ± 7.1	435 ± 144	1.3 [0.97, 1.6]	1.2 [0.91, 1.7]
NBI-136110	Normal	8	19.6 ± 6.65	3.0 [1.0, 8.0]	37 ± 7.2	837 ± 165	—	—
	Severe	8	12.9 ± 6.60	4.0 [0.75, 24]	46 ± 15	730 ± 151	0.63 [0.44, 0.91]	0.87 [0.73, 1.0]

Mean ± SD; —, Not applicable
a) Median [Min., Max.]
b) Ratio of C_{max} or $AUC_{0-\infty}$ for severe renal impairment vs. normal renal function estimated using an analysis of variance model

6.2.5 Drug interaction studies

Open-label studies of valbenazine were conducted to investigate potential drug-drug interactions. Table 33 and Table 34 show the geometric least-squares mean ratios of the plasma pharmacokinetic parameters of unchanged valbenazine or its metabolites, or coadministered drugs for coadministration vs. alone.

Table 33. Effect of coadministered drug on pharmacokinetics of unchanged valbenazine and its metabolites

Coadministered drug (Dosing regimen) Duration of dosing	Dosing regimen of valbenazine	Analyte	N	Geometric mean ratio[a] [90% CI]		Study ID CTD
				C_{max}	$AUC_{0-\infty}$	
Ketoconazole (200 mg BID for 5 days)[b]	50 mg single dose, fasted	Unchanged valbenazine	24	1.5 [1.4, 1.6]	2.1 [2.0, 2.2]	NBI-98854-1302 Reference data 5.3.2.2-1
		NBI-98782	24	1.6 [1.5, 1.7]	2.1 [2.0, 2.2]	
		NBI-136110	24	0.22 [0.19, 0.25]	0.46 [0.42, 0.50][e]	
Rifampicin (600 mg QD for 10 days)[c]	80 mg single dose, fasted	Unchanged valbenazine	11	0.68 [0.58, 0.80]	0.28 [0.26, 0.30]	NBI-98854-1502 Reference data 5.3.2.2-2
		NBI-98782	11	0.49 [0.41, 0.57]	0.23 [0.21, 0.25]	
		NBI-136110	11	1.4 [1.1, 1.7]	0.32 [0.29, 0.35]	
Paroxetine (20 mg QD for 15 days)[d]	40 mg single dose, fasted	Unchanged valbenazine	24	0.76 [0.62, 0.93]	0.91 [0.77, 1.08]	NBI-98854-1703 Reference data 5.3.2.2-5
		NBI-98782	24	1.42 [1.18, 1.71]	1.90 [1.58, 2.30]	
		NBI-136110	24	0.977 [0.824, 1.157]	1.075 [0.926, 1.249]	

a) Ratio of C_{max} or $AUC_{0-\infty}$ for coadministration vs. alone estimated using a mixed model
b) Valbenazine was administered orally on Days 1 and 6, and ketoconazole was administered orally twice daily on Days 5-9.
c) Valbenazine was administered orally on Days 1 and 11, and rifampicin was administered orally once daily on Days 5-14.
d) Valbenazine was administered orally on Days 1 and 17, and paroxetine was administered orally once daily on Days 8-22.
e) AUC_{0-last}

Table 34. Effect of valbenazine on pharmacokinetics of coadministered drug

Dosing regimen of valbenazine	Coadministered drug (Dosing regimen)	Analyte	N	Geometric mean ratio[a] [90% CI]		Study ID CTD
				C_{max}	AUC_{0-24h}	
80 mg QD for 7 days[b]	Digoxin (0.5 mg single dose)	Digoxin	17	1.9 [1.7, 2.2]	1.4 [1.3, 1.5]	NBI-98854-1503 Reference data 5.3.2.2-3
80 mg single dose	Midazolam (2 mg single dose)	Midazolam	12	1.0 [0.86, 1.2]	1.1 [1.0, 1.1]	NBI-98854-1507 Reference data 5.3.2.2-4

a) Ratio of C_{max} or $AUC_{0-\infty}$ for coadministration vs. alone estimated using a mixed model
b) Digoxin was administered orally on Days 1 and 14, and valbenazine was administered orally once daily on Days 10-16.

6.2.6 Pharmacodynamic study

6.2.6.1 Effect on QT/QTc interval (CTD 5.3.4.1-1, Study 1401)

A double-blind study was conducted to evaluate the effect of valbenazine on the QT/QTc interval in non-Japanese healthy adult subjects (48 subjects included in pharmacodynamic assessment).

A single oral dose of valbenazine 160 mg was to be administered under fasting conditions, or a single oral dose of moxifloxacin 400 mg was to be administered.

Table 35 shows the plasma pharmacokinetic parameters of unchanged valbenazine and its major metabolites, NBI-98782 and NBI-136110, following a single oral dose of valbenazine 160 mg under fasting conditions. Table 36 shows the time-matched mean difference in the change from baseline in the QTcF interval between valbenazine and placebo (ΔΔQTcF interval) and its 90% confidence interval. In the valbenazine 160 mg group, the upper bound of the 90% confidence interval was above 10 msec at 8 and 12 hours post-dose. Following administration of valbenazine 160 mg, 2 subjects had a QTcF >450 msec, and 3 subjects had a >30 msec increase from baseline in QTcF, whereas no subjects had a QTcF >500 msec or a >60 msec increase from baseline in QTcF.

Table 35. Pharmacokinetic parameters following administration of valbenazine 160 mg in non-Japanese healthy adult subjects

Analyte	N	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-last} (ng·h/mL)	AUC_{0-24h} (ng·h/mL)
Unchanged valbenazine	46	1800 ± 496	0.550 [0.550, 3.05]	12200 ± 2550	10400 ± 2160
NBI-98782	46	44.6 ± 8.11	5.05 [3.05, 12.1]	1220 ± 319	807 ± 180
NBI-136110	46	99.4 ± 23.7	3.05 [1.05, 12.1]	2650 ± 550	1700 ± 381

Mean ± SD
a) Median [Min., Max.]

Table 36. ΔΔQTcF interval following administration of valbenazine or moxifloxacin in non-Japanese healthy adult subjects

	Drug	N	Time after dosing								
			0.5 hours	2 hours	3 hours	4 hours	5 hours	6 hours	8 hours	12 hours	24 hours
ΔΔQTcF interval	Valbenazine (160 mg)	46	-1.22 [-3.84, 1.40]	2.28 [-0.03, 4.59]	3.07 [1.13, 5.01]	3.01 [0.82, 5.21]	5.41 [2.95, 7.87]	4.98 [2.72, 7.25]	8.96 [6.84, 11.08]	8.17 [5.85, 10.49]	6.12 [3.77, 8.47]
	Moxifloxacin (400 mg)	48	—	11.74 [9.01, 14.46][a)]	8.65 [4.97, 12.32][a)]	9.52 [5.58, 13.46][a)]	—	—	—	—	—

Least-squares mean (msec) [90% CI], —, Not applicable
a) 97.5% CI

6.2.7 PPK analyses (Reference data CTD 5.3.3.5-1, 2016-PK-056 analyses)

Using the plasma pharmacokinetic data of unchanged valbenazine and NBI-98782 (a total of 4793 PK samples from a total of 305 subjects) obtained from 2 foreign phase I studies in non-Japanese healthy adult subjects (CTD 5.3.4.1-3, Study 0901; Reference data CTD 5.3.1.1-2, Study 1504), 2 foreign phase II studies in non-Japanese patients with tardive dyskinesia (Reference data CTD 5.3.5.1-3, Study 1201; Reference data CTD 5.3.5.1-4, Study 1202), and a foreign phase III study in non-Japanese patients with tardive dyskinesia (Reference data CTD 5.3.5.1-5, Study 1304), population pharmacokinetic analyses were conducted. The pharmacokinetics of unchanged valbenazine were described by a 2-compartment model with lagged first-order absorption, and the pharmacokinetics of NBI-98782 were described by a 2-compartment model. The influence of covariates on the pharmacokinetic parameters of valbenazine was explored.[41)] Body weight was selected as a statistically significant covariate on the CL/F and volume of distribution of unchanged valbenazine and NBI-98782, and CYP2D6 genotype status was selected as a statistically significant covariate on the CL/F of NBI-98782. The CL/F of unchanged valbenazine and NBI-98782 was predicted to be 22% lower in patients weighing 56 kg (5 percentile body weight of the population) compared with patients weighing 78 kg (the median body weight of the population).

6.2.8 Exposure-response analyses (Reference data CTD 5.3.3.5-1, 2016-PK-056 analyses)

6.2.8.1 Exposure-efficacy analyses

The data from a foreign phase III study in patients with tardive dyskinesia (Reference data CTD 5.3.5.1-5, Study 1304) were used to explore relationships between the exposures (the C_{max} and $AUC_{0\text{-}tau}$ at Week 6) of unchanged valbenazine and its active metabolite, NBI-98782, and efficacy (the Abnormal Involuntary Movement Scale [AIMS] total score [the percent change from baseline and the change from baseline] and the Clinical Global Impression of Change-Tardive Dyskinesia [CGI-TD] score at Week 6). The C_{max} and $AUC_{0\text{-}tau}$ of unchanged valbenazine and NBI-98782 at Week 6 were calculated based on the PK parameter estimates from the PPK model [see Section 6.2.7] and Week 6 doses of valbenazine. The percent change from baseline in the AIMS total score, the change from baseline in the AIMS total score, and the CGI-TD score at Week 6 were calculated by unchanged valbenazine or NBI-98782 exposure quartiles. All of the percent change from baseline in the AIMS total score, the change from baseline in the AIMS total score, and the CGI-TD score tended to improve with increasing exposures.

41) Covariates tested: gender, age, BMI, race, concomitant use of CYP2D6 inhibitors, concomitant use of CYP3A inhibitors, body weight, CYP2D6 genotype status

6.2.8.2 Exposure-safety analyses

The data from a foreign phase III study in non-Japanese patients with tardive dyskinesia (Reference data CTD 5.3.5.1-5, Study 1304) were used to explore relationships between the C_{max} and $AUC_{0-\tau}$ of NBI-98782 and safety (the proportion of subjects who had the occurrence of the Barnes Akathisia Rating Scale [BARS] event for the assessment of akathisia,[42)] the proportion of subjects who had the occurrence of the Calgary Depression Scale for Schizophrenia [CDSS] event for the assessment of depressive symptoms in patients with schizophrenia,[43)] the proportion of subjects with a ≥2- or ≥4-fold increase from baseline in serum prolactin concentrations, the proportion of subjects who had the occurrence of the Simpson-Angus extrapyramidal side effects scale [SAS] event for the assessment of extrapyramidal side effects[44)]). In Foreign Study 1304, the proportion of patients with a ≥2-fold increase from baseline in serum prolactin concentrations tended to increase with increasing C_{max} of NBI-98782, but no relationship was found between the exposures and other safety endpoints.

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in pharmacokinetics

The applicant's explanation about differences in the pharmacokinetics of valbenazine between Japanese and non-Japanese populations:

- Table 37 shows the pharmacokinetic parameters of unchanged valbenazine and its active metabolite, NBI-98782, following a single oral dose of valbenazine 40, 80, or 160 mg in CYP2D6 EMs or IMs in a Japanese phase I study in Japanese healthy adult subjects (CTD 5.3.3.1-1, Study J01) and foreign phase I studies in non-Japanese healthy adult subjects (CTD 5.3.4.1-1, Study 1401; Reference data CTD 5.3.2.2-2, Study 1502; Reference data CTD 5.3.1.1-2, Study 1504; Reference data CTD 5.3.1.2-1, Study 1602). Although the C_{max} and AUC_{0-24h} of unchanged valbenazine were higher in Japanese subjects than in non-Japanese subjects, there were no clear differences in the C_{max} and AUC_{0-24h} of NBI-98782 between Japanese and non-Japanese subjects.

Table 37. Pharmacokinetic parameters of unchanged valbenazine and NBI-98782 in Japanese and non-Japanese subjects

Analyte	Dose (mg)	Japanese		Non-Japanese	
		C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
Unchanged valbenazine	40	550 [335, 779]	2551.3 [2140.0, 4181.0]	343 [173, 717]	2233.3 [1284.2, 3565.8]
	80	1260 [783, 1720]	7320.0 [4285.9, 8629.1]	774 [344, 1750]	4765.4 [2234.6, 8909.3]
	160	2670 [2210, 4450]	14296.1 [8812.4, 19392.8]	1770 [938, 3100]	10289.4 [5454.2, 15461.0]
NBI-98782	40	9.48 [5.34, 13.9]	176.4 [101.4, 248.6]	11.7 [7.06, 26.6]	189.8 [115.1, 541.3]
	80	24.3 [15.9, 33.0]	446.3 [269.5, 610.1]	26.2 [13.2, 45.0]	398.7 [255.8, 718.5]
	160	51.5 [38.4, 84.6]	926.8 [682.7, 1420.4]	43.0 [31.4, 69.3]	776.2 [528.9, 1295.9]

Median [Min., Max.]

- In the PPK analyses [see Section 6.2.7], body weight was selected as a significant covariate on the CL/F and volume of distribution of unchanged valbenazine and NBI-98782, and CYP2D6 genotype status was selected as a significant covariate on the CL/F of NBI-98782. Thus, the C_{max} and AUC_{0-24h} of unchanged valbenazine were adjusted for body weight (normalized to 70 kg body weight), and the C_{max} and AUC_{0-24h}

42) As to the BARS Item #4, the global clinical assessment of akathisia (rated on a scale of 0-5), the occurrence of the event was defined as the absolute value of score ≥3 or the change from baseline in score of ≥2 in subjects with baseline BARS score <3 or the change from baseline in score of ≥2 in subjects with baseline BARS score ≥3.

43) As to the first item score of the CDSS (scored on a scale of 0-3), the occurrence of the event was defined as post-baseline score of 2 or 3 in subjects with baseline CDSS score <2, and subjects with baseline CDSS score ≥2 were excluded from the analysis.

44) The occurrence of the event was defined as SAS score ≥0.65, and subjects with baseline SAS score >0.65 were excluded from the analysis.

of NBI-98782 were adjusted for body weight (normalized to 70 kg body weight) by CYP2D6 genotype status (EM or IM). Then, the pharmacokinetics of unchanged valbenazine and NBI-98782 in Japanese subjects were compared with those in non-Japanese subjects. The results are shown in Table 38 and Table 39. The ranges of individual values of the C_{max} and $AUC_{0\text{-}24h}$ of unchanged valbenazine and NBI-98782 largely overlapped.

Table 38. Pharmacokinetic parameters of unchanged valbenazine adjusted for body weight (normalized to 70 kg body weight) in Japanese and non-Japanese subjects

Dose (mg)	Japanese		Non-Japanese	
	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
40	546 [282, 674]	2431.5 [1831.2, 3601.6]	349 [177, 610]	2214.2 [1335.2, 3063.7]
80	1240 [751, 1490]	6388.1 [4518.5, 7692.0]	858 [405, 1930]	4996.4 [2752.0, 7840.3]
160	2460 [1920, 4420]	13099.6 [7641.6, 19607.8]	1930 [1070, 3070]	10637.6 [7264.0, 16929.2]

Median [Min., Max.]

Table 39. Pharmacokinetic parameters of NBI-98782 adjusted for body weight (normalized to 70 kg body weight) in Japanese and non-Japanese subjects

CYP2D6 genotype status	Dose (mg)	Japanese		Non-Japanese	
		C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
EM	40	8.34 [5.34, 13.9]	155.9 [101.4, 248.6]	10.9 [7.06, 19.5]	177.1 [115.1, 284.9]
	80	20.5 [15.9, 25.3]	336.8 [269.5, 448.3]	23.9 [13.2, 40.5]	368.6 [255.8, 642.5]
	160	52.7 [43.1, 69.1]	969.4 [682.7, 1140.7]	42.9 [34.9, 58.8]	767.3 [528.9, 1179.1]
IM	40	10.8 [8.17, 13.4]	215.5 [149.7, 244.4]	14.9 [10.1, 26.6]	265.0 [186.1 541.3]
	80	29.3 [23.2, 33.0]	526.7 [444.4, 610.1]	29.3 [17.9, 45.0]	489.9 [309.4 718.5]
	160	51.5 [38.4, 84.6]	888.5 [731.4, 1420.4]	43.8 [31.4, 69.3]	867.3 [608.4 1295.9]

Median [Min., Max.]

- Using the dataset consisting of the non-Japanese data used for the development of the PPK model [see Section 6.2.7] and the plasma pharmacokinetic data of unchanged valbenazine and NBI-98782 obtained from Japanese clinical studies (Japanese Study J01 and a Japanese phase II/III study [CTD 5.3.5.1-1, Study J02]) (unchanged valbenazine, a total of 3719 PK samples from a total of 508 subjects; NBI-98782, a total of 3715 PK samples from a total of 512 subjects), PPK analyses were conducted. Table 40 shows the model-predicted exposures in Japanese patients with tardive dyskinesia weighing 61.96 kg (the mean body weight in Japanese Study J02) or 34.8 kg (the minimum body weight in Japanese Study J02) following oral administration of valbenazine 40 or 80 mg. The results suggested higher exposures of unchanged valbenazine and NBI-98782 in lighter patients.

Table 40. Predicted pharmacokinetic parameters of unchanged valbenazine and NBI-98782 in Japanese patients with tardive dyskinesia

Dose (mg)	Body weight 61.96 kg				Body weight 34.8 kg			
	Unchanged valbenazine		NBI-98782		Unchanged valbenazine		NBI-98782	
	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
40	345.9	3223.7	26.4	536.2	586.8	4968.5	42.5	826.8
80	691.7	6447.4	52.9	1072.5	1173.5	9937.0	85.1	1653.6

- The above results indicate that there are no clinically relevant ethnic differences in the pharmacokinetics of unchanged valbenazine and NBI-98782.

PMDA's view:

- No clinically relevant ethnic differences in the pharmacokinetics of unchanged valbenazine and NBI-98782 have been suggested. Meanwhile, as to the pharmacokinetic parameters unadjusted for body weight in healthy adult subjects, the exposures of unchanged valbenazine were higher in Japanese subjects than

in non-Japanese subjects (Table 37), and the mean body weights of patients with tardive dyskinesia in Japanese Study J02 and a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304) were 62 kg and 81 kg, respectively, showing that Japanese patients tended to be lighter than non-Japanese patients. Based on the above, the possibility that the exposures of unchanged valbenazine are higher in Japanese patients than in non-Japanese patients cannot be ruled out.

- The appropriateness of the dosing regimen for Japanese patients and dose adjustment for patients with factors associated with increased exposure will be discussed in Sections 6.R.2 and 6.R.4.

6.R.2 Selection of dosing regimen from a clinical pharmacological standpoint

PMDA asked the applicant to explain the appropriateness of the dosing regimen of valbenazine from a clinical pharmacological standpoint, taking also account of the rationale for the dosing regimen used in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02).

The applicant's explanation:

- Based on foreign phase II studies and exposure-efficacy analyses, valbenazine 40 mg/day and 80 mg/day were selected for a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304). Namely, the foreign phase II studies (Reference data CTD 5.3.5.2-1, Study 1001; Reference data CTD 5.3.5.1-2, Study 1101; Reference data CTD 5.3.5.1-3, Study 1201; Reference data CTD 5.3.5.1-4, Study 1202) showed the tolerability of multiple doses of valbenazine 12.5 to 100 mg/day and dose-dependent efficacy of valbenazine. According to the exposure-efficacy analyses, the efficacy of valbenazine 40 mg in CYP2D6 PMs was predicted to be comparable to the efficacy of valbenazine 80 mg/day in non-PMs, and the efficacy of valbenazine 80 mg/day and 100 mg/day was predicted to be comparable between CYP2D6 PMs and non-PMs. Thus, the percent change from baseline in the AIMS total score was predicted to plateau at 40 to 80 mg/day of valbenazine, and valbenazine 100 mg was not expected to be more effective than 80 mg. Thus, valbenazine 40 mg/day and 80 mg/day were selected.
- Valbenazine 40 mg/day and 80 mg/day were selected for Japanese Study J02 as in Foreign Study 1304 because a Japanese phase I study (CTD 5.3.3.1-1, Study J01) and foreign phase I studies (CTD 5.3.4.1-1, Study 1401; Reference data CTD 5.3.2.2-2, Study 1502; Reference data CTD 5.3.1.1-2, Study 1504; Reference data CTD 5.3.1.2-1, Study 1602) showed no major differences in the pharmacokinetics and safety of valbenazine between Japanese and non-Japanese subjects [see Section 6.R.1], and valbenazine was expected to be effective at both doses (40 and 80 mg/day). However, considering patients with factors associated with increased exposure, the starting dose was 40 mg/day for all patients.

PMDA's view:

There is no problem with the dosing regimen selected for Japanese Study J02 from a clinical pharmacological standpoint based on the exposure-response analyses. The appropriateness of the proposed dosing regimen of valbenazine will be discussed in Section 7.R.5, taking account of efficacy and safety results from clinical studies.

6.R.3 Food effect on pharmacokinetics and the timing of dosing relative to meals

The applicant's explanation about the effect of food on the pharmacokinetics of valbenazine and the timing of dosing relative to meals in the proposed dosage and administration section:

- In a phase I study in non-Japanese healthy adult subjects (Reference data CTD 5.3.1.1-2, Study 1504), ingestion of high-fat and high-calorie meal delayed the t_{max} of unchanged valbenazine and decreased the C_{max} compared with fasting conditions [see Section 6.1.3]. These findings are likely due to slower gastric emptying after ingestion of meal, resulting in the delayed t_{max} and decreased C_{max} of unchanged valbenazine. On the other hand, the AUC of unchanged valbenazine and the C_{max} and AUC of its active metabolite, NBI-98782, were largely unchanged in the presence of food. Thus, food effect was not considered clinically relevant, and valbenazine was administered without regard to food in a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304), which demonstrated the efficacy and safety of valbenazine.
- Study drug was administered without regard to food in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) as in Foreign Study 1304, but subjects were required to take study drug during the same period of time every day wherever possible. Information regarding the timing of dosing of study drug relative to meals was not collected.
- Japanese Study J02, in which study drug was administered without regard to food, demonstrated the efficacy and safety of valbenazine. Although valbenazine 160 mg resulted in QT interval prolongation in a foreign phase I study (CTD 5.3.4.1-1, Study 1401), the predicted steady-state C_{max} of NBI-98782 following multiple dosing of valbenazine 80 mg in Japanese patients under fasting conditions is 48.5 ng/mL, and the ΔQTcF interval at this exposure level and the upper bound of the 95% confidence interval are estimated to be 4.74 and 6.52 msec, respectively [see Section 6.R.5]. Thus, the risk of QT interval prolongation is not high even in patients receiving multiple doses of valbenazine 80 mg under fasting conditions.
- If patients who have been taking valbenazine after a meal and titrated to their optimal dose receive valbenazine under fasting conditions, the possibility that fasted administration will result in an increase in the C_{max} of unchanged valbenazine, affecting safety, cannot be ruled out. However, this is unlikely to become a clinically relevant problem, as long as the package insert advises physicians to take appropriate measures, e.g., closely monitor patients for the occurrence of adverse drug reactions. Thus, there is no need to specify the timing of dosing relative to meals in the DOSAGE AND ADMINISTRATION section.

PMDA's view:

- Given that Japanese Study J02, in which valbenazine was administered without regard to food, demonstrated the efficacy and safety of valbenazine, there is no problem with the applicant's idea (the timing of dosing relative to meals will not be specified in the DOSAGE AND ADMINISTRATION section).
- However, if patients who have been taking valbenazine after a meal and titrated to their optimal dose receive valbenazine under fasting conditions, the possibility that fasted administration will result in an increase in the C_{max} of unchanged valbenazine, affecting safety, cannot be ruled out. Thus, the package insert should advise that if the dose of valbenazine is increased, the timing of dosing relative to meals should be consistent before and after dose adjustment.

6.R.4 Need for dose adjustment in patients with factors associated with increased exposure of valbenazine

6.R.4.1 Exposure-safety relationship

In exposure-safety analyses, the exposure-safety relationship was discussed based on the data from a foreign clinical study [see Section 6.2.8.2]. PMDA asked the applicant to explain the exposure-safety relationship in Japanese patients with tardive dyskinesia based on the data from a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02).

The applicant's explanation:

- PPK analyses were conducted using the dataset consisting of the non-Japanese data used for the development of the PPK model [see Section 6.2.7] and the plasma pharmacokinetic data of unchanged valbenazine and its active metabolite NBI-98782 obtained from Japanese clinical studies (a Japanese phase I study [CTD 5.3.3.1-1, Study J01] and Japanese Study J02). Relationships were explored between the PPK model-predicted steady-state exposures of unchanged valbenazine and NBI-98782 ($C_{max,ss}$ and $AUC_{0-\tau,ss}$) in individual subjects in Japanese Study J02 and the incidence of adverse events. The assessment suggested a relationship between the incidences of somnolence-related adverse events,[45)] parkinsonism-related adverse events,[46)] and akathisia-related adverse events[47)] and the exposures of unchanged valbenazine and NBI-98782 (C_{max} and AUC).
- Based on the above, given that the incidences of somnolence-related adverse events, parkinsonism-related adverse events, and akathisia-related adverse events tended to increase with increasing exposures in Japanese Study J02, the package insert will advise that the dose should not be increased to 80 mg in patients with factors associated with increased exposure.

6.R.4.2 Need for dose adjustment according to CYP2D6 genotype

The applicant's explanation about the need for dose adjustment and a precaution according to CYP2D6 genotype:

- In a Japanese phase I study (CTD 5.3.3.1-1, Study J01), there were no clear differences in the exposures of unchanged valbenazine following a single oral dose of valbenazine 40 mg under fasting conditions according to CYP2D6 genotype. On the other hand, the exposures of its active metabolite NBI-98782 were highest in PMs, followed by IMs, EMs, and UMs [see Section 6.2.2.1].
- Table 41 shows the steady-state C_{max} and AUC_{tau} of unchanged valbenazine and NBI-98782 in Japanese patients with tardive dyskinesia who are CYP2D6 PMs or non-PMs (UM, EM, or IM)[48)] following administration of valbenazine 40 or 80 mg, predicted by simulations using the PPK model including Japanese clinical study data [see Section 6.R.1]. While there were no differences in the exposures of

45) Events coded to MedDRA PTs "somnolence," "sedation," "fatigue," "asthenia," "lethargy," "malaise," "hypersomnia," "sedation complication," and "decreased activity"
46) Events in the MedDRA SMQ "parkinson-like events (broad)" and events coded to PT "salivary hypersecretion"
47) Events in the MedDRA SMQ "akathisia (broad)"
48) The applicant's explanation: In the PPK analyses, the impact of CYP2D6 genotype as a covariate on the CL/F of NBI-98782 was evaluated. Since the differences in the CL/F of NBI-98782 among EMs, IMs, and UMs were within less than ± 20%, UMs, EMs, and IMs were grouped together as "non-PMs."

unchanged valbenazine between CYP2D6 PMs and non-PMs, the exposures of NBI-98782 were predicted to be approximately 2-fold higher in CYP2D6 PMs than in non-PMs.

Table 41. Predicted steady-state pharmacokinetic parameters of unchanged valbenazine and NBI-98782 in Japanese patients with tardive dyskinesia

Analyte	Dose (mg)	PMs		Non-PMs (UM, EM, or IM)	
		C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)
Unchanged valbenazine	40	348	3237	348	3237
	80	695	6475	695	6475
NBI-98782	40	47.8	1050	26.5	538
	80	95.6	2100	53.1	1076

Mean

- Table 42 shows the incidence of adverse events by CYP2D6 genotype status according to the pooled analyses of foreign clinical studies.[49)] There were no clear differences in the incidence of adverse events between CYP2D6 PMs and non-PMs. No patients who were CYP2D6 PMs were enrolled in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02).

Table 42. Incidence of adverse events by CYP2D6 genotype status according to pooled analyses of foreign clinical studies (Safety population)

	PMs					Non-PMs (UM, EM, or IM)				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	7	8	4	12	11	171	101	107	185	218
All adverse events	0	4 (50.0)	1 (25.0)	8 (66.7)	8 (72.7)	71 (41.5)	43 (42.6)	51 (47.7)	109 (58.9)	133 (61.0)
Somnolence-related adverse events[a)]	0	1 (12.5)	1 (25.0)	2 (16.7)	0	5 (2.9)	9 (8.9)	5 (4.7)	15 (8.1)	13 (6.0)
Parkinsonism-related adverse events[b)]	0	0	0	1 (8.3)	0	0	0	2 (1.9)	4 (2.2)	5 (2.3)
Akathisia-related adverse events[c)]	0	0	0	0	0	1 (0.6)	3 (3.0)	3 (2.8)	7 (3.8)	1 (0.5)

n (incidence [%])
a) Events coded to MedDRA PTs "sedation" and "somnolence"
b) Events coded to MedDRA PTs "cogwheel rigidity," "muscle rigidity," "parkinsonism," and "tremor"
c) Events coded to MedDRA PT "akathisia"

- In the PPK analyses, the impact of CYP2D6 genotype as a covariate on the CL/F of NBI-98782 was evaluated. Since the differences in the CL/F of NBI-98782 among EMs, IMs, and UMs were within less than ± 20%, a precaution about patients with low CYP2D6 activity (intermediate CYP2D6 metabolizing capacity, IMs) is unnecessary. Meanwhile, as CYP2D6 PMs seem to show approximately 2-fold higher exposures of NBI-98782 following administration of valbenazine, the package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients who are known to have genetically deficient CYP2D6 activity.
- In Japanese Study J02 and a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304), the starting dose was 40 mg also in the valbenazine 80 mg group. Although exposures may be increased at the start of treatment in CYP2D6 PMs compared with non-PMs, given that no serious adverse events were reported

49) Pooled data from foreign phase II studies (Reference data CTD 5.3.5.1-3, Study 1201; Reference data CTD 5.3.5.1-4, Study 1202) and foreign phase III studies (Reference data CTD 5.3.5.1-5, Study 1304; Reference data CTD 5.3.5.2-2, Study 1402) were used. Subjects treated with valbenazine 50 mg (28 subjects and 10 subjects) during the double-blind phases of Foreign Studies 1201 and 1202 and subjects treated with valbenazine 50 mg (46 subjects) during the long-term treatment phase of Foreign Study 1201 were counted as the valbenazine 40 mg group, and subjects treated with valbenazine 75 mg (33 subjects) during the double-blind phase of Foreign Study 1202 were counted as the valbenazine 80 mg group. In the pooled analysis of data during the long-term treatment phase, the interim data were used for Foreign Studies 1304 and 1402 (78 subjects and 12 subjects who completed 48-week treatment). Subjects treated with valbenazine 25 mg (5 subjects) in Foreign Study 1202 and subjects treated with valbenazine 100 mg (27 subjects) in Foreign Study 1201 were not included.

when valbenazine was initiated at 100 mg/day in a foreign phase II study in non-Japanese patients with tardive dyskinesia (Reference data CTD 5.3.5.1-3, Study 1201), the starting dose of 40 mg for CYP2D6 PMs is acceptable. The package insert will advise that patients who are CYP2D6 PMs should be closely monitored for the possible occurrence of adverse drug reactions during the early phase of treatment.

6.R.4.3 Need for dose adjustment due to drug interactions

The applicant's explanation about the need for dose adjustment in patients receiving concomitant CYP2D6 inhibitors or CYP3A inhibitors:

- Coadministration of valbenazine with a strong CYP2D6 inhibitor, paroxetine, did not alter the C_{max} or AUC of unchanged valbenazine, but increased the C_{max} and AUC of its active metabolite NBI-98782 by 1.4- and 1.9-fold, respectively. Coadministration of valbenazine with a strong CYP3A inhibitor, ketoconazole, increased the C_{max} and AUC of unchanged valbenazine by 1.5- and 2.1-fold, respectively, and the C_{max} and AUC of NBI-98782 by 1.6- and 2.1-fold, respectively [see Section 6.2.5]. Thus, the package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients receiving concomitant strong CYP2D6 inhibitors or strong CYP3A inhibitors.
- On the other hand, the effect of concomitant use of valbenazine with moderate CYP3A inhibitors was assessed using a physiologically based pharmacokinetic model.[50)] Though 1.17- and 1.61-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and 1.37- and 1.77-fold increases in the C_{max} and AUC of NBI-98782, respectively, were predicted, a >2-fold increase in exposures is not anticipated. Thus, the dose of valbenazine may be increased to 80 mg in patients receiving concomitant moderate CYP3A inhibitors.
- Although the protocol for a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) prohibited concomitant use with strong CYP3A inhibitors or strong CYP2D6 inhibitors during the double-blind phase, concomitant use with these medications was permitted during the long-term treatment phase. In Japanese Study J02, there were no subjects who received concomitant strong CYP2D6 inhibitors, but 9 subjects received concomitant clarithromycin, a strong CYP3A inhibitor. Table 43 shows the incidence of adverse events in subjects treated with valbenazine with or without clarithromycin. Although the incidences of somnolence-related adverse events,[45)] parkinsonism-related adverse events,[46)] and akathisia-related adverse events [47)] tended to be higher in subjects receiving concomitant clarithromycin than in subjects not receiving concomitant clarithromycin, among a total of 17 events reported in subjects receiving concomitant clarithromycin, 15 had occurred prior to the concomitant use of clarithromycin and were not related to concomitant clarithromycin.

Table 43. Incidence of adverse events by concomitant use of a strong CYP3A inhibitor during the long-term treatment phase of Japanese Study J02 (Safety population)

	Without strong CYP3A inhibitor	With strong CYP3A inhibitor
N	240	9
All adverse events	220 (91.7)	9 (100)
Somnolence-related adverse events	67 (27.9)	5 (55.6)
Parkinsonism-related adverse events	69 (28.8)	5 (55.6)
Akathisia-related adverse events	28 (11.7)	3 (33.3)

n (incidence [%])

50) Simcyp version 19 was used for physiologically based pharmacokinetic model analysis.

PMDA asked the applicant to explain the need for dose adjustment in CYP2D6 PMs receiving concomitant CYP3A inhibitors or patients without factors associated with increased exposure concomitantly receiving both CYP2D6 and CYP3A inhibitors.

The applicant's explanation:

- Using a physiologically based pharmacokinetic model,[50)] the steady-state C_{max} and AUC of unchanged valbenazine and NBI-98782 in CYP2D6 PMs concomitantly receiving a strong or moderate CYP3A inhibitor or a population without factors associated with increased exposure[51)] concomitantly receiving both a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor were predicted. Table 44 shows the ratios of these predicted values to the predicted C_{max} and AUC following administration of valbenazine alone in a population without factors associated with increased exposure.

Table 44. Predicted unchanged valbenazine and NBI-98782 exposure ratios

Factors associated with increased exposure	Exposure ratios[a)]			
	Unchanged valbenazine		NBI-98782	
	C_{max}	AUC	C_{max}	AUC
CYP2D6 PM/Concomitant strong CYP3A inhibitor[b)]	1.25	2.09	2.69	5.80
CYP2D6 PM/Concomitant moderate CYP3A inhibitor[c)]	1.17	1.61	2.16	3.98
Concomitant strong CYP2D6 inhibitor[d)]/strong CYP3A inhibitor[b)]	1.25	2.12	2.56	5.28
Concomitant strong CYP2D6 inhibitor[d)]/moderate CYP3A inhibitor[c)]	1.19	1.65	2.12	3.71
Concomitant moderate CYP2D6 inhibitor[e)]/moderate CYP3A inhibitor[c)]	1.17	1.63	1.97	3.27

a) Ratios to predicted C_{max} and AUC following administration of valbenazine alone in a population without factors associated with increased exposure
b) Ketoconazole, c) Fluconazole, d) Paroxetine, e) Mirabegron

- The predicted steady-state C_{max} and AUC of unchanged valbenazine and NBI-98782 in CYP2D6 PMs concomitantly receiving a strong CYP3A inhibitor were compared with those following administration of valbenazine alone in a population without factors associated with increased exposure.[51)] There were 1.25- and 2.09-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and 2.69- and 5.80-fold increases in the C_{max} and AUC of NBI-98782, respectively (Table 44). The predicted steady-state C_{max} and AUC of unchanged valbenazine and NBI-98782 in a population without factors associated with increased exposure concomitantly receiving both a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor were compared with those following administration of valbenazine alone in a population without factors associated with increased exposure. There were approximately 1.2- to 1.3-fold and approximately 1.6- to 2.1-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and approximately 2.0- to 2.6-fold and approximately 3.3- to 5.3-fold increases in the C_{max} and AUC of NBI-98782, respectively (Table 44). Based on the results of exposure-safety analyses of the data from Japanese Study J02 [see Section 6.R.4.1], the risks anticipated in patients with exposures above those at 80 mg of valbenazine in patients without factors associated with increased exposure are somnolence-related adverse events, parkinsonism-related adverse events, and akathisia-related adverse events. Safety can be ensured, provided that patients are closely monitored for the possible occurrence of these events, and that if abnormalities are observed, appropriate measures, e.g., treatment discontinuation, will be taken. Thus, valbenazine may be used in patients with factors associated with increased exposure, provided that the package insert advises that valbenazine 40 mg should be administered, and the dose should not be increased

51) Taking account of CYP2D6 phenotype frequencies in the generation population, a virtual population consisting of 86.5% EMs, 8.2% PMs, and 5.3% UMs

to 80 mg. The package insert will advise that patients with factors associated with increased exposure should be closely monitored for the possible occurrence of adverse drug reactions during the early phase of treatment.

- If patients are unable to tolerate the 40 mg dose of valbenazine, there will be no option for dose reduction. Thus, the 20-mg formulation of valbenazine is currently under development in Japan.

6.R.4.4 Use in patients with hepatic impairment

The applicant's explanation about the need for dose adjustment and a precaution for patients with hepatic impairment:

- In a pharmacokinetic study in subjects with hepatic impairment (Reference data CTD 5.3.3.3-2, Study 1303), the C_{max} and AUC of unchanged valbenazine and NBI-98782 following a single oral dose of valbenazine 50 mg increased with increasing severity of hepatic impairment. In subjects with mild, moderate, or severe hepatic impairment compared with subjects with normal hepatic function, the C_{max} of unchanged valbenazine increased by 1.4-, 2.0-, and 2.5-fold, respectively, the AUC of unchanged valbenazine increased by 1.2-, 1.9-, and 2.4-fold, respectively, the C_{max} of its active metabolite NBI-98782 increased by 1.2-, 2.1-, and 2.2-fold, respectively, and the AUC of NBI-98782 increased by 1.2-, 2.8-, and 3.4-fold, respectively [see Section 6.2.4.1].
- With regard to adverse events by severity of hepatic impairment in Foreign Study 1303, the incidences of adverse events in subjects with normal hepatic function, subjects with mild hepatic impairment, subjects with moderate hepatic impairment, and subjects with severe hepatic impairment were all 33.3% (2 of 6 subjects), and no adverse events were reported by ≥2 subjects. There were no deaths, serious or severe adverse events, or adverse events leading to treatment discontinuation. Though these are the results from a small number of subjects, there was no trend towards differences in the incidences of adverse events and serious adverse events according to the severity of hepatic impairment.
- In a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02), the incidence of adverse events according to the presence or absence of abnormal liver function tests at baseline (defined as alanine aminotransferase [ALT], aspartate aminotransferase [AST], or gamma-glutamyltransferase [γ-GTP] exceeding the upper limit of normal [ULN]) is as follows: The incidences of adverse events among subjects with abnormal liver function tests were 57.1% (8 of 14 subjects) in the placebo group, 75.0% (9 of 12 subjects) in the valbenazine 40 mg group, and 68.8% (11 of 16 subjects) in the valbenazine 80 mg group, and the incidences of adverse events among subjects without abnormal liver function tests were 41.4% (29 of 70 subjects) in the placebo group, 61.6% (45 of 73 subjects) in the valbenazine 40 mg group, and 82.4% (56 of 68 subjects) in the valbenazine 80 mg group. There were no major differences according to the presence or absence of abnormal liver function tests at baseline.
- Based on the above, approximately 2- to 3-fold increases in the exposures of unchanged valbenazine and NBI-98782 may be observed in patients with moderate or severe hepatic impairment compared with patients with normal hepatic function, and the exposures of unchanged valbenazine and NBI-98782 following administration of valbenazine 40 mg in patients with severe hepatic impairment may be equivalent to or higher than the exposures following administration of valbenazine 80 mg in patients with normal hepatic function. However, the exposures of NBI-98782 following administration of valbenazine 40 mg in patients

with severe hepatic impairment are considered to be lower than the exposures following administration of valbenazine 80 mg in CYP2D6 PMs, and the pooled analyses of foreign clinical studies[49)] found no major safety concerns about administration of valbenazine 80 mg in CYP2D6 PMs, though only a limited number of subjects were assessed. Given these findings, administration of valbenazine 40 mg in patients with severe hepatic impairment will also raise no major safety concerns. Thus, there is no need to contraindicate valbenazine in patients with severe hepatic impairment, and valbenazine may be used in patients with moderate or severe hepatic impairment, provided that the package insert advises that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg. The package insert will advise that these patients should be closely monitored for the possible occurrence of adverse drug reactions during the early phase of treatment.

PMDA's view on the need for dose adjustment in patients with factors associated with increased exposure of valbenazine pertaining to Sections 6.R.4.1 to 6.R.4.4:

- Regarding efficacy, Japanese Study J02 showed a trend towards improvement in the AIMS total score, as assessed by central raters, in the valbenazine 80 mg group compared with the valbenazine 40 mg group (Table 48), whereas the exposure-safety analyses of the data from Japanese Study J02 showed a trend towards increasing incidences of somnolence-related adverse events, parkinsonism-related adverse events, and akathisia-related adverse events with increasing exposures of unchanged valbenazine and its active metabolite NBI-98782 (C_{max} and AUC) [see Section 6.R.4.1]. The maximum tolerated dose of valbenazine in patients with tardive dyskinesia is 100 mg/day. Thus, there is no problem with the applicant's idea (The package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients with factors associated with increased exposure).
- <u>The need for dose adjustment according to CYP2D6 genotype</u>
  CYP2D6 PMs seem to show approximately 1.8-fold and approximately 2.0-fold increases in the C_{max} and AUC of NBI-98782, respectively, following administration of valbenazine (Table 41). Plasma concentrations in CYP2D6 PMs are predicted to be highly variable from patient to patient. Thus, there is no problem with the applicant's idea (The package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients who are known to have genetically deficient CYP2D6 activity).
- Coadministration of valbenazine with a strong CYP2D6 inhibitor, paroxetine, in non-PMs, did not alter the exposures of unchanged valbenazine, but increased the C_{max} and AUC of NBI-98782 by approximately 1.4-fold and approximately 1.9-fold, respectively (Table 33). Thus, there is no problem with the applicant's idea (The package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients receiving concomitant CYP2D6 inhibitors (strong CYP2D6 inhibitors).
- Coadministration of valbenazine with a strong CYP3A inhibitor, ketoconazole, in non-PMs, increased the C_{max} and AUC of unchanged valbenazine by 1.5- and 2.1-fold, respectively, and the C_{max} and AUC of NBI-98782 by 1.6- and 2.1-fold, respectively (Table 33). Thus, there is no problem with the applicant's idea (The package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients receiving concomitant strong CYP3A inhibitors).

- In the case of concomitant use of valbenazine with moderate CYP3A inhibitors in non-PMs, 1.17- and 1.61-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and 1.37- and 1.77-fold increases in the C_{max} and AUC of NBI-98782, respectively, were predicted [see Section 6.R.4.3], and a >2-fold increase in exposures is not anticipated. Thus, the applicant explained that the dose of valbenazine may be increased to 80 mg in these patients. The maximum tolerated dose of valbenazine in patients with tardive dyskinesia is 100 mg/day. The exposure-safety analyses of the data from Japanese Study J02 showed a trend towards increasing incidences of somnolence-related adverse events, parkinsonism-related adverse events, and akathisia-related adverse events with increasing exposures of unchanged valbenazine and NBI-98782 [see Section 6.R.4.1]. Although the inhibition potency of moderate CYP3A inhibitors is not necessarily definitely established, it is preferable not to increase the dose to 80 mg from a safety point of view.
- In CYP2D6 PMs concomitantly receiving a strong or moderate CYP3A inhibitor, approximately 1.2- to 1.3-fold and approximately 1.6- to 2.1-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and approximately 2.2- to 2.7-fold and approximately 4.0- to 5.8-fold increases in the C_{max} and AUC of NBI-98782, respectively, were predicted (Table 44). In patients without factors associated with increased exposure concomitantly receiving both a CYP2D6 inhibitor (a strong or moderate CYP2D6 inhibitor) and a strong or moderate CYP3A inhibitor, approximately 1.2- to 1.3-fold and approximately 1.6- to 2.1-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and approximately 2.0- to 2.6-fold and approximately 3.3- to 5.3-fold increases in the C_{max} and AUC of NBI-98782, respectively, were predicted (Table 44). The maximum tolerated dose of valbenazine in patients with tardive dyskinesia is 100 mg/day. In these cases, even when the proposed commercial formulation in Japan, i.e., the 40-mg capsule is administered, the levels of exposure are predicted to well exceed those experienced in clinical studies. Thus, concomitant use of valbenazine with a strong or moderate CYP3A inhibitor in CYP2D6 PMs and concomitant use of valbenazine with both a CYP2D6 inhibitor (a strong or moderate CYP2D6 inhibitor) and a strong or moderate CYP3A inhibitor in patients without factors associated with increased exposure should be avoided wherever possible. However, since there is no drug approved for the treatment of tardive dyskinesia in Japan, coadministration of valbenazine with these drugs may become unavoidable. In this case, valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg. The patient's condition should be closely monitored during treatment with valbenazine, with adequate attention to the possible occurrence of adverse drug reactions. These precautionary statements should be included in the package insert. At present, the proposed commercial formulation in Japan is the 40-mg capsule only. If these patients are unable to tolerate the 40 mg dose of valbenazine, there will be no option for dose reduction. Given that there is no drug approved for the treatment of tardive dyskinesia in Japan, and that the applicant explained that the 20-mg formulation of valbenazine is currently under development, an investigation should be conducted so that the 20-mg formulation can be administered to these patients.
- In patients with moderate or severe hepatic impairment compared with patients with normal hepatic function, the C_{max} of unchanged valbenazine increases by 2.0- and 2.5-fold, respectively, the AUC of unchanged valbenazine increases by 1.9- and 2.4-fold, respectively, the C_{max} of NBI-98782 increases by 2.1- and 2.2-fold, respectively, and the AUC of NBI-98782 increases by 2.8- and 3.4-fold, respectively (Table 31). The maximum tolerated dose of valbenazine in patients with tardive dyskinesia is 100 mg/day. Even when the proposed commercial formulation in Japan, i.e., the 40-mg capsule is administered to these patients, the

levels of exposure are predicted to well exceed those experienced in clinical studies. Thus, the package insert should advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients with moderate or severe hepatic impairment, and that the patient's condition should be closely monitored during treatment with valbenazine, with adequate attention to the possible occurrence of adverse drug reactions. An investigation should be conducted so that the 20-mg formulation can be administered to these patients as well.

- A final conclusion on the appropriateness of dose adjustment in patients with factors associated with increased exposure will be made, taking account of comments from the Expert Discussion.

6.R.5 QT/QTc prolongation effect

PMDA asked the applicant to explain the QT/QTc prolongation effect of valbenazine.

The applicant's explanation:

- In a safety pharmacology study, valbenazine and its active metabolite, NBI-98782, inhibited hERG current. The IC_{50} values for the inhibition of hERG channel current were approximately 1500-fold and approximately 790-fold the plasma concentration after multiple-dose administration at the MRHD of 80 mg, respectively [see Section 3.R.2]. QT prolongation was observed in a safety pharmacology study (the cardiovascular system) and repeated oral dose toxicity studies in dogs, but the changes were slight and transient [see Sections 3.R.2 and 5.2].
- In a clinical pharmacology study that evaluated the effect of valbenazine on the QT/QTc interval (CTD 5.3.4.1-1, Study 1401), the upper bound of the 90% confidence interval for ΔΔQTcF was above 10 msec at 8 and 12 hours post-dose in the valbenazine 160 mg group [see Section 6.2.6.1].
- A pooled concentration-QT analysis of data from 3 phase I studies in non-Japanese healthy adult subjects (Foreign Study 1401 in which a single dose of valbenazine 160 mg was administered under fasting conditions, Foreign Study 1301 in which a single dose of valbenazine 150 or 300 mg was administered under fed conditions [CTD 5.3.4.1-2], Foreign Study 0901 in which multiple doses of valbenazine 75-100 mg were administered under fasting conditions [CTD 5.3.4.1-3]) was performed. While unchanged valbenazine did not cause concentration-dependent increases in the QTc interval, NBI-98782 caused plasma concentration-dependent increases in the QTc interval. The mean change from baseline in the QTcF interval at the C_{max} of NBI-98782 at steady state following multiple dosing of valbenazine 80 mg in non-PMs was estimated to be 3.07 msec, and the mean change from baseline in the QTcF interval at the C_{max} of NBI-98782 at steady state following multiple dosing of valbenazine 80 mg in CYP2D6 PMs was estimated to be 8.59 msec (Table 45). The upper bound of the 95% confidence interval for the predicted ΔQTcF at the NBI-98782 C_{max} of >66 ng/mL was above 10 msec.

Table 45. Estimated change from baseline in QTcF following multiple dosing of valbenazine (ΔQTcF)

Dose (mg)	PM		Non-PM (UM, EM, or IM)	
	C_{max} (ng/mL)	ΔQTcF (msec)	C_{max} (ng/mL)	ΔQTcF (msec)
40	35.70	2.48	19.50	-0.37
80	70.41	8.59	39.01	3.07

Mean

- Then, in order to assess the risk of QT prolongation following administration of valbenazine in the Japanese population, ΔQTcF was predicted using the NBI-98782 C_{max} values at steady state following multiple dosing of valbenazine 40 or 80 mg in Japanese subjects in Japanese Study J01. The predicted ΔQTcF at the mean C_{max} of NBI-98782 at steady state (48.5 ng/mL) following administration of valbenazine 80 mg and the upper bound of the 95% confidence interval were 4.74 and 6.52 msec, respectively. Thus, as in the above case of using the C_{max} predicted from the PPK model developed with the non-Japanese data, the degree of QT prolongation is not clinically significant at the plasma concentrations of NBI-98782 expected with the human doses in the Japanese population.
- Table 46 shows the results of categorical analysis of QTcF and changes in QTcF for a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) and pooled foreign clinical studies.[52)]

Table 46. Categorical analysis of QTcF interval data for Japanese and foreign clinical studies

		Japanese Study J02					Pooled foreign clinical studies				
		Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
		Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N		84	85	84	126	123	178	110	112	200	230
Post-dose QTcF	> 450 msec	3 (3.6)	3 (3.5)	5 (6.0)	12 (9.5)	15 (12.2)	11 (6.2)	11 (10.0)	5 (4.5)	24 (12.0)	37 (16.1)
	> 480 msec	0	0	0	0	0	2 (1.1)	0	0	2 (1.0)	3 (1.3)
	> 500 msec	0	0	0	0	0	0	0	0	0	1 (0.4)
Change from baseline	> 30 msec	2 (2.4)	4 (4.7)	7 (8.3)	16 (12.7)	20 (16.3)	11 (6.2)	3 (2.7)	6 (5.4)	21 (10.5)	38 (16.5)
	> 60 msec	0	0	0	0	2 (1.6)	1 (0.6)	1 (0.9)	0	3 (1.5)	6 (2.6)

n (Proportion [%])

- During the double-blind phase of Japanese Study J02, no cardiovascular or prolonged QT interval-related adverse events[53)] were reported. During the long-term treatment phase of Japanese Study J02, the incidences of cardiovascular and prolonged QT interval-related adverse events were 3.2% (4 of 126 subjects) (death; long QT syndrome; loss of consciousness; and myocardial ischaemia [1 subject each]) in the valbenazine 40 mg group and 0.8% (1 of 123 subjects) (death [1 subject]) in the valbenazine 80 mg group. The events for which a causal relationship to study drug could not be ruled out were death and loss of consciousness in the valbenazine 40 mg group. In the case of death, the subject complained of palpitations, but the ECG etc. showed no abnormalities, and the cause of death was unknown. Also in the case of loss of consciousness, the ECG showed no clinically relevant changes. Thus, these events are not considered associated with QT prolongation.

52) Pooled data from foreign phase II studies (Reference data CTD 5.3.5.1-3, Study 1201; Reference data CTD 5.3.5.1-4, Study 1202) and foreign phase III studies (Reference data CTD 5.3.5.1-5, Study 1304; Reference data CTD 5.3.5.2-2, Study 1402) were used. Subjects treated with valbenazine 50 mg (28 subjects and 10 subjects) during the double-blind phases of Foreign Studies 1201 and 1202 and subjects treated with valbenazine 50 mg (46 subjects) during the long-term treatment phase of Foreign Study 1201 were counted as the valbenazine 40 mg group, and subjects treated with valbenazine 75 mg (33 subjects) during the double-blind phase of Foreign Study 1202 were counted as the valbenazine 80 mg group. In the pooled analysis of data during the long-term treatment phase, the interim data were used for Foreign Study 1402 (33 subjects who completed 48-week treatment). Subjects treated with valbenazine 25 mg (5 subjects) in Foreign Study 1202 and subjects treated with valbenazine 100 mg (27 subjects) in Foreign Study 1201 were not included.

53) Events in the MedDRA SMQ "torsade de pointes/QT prolongation (broad)" and events coded to PTs "cardiac failure," "chest pain," "myocardial infarction," "death," and "myocardial ischaemia"

- According to the pooled analyses of foreign clinical studies,[49)] the incidences of cardiovascular and prolonged QT interval-related adverse events during the double-blind phase were 0% (0 of 178 subjects) in the placebo group, 0% (0 of 110 subjects) in the valbenazine 40 mg group, and 0.9% (1 of 112 subjects) (sudden death [1 subject]) in the valbenazine 80 mg group. The incidences of cardiovascular and prolonged QT interval-related adverse events during the long-term treatment phase were 2.0% (4 of 197 subjects) (syncope [4 subjects]) in the valbenazine 40 mg group and 1.7% (4 of 230 subjects) (syncope [2 subjects]; electrocardiogram QT prolonged [1 subject]; sudden death [1 subject]) in the valbenazine 80 mg group. Sudden death in the valbenazine 80 mg group during the double-blind phase was the same event as sudden death in the valbenazine 80 mg group during the long-term treatment phase, and the subject had sinus bradycardia and right bundle branch block at baseline. However, the QTcF interval was stable throughout the study period, with no changes from baseline in the ECG, and its causal relationship to study drug was denied. Thus, the event is not considered associated with QT prolongation.
- Based on the above, the Japanese and foreign clinical studies showed no clear relationship between valbenazine and cardiovascular and prolonged QT interval-related adverse events. However, since the pooled concentration-QT analysis suggested that NBI-98782 causes plasma concentration-dependent increases in the QT interval, an increased plasma concentration of NBI-98782 is considered associated with increased risk of QT prolongation in patients who are known to have genetically deficient CYP2D6 activity, patients concomitantly receiving a CYP2D6 inhibitor or a strong CYP3A inhibitor, patients with moderate or severe hepatic impairment, etc. Thus, the package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in these patients, and that the patients should be closely monitored for the possible occurrence of adverse drug reactions.
- As to concomitant use of valbenazine with drugs that prolong the QT interval, although there were no clear differences in the proportion of subjects receiving concomitant drugs that prolong QT interval between subjects with and without adverse events in Japanese Study J02, the possibility that factors associated with increased exposure together with these drugs increase the risk of QT prolongation cannot be ruled out. Thus, the package insert will advise that as coadministration with these drugs may cause an increase in the QT interval, patients should be monitored appropriately, paying attention to the possible occurrence of adverse drug reactions. In addition, the package insert will advise that valbenazine may cause an increase in the QT interval also in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval, and that the patient's condition should be closely monitored by, e.g., regular ECG monitoring prior to and during treatment with valbenazine.
- Following administration of valbenazine in CYP2D6 PMs concomitantly receiving a strong CYP3A inhibitor, a 2.69-fold increase in the C_{max} of NBI-98782 was predicted (Table 44), and the predicted ΔQTc and the upper bound of the 95% confidence interval were 9.9 and 12.3 msec, respectively. In patients without factors associated with increased exposure concomitantly receiving both a strong CYP2D6 inhibitor and a strong CYP3A inhibitor, a 2.56-fold increase in the C_{max} of NBI-98782 was predicted (Table 44), and the predicted ΔQTcF and the upper bound of the 95% confidence interval were 9.3 and 11.5 msec, respectively. Thus, the package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in CYP2D6 PMs concomitantly receiving a strong CYP3A inhibitor and patients without factors associated with increased exposure concomitantly receiving both a strong

CYP2D6 inhibitor and a strong CYP3A inhibitor, and that the patient's condition should be closely monitored by, e.g., regular ECG monitoring prior to and during treatment with valbenazine.

PMDA's view:

- In a clinical pharmacology study that evaluated the effect of valbenazine on the QT/QTc interval (Foreign Study 1401), the upper bound of the 90% confidence interval for ΔΔQTcF was above 10 msec at 8 and 12 hours post-dose in the valbenazine 160 mg group [see Section 6.2.6.1]. According to a pooled concentration-QT analysis, NBI-98782 caused plasma concentration-dependent increases in the QT/QTc interval, and the upper bound of the 95% confidence interval for the predicted ΔQTcF at the NBI-98782 C_{max} of >66 ng/mL was above 10 msec. As the predicted C_{max} following multiple dosing of valbenazine 40 mg in the Japanese population is 29.0 ng/mL, a ≥2.3-fold increase in the the C_{max} of NBI-98782 is considered to increase the risk of QT/QTc prolongation. Thus, although the degree of QT prolongation is not clinically significant at the plasma concentrations of NBI-98782 expected with the human doses in patients without factors associated with increased exposure of NBI-98782, the risk of QT prolongation is increased in patients with factors associated with increased exposure of NBI-98782.
- With respect to patients with factors associated with increased exposure of NBI-98782 compared with patients without factors associated with increased exposure, the C_{max} of NBI-98782 following multiple dosing of valbenazine 40 mg may increase by ≥2-fold in CYP2D6 PMs concomitantly receiving a strong or moderate CYP3A inhibitor, non-PMs concomitantly receiving both a CYP2D6 inhibitor (a strong or moderate CYP2D6 inhibitor) and a strong or moderate CYP3A inhibitor, and patients with moderate or severe hepatic impairment [see Section 6.R.4], and the possibility that the risk of QT prolongation is increased cannot be ruled out. Thus, the package insert should advise that the dose of valbenazine should not be increased to 80 mg in these patients, and that the patient's condition should be closely monitored by, e.g., regular ECG monitoring prior to and during treatment with valbenazine.
- There is no problem with the applicant's explanation ("The package insert will advise that valbenazine may cause an increase in the QT interval in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval, and that the patient's condition should be closely monitored by, e.g., regular ECG monitoring prior to and during treatment with valbenazine. The package insert will include a precautionary statement about coadministration with drugs that prolong the QT interval").
- A final conclusion on the appropriateness of the above conclusions will be made, taking account of comments from the Expert Discussion.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the efficacy and safety evaluation data, in the form of the results from clinical studies presented in Table 47. The applicant submitted the results from foreign clinical studies as reference data. The main study results are described below. Unless otherwise specified, doses are expressed in terms of valbenazine.

Table 47. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID CTD	Phase	Subjects	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Japan	Japanese Study J01 5.3.3.1-1	I	Healthy adult male subjects	Single-dose cohort: 33 Multiple-dose cohort: 26	Single-dose cohort: A single oral dose of placebo or valbenazine 40, 80, or 160 mg Multiple-dose cohort: Placebo or valbenazine 40 or 80 mg orally once daily for 8 days	Safety PK
	Japan	Japanese Study J02 5.3.5.1-1	II/III	Patients with tardive dyskinesia	256	Double-blind period: Placebo or valbenazine 40 or 80 mg orally once daily for 6 weeks Extension period: Valbenazine 40 or 80 mg orally once daily for 42 weeks	Efficacy Safety

7.1 Phase I study

7.1.1 Japanese phase I study (CTD 5.3.3.1-1, Study J01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A clinical study was conducted to evaluate the safety and pharmacokinetics of valbenazine in Japanese healthy adult male subjects (target sample size, 56-64 subjects). The study included single-dose and multiple-dose cohorts [for pharmacokinetics, see Section 6.2.2.1]. Subjects who were CYP2D6 EMs or IMs were enrolled in the placebo-controlled, randomized, double-blind cohort, i.e., the single-dose cohort (Cohorts S1, S2, and S3) or the multiple-dose cohort (Cohorts M1 and M2). Subjects who were CYP2D6 UMs or PMs were enrolled in the open-label cohort, i.e., the single-dose cohort (Cohort A1). Study drug administration was to begin in Cohort S1, and based on the decision of the investigator, medical expert, and sponsor,[54)] the study was to proceed to Cohorts S2, M1, and A1. Then, based their decision,[55)] the study was to proceed to Cohorts S3 and M2.

(1) Single-dose cohort

A single oral dose of valbenazine 40 mg (Cohort S1), 80 mg (Cohort S2), or 160 mg (Cohort S3) or placebo was to be administered. In Cohort A1, a single oral dose of valbenazine 40 mg was to be administered.

All of 33 subjects who received study drug (6 in the placebo group, 11 in the valbenazine 40 mg group, 8 in the valbenazine 80 mg group, 8 in the valbenazine 160 mg group) were included in the safety population, and there were no subject discontinuations.

The incidences of adverse events (including laboratory test abnormalities) were 16.7% (1 of 6 subjects) in the placebo group, 0% (0 of 11 subjects) in the valbenazine 40 mg group, 12.5% (1 of 8 subjects) in the valbenazine 80 mg group, and 100.0% (8 of 8 subjects) in the valbenazine 160 mg group. There were no serious adverse events including deaths or adverse events leading to study drug discontinuation. The incidences of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be ruled out were 16.7% (1 of 6 subjects) in the placebo group, 0% (0 of 11 subjects) in the valbenazine 40 mg group, 12.5% (1 of 8 subjects) in the valbenazine 80 mg group, and 100.0% (8 of 8 subjects) in the valbenazine 160 mg group, and the main events were somnolence (8 subjects) (8 subjects in the valbenazine 160 mg group).

54) The decision to proceed was based on safety data on Days 1-5 and plasma drug concentration data on Day 1 from the previous cohort.
55) The decision to proceed was based on safety data on Days 1-5 and plasma drug concentration data on Day 1 from Cohort S2.

There were no clinically relevant changes in vital signs or ECG.

(2) Multiple-dose cohort
Valbenazine 40 mg (Cohort M1) or 80 mg (Cohort M2) or placebo was to be administered orally once daily for 8 days.

All of 26 subjects who received study drug (6 in the placebo group, 10 in the valbenazine 40 mg group, 10 in the valbenazine 80 mg group) were included in the safety population. While there were no discontinuations in the valbenazine 40 mg group, 5 discontinuations occurred in the valbenazine 80 mg group (discontinuations due to adverse events specified in the protocol [2 subjects], other adverse events [2 subjects], and subject request [1 subject]). Since 3 subjects in the valbenazine 80 mg group had depression, in accordance with the protocol, the decision to terminate Cohort M2 was made after discussion among the sponsor, medical expert, and investigator, and 8 subjects on study treatment (3 in the placebo group, 5 in the valbenazine 80 mg group) discontinued study drug.

The incidences of adverse events (including laboratory test abnormalities) were 33.3% (2 of 6 subjects) in the placebo group, 20.0% (2 of 10 subjects) in the valbenazine 40 mg group, and 80.0% (8 of 10 subjects) in the valbenazine 80 mg group. No serious adverse events including deaths were reported. No adverse events leading to treatment discontinuation were reported in the placebo and valbenazine 40 mg groups. Adverse events leading to treatment discontinuation occurred in 40.0% (4 of 10) of subjects in the valbenazine 80 mg group (depression [2 subjects]; and somnolence and malaise; and nausea and vomiting [1 subject each]). The incidences of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be ruled out were 33.3% (2 of 6 subjects) in the placebo group, 20.0% (2 of 10 subjects) in the valbenazine 40 mg group, and 80.0% (8 of 10 subjects) in the valbenazine 80 mg group, and the main events were somnolence (6 subjects) (1 subject in the placebo group, 0 subjects in the valbenazine 40 mg group, 5 subjects in the valbenazine 80 mg group), insomnia (5 subjects) (0 subjects, 0 subjects, 5 subjects), libido decreased (4 subjects) (0 subjects, 0 subjects, 4 subjects), vision blurred (4 subjects) (0 subjects, 0 subjects, 4 subjects), conjunctival hyperaemia (3 subjects) (0 subjects, 0 subjects, 3 subjects), depression (3 subjects) (0 subjects, 0 subjects, 3 subjects), disturbance in attention (3 subjects) (0 subjects, 1 subject, 2 subjects), diarrhoea (3 subjects) (2 subjects, 0 subjects, 1 subject), malaise (3 subjects) (1 subject, 0 subjects, 2 subjects), and nausea (2 subjects) (0 subjects, 0 subjects, 2 subjects).

There were no clinically relevant changes in vital signs or ECG.

7.2 Phase II/III study

7.2.1 Japanese phase II/III study (CTD 5.3.5.1-1, Study J02 [June 2017 to September 2020])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of valbenazine in patients with tardive dyskinesia and underlying schizophrenia, schizoaffective

disorder, bipolar disorder, or depressive disorder[56] (target sample size, 240 subjects[57]: 80 each in the placebo, valbenazine 40 mg, and valbenazine 80 mg groups[58]) [for pharmacokinetics, see Section 6.2.3.1].

The study consisted of a double-blind period (6 weeks), an extension period (42 weeks), and a follow-up period (4 weeks).

(1) Double-blind period

During the double-blind period, placebo or valbenazine 40 or 80 mg was to be administered orally once daily.[59] In the valbenazine 80 mg group, dosing was to be started at 40 mg once daily and increased to 80 mg once daily after the first week. The duration of treatment was 6 weeks.

Among 256 randomized subjects (85 in the placebo group, 86 in the valbenazine 40 mg group, 85 in the valbenazine 80 mg group), 253 subjects (84 in the placebo group, 85 in the valbenazine 40 mg group, 84 in the valbenazine 80 mg group) after excluding 3 subjects who did not receive study drug (1 in the placebo group, 1 in the valbenazine 40 mg group, 1 in the valbenazine 80 mg group) were included in the safety population. After excluding 4 subjects who did not have any post-baseline AIMS assessments (AIMS total score)[60] during the double-blind period (0 in the placebo group, 2 in the valbenazine 40 mg group, 2 in the valbenazine 80 mg group), 249 subjects (84 in the placebo group, 83 in the valbenazine 40 mg group, 82 in the valbenazine 80 mg group) were included in the efficacy population, i.e., the intent-to-treat (ITT) population. Among the randomized subjects, 45 discontinued (5 in the placebo group, 15 in the valbenazine 40 mg group, 25 in the valbenazine 80 mg group), and the main reasons for discontinuations were adverse events (3 in the placebo group, 5 in the valbenazine 40 mg group, 14 in the valbenazine 80 mg group) and subject's request (2 in the placebo group, 8 in the valbenazine 40 mg group, 10 in the valbenazine 80 mg group).

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56) The inclusion and exclusion criteria are shown below.
Key inclusion criteria: (1) 20-85 years of age at the time of giving consent, (2) a diagnosis of tardive dyskinesia according to the DSM-5 criteria prior to giving consent, and (3) moderate or severe tardive dyskinesia, as indicated by a score on AIMS item 8 (the severity of abnormal involuntary movements) of either 3 or 4 based on assessment of screening videos by central reviewers.
Key exclusion criteria: (1) comorbid abnormal involuntary movements (e.g., dystonia, akathisia, parkinsonism) more prominent than tardive dyskinesia based on assessment of screening videos by central AIMS reviewers, which precluded appropriate assessment of tardive dyskinesia, and (2) a score ≥3 on 2 or more items of the SAS at baseline, excluding items 8 (glabella tap) and 10 (salivation).
Additional key exclusion criteria for subjects with schizophrenia or schizoaffective disorder: (1) CDSS total score of ≥10 at baseline, (2) PANSS total score of ≥70 at baseline
Additional key exclusion criteria for subjects with bipolar disorder or depressive disorder: (1) hospitalized for bipolar disorder or major depressive disorder within 6 months prior to initial randomization, (2) mood episodes (manic symptom, depressive symptom) within 3 months prior to initial randomization, (3) a history of rapid cycling (>4 episodes per year) or ultra-rapid cycling (>4 episodes per month), (4) MADRS total score of >13 at baseline, and (5) YMRS total score of >10 at baseline

57) Based on the results from a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304), the differences between the valbenazine 40 mg or 80 mg and placebo groups were estimated at −1.8 and −3.1, respectively, for the change from baseline in AIMS total score at Week 6, with a standard deviation of 3.8. It was estimated that 216 subjects (72 per group) would be needed to detect statistically significant differences between valbenazine (40 and 80 mg) and placebo at 0.8 power using a t-test with two-sided significance level of 0.05. Assuming a dropout rate of 10% during the double-blind period, a target sample size of 240 subjects (80 per group) was chosen.

58) Randomization was stratified by underlying disease category (schizophrenia or schizoaffective disorder, bipolar disorder or depressive disorder), and subjects were randomized to the placebo, valbenazine 40 mg, or valbenazine 80 mg group.

59) Study drug was to be administered without regard to food, and as a rule, study drug was to be administered during the same period of time every morning throughout the treatment period. However, if considered necessary by the investigator for the management of adverse events etc., subjects were allowed to change the time period for taking their study drug once.

60) The sum of scores from AIMS items 1-7 (muscles of facial expression, lips and perioral area, jaw, tongue, upper extremities, lower extremities, trunk). The severity of dyskinesia in each body region was rated on a 5-point scale (0: None – No dyskinesia, 1: Minimal or slight dyskinesia – Low amplitude, present during some but not most of the exam, 2: Mild dyskinesia – Low amplitude and present during most of the exam (or moderate amplitude and present during some of exam), 3: Moderate dyskinesia – Moderate amplitude and present during most of exam, 4: Severe dyskinesia – Maximal amplitude and present during most of exam).

Table 48 shows the primary endpoint of the change from baseline in the AIMS total score as assessed by central raters[61] at Week 6 in the ITT population, and statistically significant differences between valbenazine 40 or 80 mg and placebo were detected.

Table 48. AIMS total score as assessed by central raters at Week 6 (ITT population, MMRM)

Treatment group	Baseline	Week 6	Change from baseline[a) b)]	Comparison between valbenazine and placebo[b)]	
				Placebo-subtracted difference [95% CI]	*P*-value[c)]
Placebo	8.0 ± 4.2 (84)	7.9 ± 4.2 (80)	-0.1 ± 0.3		
Valbenazine 40 mg	7.7 ± 3.8 (83)	5.9 ± 3.7 (68)	-2.3 ± 0.3	-2.2 [-3.0, -1.3]	<0.001
Valbenazine 80 mg	7.4 ± 4.3 (82)	3.9 ± 4.0 (57)	-3.7 ± 0.3	-3.6 [-4.5, -2.6]	<0.001

Mean ± SD (N)
a) Least-squares mean ± SE
b) MMRM model that included treatment group, underlying disease category, and study visit (Week 2, 4, or 6) as fixed effects, baseline AIMS total score as a covariate, and treatment-by-week and baseline score-by-week interaction terms. An unstructured variance-covariance matrix for scores within subjects was used.
c) Two-sided significance level of 5%. A fixed-sequence testing procedure was used to control the overall type I error rate for two valbenazine treatment group comparisons to placebo. If the comparison of valbenazine 80 mg vs. placebo was significant, the comparison of valbenazine 40 mg vs. placebo was to be made.

The incidences of adverse events (including laboratory test abnormalities) were 44.0% (37 of 84 subjects) in the placebo group, 63.5% (54 of 85 subjects) in the valbenazine 40 mg group, and 79.8% (67 of 84 subjects) in the valbenazine 80 mg group. No deaths were reported. The incidences of serious adverse events excluding deaths were 1.2% (1 of 84 subjects) (suicide attempt [1 subject]) in the placebo group, 4.7% (4 of 85 subjects) (panic attack; schizophrenia;, suicidal ideation; and head injury [1 subject each]) in the valbenazine 40 mg group, and 1.2% (1 of 84 subjects) (dehydration [1 subject]) in the valbenazine 80 mg group, and a causal relationship to study drug was denied for all those events.

The incidences of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be ruled out were 13.1% (11 of 84 subjects) in the placebo group, 32.9% (28 of 85 subjects) in the valbenazine 40 mg group, and 54.8% (46 of 84 subjects) in the valbenazine 80 mg group. The main events were somnolence (1 subject in the placebo group, 9 subjects in the valbenazine 40 mg group, 20 subjects in the valbenazine 80 mg group), salivary hypersecretion (1 subject, 2 subjects, 8 subjects), akathisia (1 subject, 4 subjects, 4 subjects), malaise (0 subjects, 5 subjects, 3 subjects), tremor (0 subjects, 0 subjects, 5 subjects), nausea (1 subject, 0 subjects, 3 subjects), decreased appetite (0 subjects, 1 subject, 2 subjects), thirst (1 subject, 2 subjects, 0 subjects), extrapyramidal disorder (0 subjects, 0 subjects, 2 subjects), schizophrenia (0 subjects, 2 subjects, 0 subjects), constipation (0 subjects, 2 subjects, 0 subjects), and fatigue (0 subjects, 0 subjects, 2 subjects).

There were no clinically relevant changes in vital signs (blood pressure, pulse rate, body temperature).

As to the ECGs, the proportions of subjects with a change from baseline in QTcF of >30 msec were 2.4% (2 of 84 subjects) in the placebo group, 4.7% (4 of 85 subjects) in the valbenazine 40 mg group, and 8.3% (7 of 84 subjects) in the valbenazine 80 mg group, but no subjects had a change from baseline in QTcF of > 60 msec.

61) A pair of physicians familiar with the diagnosis and assessment of tardive dyskinesia who were blinded to treatment and study visit sequence were to provide consensus scores of 0-4 for AIMS items 1-7.

The proportions of subjects with a QTcF >450 msec were 3.6% (3 of 84 subjects) in the placebo group, 3.5% (3 of 85 subjects) in the valbenazine 40 mg group, and 6.0% (5 of 84 subjects) in the valbenazine 80 mg group, but no subjects had a QTcF >480 msec.

(2) Extension period

Subjects who were initially randomized to receive placebo during the double-blind period were re-randomized in a 1:1 ratio to receive either valbenazine 40 or 80 mg in a blinded manner. Subjects who were initially randomized to receive valbenazine during the double-blind period were to continue their current dose in a blinded manner.

Valbenazine 40 or 80 mg was to be administered orally once daily.[59)] If serious adverse events, significant adverse events, parkinsonian events, or clinically significant laboratory abnormalities etc. occurred during the extension period and the investigator considered that a dose reduction was needed to ensure the safety of subjects, the doses could be reduced, but a dose increase after a dose reduction was not allowed.[62)] In subjects receiving placebo during the double-blind period who were re-randomized to valbenazine 80 mg during the extension period, dosing was to be started at 40 mg once daily and increased to 80 mg once daily after the first week. The extension period was 42 weeks, and a 4-week follow-up period was included for post-treatment assessments.

Among 211 subjects who completed the double-blind treatment period and entered the extension period (112 in the valbenazine 40 mg group, 99 in the valbenazine 80 mg group), 203 subjects (108 in the valbenazine 40 mg group, 95 in the valbenazine 80 mg group) received study drug during the extension period. Among the subjects who entered the extension period, 94 subjects (45 in the valbenazine 40 mg group, 49 in the valbenazine 80 mg group) discontinued. The reasons for discontinuations were subject's request (24 in the valbenazine 40 mg group, 26 in the valbenazine 80 mg group), adverse events (15 in the valbenazine 40 mg group, 18 in the valbenazine 80 mg group), death (3 in the valbenazine 40 mg group, 4 in the valbenazine 80 mg group), and physician's decision (3 in the valbenazine 40 mg group, 1 in the valbenazine 80 mg group).

Table 49 shows the efficacy endpoint of the time course of change from double-blind baseline in the AIMS total score as assessed by central raters.

Table 49. Time course of AIMS total score as assessed by central raters (ITT population)

	Valbenazine 40 mg		Valbenazine 80 mg	
	AIMS total score	Change from baseline	AIMS total score	Change from baseline
Double-blind baseline[a)]	7.9 ± 4.1 (125)		7.6 ± 4.2 (124)	
Week 16	5.3 ± 4.0 (93)	-3.0 ± 3.8	3.3 ± 3.2 (72)	-5.2 ± 4.3
Week 32	4.9 ± 4.1 (80)	-3.5 ± 3.9	3.4 ± 3.5 (57)	-5.6 ± 4.3
Week 48 (at the end of study treatment)	5.0 ± 4.2 (64)	-3.7 ± 4.2	3.3 ± 3.3 (49)	-5.7 ± 4.6
Week 52 (at the end of follow-up period)	8.1 ± 4.3 (65)	-0.6 ± 3.6	8.1 ± 5.0 (47)	-0.5 ± 4.1

Mean ± SD (N)

a) Double-blind baseline was used for both subjects in the placebo and valbenazine groups during the double-blind period.

62) The dose of study drug was to be reduced from 2 capsules to 1 capsule. Subjects were allowed 1 dose reduction, and a dose increase from 1 capsule to 2 capsules was not allowed. In the valbenazine 40 mg group, 1 valbenazine 40-mg capsule and 1 placebo capsule were administered, and if a dose reduction of study drug was considered necessary, the valbenazine 40-mg capsule only was continued in a blinded manner.

During the valbenazine treatment period including the double-blind and extension periods,[63] the incidences of adverse events (including laboratory test abnormalities) were 89.7% (113 of 126 subjects) in the valbenazine 40 mg group and 94.3% (116 of 123 subjects) in the valbenazine 80 mg group. There were 7 deaths[64] during the extension period (3 subjects in the valbenazine 40 mg group [myocardial ischaemia; death; and marasmus [1 subject each], 4 subjects in the valbenazine 80 mg group [pneumonia; respiratory failure; death; and pneumonia aspiration [1 subject each]), and a causal relationship to study drug was denied for all cases except for 1 case of death in the valbenazine 40 mg group. The incidences of serious adverse events excluding deaths were 11.9% (15 of 126 subjects) in the valbenazine 40 mg group and 10.6% (13 of 123 subjects) in the valbenazine 80 mg group. Table 50 shows new serious adverse events excluding deaths occurring in the extension period.

Table 50. Serious adverse events excluding deaths occurring in the extension period

Valbenazine 40 mg group 9.5% (12 of 126 subjects)	schizophrenia (3 subjects); heat illness; fatigue; suicide attempt and intentional overdose; spinal compression fracture; osteoarthritis; schizophrenia* and hypokalaemia*; deep vein thrombosis and pulmonary embolism; extrapyramidal disorder; and cerebral concussion, schizophrenia, and road traffic accident (1 subject each)
Valbenazine 80 mg group 9.8% (12 of 123 subjects)	depression*; schizophrenia*; movement disorder* and disturbance in attention*; femoral neck fracture; blood CPK increased; rash*; stupor*; rhabdomyolysis*; somnolence*; ankle fracture; bacterial pneumonia; and depression (1 subject each)

* Events for which a causal relationship to study drug could not be ruled out

During the valbenazine treatment period including the double-blind and extension periods, the incidences of adverse events (including laboratory test abnormalities) for which a causal relationship to study drug could not be ruled out were 50.8% (64 of 126 subjects) in the valbenazine 40 mg group and 74.8% (92 of 123 subjects) in the valbenazine 80 mg group. The main events were somnolence (42 subjects) (16 subjects in the valbenazine 40 mg group, 26 subjects in the valbenazine 80 mg group), salivary hypersecretion (24 subjects) (6 subjects, 18 subjects), tremor (18 subjects) (4 subjects, 14 subjects), malaise (18 subjects) (9 subjects, 9 subjects), akathisia (17 subjects) (7 subjects, 10 subjects), dizziness (7 subjects) (3 subjects, 4 subjects), parkinsonism (6 subjects) (4 subjects, 2 subjects), depression (6 subjects) (3 subjects, 3 subjects), and weight increased (6 subjects) (3 subjects, 3 subjects).

During the valbenazine treatment period including the double-blind and extension periods, there were no clinically relevant changes in vital signs (blood pressure, pulse rate, body temperature). As to the ECGs, the proportions of subjects with a change from baseline in QTcF of >30 msec were 12.7% (16 of 126 subjects) in the valbenazine 40 mg group and 16.3% (20 of 123 subjects) in the valbenazine 80 mg group, and the proportions of subjects with a change from baseline in QTcF of >60 msec were 0% (0 of 126 subjects) in the valbenazine 40 mg group and 1.6% (2 of 123 subjects) in the valbenazine 80 mg group. The proportions of subjects with a QTcF >450 msec were 9.5% (12 of 126 subjects) in the valbenazine 40 mg group and 12.2% (15 of 123 subjects) in the valbenazine 80 mg group, but no subjects had a QTcF >480 msec.

63) Subjects who received at least 1 dose of valbenazine during the double-blind or extension period were included. Subjects initially randomized to placebo during the double-blind period who discontinued before entering the extension period and did not receive valbenazine were excluded. Subjects who were initially randomized to receive placebo during the double-blind period and received valbenazine during the extension period were included as safety data during the valbenazine treatment period.

64) One death occurred (valbenazine 80 mg group: acute hepatic failure) during the follow-up period, but its causal relationship to study drug was denied.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of valbenazine.

The applicant's explanation:

- Tardive dyskinesia is a neurologic disorder characterized by involuntary movements of the orofacial region (the tongue, lips, jaw, face), extremities, and torso. It is defined by the DSM-5 as "involuntary athetoid or choreiform movements (lasting at least a few weeks) developing in association with the use of a neuroleptic medication for at least a few months." Initial symptoms of tardive dyskinesia are generally mild involuntary movements, which rarely need treatment due to the lack of awareness of tardive dyskinesia (*Eur Psychiatry*. 2011; 26: 293-6). However, as the severity of physical impairment increases, speech disturbance, joint inflammation, gait disturbance, falls, etc. may occur (*Psychosomatics*. 1985; 26: 305-13, *CNS Spectrums*. 2018; 23: 370-7). The risk factors for tardive dyskinesia include older age, schizophrenia, and cognitive impairment, in addition to the duration of use and dosage of causative agents (*Can J Psychiatry*. 2005; 50: 541-7).
- In Japan, no drugs have been approved for the treatment of tardive dyskinesia.
  The Japanese Society of Neuropsychopharmacology's Guideline for Pharmacological Therapy of Schizophrenia (Guideline for Pharmacological Therapy of Schizophrenia [in Japanese]. *Igakushoin*; 2017) provides the following recommendations: In the event of extrapyramidal adverse reactions including tardive dyskinesia, as in the case of other drug-induced adverse reactions, as a general rule, the dose of the causative drug should be reduced, and if those adverse reactions are serious, the causative drug should be withdrawn. However, since only a very small study in 8 patients suggested that antipsychotic dose reduction is effective, the causative drug should not be reduced or withdrawn unfoundedly.
  In psychotic patients who require stable maintenance antipsychotic treatment, dose reduction or discontinuation of the causative drug for the management of tardive dyskinesia has been reported to lead to increased risks of psychotic exacerbation and relapse even through it might improve tardive dyskinesia (*BMC Psychiatry.* 2018; 18: 330-40).
- Outside Japan, valbenazine and deutetrabenazine[65)] were approved for the treatment of tardive dyskinesia in in 2017 in the US. The 2018 article (*J Neurol Sci.* 2018; 389: 67-75) published by the members for the development of the American Academy of Neurology guideline regarding management of tardive dyskinesia (*Neurology*. 2013; 81: 463-9) released in 2013 recommended valbenazine and deutetrabenazine as the first-line drugs (Level A) (strongest recommendation, established as effective). The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, third edition[66)] released in 2020 recommends that patients with moderate to severe tardive dyskinesia should be treated with a VMAT2 inhibitor, and advises that treatment with a VMAT2 inhibitor can also be considered for patients with mild tardive dyskinesia on the basis of such factors as patient preference or effect on

65) Deutetrabenazine contains deuterium, which replaces hydrogen at 6 positions within the tetrabenazine molecule. Deutetrabenazine is unapproved in Japan.
66) https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841 (as of December 24, 2021)

psychosocial functioning. In Canada, the UK, etc., tetrabenazine has been approved for the treatment of tardive dyskinesia, but valbenazine is unapproved.

- Since a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) has demonstrated the efficacy and safety of valbenazine in patients with tardive dyskinesia, valbenazine will offer a new treatment option for patients with tardive dyskinesia.

PMDA's view:

No drugs have been approved for the treatment of tardive dyskinesia in Japan. Valbenazine has efficacy in patients with tardive dyskinesia [see Section 7.R.2] and acceptable safety [see Section 7.R.3]. Thus, valbenazine is clinically meaningful because it offers a new treatment option for patients with tardive dyskinesia.

7.R.2 Efficacy

7.R.2.1 Appropriateness of primary endpoint and efficacy assessment

PMDA asked the applicant to explain the appropriateness of the primary efficacy endpoint of the AIMS scored by central video raters for a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02).

The applicant's explanation:

- The AIMS is a rating scale to assess involuntary movements. It includes 12 items with 7 items rating involuntary movements in the muscles of facial expression, lips and perioral area, jaw, tongue, upper extremities, lower extremities, and trunk (items 1-7); 3 items of global judgment (items 8-10); and 2 items concerning problems with teeth and dentures (items 11 and 12). Each of items 1 to 10 is rated on a 5-point scale (0: None, 1: Minimal or slight, 2: Mild, 3: Moderate, 4: Severe).
- In a foreign phase II study of valbenazine (Reference data CTD 5.3.5.1-3, Study 1201[67]), 3 AIMS items of global judgment (items 8-10) were considered to reflect assessments of severity by body region (items 1-7) and excluded in order to avoid duplication of scores. Two AIMS items concerning teeth and dentures (items 11 and 12) were also excluded because these are items to eliminate the effect of dentures on the symptoms. Thus, in Foreign Study 1201, the AIMS total score (the sum of items 1-7) as assessed by an on-site, trained, certified rater was used as the primary endpoint.
- While the results of Foreign Study 1201 failed to show a statistically significant difference between placebo and valbenazine, post-hoc analyses using 1 central blinded video rater[68] showed a statistically significant difference in the AIMS total score of items 1-7 at Week 2 between the placebo and valbenazine 100 mg groups. The AIMS rating methodology in Foreign Study 1201 was reviewed by the Scientific Advisory Board,[69] which indicated that raters are vulnerable to sequence/expectancy bias, which might occur with clinical assessments over the course of a study, etc. Thus, the protocol for the ongoing foreign phase II study

67) Foreign Study 1201 was a placebo-controlled, parallel-group, double-blind study. The study consisted of a double-blind period (6 weeks), an open-label period (6 weeks), and a follow-up period (4 weeks) and evaluated the efficacy and safety of placebo or valbenazine 50 or 100 mg administered once daily for 2 weeks, the efficacy and safety of placebo or valbenazine 50 mg administered once daily for up to 6 weeks (double-blind period), and the safety of valbenazine 50 mg administered for up to 12 weeks (open-label period) in patients with schizophrenia or schizoaffective disorder and tardive dyskinesia.

68) The rater was blinded to treatment assignment only, not study visit sequence.

69) Scientific Advisory Board was comprised of 6 experts in the assessment of tardive dyskinesia.

(Reference data CTD 5.3.5.1-4, Study 1202[70]) was amended accordingly, and in the subsequent clinical studies, AIMS ratings were performed by using 2 neurologists specialized in movement disorders as central video raters who were blinded to study treatment and visit sequence.

- The results of Foreign Study 1202 showed a statistically significant difference in the change from baseline in the AIMS total score as assessed by central raters at Week 6 between the placebo and valbenazine groups. Thus, the change from baseline in the AIMS total score as assessed by central video raters at Week 6 was selected as the primary endpoint for a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304[71]). The results of the study showed a statistically significant difference in the primary endpoint between the placebo and valbenazine groups.
- Based on the above, in Japanese Study J02 as in Foreign Study 1304, the change from baseline in the AIMS total score as assessed by central video raters at Week 6 was selected as the primary endpoint. In Japanese Study J02, the AIMS scored by on-site, trained, certified investigators (sub-investigators) and the CGI-TD, which is a 7-point scale[72] that requires the investigator (the sub-investigator) to rate the clinical global impression of improvement from baseline in tardive dyskinesia symptoms, were also selected as secondary endpoints, so that the efficacy of valbenazine would be assessed from on-site ratings as well as central ratings. In Foreign Study 1304, on-site AIMS ratings were not performed.

PMDA asked the applicant to explain the results of the primary and secondary efficacy endpoints in Japanese Study J02 and then the clinical meaningfulness of the changes from baseline in the AIMS total score observed in Japanese Study J02.

The applicant's explanation:

- There were statistically significant differences in the primary endpoint of the change from baseline in the AIMS total score as assessed by central raters at Week 6 between the valbenazine 40 or 80 mg and placebo groups (Table 48).
- During the double-blind period of Japanese Study J02, more discontinuations due to adverse events etc. occurred and more subjects had missing post-baseline AIMS total scores in the valbenazine group than in the placebo group. In order to evaluate the influences of discontinuations and missing data on the efficacy assessment of valbenazine, post-hoc sensitivity analyses of the primary endpoint of the change from baseline in the AIMS total score as assessed by central raters at Week 6 were performed using different imputation methods to assess the impact of deviations from the missing at random assumption of the MMRM analysis. The tipping point sensitivity analysis indicated that the centrally rated AIMS total score difference for the 40 mg and 80 mg groups vs. placebo comparison at Week 6 remained statistically significant up until the scores for the valbenazine 40 and 80 mg group subjects with missing Week 6 data were worsened by 120% (P = 0.0418) and 150% (P = 0.0334), respectively. Table 51 shows the results of

70) Foreign Study 1202 was a placebo-controlled, dose-titration, double-blind study to evaluate the efficacy and safety of placebo or valbenazine 25 to 75 mg (valbenazine initiated at 25 mg and titrated to an optimal dose [increased in increments of 25 mg every 2 weeks to a maximum of 75 mg]) administered once daily for 6 weeks in patients with schizophrenia, schizoaffective disorder, mood disorder, or gastrointestinal disorder; and tardive dyskinesia.
71) Foreign Study 1304 was a placebo-controlled, parallel-group, double-blind study to evaluate the efficacy and safety of placebo or valbenazine 40 or 80 mg administered once daily for 6 weeks in patients with schizophrenia, schizoaffective disorder, or mood disorder; and tardive dyskinesia.
72) Rated on a 7-point scale: 1: Very much improved, 2: Much improved, 3: Minimally improved, 4: No change, 5: Minimally worse, 6: Much worse, 7: Very much worse

the jump to reference sensitivity analysis and the baseline observation carried forward (BOCF) sensitivity analysis, and as with the MMRM analysis, these analyses indicated improvement in the AIMS total score in the valbenazine group vs. placebo. Based on the above, discontinuations are unlikely to have affected efficacy assessment materially.

Table 51. Change from baseline in AIMS total score as assessed by central raters at Week 6 (Japanese Study J02, ITT population)

Treatment group	Jump to Reference		BOCF	
	Change from baseline[a) b)]	Placebo-subtracted difference[b)] [95% CI]	Change from baseline[a) b)]	Placebo-subtracted difference[b)] [95% CI]
Placebo	-0.1 ± 0.3 (84)		-0.1 ± 0.3 (84)	
Valbenazine 40 mg	-1.8 ± 0.3 (83)	-1.7 [-2.6, -0.8]	-1.8 ± 0.3 (83)	-1.7 [-2.6, -0.9]
Valbenazine 80 mg	-2.6 ± 0.4 (82)	-2.5 [-3.4, -1.6]	-2.6 ± 0.3 (82)	-2.5 [-3.3, -1.6]

a) Least-squares mean ± SE (N)
b) ANCOVA model that included treatment group and underlying disease category as fixed effects and baseline AIMS total score as a covariate

- Table 52 and Table 53 show the secondary endpoints of the change from baseline in the AIMS total score as assessed by on-site raters at Week 6 and the CGI-TD at Week 6, respectively. As with the results of the primary endpoint, there was a trend towards improvement in the valbenazine group vs. placebo.

Table 52. Change from baseline in AIMS total score as assessed by on-site raters at Week 6 (Japanese Study J02, ITT population, MMRM)

Treatment group	Baseline	Week 6	Change from baseline[a) b)]	Placebo-subtracted difference[b)] [95% CI]
Placebo	11.2 ± 4.9 (84)	8.9 ± 4.8 (80)	-2.3 ± 0.3	
Valbenazine 40 mg	11.7 ± 4.2 (83)	7.7 ± 4.7 (68)	-4.1 ± 0.5	-1.5 [-2.7, -0.3]
Valbenazine 80 mg	10.5 ± 3.9 (82)	5.9 ± 4.8 (57)	-4.9 ± 0.6	-2.3 [-3.5, -1.1]

Mean ± SD (N)
a) Least-squares mean ± SE
b) MMRM model that included treatment group, underlying disease category, and study visit (Week 2, 4, or 6) as fixed effects, baseline AIMS total score as a covariate, and treatment-by-week and baseline score-by-week interaction terms. An unstructured variance-covariance matrix for scores within subjects was used.

Table 53. CGI-TD at Week 6 (Japanese Study J02, ITT population)

	Placebo	Valbenazine 40 mg	Valbenazine 80 mg
N[a)]	84	83	82
Very much improved	0	7 (8.4)	6 (7.3)
Much improved	13 (15.5)	14 (16.9)	27 (32.9)
Minimally improved	24 (28.6)	21 (25.3)	7 (8.5)
No change	42 (50.0)	27 (32.5)	16 (19.5)
Minimally worse	1 (1.2)	1 (1.2)	4 (4.9)
Much worse	0	0	0
Very much worse	0	0	0

n (Proportion [%])
a) Including discontinued subjects or subjects with missing data (4.8% [4 of 84 subjects] in the placebo group, 15.7% [13 of 83 subjects] in the valbenazine 40 mg group, 26.8% [22 of 82 subjects] in the valbenazine 80 mg group).

- There are no specific criteria as to what represents a clinically meaningful change from baseline in the AIMS total score. According to a pooled efficacy analysis of foreign clinical studies of valbenazine,[73)] subjects who were assessed as being "very much improved, "much improved," or "minimally improved on the CGI-TD scale at Week 6 had a change from baseline in the AIMS total score (mean ± SD) of −2.2 ± 0.2 (*Mov Disord.* 2019; 34: 1203-9). Since a decrease of ≥2 points in the AIMS total score from baseline corresponds to "very much improved, "much improved," or "minimally improved on the CGI-TD scale, a decrease of ≥2 points in the AIMS total score from baseline is considered clinically meaningful.
- In Japanese Study J02, the difference in the change from baseline in the AIMS total score for the 40 mg and 80 mg groups vs. placebo were −2.2 and −3.6, respectively, i.e. both ≥2-point decreases (Table 48).

73) Foreign phase II studies (Reference data CTD 5.3.5.1-3, Study 1201; Reference data CTD 5.3.5.1-4, Study 1202) and a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304)

Thus, the placebo-subtracted differences observed in Japanese Study J02 are considered clinically meaningful improvements. As a secondary endpoint, a responder was defined as a subject with ≥50% reduction from baseline in the AIMS total score, and Table 54 shows the proportion of AIMS responders at Week 6. As with the results of the primary endpoint, the proportion of AIMS responders was higher in the valbenazine group than in the placebo group and tended to be higher in the valbenazine 80 mg group than in the valbenazine 40 mg group.

Table 54. Proportion of AIMS responders at Week 6 (Japanese Study J02, ITT population)

	Placebo	Valbenazine 40 mg	Valbenazine 80 mg
N[a)]	84	83	82
Responder	8 (9.5)	16 (19.3)	25 (30.5)

n (Proportion [%])

a) Including discontinued subjects or subjects with missing data (7.1% [6 of 84 subjects] in the placebo group, 19.3% [16 of 83 subjects] in the valbenazine 40 mg group, 35.4% [29 of 82 subjects] in the valbenazine 80 mg group)

- Table 55 shows the changes from baseline in the scores for AIMS items 1 to 7 in Japanese Study J02. The changes from baseline in the scores for item 5 (upper extremities) and item 6 (lower extremities) at Week 6 were smaller than those in the scores for other items. These findings are considered attributable to the following: Since the mean baseline scores were low, and the median baseline scores were 0.0 (no symptoms), there was no room for improvement, resulting in minimal changes. The time course of the changes in the scores for items 5 and 6 were similar to those for other items. As with the results of the primary endpoint, all of the scores for AIMS items 1 to 7 improved in the valbenazine group vs. placebo, and there was a trend towards greater improvement in the valbenazine 80 mg group than in the valbenazine 40 mg group.

Table 55. Change from baseline in scores for AIMS items 1-7 at Week 6 (Japanese Study J02, ITT population)

	Treatment group	Baseline	Week 6	Change from baseline
Item 1 Muscles of facial expression	Placebo	1.1 ± 1.2 (84)	1.1 ± 1.2 (80)	0.0 ± 0.7
	Valbenazine 40 mg	1.3 ± 1.1 (83)	1.1 ± 1.1 (68)	-0.2 ± 0.9
	Valbenazine 80 mg	1.2 ± 1.1 (82)	0.7 ± 1.1 (57)	-0.4 ± 1.1
Item 2 Lips and perioral area	Placebo	1.6 ± 1.1 (84)	1.4 ± 1.1 (80)	-0.2 ± 0.8
	Valbenazine 40 mg	1.6 ± 1.2 (83)	1.1 ± 1.1 (68)	-0.5 ± 0.9
	Valbenazine 80 mg	1.3 ± 1.2 (82)	0.6 ± 0.9 (57)	-0.8 ± 1.1
Item 3 Jaw	Placebo	1.5 ± 1.2 (84)	1.4 ± 1.2 (80)	-0.1 ± 0.9
	Valbenazine 40 mg	1.5 ± 1.2 (83)	0.9 ± 1.1 (68)	-0.6 ± 0.8
	Valbenazine 80 mg	1.4 ± 1.3 (82)	0.5 ± 0.9 (57)	-0.9 ± 1.2
Item 4 Tongue	Placebo	1.6 ± 1.2 (84)	1.6 ± 1.3 (80)	-0.1 ± 0.8
	Valbenazine 40 mg	1.6 ± 1.2 (83)	1.2 ± 1.1 (68)	-0.5 ± 1.0
	Valbenazine 80 mg	1.4 ± 1.1 (82)	0.6 ± 0.8 (57)	-0.8 ± 1.1
Item 5 Upper extremities	Placebo	0.7 ± 1.0 (84)	0.7 ± 1.0 (80)	0.0 ± 0.6
	Valbenazine 40 mg	0.4 ± 0.8 (83)	0.4 ± 0.8 (68)	-0.1 ± 0.5
	Valbenazine 80 mg	0.6 ± 1.0 (82)	0.5 ± 0.9 (57)	-0.2 ± 0.7
Item 6 Lower extremities	Placebo	0.6 ± 0.9 (84)	0.7 ± 0.9 (80)	0.1 ± 0.5
	Valbenazine 40 mg	0.4 ± 0.7 (83)	0.3 ± 0.5 (68)	-0.2 ± 0.6
	Valbenazine 80 mg	0.5 ± 0.9 (82)	0.3 ± 0.7 (57)	-0.2 ± 0.9
Item 7 Neck/Shoulders/Hips	Placebo	0.9 ± 1.3 (84)	1.1 ± 1.3 (80)	0.1 ± 0.6
	Valbenazine 40 mg	0.9 ± 1.4 (83)	0.9 ± 1.3 (68)	-0.3 ± 0.8
	Valbenazine 80 mg	1.0 ± 1.3 (82)	0.8 ± 1.2 (57)	-0.4 ± 0.9

Mean ± SD (N)

- Based on the above, the results of both the primary and secondary endpoints showed the efficacy of valbenazine in patients with tardive dyskinesia, and the changes from baseline in the AIMS total score observed in Japanese Study J02 were clinically meaningful.

7.R.2.2 Factors affecting the efficacy of valbenazine

PMDA asked the applicant to explain the factors affecting the efficacy of valbenazine.

The applicant's explanation:

Table 56 shows the results of subgroup analyses of the change from baseline in the AIMS total score as assessed by central raters at Week 6 by patient characteristics in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02). Improvement in the AIMS total score was observed in the valbenazine group vs. placebo across all subgroups, and there was a similar trend as in the overall population. Thus, these patient characteristics are unlikely to affect the efficacy of valbenazine.

Table 56. Subgroup analyses of AIMS total score as assessed by central raters at Week 6 by patient characteristics (Japanese Study J02, ITT population)

		Treatment group	Baseline	Week 6	Change from baseline[a) b)]	Comparison between valbenazine and placebo[b)] Placebo-subtracted difference [95% CI]
Baseline AIMS total score as assessed by central raters	<8.0	Placebo	4.6 ± 2.2 (41)	5.0 ± 3.1 (38)	0.4 ± 0.4	
		Valbenazine 40 mg	4.7 ± 1.7 (42)	3.8 ± 2.2 (29)	-0.9 ± 0.4	-1.2 [-2.5, 0.0]
		Valbenazine 80 mg	3.9 ± 2.2 (40)	1.7 ± 2.0 (28)	-1.9 ± 0.5	-2.3 [-3.5, -1.0]
	≥8.0	Placebo	11.4 ± 2.8 (43)	10.5 ± 3.3 (42)	-0.9 ± 0.4	
		Valbenazine 40 mg	10.8 ± 2.8 (41)	7.5 ± 3.9 (39)	-3.4 ± 0.4	-2.5 [-3.9, -1.1]
		Valbenazine 80 mg	10.8 ± 2.9 (42)	6.0 ± 4.4 (29)	-5.3 ± 0.8	-4.5 [-6.0, -2.9]
Underlying disease category	Schizophrenia/ Schizoaffective disorder	Placebo	8.4 ± 4.4 (53)	8.1 ± 4.5 (52)	-0.4 ± 0.3	
		Valbenazine 40 mg	7.0 ± 3.7 (54)	5.1 ± 3.5 (44)	-2.2 ± 0.5	-1.8 [-3.2, -0.5]
		Valbenazine 80 mg	6.8 ± 4.4 (53)	3.3 ± 3.7 (38)	-3.7 ± 0.7	-3.3 [-4.7, -1.9]
	Bipolar disorder/ Depressive disorder	Placebo	7.5 ± 4.0 (31)	7.4 ± 3.7 (28)	-0.1 ± 0.5	
		Valbenazine 40 mg	9.1 ± 3.8 (29)	7.4 ± 3.8 (24)	-2.5 ± 0.4	-2.4 [-3.9, -0.9]
		Valbenazine 80 mg	8.6 ± 4.0 (29)	5.1 ± 4.6 (19)	-3.6 ± 0.7	-3.5 [-5.1, -1.9]
Baseline MADRS total score[c)]	<5.0	Placebo	7.4 ± 3.0 (17)	7.1 ± 3.7 (16)	-0.4 ± 0.7	
		Valbenazine 40 mg	9.1 ± 2.7 (12)	6.4 ± 2.7 (11)	-3.1 ± 0.5	-2.7 [-4.9, -0.4]
		Valbenazine 80 mg	6.8 ± 3.8 (13)	2.7 ± 2.5 (9)	-3.4 ± 1.3	-3.0 [-5.4, -0.7]
	≥5.0	Placebo	7.6 ± 5.1 (14)	7.9 ± 3.7 (12)	0.3 ± 0.9	
		Valbenazine 40 mg	9.1 ± 4.5 (17)	8.3 ± 4.4 (13)	-2.0 ± 0.7	-2.3 [-4.5, -0.1]
		Valbenazine 80 mg	10.0 ± 3.6 (16)	7.2 ± 5.0 (10)	-3.7 ± 0.8	-4.0 [-6.4, -1.7]
Baseline PANSS total score[d)]	<58.5	Placebo	8.6 ± 4.6 (22)	8.8 ± 4.4 (21)	-0.1 ± 0.5	
		Valbenazine 40 mg	6.9 ± 3.4 (28)	4.9 ± 4.1 (23)	-2.1 ± 0.7	-1.9 [-4.3, 0.4]
		Valbenazine 80 mg	7.5 ± 4.9 (30)	3.4 ± 4.5 (18)	-4.8 ± 1.3	-4.6 [-7.2, -2.1]
	≥58.5	Placebo	8.2 ± 4.3 (31)	7.7 ± 4.6 (31)	-0.5 ± 0.4	
		Valbenazine 40 mg	7.0 ± 4.1 (26)	5.3 ± 2.7 (21)	-2.3 ± 0.6	-1.8 [-3.3, -0.3]
		Valbenazine 80 mg	5.8 ± 3.7 (23)	3.2 ± 2.9 (20)	-2.7 ± 0.7	-2.1 [-3.7, -0.6]
Baseline CDSS total score[d)]	<2.0	Placebo	8.0 ± 4.7 (25)	8.1 ± 4.9 (24)	-0.2 ± 0.5	
		Valbenazine 40 mg	7.9 ± 4.5 (20)	5.3 ± 5.1 (16)	-2.6 ± 1.0	-2.4 [-4.6, -0.2]
		Valbenazine 80 mg	6.9 ± 4.8 (21)	3.3 ± 4.7 (15)	-4.3 ± 1.1	-4.1 [-6.3, -1.8]
	≥2.0	Placebo	8.7 ± 4.1 (28)	8.2 ± 4.2 (28)	-0.5 ± 0.4	
		Valbenazine 40 mg	6.4 ± 3.0 (34)	5.0 ± 2.1 (28)	-2.0 ± 0.5	-1.5 [-3.2, 0.3]
		Valbenazine 80 mg	6.8 ± 4.3 (32)	3.3 ± 2.9 (23)	-3.3 ± 1.0	-2.8 [-4.6, -0.9]

Mean ± SD (N)
a) Least-squares mean ± SE
b) MMRM model that included treatment group, underlying disease category, and study visit (Week 2, 4, or 6) as fixed effects, baseline AIMS total score as a covariate, and treatment-by-week and baseline score-by-week interaction terms. An unstructured variance-covariance matrix for scores within subjects was used.
c) Patients with bipolar disorder/depressive disorder only were assessed.
d) Patients with schizophrenia/schizoaffective disorder only were assessed.

PMDA's view:

Based on Sections 7.R.2.1 to 7.R.2.2, the applicant's explanation about the efficacy of valbenazine is acceptable. The primary endpoint of the AIMS scored by central video raters is appropriate, and the efficacy

of valbenazine was shown with respect to the primary and secondary endpoints. In addition, no factors clearly affecting the efficacy of valbenazine have been found.

7.R.3 Safety

7.R.3.1 Safety profile of valbenazine

PMDA asked the applicant to explain the safety profile of valbenazine.

The applicant's explanation:

- In a Japanese phase I study (CTD 5.3.3.1-1, Study J01), since 3 subjects treated with valbenazine 80 mg in the valbenazine 80 mg multiple-dose cohort had depression, the cohort was terminated. Thus, the tolerability of valbenazine 80 mg in healthy adult subjects could not be assessed [see Section 7.1.1].
- Table 57 shows the incidence of adverse events during the double-blind phase or the long-term treatment phase[74)] of a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) or pooled foreign clinical studies.[52)]

Table 57. Incidence of adverse events (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
All adverse events	37 (44.0)	54 (63.5)	67 (79.8)	113 (89.7)	116 (94.3)	71 (39.9)	48 (43.6)	53 (47.3)	122 (61.0)	164 (71.3)
Deaths	0	0	0	3 (2.4)	4 (3.3)	1 (0.6)	0	1 (0.9)	0	3 (1.3)
Serious adverse events	1 (1.2)	4 (4.7)	1 (1.2)	18 (14.3)	16 (13.0)	6 (3.4)	6 (5.5)	6 (5.4)	23 (11.5)	38 (16.5)
Adverse events leading to treatment discontinuation	3 (3.6)	6 (7.1)	14 (16.7)	23 (18.3)	36 (29.3)	8 (4.5)	4 (3.6)	5 (4.5)	32 (16.0)	31 (13.5)
Adverse events leading to dose reduction	0	1 (1.2)	10 (11.9)	16 (12.7)	39 (31.7)	4 (2.2)	2 (1.8)	5 (4.5)	10 (5.0)	19 (8.3)
Depression- and suicide-related adverse events[a)]	1 (1.2)	6 (7.1)	3 (3.6)	19 (15.1)	19 (15.4)	6 (3.4)	8 (7.3)	4 (3.6)	21 (10.5)	20 (8.7)
Cardiovascular and prolonged QT interval-related adverse events[b)]	0	0	0	4 (3.2)	1 (0.8)	0	0	1 (0.9)	4 (2.0)[c)]	4 (1.7)[c)]

n (Incidence [%])

a) Events in the MedDRA SMQ "depression (excluding suicide/self-injury) (broad)" or "suicide/self-injury"

b) Events in the MedDRA SMQ "torsade de pointes/QT prolongation (broad)" and events coded to PTs "cardiac failure," "chest pain," "myocardial infarction," "death," and "myocardial ischaemia" in Japanese Study J02. Events in the MedDRA SMQ "torsade de pointes/QT prolongation (broad)" in pooled foreign clinical studies.

c) No. of subjects evaluated: 197 subjects in the valbenazine 40 mg group and 230 subjects in the valbenazine 80 mg group (counted based on interim data [78 subjects and 12 subjects who completed 48-week treatment] for Foreign Studies 1304 and 1402)

- During the double-blind phase of Japanese Study J02, the incidences of all adverse events, adverse events leading to treatment discontinuation, and adverse events leading to dose reduction were higher in the valbenazine group than in the placebo group and in the valbenazine 80 mg group than in the valbenazine 40 mg group. On the other hand, the incidence of serious adverse events was not dose-dependent, and no deaths were reported. During the double-blind phase of pooled foreign clinical studies, the incidence of all adverse events was higher in the valbenazine group than in the placebo group and in the valbenazine 80 mg

74) The long-term treatment phase was up to 48 weeks of treatment with valbenazine and included a double-blind period (6 weeks) and an extension period (up to 42 weeks) in phase III studies. Safety data during placebo treatment were excluded.

group than in the valbenazine 40 mg group. On the other hand, the incidence of serious adverse events was not dose-dependent, and there were no major differences in the incidence of adverse events leading to treatment discontinuation or death between the placebo and valbenazine groups.

- During the long-term treatment phase of Japanese Study J02, the incidences of all adverse events, adverse events leading to treatment discontinuation, and adverse events leading to dose reduction were higher in the valbenazine 80 mg group than in the valbenazine 40 mg group, while there were no major differences in the incidence of serious adverse events or death between the valbenazine 40 mg and 80 mg groups. During the long-term treatment phase of pooled foreign clinical studies, although the incidence of all adverse events was higher in the valbenazine 80 mg group than in the valbenazine 40 mg group, there were no major differences in the incidence of adverse events leading to treatment discontinuation between the valbenazine 40 mg and 80 mg groups. Deaths were reported in the 80 mg group only.
- As to adverse events leading to treatment discontinuation in Japanese Study J02, the main events during the double-blind phase were akathisia (4 subjects) (0 subjects in the placebo group, 1 subject in the valbenazine 40 mg group, 3 subjects in the valbenazine 80 mg group) and malaise (3 subjects) (0 subjects, 2 subjects, 1 subject), and the main events during the long-term treatment phase were schizophrenia (5 subjects) (5 subjects in the valbenazine 40 mg group, 0 subjects in the valbenazine 80 mg group), akathisia (5 subjects) (2 subjects, 3 subjects), malaise (4 subjects) (2 subjects, 2 subjects), suicidal ideation (3 subjects) (3 subjects, 0 subjects), and suicide attempt (3 subjects) (2 subjects, 1 subject). Adverse events leading to treatment discontinuation tended to occur frequently during the early phase of treatment in the valbenazine 80 mg group.
- As to adverse events leading to dose reduction in Japanese Study J02, the main events during the double-blind phase were salivary hypersecretion (5 subjects) (0 subjects in the placebo group, 1 subject in the valbenazine 40 mg group, 4 subjects in the valbenazine 80 mg group) and somnolence (4 subjects) (0 subjects, 0 subjects, 4 subjects), and the main events during the long-term treatment phase were salivary hypersecretion (12 subjects) (2 subjects in the valbenazine 40 mg group, 10 subjects in the valbenazine 80 mg group), somnolence (7 subjects) (2 subjects, 5 subjects), malaise (5 subjects) (1 subject, 4 subjects), and tremor (4 subjects) (1 subject, 3 subjects). Adverse events leading to dose reduction tended to occur frequently during the early phase of treatment in the valbenazine 80 mg group.
- Exposure-safety analyses [see Section 6.R.4.1] suggested a relationship between the exposures and the incidences of somnolence-related adverse events, parkinsonism-related adverse events, and akathisia-related adverse events. Safety can be ensured, provided that patients are closely monitored for the possible occurrence of these events, and that appropriate measures, e.g., treatment discontinuation, are taken. Thus, there should be no major problem with the safety profile of valbenazine 40 mg and 80 mg.

There were 7 deaths (3 in the valbenazine 40 mg group, 4 in the valbenazine 80 mg group) during valbenazine treatment and 1 death (valbenazine 80 mg group) during the follow-up period in Japanese Study J02. PMDA asked the applicant to explain the details of the deaths reported in Japanese Study J02 and then the possibility that the risk of death will become a clinically relevant problem in Japanese patients with tardive dyskinesia.

The applicant's explanation:

- In Japanese Study J02, there were 3 deaths in the valbenazine 40 mg group (marasmus; death; and myocardial ischaemia [1 subject each]) and 5 deaths in the valbenazine 80 mg group (pneumonia; respiratory failure; death; pneumonia aspiration; and acute hepatic failure [the follow-up period] [1 subject each]). An adverse event leading to death could not be identified in 2 subjects with "death" reported as an adverse event term. The time to death from the start of treatment with valbenazine was 71 to 270 days (excluding 1 subject who died during the follow-up period), and there was no clear trend in the dose and duration of valbenazine in the death cases. The details of the deaths are described below.
  - ➢ Marasmus in the valbenazine 40 mg group (Case 1) was reported from a 7[redacted]-year-old female patient with schizophrenia. After taking valbenazine in the morning of Day 228, the patient was found lying at around noon and confirmed dead. The investigator (sub-investigator) denied a causal relationship between marasmus and study drug, considering that the event occurred mainly because the patient could not eat regularly and became weaker due to oral discomfort caused by tardive dyskinesia. The patient had no change in the CDSS score (4 points at baseline, 4 points at the last time point).
  - ➢ Death in the valbenazine 40 mg group (Case 2) was reported from a 6[redacted]-year-old female patient with depressive disorder. Since the subject had palpitations[75)] and requested withdrawal from the study on Day 257, the investigator (sub-investigator) told the subject that her withdrawal from the study would be determined at an unscheduled visit on Day 268. The subject did not visit and was found lying and confirmed dead on Day 268. The event was assessed by the investigator (sub-investigator) as causally related to study drug because the cause of death was unknown, and its causal relationship to study drug could not be ruled out. The subject had a worsening in the MADRS score (10 points at baseline, 22 points at the last time point).
  - ➢ Myocardial ischaemia in the valbenazine 40 mg group (Case 3) was reported from a 6[redacted]-year-old male patient with bipolar disorder. On Day 97, the patient was taken to hospital by ambulance with a chief complaint of swallowing difficulties, but the results of examinations revealed no abnormalities. The patient was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) on Day 112 and considered to have had suicidal ideation. On Day 140, it was considered that suicidal ideation resolved, and swallowing difficulties improved. On Day 153, the patient was found dead, and a postmortem examination determined that the patient died of acute ischemic heart disease. The investigator (sub-investigator) denied a causal relationship between myocardial ischaemia and study drug because the patient had a tendency to tachycardia before participation in the study, and the ECG during the study showed right atrial enlargement. The patient had a slight worsening in the MADRS score (8 points at baseline, 11 points at the last time point).
  - ➢ Pneumonia in the valbenazine 80 mg group (Case 4) was reported from a 7[redacted]-year-old male patient with bipolar disorder. On Day 155, the patient had decreased oxygen saturation, increased white blood cells, and increased C-reactive protein (CRP) and received antibiotics and fluids. On Day 166, the patient had respiratory failure and was confirmed dead. A forensic autopsy found that the cause of death was pneumonia. The investigator (sub-investigator) denied a causal relationship between pneumonia and

75) The subject reported that she visited another medical institution for palpitations, but no abnormalities were indicated.

study drug, considering that the event occurred mainly because the patient became weaker due to poor eating associated with worsening of bipolar disorder. The patient had a worsening in the MADRS score (5 points at baseline, 18 points at the last time point).

- ➢ Respiratory failure in the valbenazine 80 mg group (Case 5) was reported from a 7[redacted]-year-old male patient with depressive disorder. On Days 50 and 64, the patient visited the study site due to worsening of asthma. Although an unscheduled visit on Day 70 was arranged, the subject did not visit. Then, the subject was found lying and confirmed dead. A forensic autopsy found that the estimated date of death was Day 71, and that the cause of death was respiratory failure. The investigator (sub-investigator) denied a causal relationship between respiratory failure and study drug, considering that the event was caused by worsening of comorbid asthma. The patient had a worsening in the MADRS score (13 points at baseline, 29 points at the last time point).
- ➢ Death in the valbenazine 80 mg group (Case 6) was reported from a 7[redacted]-year-old male patient with schizophrenia. The ECGs on Days 196 and 252 revealed supraventricular extrasystoles, which were not associated with any abnormality in other test results and were not considered clinically relevant. On Day 270, the patient was found lying and confirmed dead. No autopsy was performed, and the cause of death was unknown. The investigator (sub-investigator) denied a causal relationship between death and study drug, considering that the event was incidental. The patient had no change in the CDSS score (1 point at baseline, 1 point at the last time point).
- ➢ Pneumonia aspiration in the valbenazine 80 mg group (Case 7) was reported from a 7[redacted]-year-old male patient with schizophrenia. On Day 212, the patient choked at breakfast, and oxygen saturation (SpO_2) fell to 50% to <60%, which improved following suction and supplemental oxygen. Then, the patient had fever and respiratory murmur and was given antibiotics for possible pneumonia aspiration. The patient had cardiac arrest on Day 215 and was confirmed dead on the following day. The investigator (sub-investigator) denied a causal relationship between pneumonia aspiration and study drug because the patient had a history of pneumonia aspiration due to comorbidity of swallowing difficulties before participation in the study. The patient had a slight worsening in the CDSS score (3 points at baseline, 5 points at the last time point).
- ➢ Acute hepatic failure in the valbenazine 80 mg group (Case 8) was reported from a 5[redacted]-year-old male patient with schizophrenia. The patient received placebo during the double-blind period and valbenazine 80 mg during the extension period, beginning on Day 43. The patient had aspiration and asphyxia on Day 132, and the dose was reduced to 40 mg on Day 141. The patient fasted due to fever, increased white blood cells, a slight increase in CRP, and decreased swallowing function, beginning on Day 299, and study drug was discontinued on Day 301. The patient had hepatic dysfunction on Day 316 and died on Day 321. The investigator (sub-investigator) denied a causal relationship between acute hepatic failure and study drug because hepatic dysfunction was not noted during the study treatment period and occurred 2 weeks after the last dose of study drug. The patient had a worsening in the CDSS score (6 points at baseline, 21 points at the last time point).

- Comparison of patient characteristics between death and non-death cases in Japanese Study J02 was made. There were differences in the age at the time of giving consent (67.9 ± 5.9 years in death cases, 58.6 ± 13.8

years in non-death cases [mean ± SD]), body mass index (BMI) (18.80 ± 1.59 kg/m^2 in death cases, 23.90 ± 4.01 kg/m^2 in non-death cases [mean ± SD]), and the proportion of men (75.0% [6 of 8 subjects] in death cases, 49.4% [121 of 245 subjects] in non-death cases). However, due to only 8 death cases, whether there was a clear association was unknown. An assessment of the association of the death cases with concomitant/previous illnesses or concomitant medications suggested no specific factors associated with mortality.

- Using the PPK model-predicted steady-state exposures of unchanged valbenazine and its active metabolite NBI-98782 ($C_{max,ss}$ and $AUC_{0-\tau,ss}$) in individual subjects in Japanese Study J02, the exposures in death (8 subjects) and non-death (230 subjects) cases in Japanese Study J02 were compared. There was no trend towards higher exposures of unchanged valbenazine and NBI-98782 in death cases than in non-death cases.[76)]
- In foreign clinical studies of valbenazine,[77)] 9 of 821 subjects died (1 in the placebo group, 8 in the valbenazine group), and all of the 8 subjects in the valbenazine group received 80 mg (after a dose reduction to 40 mg in 1 subject). However, among the 8 deaths in the valbenazine group, only 1 death was reported in a randomized study in which subjects were equally randomized to receive valbenazine 40 mg or 80 mg (Foreign Study 1304), and the other 7 deaths occurred in studies in which subjects were up-titrated to 80 mg. Thus, it could not be concluded that the incidence of death was higher with valbenazine 80 mg compared with 40 mg. The time to death from the start of treatment with valbenazine was 33 to 334 days, and there was no clear trend in the duration of treatment with valbenazine.
- Table 58 shows subject characteristics in Japanese Study J02 and pooled foreign clinical studies. There were no major differences in patient characteristics between Japanese and foreign clinical studies.

Table 58. Demographic and baseline characteristics (Safety population)

	Japanese Study J02			Pooled foreign clinical studies[a)]		
	Placebo	Valbenazine 40 mg	Valbenazine 80 mg	Placebo	Valbenazine 40 mg	Valbenazine 80 mg
N	84	85	84	178	110	112
Mean age (Mean ± SD)	60.0 ± 13.4	58.6 ± 14.0	58.0 ± 13.8	55.8 ± 10.5	55.4 ± 8.5	56.3 ± 10.3
No. of women (%)	48 (57.1)	45 (52.9)	33 (39.3)	76 (42.7)	44 (44.0)	51 (45.5)
BMI (Mean ± SD)	23.75 ± 3.82	23.38 ± 4.01	24.08 ± 4.33	28.3 ± 5.5	28.8 ± 5.6	28.1 ± 5.9
Tardive dyskinesia						
Age at diagnosis (Mean ± SD)	57.0 ± 12.8	55.0 ± 14.3	54.1 ±15.1	48.4 ± 11.9	48.1 ± 9.8	48.0 ± 12.3
Schizophrenia/Schizoaffective disorder						
n (%)	53 (63.1)	55 (64.7)	54 (64.3)	134 (75.3)	82 (74.5)	70 (62.5)
Age at diagnosis (Mean ± SD)	42.4 ± 16.4	40.4 ± 15.1	36.6 ± 15.7	29.0 ± 12.4	31.1 ± 12.6	30.9 ± 12.6
Bipolar disorder/Depressive disorder						
n (%)	31 (36.9)	30 (35.3)	30 (35.7)	44 (24.7)	28 (25.5)	42 (37.5)
Age at diagnosis (Mean ± SD)	46.4 ± 13.9	45.1 ± 15.1	47.2 ± 14.4	34.7 ± 13.8	33.7 ± 16.5	37.8 ± 13.2

a) Foreign Studies 1201, 1202, and 1304

- In the observation period from the start of treatment with valbenazine through 4 weeks after the last dose of valbenazine, i.e. the end of follow-up period, in Japanese Study J02, the mortality rate was 5.13 per 100 patient-years. According to a foreign epidemiological study in patients with tardive dyskinesia, the mortality

76) The $C_{max,ss}$ and $AUC_{0-\tau,ss}$ of unchanged valbenazine and NBI-98782 (median [min., max.]) in death cases are shown below.
Unchanged valbenazine: $C_{max,ss}$ = 553.49 [191.06, 1209.22], $AUC_{0-\tau,ss}$ = 5858.36 [1977.12, 13805.75]
NBI-98782: $C_{max,ss}$ = 34.88 [20.25, 110.39], $AUC_{0-\tau,ss}$ = 701.49 [421.15, 2386.03]
The $C_{max,ss}$ and $AUC_{0-\tau,ss}$ of unchanged valbenazine and NBI-98782 (median [min., max.]) in non-death cases are shown below.
Unchanged valbenazine: $C_{max,ss}$ = 426.52 [74.4, 1792.17], $AUC_{0-\tau,ss}$ = 4201.92 [1046.63, 16729.87]
NBI-98782: $C_{max,ss}$ = 37.85 [7.38, 175.32], $AUC_{0-\tau,ss}$ = 792.31 [93.62, 3837.32]

77) Foreign phase II studies (Study 1201, Study 1202), foreign phase III studies (Study 1304; Study 1402; Reference data CTD 5.3.5.2-3, Study 1506), and foreign phase IV studies (Reference data CTD 5.3.5.1-6, Study TD4001; Reference data CTD 5.3.5.1-7, Study TD4002)

rate was 5.07 per 100 patient-years (*Br J Psychiatry*. 2009; 194: 360-4), and the mean age at the first observation was 49.2 years, and the mean age at the last observation was 53.7 years in the study population. Taking also into account that the mean age of subjects in Japanese Study J02 was higher, 58.9 years, there should be no major differences in the mortality rate between Japanese Study J02 and patients with tardive dyskinesia.

- According to foreign post-marketing valbenazine safety information,[78)] 609 deaths (642 adverse events with a fatal outcome) were reported, and the mortality rate was estimated to be 1.80 per 100 patient-years. In 426 of the 609 death cases, the adverse event term was "death" or "sudden death," and no specific events leading to death were identified. The main events other than "death" and "sudden death" were myocardial infarction (16 events), pneumonia (15 events), cardiac arrest (12 events), and COVID-19 (11 events). No specific events associated with mortality were suggested.
- Based on the above, valbenazine is not associated with an increased risk of mortality. However, given that valbenazine is the first drug for the treatment of tardive dyskinesia in Japan, the applicant will take the following post-marketing measures.
  - ➢ Ensure the proper use of valbenazine through the package insert and information materials to be distributed to healthcare professionals and patients.
  - ➢ Especially, "depression and suicide" and "adverse events due to QT prolongation" are risks potentially leading to death. Thus, "depression and suicide" and "QT prolongation" will be categorized as important potential risks in the safety specification included in the risk management plan. Ensure that the primary physician will explain worsening of depressive symptoms, signs of suicidal ideation, and signs suggestive of QT prolongation (an irregular pulse, dizziness, palpitations, fainting, etc.) to the patient (including his/her family), using the information materials for patients, etc., and that the patient (including his/her family) will be advised to contact his/her primary physician promptly, etc., if the patient has the symptoms.
  - ➢ Strive to collect detailed case information on deaths for which a causal relationship to valbenazine is denied as well as deaths for which a causal relationship to valbenazine cannot be ruled out, wherever possible, after the market launch, and assess their relationship to valbenazine, the trend of occurrence, etc.
  - ➢ Assess the incidence of death and the association between patient characteristics such as comorbidities/concomitant medications and mortality, using the data obtained from post-marketing surveillance.
  - ➢ Seek to alert healthcare professionals promptly if post-marketing information shows any change in the trend of occurrence of death or any factor affecting the trend of occurrence of death in valbenazine-treated patients.

78) Accrual period, April 11, 2017 to December 31, 2020; Estimated exposures of 9171 patient-years (valbenazine 40 mg) and 24671 patient-years (valbenazine 80 mg)

PMDA's view:

- In Japanese Study J02, the incidences of adverse events leading to treatment discontinuation or dose reduction were higher in the valbenazine 80 mg group than in the valbenazine 40 mg group. Thus, valbenazine 80 mg is less tolerable than valbenazine 40 mg.
- In Japanese Study J01, 3 subjects treated with valbenazine 80 mg in the valbenazine 80 mg multiple-dose cohort had depression, and therefore the cohort was terminated [see Section 7.1.1]. Of 8 subjects who died in Japanese Study J02, 6 subjects had possible worsening depression (Case 2, Case 3, Case 4, Case 5, Case 7, Case 8). In Japanese Study J02, the incidence of depression- and suicide-related adverse events tended to be higher in the valbenazine group than in the placebo group. As valbenazine reduces the amount of monoamines released [see Section 3.R.1], valbenazine may increase the risk of depressive symptoms.
- An assessment of the association of death cases in Japanese Study J02 with concomitant/previous illnesses or concomitant medications suggested no specific factors associated with mortality. There was no trend towards higher exposures of unchanged valbenazine and its active metabolite NBI-98782. The mortality rate in Japanese Study J02 is not clearly higher than that in patients with tardive dyskinesia.
- Given the above findings, valbenazine has acceptable safety, provided that patients are closely monitored for the possible occurrence of adverse drug reactions during treatment with valbenazine.
- A final conclusion on the appropriateness of the above conclusions will be made, taking account of comments from the Expert Discussion.

Psychiatric disorder-related events (including depression- and suicide-related events and hostility/aggression-related events), sedation-related events, extrapyramidal symptom-related events (including dysphagia), neuroleptic malignant syndrome-related events, prolactin elevation-related events, and hypersensitivity-related events will be analyzed in the following sections. Dosage and administration of valbenazine will be discussed in Section 7.R.5.

7.R.3.2 Psychiatric disorder-related events (including depression- and suicide-related events and hostility/aggression-related events)

Valbenazine reduces the amount of monoamines released [see Section 3.R.1]. In a Japanese phase I study (CTD 5.3.3.1-1, Study J01), since 3 subjects treated with valbenazine 80 mg in the valbenazine 80 mg multiple-dose cohort had depression, the cohort was terminated [see Section 7.1.1]. PMDA asked the applicant to explain the incidence of psychiatric disorder-related events associated with valbenazine, including depression- and suicide-related events and hostility/aggression-related events.

The applicant's explanation about the incidence of psychiatric disorder-related events associated with valbenazine:

- Table 59 shows the incidence of psychiatric disorder-related events[79)] in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) or pooled foreign clinical studies.[52)] While the incidence of psychiatric disorder-related events tended to be higher in the valbenazine group than in the placebo group, there were no differences

79) Events in the MedDRA SOC "psychiatric disorders"

between the valbenazine 40 mg and 80 mg groups. There was no trend towards a higher incidence of serious adverse events in the valbenazine group.

Table 59. Incidence of psychiatric disorder-related events (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
All adverse events	5 (6.0)	17 (20.0)	16 (19.0)	52 (41.3)	57 (46.3)	14 (7.9)	14 (12.7)	12 (10.7)	43 (21.5)	38 (16.5)
Serious adverse events	1 (1.2)	3 (3.5)	0	8 (6.3)	3 (2.4)	4 (2.2)	3 (2.7)	4 (3.6)	12 (6.0)	11 (4.8)
Adverse events leading to treatment discontinuation	1 (1.2)	1 (1.2)	3 (3.6)	10 (7.9)	7 (5.7)	3 (1.7)	3 (2.7)	3 (2.7)	14 (7.0)	8 (3.5)
Adverse events leading to dose reduction	0	0	0	2 (1.6)	7 (5.7)	1 (0.6)	1 (0.9)	2 (1.8)	2 (1.0)	2 (0.9)
Main events										
Insomnia	1 (1.2)	2 (2.4)	5 (6.0)	10 (7.9)	16 (13.0)	1 (0.6)	2 (1.8)	2 (1.8)	4 (2.0)	6 (2.6)
Schizophrenia	1 (1.2)	7 (8.2)	0	21 (16.7)	13 (10.6)	1 (0.6)	1 (0.9)	0	4 (2.0)	5 (2.2)
Anxiety	0	1 (1.2)	4 (4.8)	5 (4.0)	9 (7.3)	0	1 (0.9)	2 (1.8)	7 (3.5)	8 (3.5)
Depression	1 (1.2)	1 (1.2)	3 (3.6)	6 (4.8)	10 (8.1)	2 (1.1)	0	2 (1.8)	10 (5.0)	5 (2.2)
Disinhibition	0	2 (2.4)	0	2 (1.6)	0	0	0	0	0	0
Bipolar disorder	1 (1.2)	0	2 (2.4)	2 (1.6)	2 (1.6)	0	1 (0.9)	0	1 (0.5)	0
Suicidal ideation	0	1 (1.2)	0	6 (4.8)	3 (2.4)	4 (2.2)	4 (3.6)	1 (0.9)	9 (4.5)	11 (4.8)
Suicide attempt	1 (1.2)	1 (1.2)	0	3 (2.4)	1 (0.8)	0	0	1 (0.9)	0	2 (0.9)

n (Incidence [%])

- Table 60 shows the incidence of psychiatric disorder-related events by underlying disease category in Japanese Study J02 or pooled foreign clinical studies. In both Japanese and foreign clinical studies, there was a trend towards a higher incidence in the valbenazine group than in the placebo group among patients with bipolar disorder/depressive disorder. In patients with bipolar disorder/depressive disorder, the main events during the double-blind phase of Japanese Study J02 were depression (1 subject in the placebo group, 1 subject in the valbenazine 40 mg group, 3 subjects in the valbenazine 80 mg group), anxiety (0 subjects, 1 subject, 2 subjects), and bipolar disorder (1 subject, 0 subjects, 2 subjects), and the main events during the double-blind phase of pooled foreign clinical studies were anxiety (0 subjects, 1 subject, 2 subjects) and suicidal ideation (2 subjects, 1 subject, 0 subjects). Events with a high incidence were related to the underlying disease. In patients with schizophrenia/schizoaffective disorder, the main events during the double-blind phase of Japanese Study J02 were schizophrenia (1 subject, 7 subjects, 0 subjects) and insomnia (0 subjects, 2 subjects, 4 subjects), and the main events during the double-blind phase of pooled foreign clinical studies were suicidal ideation (2 subjects, 3 subjects, 1 subject), insomnia (1 subject, 2 subjects, 1 subject), depression (1 subject, 0 subjects, 2 subjects), and psychotic disorder (2 subjects, 0 subjects, 1 subject). Many events were related to the underlying disease.

Table 60. Incidence of psychiatric disorder-related events by underlying disease category (Safety population)

		Japanese Study J02					Pooled foreign clinical studies				
		Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
		Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
Schizophrenia/ Schizoaffective disorder	N	53	55	54	82	79	134	82	70	154	155
	Adverse events	1 (1.9)	12 (21.8)	8 (14.8)	35 (42.7)	32 (40.5)	11 (8.2)	8 (9.8)	8 (11.4)	28 (18.2)	25 (16.1)
Bipolar disorder/ Depressive disorder	N	31	30	30	44	44	44	28	42	46	75
	Adverse events	4 (12.9)	5 (16.7)	8 (26.7)	17 (38.6)	25 (56.8)	3 (6.8)	6 (21.4)	4 (9.5)	15 (32.6)	13 (17.3)

n (Incidence [%])

The applicant's explanation about the incidence of depression- and suicide-related events:

- In Japanese Study J01 in health adult subjects, since 3 subjects treated with valbenazine 80 mg in the valbenazine 80 mg multiple-dose cohort (3 subjects in the placebo group, 10 subjects in the valbenazine 80 mg group) had adverse events of depression (including 2 subjects with adverse events leading to study drug discontinuation), which met the criteria for cohort termination,[80] study drug was discontinued in all subjects in this cohort [see Section 7.1.1]. Since antipsychotics (dopamine receptor blocking agents) have been reported to produce negative symptoms of schizophrenia in healthy volunteers (*Am J Psychiatry*. 2006; 163: 488-93), the response to valbenazine in healthy adult subjects is considered different from that in patients with tardive dyskinesia who have hypersensitive dopamine receptors.
- Table 61 shows the incidence of depression- and suicide-related events[81] in Japanese Study J02 or pooled foreign clinical studies in patients with tardive dyskinesia. In Japanese Study J02, though the incidence of depression- and suicide-related events was higher in either dose group of valbenazine than in the placebo group, there was no trend towards a higher incidence in the valbenazine 80 mg group than in the valbenazine 40 mg group. There was no trend towards higher incidences of serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to dose reduction in the valbenazine group than in the placebo group. In pooled foreign clinical studies, there was no trend towards a higher incidence in the valbenazine group than in the placebo group, and there was no trend towards a higher incidence in the valbenazine 80 mg group than in the valbenazine 40 mg group.

80) If adverse events of suicidal ideation, suicide attempt, depression, or depressed state (excluding serious or severe events) occurred in ≥3 subjects in the same cohort, study drug was to be discontinued in this cohort, except that there was a rational reason for continuing study drug based on discussion among the sponsor, medical expert, and investigator.

81) Events in the MedDRA SMQ "depression (excluding suicide/self-injury) (broad)" or "suicide/self-injury"

Table 61. Incidence of depression- and suicide-related events (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
All adverse events	1 (1.2)	6 (7.1)	3 (3.6)	19 (15.1)	19 (15.4)	6 (3.4)	8 (7.3)	4 (3.6)	21 (10.5)	20 (8.7)
Serious adverse events	1 (1.2)	1 (1.2)	0	2 (1.6)	3 (2.4)	0	0	3 (2.7)	3 (1.5)	7 (3.0)
Adverse events leading to treatment discontinuation	1 (1.2)	0	0	6 (4.8)	4 (3.3)	0	0	2 (1.8)	6 (3.0)	7 (3.0)
Adverse events leading to dose reduction	0	0	0	1 (0.8)	1 (0.8)	0	1 (0.9)	0	1 (0.5)	0
Main events										
Depression	1 (1.2)	1 (1.2)	3 (3.6)	6 (4.8)	10 (8.1)	2 (1.1)	0	2 (1.8)	10 (5.0)	5 (2.2)
Suicidal ideation	0	1 (1.2)	0	6 (4.8)	3 (2.4)	4 (2.2)	4 (3.6)	1 (0.9)	9 (4.5)	11 (4.8)
Suicide attempt	1 (1.2)	1 (1.2)	0	3 (2.4)	1 (0.8)	0	0	1 (0.9)	0	2 (0.9)

n (Incidence [%])

- In order to assess worsening of depressive symptoms that were not reported as adverse events, the proportion of patients with a clinically meaningful worsening in the CDSS total score or the MADRS total score[82)] (depressive symptom rating scales) after study drug administration was calculated. The results are shown in Table 62. In Japanese Study J02, the proportion was higher in either dose group of valbenazine than in the placebo group, but there were no major differences between the two doses of valbenazine. The proportion of patients with worsening by underlying disease category during the double-blind phase of Japanese Study J02 is as follows: 7.5% (4 of 53 subjects) in the placebo group, 16.4% (9 of 55 subjects) in the valbenazine 40 mg group, and 18.5% (10 of 54 subjects) in the valbenazine 80 mg group among patients with schizophrenia/schizoaffective disorder, and 0% (0 of 31 subjects) in the placebo group, 16.7% (5 of 30 subjects) in the valbenazine 40 mg group, and 6.7% (2 of 30 subjects) in the valbenazine 80 mg group among patients with bipolar disorder/depressive disorder. Although the proportion was higher in the valbenazine group than in the placebo group, regardless of underlying disease category, there were no major differences between the two doses of valbenazine. In pooled foreign clinical studies, there were no major differences in the proportion of patients with a clinically meaningful worsening after study drug administration between the placebo and valbenazine groups.

Table 62. Subjects with a clinically meaningful worsening of depressive symptoms (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
Subjects with worsening	4 (4.8)	14 (16.5)	12 (14.3)	32 (25.4)	31 (25.2)	16 (9.0)	10 (9.1)	3 (2.7)	24 (12.0)	24 (10.4)

n (Proportion [%])

- Table 63 and Table 64 show the changes from baseline in the depressive symptom rating scales (CDSS total score and MADRS total score). There was a trend towards a slight worsening in the MADRS total score in the valbenazine 80 mg group during the long-term treatment phase of Japanese Study J02. If this was an

82) Defined as "post-baseline CDSS total score being >6 points and higher than baseline" in patients with schizophrenia or schizoaffective disorder and "post-baseline MADRS total score being >19 points" in patients with bipolar disorder or depressive disorder.

effect of valbenazine, treatment discontinuation was expected to result in improvement in the MADRS total score. However, treatment discontinuation did not result in improvement, and there was no particular association between the time course of depressive symptoms and valbenazine treatment.

Table 63. Changes in depressive symptom rating scales (Safety population)

	Treatment group	Japanese Study J02			Pooled foreign clinical studies		
		Baseline	Week 6	Change from baseline	Baseline	Week 6	Change from baseline
CDSS total score	Placebo	2.4 ± 2.6 (53)	2.3 ± 3.0 (52)	-0.1 ± 1.7	2.7 ± 2.52 (134)	2.4 ± 2.73 (117)	-0.3 ± 2.45
	VBZ 40 mg	2.8 ± 2.3 (55)	2.8 ± 3.3 (46)	0.0 ± 3.3	2.6 ± 2.56 (82)	2.1 ± 3.01 (71)	-0.5 ± 2.06
	VBZ 80 mg	2.7 ± 2.6 (54)	2.8 ± 2.6 (40)	0.1 ± 2.2	2.3 ± 2.36 (70)	1.9 ± 2.14 (60)	-0.6 ± 1.62
MADRS total score	Placebo	5.2 ± 4.0 (31)	5.1 ± 5.2 (28)	0.3 ± 4.6	5.3 ± 3.45 (44)	6.0 ± 5.62 (42)	0.6 ± 4.90
	VBZ 40 mg	5.9 ± 4.2 (30)	6.3 ± 6.1 (24)	0.7 ± 4.5	7.6 ± 3.82 (28)	7.3 ± 4.42 (25)	-0.2 ± 4.13
	VBZ 80 mg	5.9 ± 3.9 (30)	7.0 ± 6.1 (20)	0.8 ± 5.3	6.0 ± 4.01 (42)	4.4 ± 3.97 (41)	-1.7 ± 4.24

Mean ± SD (N)

Table 64. Changes in depressive symptom rating scales during long-term treatment phase (Safety population)

	Japanese Study J02				Pooled foreign clinical studies			
	CDSS total score		MADRS total score		CDSS total score		MADRS total score	
Time point	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
Double-blind baseline[a)]	2.7 ± 2.4 (82)	2.6 ± 2.6 (79)	5.4 ± 4.1 (44)	5.6 ± 3.9 (44)	2.4 ± 2.31 (154)	1.9 ± 2.09 (155)	6.2 ± 3.42 (46)	5.5 ± 3.84 (75)
Week 6	2.8 ± 3.3 (46)	2.8 ± 2.6 (40)	6.3 ± 6.1 (24)	7.0 ± 6.1 (20)	1.7 ± 2.32 (78)	1.6 ± 2.15 (42)	—	—
Week 12	2.1 ± 2.9 (66)	3.1 ± 3.8 (55)	5.4 ± 6.5 (34)	8.6 ± 10.2 (26)	1.7 ± 2.22 (52)	1.7 ± 2.13 (74)	—	—
Week 24	2.0 ± 3.1 (56)	2.8 ± 3.3 (48)	6.2 ± 7.4 (30)	9.6 ± 10.8 (17)	1.8 ± 2.53 (66)	1.3 ± 1.94 (105)	7.1 ± 7.50 (27)	4.5 ± 5.98 (51)
Week 48 (at the end of study treatment)	2.0 ± 3.7 (42)	2.0 ± 2.7 (35)	5.2 ± 6.1 (25)	8.2 ± 9.9 (15)	1.7 ± 2.60 (49)	1.6 ± 2.51 (58)	4.8 ± 5.14 (19)	5.0 ± 6.18 (30)
Week 52 (at the end of follow-up period)	1.1 ± 1.7 (42)	2.3 ± 2.8 (35)	6.2 ± 7.2 (24)	9.9 ± 12.7 (14)	1.1 ± 1.89 (48)	2.3 ± 3.10 (56)	7.1 ± 7.40 (19)	5.0 ± 7.11 (28)

Mean ± SD (N); —, Not measured

a) Double-blind baseline was used for both subjects in the placebo and valbenazine groups during the double-blind period.

- In order to assess changes in suicidal ideation and suicide attempt after study drug administration, C-SSRS data from Japanese Study J02 and a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304) were analyzed. The results are shown in Table 65, and there was no trend towards an increased risk of suicidal ideation or suicide attempt following administration of valbenazine.

Table 65. Proportion of subjects with worsening of suicidal ideation or suicide attempt as assessed by C-SSRS (Safety population)

	Japanese Study J02					Foreign Study 1304				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	76	72	79	97	101
Subjects with worsening from baseline	5 (6.0)	5 (5.9)	5 (6.0)	21 (16.7)	19 (15.4)	4 (5.3)	3 (4.2)	2 (2.5)	6 (6.2)	7 (6.9)

n (Proportion [%])

The applicant's explanation about the incidence of hostility/aggression-related events:

- Table 66 shows the incidence of hostility/aggression-related events[83)] in Japanese Study J02 or pooled foreign clinical studies. There was no trend towards a higher incidence in the valbenazine group than in the placebo group.

Table 66. Incidence of hostility/aggression-related events (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
All adverse events	2 (2.4)	2 (2.4)	3 (3.6)	5 (4.0)	4 (3.3)	7 (3.9)	5 (4.5)	1 (0.9)	9 (4.5)	8 (3.5)
Serious adverse events	0	0	0	0	0	1 (0.6)	2 (1.8)	0	3 (1.5)	1 (0.4)
Adverse events leading to treatment discontinuation	0	0	1 (1.2)	0	1 (0.8)	1 (0.6)	2 (1.8)	0	4 (2.0)	0
Adverse events leading to dose reduction	0	0	0	0	1 (0.8)	2 (1.1)	0	0	0	0
Main events										
Disinhibition	0	2 (2.4)	0	2 (1.6)	0	0	0	0	0	0
Bipolar disorder	1 (1.2)	0	2 (2.4)	2 (1.6)	2 (1.6)	0	1 (0.9)	0	1 (0.5)	0

n (Incidence [%])

- According to foreign post-marketing valbenazine safety information,[78)] 950 psychiatric disorder-related events in patients treated with valbenazine 40 mg (10.36 per 100 patient-years, including 100 serious events) and 1085 psychiatric disorder-related events in patients treated with valbenazine 80 mg (4.40 per 100 patient-years, including 178 serious events) were reported. The main serious events were depression (11 events in patients treated with valbenazine 40 mg, 22 events in patients treated with valbenazine 80 mg), suicidal ideation (14 events, 19 events), psychiatric symptom (7 events, 11 events), and mental disorder (4 events, 12 events).

Based on the above, the applicant provided the following explanation about psychiatric disorder-related events:

- Although the incidence of depression- and suicide-related events was higher in the valbenazine group than in the placebo group in Japanese Study J02, given that the relapse rate of depression is generally high, it is not clear whether valbenazine increases the risk of the onset or relapse of depression in Japanese patients with tardive dyskinesia. However, as valbenazine reduces the amount of monoamines released, and the possibility that depression- and suicide-related events occur cannot be ruled out, precautionary statements about the risk of depression and suicide will be included in the IMPORTANT PRECAUTIONS and PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS sections of the package insert, in order to ensure patient safety.
- Since other psychiatric disorder-related events including hostility/aggression-related events are unlikely to become a clinically relevant problem, no particular precautionary statement is necessary in the package insert.
- The US labeling for valbenazine does not have a warning/precaution for depression/suicide, aggression, etc.

83) Events in the MedDRA SMQ "hostility/aggression (broad)"

PMDA's view:

- As to depression- and suicide-related events, valbenazine reduces the amount of monoamines released, and the occurrence of depression- and suicide-related adverse events is anticipated. Since the incidence of depression- and suicide-related adverse events tended to be higher in the valbenazine group than in the placebo group in Japanese Study J02, the risk of depressive symptoms in patients with tardive dyskinesia following administration of valbenazine cannot be ruled out. Also, as the proportion of patients with a clinically meaningful worsening in the CDSS total score or the MADRS total score after study drug administration was higher in either dose group of valbenazine than in the placebo group in Japanese Study J02, the risk of worsening of depressive symptoms in Japanese patients cannot be ruled out. Furthermore, though its causal relationship to valbenazine is unknown, there were patients who had worsening of depressive symptoms after the start of treatment with valbenazine and then died in Japanese Study J02 [see Section 7.R.3.1].
- While the US labeling for valbenazine[84)] does not have a warning/precaution for depression/suicide, aggression, etc., the UK labeling for another VMAT2 inhibitor, tetrabenazine, which has been approved for tardive dyskinesia and Huntington's disease, includes precautionary statements about depression and suicide, without specifying the disease. The package insert in Japan for tetrabenazine, which has been approved for Huntington's disease, also includes precautionary statements about depression/depressed state, suicidal ideation, suicide attempt, aggression, etc.
- Given the above points, the package insert should advise about the risk of depression and suicide following administration of valbenazine in Japan, and there is no problem with the applicant's explanation that the package insert will advise about the risk of depression and suicide.
- As there was no trend towards a higher incidence of hostility/aggression-related events in the valbenazine group than in the placebo group in Japanese Study J02 or pooled foreign clinical studies, there is no problem with the applicant's explanation that no particular precautionary statement is necessary in the package insert.
- A final conclusion on the appropriateness of the above conclusions will be made, taking account of comments from the Expert Discussion.

7.R.3.3 Sedation-related events

Valbenazine reduces the amount of monoamines released. As with tetrabenazine, valbenazine is anticipated to cause sedation-related events [see Section 3.R.1]. PMDA asked the applicant to explain the incidence of sedation-related adverse events associated with valbenazine.

The applicant's explanation:

- Table 67 shows the incidence of sedation-related events[85)] in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) or pooled foreign clinical studies.[52)] In Japanese Study J02, the incidence was higher in the valbenazine group than in the placebo group, and there was a trend towards a higher incidence in the valbenazine 80 mg group than in the valbenazine 40 mg group. On the other hand, in pooled foreign clinical

84) The US labeling for deutetrabenazine, which has been approved for tardive dyskinesia and Huntington's disease, includes a warning/precaution for depression and suicide in patients with Huntington's disease only.
85) Events coded to the MedDRA PTs "somnolence," "sedation," "fatigue," "asthenia," "lethargy," "malaise," "hypersomnia," "sedation complication," and "decreased activity"

studies, though the incidence was higher in the valbenazine group than in the placebo group, there were no major differences between the valbenazine 40 mg and 80 mg groups. Serious adverse events occurred only in 1 subject (fatigue) in the valbenazine 40 mg group and 1 subject (somnolence) in the valbenazine 80 mg group during the long-term treatment phase of Japanese Study J02 and 1 subject (sedation) in the valbenazine 80 mg group during the long-term treatment phase of pooled foreign clinical studies, and many of the events were mild or moderate in severity. Although adverse events occurred during the early phase of treatment with valbenazine in both Japanese Study J02 and foreign clinical studies, there were no major differences between the valbenazine 40 mg and 80 mg groups.

Table 67. Incidence of sedation-related events (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
All adverse events	2 (2.4)	16 (18.8)	24 (28.6)	32 (25.4)	40 (32.5)	7 (3.9)	12 (10.9)	8 (7.1)	27 (13.5)	27 (11.7)
Serious adverse events	0	0	0	1 (0.8)	1 (0.8)	0	0	0	0	1 (0.4)
Adverse events leading to treatment discontinuation	0	2 (2.4)	2 (2.4)	2 (1.6)	4 (3.3)	0	0	0	3 (1.5)	6 (2.6)
Adverse events leading to dose reduction	0	0	4 (4.8)	4 (3.2)	11 (8.9)	1 (0.6)	2 (1.8)	1 (0.9)	5 (2.5)	7 (3.0)
Main events										
Somnolence	2 (2.4)	10 (11.8)	21 (25.0)	19 (15.1)	28 (22.8)	4 (2.2)	9 (8.2)	4 (3.6)	15 (7.5)	12 (5.2)
Malaise	0	5 (5.9)	4 (4.8)	10 (7.9)	10 (8.1)	0	0	0	0	1 (0.4)
Fatigue	0	0	2 (2.4)	2 (1.6)	4 (3.3)	3 (1.7)	5 (4.5)	3 (2.7)	14 (7.0)	8 (3.5)
Sedation complication	0	1 (1.2)	0	3 (2.4)	1 (0.8)	1 (0.6)	1 (0.9)	2 (1.8)	2 (1.0)	4 (1.7)

n (Incidence [%])

- Table 68 shows the incidence of sedation-related events by underlying disease category in Japanese Study J02 or pooled foreign clinical studies. There were no differences in the incidence of sedation-related events according to the underlying disease category.

Table 68. Incidence of sedation-related events by underlying disease category (Safety population)

		Japanese Study J02					Pooled foreign clinical studies				
		Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
		Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
Schizophrenia/ Schizoaffective disorder	N	53	55	54	82	79	134	82	70	154	155
	Adverse events	1 (1.9)	9 (16.4)	17 (31.5)	20 (24.4)	28 (35.4)	6 (4.5)	5 (6.1)	5 (7.1)	19 (12.3)	15 (9.7)
Bipolar disorder/ Depressive disorder	N	31	30	30	44	44	44	28	42	46	75
	Adverse events	1 (3.2)	7 (23.3)	7 (23.3)	12 (27.3)	12 (27.3)	1 (2.3)	7 (25.0)	3 (7.1)	8 (17.4)	12 (16.0)

n (Incidence [%])

- According to foreign post-marketing valbenazine safety information,[78)] 1141 sedation-related events (12.44 per 100 patient-years, including 3 serious events) in patients treated with valbenazine 40 mg and 1086 sedation-related events (4.40 per 100 patient-years, including 25 serious events) in patients treated with valbenazine 80 mg were reported. The main serious events were asthenia (2 events in patients treated with valbenazine 40 mg, 8 events in patients treated with valbenazine 80 mg), sedation (0 events, 4

events), malaise (1 events, 3 events), somnolence (0 events, 3 events), fatigue (0 events, 3 events), and lethargy (0 events, 3 events).

- Sedation-related events may be caused by reduction of monoamine release, a pharmacological action of valbenazine, and exposure-safety analyses including the data from Japanese Study J02 showed a correlation between the incidence of somnolence-related events and the exposures (C_{max} and AUC) [see Section 6.R.4.1]. Thus, those events may occur during the early phase of treatment with valbenazine, and the incidence may increase with increasing exposures of unchanged valbenazine and its active metabolite.
- The US labeling for valbenazine has a warning/precaution for somnolence.
- Based on the above, sedation-related events may occur as an action of valbenazine. Thus, precautionary statements about somnolence and sedation will be included in the IMPORTANT PRECAUTIONS and CLINICALLY SIGNIFICANT ADVERSE REACTIONS sections of the package insert.

PMDA's view:

The incidence of sedation-related events was higher in the valbenazine group than in the placebo group, and there was a trend towards a higher incidence in the valbenazine 80 mg group than in the valbenazine 40 mg group in Japanese Study J02. The US labeling for valbenazine has a warning/precaution for somnolence. The package insert in Japan for another VMAT2 inhibitor, tetrabenazine,[86)] also advises that sedation, somnolence, etc. may occur. Given these points, there is no particular problem with the applicant's explanation that the package insert will include precautionary statements about sedation and somnolence.

7.R.3.4 Extrapyramidal symptom-related events

PMDA asked the applicant to explain the incidence of extrapyramidal symptom-related events associated with valbenazine.

The applicant's explanation:

- Table 69 shows the incidence of extrapyramidal symptom-related events[87)] in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) or pooled foreign clinical studies.[52)] In Japanese Study J02, there was a trend towards a higher incidence in the valbenazine 80 mg group than in the valbenazine 40 mg group, and extrapyramidal symptom-related events tended to occur frequently during the early phase of treatment. Though the incidences of adverse events leading to treatment discontinuation or dose reduction also tended to be higher in the valbenazine 80 mg group than in the valbenazine 40 mg group, there were no major differences in the incidence of serious adverse events between the valbenazine 40 mg and 80 mg groups. According to the pooled analyses of foreign clinical studies, while the incidence was higher in the valbenazine 80 mg group than in the valbenazine 40 mg group during the double-blind phase, there were no major differences in the incidence between the valbenazine 40 mg and 80 mg groups during the long-term treatment phase.

86) The US labeling for deutetrabenazine and the UK labeling for tetrabenazine have a precaution/warning for sedation and somnolence.
87) Events in the MedDRA SMQ "extrapyramidal syndrome (broad)" and events coded to PT "salivary hypersecretion"

Table 69. Incidence of extrapyramidal symptom-related events (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
All adverse events	3 (3.6)	10 (11.8)	23 (27.4)	40 (31.7)	61 (49.6)	3 (1.7)	6 (5.5)	11 (9.8)	22 (11.0)	23 (10.0)
Serious adverse events	0	0	0	1 (0.8)	1 (0.8)	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	1 (1.2)	6 (7.1)	4 (3.2)	10 (8.1)	0	1 (0.9)	0	4 (2.0)	3 (1.3)
Adverse events leading to dose reduction	0	1 (1.2)	5 (6.0)	9 (7.1)	21 (17.1)	1 (0.6)	1 (0.9)	3 (2.7)	3 (1.5)	7 (3.0)
Main events										
Salivary hypersecretion	1 (1.2)	3 (3.5)	9 (10.7)	9 (7.1)	21 (17.1)	0	0	2 (1.8)	3 (1.5)	7 (3.0)
Akathisia	1 (1.2)	4 (4.7)	5 (6.0)	8 (6.3)	12 (9.8)	1 (0.6)	3 (2.7)	3 (2.7)	8 (4.0)	2 (0.9)
Tremor	0	0	5 (6.0)	5 (4.0)	16 (13.0)	0	0	2 (1.8)	4 (2.0)	6 (2.6)
Parkinsonism	0	1 (1.2)	1 (1.2)	5 (4.0)	3 (2.4)	0	0	0	1 (0.5)	1 (0.4)
Extrapyramidal disorder	0	0	2 (2.4)	2 (1.6)	4 (3.3)	0	0	0	0	2 (0.9)
Tardive dyskinesia	0	0	0	3 (2.4)	2 (1.6)	1 (0.6)	0	0	1 (0.5)	2 (0.9)
Drooling	0	1 (1.2)	1 (1.2)	2 (1.6)	3 (2.4)	0	0	2 (1.8)	1 (0.5)	3 (1.3)
Dyskinesia	0	0	0	2 (1.6)	1 (0.8)	0	0	3 (2.7)	2 (1.0)	4 (1.7)
Gait disturbance	0	0	0	0	1 (0.8)	0	2 (1.8)	0	4 (2.0)	2 (0.9)

n (Incidence [%])

- Table 70 shows the incidence of extrapyramidal symptom-related events by underlying disease category in Japanese Study J02 or pooled foreign clinical studies. Japanese Study J02 showed no major differences according to the underlying disease category. According to the pooled analyses of foreign clinical studies, the incidence tended to be slightly higher in patients with bipolar disorder/depressive disorder during the double-blind phase, but no similar trend was observed during the long-term treatment phase. Thus, there should be no major differences in the incidence of extrapyramidal symptom-related events according to the underlying disease category.

Table 70. Incidence of extrapyramidal symptom-related events by underlying disease category (Safety population)

		Japanese Study J02					Pooled foreign clinical studies				
		Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
		Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
Schizophrenia/ Schizoaffective disorder	N	53	55	54	82	79	134	82	70	154	155
	Adverse events	2 (3.8)	7 (12.7)	17 (31.5)	29 (35.4)	42 (53.2)	2 (1.5)	3 (3.7)	3 (4.3)	15 (9.7)	13 (8.4)
Bipolar disorder/ Depressive disorder	N	31	30	30	44	44	44	28	42	46	75
	Adverse events	1 (3.2)	3 (10.0)	6 (20.0)	11 (25.0)	19 (43.2)	1 (2.3)	3 (10.7)	8 (19.0)	7 (15.2)	10 (13.3)

n (Incidence [%])

- According to foreign post-marketing valbenazine safety information,[78)] 1108 extrapyramidal disorder-related events in patients treated with valbenazine 40 mg (12.08 per 100 patient-years, including 50 serious events) and 1555 extrapyramidal disorder-related events in patients treated with valbenazine 80 mg (6.30 per 100 patient-years, including 56 serious events) were reported. The main serious events were tremor (9 events in patients treated with valbenazine 40 mg, 10 events in patients treated with valbenazine 80 mg),

gait disturbance (5 events, 10 events), gait inability (7 events, 4 events), dyskinesia (5 events, 4 events), tardive dyskinesia (2 events, 7 events), dystonia (4 events, 4 events), parkinsonism (5 events, 2 events), and Parkinson's disease (3 events, 4 events).

- The US labeling was revised after the market launch to advise physicians to reduce the dose or discontinue valbenazine treatment in patients who develop clinically significant parkinson-like signs or symptoms.

As with tetrabenazine, the use of valbenazine is anticipated to lead to dysphagia. PMDA asked the applicant to explain the incidence of dysphagia associated with valbenazine.

The applicant's explanation:

- Table 71 shows the incidence of dysphagia in Japanese Study J02 or pooled foreign clinical studies. During the double-blind phase, there were no major differences in the incidence between the placebo and valbenazine groups, and no clear relationship to valbenazine was found.

Table 71. Incidence of dysphagia (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
Adverse events	0	1 (1.2)	1 (1.2)	5 (4.0)	5 (4.1)	0	2 (1.8)	0	3 (1.5)	3 (1.3)
Serious adverse events	0	0	0	0	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	0	0	1 (0.8)	0	0	0	0	0	0
Adverse events leading to dose reduction	0	0	0	1 (0.8)	1 (0.8)	0	0	0	1 (0.5)	0

n (Incidence [%])

- According to foreign post-marketing valbenazine safety information,[78)] there were 13 reports of serious dysphagia.

Based on the above, the applicant provided the following explanation about extrapyramidal symptom-related events:

- Extrapyramidal symptom-related events may be caused by reduction of monoamine release, a pharmacological action of valbenazine, and especially, the occurrence of the symptoms of hypokinesia, i.e., parkinsonism, is a concern. According to exposure-safety analyses including the data from Japanese Study J02, there was a correlation between the incidences of parkinsonism-related adverse events and akathisia-related adverse events and the exposures (C_{max} and AUC) [see Section 6.R.4.1]. Thus, those events may occur during the early phase of treatment with valbenazine, and the incidence may increase with increasing exposures of unchanged valbenazine and its active metabolite. No serious akathisia was reported in Japanese or foreign clinical studies.
- The US labeling for valbenazine has a warning/precaution for parkinsonism, but not dysphagia.
- Based on the above, parkinsonism will be listed in the CLINICALLY SIGNIFICANT ADVERSE REACTIONS section of the package insert. Although dysphagia was reported in clinical studies, dysphagia

can be associated with the symptoms of tardive dyskinesia, and no serious dysphagia-related events were reported in Japanese Study J02. Thus, dysphagia will be listed in the OTHER ADVERSE REACTIONS section of the package insert.

PMDA's view:

- In Japanese Study J02, the incidence of extrapyramidal symptom-related events was higher in the valbenazine group than in the placebo group, and there was a trend towards a higher incidence in the valbenazine 80 mg group than in the valbenazine 40 mg group. The US labeling for valbenazine[88)] has a warning/precaution for parkinsonism. The package insert in Japan for another VMAT2 inhibitor, tetrabenazine, advises that akathisia, parkinsonism, etc. may occur. The UK labeling for tetrabenazine also has warnings/precautions for akathisia, restlessness, agitation, and parkinsonism. Given these points, the package insert for valbenazine should include a precautionary statement about extrapyramidal symptom-related events including parkinsonism.
- Dysphagia occurred in the valbenazine group only, but no serious events were reported in clinical studies of valbenazine. While the package insert in Japan for tetrabenazine advises that dysphagia may occur or worsen, neither the US labeling for valbenazine[89)] nor the UK labeling for tetrabenazine, which has been approved for tardive dyskinesia and Huntington's disease, basically have a warning/precaution for dysphagia.[90)] Based on the above, there is no problem with the applicant's idea (Dysphagia will be listed in the OTHER ADVERSE REACTIONS section) at present. However, dysphagia occurred in the valbenazine group only in clinical studies, and cases of serious dysphagia have been reported in the foreign marketing experience. Thus, the applicant should watch for the occurrence of dysphagia in the post-marketing setting, collect information on dysphagia via post-marketing surveillance, and take appropriate action as needed.
- A final conclusion on the appropriateness of the above precautions will be made, taking account of comments from the Expert Discussion.

7.R.3.5 Neuroleptic malignant syndrome-related events

Valbenazine reduces the amount of monoamines released. As with tetrabenazine, valbenazine is anticipated to cause neuroleptic malignant syndrome-related events [see Section 3.R.1]. PMDA asked the applicant to explain the incidence of neuroleptic malignant syndrome-related events.

The applicant's explanation:

- Table 72 shows the incidence of neuroleptic malignant syndrome-related events[91)] in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) or pooled foreign clinical studies.[52)] The incidence was high in the valbenazine 80 mg group of Japanese Study J02, which was considered attributable to a high incidence of tremor, an extrapyramidal symptom-related event, in the valbenazine 80 mg group, because the reported events included many extrapyramidal symptom-related events.

88) The US labeling for deutetrabenazine has warnings/precautions for akathisia, restlessness, agitation, and parkinsonism.
89) The US labeling for deutetrabenazine has no particular warning/precaution for dysphagia.
90) In the UK, 2 formulations of tetrabenazine have been approved for Huntington's disease only and 2 formulations of tetrabenazine have been approved for tardive dyskinesia and Huntington's disease. Only the labeling for 1 formulation of tetrabenazine approved for tardive dyskinesia and Huntington's disease has a warning/precaution for dysphagia in patients with Huntington's disease.
91) Events in the MedDRA SMQ "neuroleptic malignant syndrome (broad)"

Table 72. Incidence of neuroleptic malignant syndrome-related events (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
All adverse events	1 (1.2)	4 (4.7)	9 (10.7)	27 (21.4)	39 (31.7)	4 (2.2)	3 (2.7)	9 (8.0)	15 (7.5)	26 (11.3)
Serious adverse events	0	0	0	1 (0.8)	3 (2.4)	0	0	0	2 (1.0)	1 (0.4)
Adverse events leading to treatment discontinuation	0	0	2 (2.4)	3 (2.4)	5 (4.1)	0	0	0	3 (1.5)	1 (0.4)
Adverse events leading to dose reduction	0	0	1 (1.2)	4 (3.2)	5 (4.1)	0	0	1 (0.9)	2 (1.0)	3 (1.3)
Main events										
Tremor	0	0	5 (6.0)	5 (4.0)	16 (13.0)	0	0	2 (1.8)	4 (2.0)	6 (2.6)
Extrapyramidal disorder	0	0	2 (2.4)	2 (1.6)	4 (3.3)	0	0	0	0	2 (0.9)
Parkinsonism	0	1 (1.2)	1 (1.2)	5 (4.0)	3 (2.4)	0	0	0	1 (0.5)	1 (0.4)
Blood CPK increased	1 (1.2)	1 (1.2)	1 (1.2)	2 (1.6)	5 (4.1)	0	1 (0.9)	0	2 (1.0)	3 (1.3)
Pyrexia	0	1 (1.2)	0	3 (2.4)	3 (2.4)	1 (0.6)	0	1 (0.9)	0	2 (0.9)
Hypertension	0	1 (1.2)	0	3 (2.4)	1 (0.8)	1 (0.6)	1 (0.9)	0	2 (1.0)	8 (3.5)
Dyskinesia	0	0	0	2 (1.6)	1 (0.8)	0	0	3 (2.7)	2 (1.0)	4 (1.7)

n (Incidence [%])

- According to foreign post-marketing valbenazine safety information,[78)] 630 neuroleptic malignant syndrome-related events in patients treated with valbenazine 40 mg (6.87 per 100 patient-years, including 57 serious events) and 818 neuroleptic malignant syndrome-related events in patients treated with valbenazine 80 mg (3.32 per 100 patient-years, including 80 serious events) were reported. The main serious events were tremor (9 events in patients treated with valbenazine 40 mg, 10 events in patients treated with valbenazine 80 mg), loss of consciousness (4 events, 10 events), dyskinesia (5 events, 4 events), dystonia (4 events, 4 events), hypotension (4 events, 4 events), confusional state (5 events, 2 events), parkinsonism (5 events, 2 events), and Parkinson's disease (3 events, 4 events), and many extrapyramidal symptom-related events were reported. One event of serious neuroleptic malignant syndrome was reported following administration of valbenazine 80 mg.
- The US labeling for valbenazine does not have a warning/precaution for neuroleptic malignant syndrome.
- Based on the above, as neuroleptic malignant syndrome was not reported in clinical studies, and the majority of related events were mild or moderate in severity, a relevant precautionary statement in the package insert is unnecessary.

PMDA's view:

- Although no events of neuroleptic malignant syndrome occurred in clinical studies, serious neuroleptic malignant syndrome was reported in the foreign marketing experience. Neuroleptic malignant syndrome can be serious if it occurs.
- The US labeling for valbenazine[92)] does not have a warning/precaution for neuroleptic malignant syndrome. The package insert in Japan for another VMAT2 inhibitor, tetrabenazine, has precautions for neuroleptic malignant syndrome, in addition to akathisia, parkinsonism, etc. The UK labeling for

92) The US labeling for deutetrabenazine has warnings/precautions for neuroleptic malignant syndrome, in addition to akathisia, parkinsonism, etc.

tetrabenazine also has warnings/precautions for neuroleptic malignant syndrome, in addition to akathisia, parkinsonism, etc.

- Based on the above, considering the potential seriousness of neuroleptic malignant syndrome, the package insert should advise about the risk of neuroleptic malignant syndrome associated with valbenazine. A final conclusion on the need for a precautionary statement will be made, taking account of comments from the Expert Discussion.

7.R.3.6 Prolactin elevation-related events

Valbenazine reduces the amount of monoamines released. As with tetrabenazine, valbenazine is anticipated to cause prolactin elevation-related events [see Section 3.R.1]. PMDA asked the applicant to explain the incidence of prolactin elevation-related adverse events.

The applicant's explanation:

- In a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) and pooled foreign clinical studies,[52)] no prolactin elevation-related events occurred during the double-blind phase. The incidences of prolactin elevation-related events were 0.8% (1 of 126 subjects) (irregular menstruation) in the valbenazine 40 mg group and 0.8% (1 of 123 subjects) (galactorrhoea) in the valbenazine 80 mg group during the long-term treatment phase of Japanese Study J02 and 1.5% (3 of 200 subjects) (blood prolactin increased [2 subjects]; and galactorrhoea [1 subject]) in the valbenazine 40 mg group and 0.4% (1 of 230 subjects) (blood prolactin increased) in the valbenazine 80 mg group during the long-term treatment phase of pooled foreign clinical studies. All those events were non-serious.
- Table 73 shows the change from baseline in blood prolactin levels in Japanese Study J02 or pooled foreign clinical studies, and there was a trend towards an increase in prolactin levels following administration of valbenazine. On the other hand, Table 74 shows the proportion of subjects with clinically significant prolactin elevation, and there were no major differences between the placebo and valbenazine groups.

Table 73. Change from baseline in blood prolactin levels (Safety population)

		Japanese Study J02				Pooled foreign clinical studies			
		N	Baseline[a)]	Last dose[a)]	Change[a)]	N	Baseline[b)]	Last dose[b)]	Change[b)]
Double-blind phase	Placebo	84	22.3 ± 35.4	22.8 ± 37.1	0.6 ± 9.3	171	643.1 ± 728.5	677.4 ± 803.6	27.1 ± 374.1
	VBZ 40 mg	82	17.8 ± 21.8	26.0 ± 28.2	8.7 ± 15.4	104	656.4 ± 87.07	859.0 ± 1031.7	232.0 ± 713.0
	VBZ 80 mg	79	22.2 ± 32.2	32.7 ± 37.1	10.7 ± 25.2	110	581.9 ± 626.5	862.3 ± 885.4	287.6 ± 679.4
Long-term treatment phase	VBZ 40 mg	120	17.6 ± 22.0	26.0 ± 31.1	8.6 ± 20.9	183	651.5 ± 838.0	832.6 ± 1007.2	193.8 ± 704.7
	VBZ 80 mg	117	22.1 ± 30.0	29.6 ± 34.1	8.1 ± 21.6	223	608.0 ± 667.5	847.4 ± 906.2	243.7 ± 657.2

Mean ± SD
a) ng/mL, b) pmol/L

Table 74. Number of subjects with clinically significant worsening of blood prolactin levels (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	46	44	41	66	63	115	65	71	121	155
No. of subjects with worsening[a)]	0	0	0	2 (3.0)	1 (1.6)	0	1 (1.5)	1 (1.4)	2 (1.7)	1 (0.6)

n (Proportion [%])
a) Subjects with blood prolactin ≥5 times the upper limit of normal

- According to foreign post-marketing valbenazine safety information,[78)] only 1 case of blood prolactin increased as a prolactin elevation-related event was reported following administration of valbenazine 40 mg (0.01 per 100 patient-years, non-serious).
- Based on the above, prolactin elevation-related events reported in Japanese Study J02 and pooled foreign clinical studies were all non-serious, and there were no major differences in the incidence between the placebo and valbenazine groups. Also according to foreign post-marketing safety information, no serious events were reported. Thus, no clinically relevant prolactin elevation-related events have been reported.
- The US labeling for valbenazine[93)] has no particular warning/precaution for prolactin elevation.
- Based on the above, prolactin elevation will be listed in the OTHER ADVERSE REACTIONS section of the package insert.[94)] Post-marketing information on prolactin elevation-related adverse events will be collected.

PMDA accepted the applicant's explanation because hyperprolactinaemia was not observed in clinical studies, and no serious prolactin elevation-related adverse events have been reported.

7.R.3.7 Hypersensitivity-related events

PMDA asked the applicant to explain the incidence of hypersensitivity-related events.

The applicant's explanation:

- Table 75 shows the incidence of hypersensitivity-related events[95)] in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) or pooled foreign clinical studies.[52)] There was no trend towards a higher incidence of hypersensitivity-related events in the valbenazine group than in the placebo group. Only 1 subject in the valbenazine 80 mg group had a serious adverse event (rash) during the long-term treatment phase of Japanese Study J02.

93) The US labeling for deutetrabenazine and the UK labeling for tetrabenazine have a warning/precaution for hyperprolactinaemia.
94) The package insert in Japan for tetrabenazine advises that if prolactin elevation and menstrual abnormality, galactorrhoea, etc., occur, dose reduction or treatment discontinuation should be considered.
95) Events in the MedDRA SMQs "anaphylactic/anaphylactoid shock conditions (narrow)," "anaphylactic reaction (narrow)," "hypersensitivity (narrow)," "angioedema (narrow)," "drug reaction with eosinophilia and systemic symptoms syndrome (narrow)," and "severe cutaneous adverse reactions (broad)" and events coded to PTs "eye pruritus," "pruritus (pruritus generalised)," "genital rash," "perineal rash," "auricular swelling," "skin swelling," "rash papular," and "erythema"

Table 75. Incidence of hypersensitivity-related events in Japanese and foreign clinical studies (Safety population)

	Japanese Study J02					Pooled foreign clinical studies				
	Double-blind phase			Long-term treatment phase		Double-blind phase			Long-term treatment phase	
	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg	Placebo	VBZ 40 mg	VBZ 80 mg	VBZ 40 mg	VBZ 80 mg
N	84	85	84	126	123	178	110	112	200	230
All adverse events	6 (7.1)	5 (5.9)	7 (8.3)	23 (18.3)	18 (14.6)	2 (1.1)	1 (0.9)	0	4 (2.0)	1 (0.4)
Serious adverse events	0	0	0	0	1 (0.8)	0	0	0	0	0
Adverse events leading to treatment discontinuation	1 (1.2)	1 (1.2)	1 (1.2)	1 (0.8)	3 (2.4)	0	0	0	1 (0.5)	0
Adverse events leading to dose reduction	0	0	0	0	0	0	0	0	0	0
Main events										
Urticaria	0	2 (2.4)	2 (2.4)	3 (2.4)	2 (1.6)	0	0	0	1 (0.5)	0
Eczema	3 (3.6)	1 (1.2)	1 (1.2)	4 (3.2)	3 (2.4)	0	0	0	0	0
Stomatitis	1 (1.2)	0	0	4 (3.2)	3 (2.4)	0	0	0	0	0
Pruritus	0	0	0	2 (1.6)	2 (1.6)	2 (1.1)	1 (0.9)	0	2 (1.0)	0

n (Incidence [%])

- According to foreign post-marketing valbenazine safety information,[78)] 291 hypersensitivity-related events in patients treated with valbenazine 40 mg (3.17 per 100 patient-years, including 60 serious events) and 323 hypersensitivity-related events in patients treated with valbenazine 80 mg (1.31 per 100 patient-years, including 73 serious events) were reported. The main serious events were urticaria (20 events in patients treated with valbenazine 40 mg, 22 events in patients treated with valbenazine 80 mg), angioedema (11 events, 10 events), rash (9 events, 11 events), and hypersensitivity (5 events, 5 events).
- The US labeling for valbenazine was revised after the market launch to add a precautionary statement about hypersensitivity.
- Based on the above, many of the hypersensitivity-related events reported in Japanese Study J02 and pooled foreign clinical studies were non-serious, and there were no major differences in the incidence between the placebo and valbenazine groups. Meanwhile, serious hypersensitivity-related events were reported in the foreign marketing experience, and serious hypersensitivity symptoms may occur following administration of valbenazine. Thus, serious hypersensitivity will be listed in the CLINICALLY SIGNIFICANT ADVERSE REACTIONS section of the package insert.

PMDA accepted the applicant's explanation ("Since serious hypersensitivity-related events were reported in the foreign marketing experience, the package insert will include a precautionary statement about hypersensitivity-related events associated with valbenazine").

7.R.4 Indication

Patients with moderate or severe tardive dyskinesia were enrolled in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02). PMDA asked the applicant to explain the appropriateness of the proposed indication of "tardive dyskinesia."

The applicant's explanation:

- In Japanese Study J02 as in a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304), "moderate or severe tardive dyskinesia, as indicated by a score on AIMS item 8 (global tardive dyskinesia severity) of either 3 or 4 based on assessment of screening videos by central reviewers" was listed as an inclusion criterion, and patients with moderate or severe tardive dyskinesia were enrolled. The results of Japanese Study J02 demonstrated the efficacy and safety of valbenazine in these patients [see Section 7.2.1].
- Mild tardive dyskinesia rarely needs treatment due to the lack of awareness of involuntary movements (*Eur Psychiatry*. 2011; 26: 293-6). The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, third edition[66)] recommends treatment with a VMAT2 inhibitor in patients with moderate to severe tardive dyskinesia and states that treatment with a VMAT2 inhibitor can also be considered for patients with mild tardive dyskinesia on the basis of such factors as patient preference or effect on psychosocial functioning. This guideline also states that when using scales such as the AIMS, there is no specific score threshold that suggests a need for intervention [see Section 7.R.1].
- Based on the above, since treatment according to the patient's condition is recommended also in patients with mild tardive dyskinesia, the appropriate indication should be "tardive dyskinesia." Also in the US where valbenazine has been approved, valbenazine is indicated for all patients, regardless of the severity of the disease, and the indication is "tardive dyskinesia."
- The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, third edition[66)] states that for a diagnosis of tardive dyskinesia, assessment for other contributors to a movement disorder is warranted. Prior to the use of valbenazine, it is important to make a differential diagnosis from other diseases associated with dyskinesia symptoms. Thus, the PRECAUTIONS CONCERNING INDICATION section will advise that valbenazine should be used in patients with a diagnosis of tardive dyskinesia.

PMDA's view:

The above explanation by the applicant is acceptable. There is no problem with the proposed indication of "tardive dyskinesia" and the PRECAUTIONS CONCERNING INDICATION section advising that valbenazine should be used in patients with a diagnosis of tardive dyskinesia. A conclusion on the appropriateness of the indication and the precautionary statement will be made, taking account of comments from the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Selection of dosing regimen

PMDA asked the applicant to explain the rationale for the dosing regimen used in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) and a foreign phase III study (Reference data CTD 5.3.5.1-5, Study 1304) and then the appropriateness of the proposed dosing regimen of valbenazine.

The applicant's explanation about the rationale for the dosing regimen used in Foreign Study 1304 and the approved recommended dose of valbenazine in the US:

- Foreign phase II studies (Reference data CTD 5.3.5.2-1, Study 1001; Reference data CTD 5.3.5.1-2, Study 1101; Reference data CTD 5.3.5.1-3, Study 1201; Reference data CTD 5.3.5.1-4, Study 1202) showed the tolerability of multiple doses of valbenazine 12.5 to 100 mg/day and the dose-dependent efficacy of valbenazine. According to exposure-response analyses, the percent change from baseline in the AIMS total score was predicted to plateau at 40 to 80 mg of valbenazine, and valbenazine 100 mg was not expected to be more effective than 80 mg. Given these findings, valbenazine 40 mg and 80 mg were selected for Foreign Study 1304 [see Section 6.R.2]. Based on FDA's advice that a fixed-dose study is more appropriate than a flexible-dose study in order to evaluate the effective dose range and the dose response relationship, a fixed-dose study of valbenazine 40 mg and 80 mg was planned. However, as the tolerability and efficacy of valbenazine were considered to be affected in patients with factors associated with increased exposure, the starting dose was 40 mg for all patients, and subjects in the valbenazine 80 mg group were to receive valbenazine 40 mg for the first week.
- In Foreign Study 1304, a fixed-sequence testing procedure was used to adjust for multiplicity of between-group comparisons of the primary endpoint (AIMS total score at Week 6) and secondary endpoint (CGI-TD score at Week 6). The first step demonstrated a statistically significant difference between valbenazine 80 mg and placebo for the AIMS total score. In the second step, no statistically significant differences between valbenazine 80 mg and placebo were detected for the CGI-TD score. In the third step, comparison of valbenazine 40 mg and placebo for the AIMS total score suggested the efficacy of valbenazine 40 mg. Based on the above results, 80 mg was selected as the recommended dose of valbenazine in the US labeling, and the following dosing regimen was selected: The initial dosage for valbenazine is 40 mg once daily, and after 1 week, increase the dose to the recommended dosage of 80 mg once daily.

The applicant's explanation about the rationale for the dosing regimen used in Japanese Study J02 and the appropriateness of the proposed dosing regimen:

- Although a Japanese phase I study (CTD 5.3.3.1-1, Study J01) demonstrated the tolerability of single doses of 40 mg, 80 mg, and 160 mg of valbenazine and multiple doses of valbenazine 40 mg in healthy adult subjects, as 3 subjects treated with multiple doses of valbenazine 80 mg had depression-related adverse events, and treatment was discontinued in all subjects in the valbenazine 80 mg multiple-dose cohort based on the provisions of the protocol, the tolerability of multiple doses of 80 mg could not be demonstrated. These results showed a similar trend to the results of a foreign phase I study (CTD 5.3.4.1-3, Study 0901), which demonstrated the tolerability of single doses of valbenazine 75 to 150 mg and multiple doses of valbenazine 50 mg in healthy adult subjects, but could not demonstrate the tolerability of multiple doses of valbenazine 100 mg because adverse events leading to treatment discontinuation occurred in 37.5% (3 of 8) of subjects treated with multiple doses of valbenazine 100 mg. The possible reason for these findings is as follows: Since antipsychotics (dopamine receptor blocking agents) have been reported to produce negative symptoms of schizophrenia in healthy volunteers (*Am J Psychiatry*. 2006; 163: 488-93), the response to valbenazine in healthy adult subjects is considered different from that in patients with tardive dyskinesia who have hypersensitive dopamine receptors [see Section 7.R.3.2]. In healthy subjects, multiple dosing of

valbenazine in the maximum dose range for patients with tardive dyskinesia resulted in excessive reduction of monoamines in the CNS, leading to frequent nervous system or psychiatric disorder adverse events.

- Japanese Study J01 and foreign phase I studies (CTD 5.3.4.1-1, Study 1401; Reference data CTD 5.3.2.2-2, Study 1502; Reference data CTD 5.3.1.1-2, Study 1504; Reference data CTD 5.3.1.2-1, Study 1602) indicated that there are no major differences in the pharmacokinetics of valbenazine between Japanese and non-Japanese populations [see Section 6.R.1].
- Based on the above, in Japanese Study J02 as in Foreign Study 1304, valbenazine 40 mg and 80 mg were selected, and subjects in the valbenazine 80 mg group were to receive 40 mg for the first week.
- In Japanese Study J02, a fixed-sequence testing procedure was used to adjust for multiplicity for the primary endpoint of the AIMS total score at Week 6. Statistically significant differences between valbenazine 80 mg and placebo and between valbenazine 40 mg and placebo were detected for the AIMS total score in the first step and in the second step, respectively, and valbenazine 80 mg showed greater improvement compared with valbenazine 40 mg. The proportions of subjects with a dose reduction of study drug during the long-term treatment phase were 13.5% (17 of 126 subjects) in the valbenazine 40 mg group and 31.7% (39 of 123 subjects) in the valbenazine 80 mg group, etc., showing a trend towards a dose-dependent decrease in tolerability, while efficacy was sustained also in subjects with a dose reduction in the valbenazine 80 mg group, as in the valbenazine 40 mg group (Table 76). Also, there were no major safety problems with either 40 mg or 80 mg of valbenazine in Japanese Study J02.

Table 76. Time course of AIMS total score as assessed by central raters (Japanese Study J02, ITT population)

	Valbenazine 40 mg		Valbenazine 80 mg		Valbenazine 80 mg (Subjects with dose reduction)	
	AIMS total score	Change from baseline	AIMS total score	Change from baseline	AIMS total score	Change from baseline
Double-blind baseline[a)]	7.9 ± 4.1 (125)		7.6 ± 4.2 (124)		6.8 ± 3.9 (39)	
Week 16	5.3 ± 4.0 (93)	-3.0 ± 3.8	3.3 ± 3.2 (72)	-5.2 ± 4.3	3.0 ± 2.5 (30)	-4.7 ± 3.9
Week 32	4.9 ± 4.1 (80)	-3.5 ± 3.9	3.4 ± 3.5 (57)	-5.6 ± 4.3	2.9 ± 2.9 (23)	-4.7 ± 3.8
Week 48 (at the end of study treatment)	5.0 ± 4.2 (64)	-3.7 ± 4.2	3.3 ± 3.3 (49)	-5.7 ± 4.6	2.7 ± 2.9 (21)	-4.9 ± 3.9
Week 52 (at the end of follow-up period)	8.1 ± 4.3 (65)	-0.6 ± 3.6	8.1 ± 5.0 (47)	-0.5 ± 4.1	7.6 ± 4.6 (21)	0.0 ± 3.7

Mean ± SD (N)
a) Double-blind baseline was used for both subjects in the placebo and valbenazine groups during the double-blind period.

- Based on the above, the initial dose of valbenazine should be 40 mg, and after ≥1 week, a maintenance dose of 40 or 80 mg should be chosen according to the patient's condition.

PMDA's view:

- In Japanese Study J02, there was a trend towards improvement in the AIMS total score as assessed by central raters in the valbenazine 80 mg group compared with the valbenazine 40 mg group. On the other hand, the incidence of adverse events was higher with valbenazine 80 mg, and the proportions of subjects with a dose reduction of study drug during the long-term treatment phase were 13.5% (17 of 126 subjects) in the valbenazine 40 mg group and 31.7% (39 of 123 subjects) in the valbenazine 80 mg group, indicating that the 80 mg dose of valbenazine is less tolerable. Thus, the initial dose of valbenazine should be 40 mg, and the dose may be increased with caution, according to the patient's condition, after ≥1 week, based on tolerability.

- A final conclusion on the appropriateness of the proposed dosing regimen, including the appropriateness of dose adjustment in patients with factors associated with increased exposure [see Section 6.R.4], will be made, taking also account of comments from the Expert Discussion.

7.R.5.2 Need for dose adjustment of valbenazine in the case of modification of concomitant medications for the management of underling disease during treatment with valbenazine

Changes in the regimen of concomitant medications for the management of the underlying disease etc.[96)] were allowed during the extension period of a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02). PMDA asked the applicant to explain the need for dose adjustment of valbenazine in the case of discontinuation or dose reduction of these concomitant medications.

The applicant's explanation:

- Table 77 shows the time course of the AIMS total score as assessed by central raters in subjects who discontinued or reduced the dose of concomitant medications for the management of the underlying disease etc. without re-increasing the dose or using additional medications and other subjects in Japanese Study J02. Improvement with valbenazine was sustained throughout the extension period in both groups of subjects, and there were no major differences with or without discontinuation or dose reduction of concomitant medications.

Table 77. Time course of AIMS total score as assessed by central raters with or without discontinuation or dose reduction of concomitant medications (Japanese Study J02, ITT population)

	Subjects who discontinued or reduced the dose of concomitant medications		Other subjects[a)]	
	AIMS total score	Change from baseline	AIMS total score	Change from baseline
Double-blind baseline[b)]	7.1 ± 3.9 (29)		7.8 ± 4.2 (220)	
Week 16	6.6 ± 5.0 (14)	-2.4 ± 0.9	4.2 ± 3.6 (151)	-4.1 ± 0.3
Week 32	5.9 ± 4.3 (10)	-3.5 ± 1.1	4.2 ± 3.9 (127)	-4.4 ± 0.4
Week 48 (at the end of study treatment)	7.0 ± 3.9 (7)	-3.9 ± 1.0	4.1 ± 3.9 (106)	-4.6 ± 0.4
Week 52 (at the end of follow-up period)	9.7 ± 5.5 (7)	-1.1 ± 1.4	8.0 ± 4.5 (105)	-0.5 ± 0.4

Mean ± SD (N)

a) Subjects who increased the dose of concomitant medications at least once or who received additional medications for the management of underlying disease etc. were categorized as other subjects.

b) Double-blind baseline was used for both subjects in the placebo and valbenazine groups during the double-blind period.

- The proportions of subjects meeting the criteria for a clinically meaningful worsening in the CDSS total score or the MADRS total score were 20.0% (6 of 30 subjects) in subjects who discontinued or reduced the dose of concomitant medications and 26.0% (57 of 219 subjects) in other subjects, showing no major differences with or without discontinuation or dose reduction of concomitant medications.
- Based on the above, there were no particular efficacy or safety problems in subjects who had discontinuation or reduction of the dose of concomitant medications for the management of the underlying disease etc. during treatment with valbenazine. Thus, the dose adjustment of valbenazine is unnecessary. The inclusion of a relevant precautionary statement in the package insert is also unnecessary.

96) Maintenance medications for schizophrenia, schizoaffective disorder, bipolar disorder, or depressive disorder or hypnotics (benzodiazepines), and psychotropic medications to treat extrapyramidal symptoms etc. (including antiparkinsonian drugs, excluding hypnotics)

Since the number of subjects who discontinued or reduced the dose of concomitant medications for the management of the underlying disease etc. without re-increasing the dose or using additional medications was limited in Japanese Study J02, the impact of discontinuation or dose reduction of concomitant medications on the study results are unclear. However, these results did not suggest the need for dose adjustment of valbenazine in the case of dose modifications of concomitant medications. Thus, PMDA accepted the applicant's explanation that the inclusion of a relevant precautionary statement in the package insert is unnecessary.

7.R.5.3 Valbenazine treatment discontinuation

PMDA asked the applicant to explain the need for valbenazine discontinuation when the symptoms of tardive dyskinesia have improved after treatment with valbenazine.

The applicant's explanation:

- In a foreign phase IV study (Reference data CTD 5.3.5.1-7, Study TD4002), patients with tardive dyskinesia[97] received open-label valbenazine 80 mg[98] for 8 weeks. Then, patients were randomized to the placebo or valbenazine group and received placebo or continued with the same dose of valbenazine as taken during the open-label period for 8 weeks in a double-blind manner. Table 78 shows the time course of the AIMS total score as assessed by central raters. The persistence of the effect of valbenazine was observed during continued treatment with valbenazine, but the symptoms tended to worsen after valbenazine discontinuation (at the end of follow-up period).

Table 78. Time course of AIMS total score as assessed by central raters (Foreign Study TD4002)

	Placebo		Valbenazine	
	AIMS total score	Change from baseline[a)]	AIMS total score	Change from baseline[a)]
Open-label baseline	10.3 ± 3.7 (58)		11.0 ± 4.1 (59)	
Double-blind baseline (Week 8)	6.6 ± 3.7 (58)	-3.7 ± 4.1	7.3 ± 4.1 (59)	-3.7 ± 4.3
Week 12	7.6 ± 4.1 (56)	1.1 ± 5.1	7.1 ± 3.7 (58)	-0.3 ± 2.6
Week 16 (at the end of study treatment)	7.1 ± 3.8 (53)	0.7 ± 4.9	5.8 ± 4.4 (56)	-1.7 ± 2.7
Week 20 (at the end of follow-up period)	8.0 ± 3.7 (53)	1.6 ± 4.6	8.5 ± 3.8 (55)	1.1 ± 4.3

Mean ± SD (N)
a) Change from open-label baseline at Week 8 only, Change from double-blind baseline at other time points

- In Foreign Study TD4002, the changes from double-blind baseline in the AIMS total score (mean ± SD) by antipsychotic use at double-blind baseline were assessed. In subjects without antipsychotic use (6 subjects in the placebo group, 7 subjects in the valbenazine group), the changes from double-blind baseline in the AIMS total score at Week 12 were 0.3 ± 1.2 in the placebo group and −1.1 ± 3.8 in the valbenazine group, and the changes from double-blind baseline in the AIMS total score at Week 16 were 0.7 ± 2.0 in the placebo

97) Key inclusion criteria: (1) clinical diagnoses of schizophrenia, schizoaffective disorder, or mood disorder with neuroleptic-induced tardive dyskinesia, (2) male and female patients with moderate or severe tardive dyskinesia 18-85 years of age, and (3) psychiatrically stable (including a Brief Psychiatric Rating Scale [BPRS] score of <50 at screening)
98) Subjects were to receive valbenazine 40 mg for the first week followed by 80 mg. Subjects who were unable to tolerate the 80 mg dose were allowed to have their dose decreased to 40 mg at the discretion of the investigator.

group and −0.7 ± 2.7 in the valbenazine group. In subjects with antipsychotic use (52 subjects, 52 subjects), the changes from double-blind baseline in the AIMS total score at Week 12 were 1.2 ± 5.4 in the placebo group and −0.1 ± 2.4 in the valbenazine group, and the changes from double-blind baseline in the AIMS total score at Week 16 were 0.7 ± 5.2 in the placebo group and −1.8 ± 2.7 in the valbenazine group. Regardless of antipsychotic use, the AIMS total score tended to worsen in the placebo group, suggesting that the symptoms worsen after discontinuation of valbenazine.

- In a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02), an extension treatment period was followed by a 4-week follow-up period, and the efficacy of valbenazine after discontinuation was also evaluated. After valbenazine discontinuation (at the end of follow-up period), the AIMS total score returned to baseline values (Table 49). Among subjects with centrally rated AIMS total score at 4 weeks after the last dose of valbenazine (112 subjects) in Japanese Study J02, 89 subjects had recurrence[99)] and 23 subjects did not have recurrence. The proportions of subjects without antipsychotic use at baseline were 25.8% (23 of 89 subjects) in subjects with recurrence and 30.4% (7 of 23 subjects) in subjects without recurrence. There were no major differences in the proportion of subjects without antipsychotic use between subjects with and without recurrence, suggesting no association between antipsychotic use and recurrence of the symptoms after valbenazine discontinuation.
- Based on the above, among patients with improvement in the symptoms of tardive dyskinesia following administration of valbenazine, those who do not have recurrence of the symptoms even after valbenazine discontinuation have not been identified. Thus, even when the symptoms of tardive dyskinesia have improved after treatment with valbenazine, all patients do not have to discontinue valbenazine treatment. Thus, a particular precautionary statement about valbenazine discontinuation in the package insert is unnecessary. If the risk of adverse events etc. associated with continued treatment with valbenazine is considered to outweigh its benefit of improvement of symptoms, valbenazine treatment will be discontinued.

PMDA's view

Since even patients with improvement in the symptoms of tardive dyskinesia following administration of valbenazine showed worsening of the symptoms after valbenazine discontinuation, all patients do not have to discontinue valbenazine treatment. PMDA accepted the applicant's explanation that a precautionary statement about valbenazine discontinuation in the package insert is unnecessary.

7.R.6 Post-marketing investigations

The applicant's explanation:

As the post-marketing surveillance of valbenazine, a specified use-results survey in patients with tardive dyskinesia with an observation period of 1 year for each patient and a target sample size of 500 patients is planned to be conducted to collect information on the long-term safety and efficacy of valbenazine in clinical practice. Using the data obtained from the post-marketing surveillance, the applicant will investigate the incidence of death, the effects of patient characteristics such as comorbidities/concomitant medications, and

99) Among subjects with centrally-rated AIMS total score at 4 weeks after the last dose of valbenazine, based on the lower quartile of changes from baseline (−3 points), subjects without recurrence were defined as subjects with change from baseline of <−3 and subjects with recurrence were defined as subjects with change from baseline of ≥−3.

other issues. To investigate deaths among patients treated with valbenazine in the post-marketing experience, the applicant will collect detailed information, regardless of causality, from spontaneous reports as well as from the post-marketing surveillance, wherever possible, thereby assessing a possible association with valbenazine, the trend of incidence, etc., and exploring risk factors [see Section 7.R.3.1].

PMDA's view:

There is no particular problem with the applicant's explanation ("As the post-marketing surveillance of valbenazine, a specified use-results survey in patients with tardive dyskinesia will be conducted to collect information on the long-term safety and efficacy of valbenazine in clinical practice. Using the data obtained from the post-marketing surveillance, the applicant will investigate the incidence of death, the effects of patient characteristics such as comorbidities/concomitant medications, and other issues."). A final conclusion on the appropriateness of post-marketing investigations will be made, taking account of comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that valbenazine has efficacy in the treatment of tardive dyskinesia, and that valbenazine has acceptable safety in view of its benefits. Valbenazine is clinically meaningful because it offers a new treatment option for patients with tardive dyskinesia. PMDA considers that the safety, indication, dosage and administration, and post-marketing investigations of valbenazine, etc., need to be further discussed.

PMDA has concluded that valbenazine may be approved if valbenazine is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 4, 2022

Product Submitted for Approval

Brand Name	Dysval Capsules 40 mg
Non-proprietary Name	Valbenazine Tosilate
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	April 22, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy and indication

PMDA's conclusions:

The Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) met both its primary and secondary efficacy endpoints in patients with tardive dyskinesia, demonstrating the efficacy of valbenazine, with no factors clearly affecting the efficacy of valbenazine [see Section 7.R.2 in the Review Report (1)]. Given these and other results, there is no problem with the proposed indication of "tardive dyskinesia" [see Section 7.R.4 in the Review Report (1)].

There is no problem with the applicant's explanation ("Prior to the use of valbenazine, it is important to make a differential diagnosis from other diseases associated with dyskinesia symptoms. Thus, the PRECAUTIONS CONCERNING INDICATION section of the package insert will advise that valbenazine should be used in patients with a diagnosis of tardive dyskinesia."). In Japan, no clinical practice guidelines for tardive dyskinesia have been published yet, nor is there any written guidance on differential diagnosis of tardive dyskinesia. Thus, the package insert should advise that valbenazine should be used in patients with a diagnosis of tardive dyskinesia according to the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, third edition, which describes the differential diagnosis of tardive dyskinesia. The differential diagnosis and other relevant information described in the American Psychiatric Association

Practice Guideline for the Treatment of Patients with Schizophrenia should be disseminated using the information materials for healthcare professionals.

The expert advisors supported the above conclusions by PMDA.

The expert advisors made the following comments.

- Tardive dyskinesia is an involuntary movement disorder that occurs due to long-term treatment with dopamine D_2 receptor blocking agents such as first-generation antipsychotics. The following strategies are recommended in the management of tardive dyskinesia: The dose of the causative antipsychotic drug should be minimized or discontinued, and if psychotic symptoms worsen, atypical antipsychotics should be added (Manuals for Management of Individual Serious Adverse Drug Reactions [MHLW, 2009]). However, dopamine D_2 receptor blockade is the key pharmacological action of antipsychotics in the treatment of schizophrenia. The dose of antipsychotics cannot be reduced or discontinued uniformly even if tardive dyskinesia develops; this makes treatment difficult. Few appropriate therapies have been available for patients with tardive dyskinesia, and not a few patients have impaired daily activities. Because no drugs have been approved for the treatment of tardive dyskinesia in Japan, valbenazine can offer a new treatment option and, therefore, is highly clinically meaningful.
- If clinical practice guidelines for tardive dyskinesia are developed in Japan in future, and the differential diagnosis of tardive dyskinesia is described in the guidelines, the statement in the PRECAUTIONS CONCERNING INDICATION section of the package insert should be revised for replacement with a statement mentioning the Japanese guidelines.

Based on the above, PMDA instructed the applicant to include the following statement in the PRECAUTIONS CONCERNING INDICATION section of the package insert: Valbenazine should be used in patients with a diagnosis of tardive dyskinesia according to the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, third edition. PMDA also instructed the applicant to disseminate the differential diagnosis of tardive dyskinesia and other relevant information described in the American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, using the information materials for healthcare professionals. The applicant responded appropriately.

1.2 Safety

PMDA's view on the safety profile of valbenazine [see Section 7.R.3.1 in the Review Report (1)]:

- In a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02), the incidences of adverse events leading to treatment discontinuation or dose reduction were higher in the valbenazine 80 mg group than in the valbenazine 40 mg group. Thus, valbenazine 80 mg is less tolerable than valbenazine 40 mg.
- An assessment of the association of death cases in Japanese Study J02 with concomitant/previous illnesses or concomitant medications suggested no specific factors associated with mortality. There was no trend towards higher exposures of unchanged valbenazine and its active metabolite NBI-98782. The mortality rate in Japanese Study J02 is not clearly higher than that in patients with tardive dyskinesia.

PMDA's view on specific adverse events [see Sections 7.R.3.2 to 7.R.3.7 in the Review Report (1)]:

- As to depression- and suicide-related events, valbenazine reduces the amount of monoamines released, and the occurrence of depression- and suicide-related adverse events is anticipated. In Japanese Study J02, the incidence of depression- and suicide-related adverse events tended to be higher in the valbenazine group than in the placebo group. In Japanese Study J02, the proportion of patients with a clinically meaningful worsening in the CDSS total score or the MADRS total score after study drug administration was higher in both dose groups of valbenazine than in the placebo group. Furthermore, of 8 subjects who died in Japanese Study J02, 6 subjects had possible worsening depression. Given the above findings, the package insert in Japan should advise about the risk of depression and suicide following administration of valbenazine, although the US labeling for valbenazine does not have a warning/precaution for depression/suicide, aggression, etc.[84)]
- In Japanese Study J02, the incidence of extrapyramidal symptom-related events was higher in the valbenazine group than in the placebo group, and there was a trend towards a higher incidence in the valbenazine 80 mg group than in the valbenazine 40 mg group. Although the US labeling for valbenazine has a warning/precaution for parkinsonism only,[88)] the package insert in Japan should include a precautionary statement about extrapyramidal symptom-related events including parkinsonism.
- Dysphagia occurred in the valbenazine group only, but no serious events were reported in clinical studies of valbenazine. The US labeling for valbenazine does not have a warning/precaution for dysphagia.[89)] Thus, there is currently no problem with the applicant's idea ("Dysphagia will be listed in the OTHER ADVERSE REACTIONS section.). However, dysphagia occurred in the valbenazine group only in clinical studies. Given this fact and other findings, the applicant should watch for the occurrence of dysphagia in the post-marketing setting, collect information on dysphagia via post-marketing surveillance, and take appropriate action as needed.
- Although no events of neuroleptic malignant syndrome occurred in clinical studies, serious neuroleptic malignant syndrome was reported in the foreign marketing experience. Neuroleptic malignant syndrome can be serious if it occurs. Although the US labeling for valbenazine does not have a warning/precaution for neuroleptic malignant syndrome,[92)] the package insert should advise about the risk of neuroleptic malignant syndrome associated with valbenazine, considering its potential seriousness.

Based on the above, PMDA considered that valbenazine has acceptable safety, provided that patients are closely monitored for the possible occurrence of adverse drug reactions during treatment with valbenazine.

The expert advisors supported the above conclusions by PMDA and made the following comments.

- An assessment of the association of death cases in Japanese Study J02 with concomitant/previous illnesses or concomitant medications suggested no specific factors associated with mortality. The mortality rate in Japanese Study J02 is not clearly higher than that in patients with tardive dyskinesia. Thus, valbenazine has acceptable safety, provided that patients are closely monitored for the possible occurrence of adverse drug reactions during treatment with valbenazine.

- When the incidence of depression- and suicide-related adverse events in the long-term treatment phase of Japanese Study J02 was analyzed by underlying disease category, the incidence of depression- and suicide-related adverse events in the valbenazine group was 25.0% (22 of 88 subjects) in patients with bipolar disorder/depressive disorder, which tended to be higher than the incidence in patients with schizophrenia/schizoaffective disorder (9.9%, 16 of 161 subjects). No such differences in the incidence of adverse events according to underlying disease category were observed in foreign clinical studies. The US labeling for valbenazine does not have a precaution/warning for depression- and suicide-related adverse events. Nevertheless, given the incidence of adverse events, a trend towards worsening in the depressive symptom rating scales in the Japanese clinical study, and other findings, there is no problem with including a precautionary statement about the risk of depression and suicide following administration of valbenazine in the package insert in Japan.
- Since VMAT2 inhibitors induce extrapyramidal disorder by reducing the release of neurotransmitters, there is no problem with including a precautionary statement about extrapyramidal symptom-related events such as parkinsonism in the package insert.
- Since the incidence of adverse events of dysphagia was low, there is currently no problem with the following measures: Dysphagia will be listed in the OTHER ADVERSE REACTIONS section of the package insert, and the occurrence of dysphagia will be watched for via post-marketing surveillance. Dysphagia should be categorized as an important potential risk in the risk management plan.
- The pathophysiological etiology of neuroleptic malignant syndrome is unknown, and the risk of neuroleptic malignant syndrome associated with VMAT2 inhibitors has been reported to be low. However, clinicians should remain vigilant for early signs of neuroleptic malignant syndrome in all patients treated with any drugs that affect brain dopamine activity (*Clin Psychopharmacol Neurosci*. 2020; 18: 322-326). Thus, there is no problem with the following measure: Considering the potential seriousness of neuroleptic malignant syndrome, the package insert will advise about the risk of neuroleptic malignant syndrome associated with valbenazine.
- There is an increased risk of tardive dyskinesia associated with typical antipsychotics. The following strategies are recommended in the management of tardive dyskinesia: The dose of the causative antipsychotic drug should be minimized or discontinued, and if psychotic symptoms worsen, atypical antipsychotics should be added (Manuals for Management of Individual Serious Adverse Drug Reactions [MHLW, 2009]). Since dopamine D_2 receptor blockade is the key pharmacological action of antipsychotics in the treatment of schizophrenia, antipsychotics cannot be discontinued uniformly even if tardive dyskinesia develops; this makes treatment difficult. However, dopamine D_2 receptor blockade is not always essential in the treatment of bipolar disorder or depressive disorder. Although valbenazine will offer a new treatment option for patients with tardive dyskinesia, physicians should take care to ensure that discontinuation and dose reduction of the causative antipsychotic drug are adequately considered for each individual patient. On the other hand, it should be noted that dose reduction or discontinuation of the causative drug may lead to psychotic exacerbation and relapse.

Based on the above, PMDA instructed the applicant to include the following precaution information in the package insert, and the applicant responded appropriately. PMDA also instructed the applicant to disseminate

information on the incidence of adverse events by underlying disease category in Japanese Study J02 using the information materials for healthcare professionals, and the applicant responded appropriately [for the risk management plan, see Section "1.4 Risk management plan (draft)"].

- Depression- and suicide-related events
- Extrapyramidal symptom-related events including parkinsonism
- Neuroleptic malignant syndrome-related events
- Since tardive dyskinesia occurs due to long-term treatment with antipsychotics, dose reduction or discontinuation of the causative drug should be considered. A careful decision should be madeon dose reduction or discontinuation of the causative drug, which may lead to psychotic exacerbation and relapse.

1.3 Dosage and administration

1.3.1 Selection of dosing regimen and dosing regimen in patients with factors associated with increased exposure

PMDA's view:

In a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02), while there was a trend towards improvement in the AIMS total score as assessed by central raters in the valbenazine 80 mg group compared with the valbenazine 40 mg group, the 80 mg dose of valbenazine was considered less tolerable. Thus, the initial dose of valbenazine should be 40 mg, and the dose may be increased with caution, according to the patient's condition, after ≥1 week, based on tolerability [see Section 7.R.5.1 in the Review Report (1)].

PMDA's view on the need for dose adjustment in patients with factors associated with increased exposure of valbenazine [see Sections 6.R.4.1 to 6.R.4.4 in the Review Report (1)]:

- The exposure-safety analyses of the data from Japanese Study J02 showed a trend towards increasing incidences of somnolence-related adverse events, parkinsonism-related adverse events, and akathisia-related adverse events with increasing exposures (C_{max} and AUC) of unchanged valbenazine and its active metabolite NBI-98782. The maximum tolerated dose of valbenazine in patients with tardive dyskinesia is 100 mg/day. Thus, there is no problem with the applicant's idea ("The package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients with factors associated with increased exposure").
- CYP2D6 PMs seem to show approximately 1.8-fold and approximately 2.0-fold increases in the C_{max} and AUC of NBI-98782, respectively, following administration of valbenazine (Table 41), compared with non-PMs. Plasma concentrations in CYP2D6 PMs are predicted to be highly variable from patient to patient. Give these findings, there is no problem with the applicant's idea ("The package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients who are known to have genetically deficient CYP2D6 activity").
- Coadministration of valbenazine with a strong CYP2D6 inhibitor, paroxetine, in non-PMs, did not alter the exposures of unchanged valbenazine, but increased the C_{max} and AUC of NBI-98782 by 1.4- and 1.9-fold, respectively (Table 33). Thus, there is no problem with the applicant's idea ("The package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients receiving concomitant CYP2D6 inhibitors [strong CYP2D6 inhibitors]").

- Coadministration of valbenazine with a strong CYP3A inhibitor, ketoconazole, in non-PMs, increased the C_{max} and AUC of unchanged valbenazine by 1.5- and 2.1-fold, respectively, and the C_{max} and AUC of NBI-98782 by 1.6- and 2.1-fold, respectively (Table 33). Thus, there is no problem with the applicant's idea ("The package insert will advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients receiving concomitant strong CYP3A inhibitors").
- In the case of concomitant use of valbenazine with moderate CYP3A inhibitors in non-PMs, 1.17- and 1.61-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and 1.37- and 1.77-fold increases in the C_{max} and AUC of NBI-98782, respectively, were predicted [see Section 6.R.4.3 in the Review Report (1)], and a >2-fold increase in the exposures is not anticipated. Although the inhibition potency of moderate CYP3A inhibitors is not necessarily established, it is preferable not to increase the dose to 80 mg from a safety point of view.
- In CYP2D6 PMs concomitantly receiving a strong or moderate CYP3A inhibitor, approximately 1.2- to 1.3-fold and approximately 1.6- to 2.1-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and approximately 2.2- to 2.7-fold and approximately 4.0- to 5.8-fold increases in the C_{max} and AUC of NBI-98782, respectively, were predicted. In patients without factors associated with increased exposure concomitantly receiving both a CYP2D6 inhibitor (a strong or moderate CYP2D6 inhibitor) and a strong or moderate CYP3A inhibitor, approximately 1.2- to 1.3-fold and approximately 1.6- to 2.1-fold increases in the C_{max} and AUC of unchanged valbenazine, respectively, and approximately 2.0- to 2.6-fold and approximately 3.3- to 5.3-fold increases in the C_{max} and AUC of NBI-98782, respectively, were predicted (Table 44). In these cases, even when the proposed commercial formulation in Japan, i.e., the 40-mg capsule is administered to the patients, the levels of exposure are predicted to well exceed those experienced in clinical studies. Thus, concomitant use of valbenazine with a strong or moderate CYP3A inhibitor in CYP2D6 PMs and concomitant use of valbenazine with both a CYP2D6 inhibitor (a strong or moderate CYP2D6 inhibitor) and a strong or moderate CYP3A inhibitor in patients without factors associated with increased exposure should be avoided wherever possible. However, since there is no drug approved for the treatment of tardive dyskinesia in Japan, coadministration of valbenazine with these drugs in these patients may become unavoidable. In this case, valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg. The patient's condition should be closely monitored during treatment with valbenazine, with adequate attention to the possible occurrence of adverse drug reactions. These precautionary statements should be included in the package insert.
- In patients with moderate or severe hepatic impairment compared with patients with normal hepatic function, the C_{max} of unchanged valbenazine increased by 2.0- and 2.5-fold, respectively, the AUC of unchanged valbenazine increased by 1.9- and 2.4-fold, respectively, the C_{max} of NBI-98782 increased by 2.1- and 2.2-fold, respectively, and the AUC of NBI-98782 increased by 2.8- and 3.4-fold, respectively (Table 31). Even when the proposed commercial formulation in Japan, i.e., the 40-mg capsule is administered to these patients, the levels of exposure are predicted to well exceed those experienced in clinical studies. Thus, the package insert should advise that valbenazine 40 mg should be administered, and the dose should not be increased to 80 mg in patients with moderate or severe hepatic impairment.
- At present, the proposed commercial formulation in Japan is the 40-mg capsule only. If the above patients are unable to tolerate the 40 mg dose of valbenazine, there will be no option for dose reduction. Since there

is no drug approved for the treatment of tardive dyskinesia in Japan, an investigation should be conducted so that the 20-mg formulation can be administered to these patients.

The expert advisors supported the above conclusions by PMDA and made the following comments.

- For concomitant use of valbenazine with moderate CYP3A inhibitors in non-PMs, a dose increase to 80 mg is also acceptable, provided that valbenazine is used with adequate attention to the possible occurrence of adverse drug reactions, because (i) concomitant use with moderate CYP3A inhibitors was also allowed in Japanese Study J02 and (ii) there is no drug approved for the treatment of tardive dyskinesia in Japan.
- As to drugs that require caution when coadministered with valbenazine, drugs potentially coadministered with valbenazine in clinical practice should be specified in the information materials for healthcare professionals etc.
- Since valbenazine 80 mg is less tolerable than valbenazine 40 mg, caution is needed for the safety of valbenazine 40 mg in patients with factors associated with increased exposure. It is desirable that the 20-mg formulation can be administered to these patients as early as possible.

Based on the above comments, and given that the 20-mg formulation is currently under development, PMDA instructed the applicant to modify the proposed dosage and administration statement as shown below, and the applicant responded appropriately. PMDA also instructed the applicant to provide necessary precautions and information regarding patients with factors associated with increased exposure of valbenazine who require dose adjustment and drugs that require caution when coadministered with valbenazine in the package insert and information materials for healthcare professionals, and the applicant responded appropriately. Moreover, PMDA instructed the applicant to continue to develop the 20-mg formulation and submit a marketing application promptly so that the 20-mg formulation of valbenazine can be administered.

Dosage and Administration

The usual adult dosage is 40 mg of valbenazine administered orally once daily. The dose may be adjusted according to the patient's symptoms. The maximum dosage is 80 mg once daily.

1.3.2 Precautions about QT/QTc interval prolongation effect

PMDA's view on precautions about QT/QTc interval prolongation effect [see Section 6.R.5 in the Review Report (1)]:

- The results of a clinical pharmacology study that evaluated the effect of valbenazine on the QT/QTc interval (CTD 5.3.4.1-1, Study 1401) and of a pooled concentration-QT analysis of data from Foreign Study 1401, Foreign Study 1301 (CTD 5.3.4.1-2), and Foreign Study 0901 (CTD 5.3.4.1-3) suggest that a ≥2.3-fold increase in the C_{max} of its active metabolite NBI-98782 increases the risk of QT/QTc prolongation. Although the degree of QT prolongation is not clinically significant at the plasma concentrations of NBI-98782 expected with the human doses in patients without factors associated with increased exposure of NBI-98782, the risk of QT prolongation is likely to increase in patients with factors associated with increased exposure of NBI-98782.

- According to analyses of data from patients with factors associated with increased exposure of NBI-98782 versus those without factors associated with increased exposure, the C_{max} of NBI-98782 following multiple dosing of valbenazine 40 mg may increase by ≥2-fold in CYP2D6 PMs concomitantly receiving a strong or moderate CYP3A inhibitor, non-PMs concomitantly receiving both a CYP2D6 inhibitor (a strong or moderate CYP2D6 inhibitor) and a strong or moderate CYP3A inhibitor, and patients with moderate or severe hepatic impairment [see Section 6.R.4 in the Review Report (1)]. The possibility that the risk of QT prolongation is increased in these patient populations cannot be ruled out. Thus, the package insert should advise that the dose of valbenazine should not be increased to 80 mg in these patient populations, and that the patient's condition should be closely monitored by, e.g., regular ECG monitoring prior to and during treatment with valbenazine.
- There is no problem with the applicant's explanation ("The package insert will advise that valbenazine may cause an increase in the QT interval in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval, and that the patient's condition should be closely monitored by, e.g., regular ECG monitoring prior to and during treatment with valbenazine. The package insert will include a precautionary statement about coadministration with drugs that prolong the QT interval.").

The expert advisors largely supported the above conclusions by PMDA and made the following comments.

- It should be noted that there are limitations to discussion on the association of death cases in a Japanese phase II/III study (CTD 5.3.5.1-1, Study J02) with concomitant/previous illnesses or concomitant medications, because a very limited number of subjects were analyzed in the clinical study.
- Given that tardive dyskinesia occurs after exposure to antipsychotics, and that many antipsychotics prolong QT, the target population for valbenazine, i.e., patients with tardive dyskinesia are considered a population at increased risk of torsades de pointes and sudden death.
- Patients with prolonged QTc on baseline ECG and patients with clinically significant cardiac diseases were excluded from Japanese Study J02 and a foreign phase III study. For this reason, the applicant should establish adequate rules to prevent QT prolongation following administration of valbenazine in the post-marketing setting. Although routine ECGs for all patients receiving valbenazine are not necessary, the need for ECG to manage the risk of QT prolongation associated with valbenazine should be determined, taking account of patient factors and the situations associated with increased exposure of valbenazine.
- Regarding patient factors, the use of valbenazine should be avoided in patients with a history of congenital long QT syndrome or torsades de pointes who form a population at increased risk of excessive QT prolongation or torsades de pointes., because even regular ECG monitoring prior to and during treatment with valbenazine cannot ensure the prevention of the risk of torsades de pointes in the patient population. The safety of valbenazine is acceptable in patients receiving drugs known to prolong QT, provided that the patients are closely monitored with regular ECGs prior to and during treatment with valbenazine for the possible occurrence of adverse reactions to valbenazine. The package insert should advise that valbenazine should be used with caution in patients at risk of QT prolongation (patients with arrhythmias [such as marked bradycardia] or a history of arrhythmias, patients with congestive cardiac failure, patients with hypokalaemia or hypomagnesaemia). In addition, prior to the use of valbenazine, patients should be assessed for a history of syncope and a family history of sudden death.

- The situations associated with increased exposure of valbenazine were assessed based on a pooled concentration-QT analysis of data from Foreign Study 1401, Foreign Study 1301, and Foreign Study 0901. These data should be used as a reference, because Foreign Study 0901 included doses in the lower range (valbenazine 75-100 mg) and this study was conducted at a different site from that used for Foreign Study 1401 and Foreign Study 1301.

Based on the above comments, PMDA instructed the applicant to take the following measures, and the applicant responded appropriately.

- The package insert should specify that valbenazine is contraindicated in patients with a history of congenital long QT syndrome or torsades de pointes.
- The package insert should advise that the patient's condition should be closely monitored by, e.g., regular ECG monitoring prior to and during treatment with valbenazine, in patients at risk of QT prolongation (patients with arrhythmias [such as marked bradycardia] or a history of arrhythmias, patients with congestive cardiac failure, patients with hypokalaemia or hypomagnesaemia) and patients receiving drugs known to prolong QT.
- The risk of QT prolongation was assessed using data from Foreign Study 1401. On the basis of the exposures at 160 mg of valbenazine, the package insert should advise that the patient's condition should be closely monitored by, e.g., regular ECG monitoring prior to and during treatment with valbenazine, in the following patients.
  - ➢ Patients known to have genetically deficient CYP2D6 activity
  - ➢ Patients with moderate or severe hepatic impairment (Child-Pugh class B or C)
  - ➢ Patients receiving strong CYP2D6 inhibitors (e.g., paroxetine, quinidine)
  - ➢ Patients receiving strong CYP3A inhibitors (e.g., itraconazole, clarithromycin)
  - ➢ Patients receiving both a CYP2D6 inhibitor and a moderate or strong CYP3A inhibitor
- The information materials for healthcare professionals should advise that prior to the use of valbenazine, patients should be assessed also for a history of syncope and a family history of sudden death.

1.4 Risk management plan (draft)

Based on the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for valbenazine should include the safety specification presented in Table 79, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 80.

Table 79. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Somnolence, Sedation · Serious hypersensitivity · Extrapyramidal disorder	· Depression and suicide · QT prolongation · Adverse events due to hyperprolactinaemia · Confusion · Neuroleptic malignant syndrome · Dysphagia	None
Efficacy specification		
None		

Table 80. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
· Early post-marketing phase vigilance · Specified use-results survey	· Disseminate data gathered during early post-marketing phase vigilance · Develop information materials to be distributed to healthcare professionals · Develop information materials to be distributed to patients

Based on the following comment from the expert advisors at the Expert Discussion, PMDA requested the applicant to conduct post-marketing surveillance to investigate the above issues.

- It is important to assess the safety and efficacy of valbenazine in patients treated with valbenazine 80 mg. Since valbenazine is a drug with a novel mechanism of action for the treatment of tardive dyskinesia, it is beneficial to promptly provide healthcare professionals in clinical practice with the results of an interim analysis of surveillance data, including the incidences of depression and suicide, with an appropriate cutoff date. Accrual of additional patients should be planned if (but not limited to) a very limited number of patients treated with valbenazine 80 mg have been accrued at the interim data cutoff.

The applicant's explanation:

A specified use-results survey in patients with tardive dyskinesia presented in Table 81 will be conducted. The survey aims to accrue 150 patients treated with valbenazine 80 mg. An interim analysis at a data cutoff is planned to occur when a total of 250 patients have been accrued. The results of the interim analysis will be provided to healthcare professionals promptly. Then, additional patients will be accrued as needed.

Table 81. Outline of use-results survey (draft)

Objective	To collect information on the long-term safety and efficacy of valbenazine in clinical practice.
Survey method	Central registry system
Population	Patients with tardive dyskinesia
Observation period	1 year
Planned sample size	500 patients
Main survey items	Patient characteristics (gender, age, underlying disease, duration of tardive dyskinesia, extrapyramidal symptoms, comorbidities, the severity of hepatic impairment, etc.) Treatment status (use of valbenazine, use of concomitant medications, use of antipsychotics after discontinuation of valbenazine) CGI-TD Clinical global severity of the underlying disease Adverse events, Clinical laboratory tests

PMDA accepts the above, but considers that the results obtained from this survey should promptly be provided to healthcare professionals in clinical practice.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, after modifying the proposed dosage and administration, with the following approval condition. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Tardive dyskinesia

Dosage and Administration

The usual adult dosage is 40 mg of valbenazine administered orally once daily. The dose may be adjusted according to the patient's symptoms. The maximum dosage is 80 mg once daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

AhR	Aryl hydrocarbon receptor
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under Concentration-time Curve
BARS	Barnes Akathisia Rating Scale
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CDSS	Calgary Depression Scale for Schizophrenia
CHO	Chinese Hamster Ovary
CGI-TD	Clinical Global Impression of Change - Tardive Dyskinesia
CL	Clearance
CL/F	Apparent Total Clearance
C_{max}	Maximum Concentration
COVID-19	Coronavirus disease
CPK	Creatine Phosphokinase
CQA	Critical Quality Attribute
CRP	C-reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CTD	Common Technical Document
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eGFR	estimated Glomerular Filtration Rate
EM	Extensive Metabolizer
FDA	Food and Drug Administration
FMO	Flavin-containing monooxygenase
FOB	Functional observation battery
GC	Gas Chromatography
HEK	Human Embyonic Kidney
hERG	human ether-à-go-go-related gene
HPLC	High performance liquid chromatography
5-HT_{2B}	serotonin (5-hydroxytryptamine) 2B receptor
5-HT_7	serotonin (5-hydroxytryptamine) 7 receptor
IC_{50}	Half Maximal (50%) Inhibitory Concentration
ICH M3 guideline	"Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" (PFSB/ELD Notification No. 0219-4 dated February 19, 2010)
ICH M7 guideline	"Partial Revision (Addendum) to the Guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/PED Notification No. 0627-1 dated June 27, 2018)
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3A guideline	"Revision of the Guideline on Impurities in New Drug Substances" (PMSB/ELD Notification No.1216001 dated December 16, 2002)
ICH Q3B guideline	"Revision of the Guideline on Impurities in New Drug Products" (PMSB/ELD Notification No. 0624001 dated June 24, 2003)
IM	Intermediate Metabolizer
ITT	Intent-to-treat
IR	Infrared absorption spectroscopy

Ki	Inhibitory Constant
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
MADRS	Montgomery-Åsberg Depression Rating Scale
MATE	Multidrug and Toxin Extrusion
MDCK	Madin-darby Canine Kidney
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MMRM	Mixed-effects Model Repeated Measures
MS	Mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
NOAEL	no observed adverse effect level
NZW	New Zealand White
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
P450	Cytochrome P450
PANSS	Positive And Negative Syndrome Scale
P-gp	P-glycoprotein
PM	Poor Metabolizer
PPK	Population Pharmacokinetics
PTP	Press Through Packaging
PXR	Pregnane X receptor
QbD	Quality by Design
(Q)SAR	(Quantitative) Structure-Activity Relationship
QTc	Corrected QT
QTcF interval	Fridericia-corrected QT Interval
SAS	Simpson – Angus extrapyramidal side effects scale
SD	Sprague Dawley
Study J01	Study MT-5199-J01 (CTD 5.3.3.1-1)
Study J02	Study MT-5199-J02 (CTD 5.3.5.1-1)
Study 0901	Study NBI-98854-0901 (CTD 5.3.4.1-3)
Study 1001	Study NBI-98854-1001 (Reference data CTD 5.3.5.2-1)
Study 1101	Study NBI-98854-1101 (Reference data CTD 5.3.5.1-2)
Study 1102	Study NBI-98854-1102 (CTD 5.3.3.3-1)
Study 1201	Study NBI-98854-1201 (Reference data CTD 5.3.5.1-3)
Study 1202	Study NBI-98854-1202 (Reference data CTD 5.3.5.1-4)
Study 1204	Study NBI-98854-1204 (Reference data CTD 5.3.1.1-1)
Study 1301	Study NBI-98854-1301 (CTD 5.3.4.1-2)
Study 1303	Study NBI-98854-1303 (Reference data CTD 5.3.3.3-2)
Study 1304	Study NBI-98854-1304 (Reference data CTD 5.3.5.1-5)
Study 1401	Study NBI-98854-1401 (CTD 5.3.4.1-1)
Study 1402	Study NBI-98854-1402 (Reference data CTD 5.3.5.2-2)
Study 1504	Study NBI-98854-1504 (CTD 5.3.1.1-2)
Study 1506	Study NBI-98854-1506 (Reference data CTD 5.3.5.2-3)
Study 1602	Study NBI-98854-1602 (CTD 5.3.1.2-1)
$t_{1/2}$	Elimination Half-Life
The product	Dysval Capsules 40 mg
t_{max}	Time to Reach Maximum Concentration
UM	Ultra-rapid Metabolizer
UV-VIS	Ultraviolet-visible spectroscopy
Valbenazine	Valbenazine Tosilate
V_d	volume of distribution
V_d/F	apparent volume of distribution
VMAT1	vesicular monoamine transporter-1

VMAT2	vesicular monoamine transporter-2
YMRS	Young Mania Rating Scale
γ-GTP	Gamma-glutamyltransferase