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APPLICATION NUMBER:

209241Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology/Toxicology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO

NDA: 209241

Submission date: 8/11/2016

Drug: valbenazine

Applicant: Neurocrine Biosciences Inc.

Indication: Treatment of tardive dyskinesia

Reviewing Division: Division of Psychiatry Products

Discussion:

The pharmacology/toxicology reviewer and supervisor recommended that valbenazine could be approved from the pharmacology/toxicology perspective for the indication listed above.

Although the exact mechanism of valbenazine in the treatment of tardive dyskinesia is unknown, it and its metabolites demonstrate inhibition of vesicular monoamine transporter 2 (VMAT2) similar to the approved drug, tetrabenazine. Therefore, the established pharmacologic class of "Vesicular Monoamine Transporter 2 Inhibitor" is appropriate.

Fertility was decreased in rats treated with valbenazine although this was considered to be related to an increase in prolactin and not a direct effect. A pre/postnatal study in rats showed an increase in stillbirths and postnatal pup mortality. These effects are described in the proposed labeling.

A 6-month study in transgenic rasH2 mice and a 2-year carcinogenicity study in Sprague-Dawley rats showed no drug-related neoplasms.

Conclusions:

The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that this NDA may be approved for the above indication.

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/s/

PAUL C BROWN
04/07/2017

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 209241
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Indication: Treatment of Tardive Dyskinesia
Sponsor: Neurocrine Biosciences Inc. San Diego, CA
Review Division: Division of Psychiatry Products
Reviewer: Darren Fegley, Ph.D., DABT
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Disclaimer

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1 Executive Summary

1.1 Introduction

Valbenazine (INGREZZA) is a new molecular entity under development for the treatment of Tardive Dyskinesia (TD). The mechanism of action of valbenazine for the treatment of TD is unknown. However, its efficacy could be mediated through inhibition of the Vesicular Monoamine Transporter 2 (VMAT2). Valbenazine is not approved outside of the U.S.

1.2 Brief Discussion of Nonclinical Findings

Valbenazine displays moderate affinity for rat and human VMAT2 ($K_i \sim 110$ and 150 nM, respectively). Three metabolites of valbenazine also bind rat and human VMAT2 with moderate to relatively high affinity; alpha-dihydrotrabenazine (NBI-98782, $K_i \sim 2$ and 3 nM, respectively), M10b (NBI-679006, $K_i \sim 28$ and 74 nM, respectively), and M14 (NBI-136110, $K_i \sim 160$ and 220 nM, respectively). It should be noted that NBI-98782 is also a metabolite of the FDA approved drug XENAZINE® (trabenazine, NDA 021894).

Valbenazine and NBI-98782 have no activity at VMAT1 when tested at concentrations up to $10 \mu\text{M}$ and no appreciable affinity ($K_i > 5 \mu\text{M}$) for other targets including dopaminergic (including D_2), serotonergic (including 5-HT_{2B}), adrenergic, histaminergic, muscarinic, and NMDA receptors or other monoamine transporters such as the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT). In safety pharmacology studies, valbenazine moderately inhibited the hERG channel with an IC_{50} of $2 \mu\text{M}$ and produced a moderate prolongation of the QTc interval in dogs at a dose which is 6 times the maximum recommended human dose (MRHD) of 80 mg/day based on mg/m^2 body surface area. In-line with valbenazine's apparent lack of affinity for VMAT1 no adverse cardiovascular effects were noted in dogs at doses up to 12.5 times the MRHD of 80 mg/day based on mg/m^2 , with the exception of QTc prolongation where the NOEL across all nonclinical toxicology studies was 5 times the MRHD of 80 mg/day based on mg/m^2 .

Valbenazine and its metabolites likely act as selective inhibitors of VMAT2 in vivo. Briefly, valbenazine displayed efficacy in multiple rat models sensitive to depletion of monoamines when tested at doses ~ 0.1 to 4 times the MRHD of 80 mg based on mg/m^2 . Moreover, it should be noted that the majority of valbenazine treatment-related effects observed in nonclinical studies are consistent with depletion of monoamines from the CNS (e.g. CNS depression, ataxia, hyperprolactinemia, and ptosis).

Valbenazine is extensively metabolized in rats, dogs, and humans with little unchanged drug excreted via biliary or renal pathways. In vivo radiolabeled mass balance studies conducted in rats, dogs, and humans demonstrated that metabolism was qualitatively, but not quantitatively, similar across species. The primary difference in metabolism is related to the extent of ester hydrolysis of valbenazine to form NBI-98782 (alpha-dihydrotrabenazine), which is significantly greater in the rat than in the dog, mouse, or human. This may partially account for the increased sensitivity of rats to valbenazine

effects noted in the nonclinical studies, owing to the higher affinity (55 times) of NBI-98782 for VMAT2 relative to valbenazine.

Distribution of valbenazine-related material was extensive in both pigmented and non-pigmented rats, with the ratio of tissue to plasma radioactivity ≥ 1 for all tissues (including brain) and > 10 for highly perfused tissues (e.g. lungs, liver, kidney). Valbenazine-related material was highly distributed to the pigmented region of the eye, ratio of tissue to plasma radioactivity ~ 4000 and a $t_{1/2} \sim 1000$ hrs., suggesting extensive melanin binding. Due to the fact that the rat studies were conducted in albino animals, no valbenazine treatment-related eye findings were noted in the dog or pigmented mouse, and no phototoxicity was observed in BALB/c 3T3 mouse fibroblasts, the clinical significance of the extensive distribution of valbenazine-related material to the eye is unclear at present. A similar distribution to pigmented skin was not observed.

Pivotal toxicology studies were carried out in Sprague Dawley rats (oral gavage), CD-1 mice (oral gavage), and Beagle dogs (oral capsule). Rats were the most sensitive species, with mortality and excessive morbidity observed at exposures roughly equivalent to the MRHD of 80 mg based on both AUC and mg/m^2 . In general, other nonclinical species tended to tolerate higher exposures of valbenazine, with no adverse effects occurring at doses 2- to 5 times the MRHD based on both AUC and mg/m^2 and no mortality or excessive morbidity at therapeutically relevant exposures. It should be noted that exposure to alpha-dihydrotetrabenazine (the primary pharmacologically active circulating metabolite in human), was similar at both the no observed adverse effect level (NOAEL) and maximum tolerated doses across nonclinical species.

The primary target organ of toxicity across nonclinical species is the CNS. Clinical signs consistent with depletion of monoamines from the CNS (e.g. decreased activity, ataxia, trembling, and ptosis) were noted in rats, mice, and dogs. Rodents also exhibited increased activity prior to dosing when valbenazine levels are at trough and for a couple of days following cessation of dosing, suggestive of a potential withdrawal phenomenon, although no specific studies to address this were conducted. Valbenazine administration was also associated with tremors and convulsions in both rats and dogs. In rats, self-resolving myoclonic jerking or clonic convulsions generally lasting < 1 minute were noted at doses approximately equivalent to the MRHD of 80 mg based on mg/m^2 . This seizure-like activity was late developing, requiring at least 2 months of dosing, was not associated with t_{max} , but instead with handling (dosing, detailed clinical examinations, etc.), and was not observed following dosing cessation. In addition, extensive neuropathology examinations were undertaken in these studies and no CNS lesions were noted. Taken together these findings suggest that the convulsions are the result of chronic administration and that this process appears to be reversible. Similar effects in rats were noted with tetrabenazine (XENAZINE[®], NDA 021894), another VMAT2 inhibitor, indicating this effect may be common to this class of drugs. In dogs, tremors and wobbly gait were observed in subchronic and chronic studies at doses ≥ 2 times the MRHD of 80 mg based on mg/m^2 . These effects were related to periods of significant tremor in proximal muscles (head, neck, shoulders) with no associated electroencephalogram abnormalities or neuropathology lesions.

However, death occurred following doses ≥ 35 mg/kg/day which is at least 15 times the MRHD on mg/m². Although the toxicological significance of these findings in dogs is unclear at present, the current indication is an involuntary movement disorder affecting the tongue, lips, face, trunk, and extremities, they may be clinically meaningful.

Valbenazine was not mutagenic in the in vitro bacterial reverse mutation test (Ames) or clastogenic in the in vitro mammalian chromosomal aberration assay or in the in vivo rat bone marrow micronucleus assay. Valbenazine was not carcinogenic and did not induce tumors in rats or mice at doses up to 0.24 times and 4.6 times the MRHD of 80 mg based on mg/m², respectively. Valbenazine did not produce structural abnormalities, functional impairment, or alterations in growth in rats or rabbits at doses 2 times and 12 times the MRHD of 80 mg based on mg/m², respectively. In rats, valbenazine adversely affected male and female fertility, although this effect is likely due to changes in mating behavior and disruption of estrous cyclicity owing to hyperprolactinemia and not a direct toxic effect of valbenazine on reproductive organs. Valbenazine administration increased the incidence of stillbirths and postnatal pup mortality at doses below the MRHD of 80 mg/day based on mg/m². In addition, valbenazine and the metabolites, NBI-98782 and NBI-136110, were detected in fetuses (gestation days 11 and 13), as well as in milk and in pups (lactation day 14) following administration to pregnant or lactating rats. These data indicate risk to benefit should be considered when administering valbenazine to pregnant or breastfeeding women as fetal and infant exposure are likely to occur.

All impurities in drug substance and/or product present at levels above the qualification threshold have been adequately qualified in nonclinical studies.

1.3 Recommendations

1.3.1 Approvability

Based on the review and evaluation of data generated from administration of valbenazine to animals this application is recommended for approval from a Pharmacology/Toxicology perspective for the indication of tardive dyskinesia.

1.3.2 Additional Non Clinical Recommendations

Not applicable

1.3.3 Labeling

Sections of the labeling supported by nonclinical data were being negotiated with the Applicant at the time of completion of this review. This document will be amended with a final version of the labeling when it becomes available.

2 Drug Information

2.1 Drug

CAS Registry Number

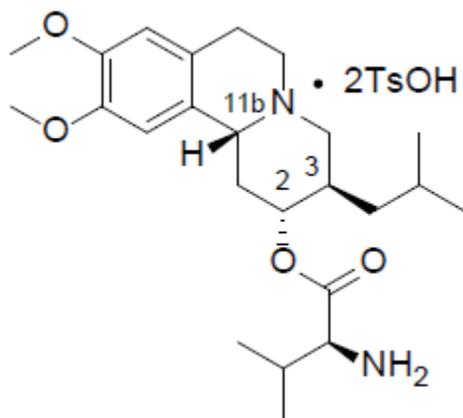
1639208-54-0

Generic Name

Valbenazine

Code Name

NBI-98854

Chemical NameIUPAC: (2*R*,3*R*,11*bR*)-3-Isobutyl-9,10-dimethoxy-1,3,4,6,7,11hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-yl *L*-valinate bis(4-methylbenzenesulfonate)**Molecular Formula/Molecular Weight**Valbenazine: $C_{24}H_{38}N_2O_4$ M.W. = 418.57 g/molValbenazine ditosylate: $C_{38}H_{54}N_2O_{10}S_2$ M.W. = 762.97 g/mol**Structure or Biochemical Description****Pharmacologic Class**

Vesicular Monoamine Transporter 2 (VMAT2) Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND111591 (Valbenazine for the treatment of Tardive Dyskinesia)

(b) (4)

2.3 Drug Formulation

Valbenazine capsules are intended for oral administration only. Each valbenazine capsule appears as a (b) (4) purple opaque cap/ (b) (4) white opaque body containing 73 mg of valbenazine ditosylate, which is equivalent to 40 mg of valbenazine free base. Components and quantitative composition of the 40 mg valbenazine capsules are shown in the following table provided by the Sponsor.

Table 1 Quantitative Composition of the Valbenazine 40 mg Capsules

Component	Quality Standard	Function	Weight (mg/unit)	% (w/w)
NBI-98854 ditosylate ^a	In-house	Drug Substance	73.0 ^b	(b) (4)
Mannitol (b) (4)	USP	(b) (4)	(b) (4)	(b) (4)
Partially pregelatinized (b) (4) starch (b) (4)	NF			
Fumed silica (b) (4)	NF			
Magnesium stearate (b) (4)	NF			
(b) (4)	(b) (4)			
(b) (4) gelatin capsules, Size 1; (b) (4) purple opaque cap, (b) (4) white opaque body; axially printed with 'VBZ' over '40' in black ink, on both the cap and body ^{e, f}	Pharmaceutical	Capsule Shell	--	1 capsule
(b) (4)				

^b NBI-98854 ditosylate theoretical quantity per unit is equivalent to 40.0 mg of NBI-98854 free base (b) (4)

^e Gelatin capsule shells contain gelatin (b) (4) FD&C Red #40 (b) (4) FD&C Blue #1 (b) (4) and candurin silver fine (b) (4)

^f Specification provided in 3.2.P.4.1.

2.4 Comments on Novel Excipients

There are no novel excipients in the valbenazine formulation. All excipients are of compendial grade with the exception of the (b) (4) gelatin capsule shell. The components of the (b) (4) gelatin capsule shell are acceptable and shown in the following table provided by the Sponsor.

Table 2 Quantitative Composition of the Valbenazine 40 mg Capsules

Capsule Shell	Component	Amount	Grade
(b) (4)	(b) (4)	(b) (4)	21 CFR §73.1350: Exempt
			NF
	Candurin Silver Fine		21 CFR §73.1350: Exempt
	FD&C Blue #1		21 CFR §74.1101: Required and listed
	FD&C Red #40		21 CFR §74.1340: Required and listed
	Gelatin		NF

2.5 Comments on Impurities/Degradants of Concern

In silico evaluation using Leadscope and DEREK Nexus was performed to evaluate the genotoxic potential of valbenazine related impurities and degradants. There were 2 potential impurities, (b) (4), and one potential impurity/degradant, (b) (4), that contained structural alerts for genotoxicity. As a result these substances were tested in vitro in the Ames assay and found to be negative for mutagenicity. In addition (b) (4) was tested in the in vitro mammalian chromosomal aberrations assay and found to be negative.

Table 3 In Vitro Qualification of potential Impurities/Degradants with Structural Alerts for Genotoxicity

Impurity	In Vitro Assay ^a	GLP Compliance	Concentrations Evaluated	Results
(b) (4)	AMES	Yes	(b) (4)	Negative
	AMES	Yes		Negative
	AMES Chrom. Ab.	Yes Yes		Negative Negative

a. Salmonella (TA98, TA100, TA1535, and TA1537) and Escherichia coli (WP2uvrA) bacterial strains were used in the Ames assay. Human peripheral blood lymphocytes were used in the chromosomal aberration assay.

In addition to the valbenazine-related impurities discussed above the Sponsor also identified several potential genotoxic impurities that may be present in the drug substance (b) (4)

The Sponsor proposes to limit these individual impurities to not more than (NMT) (b) (4) ppm/day. This proposal is acceptable based on the following considerations: Individual genotoxic impurities (GTI) should be limited to NMT the threshold of toxicological concern (TTC) of (b) (4) µg unless otherwise justified. There is no available data that indicates a lower TTC should be used and the Sponsor did not provide a rationale to use a higher TTC. 80 mg of valbenazine freebase corresponds to 145.8 mg of valbenazine ditosylate. Therefore an acceptable GTI limit would be = (b) (4) µg/day divided by (b) (4) g/day = (b) (4) ppm/day. Therefore (b) (4) ppm is acceptable.

The Sponsor proposes to limit the total potential GTIs to NMT (b) (4) ppm. This is also acceptable based on the following considerations: Multiple GTIs should be limited to a total of NMT (b) (4) µg. 80 mg of valbenazine freebase corresponds to 145.8 mg of valbenazine ditosylate. Therefore an acceptable GTI limit would be = (b) (4) µg/day divided by (b) (4) g/day = (b) (4) ppm/day. Therefore (b) (4) ppm is acceptable.

In addition to the potential valbenazine-related impurities with structural alerts for genotoxicity discussed above the Sponsor also assessed the general toxicity of several

additional impurities/degradants. The overall toxicity of organic impurities related to the drug substance was assessed in rodent and nonrodent studies to assure adequate coverage at the maximum recommended human dose of 80 mg/day. The proposed drug substance and drug product specifications are qualified from the toxicological perspective. The following table (adapted from table provided by Sponsor) summarizes the Sponsor's proposed acceptance criteria for impurities and degradants along with the supporting nonclinical information and relevant safety margins.

Table 4 In Vivo Impurity Qualification

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Valbenazine is under development for the treatment of adult patients with Tardive Dyskinesia (TD). The initial dose of valbenazine is 40 mg/day for one week after which the dose will be increased to the MRHD of 80 mg/day.

2.7 Regulatory Background

This NDA is being submitted for the approval of valbenazine for the treatment of TD.

(b) (4)

Fast Track designation was granted in January 2012 and Breakthrough Therapy designation was granted in October 2014 to Neurocrine Biosciences for the development of valbenazine for the treatment of TD. In January 2015 a full pediatric study waiver was requested and granted for the development of valbenazine for the treatment of TD. In March 2016 a rolling submission of the NDA for the development of valbenazine for the treatment of TD was granted.

3 Studies Submitted

3.1 Studies Reviewed

All study reports relevant to the development of valbenazine for the treatment of TD have been reviewed.

3.2 Studies Not Reviewed

As TD is primarily an adult indication and a full-waiver was granted for pediatric development,

(b) (4)

(b) (4)

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

In Vitro Studies

Valbenazine (NBI-98854) displays moderate affinity for VMAT2 in both rats (striatal cell membranes) and humans (platelet cell membranes) ($K_i = 110$ and 150 nM, respectively). Valbenazine is metabolized to three pharmacologically active metabolites (Table 5, adapted from table provided by Sponsor): alpha-dihydrotrabenzazine (NBI-98782), M10b (NBI-679006), and M14 (NBI-136110). Of the circulating drug-related material, including valbenazine, NBI-98782 displays the highest affinity for both rat and human VMAT2 ($K_i \sim 1.0$ to 2.8 and 2.6 to 3.3 nM, respectively). It should be noted that NBI-98782 is also a metabolite of the FDA approved drug XENAZINE® (trabenzazine, NDA 021894).

Table 5 Primary Pharmacodynamics

Test Article	Rat Striatal VMAT2	Human Platelet VMAT2	Total [14 C]valbenazine-related material in human plasma following a 50 mg dose (%)	Total [14 C]valbenazine-related material in rat plasma following a 15 mg dose (%)
	Ki Value (nM)	Ki Value (nM)		
Valbenazine	110	150	42.4	8.8
NBI-98782	1.0 to 2.8	2.6 to 3.3	9.9	18.2
NBI-136110	160	220	12.7	7.3
NBI-679006	28	74	8.2	32.3

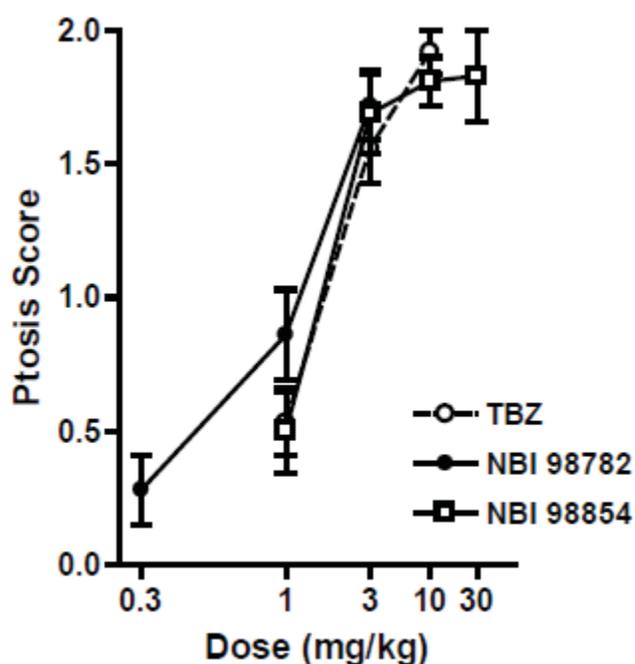
In Vivo Studies

To investigate whether valbenazine or the metabolite, NBI-98782, inhibit VMAT2 in vivo the Sponsor utilized rat models of monoamine depletion as surrogate markers. These

models included palpebral ptosis (\downarrow dopamine or norepinephrine), decreased locomotor activity (\downarrow dopamine or norepinephrine), and increased serum prolactin (\downarrow dopamine). It should be noted that although these models are also sensitive to blockade of certain receptors or inhibition of other transporters/enzymes, valbenazine and NBI-98782 lack affinity for these targets. Therefore any activity in these models is likely due to inhibition of VMAT2 as opposed to, for example, dopaminergic D2 receptor antagonism. For a detailed discussion of secondary pharmacology see section 4.2 below.

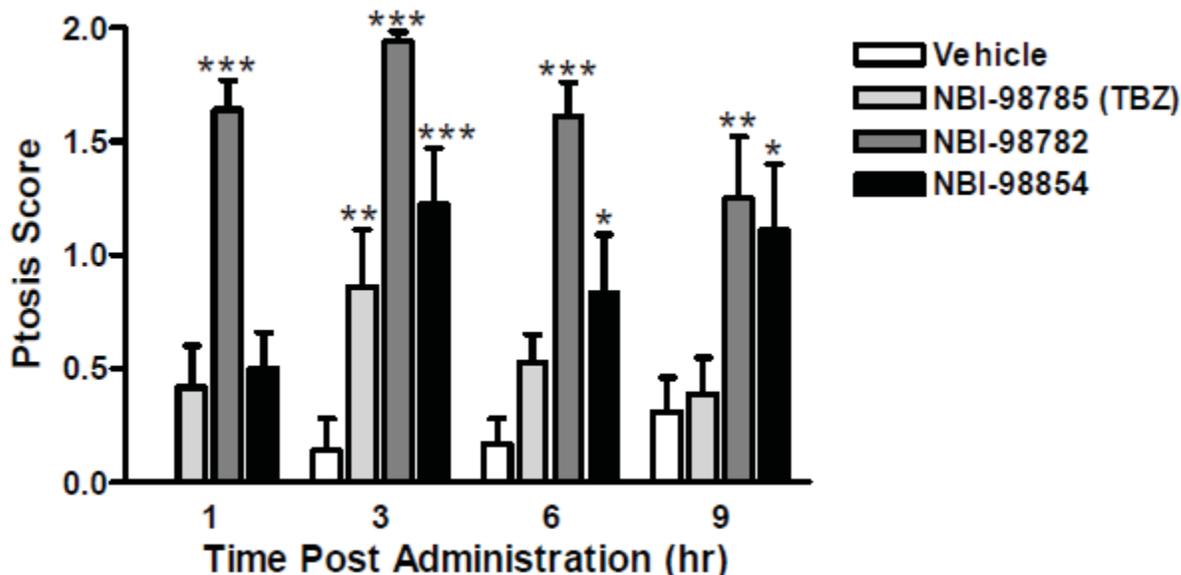
Oral administration of either valbenazine or NBI-98782 at doses of 0.3, 1.0, 3.0, 10, or 30 mg/kg induced palpebral ptosis in a dose dependent manner. Valbenazine induced ptosis beginning at a dose of 1.0 mg/kg. NBI-98782 was more potent with initial effects noted at 0.3 mg/kg and with a slightly higher degree of ptosis (Figure 1, from Sponsor).

Figure 1 Mean Palpebral Ptosis Scores 2 hrs. Following Oral Administration of Valbenazine (NBI-98854), NBI-98782, or Tetrabenazine (TBZ) to Rats



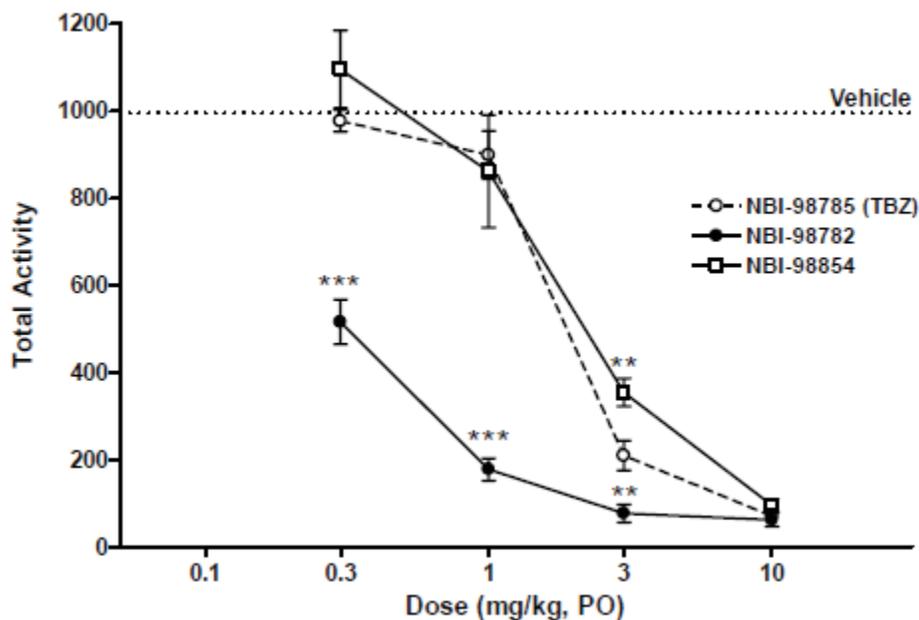
In addition the onset of ptosis was more rapid with NBI-98782 than valbenazine, occurring at 1 hr. postdose for the former and 3 hrs. postdose for the latter. 3 hrs. also represented the peak response following oral administration of valbenazine, which is more closely associated with the t_{max} of NBI-98782 following metabolism of valbenazine. A relatively consistent level of response was observed up to 9 hrs. postdose for both valbenazine and NBI-98782 followed by recovery such that ptosis was no longer observed 12 hrs. postdose (Figure 2, from Sponsor).

Figure 2 Time Course of Palpebral Ptosis Following Oral Administration of 3 mg/kg of Valbenazine (NBI-98854), NBI-98782, or Tetrabenazine (TBZ) to Rats



Oral administration of either valbenazine or NBI-98782 to rats at doses of 0.3, 1.0, 3.0, or 10 mg/kg produced a significant decrease in locomotor activity in a dose dependent manner. NBI-98782 appeared to be more potent with effects first observed at a dose of 0.3 mg/kg vs. 3 mg/kg for valbenazine (Figure 3, from Sponsor).

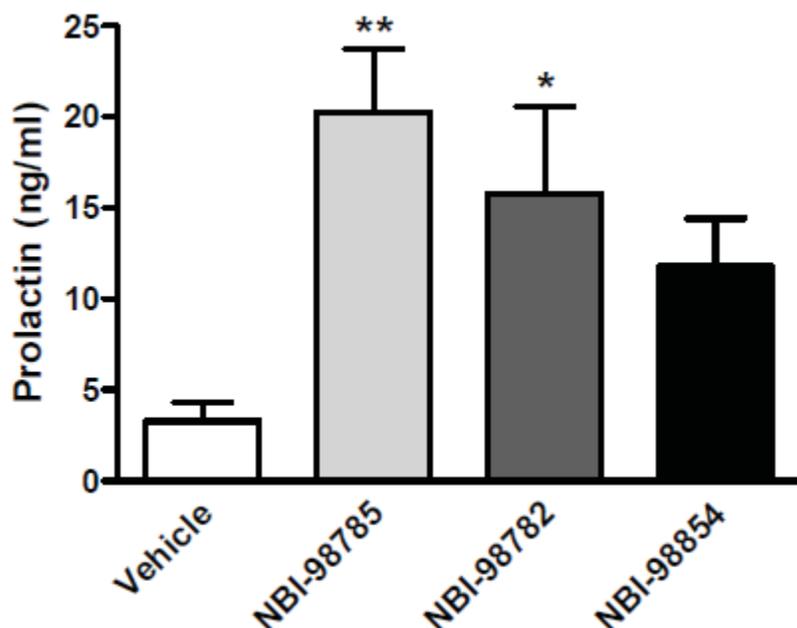
Figure 3 Mean Locomotor Activity 1 hr. Following Oral Administration of Valbenazine (NBI-98854), NBI-98782, or Tetrabenazine (TBZ) to Rats



It is known that depletion of dopamine or antagonism of dopamine D2 receptors can increase serum prolactin levels in the rat (Fitzgerald and Dinan, 2008). To investigate

the effect of valbenazine and NBI-98782 on prolactin levels, female rats were administered a dose of 3 mg/kg and blood was collected for analysis 90 minutes postdose. Both valbenazine and NBI-98782 produced an increase in serum prolactin levels following oral administration (Figure 4, from Sponsor).

Figure 4 Mean Serum Prolactin Levels 90 min. Following Oral Administration of 3 mg/kg of Valbenazine (NBI-98854), NBI-98782, or Tetrabenazine (NBI-98785) to Female Rats



Because NBI-98782 has a higher binding affinity for VMAT2, produced a more rapid onset of ptosis, and had more profound effects on serum prolactin levels than valbenazine, the Sponsor conducted a series of experiments to investigate the relative role of valbenazine and NBI-98782 in exerting the pharmacological effects of valbenazine in the rat. To this end the Sponsor assessed the relationship between plasma concentrations of valbenazine or NBI-98782, occupancy of VMAT2 in the brain, and ptosis following oral administration of valbenazine in the rat. Based on the results of these experiments the Sponsor concluded that “NBI-98782 is the primary species bound to rat brain VMAT2 following oral administration of valbenazine and is therefore responsible for the pharmacology associated with VMAT2 inhibition.”

Reviewer Comment: NBI-98782 is likely the primary pharmacologically active moiety across all species, including humans following oral administration of valbenazine. However, the total contribution of NBI-98782 versus valbenazine likely differs across species owing to the fact that NBI-98782 is formed more slowly in humans and dogs resulting in lower concentrations at steady state relative to than in the rat. In the rat NBI-98782 is estimated to contribute approximately 90% of the pharmacological activity following oral administration of valbenazine. However, in the dog and human it is estimated that NBI-98782, while still the principle pharmacologically active moiety, only contributes ~60% and ~80%, respectively, with valbenazine responsible for the majority of the remainder. NBI-136110 and NBI-679006 are likely to play a very limited role in the pharmacological profile following oral administration of valbenazine to humans. For

a more detailed discussion of the PK differences observed across species see section 5.1. (PK/ADME) below.

Conclusion: Taken together these data indicate that oral administration of valbenazine (NBI-98854) to the rat at or below the NOAEL (3 mg/kg/day) identified in the repeat-dose toxicology studies (see section 6 below) results in pharmacologically relevant behavioral/physiological effects.

4.2 Secondary Pharmacology

Valbenazine and the metabolite NBI-98782 were screened using a panel of 80 receptors, enzymes, transporters, and ion channels. Valbenazine and NBI-98782 have no activity at VMAT1 when tested at concentrations up to 10 μ M and no appreciable affinity ($K_i > 5 \mu$ M) for other targets including dopaminergic (including D_2), serotonergic (including 5-HT_{2B}), adrenergic, histaminergic, muscarinic, and NMDA receptors or other monoamine transporters such as the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT).

Reviewer Comment: The majority of toxicities identified in the toxicology studies are consistent with what is observed following monoamine depletion with other drugs that target VMAT2 (e.g. tetrabenazine, NDA 021894). This further supports the absence of identified off-target liabilities in the secondary pharmacology screen.

4.3 Safety Pharmacology

Central Nervous System (CNS):

Based on the nonclinical data the potential of valbenazine to produce adverse CNS-related events (CNS depression, extrapyramidal effects, etc.) at therapeutically relevant doses is high.

Functional Observational Battery (FOB): Valbenazine was evaluated for its potential to cause adverse CNS effects in an FOB following a single oral administration to Sprague-Dawley rats (8/sex/group) at doses of 0, 15, 25, and 50 mg/kg. The FOB was performed pre-dose, and 1.5 hrs. ($\sim C_{max}$) and 24 hrs. postdose (GLP-compliant).

One male rat at the 50 mg/kg dose level was found dead 24 hrs. postdose. Although no cause of death was determined for this rat it is considered valbenazine-related by this reviewer and possibly related to the severe CNS depression noted at this dose level.

Valbenazine treatment-related findings were noted at all dose levels, increasing in severity with increased dose. All findings were consistent with a CNS depressant effect and included \downarrow motor activity, \uparrow lacrimation, and palpebral ptosis, slight to severe gait abnormalities (ataxia, hindlimbs/forelimbs splayed/dragging, flattened body posture), slight to severe impairment of locomotion, and very low arousal. Hindlimb grip strength was also decreased (up to 15%). Depressed reflexes (miosis/abnormal pupil response, air righting) and pain perception were also noted.

Valbenazine treatment-related findings were still present 24 hrs. postdose in rats at the 50 mg/kg dose level. However, the incidence and severity of these findings was significantly decreased at this time point and were not observed at the 15 and 25 mg/kg dose levels indicating reversibility.

Reviewer Comment: Taken together these findings indicate valbenazine treatment may result in depressed neuromuscular and sensorimotor function, as well as stimulation of the parasympathetic nervous system. These effects are all consistent with monoamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. The Sponsor concluded the NOAEL for CNS findings was 25 mg/kg based on the observed reversibility. However, this reviewer concludes a NOAEL was not established based on the severity of the findings and the probability they will disrupt behavior enough to produce additional adverse effects such as decreased food intake and body weight. Therefore the LOAEL for CNS effects is 15 mg/kg/day, which is 1.8 times the MRHD of 80 mg/day based on mg/m².

Pro-convulsant Potential: In a number of the studies conducted by the Sponsor, oral administration of valbenazine was associated with tremors, myoclonic jerking, or clonic convulsions in both dogs and rats following repeat dosing.

In dogs tremors of the shoulders, neck, and head were observed at doses ≥ 5 mg/kg/day after ~1-week of dosing and jerky/uncoordinated movements as well as convulsions were observed after a single dose of 35 mg/kg. To rule out a link between tremors and seizure or pre-seizure patterns electroencephalogram (EEG) and electromyogram (EMG) recordings were taken 2 hrs. and 4 hrs. postdose ($\sim C_{max}$) on days 246/247 and 254/255 of the 9-month chronic toxicology study (study No. 20028697). Tremors were noted at the 10 and 15 mg/kg/day dose levels and increased in incidence and severity with increasing dose. Although tremors were observed during collection of EEGs no abnormal EEG patterns were observed. EMG recordings in several dogs from each treatment group demonstrated clear patterns of high-frequency, high-intensity motor unit action potentials in proximal muscles (e.g. head, neck, shoulders) manifested as the observed tremors.

Reviewer Comment: In dogs, a single administration at a dose of 35 mg/kg is likely associated with convulsions, which is ~15 times the MRHD of 80 mg/day based on mg/m². Thus there is a large margin of safety and this finding is of relatively minor clinical significance. On the other hand, although the toxicological significance of the muscle tremor in dogs is unclear at present, because the current indication is an involuntary movement disorder affecting the tongue, lips, face, trunk, and extremities, they may be clinically meaningful. Moreover, these tremors occurred at a dose ~2 times the RMHD based on mg/m².

In rats, repeat oral administration of valbenazine at doses ≥ 10 mg/kg/day for at least 64 days (study No. 8271662) resulted in self-resolving myoclonic jerking or clonic convulsions generally lasting < 1 minute. This activity was not associated with t_{max} , but rather, with handling (dosing, detailed clinical examinations, etc.), and was not observed following dosing cessation.

Reviewer Comment: These findings suggest that the convulsions are the result of a chronic process that appears to be reversible. Extensive neuropathology evaluation of these animals revealed no associated causative lesions. These convulsions tended to be observed at times when rats were exhibiting increased activity, prior to dosing when valbenazine levels are at trough, and may be part of a potential rodent specific withdrawal phenomenon, although no specific studies to address this were conducted. Similar effects in rats have been noted with tetrabenazine (XENAZINE[®], NDA 021894), another VMAT2 inhibitor, indicating this effect may be common to this class of drugs. The clinical significance of this finding, although unclear, is likely limited.

Cardiovascular System:

Based on the non-clinical data the potential of valbenazine to produce adverse cardiovascular events at therapeutically relevant exposures is minimal.

In vitro: Valbenazine and the metabolite NBI-98782 were evaluated for their potential to cause QT prolongation using cloned hERG potassium channels expressed in human embryonic kidney cells (GLP-compliant). Valbenazine inhibited hERG current by 13.1, 36.6, 66.6, and 84.1% at 0.3, 1.2, 3.6, and 12.5 μ M, respectively. NBI-98782 inhibited hERG current by 9, 26.3, 42.8, and 72.4% at 3, 10, 30, and 100 μ M, respectively. Valbenazine and NBI-98782 decreased hERG tail peak currents with IC₅₀ values of 2.0 and 36.1 μ M, respectively.

In vivo: Valbenazine was evaluated for its potential to cause adverse cardiovascular effects in a single dose study using telemetered conscious beagle dogs. Doses utilized in this study ranged from 5 to 30 mg/kg administered via the oral route. Valbenazine treatment-related effects were noted on various cardiovascular parameters at doses \geq 15 mg/kg/day with a dose-dependent increase in incidence and severity. Increased heart rate (28 to 53 bpm) and QTc (< 15 msec) were noted at dose levels \geq 15 mg/kg and increased mean arterial pressure (< 24.8 mmHg) was noted at dose levels \geq 30 mg/kg.

Reviewer Comment: A minor effect on cardiovascular parameters is not unexpected given the actions of valbenazine at VMAT2. However, in-line with valbenazine's apparent lack of affinity for VMAT1 these cardiovascular effects, other than QTc prolongation, are not considered adverse based on the relatively minor degree of change. The NOAEL for cardiovascular effects in the beagle dog, other than QTc prolongation, is 30 mg/kg, which is 12.5 times the MRHD of 80 mg/day based on mg/m². The NOEL for QTc prolongation across all studies is 12.5 mg/kg, which is 5 times the MRHD of 80 mg/day based on mg/m².

Respiratory System:

Based on the non-clinical data the potential of valbenazine to produce adverse respiratory system-related events at therapeutically relevant exposures is minimal.

Valbenazine was evaluated for its potential to cause adverse respiratory effects in a 14-day repeat dose study (study No. 08-3332) using beagle dogs. Doses utilized in this study were 5, 15, and 35 mg/kg/day administered via the oral route. Valbenazine

treatment resulted in significant decreases in respiratory rate (26% to 35%) and minute volume (4% to 17%) with compensatory increases in tidal volume (23% to 32%) and an increased incidence of sighs at doses ≥ 15 mg/kg/day.

Reviewer Comment: Although these effects are common to CNS depressants, and therefore drug related, the compensatory increase in tidal volume suggests a non-adverse effect on central respiratory centers at the doses tested. The NOAEL for respiratory effects in the beagle dog is 35 mg/kg, which is ~ 15 times the MRHD of 80 mg/day based on mg/m².

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME/Drug-Drug Interactions

Absorption

In Vitro:

The permeability of valbenazine was evaluated using human colon carcinoma-derived Caco-2 cells and the permeability of both valbenazine and the metabolite NBI-98782 was evaluated using Madin Darby canine kidney cells stably transfected with human MDR1 (MDCK-MDR1).

Valbenazine (20 μ M) was highly permeable in the absorptive direction across Caco-2 cell monolayers with greater permeability at higher pH ranges owing to increased ionization of this weakly basic compound at lower pH. The ratio of measured apparent permeability in the absorptive vs. secretive directions was less than 1 indicating valbenazine is not a substrate for the efflux transporters P-gp or BCRP expressed in these cells. In addition, when the apical medium was acidified from pH 7.4 to 6.0 transport of valbenazine from the apical side to the basolateral side decreased, indicating it is not a substrate for the PepT1 despite having a valine functional group.

Valbenazine (20 μ M) and NBI-98782 (20 μ M) were both highly permeable in the absorptive direction across MDCK-MDR1 monolayers. The ratio of measured apparent permeability in the absorptive vs. secretive directions was less than 1 for both valbenazine and NBI-98782 indicating they are not substrates for the efflux transporter P-gp.

In Vivo:

Bioavailability: Valbenazine is rapidly and extensively absorbed following oral administration, with t_{max} generally ranging from 0.25 to 2.0 hrs. postdose across species and a mean oral bioavailability in rats, dogs, and humans of 68.5%, 123%, and 48.6%, respectively. Following IV administration systemic plasma clearance was lower in humans and dogs relative to rats. The lower clearance was consistent with a longer apparent mean terminal half-life ($t_{1/2}$) in humans (16 hrs.) and dogs (5.9 hrs.) relative to rats (1.3 hrs.). However, the volume of distribution at steady state (V_{ss}) was similar across species (Table 6, adapted from table provided by Sponsor).

Table 6 Mean PK Parameters of Valbenazine Following IV and Oral Dosing

Species	Dose	Oral Dosing				IV Dosing			
		t _{max} (hr.)	C _{max} (ng/mL)	AUC _(0-∞) (ng•hr/mL)	%F	Dose	CL (mL/min/kg)	V _{ss} (L/kg)	t _{1/2} (hr.)
SD Rat	10 mg/kg	0.5-1.0	1910	4990	68.5	2.5 mg/kg	23.2	2.04	1.3
Beagle Dog	10 mg/kg	0.25-0.5	9170	27400	123	2.5 mg/kg	7.72	1.90	5.9
Human	50 mg	0.5-0.73	415	3450	48.6	0.015 mg	1.17	1.32	16

The pharmacologically active metabolite NBI-98782 was formed following both IV and oral administration in all species studied. In dogs and humans the ester hydrolysis of valbenazine to NBI-98782 is slower than in rats resulting in higher exposures to valbenazine and lower exposures to NBI-98782 in the former. This difference results in a significant difference in the percent molar ratio of metabolite to parent with dogs being more similar to humans than rats. The percent molar ratios are 110%, 10%, and 23% in rats, dogs, and human, respectively.

Following repeat oral dosing in the toxicology studies no consistent or significant gender differences in exposures were observed. In general, exposure increased with increasing dose and no significant accumulation was observed for valbenazine or its metabolites. However, in mice repeat dosing resulted in decreasing exposure of valbenazine and its metabolites, with higher doses resulting in more significant decreases in exposure. This apparent decrease in exposure in mice is consistent with in vitro data demonstrating valbenazine is a weak inducer of CYP3A4, one of the primary enzymes responsible for its metabolism.

Distribution

Valbenazine distribution was evaluated using whole body autoradiography in pigmented Long-Evans (LE) rats and non-pigmented Sprague-Dawley (SD) rats following a single 15 mg/kg oral dose. [¹⁴C]Valbenazine-related radioactivity was rapidly distributed from blood/plasma to tissues. In most tissues peak radioactivity concentrations (t_{max}) were reached 1 hr. postdose (earliest time point evaluated) and by 8 hrs. (2nd time point evaluated) for the remainder of the tissues. Distribution of valbenazine-related material was extensive with the ratio of tissue to plasma radioactivity exposures ≥ 1 for all tissues and > 10 for highly perfused tissues such as the lungs, liver, kidney and spleen. Distribution of radioactivity to the brain indicated that valbenazine-related material is able to cross the blood-brain barrier. In addition valbenazine-related radioactivity was highly distributed to pigmented region of the eye in LE rats, particularly the uveal tract with a tissue to plasma ratio > 4000 and t_{1/2} > 1000 hrs. indicating extensive binding to melanin. A similar degree of distribution to pigmented skin was not observed (Table 7, adapted from table provided by Sponsor).

Reviewer Comment: The only nonclinical study with potentially valbenazine treatment-related eye findings was the 6-month chronic rat study (study No. 8271662), in which retinal degeneration was observed. However, as these rats are albino, the relevance of this finding to accumulation of valbenazine in pigmented eye is unclear. Moreover, no valbenazine treatment-related eye findings were noted in the dog or pigmented mouse,

and no phototoxicity was observed in BALB/c 3T3 mouse fibroblasts. Moreover, no eye-related toxicities were reported in the toxicology studies conducted with the FDA approved drug XENAZINE® (tetrabenazine, NDA 021894). Therefore, the clinical significance of the extensive distribution of valbenazine-related material to the eye is unclear at present.

Table 7 Distribution of Valbenazine-Related Radioactivity in Male LE and SD Rats

Tissue	C _{max} (µg equivalents/g)	AUC (µg equivalents•hr/g)	Tissue:Plasma	t _{max} (hr.)	t _½ (hr.)
Plasma	2.45	25.3	NA	1.0	11.5
Brain	4.61	32.3	1.27	1.0	NC
Lung	31.4	301	11.9	1.0	8.7
Liver	44.7	676	26.7	1.0	44.7
Kidney	23.5	278	11.0	1.0	NC
Spleen	23.1	295	11.7	1.0	NC
Pancreas	20.0	237	9.33	1.0	32.4
Testis	6.10	202	7.99	8.0	46.5
Adrenal	25.6	367	14.5	1.0	48.1
Harderian	47.8	33310	131	8.0	38.0
Pituitary	18.5	318	12.6	1.0	NC
Thyroid	32.8	608	24.0	1.0	60.8
Eye – SD	1.35	16.6	0.66	1.0	NC
Eye – LE	46.2	19600	735	8.0	NC
Uveal tract – SD	6.47	89.3	3.52	1.0	13.9
Uveal tract – LE	243	112000	4190	8.0	1090
Skin – SD	3.95	74.0	2.92	1.0	12.4
Skin – LE	4.20	53.9	2.02	1.0	19.1

The distribution of valbenazine and the metabolite NBI-98782 to the brain was evaluated following a single 13.1 mg/kg oral dose of valbenazine to SD rats. In line with what was observed in the autoradiography study both valbenazine and NBI-98782 were detectable in the brain following oral administration. However, brain:plasma ratios were higher in this study (~5 times).

The distribution of valbenazine and the metabolites NBI-98782 and NBI-136110 from pregnant rats to the fetus was evaluated on gestation day (GD) 11 and 13. Systemic exposure of valbenazine and its metabolites was higher in fetal tissue relative to maternal plasma on both days. However, the difference in exposure was greater on GD 11 relative to 13, possibly due to the formation of the chorioallantoic placenta in rats during that time period.

Plasma protein binding of valbenazine was high across species while it was significantly lower for NBI-98782. The percentage of valbenazine bound to proteins was 95.4% in mouse, 98.3% in rat, 99.3% in rabbit, 98.8% in dog, and 99.9% in human. The percentage of NBI-98782 bound to proteins was 76.0% in mouse, 71.7% in rat, 48.0% in rabbit, 58.9% in dog, and 65.2% in human. In addition the blood:plasma ratio was approximately equal in whole blood across species indicating no preferential distribution to the cellular components of whole blood.

Metabolism

In Vivo

Enantiomeric Conversion: The potential for chiral inversion of the secondary alcohol function of NBI-98782 to form a diastereomeric variant (NBI-98795) was evaluated. Under conditions established to resolve NBI-98782 from the NBI-98795, no NBI-98795 was detected in plasma from rat, dog, or human indicating NBI-98782 undergoes little or no chiral inversion in vivo.

Species comparison: The metabolic profile of valbenazine (NBI-98854) was evaluated in rats (intact and bile duct cannulated), dogs (intact and bile duct cannulated), and humans using HPLC with parallel radiometric and mass spectrometric detection.

Plasma: The only valbenazine-related material quantifiable by radiometric methods was parent and the metabolites NBI-98782, NBI-136110, and NBI-679006 (M10b). These metabolites were detected in plasma from rat and dog at levels \geq those detected in human plasma (Table 8, adapted from table provided by Sponsor).

Table 8 Percent Total Plasma Exposure of [¹⁴C]Valbenazine-related radioactivity in Rat, Dog, and Human Following a Single Oral Administration.

Circulating Component	Rat (15 mg/kg)	Dog (10 mg/kg)	Human (50 mg)
Valbenazine	8.8%	47.0%	42.4%
NBI-98782	18.2%	5.2%	9.9%
NBI-136110	7.3%	8.1%	12.7%
NBI-679006	32.3%	8.7%	8.2%

There were several additional metabolites identified in human plasma. However, they were below the limit of quantification for the methods and less than 1% of total circulating valbenazine-related material. These metabolites were detected in plasma for rats and dogs with the exception M21a (di-oxidized valbenazine glucuronide) and M17 (mono-oxidized valbenazine glucuronide). However, M21a and M17 were detected in urine from rat and dog, are present at very low concentration, are non-toxic glucuronides, and as such are not considered of toxicological significance.

Excreta: The percent of orally administered valbenazine excreted as unchanged parent or NBI-98782 was low across species indicating metabolism is primarily responsible for systemic clearance with little contribution of renal or biliary excretion. (Table 9, adapted from table provided by Sponsor)

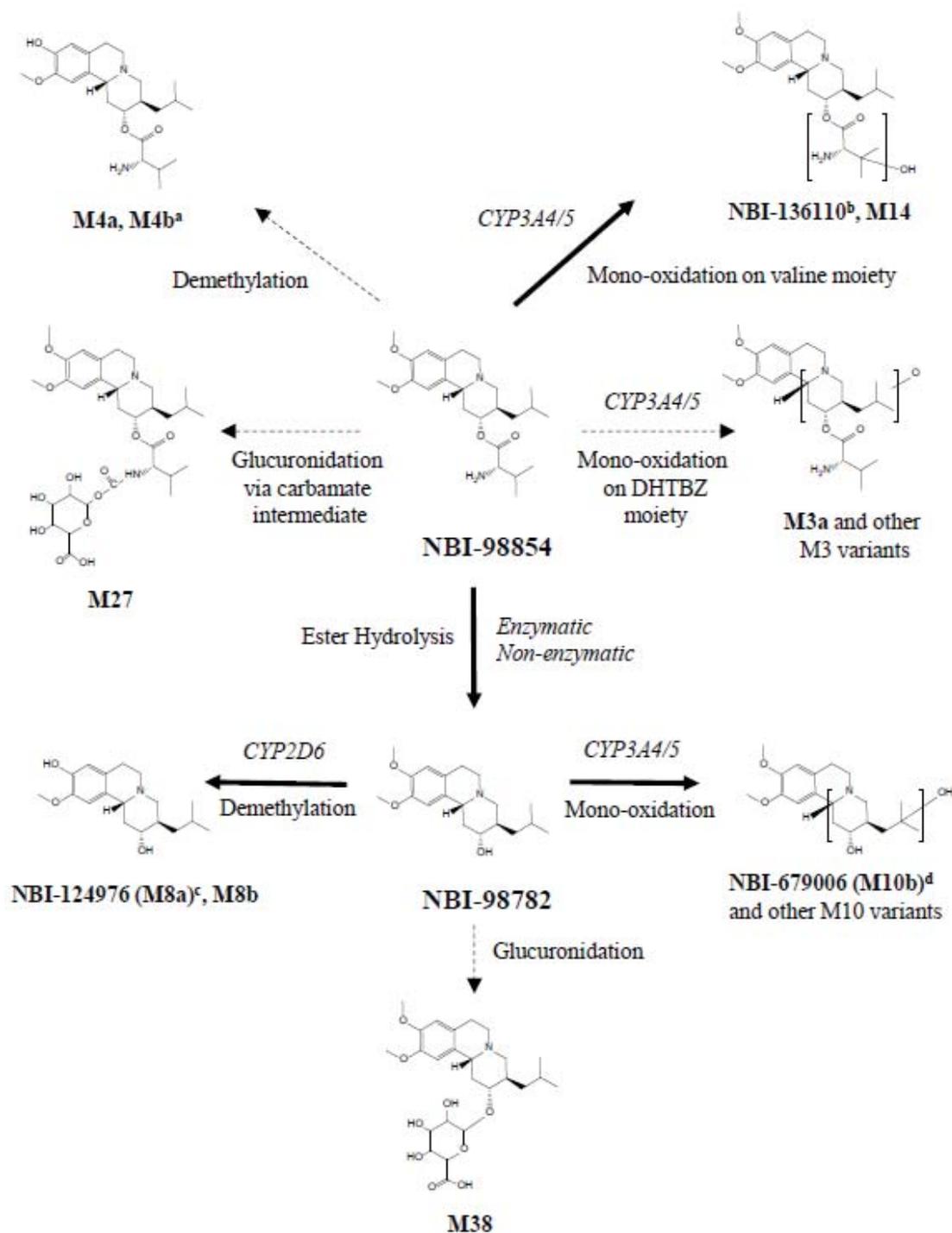
Table 9 Percent of Orally Administered [¹⁴C]Valbenazine Excreted as Unchanged Parent or NBI-98782 in Rat, Dog, and Human Urine and Feces and Rat Bile (% Administered Dose).

Matrix	Urine			Feces			Bile
Analyte	Rat	Dog	Human	Rat	Dog	Human	Rat
Valbenazine	ND	1.8%	1.8%	2.1%	13.2%	1.8%	1.0%
NBI-98782	1.3%	2.0%	1.6%	ND	2.2%	<1%	ND

ND = Not detected

Reviewer Comment: In total, more than 60 metabolites were detected in human urine and feces by radiometry or mass spectrometry. However, no single metabolite represented > 10% of the administered dose. The metabolic profile in rat and dog was similar to human, with every excretory human metabolite detected in at least one and the majority detected in both species. The structural characterization of the metabolites present in rat, dog, and human plasma and excreta suggest several metabolic clearance pathways, common to all three species. Pathway 1 is ester hydrolysis to NBI-98782 followed by mono-oxidation to NBI-679006 (primary), demethylation to NBI-124976 (minor), or glucuronidation (minor). Pathway 2 is mono-oxidation to NBI-136110. These pathways as well as lesser pathways are shown in the figure below (Figure 5 provided by Sponsor).

Figure 5 Proposed Metabolic Pathways of Valbenzazine (NBI-98854) in rats, dogs, and humans



Valbenzazine is represented as NBI-98854

Bold and dashed arrows indicate major and minor metabolic clearance pathways, respectively.

a – One of 2 potential desmethyl valbenzazine metabolites shown.

b – The structure of NBI-136110 is as shown. Brackets indicate the region where oxidation occurs to form M14, a lesser abundant valine oxidized NBI-98854 metabolite observed primarily in *in vitro* studies.

c – The structure of NBI-124976 (M8a) is as shown. M8b represents the other potential desmethyl NBI-98782 metabolite.

d – The structure of NBI-679006 is as shown. Brackets indicate the region where oxidation occurs to form other, lesser abundant, M10 variants.

In Vitro

The relative contribution of cytochrome P450 (CYP) enzymes in the metabolism of valbenazine was evaluated using pooled human liver microsomes in the presence and absence of specific inhibitors. The CYP3A4/5 inhibitor azamulin produced an 82% reduction in the intrinsic clearance (CL_{int}) of valbenazine, while the CYP2D6 inhibitor quinidine produced a much smaller 12% reduction in the CL_{int} of valbenazine.

In line with these results the CYP3A4/5 inhibitor azamulin produced a 47% reduction in the formation of NBI-98782 and an 88% reduction in the formation of NBI-136110 when co-incubated with valbenazine in human hepatocytes. In addition the only cDNA expressed human CYP enzyme capable of generating appreciable amounts of NBI-136110 was CYP3A4/5.

On the other hand when NBI-98782 was incubated with the CYP2D6 inhibitor quinidine in pooled human liver microsomes or human hepatocytes CL_{int} was reduced > 50%. In addition the only cDNA expressed human CYP enzyme capable of generating the O-desmethyl metabolites NBI-124976 (M8a) and M8b was CYP2D6. NBI-679006 was formed by the cDNA expressed human CYP enzyme CYP3A4/5.

Reviewer Comment: Taken together these data indicate that CYP3A4/5 play a primary role in the metabolism of valbenazine, while CYP3A4/5 and CYP2D6 both play a role in the subsequent metabolism of NBI-98782.

Excretion

Following oral administration, valbenazine is extensively metabolized with very little excreted as unchanged parent or the metabolite NBI-98782. Both urine and feces play a significant role in the excretion of valbenazine-related material across species. The rate of excretion was relatively rapid with more than half of the administered [¹⁴C]valbenazine-related radioactivity excreted within 72 hours postdose. Total recovery of [¹⁴C]valbenazine-related radioactivity was relatively complete across species (> 90%) (Table 10, adapted from table provided by Sponsor).

Table 10 Total Recovery and Percent of Orally Administered [¹⁴C]Valbenazine-related radioactivity Excreted in Rat, Dog, and Human.

Species	Dose	Collection Period (hrs.)	Urine	Feces	Bile	Total
Rat	15 mg/kg	0-168	36.3	57.9	NA	99.8
Rat (BDC)	15 mg/kg	0-72	36.2	8.68	49.9	96.8
Dog	10 mg/kg	0-168	35.0	56.4	NA	95.4
Human (male)	50 mg	0-312	61.2	29.5	NA	90.8

NA = Not Applicable

The excretion of valbenazine or the metabolites, NBI-98782 and NBI-136110, into rat milk was evaluated in the prenatal and postnatal development study (No. 20068205) following valbenazine administration at doses of 1, 3, and 10 mg/kg/day. Valbenazine, NBI-98782, and NBI-136110 were quantifiable in rat milk at higher levels than plasma (2.4-, 2.9-, and 1.4 times respectively) on day 14 of lactation at 3 hrs. postdose.

Reviewer Comment: These data indicate the potential for infant exposure to valbenazine or its metabolites via breast milk.

Drug-Drug Interaction Potential

The potential for valbenazine or the metabolites, NBI-98782 and NBI-136110, to perpetrate drug-drug interactions via induction or inhibition of metabolizing enzymes or drug transporters is low. No evidence of induction or inhibition of CYP enzymes or drug transporters was observed at physiologically relevant concentrations. The most notable effects were inhibition by valbenazine of P-gp ($IC_{50}=23.8 \mu\text{M}$), CYP3A4/5 ($IC_{50}=31.1 \mu\text{M}$), and CYP2D6 ($IC_{50}=9.0 \mu\text{M}$) and inhibition by NBI-98782 of CYP2D6 ($IC_{50}=14.2 \mu\text{M}$). These IC_{50} values are significantly greater than the plasma concentrations of valbenazine and NBI-98782 observed at steady state following administration the maximum recommended dose of 80 mg to humans (0.916 and 0.0394 μM , respectively). Therefore, weak inhibition of CYP3A4/5 and P-gp is likely to be limited to the gut and is of limited clinical significance.

5.2 Toxicokinetics

Table 11 Systemic Exposures for Valbenazine and the Metabolites, NBI-98782 and NBI-136110, at the NOAEL in the Repeat Dose Toxicology Studies

Study	NOAEL	Valbenazine		NBI-98782		NBI-136110	
		C_{max} (ng/mL)	AUC (ng•hr/mL)	C_{max} (ng/mL)	AUC (ng•hr/mL)	C_{max} (ng/mL)	AUC (ng•hr/mL)
Human 80 mg/day	-----	916	6150	39.4	695	124	1910
Mouse 3-month	60 mg/kg/day	6120	25300	212	1630	1339	13730
Rat 3-month	3 mg/kg/day	131	402	83	775	ND	ND
Rat 6-month	3 mg/kg/day ^a	392	1300	118	1020	65	536
Dog 3-month	5 mg/kg/day	2790	11808	114	1138	ND	ND
Dog 9-month	3 mg/kg/day	1725	8825	41	407	136	1670

ND = Not Determined

^a LOAEL based on retinal degeneration

6 General Toxicology

6.1 Acute Toxicity

Single dose toxicology studies were conducted in the rat and dog in an effort to determine a maximum tolerated dose (MTD) and to inform dose selection in the repeat-dose toxicology studies.

Rat

In an initial MTD study, male rats were administered valbenazine by oral gavage at doses of 50, 100, and 200 mg/kg. No mortality was reported. At 2 hrs. postdose hunched posture was noted at all dose levels. Splayed front legs, ptosis, and tremors were noted only at the 50 and 100 mg/kg dose level and abnormal gait was noted only at the 100 mg/kg dose level. At 24 hrs. postdose no clinical signs were noted at the 50 mg/kg/day dose level and were partially reversed at the 100 mg/kg/day dose level. At the 200 mg/kg dose level hunched posture was still noted and the rats also displayed ptosis and diarrhea. The Sponsor concluded that 200 mg/kg exceeded an MTD.

In a subsequent MTD study, male and female rats were administered valbenazine by oral gavage at doses of 60, 80, 100, and 150 mg/kg. Four rats (1/3♂, & 3/3♀) at the 150 mg/kg dose level and one rat (1/3♀) at the 100 mg/kg dose level were sacrificed in moribund condition. In the surviving rats clinical signs consisting of decreased activity, lethargy, palpebral closure, piloerection, and hunched posture were noted at all dose levels. In addition a significant (up to 14%) decrease in body weight was noted 2 days postdose at all dose levels. Based on the significant decrease in body weight and adverse clinical signs noted at all doses in this study the Sponsor concluded that the lowest dose, 60 mg/kg, exceeded an MTD.

Dog

In an MTD study, male and female dogs were administered valbenazine by oral intubation at doses of 50 or 80 mg/kg and by oral capsule at a dose of 80 mg/kg. Three dogs (2/2♂, & 1/2♀) at the 80 mg/kg dose level were sacrificed due to convulsions 1 hr. or 32 hrs. postdose. In the surviving dogs clinical signs consisting of ataxia, trembling, decreased activity, lethargy, recumbency, excessive salivation, and emesis were noted at all dose levels. The Sponsor concluded that the MTD in this study was 50 mg/kg based on the convulsions noted at the 80 mg/kg dose level.

Reviewer Comment: This reviewer considers 50 mg/kg to have exceeded an MTD based on the severity of the clinical signs noted at this dose level. In line with this a dose of 35 mg/kg was not tolerated in a 14-day toxicology study in dogs and lower doses (20 and 15 mg/kg/day) were employed in the subchronic and chronic toxicology studies.

6.2 Repeat-Dose Toxicity

The general toxicology program for valbenazine included repeat-dose general toxicity studies in mouse, rat, and dog.

6.2.1 Rodent

Exploratory Studies in Mice

Study title: 24-Day Oral Safety Assessment and Toxicokinetics of NBI-98854 in CD-1 Mice

Study no.:	11-98854-007-TX
Sponsor Reference No.	2011-TX-040
Study report location:	SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location:	Neurocrine Biosciences, Inc., San Diego, CA
GLP compliance:	No
Drug, lot #, and % purity:	Valbenazine, 04-110323-03B/03-54-01, 99%

Methods: Valbenazine was administered to groups of CD-1 mice (~8 wks. of age) by oral gavage at doses of 0, 30, 100, and 300 mg/kg/day (10/sex/group) for 24-days followed by a 15-day recovery period. The Sponsor concluded a dose of 300 mg/kg/day did not exceed an MTD and therefore a 600 mg/kg/day dose group (6/sex) was added.

Results: Valbenazine treatment-related mortality was observed at doses ≥ 300 mg/kg/day. Following a single dose of valbenazine at 600 mg/kg 2 male and 4 female mice died within 1 hr. of dosing. Therefore this treatment group was terminated prior to dosing on day 2. Two female mice at the 300 mg/kg/day dose level were found dead during the dosing phase. One female was found dead on day 25 prior to dosing and may be treatment related and one female died ~10 minutes postdose on day 4. Clinical signs in these two mice were consistent with those observed other mice at this dose level. In the surviving mice clinical signs consisting of decreased activity and ptosis were noted from 1 to 4 hrs. postdose and increased activity/aggressiveness was noted during the pre-dose period at doses ≥ 100 mg/kg/day. A significant reduction in mean body weight (12.5%) relative to control was noted in male mice at the 300 mg/kg/day dose level. **Reviewer Comment:** The female mortality that was noted on day 25 prior to dosing may be treatment related, although no cause of death was determined and clinical signs in this mouse were consistent with those observed in other mice at this dose level. The female mortality that occurred ~10 minutes postdose on day 4 is not likely treatment related. Although no cause of death was determined the proximity of this death to dosing suggests dosing related trauma. The minimal severity of clinical signs and the absence of mortality in males together with only 1 possibly treatment related death in females suggest that mice can tolerate repeat-doses of valbenazine up to 300 mg/kg/day. However, the reduction in body weight relative to control suggest this

dose may exceed an MTD and not be tolerated for longer-term studies. With that said, in a subsequent 91-day toxicology study in CD-1 mice (study No. 20021098) a single administration of valbenazine at the 300 mg/kg/day dose level resulted in excessive mortality and early termination of the entire dose group. The reason for this apparent decrease in MTD is unknown.

Pivotal Studies in Mice

Study title: A 91-Day Study of NBI-98854 by Oral Gavage in Mice with a 28-Day Recovery Period

Study no.:	20021098
Sponsor Reference No.	2011-TX-042
Study report location:	SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	12/08/2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Valbenazine, 04-110323-03B/03-54-01, 99%

Key Study Findings

Valbenazine treatment resulted in mortality/morbidity at doses \geq 100 mg/kg/day.

Clinically relevant valbenazine treatment-related toxicities included the following:

- Mortality at 300 mg/kg/day resulted in termination of the dose group following a single administration.
- 1 ♂ and 1 ♀ at the 100 mg/kg/day were found dead or sacrificed in moribund condition.
- Clinical signs \geq 30 mg/kg/day; decreased activity, \geq 100 mg/kg/day; increased pre-dose activity, 300 mg/kg/day; adverse clinical signs indicative of significant CNS depression
- \downarrow body weight gain relative to control in male mice at \geq 30 mg/kg/day
- Lobular hyperplasia in the mammary gland of females at all dose levels
- The NOAEL was judged to be 60 mg/kg/day based on mortality at 100 mg/kg/day.

Exposures at the NOAEL are: C_{max} of 5229 and 7012 ng/mL and an AUC_{0-24} of 29396 and 21161 ng•hr/mL in males and females, respectively for valbenazine, which are ~7 times and 4 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (916 ng/mL and 6150 ng•hr/mL, respectively).

Exposures for NBI-98782 at the NOAEL are: C_{max} of 196 and 227 ng/mL and an AUC_{0-24} of 1903 and 1360 ng•hr/mL in males and females, respectively, which are ~5 times and 2 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (39.4 ng/mL and 695 ng•hr/mL, respectively).

Exposures for NBI-136110 at the NOAEL are: C_{max} of 1603 and 1076 ng/mL and an AUC_{0-24} of 16972 and 10489 ng•hr/mL in males and females, respectively, which are ~10 times and 7 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (124 ng/mL and 1910 ng•hr/mL, respectively).

The margin at the NOAEL based on mg/m² is ~3.6 times the MRHD of 80 mg/day.

Methods

Doses: 0, 10, 30, 60, 100, or 300 mg/kg
Frequency of dosing: Daily
Route of administration: Oral
Dose volume: 10 mL/kg
Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain: Mouse/ CD-1, (b) (4)
Number/Sex/Group: 10/sex/group and 5/sex/group for recovery
Age: 10 to 11 weeks of age at initiation of dosing
Weight: 28.9 to 39.4 g for males and 21.7 to 31.8 g for females
Satellite groups: TK, 36/sex/ treatment group, No TK mice included for control group.
Unique study design: Due to lack of tolerability the 300 mg/kg/day dose group was terminated on day 7 of the treatment phase following a single administration of valbenazine and replaced by a 60 mg/kg/day dose group.
Deviation from study protocol: None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Mortality

Valbenazine treatment-related mortalities and moribund sacrifice occurred at doses ≥ 100 mg/kg/day.

At the 300 mg/kg/day dose level 2 male mice were found dead and 7 males were euthanized in moribund condition following a single administration of valbenazine. Due to excessive mortality and clinical signs the entire 300 mg/kg/day dose group was placed on a dosing holiday on day 2 and terminated on day 7. Clinical signs leading to moribund sacrifice consisted of lateral/sternal recumbency, labored/shallow breathing, ataxia, body rigidity, and hunched posture.

At the 100 mg/kg/day dose level 1 female (No. 1108) was found dead on day 74 and 1 male (No. 1043) was euthanized on day 89 of the dosing phase.

Reviewer Comment: Clinical signs leading to moribund sacrifice in the male were similar to those observed at the 300 mg/kg/day dose and, therefore, this death is considered treatment-related. No adverse clinical signs were noted in the female found dead on day 74 and a cause of death was not determined, nevertheless a relationship to valbenazine treatment cannot be ruled out.

Mice were observed for general health/mortality and morbidity twice daily, once in the morning and afternoon, throughout the study.

Clinical Signs

Valbenazine treatment-related findings were noted at dose levels ≥ 30 mg/kg/day. At doses ≥ 30 mg/kg/day clinical signs consisted of decreased activity throughout the first week of the dosing phase lasting 30 min to 1 hr. postdose. Increased activity was noted prior to dosing, beginning on day 18 of the dosing phase, at 100 mg/kg/day.

Adverse clinical signs indicative of significant CNS depression were noted at 300 mg/kg/day and resulted in the termination of this group on day 7 of the dosing phase following a single administration of valbenazine and subsequent dosing holiday. Clinical signs at this dose level consisted of decreased activity, hypothermia, palpebral closure, hunched posture, lateral/sternal recumbency, labored/shallow breathing, ataxia, body rigidity, rough/urine-stained hair coat, and dehydration.

Reviewer Comment: In a previous study (No. 2011-TX-040) in mice a dose of 300 mg/kg/day was tolerated with a non-adverse decrease in activity noted and only one possibly treatment related mortality prior to study termination following 24 daily valbenazine administrations. The reason for this apparent discrepancy in tolerability is unclear.

No adverse valbenazine treatment-related clinical signs were noted during the recovery phase. A few incidences of rough/urine stained hair coat were noted in males at the 100 mg/kg/day dose level.

Cageside observations were conducted approximately 1 and 7 hrs. postdose during the dosing phase and once daily on non-dosing days. Detailed observations were conducted for each animal once during the predose phase and weekly throughout the dosing and recovery phases.

Body Weights

Valbenazine treatment resulted in a significant decrease in body weight and body weight gain in male mice at dose levels ≥ 30 mg/kg/day throughout the dosing phase, relative to control rats. The effect on body weight was not correlated with a decrease in food consumption. Although mean body weight remained statistically lower relative to controls during the recovery period, body weight gains were generally greater, indicating recovery.

Reviewer Comment: Although body weight was determined for mice in the 60 mg/kg/day dose group they were part of a separate shipment and dosing was initiated on a different day potentially confounding the results. Moreover, although body weight gain was reduced at the 60 mg/kg/day dose level, consistent with what was observed in the other dose groups, these mice had significantly higher mean body weights than all other dose groups throughout the course of the study. Therefore, the 60 mg/kg/day dose level is omitted from the table below as the values are not reflective of the effect of valbenazine on body weight.

Table 12 Mean Body Weight Effects in the 91-Day Mouse General Toxicology Study – Dosing Phase

Dose (mg/kg)	Male	Female
	Mean Body weight (% Control)	Mean Body weight (% Control)
0	----	----
10	-4.1%	+2.2%
30	-9.0%	-1.5%
100	-12.7%	+0.8%

Each animal was weighed on the day of randomization and on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 90, 97, 104, 111, and 119. A final fasted body weight was recorded for each animal on the day of scheduled euthanasia for calculation of organ to body weight ratios. Food consumption was measured weekly.

Ophthalmoscopy

No valbenazine treatment-related ophthalmic findings were observed during the dosing or recovery phases.

Ophthalmic examinations were conducted once during the pre-dose phase on all rats and once during the last week of the dosing phase on each toxicity animal. The eyes were dilated with a mydriatic agent, and examinations were performed using an indirect ophthalmoscope.

ECG

No assessment performed.

Hematology

Non-adverse valbenazine treatment-related effects were noted on several hematology parameters at the 60 mg/kg/day dose levels at the end of the dosing phase. These effects were considered non-adverse due to their relatively small magnitude (+2.8% to +86%), lack of a dose response (they were not present at the 100 mg/kg/day dose level), lack of microscopic correlates, and absence following recovery.

No valbenazine treatment-related effects on coagulation parameters were noted.

Reviewer Comment: Analysis of hematology and coagulation parameters was performed for mice at the 300 mg/kg/day dose level only on day 3 due to this group's early termination. No significant effects were noted. However, this dose is 18 times the MRHD of 80 mg/day based on mg/m². Therefore the absence of longer term dosing data is of limited clinical significance.

An adequate battery of hematology and coagulation parameters was assessed. Blood samples were collected from fasted mice from the vena cava at necropsy.

Clinical Chemistry

Non-adverse valbenazine treatment-related effects were noted on multiple clinical chemistry parameters at doses \geq 60 mg/kg/day in male and female mice. These effects were considered non-adverse due to their relatively small magnitude (+100% to -45.2%), lack of dose response (occurring at 60 but not 100 mg/kg/day), absence of microscopic correlates, and tendency to reverse during the recovery phase. In addition the majority of the findings noted were within the Testing Facility's historical control ranges.

Reviewer Comment: Analysis of clinical chemistry parameters was performed for mice at the 300 mg/kg/day dose level only on day 3 due to this group's early termination. Significant increases in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, and urea nitrogen were noted. However, these findings were noted at a dose that exceeded the MTD and is 18 times the MRHD of 80 mg/day based on mg/m². Therefore the absence of longer term dosing data is of limited clinical significance.

An adequate battery of clinical chemistry parameters was assessed. Blood samples were collected from fasted mice from the vena cava at necropsy.

Urinalysis

No assessment performed.

Gross Pathology

No gross pathology findings related to valbenazine treatment were observed.

Mice were fasted overnight, anesthetized by isoflurane inhalation, exsanguinated, and necropsied. Terminal body weights were recorded for all sacrificed toxicity animals and an examination of the external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues was performed.

Organ Weights

Valbenazine treatment resulted in a significant but non-adverse decrease in the weight of the thymus in male mice at doses \geq 30 mg/kg/day. No organ weight changes were noted at the end of the recovery period.

Therefore, given the tendency to recover, the small magnitude of the relative to brain weight decrease (27% to 40% relative to control), and a lack of microscopic correlates the finding in the thymus was considered non-adverse and potentially related to differences in sexual maturity or stress secondary to valbenazine treatment and not direct action of the test-article.

Organ weights were recorded at each scheduled sacrifice and paired organs were weighed together. Weight were determined for the following organs; adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, prostate gland, spleen, testis, thymus, uterus.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Valbenazine treatment resulted in minimal to mild lobuloalveolar hyperplasia of the mammary gland in female mice at doses ≥ 10 mg/kg/day. This finding is consistent with increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. Lobuloalveolar hyperplasia was still present in female mice, although at a reduced incidence, at doses ≥ 60 mg/kg/day at the end of the recovery phase. The absence of this effect at the 10 and 30 mg/kg/day dose levels and the reduced incidence at doses ≥ 60 mg/kg/day indicate the potential for recovery.

Reviewer Comment: Although no effects were noted in mammary tissue from male mice, only limited numbers of mammary tissue were present for evaluation, owing to the difficulty of obtaining mammary tissue from male mice. Therefore, a potential effect on male mammary tissue (e.g. feminization) cannot be ruled out under the conditions of this study.

Special Evaluation

The brain of all main study mice was subject to expanded histopathology, performed by a neuropathologist at (b) (4). Six to 8 coronal sections were obtained and confirmed to include (at minimum) meninges, paleocortex, midbrain including substantia nigra, and medulla oblongata. Special staining with Glial Fibrillary Acidic Protein (astrocytes), Fluoro-Jade B (neuronal necrosis), and Tyrosine hydroxylase was undertaken. No CNS lesions were noted at doses up to 100 mg/kg/day under the conditions of this study. In particular no lesions were noted in the pars compacta region of the substantia nigra or striatum.

Toxicokinetics

No quantifiable concentrations of valbenazine or related metabolites were observed in the control group.

Valbenazine exposure increased with increasing dose on day 1 and 91. C_{max} increased in an ~ dose proportional manner while AUC increased in a > dose proportional manner across the dose range. No consistent difference in exposure was noted between male

and female mice on day 1. However, AUC values were increased (1.4- to 2.2 times) in male mice relative to female mice on day 91. A moderate, but generally < 2 times, decrease in valbenazine exposure was noted over the course of the dosing phase.

Table 13 Mean Valbenazine TK Parameters in the 91-Day Mouse General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 91	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
10	Male	697	2793	914	3112
	Female	870	2969	500	1414
30	Male	4061	21126	2462	11504
	Female	3348	18575	3269	8372
60	Male	8177	81234	5229	29396
	Female	9025	67530	7012	21161
100	Male	16389	120754	4290	42580
	Female	12135	133142	6026	28507

NBI-98782 (pharmacologically active metabolite) C_{max} increased in a < dose proportional manner and AUC increased in an approximately dose proportional manner across groups on day 1 and day 91. Exposures were generally similar in male and female mice. Exposures tended to decrease following repeated exposure with the most significant decrease occurring in female mice at the 60 and 100 mg/kg/day dose levels. The molar ratio of NBI-98782 to valbenazine ranged from 0.0119 to 0.239 on dosing days 1 and 91.

Table 14 Mean NBI-98782 TK Parameters in the 91-Day Mouse General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 91	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
10	Male	45.1	361	44.8	316
	Female	92.1	333	75.2	257
30	Male	172	1203	119	980
	Female	273	1365	186	856
60	Male	217	2827	196	1903
	Female	382	3343	227	1360
100	Male	307	3162	248	2736
	Female	639	6015	207	1810

NBI-136110 (pharmacologically active metabolite) exposure increased in a an approximately dose proportional manner across dose groups on day 1 and day 91. Exposures were generally similar in male and female mice. Exposures tended to decrease following repeated exposure with the most significant decrease occurring in female mice at the 60 and 100 mg/kg/day dose levels. The molar ratio of NBI-98782 to valbenazine ranged from 0.109 to 0.803 on dosing days 1 and 91.

Table 15 Mean NBI-136110 TK Parameters in the 91-Day Mouse General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 91	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
10	Male	218	1878	270	1870
	Female	340	2267	199	1179
30	Male	1007	9210	764	7207
	Female	1129	9721	585	4530
60	Male	2275	31584	1603	16972
	Female	1831	26434	1076	10489
100	Male	2201	30030	2089	24131
	Female	2626	36661	925	13553

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations were within $\pm 15\%$ of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Exploratory Studies in Rats

Study title: NBI-98854: A 2-Phase Maximum Tolerated Oral Single Dose and 7-Day Repeat Dose Study in Rats (Non-GLP)

Study no.: 08-2059
Study report location: SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location: (b) (4)
GLP compliance: No
Drug, lot #, and % purity: Valbenazine, MD-2139-154A, 97.18%

Methods: Valbenazine was administered to groups of Sprague Dawley rats (~8 wks. of age) by oral gavage at doses of 0, 60, 80, and 100 mg/kg/day (6/sex/group) for 7-days.

Results: Two rats at the 100 mg/kg/day dose level (1/6♂, and 1/6♀) and one rat at the 80 mg/kg/day dose level (1/6♀) were found dead on dosing day 2 or 3. As a result dosing was discontinued at the 80 and 100 mg/kg/day dose levels. In the surviving rats clinical signs consisting of decreased activity, lethargy, palpebral closure, and hunched posture were noted at all dose levels. In addition a significant (up to 28%) decrease in body weight was noted on dosing day 6 at the 60 mg/kg/day dose level. Based on the significant decrease in body weight and adverse clinical signs noted at all doses in this study the Sponsor confirmed that the lowest dose, 60 mg/kg, exceeded an MTD.

Study title: 12 Day Oral Safety Assessment and Toxicokinetics of Daily HTBZ NBI-98854 Administration in the Male Sprague Dawley Rat (Non-GLP)

Study no.: Tox-HTBZ-98854-07-02
Study report location: SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location: Neurocrine Biosciences, Inc., CA
GLP compliance: No
Drug, lot #, and % purity: Valbenazine, TG-1790-021-Q, 97.18%

Methods: Valbenazine was administered to groups of male Sprague Dawley rats (~8 wks. of age) by oral gavage at doses of 0, 15, 30, and 60 mg/kg/day (4/group) for 12-days. The doses in this study were selected based on the above study where 60 mg/kg/day (the lowest dose tested) exceeded an MTD based on adverse body weight effects and clinical signs.

Results: No mortality was reported. Clinical signs consisting of hunched posture, ptosis, lethargy, rigidity, and stiff limbs were noted at all doses. At 24 hrs. postdose no

clinical signs were noted with the exception of days 7 to 12 when pre-dose hyperactivity was observed. On day 12 body weight was decreased by ~19% relative to control at the 60 mg/kg/day dose level. The Sponsor concluded that 30 mg/kg/day was the MTD in this study based on the clinical signs and decreased body weight observed at the 60 mg/kg/day dose level.

Reviewer Comment: The brain of all rats was subject to expanded histopathology performed by a neuropathologist at (b) (4). Eight coronal sections were obtained and, although sectioning varied slightly among rats, the following subanatomic areas were evaluated at a minimum: meninges, forebrain, striatum, cerebral cortex, thalamus/hypothalamus, midbrain, substantia nigra, pons, and cerebellum. Special staining with Fluoro-Jade B (neuronal necrosis) in addition to standard H&E was utilized. No CNS lesions were noted at doses up to 60 mg/kg/day under the conditions of this study. In particular no lesions were noted in the substantia nigra or striatum.

Study title: A 14-Day Oral Toxicity Study in Rats With a Minimum of 1-Week Recovery Period

Study no.:	08-2064
Study report location:	SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/29/2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Valbenazine, 08KL014D, 98.7%

Key Study Findings

Valbenazine treatment resulted in mortality at doses \geq 25 mg/kg/day.

Clinically relevant valbenazine treatment-related toxicities included the following:

- Clinical signs \geq 15 mg/kg/day; decreased activity, palpebral closure
- \downarrow body weight gain relative to control at all doses (σ , 44 to 127% and f , 53 to 136%)
- Histopathology changes in female and male reproductive tissues likely due to increased prolactin levels (not measure in this study).
- The Sponsor judged the NOAEL to be 15 mg/kg/day.
- This reviewer judged a NOAEL to have not been achieved based on the significant decrease in bodyweight gain observed at all dose levels. Therefore 15 mg/kg/day was judged to be the LOAEL in the current study.

Exposures for valbenazine at the LOAEL are: C_{max} of 1510 and 1400 ng/mL and an AUC_{0-24} of 7860 and 4440 ng•hr/mL in males and females, respectively for valbenazine, which are ~1.5 times and 1 times the human C_{max} and $AUC_{(0-24\text{hr})}$ expected at the MRHD of 80 mg/day (916 ng/mL and 6150 ng•hr/mL, respectively).

Exposures for NBI-98782 at the LOAEL are: C_{max} of 502 and 645 ng/mL and an AUC_{0-24} of 4310 and 6010 ng•hr/mL in males and females, respectively for valbenazine, which are ~12 times and 7 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (39.4 ng/mL and 695 ng•hr/mL, respectively).

The margin at the LOAEL based on mg/m² is 1.8 times the MRHD of 80 mg/day.

Methods

Doses:	0, 15, 25, or 50 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain:	Rat/Crl:CD(SD) (b) (4)
Number/Sex/Group:	10/sex/group and 5/sex/group for recovery
Age:	9 weeks of age at initiation of dosing
Weight:	253 to 357 g for males and 171 to 237 g for females
Satellite groups:	TK, 10/sex/group
Unique study design:	None
Deviation from study protocol:	None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Mortality

Three potentially valbenazine treatment-related mortalities occurred.

One female rat at the 25 mg/kg/day dose level and two female rats at the 50 mg/kg/day dose level were found dead. Although a cause of death was not determined an effect of treatment cannot be ruled out and therefore are considered valbenazine treatment-related.

Rats were observed for general health/mortality and morbidity twice daily, once in the morning and afternoon, throughout the study.

Clinical Signs

Valbenazine treatment-related findings were noted at all dose levels and consisted of hypoactivity and palpebral closure. These findings were generally observed 2 to 6 hrs. postdose, in association with C_{max} , and increased in incidence and severity with increasing dose. These findings are consistent with monoamine depletion a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. In addition, during the weekly physical examinations (Day 6) 2 males at the 25 mg/kg/day dose level and 1 male at the 50 mg/kg/day dose level exhibited trembling.

Hyperactivity was noted on the first day of the recovery period in rats at the 25 and 50 mg/kg/day dose levels.

Cageside observations were conducted pre-dose and approximately 2 to 6 hours postdose during the dosing phase and once daily on non-dosing days. Detailed observations were conducted for each animal once during the pre-dose phase and weekly throughout the dosing and recovery phases.

Body Weights

Valbenazine treatment resulted in a decrease in body weight gain in both male and female rats at all dose levels throughout the dosing phase. In male and female rats this effect resulted in a significant decrease in body weight relative to control rats at doses ≥ 25 and ≥ 15 mg/kg/day, respectively. The effect on body weight correlated with a decrease in food consumption during this period. Although mean body weight remained statistically lower relative to controls during the recovery period, body weight gains were generally greater, indicating recovery.

Table 16 Mean Body Weight Effects in the 91-Day Rat General Toxicology Study – Dosing Phase

Dose (mg/kg)	Male	Female
	Body weight Gain (% Control)	Body weight Gain (% Control)
0	----	----
15	-44%	-53%
25	-71%	-90%
50	-127%	-136%

Each animal was weighed on the day of randomization and daily during the dosing and recovery phases. A final fasted body weight was recorded for each animal on the day of scheduled euthanasia for calculation of organ to body weight ratios. Food consumption was measured daily throughout the study.

Ophthalmoscopy

No valbenazine treatment-related ophthalmic findings were observed during the dosing or recovery phases.

Ophthalmic examinations were conducted once during the pre-dose phase, on day 12 of the dosing phase and at the end of the recovery phase. The eyes were dilated with a mydriatic agent, and examinations were performed using an indirect ophthalmoscope.

ECG

No assessment performed.

Hematology

Non-adverse valbenazine treatment-related effects were noted on several hematology parameters at all dose levels at the end of the dosing phase. These effects were considered non-adverse due to their relatively small magnitude (+40% to -33%) and tendency to reverse during the recovery phase. In addition the majority of the findings noted are typical of those observed in rats with decreased food intake/body weight gain.

Valbenazine administration had no effect on coagulation parameters.

An adequate battery of hematology and coagulation parameters was assessed. Blood samples were collected from fasted rats from the vena cava at necropsy.

Clinical Chemistry

Non-adverse valbenazine treatment-related effects were noted on multiple clinical chemistry parameters at all dose levels. These effects were considered non-adverse due to their relatively small magnitude (+36% to -56%), the absence of any histopathology correlates and tendency to reverse during the recovery phase. In addition the majority of the findings noted are typical of those observed in rats with decreased food intake/body weight gain.

An adequate battery of clinical chemistry parameters was assessed. Blood samples were collected from fasted rats from the vena cava at necropsy.

Urinalysis

Non-adverse valbenazine treatment-related effects were noted on several urinalysis parameters at all dose levels. These effects were considered non-adverse due to their relatively small magnitude (+2% to -77%) and tendency to reverse during the recovery phase. In addition the majority of the findings noted are typical of those observed in rats with decreased food intake/body weight gain.

An adequate battery of urinalysis parameters was assessed. Urine samples for were collected into ice-chilled containers during the overnight period prior to necropsy from animals fasted overnight.

Gross Pathology

No gross pathology findings related to valbenazine treatment were observed.

Rats were fasted overnight, anesthetized by isoflurane inhalation, exsanguinated, and necropsied. Terminal body weights were recorded for all sacrificed toxicity animals and an examination of the external features of the carcass, external body orifices, abdominal, thoracic, and cranial cavities, organs, and tissues was performed.

Organ Weights

Valbenazine treatment resulted in significant but non-adverse changes in the weight of the uterus/cervix, thymus, and pituitary.

Uterine/cervix weight was significantly decreased (both absolute and relative) at doses ≥ 25 mg/kg/day in females. Thymus weight was significantly decreased (both absolute and relative) at doses ≥ 25 mg/kg/day in females. Pituitary weight was significantly decreased (both absolute and relative) at the 50 mg/kg/day dose level in males and females. No organ weight changes were noted at the end of the recovery period.

Therefore, given the tendency to recovery, the small magnitude of the findings (-10% to -54%), and a lack of microscopic correlates these findings were considered non-adverse.

Organ weights were recorded at each scheduled sacrifice and paired organs were weighed together. Weight was determined for the following organs; adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, pituitary gland, prostate gland, Salivary gland, spleen, testis, thymus, thyroid gland, uterus.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Valbenazine treatment resulted in minimal to slight acinar hyperplasia of the mammary gland in females at doses ≥ 15 mg/kg/day. Feminization of the mammary gland, change from lobuloalveolar morphology to tubuloalveolar morphology, occurred in 4 and 7 male rats at the 25 and 50 mg/kg/day dose levels, respectively. These findings are consistent with increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. The incidence of findings in male and female reproductive tissues was similar to control following the recovery phase indicating reversibility.

A minimal to slight decrease in bone marrow cellularity (femur and sternum) was noted in males and females at the 25 mg/kg/day dose level. A minimal to marked decrease in bone marrow cellularity (femur and sternum) was noted in males and females at the 50 mg/kg/day dose level. This finding is consistent with an indirect effect secondary to the decreased food intake/body weight gain noted in these rats.

Special Evaluation

The brain of all main study rats was subject to expanded histopathology, performed by a neuropathologist at (b) (4). Eight coronal sections were obtained and confirmed to include (at minimum) meninges, paleocortex, midbrain including substantia nigra, and medulla oblongata. Special staining with Fluoro-Jade B (neuronal necrosis) in addition to standard H&E staining was performed. No CNS lesions were noted at doses up to 50 mg/kg/day under the conditions of this study. In particular no lesions were noted in the pars compacta region of the substantia nigra or striatum.

Toxicokinetics

No quantifiable concentrations of valbenazine or related metabolites were observed in the control group.

Valbenazine exposure increased with increasing dose on day 1 and 14. Slightly higher exposures were noted in female rats. A moderate, but generally < 2 times, increase in valbenazine exposure was noted over the course of the dosing phase. Valbenazine exposures tended to be highly variable.

Table 17 Mean Valbenazine TK Parameters in the 14-Day Rat General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 14	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
15	Male	832	3130	1510	7860
	Female	1670	5880	1400	4440
25	Male	1050	5670	2030	11900
	Female	1440	15000	2030	11800
50	Male	3270	40500	2290	16500
	Female	4280	40500	3080	19800

NBI-98782 (pharmacologically active metabolite) C_{max} and AUC increased in an approximately dose proportional manner across groups on day 1 and day 14. Slightly higher exposures were noted in female rats. No significant accumulation was observed. The molar ratio of NBI-98782 to valbenazine ranged from 0.6 to 1.6 on dosing days 1 and 14.

Table 18 Mean NBI-98782 TK Parameters in the 14-Day Rat General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 14	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
15	Male	550	4760	502	4310
	Female	741	7100	645	6010
25	Male	773	6350	712	7950
	Female	923	11100	880	8420
50	Male	1120	15900	1070	12700
	Female	1730	21400	1460	16900

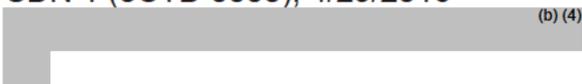
NBI-136110 (pharmacologically active metabolite) levels were not measured in this study.

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations were within $\pm 15\%$ of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Pivotal Studies in Rats

Study title: A 91-Day Study of NBI-98854 by Oral Gavage in Rats with a 6-Week Recovery Period

Study no.:	20008481
Sponsor Reference No.:	2011-TX-001
Study report location:	SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	5/21/2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Valbenazine, 04-110323-03B/03-54-01, 99%

Key Study Findings

Valbenazine treatment was generally tolerated in rats at doses up to 15 mg/kg/day for 91 days.

Clinically relevant valbenazine treatment-related toxicities included the following:

- Clinical signs ≥ 3 mg/kg/day; decreased activity, palpebral closure
- Dose related \downarrow body weight gain relative to control (σ , 5 to 21% and f , 7 to 13%)
- Lobuloalveolar hyperplasia of the mammary gland in females at dose ≥ 10 mg/kg/day and feminization of the mammary gland in males at 15 mg/kg/day.
- Levels of the metabolite NBI-136110 were not measured in this study.
- The Sponsor judged the NOAEL to be 15 mg/kg/day, the highest dose tested, corresponding to a C_{\max} of 589 and 967 ng/mL and an AUC_{0-24} of 3210 and 3471 ng•hr/mL in males and females, respectively.
- This reviewer judged the NOAEL to be 3 mg/kg/day based on clinical signs leading to a significant reduction in food consumption and bodyweight gain observed at doses ≥ 10 mg/kg/day.

Exposures for valbenazine at the NOAEL of 3 mg/kg/day are: C_{\max} of 76.8 and 186 ng/mL and an AUC_{0-24} of 269 and 534 ng•hr/mL in males and females, respectively, which are < 1 times the human C_{\max} and $AUC_{(0-24\text{hr})}$ expected at the MRHD of 80 mg/day (916 ng/mL and 6150 ng•hr/mL, respectively).

Exposures for NBI-98782 at the NOAEL of 3 mg/kg/day are: C_{\max} of 72.2 and 93.1 ng/mL and an AUC_{0-24} of 664 and 885 ng•hr/mL in males and females, respectively, which are ~ 2 times and 1 times the human C_{\max} and $AUC_{(0-24\text{hr})}$ expected at the MRHD of 80 mg/day (39.4 ng/mL and 695 ng•hr/mL, respectively).

The margin at the NOAEL based on mg/m² is <1 times the MRHD of 80 mg/day.

Methods

Doses: 0, 1, 3, 10, or 15 mg/kg
Frequency of dosing: Daily
Route of administration: Oral
Dose volume: 10 mL/kg
Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain: Rat/Crl:CD(SD), (b) (4)
Number/Sex/Group: 10/sex/group and 5/sex/group for recovery
Age: 6 to 7 weeks of age at initiation of dosing
Weight: 190 to 258 g for males and 152 to 224 g for females
Satellite groups: TK, 6/sex/group
Unique study design: None
Deviation from study protocol: None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Mortality

No valbenazine treatment-related mortalities occurred.

One male rat at the 10 mg/kg/day dose level and one female rat at the 3 mg/kg/day dose level were found dead. Cause of death was attributed to esophageal perforation.

Rats were observed for general health/mortality and morbidity twice daily, once in the morning and afternoon, throughout the study.

Clinical Signs

Valbenazine treatment-related findings were noted at dose levels ≥ 3 mg/kg/day and consisted of hypoactivity and palpebral closure. These findings were generally observed 1 to 4 hrs. postdose, in association with C_{max} , and increased in incidence and severity with increasing dose. These findings are consistent with monoamine depletion a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. In addition apparent rebound hyperactivity was noted just prior to dose administration beginning approximately 4-weeks following study initiation. Hyperactivity was also observed during the first week of the recovery period.

Cageside observations were conducted approximately 1 to 4 hours postdose during the dosing phase and once daily on non-dosing days. Detailed observations were conducted for each animal once during the predose phase, prior to dosing on day 1, and weekly throughout the dosing and recovery phases. Detailed observations were conducted prior to dosing on dosing days.

Body Weights

Valbenazine treatment resulted in a decrease in body weight gain in both male and female rats at dose levels ≥ 3 mg/kg/day throughout the dosing phase. In both sexes this effect resulted in a significant decrease in body weight relative to control rats at doses ≥ 10 and ≥ 3 mg/kg/day, respectively. The effect on body weight was most significant during the first 3 weeks of dosing and correlated with a decrease in food consumption during this period. Although mean body weight remained statistically lower relative to controls during the recovery period, body weight gains were generally greater, indicating recovery.

Table 19 Mean Body Weight Effects in the 91-Day Rat General Toxicology Study – Dosing Phase

Dose (mg/kg)	Male	Female
	Body weight Gain (% Control)	Body weight Gain (% Control)
0	----	----
3	-5%	-7%
10	-14%	-8%
15	-21%	-13%

Each animal was weighed on the day of randomization and on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 91, 98, 105, 112, 119, 123, 126, 130, and 133. A final fasted body weight was recorded for each animal on the day of scheduled euthanasia for calculation of organ to body weight ratios.

Ophthalmoscopy

No valbenazine treatment-related ophthalmic findings were observed during the dosing phase. As a result no ophthalmic assessment was performed during the recovery phase.

Ophthalmic examinations were conducted once during the predose phase on all rats and once during the last week of the dosing phase on each toxicity animal. The eyes were dilated with a mydriatic agent, and examinations were performed using an indirect ophthalmoscope.

ECG

No assessment performed.

Hematology

Non-adverse valbenazine treatment-related effects were noted on several hematology parameters at the 10 and 15 mg/kg/day dose levels at the end of the dosing phase. These effects were considered non-adverse due to their relatively small magnitude (+20% to -48%) and tendency to reverse during the recovery phase.

Reviewer Comment: Although statistically significant effects were noted on white cell counts, these were likely secondary to stress (endogenous corticosteroid response) associated with valbenazine administration and not a direct action on the immune system. In addition the effects noted in red cell parameters are typical of those observed in rats with decreased food intake/body weight gain.

Valbenazine administration resulted in a non-adverse increase in prothrombin time (+8 to +20%) in males and females at doses ≥ 3 mg/kg/day and ≥ 1 mg/kg/day, respectively.

An adequate battery of hematology and coagulation parameters was assessed. Blood samples were collected from fasted rats from the vena cava at necropsy.

Clinical Chemistry

Non-adverse valbenazine treatment-related effects were noted on multiple clinical chemistry parameters at all dose levels. These effects were considered non-adverse due to their relatively small magnitude (+10% to -20%), the absence of any histopathology correlates and tendency to reverse during the recovery phase.

Reviewer Comment: The majority of the findings noted are typical of those observed in rats with decreased food intake/body weight gain.

An adequate battery of clinical chemistry parameters was assessed. Blood samples were collected from fasted rats from the vena cava at necropsy.

Urinalysis

No valbenazine treatment-related changes in urinalysis parameters were observed.

An adequate battery of urinalysis parameters was assessed. Urine samples were collected on wet ice during the overnight period before blood collection from animals fasted overnight.

Gross Pathology

No gross pathology findings related to valbenazine treatment were observed.

Rats were fasted overnight, anesthetized by isoflurane inhalation, exsanguinated, and necropsied. Terminal body weights were recorded for all sacrificed toxicity animals and an examination of the external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues was performed.

Organ Weights

Valbenazine treatment resulted in significant but non-adverse changes in the weight of the adrenal gland, ovary, and pituitary.

Adrenal weight was significantly increased (both absolute and relative) at doses ≥ 10 mg/kg/day in males and ≥ 1 mg/kg/day in females. Ovary weight was significantly increased (both absolute and relative) at doses ≥ 10 mg/kg/day in females. Pituitary weight was significantly decreased (both absolute and relative) at doses ≥ 3 mg/kg/day

in males and ≥ 1 mg/kg/day in females. No organ weight changes were noted at the end of the recovery period.

Therefore, given the tendency to recovery, the small magnitude of the findings (+50% to -35%), and a lack of microscopic correlates these findings were considered non-adverse.

Organ weights were recorded at each scheduled sacrifice and paired organs were weighed together. Weight were determined for the following organs; adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, pituitary gland, prostate gland, spleen, testis, thymus, thyroid gland, uterus.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Valbenazine treatment resulted in lobuloalveolar hyperplasia of the mammary gland in females at the 10 and 15 mg/kg/day dose levels. Feminization of the mammary gland, change from lobuloalveolar morphology to tubuloalveolar morphology, occurred in 1 male rat at the 15 mg/kg/day dose level.

Reviewer Comment: These findings are consistent with increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. The incidence of findings in male and female reproductive tissues was similar to control following the recovery phase indicating reversibility. Although prolactin was not measured in the current study, oral administration of valbenazine was previously demonstrated to significantly increase serum prolactin levels in rats at a dose of 3 mg/kg/day (study No. 08-98854-002-PH).

A minimal increase in bone marrow cellularity (femur and sternum) was noted in males at the 15 mg/kg/day dose level and females at doses ≥ 3 mg/kg/day. This finding was judged to be of no toxicological significance due to the minimal severity score.

Special Evaluation

The brain of all main study rats was subject to expanded histopathology, performed by a neuropathologist at (b) (4) Eight coronal sections were obtained and confirmed to include (at minimum) meninges, paleocortex, midbrain including substantia nigra, and medulla oblongata. Special staining with Glial Fibrillary Acidic Protein (astrocytes), Fluoro-Jade B (neuronal necrosis), and Tyrosine hydroxylase was undertaken. No CNS lesions were noted at doses up to 15 mg/kg/day under the conditions of this study. In particular no lesions were noted in the pars compacta region of the substantia nigra or striatum.

Toxicokinetics

No quantifiable concentrations of valbenazine or related metabolites were observed in the control group.

Valbenazine exposure increased with increasing dose on day 1 and 91. C_{max} and AUC increased in a > dose proportional manner between 1 and 10 mg/kg/day and ~ dose proportional manner between 10 and 15 mg/kg/day. Slightly higher exposures were noted in female rats. A moderate, but generally < 2 times, increase in valbenazine exposure was noted over the course of the dosing phase.

Table 20 Mean Valbenazine TK Parameters in the 91-Day Rat General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 91	
		C_{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C_{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
1	Male	12.2	31.0	25.9	40.5
	Female	16.7	39.1	35.8	141
3	Male	44.8	171	76.8	269
	Female	81.9	310	186	534
10	Male	272	1252	526	1456
	Female	392	1469	686	1563
15	Male	659	2891	589	3210
	Female	1006	3391	967	3471

NBI-98782 (pharmacologically active metabolite) C_{max} and AUC increased in an approximately dose proportional manner across groups on day 1 and day 91. Slightly higher exposures were noted in female rats. No significant accumulation was observed. The molar ratio of NBI-98782 to valbenazine ranged from 1 to 5 on dosing days 1 and 91.

Table 21 Mean NBI-98782 TK Parameters in the 91-Day Rat General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 91	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
1	Male	19.4	110	20.8	135
	Female	29.9	171	29.9	190
3	Male	64.6	480	72.2	664
	Female	102	557	93.1	885
10	Male	256	2210	249	2913
	Female	415	3392	404	3123
15	Male	413	4008	423	4320
	Female	798	5562	660	5061

NBI-136110 (pharmacologically active metabolite) levels were not measured in this study.

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations were within $\pm 15\%$ of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Study title: A 6-Month Oral Gavage Toxicity and Toxicokinetic Study with NBI-98854 in Rats with a 6-Week Recovery

Study no.: 8271662
 Sponsor Reference No. 2012-TX-108
 Study report location: SDN 1 (eCTD 0000), 4/29/2016
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 11/16/2010
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Valbenazine, Z534FP-12-001, 99.9%

Key Study Findings

Adverse potentially valbenazine treatment-related toxicity was noted at all dose levels. Clinically relevant adverse toxicities included the following:

- Mortality ≥ 10 mg/kg/day
- Clinical signs ≥ 10 mg/kg/day; myoclonic jerking/clonic convulsions
- Dose dependent \downarrow body weight gain relative to control at all dose levels (σ , 54 to 72% and ♀ , 66 to 81%)

- Retinal degeneration ≥ 3 mg/kg/day, possibly an exacerbation of light-induced retinopathy but based on the evidence a direct effect of valbenazine on the retina cannot be ruled out.
- The Sponsor judged the NOAEL to be 3 mg/kg/day, the lowest dose tested. However this reviewer disagrees with this assessment.
- Based on the retinal degeneration and clinical signs associated with \downarrow food consumption/bodyweight gain observed at 3 mg/kg/day this reviewer conclude that 3 mg/kg/day is the LOAEL, corresponding to a C_{\max} of 311 and 472 ng/mL and an AUC_{0-24} of 945 and 1650 ng·hr/mL in males and females, respectively.
- Findings in this chronic rat toxicology study were consistent with findings from the prior rat toxicity studies except for the retinal degeneration myoclonic jerking/clonic convulsions.
- An MTD was exceeded in this study at the 10 mg/kg/day dose level based on excessive morbidity in males and bodyweight effects in females.

Exposures for valbenazine at the LOAEL of 3 mg/kg/day are: C_{\max} of 311 and 472 ng/mL and an AUC_{0-24} of 945 and 1650 ng·hr/mL in males and females, respectively, which are < 1 times the human C_{\max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (916 ng/mL and 6150 ng·hr/mL, respectively).

Exposures for NBI-98782 at the LOAEL of 3 mg/kg/day are: C_{\max} of 110 and 125 ng/mL and an AUC_{0-24} of 897 and 1150 ng·hr/mL in males and females, respectively, which are ~ 3 times and 1.5 times the human C_{\max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (39.4 ng/mL and 695 ng·hr/mL, respectively).

Exposures for NBI-136110 at the LOAEL of 3 mg/kg/day are: C_{\max} of 66.4 and 64.2 ng/mL and an AUC_{0-24} of 472 and 599 ng·hr/mL in males and females, respectively, which are ~ 0.5 times and 0.3 times the human C_{\max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (124 ng/mL and 1910 ng·hr/mL, respectively).

The margin at the LOAEL based on mg/m² is < 1 times the MRHD of 80 mg/day.

Methods

Doses: 0, 3, 10, or 15 mg/kg
Frequency of dosing: Daily
Route of administration: Oral
Dose volume: 10 mL/kg
Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain: Rat/Crl:CD(SD), (b) (4)
Number/Sex/Group: 10/sex/group and 5/sex/group for recovery
Age: 6 to 7 weeks of age at initiation of dosing
Weight: 190 to 258 g for males and 152 to 224 g for females
Satellite groups: TK, 3/sex/control and 7/sex/treated group
Unique study design: None
Deviation from study protocol: None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Mortality

Possible valbenazine treatment-related mortality occurred in 3 male rats at the 10 and 15 mg/kg/day dose levels during the study.

One male rat (No. B55805) at the 10 mg/kg/day dose level was sacrificed on day 100 of the dosing phase due to repeated clonic convulsions. Convulsions were noted in this rat beginning on day 97 of the dosing phase and were present on each subsequent day but not related to C_{max} , generally occurring in conjunction with handling (dosing, detailed clinical examinations, etc.). The frequency and severity of convulsions in this rat resulted in adverse body weight loss and the association of convulsions with handling made it difficult to safely conduct study procedures. Therefore this animal was sacrificed early.

Reviewer Comment: Convulsions were noted in both sexes at the 15 mg/kg/day dose level and were judged to be valbenazine treatment-related. However, the convulsions in these rats tended to be of shorter duration and less severe.

Two male rats at the 15 mg/kg/day dose level were found dead, one on day 161 of the dosing phase and the other on day 15 of the recovery phase. Clinical signs were consistent with those seen in other rats at this dose level and no cause of death was determined at necropsy. However, an effect of valbenazine treatment cannot be ruled out.

Two additional mortalities occurred in male rats during the course of the study and were judged to be non-valbenazine treatment-related. One rat in the control group was found dead (cause unknown) and another rat at the 10 mg/kg/day dose level was sacrificed on day 26 of the dosing phase due to an incidental eye injury.

Rats were observed for general health/mortality and morbidity twice daily, once in the morning and afternoon, throughout the study.

Clinical Signs

Valbenazine treatment-related clinical signs were noted at all dose levels.

Adverse clinical signs were noted at the 10 and 15 mg/kg/day dose levels and consisted of myoclonic jerking and/or clonic convulsions in one male at the 10 mg/kg/day dose level (No. B55805, pre-terminal sacrifice) and two males (No. B55821 and B55831) and one female (No. B55906) at the 15 mg/kg/day dose level. Convulsions tended to last less than 1 minute but occasionally exceeded this time. The timing of convulsions was not associated with t_{max} , but instead with handling of the rats (dosing, detailed clinical examinations, etc.).

Reviewer Comment: Convulsions didn't develop until late in the dosing phase with the earliest evidence noted on dosing day 64 but generally occurring after day 97 and were not observed following cessation of dosing during the recovery period. In addition extensive neuropathology examination (see histopathology section for more detail) revealed no associated CNS lesions. Convulsions were not observed during a prior 3-month general toxicology study (No. 20008481) at comparable doses (up to 15 mg/kg/day) further suggesting a long latency period. These findings indicate that the convulsions are the result of a chronic process that appears to be reversible following cessation of dosing.

Additional valbenazine treatment-related findings were noted at all dose levels and consisted of hypoactivity and palpebral closure. These findings were generally observed 1 to 4 hrs. postdose, in association with C_{max} , and increased in incidence and severity with increasing dose. These findings are consistent with monoamine depletion a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. In addition apparent rebound hyperactivity was noted just prior to dose administration on most days.

Table 22 Clinical Signs Observed in the 6-Month Rat General Toxicology Study (# animals)

Dose Group (mg/kg/day)	Males	Females
0	None	None
3	Postdose Hypoactivity (8/15) Predose Hyperactivity (11/15)	Postdose Hypoactivity (8/15) Predose Hyperactivity (15/15)
10	Convulsions/Myoclonic jerking (1/15) Postdose Hypoactivity (14/15) Predose Hyperactivity (15/15)	Postdose Hypoactivity (14/15) Predose Hyperactivity (15/15)
15	Convulsions/Myoclonic jerking (3/15) Postdose Hypoactivity (15/15) Predose Hyperactivity (15/15)	Convulsions/Myoclonic jerking (1/15) Postdose Hypoactivity (15/15) Predose Hyperactivity (15/15)

Cageside observations were conducted approximately 2 to 4 hours and 22 to 23 hours postdose (prior to dosing on the following day). Postdose observation start times for each toxicity group were based on the dosing completion time for each group. Detailed

observations were conducted for each animal once during the predose phase, prior to dosing on day 1, and weekly (based on day 1) throughout the dosing and recovery phases for each toxicity animal. Detailed observations were also collected on the days of scheduled sacrifice (all surviving toxicity animals). Observations of animal behavior and movement were made while approaching the cage.

Body Weights

Valbenzazine treatment resulted in a significant decrease in body weight and body weight gain, relative to vehicle control, in both male and female rats at all dose levels throughout the dosing phase. In male rats this effect correlated with a significant reduction in food intake throughout the entire dosing phase. However, in female rats this effect correlated with a significant reduction in food intake only during the first two weeks of the dosing phase. During weeks 3 to 26 of the dosing phase food consumption was greater than or equal to control in the valbenzazine treated rats.

Figure 3 Mean Body weight Data from the Rat 6-Month General Toxicology Study – Male

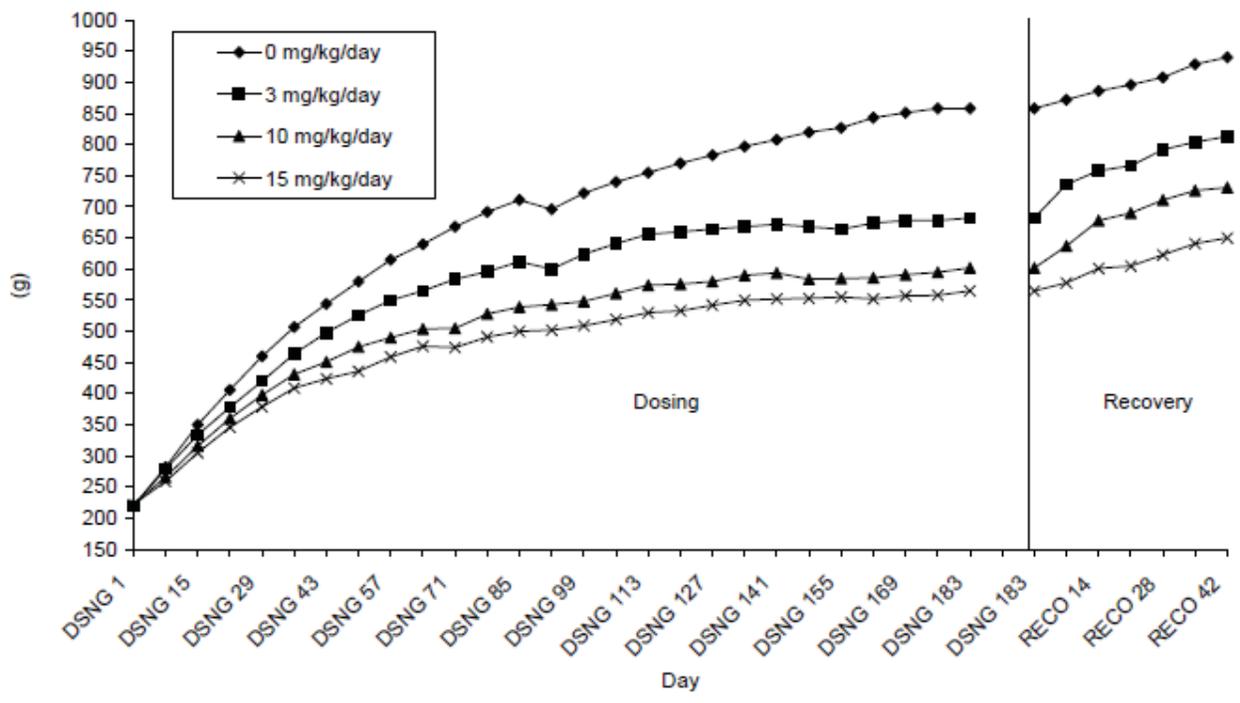


Figure 3 Mean Body weight Data from the Rat 6-Month General Toxicology Study – Female

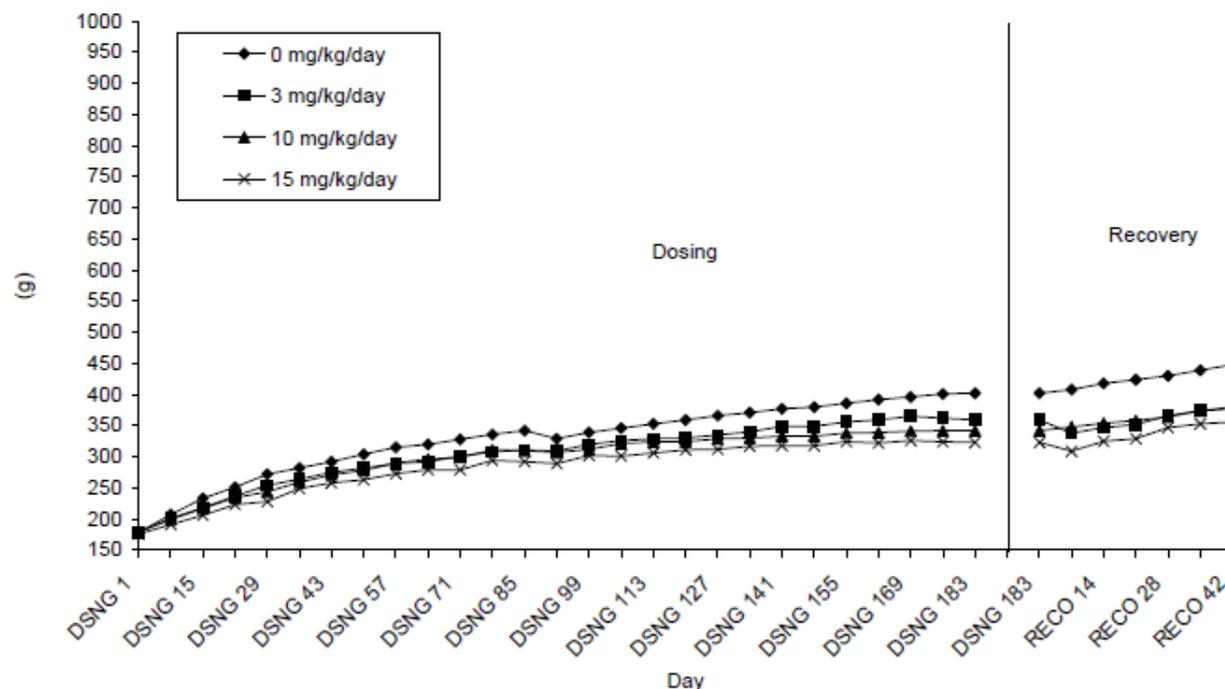


Table 23 Mean Body Weight Effects in the 6-Month Rat General Toxicology Study – Male, Dosing Phase

Sex	Dose (mg/kg)	Terminal Body weight (g)	Body weight Gain (g)	Body weight Gain (% Control)
Male	0	858 ± 71.3	640 ± 67.2	100%
	3	682 ± 72.1	462 ± 62.4	72%
	10	602 ± 52.2	380 ± 43.5	59%
	15	565 ± 37.1	342 ± 30.4	54%

Table 24 Mean Body Weight Effects in the 6-Month Rat General Toxicology Study – Female, Dosing Phase

Sex	Dose (mg/kg)	Terminal Body weight (g)	Body weight Gain (g)	Body weight Gain (% Control)
Female	0	402 ± 54.5	224 ± 44.3	100%
	3	359 ± 43.5	181 ± 36.4	81%
	10	342 ± 27.5	162 ± 18.5	72%
	15	323 ± 28.7	148 ± 24.0	66%

During the recovery phase body weight gain in valbenazine treated rats was greater than or equal to control rats. However, terminal body weight at the end of the recovery phase was still significantly reduced relative to controls.

Table 25 Mean Body Weight Effects in the 6-Month Rat General Toxicology Study – Male, Recovery

Sex	Dose (mg/kg)	Terminal Body weight (g)	Body weight Gain (g)	Body weight Gain (% Control)
Male	0	940 ± 98.6	72 ± 17.4	100%
	3	813 ± 84.3	94 ± 27.8	131%
	10	731 ± 37.6	101 ± 41.4	140%
	15	650 ± 9.4	104 ± 6.4	144%

Table 26 Mean Body Weight Effects in the 6-Month Rat General Toxicology Study – Female, Recovery

Sex	Dose (mg/kg)	Terminal Body weight (g)	Body weight Gain (g)	Body weight Gain (% Control)
Female	0	448 ± 45.5	39 ± 16.5	100%
	3	377 ± 50.3	40 ± 12.9	103%
	10	380 ± 29.7	34 ± 16.2	87%
	15	356 ± 38.1	42 ± 21.5	108%

Body weights were recorded for all animals once during the predose phase, prior to dosing on day 1, and weekly thereafter during the dosing and recovery phases.

Food Consumption

Valbenazine treatment resulted in a significant decrease in food consumption in male rats at all dose levels throughout the entire dosing phase. The magnitude of the effect was dose-responsive and correlated with a significant reduction in body weight gain in these rats. In female rats a valbenazine treatment-related decrease in food consumption was only noted during the first two weeks of the dosing phase. Food consumption was greater than or equal to control in valbenazine treated female rats during weeks 3 to 26 of the dosing phase. During the recovery period food consumption in valbenazine treated male rats tended to be comparable to controls. However, food consumption was greater in valbenazine treated female rats relative to controls at the 10 and 15 mg/kg/day dose levels during recovery. This is in contrast to the effects on body weight where the greatest recovery was observed in male rats.

Reviewer Comment: Together the effects on food consumption and body weight suggest that, although there is some correlation, it is likely valbenazine has a direct effect on body weight that is also independent of its effects on food consumption.

Food consumption was quantitatively assessed for each toxicity animal weekly during the dosing and recovery phases.

Ophthalmoscopy

No valbenazine treatment-related ophthalmic findings were observed during the dosing phase. As a result not ophthalmic assessment was performed during the recovery phase.

Ophthalmic examinations were conducted once during the predose phase on all rats and once during week 26 of the dosing phase on each toxicity animal. The eyes were dilated with a mydriatic agent, and examinations were performed using an indirect ophthalmoscope.

ECG

No assessment performed.

Hematology

Non-adverse valbenazine treatment-related effects were noted on several hematology parameters at the 10 and 15 mg/kg/day dose levels at the end of the dosing phase. These effects were considered non-adverse due to their relatively small magnitude (+7% to -64%) and tendency to reverse during the recovery phase.

Reviewer Comment: Although statistically significant effects were noted on white cell counts, these were likely secondary to stress (endogenous corticosteroid response) associated with valbenazine administration and not a direct action on the immune system. In addition the effects in red cell parameters are typical of those observed in rats with decreased food intake/body weight gain.

Valbenazine administration had no effect on coagulation parameters.

An adequate battery of hematology and coagulation parameters was assessed. Blood samples were collected from fasted rats via a jugular vein. Blood samples were collected during week 13 of the dosing phase and on days of scheduled sacrifice. Blood was also collected from toxicity animals sacrificed at an unscheduled interval.

Clinical Chemistry

Non-adverse valbenazine treatment-related effects were noted on multiple clinical chemistry parameters at all dose levels. These effects were considered non-adverse

due to their relatively small magnitude (+60% to -80%), the absence of any histopathology correlates and tendency to reverse during the recovery phase.

Reviewer Comment: The majority of the findings noted are typical of those observed in rats with decreased food intake/body weight gain.

An adequate battery of clinical chemistry parameters was assessed. Blood samples were collected from fasted rats via a jugular vein. Blood samples were collected during week 13 of the dosing phase and on days of scheduled sacrifice. Blood was also collected from toxicity animals sacrificed at an unscheduled interval.

Urinalysis

Urine volume and concentration were higher, relative to vehicle control, at all dose levels at the end of the dosing phase.

Reviewer Comment: Water intake was not measured during the study, so an effect on water intake cannot be ruled out. However, increased prolactin secretion secondary to dopamine depletion can produce hemoconcentration resulting in the effects noted here and in the clinical chemistry and hematology parameters.

An adequate battery of urinalysis parameters was assessed. Urine samples for were collected on wet ice during the overnight period before blood collection from animals fasted overnight. Urine samples were collected during week 13 of the dosing phase and on days of scheduled sacrifice.

Gross Pathology

Cysts on the right horn of the uterus were noted in a single rat at the 15 mg/kg/day dose level. Although this finding was present in only one rat it was judged to be valbenazine treatment-related.

Reviewer Comment: Microscopic diagnosis confirmed that these were decidual reactions (non-neoplastic proliferative changes in the endometrium) consistent with pseudopregnancy. The decidual reactions are likely the result of increased serum prolactin levels. Although prolactin was not measured in the current study, oral administration of valbenazine was previously demonstrated to significantly increase serum prolactin levels in rats at a dose of 3 mg/kg/day (study No. 08-98854-002-PH).

Rats were fasted overnight, anesthetized with sodium pentobarbital, exsanguinated, and necropsied. Terminal body weights were recorded for all sacrificed toxicity animals and an examination of the external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues was performed.

Organ Weights

Valbenazine treatment resulted in a significant decrease in uterine weights (both absolute and relative) at the 10 and 15 mg/kg/day dose levels. This finding correlated with decreased cell size in the uterine myometrium.

Reviewer Comment: The effect on the uterus is likely secondary to increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of

valbenazine acting as a VMAT2 inhibitor. Although prolactin was not measured in the current study, oral administration of valbenazine was previously demonstrated to significantly increase serum prolactin levels in rats at a dose of 3 mg/kg/day (study No. 08-98854-002-PH).

The effect on the uterus reversed during the recovery phase.

Table 27 Organ Weights in the 6-Month Rat General Toxicology Study – Female

Dose, mg/kg	Uterus		
	Absolute Weight	Body Weight Ratio (%)	Brain Weight ratio (%)
0	0.6916	100%	100%
3	0.7353	112%	64%
10	0.4896	82%	78%
15	0.4416	78%	57%

Organ weights were recorded at each scheduled sacrifice and paired organs were weighed together. Weight were determined for the following organs; adrenal, brain, epididymis, heart, kidney, liver, lung, ovary, pituitary, prostate, salivary gland, seminal vesicle, spleen, testis, thymus, thyroid, uterus.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Retinal degeneration was noted at terminal sacrifice in male (2/10, both doses) and female (2/10, both doses) rats at the 10 and 15 mg/kg/day dose levels vs. none in the vehicle control groups. At the end recovery retinal degeneration was noted in females (1/5, all doses) at all valbenazine dose levels. This finding was characterized by bilaterally symmetric degeneration of the photoreceptors and outer nuclear layer. The Sponsor concluded the characteristics of this finding were consistent with light-induced retinopathy. **Reviewer Comment:** Although light-induced retinopathy is a potentially spontaneous background finding in albino rats, the presence of retinal degeneration in only the valbenazine treatment groups together with the apparent dose responsiveness of the severity suggest it is treatment-related. Prolactin is known to directly affect the retina and potentiate light damage (De Vera Mudry, 2013). Moreover, hyperactivity was noted in these rats prior to dosing each day and this hyperactivity occurred during the period when room lights were on. Therefore, it is possible that the observed retinal degeneration is a treatment-related exacerbation of a spontaneous background change due to hyperactivity and prolactin-induced increased sensitivity. However, a direct effect of valbenazine on the retina cannot be ruled out at this time. No retinal degeneration or eye related toxicities were observed in any of the other studies conducted with valbenazine, including the 6-month carcinogenicity assay in pigmented mice (study No. AD20XW.7G8R. (b) (4)) or the 9-month chronic toxicology

study in beagle dogs (study No. 20028697) or in the chronic toxicology studies conducted with the FDA approved drug XENAZINE® (tetrabenazine, NDA 021894).

Table 28 Histopathology (Eye) from the 6-Month Rat General Toxicology Study – Male

Finding	Severity	0 mg/kg	3 mg/kg	10 mg/kg	15 mg/kg
Retinal Degeneration	Not present	10	10	8	8
	Minimal	0	0	1	0
	Moderate	0	0	1	1
	Marked	0	0	0	1

Table 29 Histopathology (Eye) from the 6-Month Rat General Toxicology Study – Female

Finding	Severity	0 mg/kg	3 mg/kg	10 mg/kg	15 mg/kg
Retinal Degeneration – <u>Terminal Sacrifice</u>	Not present	10	10	8	8
	Slight	0	0	2	0
	Marked	0	0	0	2
Retinal Degeneration – <u>Recovery Sacrifice</u>	Not Present	5	4	4	4
	Moderate	0	1	0	0
	Marked	0	0	1	1

Numerous valbenazine treatment-related histopathology findings were noted in male and female reproductive tissues at all dose levels. Male and female reproductive tissue findings consisted of lobular hyperplasia of the mammary gland. Additionally in females, increased eosinophilic nondegenerate corpora lutea in the ovary, and decidual reaction of the uterus and mucification/atrophy of the vagina, consistent with pseudopregnancy/prolonged diestrus were observed

Reviewer Comment: These findings are consistent with increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. Although prolactin was not measured in the current study, oral administration of valbenazine was previously demonstrated to significantly increase serum prolactin levels in rats at a dose of 3 mg/kg/day (study No. 08-98854-002-PH).

The incidence of findings in male and female reproductive tissues was similar to control following the recovery phase indicating reversibility.

Table 30 Histopathology (Reproductive Tissue) from the 6-Month Rat General Toxicology Study – Male

Finding	Severity	0 mg/kg	3 mg/kg	10 mg/kg	15 mg/kg
Mammary Gland Lobular Hyperplasia	Not present	7	10	1	3
	Minimal	0	0	8	6

Table 31 Histopathology (Reproductive Tissue) from the 6-Month Rat General Toxicology Study – Female

Finding	Severity	0 mg/kg	3 mg/kg	10 mg/kg	15 mg/kg
Mammary Gland Lobular Hyperplasia	Not present	8	4	0	1
	Minimal	2	3	3	0
	Slight	0	3	7	9
Ovary – ↑ Eosinophilic Nondegenerative Corpora Lutea	Not Present	7	8	3	0
	Present	3	2	7	10
Vagina - Epithelial Mucification/Atrophy	Not Present	10	6	1	2
	Present	0	4	9	8
Uterus – ↓ Myometrium cell size	Not Present	10	10	3	3
	Minimal	0	0	1	0
	Slight	0	0	4	2
	Moderate	0	0	2	5
Uterus – Decidual Reaction	Not Present	10	10	10	9
	Present	0	0	0	1

Angiectasis of the adrenal cortex was noted in female rats at all valbenazine dose levels. Angiectasis is a lesion consisting of widely dilated, blood-filled vascular channels causing compression of adjacent tissues. While it occurs as a spontaneous age-related change in rats, the apparent dose responsiveness of the incidence and severity suggest it is valbenazine treatment-related. Non-age-related angiectasis is typically secondary to other adrenal lesions such as inflammation, atrophy, degeneration, and neoplasia. In the absence of associated lesions this finding is likely a treatment-related exacerbation of a spontaneous background change. In addition this finding was not observed during the recovery period indicating reversibility. This finding was therefore judged to be of limited toxicological significance.

Table 32 Histopathology (Adrenal) from the 6-Month Rat General Toxicology Study – Female

Finding	Severity	0 mg/kg	3 mg/kg	10 mg/kg	15 mg/kg
Adrenal Cortex – Angiectasis	Not present	10	6	7	4
	Minimal	0	1	1	4
	Slight	0	2	2	1
	Moderate	0	1	0	1

A valbenazine treatment-related decrease in adipocytes was noted in the femoral and sternal bone marrow or both male and female rats at all dose levels. This finding is likely secondary to the significant decrease in body weight gain noted over the course of the study and is of limited toxicological significance.

All other microscopic observations were considered non-valbenazine treatment-related as they were caused by testing procedures or occurred in control rats at the same or higher incidence/severity when compared to valbenazine treatment groups.

Special Evaluation

The brain of all main study rats was subject to expanded histopathology, performed by a neuropathologist at (b) (4) due to the convulsions noted at the 10 and 15 mg/kg/day dose levels. Eight coronal sections were obtained and confirmed to include (at minimum) meninges, paleocortex, midbrain including substantia nigra, and medulla oblongata. The convulsions noted in this study did not have any morphological correlates in the brain.

Toxicokinetics

No quantifiable concentrations of valbenazine or related metabolites were observed in the control group.

Valbenazine exposure increased with increasing dose on day 1 and 180 except for females where exposures were comparable between 10 and 15 mg/kg/day on day 180. C_{max} and AUC increased in an approximately dose proportional manner for males and less than dose proportional manner for females on day 180. No consistent sex-related exposure difference was noted. Valbenazine exposure increased 4- to 6 times at 3 mg/kg/day and 2- to 3 times at 10 mg/kg/day over the course of the dosing phase. No accumulation was noted at 15 mg/kg/day.

Table 33 Mean Valbenazine TK Parameters in the 6-Month Rat General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 180	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
3	Male	37.7	215	311	954
	Female	52.2	289	472	1650
10	Male	287	1570	822	3940
	Female	258	2050	1180	4840
15	Male	690	3850	1570	7270
	Female	869	5300	971	5430

NBI-98782 (pharmacologically active metabolite) C_{max} and AUC increased in an approximately dose proportional manner across groups on day 1 and day 180. No consistent sex-related exposure difference was noted. No significant accumulation was observed. The molar ratio of NBI-98782 to valbenazine ranged from 1 to 4 on day 1 and was approximately 1 at all dose levels on day 180.

Table 34 Mean NBI-98782 TK Parameters in the 6-Month Rat General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 180	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
3	Male	68.1	626	110	897
	Female	68.1	773	125	1150
10	Male	262	2270	326	3050
	Female	281	3070	383	3350
15	Male	461	4050	412	4720
	Female	595	5530	476	4310

NBI-136110 (pharmacologically active metabolite) exposure increased with increasing dose on day 1 and 180 except for females where exposures were comparable between 10 and 15 mg/kg/day on day 180. C_{max} and AUC increased in an approximately dose proportional manner for males and less than dose proportional manner for females on day 180. No consistent sex-related exposure difference was noted. NBI-136110 exposure increased 2- to 3 times at 3 mg/kg/day over the course of the dosing phase. No accumulation was noted at the 10 or 15 mg/kg/day dose levels. The molar ratio of

NBI-136110 to the parent valbenzazine ranged from 0.28 to 1.08 on day 1 and from 0.27 to 0.48 on day 180.

Table 35 Mean NBI-136110 TK Parameters in the 6-Month Rat General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 180	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
3	Male	21.8	240	66.4	472
	Female	15.5	210	64.2	599
10	Male	85.1	1050	134	1560
	Female	59.5	864	121	1350
15	Male	165	2340	208	1590
	Female	104	1540	109	2680

Dosing Solution Analysis

Concentration verification results indicated that all the valbenzazine dose formulations were within $\pm 15\%$ of the target concentration. All formulations met analytical criteria and were thus suitable for use.

6.2.2 Non-rodent

Exploratory Studies in Dogs

Study title: NBI-98854 and NBI-98782: A 14-Day Oral (Capsule) Toxicity Study in Dogs with a Minimum of 1-Week Recovery Period

Study no.: 08-3332
 Study report location: SDN 1 (eCTD 0000), 4/29/2016
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 5/20/2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Valbenzazine, 08KL014D, 98.7%

Key Study Findings

Valbenzazine treatment-related mortality occurred at the 35 mg/kg/day dose level. The top dose was lowered to 30 mg/kg/day on day 11.

Adverse valbenzazine treatment-related toxicity consisted of the following:

- Clinical signs at 35/30 mg/kg/day; seizure-like activity (jerky/uncoordinated movement, convulsions), trembling, ataxia, difficulty standing, head bobbing, weak pulse, and excessive salivation
- The Sponsor judged the NOAEL to be 15 mg/kg/day due to mortality and clinical signs observed at the highest dose, corresponding to a C_{max} of 6470 and 9410 ng/mL and an AUC_{0-24} of 31900 and 36400 ng·hr/mL in males and females, respectively.
- This reviewer judged the NOAEL to be 5 mg/kg/day, based on clinical signs (CNS depression, muscle tremors) noted at 15 mg/kg/day.

Exposures for valbenazine at the NOAEL of 5 mg/kg/day are: C_{max} of 1730 and 1680 ng/mL and an AUC_{0-24} of 7760 and 6770 ng·hr/mL in males and females, respectively, which are ~2 times and ~1 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (916 ng/mL and 6150 ng·hr/mL, respectively).

Exposures for NBI-98782 at the NOAEL of 5 mg/kg/day are: C_{max} of 79.8 and 72.4 ng/mL and an AUC_{0-24} of 603 and 547 ng·hr/mL in males and females, respectively, which are ~2 times and ~1 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (39.4 ng/mL and 695 ng·hr/mL, respectively).

The margin at the NOAEL based on mg/m² is ~2 times the MRHD of 80 mg/day.

Although NBI-98782 was administered neat as part of this study the findings in those dogs are not discussed here as they were not materially different than the effects associated with valbenazine administration.

Methods

Doses:	Valbenazine; 0, 5, 15, or 35/30 mg/kg NBI-98782; 0, 7.5, or 15 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral (Capsule)
Dose volume:	NA
Formulation/Vehicle:	Empty Capsule
Species/Strain:	Dog/Beagle, [REDACTED] (b) (4)
Number/Sex/Group:	4 to 6/sex/group and 2/sex/group for recovery
Age:	5 to 6 months of age at initiation of dosing
Weight:	6 to 9.5 kg
Satellite groups:	4 to 6/sex/group for TK
Unique study design:	In addition to valbenazine, the active metabolite NBI-98782 was also administered neat in this study. The effects of NBI-98782 administration are not discussed in this review as they were materially similar to those observed following administration of valbenazine.
Deviation from study protocol:	None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Mortality

Valbenazine treatment-related mortality occurred at the 35 mg/kg/day dose level. One male dog had clonic/tonic convulsions lasting for 15 minutes on dosing day 10. This dog was euthanized when the convulsions failed to terminate. As a result doses were lowered to from 35 mg/kg/day to 30 mg/kg/day for this group on dosing day 11. All remaining dogs survived until study termination.

Dogs were observed for general health/mortality and morbidity twice daily, once in the morning and afternoon, throughout the study.

Clinical Signs

Valbenazine treatment-related adverse clinical signs were noted at the 35 mg/kg/day dose level, consisting of seizure-like activity. One female dog (No. 4762) displayed jerky/uncoordinated movement, excess salivation, pale gums, difficulty standing, and head bobbing on dosing day 3. Another female dog (No. 4763) displayed convulsions, excessive salivation, recumbency, trembling, weak pulse, and grey gums on dosing day 6. One male dog (No. 4261) displayed clonic/tonic convulsion accompanied by thrashing, grey gums, weak pulse, and vomiting prior to moribund sacrifice on dosing day 10. The top dose was subsequently lowered from 35 mg/kg/day to 30 mg/kg/day on dosing day 11.

In addition, ataxia, trembling, unsteady head, and excessive salivation were noted throughout the dosing phase at doses ≥ 15 mg/kg/day.

Valbenazine treatment-related clinical signs noted at all dose levels consisted of hypoactivity lethargy, and recumbency.

These findings were generally observed, in association with C_{max} , and increased in incidence and severity with increasing dose. With the exception of seizure-like activity, these findings are consistent with monoamine depletion a known pharmacological action of valbenazine acting as a VMAT2 inhibitor.

No valbenazine treatment-related clinical signs were noted during the recovery phase.

Cage side observations were performed predose, 1, 3, and 6 hrs. postdose. Detailed clinical examinations were performed twice during the predose phase and weekly during the dosing and recovery phases.

Body Weights

No adverse valbenazine treatment-related effects were noted on body weight.

A slight decrease in body weight gain in female dogs was observed at the 35/30 mg/kg/day (13%) and 15 mg/kg/day dose levels (11%). No effect on body weight was noted in male dogs at any dose level.

Each animal was weighed during the predose phase and twice weekly during the dosing and recovery phases. A final fasted body weight was recorded for each animal on the day of scheduled euthanasia for calculation of organ to body weight ratios.

Food Consumption

Food consumption was reduced sporadically in valbenazine treated dogs at doses ≥ 15 mg/kg/day.

A visual estimate of the amount of food consumed per day was made for each dog daily beginning one week prior to study initiation.

Ophthalmoscopy

No valbenazine treatment-related ophthalmic findings were observed during the dosing or recovery phase.

Ophthalmological examinations were performed prior to the dosing phase on day 12 or 13 of the dosing phase. The ocular examinations were conducted using a hand-held slit lamp and indirect ophthalmoscope. A short-acting mydriatic solution was used to dilate the eyes.

Respiratory Parameters

Valbenazine treatment resulted in significant decreases in respiratory rate (26% to 35%) and minute volume (4% to 17%) with compensatory increases in tidal volume (23% to 32%) and an increased incidence of sighs at doses ≥ 15 mg/kg/day. Although these

effects are common to CNS depressants the compensatory increase in tidal volume suggests a non-adverse effect on central respiratory centers at the doses tested.

Respiratory parameters were examined utilizing the Biosystem XA Software for Windows Version 2.5, designed by Buxco Electronics Inc., in accordance with the Standard Operating Procedures of the Testing Facility. All animals were acclimated to the facemask on at least 3 occasions for 5 minutes each before the pretreatment respiratory measurements were recorded.

Respiratory assessments were performed prior to the dosing phase (3 occasions) and day 2 of the dosing phase at the presumed T_{max} and 20 to 24 hours post dose (prior to the day 3 dose). An assessment at the end of recovery was not necessary based on the findings at the end of dosing.

ECG

Not assessed.

Hematology

No adverse valbenazine treatment-related effects were noted on any hematology or coagulation parameters. Reticulocyte counts were lower in male dogs at the 35/30 mg/kg/day dose level and in female dogs at all dose levels. However, all differences noted between control and valbenazine dose groups were small in magnitude (24 to 44%) and within the Testing Facility's historical control ranges.

An adequate battery of hematology and coagulation parameters was analyzed. Blood was collected by venipuncture of the jugular and cephalic vein during the predose phase, at the end of the dosing phase, and at the end of the recovery phase. The animals were fasted overnight but had access to water ad libitum.

Clinical Chemistry

No valbenazine treatment-related effects were noted on any clinical chemistry parameters. All differences noted between control and valbenazine dose groups were small in magnitude (12 to 25%) and statistically significant values were within the Testing Facility's historical control ranges.

An adequate battery of clinical chemistry parameters was analyzed. Blood was collected by venipuncture of the jugular and cephalic vein during the predose phase, at the end of the dosing phase, and at the end of the recovery phase. The animals were fasted overnight but had access to water ad libitum.

Urinalysis

No valbenazine treatment-related effects were noted on any urinalysis parameters.

Urine was collected overnight by cage pan drainage. The animals were fasted and water deprived overnight.

Gross Pathology

No valbenazine treatment-related effects were noted.

Dogs were euthanized by acepromazine sedation followed by sodium pentobarbital injection then exsanguination. Main study and recovery animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Organ Weights

Valbenazine treatment resulted in a decrease in thymus weights correlated with a decrease in thymus cellularity across all dose groups with no clear dose response. However, because no changes in hematology parameters (e.g. lymphocytes) indicative of a direct toxic effect were observed and these changes in the thymus are often secondary to stress they are judged to be of minimal toxicological significance.

In addition to the effect on thymus weights, a minimal increase in the weight of adrenals and a minimal decrease in the weight of the spleen were noted in males at all dose levels (both absolute and relative). Due to the relatively small magnitude of the change (15% to 31%) combined with a lack of histopathology correlates these effects were judged to be of limited toxicological significance.

No effects were noted at the end of the recovery period with the exception of decreased thymus weights which only showed a partial recovery in both sexes.

Organs were weighed at necropsy for all scheduled euthanasia animals. Paired organs were weighed together. Organ to body weight ratio (using the terminal body weight) and organ to brain weight ratios were calculated. The following organs were weighed; brain, epididymis, adrenal gland, pituitary gland, prostate gland, thyroid gland, heart, kidney, liver, lung, ovary, spleen, testis, thymus, and uterus.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Decreased thymus cellularity was noted across all dose levels. Unlike the correlated finding of decreased thymus weight, the incidence and severity of this microscopic finding increased in a dose responsive manner. This finding was characterized by decreased corticomedullary lymphocyte ratio.

Table 36 Histopathology from the 14-Day Dog General Toxicology Study

		Male				Female			
Finding	Severity	0 mg/kg	5 mg/kg	15 mg/kg	35/30 mg/kg	0 mg/kg	5 mg/kg	15 mg/kg	35/30 mg/kg
Thymus – Decreased Cellularity	Not present	4	2	1	0	4	4	2	0
	Minimal	0	0	1	3	0	0	2	1
	Slight	0	1	2	1	0	0	0	2
	Moderate	0	0	0	0	0	0	0	1

Special Evaluation

The brain of all main study dogs was subject to expanded histopathology performed by a neuropathologist at (b) (4) to allow an extensive examination of dopamine-rich areas (substantia nigra, ventral tegmental area, and striatum). Sections were stained with Fluoro-Jade B (neuronal necrosis) in addition to standard H&E staining. No valbenazine treatment-related gross or microscopic lesions were noted in the brain. The seizure-like activity noted in this study did not have any morphological correlates in the brain.

Toxicokinetics

No quantifiable concentrations of valbenazine or related metabolites were observed in the control group.

Valbenazine exposure increased with increasing dose in a dose-proportional to slightly greater than dose-proportional manner on day 1 and day 14. No consistent sex-related exposure difference was noted. Valbenazine exposure increased less than 2 times over the course of the dosing phase.

Table 37 Mean Valbenazine TK Parameters in the 14-Day Dog General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 14	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
5	Male	1510	6410	1730	7760
	Female	1530	5580	1680	6770
15	Male	6880	26100	6470	37900
	Female	6780	29700	9410	36400
35/30	Male	13100	77000	13900	78100
	Female	19500	72300	15000	83300

NBI-98782 (pharmacologically active metabolite) C_{max} and AUC increased in an approximately dose-proportional manner across groups on day 1 and day 14. No consistent sex-related exposure difference was noted. NBI-98782 exposure was similar to slightly increased (<2 times) on day 14 compared to day 1 of the dosing phase. The molar ratio of NBI-98782 to valbenazine ranged from 0.06 to 0.8 on day 1 and from 0.04 to 0.08 on day 14.

Table 38 Mean NBI-98782 TK Parameters in the 14-Day Dog General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 14	
		C_{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C_{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
5	Male	68.9	508	79.8	603
	Female	65.8	449	72.4	547
15	Male	244	1920	298	2720
	Female	209	1840	290	2320
35/30	Male	418	4870	404	4170
	Female	381	4050	357	3520

NBI-136110 (pharmacologically active metabolite) exposure was not determined in this study.

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations were within $\pm 15\%$ of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Pivotal Studies in Dogs

Study title: A 91-Day Study of NBI-98854 by Oral Capsule in Dogs with a 28-Day Recovery Period

Study no.: 20008482
 Sponsor Reference No. 2011-TX-002
 Study report location: SDN 1 (eCTD 0000), 4/29/2016
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 5/11/2011
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Valbenazine, 04-110323-03B/03-54-01, 99%

Key Study Findings

Valbenazine treatment-related toxicity consisted of the following:

- Clinical signs \geq 5 mg/kg/day; tremors, ataxia, hypoactivity
- \downarrow body weight gain and food consumption at \geq 12.5 mg/kg/day during the dosing phase. \downarrow body weight gain at 5 mg/kg/day during the recovery phase.
- The Sponsor judged the NOAEL to be 20 mg/kg/day, the highest dose tested corresponding to a C_{max} of 8189 and 7407 ng/mL and an AUC_{0-24} of 47649 and 49394 ng·hr/mL in males and females, respectively.
- This reviewer judged the NOAEL to be 2 mg/kg/day, based on clinical signs (CNS depression, muscle tremors) and decreased body weight gain noted at doses \geq 5 mg/kg/day.

Exposures for valbenazine at the NOAEL of 2 mg/kg/day are: C_{max} of 1037 and 1162 ng/mL and an AUC_{0-24} of 4090 and 4010 ng·hr/mL in males and females, respectively, which are \sim 1 times and \sim 0.7 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (916 ng/mL and 6150 ng·hr/mL, respectively).

Exposures for NBI-98782 at the NOAEL of 2 mg/kg/day are: C_{max} of 28.3 and 29.8 ng/mL and an AUC_{0-24} of 284 and 266 ng·hr/mL in males and females, respectively, which are \sim 0.7 times and 0.4 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (39.4 ng/mL and 695 ng·hr/mL, respectively).

The margin at the NOAEL of 2 mg/kg/day based on mg/m² is \sim 0.8 times the MRHD of 80 mg/day.

Methods

Doses:	0, 2, 5, 12.5, or 20 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral (Capsule)
Dose volume:	NA
Formulation/Vehicle:	Empty Capsule
Species/Strain:	Dog/Beagle, (b) (4)
Number/Sex/Group:	4/sex/group and 2/sex/group for recovery
Age:	6 months of age at initiation of dosing
Weight:	6.1 to 9.7 kg
Satellite groups:	None
Unique study design:	Assessment of serum prolactin levels was performed.
Deviation from study protocol:	None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Mortality

No deaths occurred during the in-life phase of the study.

Dogs were observed for general health/mortality and morbidity twice daily, once in the morning and afternoon, throughout the study.

Clinical Signs

Adverse valbenazine treatment-related clinical signs were noted at doses ≥ 5 mg/kg/day, consisting of hypoactivity, tremors, and ataxia (i.e. wobbly gate). These findings were generally observed 1 to 4 hrs. postdose, in association with C_{max} , and increased in incidence and severity with increasing dose. Hypoactivity was first observed late in the first week, tremors were first observed in the second week, and ataxia was observed intermittently throughout the dosing phase. These findings are consistent with CNS depression associated with monoamine depletion a known pharmacological action of valbenazine acting as a VMAT2 inhibitor.

No valbenazine treatment-related clinical signs were noted during the recovery phase.

Cage side observations were performed once daily (days 1 to 119) between 1 and 4 hours following dosing on dosing days and during the recovery period. Detailed clinical examinations were performed on the day of randomization (day -2 females/day -1 males) and weekly starting the last week of the predosing phase through the dosing and recovery phase.

Body Weights

Valbenazine treatment-related effects on body weight were observed at the 12.5 and 20 mg/kg/day dose levels. Body weight gain was decreased in both male and female dogs, especially during the first two weeks of the dosing phase resulting in terminal body weights that ranged from 8% to 15% lower in males and 5% to 13% lower in females on day 91 relative to control dogs. This effect correlated with decreased food consumption during the early dosing phase as food was only available during the 4 hour postdose period of hypoactivity. As a result food was not removed allowing the dogs more time to eat. This protocol change resulted in a more normalized body weight gain.

The decrease in body weight gain peaked in male dogs during the 1st two weeks of the recovery phase (22%) and at the end of the recovery period body weights were 12% lower in males at the 12.5 mg/kg/day dose level (dose with largest effect) indicating a trend toward recovery. The decrease in body weight gain remained steady in female dogs throughout the recovery period at the 12.5 and 20 mg/kg/day dose levels and worsened at the 5 mg/kg/day dose level resulting in body weights that were 16 to 18% lower at doses ≥ 5 mg/kg/day relative to control dogs. At the 5 mg/kg/day dose level decreased food consumption was noted during this period. No effect on food consumption was noted at the 12.5 or 20 mg/kg/day dose levels. The toxicological significance of the findings in female dogs is unclear.

Each animal was weighed on the day of randomization (day -2 females/day -1 males) and on days -1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 91, 98, 105, 112, and 119.

A final fasted body weight was recorded for each animal on the day of scheduled euthanasia for calculation of organ to body weight ratios (day 92 or 120).

Food Consumption

Food consumption was reduced in valbenazine treated dogs primarily during the first two weeks of dosing when food was available only during the postdose period of hypoactivity. Starting on day 15 when food was left in the cage overnight food consumption tended to normalized. However, food consumption remained low in females at the 20 mg/kg/day dose level and was noted during the recovery period in females at the 5 mg/kg/day dose level. The toxicological significance of the findings in female dogs is unclear.

Food consumption was quantitatively measured on each day for each animal and reported in weekly intervals. From day 1 to 14 of the dosing phase, the food was offered 2 hrs. after dosing and left in the dog's cage for a period of 2 to 4 hours and then removed. From day 15 of the dosing phase until the end of the study, the food was left in the dog's cage overnight and weighed the following morning.

Ophthalmoscopy

No valbenazine treatment-related ophthalmic findings were observed during the dosing phase. As a result no ophthalmic assessment was performed during the recovery phase.

Ophthalmological examinations were performed prior to the dosing phase (Day -3 females/Day -2 males) and during the last week of the dosing phase (Day 89 females/Day 90 males). The ocular examinations were conducted using a hand-held slit lamp and indirect ophthalmoscope. A short-acting mydriatic solution was used to dilate the eyes.

ECG

A statistically significant prolongation of QTc (25 msec, 11%) in female dogs at the 20 mg/kg/day dose level was observed on day 85 of the dosing phase. No other valbenazine treatment-related effects were observed.

Reviewer Comment: A similar degree of QTc prolongation was observed in male but not female dogs on day 137 (but not 270) of the 9-month general toxicology study (No. 20028697). Because valbenazine has been shown to significantly increase QTc (15 to 25 msec) across multiple studies and also inhibits hERG tail currents at relevant concentrations (IC₅₀ 2 µM) this effect may be treatment related. However, because the effect is not observed consistently the toxicological significance is unclear.

Electrocardiogram (ECG) measurements were obtained from all animals using leads I, II, III, aVR, aVL, and aVF and a chart speed of 50 mm/second. The ECG measurements were obtained once during the predose phase (day -6 females/day -5 males), during the last week of the dosing phase (day 85 females/day 86 males), and during the last week of the recovery period (day 118 females/day 119 males). Only lead II was evaluated by a board-certified veterinary cardiologist.

Hematology

No valbenazine treatment-related effects were noted on any hematology or coagulation parameters. All differences noted between control and valbenazine dose groups were small in magnitude (-9.4 to 2%), not dose related, and statistically significant values were similar to pretest values or within the Testing Facility's historical control ranges.

An adequate battery of hematology and coagulation parameters was analyzed. Blood was collected by venipuncture of the jugular vein during the predose phase (Week -1), day 92 of the dosing phase, and day 120 of the recovery period. The animals were fasted overnight but had access to water ad libitum.

Clinical Chemistry

No valbenazine treatment-related effects were noted on any clinical chemistry parameters. All differences noted between control and valbenazine dose groups were small in magnitude (7 to 15%) and statistically significant values were similar to pretest values or within the Testing Facility's historical control ranges.

An adequate battery of clinical chemistry parameters was analyzed. Blood was collected by venipuncture of the jugular vein during the predose phase (Week -1), day 92 of the dosing phase, and day 120 of the recovery period. The animals were fasted overnight but had access to water ad libitum.

Urinalysis

No valbenazine treatment-related effects were noted on any urinalysis parameters.

Urine was collected overnight by cage pan drainage or via cystocentesis at gross necropsy if an adequate sample was not obtained. The animals were fasted overnight but had access to water ad libitum.

Serum Prolactin Levels

No valbenazine treatment-related effects were noted on serum prolactin concentrations.

Serum prolactin concentrations were < 5 ng/mL and mean values were generally comparable to those reported in the peer reviewed literature for Beagle dogs. Serum prolactin concentrations were similar between control and valbenazine treated dogs on both day 1 and day 91 of the dosing phase.

Blood was collected by venipuncture of the jugular vein during the predose phase (Week -1), day 92 of the dosing phase, and day 120 of the recovery period. The animals were fasted overnight but had access to water ad libitum. Serum prolactin concentrations were determined using a commercially available ELISA prolactin (canine) kit (ALPCO, Salem, NH).

Gross Pathology

Thymic size was visibly decreased in two male dogs, one each at the 12.5 and 20 mg/kg/day dose levels. No other valbenazine treatment related effects were noted at gross necropsy.

Reviewer Comment: The effect on the thymus was associated with decreased thymic weight at these dose levels and microscopic findings of minimal to mild lymphoid depletion. This effect is likely an adaptive change related to stress and not a direct action of valbenazine on the thymus.

Dogs were euthanized by sodium pentobarbital injection, followed by exsanguination. When possible, the animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied at similar times throughout the day. Animals were fasted (overnight) before their scheduled necropsy. Main study and recovery animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Organ Weights

There was a statistically significant trend for decreasing thymic weight at the 12.5 and 20 mg/kg/day dose levels associated with microscopic findings of minimal to mild thymic lymphoid depletion. At recovery this trend was reversed.

Reviewer Comment: This effect is likely an adaptive change related to stress and not a direct action of valbenazine on the thymus.

Organs were weighed at necropsy for all scheduled euthanasia animals. Paired organs were weighed together. Organ to body weight ratio (using the terminal body weight) and organ to brain weight ratios were calculated. The following organs were weighed; brain, epididymis, adrenal gland, pituitary gland, prostate gland, thyroid gland, heart, kidney, liver, lung, ovary, spleen, testis, thymus, and uterus.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Minimal to mild thymic lymphoid depletion was noted in male dogs with grossly observed small thymuses and 7 females with grossly normal thymuses. This effect was observed at the 12.5 and 20 mg/kg/day dose levels in male dogs and in control, 2, 12.5, and 20 mg/kg/day dose levels in female dogs.

Reviewer Comment: Given the relatively minor nature of the finding based on severity score and the association of these findings with stress it is likely secondary to an adaptive stress response and not a direct action of valbenazine on the thymus.

Other findings were considered incidental (minimal, multifocal mononuclear cell infiltrates, minimal, multifocal granulocytic infiltrates, minimal Kupffer cell hyperplasia, and mild chronic pericholangial inflammation in the liver of 1 dog at the 20 mg/kg/day

dose level) or of unknown toxicological significance (perivascular inflammation in the oviducts (1 ♀ 20 mg/kg/day), heart (1♀ 12.5 mg/kg/day), and cervix (1 ♀ 2 mg/kg/day)).

Reviewer Comment: These findings were absent in the 9-month chronic toxicology study in dogs (study No. 20028697) at comparable doses (up to 15 mg/kg/day). Therefore these changes are likely incidental and unrelated to valbenazine treatment.

No valbenazine treatment-related effects were noted at recovery.

Special Evaluation

The brain of all main study dogs was subject to expanded histopathology performed by a neuropathologist at (b) (4) to allow an extensive examination of dopamine-rich areas (substantia nigra, ventral tegmental area, and striatum). Sections were stained with GFAP (astrocytes), Fluoro-Jade B (neuronal necrosis), and tyrosine hydroxylase in addition to standard H&E staining. No valbenazine treatment-related gross or microscopic lesions were noted in the brain.

Toxicokinetics

No quantifiable concentrations of valbenazine or related metabolites were observed in the control group.

Valbenazine exposure increased with increasing dose in a dose-proportional manner on day 1 and 91. No consistent sex-related exposure difference was noted. Valbenazine exposure did not increase with repeated dosing over the course of the dosing phase indicating limited potential for accumulation.

Table 39 Mean Valbenazine TK Parameters in the 91-Day Dog General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 91	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
2	Male	721	2265	1037	4090
	Female	779	2347	1162	4010
5	Male	2213	6239	2656	11857
	Female	2229	7781	2924	11759
12.5	Male	7909	25600	7110	33885
	Female	4784	18907	4762	24285
20	Male	11241	37288	8189	47649
	Female	10019	45853	7407	49394

NBI-98782 (pharmacologically active metabolite) C_{max} and AUC increased in an approximately dose-proportional manner across groups on day 1 and 91. No consistent

sex-related exposure difference was noted. NBI-98782 exposure increased 1.3- to 2.9 times over the course of the dosing phase. The molar ratio of NBI-98782 to valbenazine was ~0.1 on day 1 and ranged from 0.09 to 0.18 on day 91.

Table 40 Mean NBI-98782 TK Parameters in the 91-Day Dog General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 91	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
2	Male	22.0	174	28.3	284
	Female	23.7	172	29.8	266
5	Male	56.2	433	119	1252
	Female	55.1	510	108	1024
12.5	Male	194	2033	348	3808
	Female	121	1266	227	2474
20	Male	253	2511	504	6457
	Female	219	2896	401	5485

NBI-136110 (pharmacologically active metabolite) exposure was not characterized in this study.

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations were within ±15% of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Study title: A 9-Month Study of NBI-98854 by Oral Capsule Administration in Dogs with a 1-month Recovery Period

Study no.: 20028697
 Sponsor Reference No. 2012-TX-090
 Study report location: SDN 1 (eCTD 0000), 4/29/2016
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 10/09/2012
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Valbenazine, 04-110323-03B/03-54-01, 97%

Key Study Findings

Valbenazine treatment-related toxicity consisted of the following:

- Clinical signs ≥ 10 mg/kg/day; tremors, palpebral ptosis, hypoactivity
- \downarrow body weight gain and food consumption in females at ≥ 10 mg/kg/day
- The Sponsor judged the NOAEL to be 15 mg/kg/day, the highest dose tested corresponding to a C_{max} of 10900 and 9730 ng/mL and an AUC_{0-24} of 73000 and 52200 ng·hr/mL in males and females, respectively.
- This reviewer judged the NOAEL to be 3 mg/kg/day, the lowest dose tested, based on clinical signs (CNS depression, muscle tremors) noted at doses ≥ 10 mg/kg/day.

Exposures for valbenazine at the NOAEL of 3 mg/kg/day are: C_{max} of 1780 and 1670 ng/mL and an AUC_{0-24} of 10200 and 7450 ng·hr/mL in males and females, respectively, which are ~ 2 times and ~ 1.4 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (916 ng/mL and 6150 ng·hr/mL, respectively).

Exposures for NBI-98782 at the NOAEL of 3 mg/kg/day are: C_{max} of 42.9 and 39.4 ng/mL and an AUC_{0-24} of 445 and 369 ng·hr/mL in males and females, respectively, which are ~ 1 times and 0.6 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (39.4 ng/mL and 695 ng·hr/mL, respectively).

The margin at the NOAEL of 3 mg/kg/day based on mg/m² is ~ 1 times the MRHD of 80 mg/day.

Methods

Doses:	0, 3, 10, or 15 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral (Capsule)
Dose volume:	NA
Formulation/Vehicle:	Empty Capsule
Species/Strain:	Dog/Beagle, [REDACTED] (b) (4)
Number/Sex/Group:	5/sex/group and 2/sex/group for recovery
Age:	6 months of age at initiation of dosing
Weight:	6.5 to 9 kg
Satellite groups:	None
Unique study design:	Electroencephalograms (EEGs) were collected on approximately half of the animals each day on days 246/247 and 254/255 of the dosing phase. Electromyograms (EMGs) were collected on approximately half of the animals each day for the day 254/255 interval only. EEGs and EMGs were recorded on Day 254/255 prior to dose administration, approximately 2 hours postdose, and at approximately 4 to 5 hours postdose. Prior to recording, each dog was positioned in a restraining sling. The dogs were acclimated to the slings the week prior to the first evaluation period (approximately 10 minutes each time, for a total of 3 times).
Deviation from study protocol:	None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Mortality

No deaths occurred during the in-life phase of the study.

Dogs were observed for general health/mortality and morbidity twice daily, once in the morning and afternoon, throughout the study.

Clinical Signs

Valbenazine treatment-related clinical signs were noted at the 10 and 15 mg/kg/day dose levels, consisting of hypoactivity and palpebral closure. These findings were generally observed 1 to 4 hrs. postdose, in association with C_{max} , and increased in incidence and severity with increasing dose. These findings are consistent with monoamine depletion a known pharmacological action of valbenazine acting as a VMAT2 inhibitor.

Tremors were noted at the 10 and 15 mg/kg/day dose levels and increased in incidence and severity with increasing dose. To rule out a link between tremors and seizure or pre-seizure patterns EEGs were collected on days 246/247 and 254/255 prior to valbenazine administration, approximately 2 hours postdose, and at approximately 4 to 5 hours postdose. Although tremors were observed during collection of EEGs no abnormal EEG patterns were observed. EMGs were collected on days 254/255 in conjunction with EEG. Several dogs in each treated group demonstrated clear patterns of high-frequency, high-intensity motor unit action potentials in proximal muscles (e.g. head, neck, shoulders) manifesting as the observed tremors.

Reviewer Comment: Although the toxicological significance of the muscle tremor in dogs is unclear at present, because the current indication is an involuntary movement disorder affecting the tongue, lips, face, trunk, and extremities, they may be clinically meaningful.

No valbenazine treatment-related clinical signs were noted during the recovery phase.

Cage side observations were performed once daily (days 1 to 301) between 1 and 4 hours following dosing (postdose observations) on dosing days and during the recovery period. Detailed clinical examinations were performed weekly starting the last week of the predosing phase through the dosing and recovery phase.

Body Weights

No adverse valbenazine treatment-related effects were noted on body weight.

A slight decrease in body weight gain in female dogs was noted during the first two weeks of the dosing phase. Throughout the remainder of the dosing phase body weight gains were sporadically lower in female dogs at the 10 and 15 mg/kg/day dose level. This effect correlated with decreased food consumption during the early dosing phase as food was only available during the 2 to 4 hour postdose period of hypoactivity. As a result food was made available prior to dosing resulting in a more normalized body weight gain. The decrease in body weight gain was not considered adverse. No effect on body weight was noted in male dogs at any dose level.

Each animal was weighed on the day of randomization and on days -1, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168, 175, 182, 189, 196, 203, 210, 217, 224, 231, 238, 245, 252, 259, 266, 272, 279, 286, 293, and 300. A final fasted body weight was recorded for each animal on the day of scheduled euthanasia for calculation of organ to body weight ratios (day 274/275 or 302).

Food Consumption

Food consumption was reduced in valbenazine treated dogs during the first week of dosing when food was available only during the postdose period of hypoactivity. Once food was made available for 3 hours prior to dosing food consumption normalized.

Food consumption was quantitatively measured for each animal twice weekly throughout the dosing and recovery phases. On Days 1 through 3, food was offered up to 2 hours after dosing and was left in the dog's cage for a period of 2 to 4 hours and then removed. From day 4 throughout the remainder of the study, food was provided to the animals approximately 2 to 3 hours prior to dose administration and remained in the animal's individual cage throughout the day. In general, the dogs received a minimum of 6 hours of access to their food. If necessary, the food ration was left in the dog's cage overnight and weighed the following morning.

Ophthalmoscopy

No valbenazine treatment-related ophthalmic findings were observed during the dosing phase. As a result no ophthalmic assessment was performed during the recovery phase.

Ophthalmological examinations were performed prior to the dosing phase (day -6 males) during week 19 (day 130) and during the last week of the dosing phase (day 273). The ocular examinations were conducted using a hand-held slit lamp and indirect ophthalmoscope. A short-acting mydriatic solution was used to dilate the eyes.

ECG

A statistically significant prolongation of QTc in males at the 15 mg/kg/day dose level (20 msec, 9%) was observed on day 137 of the dosing phase. No effect was noted in females on day 137 or in either sex on day 270 of the dosing phase. No other valbenazine treatment-related effects were observed.

Reviewer Comment: A similar degree of QTc prolongation was observed in female but not male dogs during the 91-day general toxicology study (No. 20008482). Because valbenazine has been shown to significantly increase QTc (15 to 20 msec) across multiple studies and also inhibits hERG tail currents at relevant concentrations (IC₅₀ 2 µM) this effect may be treatment related. However, because the effect is not observed consistently the toxicological significance is unclear.

Electrocardiogram (ECG) measurements were obtained from all animals using leads I, II, III, aVR, aVL, and aVF and a chart speed of 50 mm/second. The ECG measurements were obtained once during the predose phase (day -4 and -3), during week 19 (day 137) during the last week of the dosing phase (day 270) at ~2hrs postdose, and during the last week of the recovery period (day 298). Recordings were timed to coincide with C_{max}. Only lead II was evaluated by a board-certified veterinary cardiologist.

Hematology

No valbenazine treatment-related effects were noted on any hematology or coagulation parameters. All differences noted between control and valbenazine dose groups were small in magnitude (3.8 to 9.9%) and statistically significant values were within the Testing Facility's historical control ranges.

An adequate battery of hematology and coagulation parameters was analyzed. Blood was collected by venipuncture of the jugular vein during the predose phase (day -6),

day 127 and 274 of the dosing phase, and day 302 of the recovery period. The animals were fasted overnight but had access to water ad libitum.

Clinical Chemistry

No valbenazine treatment-related effects were noted on any clinical chemistry parameters. All differences noted between control and valbenazine dose groups were small in magnitude (9.9 to 35.4%) and statistically significant values were within the Testing Facility's historical control ranges.

An adequate battery of clinical chemistry parameters was analyzed. Blood was collected by venipuncture of the jugular vein during the predose phase (day -6), day 127 and 274 of the dosing phase, and day 302 of the recovery period. The animals were fasted overnight but had access to water ad libitum.

Urinalysis

No valbenazine treatment-related effects were noted on any urinalysis parameters.

Urine was collected overnight by cage pan drainage or via cystocentesis at gross necropsy if an adequate sample was not obtained. The animals were fasted overnight but had access to water ad libitum.

Gross Pathology

No valbenazine treatment-related effects were noted.

Non-valbenazine related changes occurred bilaterally in the kidneys of one female at the 15 mg/kg/day dose level at terminal necropsy (irregular surface coincident with pale areas) and unilaterally in the kidney of one male at the 10 mg/kg/day dose level at the recovery necropsy (irregular surface of the renal capsule).

Reviewer Comment: These findings correlated microscopically with multifocal loss of cortical medullary tubules, interstitial fibrosis, and occasional foci of mononuclear cell infiltrates. Based on the small incidence (although above historical control) and lack of dose response in males these findings are considered idiosyncratic non-treatment related changes.

Dogs were euthanized by sodium pentobarbital injection, followed by exsanguination. When possible, the animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied at similar times throughout the day. Animals were fasted (overnight) before their scheduled necropsy. Main study and recovery animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Organ Weights

Valbenazine treatment resulted in a decrease in prostate weights (absolute, 30% and relative, 7%) at the 15 mg/kg/day dose levels. This finding correlated with minimal to moderate dilatation of acini and minimal mononuclear cell infiltrates.

Organs were weighed at necropsy for all scheduled euthanasia animals. Paired organs were weighed together. Organ to body weight ratio (using the terminal body weight) and organ to brain weight ratios were calculated. The following organs were weighed; brain, epididymis, adrenal gland, pituitary gland, prostate gland, thyroid gland, heart, kidney, liver, lung, ovary, spleen, testis, thymus, and uterus.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Bilateral degenerative/inflammatory changes were noted in the kidney of one female dog at the 15 mg/kg/day dose level at terminal necropsy.

Unilateral degenerative/inflammatory changes were noted in one male dog at the 10 mg/kg/day dose level at recovery necropsy. In both instances these changes consisted of multiple infarcts and interpreted as possibly idiosyncratic by the study pathologist.

Reviewer Comment: Although a direct effect of valbenazine treatment cannot be ruled out, given the limited incidence (though above historical control) and lack of dose-response in males they are unlikely to be related to valbenazine treatment. Moreover, in the female with bilateral renal findings, blood urea nitrogen (BUN) and creatinine levels were double concurrent control values and at the upper limits of the historical control data at baseline suggesting this female may have had marginally compromised renal function prior to valbenazine exposure. Importantly, these values did not increase with repeated valbenazine administration indicating renal function was not further compromised over the course of the study.

Special Evaluation

The brain of all main study dogs was subject to expanded histopathology (at least 15 total sections) performed by a neuropathologist at (b) (4) to allow an extensive examination of dopamine-rich areas (substantia nigra, ventral tegmental area, and striatum). Sections were stained with standard H&E staining. No valbenazine treatment-related gross or microscopic lesions were noted in the brain.

Toxicokinetics

No quantifiable concentrations of valbenazine or related metabolites were observed in the control group.

Valbenazine exposure increased with increasing dose in a dose-proportional manner on day 1 and a greater than dose-proportional manner on day 273. No consistent sex-related exposure difference was noted. Valbenazine exposure increased 1.8- to 2.6 times over the course of the dosing phase.

Table 41 Mean Valbenazine TK Parameters in the 9-Month Dog General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 273	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
3	Male	1280	4280	1780	10200
	Female	1340	4160	1670	7450
10	Male	4310	14600	6620	36700
	Female	4110	15000	6360	28700
15	Male	8120	30900	10900	73000
	Female	6510	25900	9730	52200

NBI-98782 (pharmacologically active metabolite) C_{max} and AUC increased in an approximately dose-proportional manner across groups on day 1 and day 273. No consistent sex-related exposure difference was noted. NBI-98782 exposure increased 1.1- to 2 times over the course of the dosing phase. The molar ratio of NBI-98782 to valbenazine ranged from 0.08 to 0.1 on day 1 and from 0.06 to 0.07 on day 273.

Table 42 Mean NBI-98782 TK Parameters in the 9-Month Dog General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 273	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
3	Male	41.3	336	42.9	445
	Female	45.4	329	39.4	369
10	Male	124	1130	175	2100
	Female	98.4	994	128	1350
15	Male	176	2000	290	3890
	Female	167	1850	238	2880

NBI-136110 (pharmacologically active metabolite) C_{max} and AUC increased in an approximately dose-proportional manner across groups on day 1 and day 273. No consistent sex-related exposure difference was noted. NBI-136110 exposure increased 1.4- to 2.2 times over the course of the dosing phase. The molar ratio of NBI-136110 to the valbenazine ranged from 0.16 to 0.24 on day 1 and from 0.14 to 0.19 on day 273.

Table 43 Mean NBI-136110 TK Parameters in the 9-Month Dog General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 273	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
3	Male	75.6	866	135	1890
	Female	126	1040	136	1450
10	Male	339	3460	423	6260
	Female	238	3170	433	5200
15	Male	482	5140	677	10800
	Female	390	5190	539	8350

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations were within ±15% of the target concentration. All formulations met analytical criteria and were thus suitable for use.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay with a Confirmatory Assay for NBI-98854

Study no.:	6944-354
Study report location:	SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6/5/2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Valbenazine, 08KL014D, 98.7%

Key Study Findings

Valbenazine, at concentrations up to 5000 µg, was judged to be negative for mutagenicity under the conditions of this study.

Methods

- Strains: TA98, TA100, TA1535, TA1537 and WP2uvrA
- Concentrations in definitive study: 10.0, 33.3, 100, 393, 1160, 2000, and 5000 µg/plate
- Basis of concentration selection: Ten doses of test article, from 6.67 to 5000 µg/plate, were evaluated with and without S9. Indications of cytotoxicity (reduced bacterial background lawns and/or decreases in revertant frequency) were observed at ≥ 3330 µg/plate with and without S9. The test article was observed to be freely soluble at all doses evaluated with and without S9.
- Negative control: Vehicle (DMSO)
- Positive control: Benzo[a]pyrene (2.5 µg/plate), 2 aminoanthracene (2.5 µg/plate and (2.5.0µg/plate for WP2uvrA), 2-nitrofluorene (1.0 µg/plate), Sodium Azide (2.0 µg/plate), ICR-191 (2.0 µg/plate), 4-nitroquinolone-N-oxide (1.0 µg/plate).
- Formulation/Vehicle: Dimethylsulfoxide (DMSO)
- Incubation & sampling time: 100 µL tester strain and 50 µL of test or control article were added to 2.5 mL of molten selective top agar ($45 \pm 2^\circ\text{C}$). The mixture vortexed and overlaid onto the surface of a 15 x 100 mm petri dish. After the overlay solidified, the plates were inverted and incubated for 52 ± 4 hours at $37 \pm 2^\circ\text{C}$. Cultures were treated in the presence of S9 in an identical manner, except using 2.0 mL undiluted molten selective top agar and adding 500 µL S9 mix. Plates which were not evaluated immediately following the incubation period were held at 0 to 10°C until counted.

Study Validity

All positive and vehicle control values were within acceptable ranges and all criteria for a valid study were met. A positive response was defined as one that resulted in a dose dependent increase in revertant frequency ≥ 2.0 times vehicle control values for tester strains TA98, TA100, and WP2uvrA, or ≥ 3.0 times vehicle control values for tester strains TA1535 and TA1537.

Results

No concentration of valbenazine (up to 5000 µg/plate) produced positive increases in the mean number of revertants per plate in any of the tester strains in the presence or absence of metabolic activation. Therefore valbenazine was judged to negative for mutagenicity under the conditions of this study.

7.2 *In Vitro* Assays in Mammalian Cells**Study title: Chromosomal Aberrations Assay in Cultured Human Peripheral Blood Lymphocytes for NBI-98854**

Study no.: 6944-355
 Study report location: SDN 1 (eCTD 0000), 4/29/2016
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 6/23/2008
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Valbenazine, 08KL014D, 98.7%

Key Study Findings

Valbenazine, at concentrations resulting in a >50% reduction in mitotic index, was judged to be negative for clastogenicity under the conditions of this study.

Methods

Cell line: Human peripheral blood lymphocytes
 Concentrations in definitive study: -S9: 13.0, 24.2, 46.8, 59.8, 75.0, 134, 150, 200, 300, and 400 µg/mL
 +S9: 75.0, 150, 200, 250, 300, 350, 400, 550, and 650 µg/mL
 Basis of concentration selection: Concentrations in the definitive study were based on findings from an initial assay where mitotic index was reduced 52% at concentrations of 154 µg/mL in the absence of metabolic activation or 402 µg/mL in the presence of metabolic activation.
 Negative control: Vehicle (DMSO)
 Positive control: Mitomycin C (0.75, 1.0, 1.5, 0.2, 0.3, and 0.4 µg/mL) was used as a positive control in the absence of metabolic activation. Cyclophosphamide (20, 25, and 40 µg/mL) was used as a positive control in the presence of metabolic activation.
 Formulation/Vehicle: Highest concentration of DMSO used was 10.0 µL/mL
 Incubation & sampling time: The cells were incubated with or without metabolic activation in a cell culture incubator at 37°C, 5% CO₂.
 For the assays without metabolic activation

cells were incubated with the test article at predetermined concentrations, vehicle control, or positive controls for either 3 hours, and then the cultures were washed with phosphate-buffered saline and harvested ~22 hrs. after initiation, or for 22 hours and the cultures were then harvested.

For the assay with metabolic activation cells were incubated with the test article at predetermined concentrations, vehicle control, positive controls, and S9 for 3 hours. The cultures were then washed with phosphate-buffered saline and the cultures were harvested ~22 hrs. after initiation of treatment.

Study Validity

All positive and vehicle control values were within acceptable ranges and all criteria for a valid study were met. A positive response was defined as one that resulted in a significant ($p \leq 0.01$) increase in the number of cells with chromosomal aberrations.

Results

In the assay without metabolic activation the high dose selected for analysis was 134 $\mu\text{g}/\text{mL}$ based on decreased mitotic index of 51%. No significant increase in cells with chromosomal aberrations, polyploidy, or endoreduplications was observed.

In the assay with metabolic activation the high dose selected for analysis was 650 $\mu\text{g}/\text{mL}$ based on decreased mitotic index of 51%. No significant increase in cells with chromosomal aberrations, polyploidy, or endoreduplications was observed.

Valbenazine was judged to be negative for induction of chromosome aberrations, polyploidy, or endoreduplication under the conditions of this study.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Rat Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of NBI-98854

Study no:	AD20XW.125 (b) (4)
Study report location:	Sponsor Reference no. 2011-TX-003 SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8/8/2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Valbenazine, 04-110323-03B/03-54-01,

100%

Key Study Findings

Valbenazine was judged to be negative in the rat micronucleus assay following a single oral dose up to 60 mg/kg.

Methods

Doses in definitive study: 0, 15, 30, and 60 mg/kg
Frequency of dosing: Single dose
Route of administration: Oral gavage
Dose volume: 10 mL/kg
Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain: Rat/Sprague Dawley, (b) (4)
Number/Sex/Group: 5 male rats/dose group
Satellite groups: None
Basis of dose selection: Based on prior nonclinical toxicity studies valbenazine at doses > 60 mg/kg/day resulted in excess morbidity and mortality. Therefore, 60 mg/kg was used as the top dose.
Negative control: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Positive control: Cyclophosphamide, 40 mg/kg

Study Validity

The incidence of micronucleated polychromatic erythrocytes (PCE) per 2000 PCEs for each animal and per 10,000 PCEs for each treatment group was determined.

The test article would have been considered to induce a positive response if the incidence of micronucleated polychromatic erythrocytes at one or more doses was statistically elevated relative to the concurrent negative (vehicle) control.

The incidence of micronucleated polychromatic erythrocytes in the vehicle control groups did not exceed the historical vehicle control range.

The incidence of micronucleated polychromatic erythrocytes in the positive control groups was significantly increased relative to the respective vehicle control groups.

The top dose of 60 mg/kg is an acceptable top dose as it resulted in adverse clinical signs indicative of toxicity.

Results

Bone marrow cells collected 24 and 48 hours postdose were examined microscopically for the presence of micronuclei. Valbenazine did not significantly increase the incidence of micronucleated polychromatic erythrocytes relative to the vehicle control following a single oral dose up to 60 mg/kg.

8 Carcinogenicity

Mouse Dose-Range Finding Study

Study title: 28-Day Repeated Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Mice with a Preliminary 5 Day Range-finding Toxicity Study

Study no.: AD20XW.2G3R. (b) (4)
Sponsor Reference No. 2012-TX-082
Study report location: SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location: (b) (4)
Date of study initiation: 09/05/2012
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Valbenazine, 04-110323-03B/03-54-01, 100%

Key Study Findings

Valbenazine treatment resulted in mortality/morbidity at 200 mg/kg/day.

Clinically relevant valbenazine treatment-related toxicities included the following:

- Mortality at 200 mg/kg/day generally occurring from day 3 to 5 of the dosing phase.
- Clinical signs – 200 mg/kg/day; decreased activity, ataxia, seizures/tremors, and labored breathing indicative of significant CNS affects.
- Mice at the 200 mg/kg/day dose level tended to tolerate valbenazine better following 5 days of dosing. This may be due to tolerance and/or increased clearance/metabolism as indicated by decreased valbenazine exposure at the end of the dosing phase relative to day one exposures.
- The NOAEL was judged to be 100 mg/kg/day based on mortality and adverse clinical signs observed at 200 mg/kg/day.
- Based on mortality and adverse clinical signs observed at the 200 mg/kg/day dose level, doses of 0, 10, 30, and 75 mg/kg/day were chosen for the 26-week Tg.rash2 mouse carcinogenicity study.

Exposures at the NOAEL of 100 mg/kg/day are: C_{max} of 3340 and 2990 ng/mL and an AUC_{0-24} of 29100 and 28600 ng·hr/mL in males and females, respectively for valbenazine, which are ~3.5 times and 4.5 times the human C_{max} and $AUC_{(0-24hr)}$ expected at the MRHD of 80 mg/day (916 ng/mL and 6150 ng·hr/mL, respectively).

At the NOAEL, the combined $AUC_{(0-24hr)}$ values for valbenazine, and the 2 major metabolites, NBI-98782 and NBI-113610, are 53510 and 46720 ng·hr/mL in male and

female mice, respectively, which are ~6 times the combined human $AUC_{(0-24hr)}$ value for these moieties, expected at the MRHD of 80 mg/day (8755 ng·hr/mL).

Methods

Doses: 0, 50, 100, or 200 mg/kg
Frequency of dosing: Daily
Route of administration: Oral
Dose volume: 10 mL/kg
Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain: Mouse/CByB6F1, (b) (4)
Number/Sex/Group: 10/sex/group
Age: 7 weeks of age at initiation of dosing
Weight: 20.1 to 26.5 g for males and 15.3 to 21.5 g for females
Satellite groups: TK, 35/sex/ treatment group, 8 TK mice included for control group.
Unique study design: None
Deviation from study protocol: None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Mortality

Valbenazine treatment-related mortalities occurred at 200 mg/kg/day. In the main study group 2/10 male mice and 4/10 female mice were found dead during the study. In the TK satellite group 3/36 male mice and 5/36 female mice were found dead during the study while an additional female was sacrificed in moribund condition. All but one male and one female were found dead on dosing days 3 to 5. The exceptions were one male found dead on dosing day 28 and one female sacrificed in moribund condition on dosing day 10.

No mortality or excessive morbidity was noted at the 50 or 100 mg/kg/day dose levels.

Mice were observed for general health/mortality and morbidity twice daily, once in the morning and afternoon, throughout the study.

Clinical Signs

Valbenazine treatment-related clinical signs were observed in the majority of male and female mice in the 200 mg/kg/day dose group and consisted of decreased activity, ataxia, seizures/tremors, and labored breathing. These clinical signs were observed primarily in association with C_{max} throughout the first 5 days of the dosing phase. No clinical signs were noted at the 50 or 100 mg/kg/day dose levels. **Reviewer Comment:** These clinical signs are similar to those observed in CB-1 mice following oral administration of 300 mg/kg/day (Study No. 20021098).

Cageside observations were conducted approximately 1 hr. postdose. Detailed observations were conducted for each animal once during the predose phase and weekly throughout the dosing phase.

Body Weights

Valbenazine treatment had no significant effect on body weight at any dose.

Each animal was weighed and food consumption was recorded on the day of randomization and on days 1, 8, 15, 22, and 29. A final fasted body weight was recorded for each animal on the day of scheduled euthanasia for calculation of organ to body weight ratios.

Hematology

No significant valbenazine treatment-related effects were noted on hematology parameters were noted.

An adequate battery of hematology and coagulation parameters was assessed. Blood samples were collected from fasted mice from the retro-orbital sinus.

Clinical Chemistry

No significant valbenazine treatment-related effects were noted on clinical chemistry parameters.

An adequate battery of clinical chemistry parameters was assessed. Blood samples were collected from fasted mice from the retro-orbital sinus.

Gross Pathology

No gross pathology findings related to valbenazine treatment were observed.

Mice were fasted overnight, sacrificed with CO₂ inhalation, and necropsied. Terminal body weights were recorded for all sacrificed toxicity animals and an examination of the external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues was performed.

Organ Weights

No organ weight changes related to valbenazine treatment were observed.

Organ weights were recorded at each scheduled sacrifice and paired organs were weighed together. Weight were determined for the following organs; adrenal gland, brain, epididymis, heart, kidney, liver, ovary, spleen, testis, thymus, uterus.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Valbenazine treatment resulted in exudative inflammation of the nasal cavity in male and female mice at the 200 mg/kg/day dose level. In addition 2 female mice presented with this finding at the 50 mg/kg/day dose level. The Sponsor attributed this finding to the acidic pH of the dose formulations combined with reflux during oral gavage. **Reviewer Comment:** A similar finding was observed during the 26-week carcinogenicity study but not the studies utilizing CB-1 mice. The reason for this discrepancy is unclear and cannot be attributed to a change in test article formulation. However, this finding is likely to be of relatively little clinical relevance.

Centrilobular hypertrophy was not in the livers of male and female mice at the 200 mg/kg/day dose level. **Reviewer Comment:** This effect is likely an adaptive change due to enzyme induction and not toxicologically meaningful.

Toxicokinetics

No quantifiable concentrations of valbenazine or related metabolites were observed in the control group.

Valbenazine exposure increased with increasing dose on day 1 and 91. C_{max} and AUC increased in an ~ dose proportional manner on day 1. On day 28 exposure increased in an ~ dose proportional manner from 100 to 200 mg/kg/day and less than dose proportional from 50 to 100 mg/kg/day. No consistent different in exposure was noted between male and female mice on day 1. A moderate decrease in valbenazine exposure was noted over the course of the dosing phase. This reduction in exposure was greater at the higher doses and most significant in females at the 200 mg/kg/day dose level.

Table 44 Mean Valbenazine TK Parameters in the 28-Day Mouse General Toxicology Study

Dose Group (mg/kg/day)	Sex	Day 1		Day 28	
		C_{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C_{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
50	Male	4530	28900	3150	24600
	Female	3550	28600	3960	22100
100	Male	6740	60700	3340	29100
	Female	6440	62200	2990	28600
200	Male	11300	208000	8930	57700
	Female	14200	208000	6110	29900

NBI-98782 (pharmacologically active metabolite) C_{max} and AUC increased in a < dose proportional manner across groups on day 1 and day 28. Exposures were generally similar in male and female mice. Exposures tended to decrease following repeated exposure with the most significant decrease occurring in female mice at the 100 and

200 mg/kg/day dose levels. The molar ratio of NBI-98782 to valbenazine ranged from 0.0256 to 0.777 on dosing days 1 and 28.

Table 45 Mean NBI-98782 TK Parameters in the 28-Day Mouse General Toxicology Study

Valbenazine Dose Group (mg/kg/day)	Sex	Day 1		Day 28	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
50	Male	180	2020	142	1830
	Female	205	1940	175	1540
100	Male	241	4020	174	2310
	Female	255	3420	150	1920
200	Male	225	3600	306	3770
	Female	346	4950	226	2230

NBI-136110 (pharmacologically active metabolite) exposure increased in < dose proportional manner across dose groups on day 1 and day 28. Exposures were generally similar in male and female mice. Exposures tended to decrease following repeated exposure with the most significant decrease occurring in female mice at the 100 and 200 mg/kg/day dose levels. The molar ratio of NBI-136110 to valbenazine ranged from 0.149 to 0.750 on dosing days 1 and 28.

Table 46 Mean NBI-136110 TK Parameters in the 28-Day Mouse General Toxicology Study

Valbenazine Dose Group (mg/kg/day)	Sex	Day 1		Day 28	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
50	Male	808	10800	1110	13600
	Female	753	11400	862	10300
100	Male	1350	21800	1610	22100
	Female	1170	18900	1180	16200
200	Male	1290	20900	3120	37600
	Female	1730	32800	1780	22500

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations were within ±15% of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Pivotal Carcinogenicity Studies**Study title: NBI-98854 di-tosylate: 26-Week Repeated Dose Oral Carcinogenicity Study in Tg.rasH2 Mice**

Study no.: AD20XW.7G8R. (b) (4)
Sponsor Reference no. 2014-TX-083
SDN 1 (eCTD 0000), 4/29/2016
Study report location: (b) (4)
Conducting laboratory and location: (b) (4)
Date of study initiation: 9/30/2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Valbenazine, Z534FP-12-002, 99.8%

CAC concurrence

The Exec CAC reviewed the protocol on April 1, 2014. The Exec CAC recommended doses of 0, 10, 30, and 75 mg/kg/day for both male and female mice based on MTD (deaths at 200 mg/kg/day in a 28-day DRF study in CByB6F1 mice). No changes were made during the course of the study and there were no deviations that impacted the validity of the study.

Key Study Findings

- No valbenazine treatment-related increase in neoplastic lesions.
- Non-adverse valbenazine treatment-related clinical signs noted at the 75 mg/kg/day dose level in female mice consisting of thin appearance (6/25) and hunched posture (6/25)
- Increase in the incidence of nasal cavity lesions. Of limited clinical significance and likely caused by back-flow of test formulation into the nasal cavity during dosing.

The high doses of 75 mg/kg/day in male and female mice is ~4.6 times the maximum recommended human dose (MRHD) of 80 mg/day based on mg/m² body surface area.

The NOAEL for neoplastic and non-neoplastic lesions in male and female mice is 75 mg/kg/day. The AUC_(0-24hr) values for valbenazine at 75 mg/kg/day during week 26 were 19100 and 24900 ng·hr/mL in male and female mice, respectively, which are ~3- and 4 times the AUC_(0-24hr) values expected in humans at the MRHD of 80 mg/day (6150 ng·hr/mL). The AUC_(0-24hr) values for NBI-98782 were 1580 and 1460 ng·hr/mL in male and female mice, respectively, which are ~2 times the human AUC_(0-24hr) value for this moiety, expected at the MRHD of valbenazine of 80 mg/day (695 ng·hr/mL). The AUC_(0-24hr) values for NBI-136110 were 14100 and 11300 ng·hr/mL in male and female mice, respectively, which are ~6.5 times the human AUC_(0-24hr) value for this moiety, expected at the MRHD of valbenazine of 80 mg/day (1910 ng·hr/mL).

Adequacy of Carcinogenicity Study

This 26-Week Tg.rasH2 mouse carcinogenicity study is considered adequate. The route of administration, dose selection, number of animals/sex/group, and overall study

conduct were appropriate. A positive control group (urethane, 1000 mg/kg/day) demonstrated sensitivity of the test system.

Appropriateness of Test Model

The Tg.rasH2 mouse is an acceptable model. Two major human metabolites, NBI-98782 and NBI-136110, are present at sufficient levels in the mouse to evaluate their carcinogenic potential.

Evaluation of Tumor Findings

There was no statistically significant increase in tumor incidence in Tg.rasH2 mice treated with valbenazine for 28 weeks when compared to the vehicle control group. According to the FDA biostatistics Reviewer (Hepei Chen) the only statistically significant results were for comparisons between the positive control (urethane) and vehicle control groups for alveolar-bronchiolar adenoma in lungs with bronchi and hemangiosarcoma in spleen for both male and female mice (all p-values < 0.0001).

Methods

Doses:	0, 10, 30, 75 mg/kg/day (Consistent with Exec CAC recommendations)
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.25% (w/v) methylcellulose in reverse osmosis deionized water
Basis of dose selection:	Based on deaths at a dose of 200 mg/kg/day in a 28-day dose range findings study.
Species/Strain:	Mouse/CByB6F1-Tg(HRAS)2Jic (+/- hemizygous c-Ha-ras)
Number/Sex/Group:	25/sex/dose level
Age:	8 weeks at initiation of dosing
Animal housing:	Individually housed
Dual control utilized:	Positive control, urethane (1000 mg/kg/day) in 0.9% NaCl (saline)
Satellite groups:	TK cohort (CByB6F1 mice), 32/sex/dose level.
Deviation from study protocol:	There were no deviations reported by the Sponsor that impacted the validity of this study.

Observations and Results

Mortality

No valbenazine treatment-related mortalities were reported.

In total 3 male and 2 female mice from the main study cohort died during the course of the study. The cause of these deaths were undetermined or due to spontaneous tumors. **Reviewer Comment:** These mortalities are not considered treatment-related. The incidence of mortality is within the historical control range for a 26-week mouse study conducted at this test facility and not associated with test article-related toxicities.

There are a sufficient number of animals remaining for statistical evaluation.

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Table 1 Causes of Death from the 26-Week Tg.rasH2 Mouse Carcinogenicity Study

Sex	Dose Group (mg/kg/day)	Mode of Death	Animal Number	Day of Death	Cause of Death
Male	30	Moribund Sacrifice	6251	94	Undetermined
		Moribund Sacrifice	6267	137	Skin, Squamous Cell Carcinoma
	75	Found Dead	6286	151	Undetermined
Female	75	Found Dead	6349	112	Undetermined
		Found Dead	6403	165	Mesothelioma

There are a sufficient number of animals remaining for statistical evaluation.

Clinical Signs

Non-adverse valbenazine treatment-related clinical signs were primarily noted at the 75 mg/kg/day dose level in female mice and generally consistent with those observed at similar doses in the previous 28-day and 91-day toxicology studies conducted in mice. These signs consisted of thin appearance (6/25) and hunched posture (6/25) noted during the weekly detailed examinations. **Reviewer Comment:** Decreased postdose activity was not observed during the current study unlike the previous studies in mice. This may be due to the fact that detailed clinical examinations were only performed weekly during the dosing phase and the time of the examination is not provided. In addition there is no indication if the daily morbidity/mortality checks coincided with C_{max} . Therefore, it is likely that hypoactivity may have been missed if it was present.

Body Weights

No significant valbenazine treatment-related changes in body weight that would be likely to affect tumor incidence were reported. Body weight was slightly increased in female mice at the 75 mg/kg/day dose level relative to vehicle control.

Table 2 Percent Mean Body weight from the 26-Week Tg.rasH2 Mouse Carcinogenicity Study

Sex	Male		Female	
	% Control Body weight at Day 86	% Control Body weight at Day 183	% Control Body weight at Day 86	% Control Body weight at Day 183
0	100	100	100	100
10	98	101	99	100
30	99	100	101	100
75	100	102	104	105

Food Consumption

No significant valbenazine treatment-related changes in food consumption were reported.

Gross Pathology

No significant valbenazine treatment-related effects were reported.

Macroscopic lesions in the urethane positive control group were noted in the lungs (dark or pale nodules) and spleen (nodules) of both male and female mice. These findings are expected and associated with neoplasms in these organs.

Histopathology

Peer Review: Peer review was conducted and differences in opinion between the study and reviewing pathologists were resolved. The final study report reflects the mutually agreed-on diagnoses.

Neoplastic: There was no statistically significant increase in tumor incidence in Tg.rasH2 mice treated with valbenazine for 28 weeks when compared to the vehicle control group. According to the FDA biostatistics Reviewer (Hepei Chen) the only statistically significant results were for comparisons between the positive control (urethane) and vehicle control groups for alveolar-bronchiolar adenoma in lungs with bronchi and hemangiosarcoma in spleen for both male and female mice (all p-values < 0.0001). The positive control article produced the expected increases in pulmonary and splenic tumors confirming the sensitivity of the assay under these conditions.

Non Neoplastic: A valbenazine treatment-related increase in the incidence of nasal cavity lesions was noted. The Sponsor concluded these findings were likely caused by back-flow of test formulation into the nasal cavity during dosing. **Reviewer Comment:** This would not explain the dose-related increase in incidence and severity. These findings are similar to those noted in the 28-day dose range finding study (No. AD20XW.2G3R. (b) (4)) although no similar finding was noted in a longer 91-day toxicology study. However, this reviewer anticipates this finding to be of relatively little clinical relevance. In a 91-day general toxicology study in mice (No. 20021098) doses \geq 10 mg/kg/day resulted in lobuloalveolar hyperplasia of the mammary gland in female mice. It is unclear why a similar pharmacologically relevant effect was not noted in the current 6-month study.

Toxicokinetics

Concentrations of valbenazine and the metabolites NBI-98782 and NBI-136110 were below the limit of quantification in samples taken from the vehicle control groups.

Valbenazine exposure, both C_{max} and AUC, increased with increasing dose. C_{max} increased in a dose proportional manner across groups on day 1 and a less than dose proportional manner during week 26, while AUC_{0-24} increased in a greater than dose proportional manner across groups on day 1 and a dose proportional manner during

week 26. Exposures were ~ one half (1/2) their day one values during week 26 indicating a decrease in exposure with time. No consistent sex difference in exposure was observed.

Table 3 Mean Valbenazine TK Parameters on Day 1 and Week-26 in the 26-Week Tg.rasH2 Mouse Carcinogenicity Study

Dose Group (mg/kg/day)	Sex	Day 1		Week 26	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
10	Male	1030	3550	699	3090
	Female	848	2890	660	2300
30	Male	4770	21800	2230	11300
	Female	4110	15100	1490	8150
75	Male	6350	52900	2350	19100
	Female	5860	45600	2760	24900

NBI-98782 (pharmacologically active metabolite) exposure, both C_{max} and AUC, increased with increasing dose in a less than dose proportional manner across groups on day 1 and during week 26. Exposures were generally similar in male and female mice. No accumulation of NBI-98782 was observed following 26 weeks of valbenazine administration. The molar ratio of NBI-98782 to valbenazine ranged from 0.0428 to 0.076 on day 1 and from 0.0691 to 0.187 during week 26.

Table 4 Mean NBI-98782 TK Parameters on Day 1 and Week-26 in the 26-Week Tg.rasH2 Mouse Carcinogenicity Study

Valbenazine Dose Group (mg/kg/day)	Sex	Day 1		Week 26	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
10	Male	44.6	319	47.6	407
	Female	51.1	307	47.8	305
30	Male	116	1020	105	1000
	Female	151	1100	88.2	761
75	Male	184	1800	130	1580
	Female	207	2100	130	1460

NBI-136110 (pharmacologically active metabolite) exposure, both C_{max} and AUC, increased with increasing dose. C_{max} increased in a dose proportional manner from 10 to 30 mg/kg/day and in a less than dose proportional manner from 30 to 75 mg/kg/day

on day 1 and during week 26. $AUC_{(0-24)}$ increased in a greater than dose proportional manner from 10 to 30 mg/kg/day and in a dose proportional manner from 30 to 75 mg/kg/day on day 1 and during week 26. Exposures were ~1/2 their day one values during week 26 indicating a decrease in exposure with time. No consistent sex difference in exposure was observed. NBI-136110 exposures were similar at 10 mg/kg/day and decreased by ~1/3 at 30 and 75 mg/kg/day following 26 weeks of valbenazine administration. The molar ratio of NBI-136110 to valbenazine ranged from 0.385 to 0.720 on day 1, and from 0.563 to 0.844 during week 26.

Table 5 Mean NBI-136110 TK Parameters on Day 1 and Week-26 in the 26-Week Tg.rasH2 Mouse Carcinogenicity Study

Valbenazine Dose Group (mg/kg/day)	Sex	Day 1		Week 26	
		C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·hr/mL)
10	Male	309	1880	263	1830
	Female	272	1650	214	1380
30	Male	1090	9330	645	6490
	Female	839	6890	498	4440
75	Male	1410	20100	1200	14100
	Female	1070	15100	833	11300

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations were within $\pm 15\%$ of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Study title: NBI-98854 di-tosylate: 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with NBI-98854 in Rats

Study no.: 8299648
 Sponsor Reference No. 2014-TX-010
 Study report location: SDN 1 (eCTD 0000), 4/29/2016
 Conducting laboratory and location: (b) (4)
 Date of study initiation: 5/12/2014
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Valbenazine, 13-1249, 99.8%

CAC concurrence

The Exec CAC reviewed the protocol on April 1, 2014. The Exec CAC recommended doses of 0, 0.5, 1, and 2 mg/kg/day for both male and female rats based on MTD

(deaths/adverse CNS effects at doses \geq at 10 mg/kg/day and decreased body weight at doses \geq 3 mg/kg/day in the 3- and 6-month studies in rats). During the conduct of this carcinogenicity study predetermined criteria for early termination were reached prior to week 102. All male dose groups were terminated during week 91 when only 20 male rats remained in the control group. Females at the 0.5 mg/kg/day dose level were terminated early during week 91 when only 15 rats remained. The remaining females were terminated later during week 91 when only 20 rats remained in the control group. The Exec CAC concurred with the early study termination, but requested the Sponsor address the apparent increase in survival at the high dose.

Key Study Findings

- Increased incidence of benign and malignant mammary gland neoplasms (fibroadenoma, adenoma, and carcinoma) at the 2 mg/kg/day dose level in female rats. Increase was significant only for adenoma at the 0.05 level. These types of tumors are common in female rats. Therefore, the increased incidence was judged to be nonsignificant.
- Increased incidence of benign and malignant neoplasms in the skin/subcutis in male rats. The incidence of malignant fibrosarcoma was significantly increased at the 0.5 mg/kg/day dose level and the incidence of benign trichoepithelioma was significantly increased at the 1 mg/kg/day dose level. Only the incidence of malignant fibrosarcoma was significantly increased according to the FDA biostatistics Reviewer (Hepei Chen). Although the incidence of fibrosarcoma was higher at the low dose (5/59, 8.5%) than what is reported for CrI:CD(SD) rats (1.74%; range 1.0% to 6.0%) it is not a rare tumor. This together with the lack of a dose response would suggest the finding is incidental and of no relevance to human risk.
- Enhanced survival at the 2mg/kg/day dose level for both male and female rats. Statistically significant for males only.
- Marked decrease in body weight and body weight gain in males at the 2 mg/kg/day dose level. Less profound but still significant decrease in body weight and body weight gain in females at the 2 mg/kg/day dose and males at the lower doses.
- Slight to moderate decreases in food consumption in males associated with decreased body weight. Decreased food consumption was more intermittent in females and did not correlate well with observed decrease in body weight.
- Decreased body weight and associated decrease in lethal pituitary tumors observed in males and females likely responsible for enhanced survival at the 2 mg/kg/day dose level.

The high dose of 2 mg/kg/day in male and female rats is \sim 0.24 times the maximum recommended human dose (MRHD) of 80 mg/day based on mg/m² body surface area.

The NOAEL for neoplastic and non-neoplastic lesions is 2 mg/kg/day. The AUC_(0-24hr) values for valbenazine at 2 mg/kg/day during week 26 were 369 and 825 ng·hr/mL in male and female rats, respectively, which are \sim 0.06 and 0.13 times the AUC_(0-24hr) values expected in humans at the MRHD of 80 mg/day (6150 ng·hr/mL). The combined

AUC_(0-24hr) values for valbenazine, NBI-98782, and NBI-113610 (the 2 major human and active metabolites), are 1354 and 2055 ng·hr/mL in male and female rats, respectively, which are ~0.15 and 0.23 times the combined human AUC_(0-24hr) value for these moieties, expected at the MRHD of 80 mg/day (8755 ng·hr/mL).

Adequacy of Carcinogenicity Study

This rat carcinogenicity study is considered adequate. The route of administration, dose selection, number of animals/sex/group, and overall study conduct were appropriate.

Appropriateness of Test Model

The CrI:CD(SD) Rat is an appropriate model. All major circulating human metabolites are present at sufficient levels in the rat to evaluate their carcinogenic potential.

Evaluation of Tumor Findings

For female rats the Sponsor reported an increase in the combined incidence of benign and malignant neoplastic lesions of the mammary gland (fibroadenoma, adenoma, and carcinoma) at the high-dose level. However, the increase was significant (Log-Rank $p = 0.0454$) only for adenoma at the 0.05 level. Since these tumors are considered common the increased incidence was interpreted as non-significant by the Sponsor.

For male rats the Sponsor reported statistically significant increases in the incidence of benign and malignant neoplastic lesions of the skin/subcutis. The incidence of malignant fibrosarcoma was significantly increased at the low-dose level ($p = 0.0143$ and $p = 0.0156$ for Log-rank test and Wilcoxon test, respectively) and the incidence of benign trichoepithelioma was significantly increased at the mid-dose level ($p = 0.0227$ and $p = 0.0265$ for Log-rank test and Wilcoxon test, respectively). **Reviewer**

Comments: Only the incidence of malignant fibrosarcoma was significantly increased ($p = 0.0406$) according to the FDA biostatistics Reviewer (Hepei Chen). Although the incidence of fibrosarcoma was higher at the low dose (5/59, 8.5%) than what is reported for CrI:CD(SD) rats (1.74%; range 1.0% to 6.0%) it is not a rare tumor. This together with the lack of a dose response would suggest the finding is incidental and of no relevance to human risk.

In addition when all benign and malignant tumors of the skin/subcutis were combined the Sponsor reported a significant increase at the 1 mg/kg/day dose level. **Reviewer Comments:** This finding was primarily driven by increases in benign trichoepithelioma, benign keratoacanthoma, and malignant sebaceous cell carcinoma, three tumor types that should not be combined as they arise from different cell types. Finally this increase was not judged as significant according to the FDA biostatistics Reviewer (Hepei Chen). Therefore this finding is considered incidental and of no relevance to human risk.

No other statistically significant or biologically meaningful increases in neoplastic lesions were observed.

Reviewer Comments: Survival was higher for both male and female rats at the high dose level as compared to all other dose groups and vehicle control beginning at ~

week 60 through study termination. Increased survival reached statistical significance in male rats at the end of the study. The increased survival is likely due to lower mean body weight (83% for male and 92 % for female relative to control at week 90) observed with no correlated evidence of adverse toxicity in combination with an associated decrease in fatal pituitary tumors in the high dose group relative to the other treatment groups.

Methods

Doses: 0, 0.5, 1, 2 mg/kg/day (Consistent with Exec CAC recommendations)

Frequency of dosing: Once daily

Dose volume: 10 mL/kg

Route of administration: Oral gavage

Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water

Basis of dose selection: Based on adverse effects and deaths at doses ≥ 10 mg/kg/day in a 6-month dose range finding study.

Species/Strain: Rat/Crl:CD(SD), (b) (4)

Number/Sex/Group: 60/sex/dose level

Age: 47 to 55 days old at initiation of dosing

Animal housing: Individually housed

Dual control utilized: No

Satellite groups: TK cohort, 6/sex/dose level, 3/sex for control.

Deviation from study protocol: The study achieved predetermined criteria for early termination prior to week 102. All male dose groups were terminated during week 91 when only 20 male rats remained in the control group. Females at the 0.5 mg/kg/day dose level were terminated early during week 91 when only 15 rats remained. The remaining females were terminated later during week 91 when only 20 rats remained in the control group. The Exec CAC concurred with the early study termination, but requested the Sponsor address the apparent increase in survival at the high dose. As the dosing period was longer than 90 weeks for all groups prior to early termination it was judged to have not impacted the validity of this study.

Observations and Results

Mortality

Administration of valbenazine was associated with enhanced survival at the 2 mg/kg/day dose level (highest dose tested) in both male and female rats.

However, a majority of the rats assigned to the control and valbenazine treatment groups were sacrificed at an unscheduled interval or died prior to study termination. All surviving male rats were terminated during week 91 when only 20 remained in the control group. Female rats at the 0.5 mg/kg/day dose level were terminated early during week 91 when only 15 remained. The remaining female rats were terminated later during week 91 when only 20 remained in the control group. The Sponsor received agreement from both the Division and the Exec CAC prior to early study termination.

Survival was $\geq 88\%$ for all dose groups through week 52. Survival was higher for both male and female rats in the 2 mg/kg/day dose group as compared to all other dose groups and vehicle control beginning at \sim week 60 through study termination. For male rats, at study termination, survival was 33%, 37%, 38%, and 55% at the 0, 0.5, 1, and 2 mg/kg/day dose levels, respectively. For female rats, at study termination, survival was 33%, 25%, 30%, and 45% at the 0, 0.5, 1, and 2 mg/kg/day dose levels, respectively. Increased survival reached statistical significance in male rats ($p = 0.0216$ and $p = 0.0395$ for the Log-Rank and Wilcoxon tests, respectively) and was attributed to lower body weight gain observed in these rats with no correlated evidence of toxicity. In addition both male and female rats in the 2 mg/kg/day dose group had significantly fewer fatal pituitary tumors relative to the other treatment groups.

Reviewer Comments: It is well established that decreased body weight due to dietary restriction enhances survival in rodents. In addition dietary restriction has been demonstrated to decrease pituitary neoplasm incidence in aged rats (Duffy et al, 2008). Therefore, the decreased food consumption that correlated with decrease in body weight at the high dose is likely the cause of the enhanced survival observed in this dose group.

Table 1 Causes of Death from the Rat 102-Week Carcinogenicity Study

Sex	Male				Female			
	0	0.5	1	2	0	0.5	1	2
Dose Level (mg/kg/day)								
Total pre-terminal deaths	40	38	37	27	40	45	42	33
Pituitary neoplasm	22	20	15	9	29	28	27	20
Mammary gland neoplasm	1	0	3	0	4	14	9	10
Skin/subcutis neoplasm	2	5	3	2	2	1	1	0
Undetermined	7	6	7	9	1	1	1	1

Sufficient number of animals remained for statistical evaluation.

Kaplan-Meier survival curves taken from Dr. Hepei Chen's statistical review are provided below.

Figure 1 Kaplan-Meier Survival Functions from the Rat 102-Week Carcinogenicity Study - Male

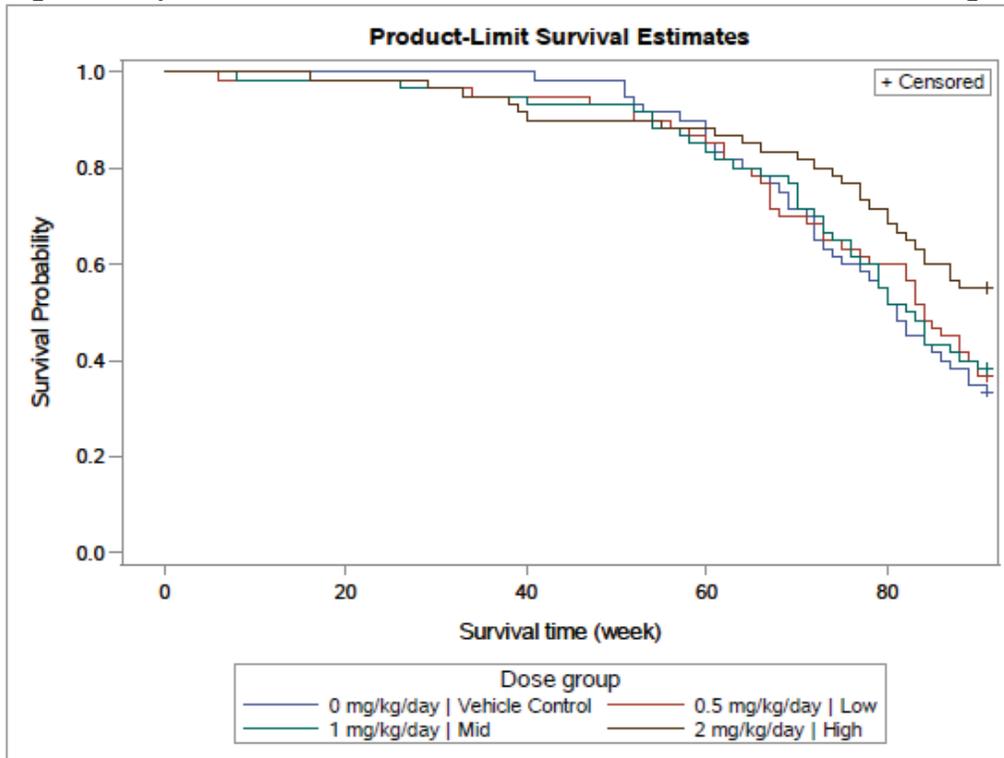


Figure 2 Kaplan-Meier Survival Functions from the Rat 102-Week Carcinogenicity Study – Female

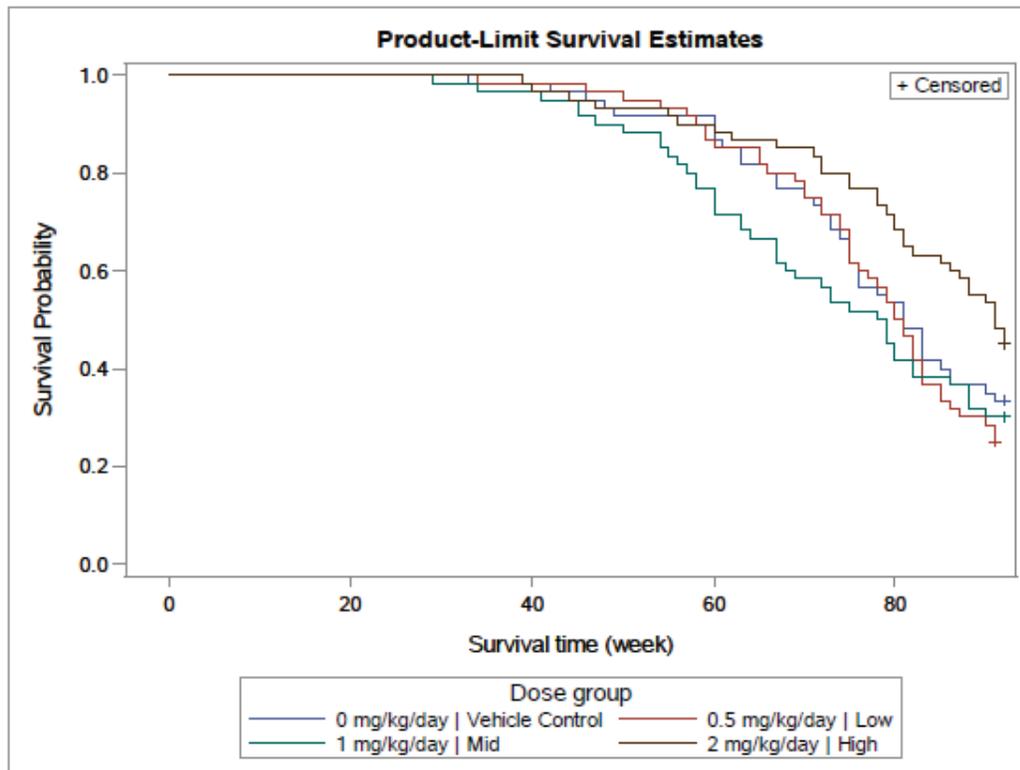


Table 2 Mortality rate in the Rat 102-Week Carcinogenicity Study – Male

Week / Type of Death	Vehicle Control		Low		Mid		High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	4	6.67	6	10.00	5	8.33	6	10.00
53 - 78	22	43.33	18	40.00	19	40.00	11	28.33
79 - 91	14	66.67	14	63.33	13	61.67	10	45.00
Terminal sacrifice	20	33.33	22	36.67	23	38.33	33	55.00
Total	60		60		60		60	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.0190*		0.6731		0.6586		0.0227*	
Homogeneity (Log-Rank)	0.1132		0.6702		0.6556		0.0216*	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level;

Table 3 Mortality rate in the Rat 102-Week Carcinogenicity Study – Female

Week / Type of Death	Vehicle Control		Low		Mid		High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	5	8.33	3	5.00	7	11.67	4	6.67
53 - 78	22	45.00	23	43.33	23	50.00	12	26.67
79 - 91	13	66.67	19	75.00	12	70.00	15	51.67
92 - 104							2	3.33
Terminal sacrifice	20	33.33	15	25.00	18	30.00	27	45.00
Total	60		60		60		60	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.0534		0.4849		0.3846		0.0958	
Homogeneity (Log-Rank)	0.0480*		0.4770		0.3776		0.0909	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level;

Clinical Signs

Non-adverse valbenazine treatment-related clinical signs were primarily noted at the 2 mg/kg/day dose level and generally consistent with those observed at similar doses in the subchronic and chronic toxicology studies in rat. These signs consisted of increased reactivity to stimulus, pre-dose hyperactivity, sensitivity to touch, straub tail (also observed in males at 1 mg/kg/day), and increased struggling (all doses). In general these findings were noted during the 1st year of dosing then waned, with the exception of sensitivity to touch, which was noted primarily during the 2nd year.

Reviewer Comment: Decreased postdose activity was not observed during the current study unlike the previous studies in rats. This may be due, in part, to the dose selection, as the high dose of 2 mg/kg/day utilized in the carcinogenicity study was slightly below the low dose of 3 mg/kg/day utilized in the previous general toxicology studies. In addition, because detailed clinical examinations were only performed weekly

during the dosing phase and the time of the examination is not provided, hypoactivity may have been missed.

Body Weights

Valbenazine treatment-related decreases in body weight gain were observed in both male and female rats at the 2 mg/kg/day dose level. As a result mean body weight was reduced beginning on week 3 in females and week 5 in males at the 2 mg/kg/day dose level relative to control rats. This effect was more pronounced in male rats where it correlated with minor differences in food consumption over the course of the study. A less significant decrease in body weight was noted in male rats at the 0.5 and 1 mg/kg/day dose levels at the end of the study.

Table 4 Percent Mean Body weight from the Rat 102-Week Carcinogenicity Study

Sex	Male		Female	
	% Control Body weight at Week 52	% Control Body weight at Week 90	% Control Body weight at Week 52	% Control Body weight at Week 90
0	100	100	100	100
0.5	99	92	101	106
1	92	93	94	103
2	85	83	90	92

Figure 3 Mean Body weight Data from the Rat 102-Week Carcinogenicity Study – Male

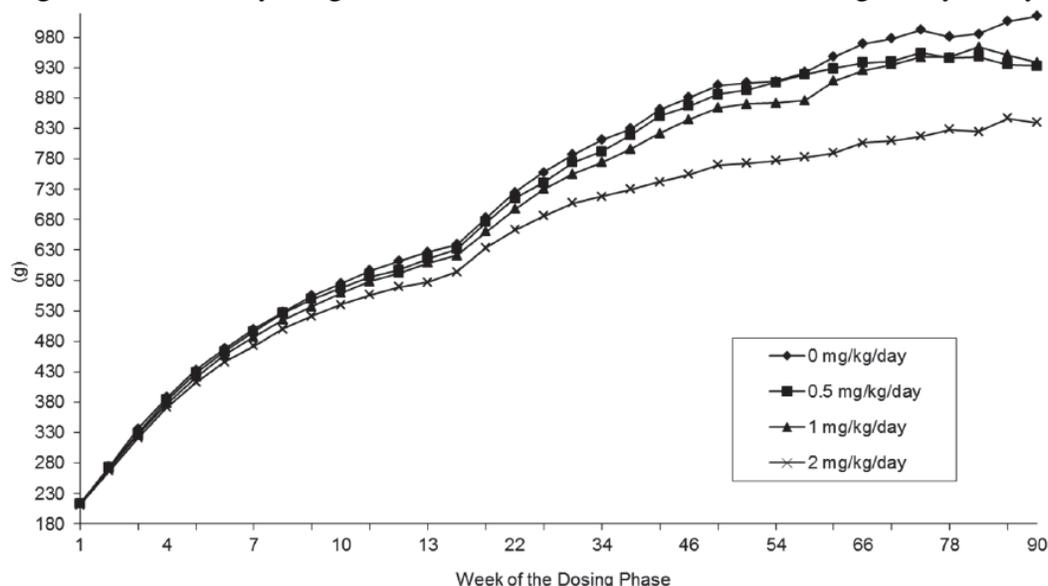
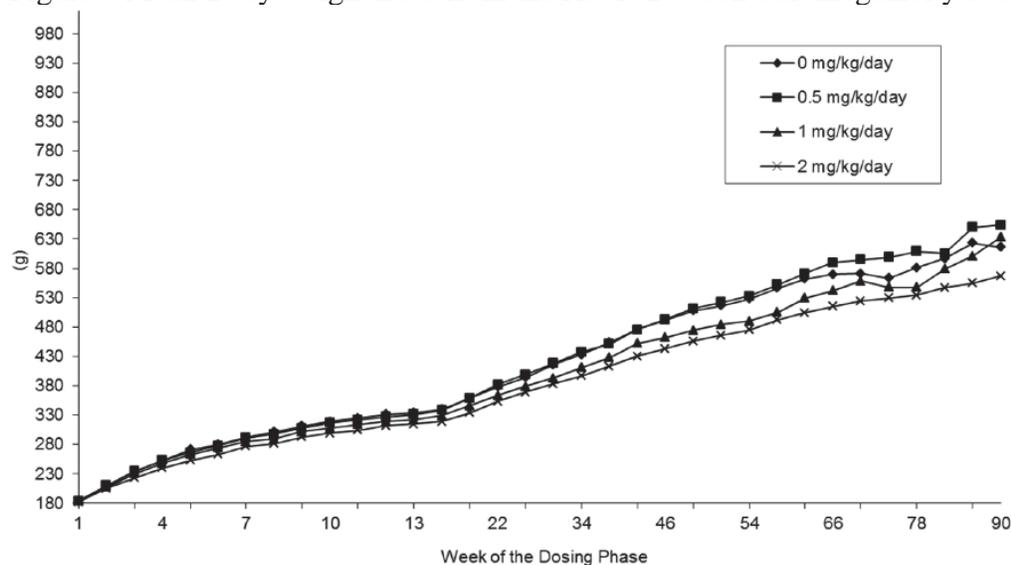


Figure 4 Mean Body weight Data from the Rat 102-Week Carcinogenicity Study – Female



Food Consumption

Food consumption was decreased throughout the course of study in male and female rats at the 2 mg/kg/day dose level. This effect was most pronounced in males and correlated with a larger decrease in body weight gain and mean terminal body weight in these rats. Although food consumption was sporadically lower in females it did not correlate as well with decreased body weight in these rats. No consistent valbenzine treatment-related effects on food consumption were noted at any other dose level.

Gross Pathology

No valbenzine treatment-related effect on total palpable masses was reported. However, there was an increase in the incidence of skin masses, which were generally palpable, noted in females at the 2 mg/kg/day dose level. With one exception (abscess) these masses were determined to be mammary gland hyperplasia or neoplasms.

Table 5 Incidence of Skin Masses from the Rat 102-Week Carcinogenicity Study

Sex	Male				Female			
Dose Level (mg/kg/day)	0	0.5	1	2	0	0.5	1	2
Number Examined	60	60	60	60	60	60	60	60
Skin Mass	8	10	9	5	16	14	13	28

No other gross pathology findings related to valbenzine treatment were reported.

Reviewer Comment: The lack of valbenzine treatment-related gross pathology findings in the current study is in line with results from the subchronic and chronic toxicology studies in rats, in which no gross pathology findings were reported at doses up to 10 mg/kg/day.

Histopathology

Peer Review: Peer review was conducted and differences in opinion between the study and reviewing pathologists were resolved. The final study report reflects the mutually agreed-on diagnoses.

Neoplastic: For female rats the Sponsor reported an increase in the incidence of benign and malignant neoplastic lesions of the mammary gland (fibroadenoma, adenoma, and carcinoma) at the high-dose level. However, the increase was significant (Log-Rank $p = 0.0454$) only for adenoma at the 0.05 level. Since these tumors are considered common the increased incidence was interpreted as non-significant by the Sponsor. **Reviewer Comments:** Although these types of tumors are common in female rats, valbenazine has been shown to increase circulating prolactin level. Therefore, the increased incidence is likely test article-related and of relevance to human risk (Harvey, 2011).

Table 6 Incidences of Primary Mammary Gland Neoplasms in the Rat 102-Week Carcinogenicity Study – Female

	Sex	Female			
		Dose Level (mg/kg/day)	0	0.5	1
Mammary gland	Number examined	59	59	60	60
B-Fibroadenoma		21	23	23	29
B-Adenoma		1	0	0	4
M-Carcinoma		17	23	19	24
Combined		32	37	31	42

For male rats the Sponsor reported statistically significant increases in the incidence of benign and malignant neoplastic lesions of the skin/subcutis. The incidence of malignant fibrosarcoma was significantly increased at the low-dose level ($p = 0.0143$ and $p = 0.0156$ for Log-rank test and Wilcoxon test, respectively) and the incidence of benign trichoepithelioma was significantly increased at the mid-dose level ($p = 0.0227$ and $p = 0.0265$ for Log-rank test and Wilcoxon test, respectively). **Reviewer Comments:** Only the incidence of malignant fibrosarcoma was significantly increased ($p = 0.0406$) according to the FDA biostatistics Reviewer (Hepei Chen). Although the incidence of fibrosarcoma was higher at the low dose (5/59, 8.5%) than what is reported for CrI:CD(SD) rats (1.74%; range 1.0% to 6.0%) it is not a rare tumor. This together with the lack of a dose response, as an increased incidence was only noted at the low-dose, would suggest the finding is incidental and of no relevance to human risk.

Table 7 Incidences of Fibroma and Fibrosarcoma in the Skin from the Rat 102-Week Carcinogenicity Study – Male

	Sex	Male			
		Dose Level (mg/kg/day)	0	0.5	1
Subcutis	Number examined	58	59	59	59
B-Fibroma		2	1	1	0
M-Fibrosarcoma		0	5	0	2
Combined		2	6	1	2

Table 8 Incidences of Epithelial Neoplasms in the Skin from the Rat 102-Week Carcinogenicity Study – Male

	Sex	Male			
		Dose Level (mg/kg/day)	0	0.5	1
Skin	Number examined	58	59	59	59
B-Basal cell tumor		0	1	1	0
B-Adenoma, sebaceous cell		0	2	0	0
M-Carcinoma, sebaceous cell		0	0	2	0
B-Keratoacanthoma		1	0	3	0
B-Papilloma, squamous cell		1	1	0	0
M-Carcinoma, squamous cell		1	0	0	1
B-Trichoepithelioma		0	1	4	0
M-Carcinoma, trichoepithelial		0	0	0	0
Combined		3	5	10	1

In addition when all benign and malignant tumors of the skin/subcutis were combined the Sponsor reported a significant increase at the 1 mg/kg/day dose level. **Reviewer Comments:** This finding was primarily driven by increases in benign trichoepithelioma, benign keratoacanthoma, and malignant sebaceous cell carcinoma, three tumor types that should not be combined as they arise from different cell types. Finally this increase was not judged as significant according to the FDA biostatistics Reviewer (Hepei Chen). Therefore this finding is considered incidental and of no relevance to human risk.

No other statistically significant or biologically meaningful increases in neoplastic lesions were observed.

Non Neoplastic: No valbenazine treatment-related non-neoplastic lesions were reported. All non-neoplastic microscopic findings were considered spontaneous or incidental because they occurred at a low incidence that was within the historical control range for Crl:CD(SD) rats or lacked dose response. **Reviewer Comment:** The lack of valbenazine treatment-related non-neoplastic microscopic findings in the current study is in line with results from the subchronic and chronic toxicology studies, in which no microscopic lesions were reported at a dose of 3 mg/kg/day.

Toxicokinetics

Concentrations of valbenazine and the metabolites NBI-98782 and NBI-136110 were below the limit of quantification in samples taken from the vehicle control groups.

Valbenazine exposure, both C_{max} and AUC, increased with increasing dose in a greater than dose proportional manner across groups on day 1 and week 26. Significant accumulation of valbenazine was noted at week 26 with exposure ($AUC_{(0-24)}$) increasing 5- to 11 times for at the low-dose, 2 to 4 times at the mid-dose, and ~3 times for the high-dose. Exposure to valbenazine was 2 to 5 times greater in females than in males.

Reviewer Comment: Accumulation was higher in the current study than was previously observed in rats. However, similar to what was observed previously, the amount of accumulation decreased with increasing dose. In addition, as discussed below, real valbenazine concentrations in the dose formulations were significantly below nominal (56% to 85%) on day 1 relative to week 26. This formulation error likely contributed to the apparent accumulation observed here. With that said, the formulation issue was corrected at week 7 and therefore week 26 values are relevant to calculation of steady state exposures. Finally it should be noted that, although C_{max} was similar at week 26 in both this carcinogenicity assay and the previous 3-month general toxicology study, $AUC_{(0-24)}$ exposures were significantly higher in the current study (> 2 times).

Table 9 Mean Valbenazine TK Parameters on Day 1 and Week-26 in the Rat 102-Week Carcinogenicity Study

Dose Group (mg/kg/day)	Sex	Day 1		Week 26	
		C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·hr/mL)
0.5	Male	NC	NC	7.22	22.4
	Female	4.66	23.3	20.9	119
1	Male	10.9	46.9	26.4	112
	Female	12.6	80.6	65.4	321
2	Male	22.8	115	62.6	369
	Female	37.8	274	181	825

NBI-98782 (pharmacologically active metabolite) exposure, both C_{max} and AUC, increased with increasing dose in an approximately dose proportional manner across groups on day 1 and during week 26. Unlike exposure to valbenazine, no significant accumulation of NBI-98782 was noted at week 26 with exposure ($AUC_{(0-24)}$) increasing < 2 times for at all dose levels. In addition, no significant sex difference in exposure was noted, although female rats had slightly higher plasma levels (< 2 times increase) at all doses and time points. The molar ratio of NBI-98782 to valbenazine was between 2.75 and 6.52 on day 1 and between 1.26 and 7.72 during week 26.

Reviewer Comment: Similar to what was observed previously in rats, no significant accumulation was noted. However, because of the formulation issue interpretation of

this data is confounded. With that said, the formulation issue was corrected at week 7 and therefore week 26 values are relevant to calculation of steady state exposures. Finally it should be noted that, although C_{max} was similar at week 26 in both this carcinogenicity assay and the previous 3-month general toxicology study in rats, $AUC_{(0-24)}$ exposures were significantly higher in the current study (> 2 times).

Table 10 Mean NBI-98782 TK Parameters on Day 1 and Week-26 in the Rat 102-Week Carcinogenicity Study

Valbenazine Dose Group (mg/kg/day)	Sex	Day 1		Week 26	
		C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·hr/mL)
0.5	Male	9.65	84.3	14.0	132
	Female	11.5	116	18.2	177
1	Male	20.4	169	30.3	295
	Female	22.8	302	38.5	450
2	Male	40.9	381	66.8	641
	Female	51.2	574	76.8	794

NBI-136110 (pharmacologically active metabolite) exposure, both C_{max} and AUC, increased with increasing dose in an approximately dose proportional manner across groups on day 1 and during week 26. Unlike exposure to valbenazine, no significant accumulation of NBI-98782 was noted at week 26 with exposure (AUC_{0-24}) increasing < 2 times for at all dose levels, except at the low dose where exposure increased ~2 times. In addition, no significant sex difference in exposure was noted, although female rats had slightly higher plasma levels (< 2 times increase) at all doses and time points, except at the low dose where exposure was ~2 times higher in female rats on day 1. The molar ratio of NBI-136110 to valbenazine ranged from 0.78 to 2.07 on day 1, and from 0.51 to 3.51 during week 26.

Table 11 Mean NBI-136110 TK Parameters on Day 1 and Week-26 in the Rat 102-Week Carcinogenicity Study

Valbenazine Dose Group (mg/kg/day)	Sex	Day 1		Week 26	
		C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)
0.5	Male	2.81	19.1	6.66	81.7
	Female	4.39	50.0	9.00	106
1	Male	8.11	74.9	14.2	154
	Female	8.27	74.9	20.3	235
2	Male	14.5	168	30.2	344
	Female	14.1	223	39.2	436

Dosing Solution Analysis

Dose analysis revealed that rats were under dosed during the first 6 weeks of the study. Samples collected for day 1, week 4, and week 5 had mean real concentrations ~56% of nominal at the low-dose, ~74% of nominal at the mid-dose, and ~85% of nominal at the high-dose. No formulation or analytical procedure error was identified that could explain these results. However, chromatograms suggested an issue with degradation. Subsequent changes to pH limit directives for the formulations were made beginning week 7 and this change corrected the low recoveries. Remaining dose analysis intervals for valbenazine formulations had mean sample results within ±10% of their target concentration. **Reviewer Comment:** The length of under dosing represents a sufficiently short period (~7% of total study length) and therefore is not considered to have impacted overall study validity.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title:

Study no.:	8235039
Study report location:	Sponsor Reference No. 2010-TX-020 SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/16/2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Valbenazine, 08KL014D, 98.8%

Key Study Findings

- Signs of parental toxicity consisting of palpebral ptosis and significantly lower body weight gain were noted in both males and females at the 10 mg/kg/day dose level.
- Lower fertility index (77%) was noted in males and lower pregnancy rate (81%) and fertility index (77%) were noted in females at the 10 mg/kg/day dose level.
- No valbenazine treatment-related findings were noted on male gonadal function or mating behavior.
- No valbenazine treatment-related findings were noted on cesarean section or parental necropsy.
- The NOAEL for male and female fertility was 3 mg/kg/day.
- The NOEL for early embryonic development was 10 mg/kg/day, the highest dose tested.

Methods

Doses:	0, 1, 3, 10 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain:	Rats, Crl:CD(SD), (b) (4)
Number/Sex/Group:	22/sex/group
Satellite groups:	none
Study design:	Valbenazine was administered daily via oral gavage to male and female rats prior to mating for 28 and 14 days, respectively, and until termination (males, at least 10 weeks of dosing) or through gestation day (GD) 7 (females). Potential effects on general toxicity, gonadal function, mating behavior, implantation, general fertility of male and female rats, and early embryonic survival of their offspring were assessed.
Deviation from study protocol:	None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Observations and Results

Mortality

No valbenazine treatment-related morbidity-related early terminations or mortalities were noted during the course of this study.

Clinical Signs

Valbenazine treatment-related palpebral ptosis was noted in most male and female rats at the 10 mg/kg/day dose level and a few females at the 3 mg/kg/day dose level. This finding was noted beginning about 2 hrs. postdose and is consistent with monoamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor.

In addition transient hypoactivity (females) or hyperactivity (males) was noted in rats at the 10 mg/kg/day dose level. The toxicological significance of this finding is unclear. However, monoamine depletion is known to cause transient hyper/hypoactivity.

Body Weight

Male body weight gain was significantly reduced at the 3 and 10 mg/kg/day dose levels during the dosing period (11.1 and 35.2%, respectively). The effect was considered adverse in male at the 10 mg/kg/day dose, where lower overall mean body weight relative to control males was noted beginning on dosing day 7 resulting in a 17.7% reduction relative to control at the end of the dosing period.

Female body weight gain was significantly reduced at the 10 mg/kg/day dose level during the pre-mating period and gestation period (51.7 and 11.1%, respectively). Based on the magnitude of this effect it was considered adverse.

Effects on body weight gain correlated with reduced food intake in both sexes.

Estrus Cycling

Twenty out of 22 females at the 10 mg/kg/day dose level were in a state of persistent diestrus (≥ 4 consecutive Days) with the majority of females cycling back to metestrus. **Reviewer Comment:** These findings are consistent with increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. Although prolactin was not measured in the current study, oral administration of valbenazine was previously demonstrated to significantly increase serum prolactin levels in rats at a dose of 3 mg/kg/day (study No. 08-98854-002-PH). Although mating behavior was unaffected in these female rats their fertility index was significantly decreased likely due to anovulation.

Toxicokinetics

Not analyzed

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations prepared at weeks 1, 3, 7, and 10 were within 10.1% of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Necropsy

Macroscopic Findings and Organ Weights: No adverse valbenazine treatment-related findings were noted. Mean prostate, testes, epididymis, and seminal vesicles weights

were slightly lower compared to control in males at the 10 mg/kg/day dose level. No findings were noted at the lower dose levels.

Reviewer Comment: These findings are consistent with increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. Although prolactin was not measured in the current study, oral administration of valbenazine was previously demonstrated to significantly increase serum prolactin levels in rats at a dose of 3 mg/kg/day (study No. 08-98854-002-PH).

Reproductive parameters:

Females (6/22) at the 10 mg/kg/day dose level showed extended pre-coital interval. In addition, although mating behavior was not significantly affected, as indicated by coital rate, fewer females (81% vs. 100%) were pregnant following cohabitation contributing to a marked reduction in the fertility index (77%) at this dose level.

Reviewer Comment: This is likely due to the state of persistent diestrus observed in these females resulting in anovulation. Although prolactin was not measured in the current study, oral administration of valbenazine was previously demonstrated to significantly increase serum prolactin levels in rats at a dose of 3 mg/kg/day (study No. 08-98854-002-PH).

Males at the 10 mg/kg/day dose level also had a decreased fertility index (77%). However, sperm count and sperm motility parameters were unremarkable. In addition, although males sex organ weights were reduced, the magnitude of the change was not significant enough to clearly establish a causative role in the observed decreased fertility.

Table 47 Fertility and Pregnancy Parameters

Endpoints	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
Number of males mated	22	22	21	21
Number of males successfully mated	22	20	20	17
Number of females mated	22	22	22	21
Number of females pregnant	22	20	21	17
Male coital rate (%)	100	100	100	95
Female coital rate (%)	100	100	100	95
Conception index (%)	100	91	91	81
Male fertility index (%)	100	91	95	77
Female fertility index (%)	100	91	95	77

No valbenazine treatment-related effects were observed in any cesarean section parameters, including number of corpora lutea, implantation sites, and fetal viability.

9.2 Embryonic Fetal Development - Rat

Study title: Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetic with NBI-98854 in Rats

Study no.: 8235041
Sponsor Reference No. 2010-TX-030
Study report location: SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location: (b) (4)
Date of study initiation: 1/17/2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Valbenazine, 08KL014D, 98.8%

Key Study Findings

- Maternal toxicity evidenced by significantly lower body weight gain was noted at the 5 and 15 mg/kg/day dose levels.
- Clinical signs (hypoactivity and palpebral ptosis) consistent with the known pharmacology of valbenazine were noted at 15 mg/kg/day.
- No valbenazine treatment-related findings were noted on maternal necropsy or cesarean section.
- The NOAEL for maternal toxicity based on decreased body weight gain was 1 mg/kg/day.
- The NOAEL for embryo/fetal viability, growth, and development was 15 mg/kg/day, the highest dose tested corresponding to a C_{max} of 480 ng/mL and an AUC_{0-24} of 4230 ng•hr/mL.

Methods

Doses: 0, 1, 5, and 15 mg/kg
Frequency of dosing: Daily
Dose volume: 10 mL/Kg
Route of administration: Oral
Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain: Rat/Crl:CD(SD), (b) (4)
Number/Sex/Group: 25/group main study
Satellite groups: 5/control and 10/treatment group for TK analysis
Study design: 135 pregnant female (F0 generation) rats were randomly assigned to 4 groups (25 females per group). An additional 35 pregnant females rats were randomly assigned to 4 groups for TK sample collections. Valbenazine or vehicle were administered via oral gavage once daily from gestation day (GD) 6 through 17. The high-dose level was chosen based on signs of maternal

toxicity evidenced by clinical signs (hypoactivity, hunched posture, irregular respiration, palpebral ptosis) and reduced body weight gain observed in a prior dose range finding study at doses up to 15 mg/kg/day. Although 15 mg/kg/day was judged to be a maternally toxic dose there were no dose-dependent effects on cesarean parameters, fetal weight, or fetal evaluations and was therefore chosen as the top-dose in the current study. Doses of 1 and 5 mg/kg/day were chosen as the low- and mid-dose to provide adequate exposure separation and explore any potential dose-response.

Deviation from study protocol: None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Observations and Results

Mortality

No mortality occurred during the course of the study.

Clinical Signs

Valbenazine treatment-related clinical signs were observed at the 15 mg/kg/day dose level and consisted of hypoactivity and palpebral ptosis. These effects were not present prior to dosing the next day and were not observed following dosing cessation (GD 18-21). These findings are consistent with monoamine depletion a known pharmacological action of valbenazine acting as a VMAT2 inhibitor.

Body Weight

Maternal body weight gains were significantly reduced during gestation at the 5 and 15 mg/kg/day dose levels. At the 15 mg/kg/day dose level female rats lost body weight from GD 6 to 8 indicating adverse maternal toxicity. In addition, reduction in maternal body weight gain was noted both during the early- and late-gestation intervals, including the period following dosing cessation (GD18-21) at the 5 and 15 mg/kg/day dose levels.

Reviewer Comment: The effect on maternal bodyweight during the late-gestation interval is indicative of delayed fetal development as well as maternal toxicity. These effects are in-line with observations of increased duration of gestation, reduced fetal weight, and still births noted in the rat PPND study (No. 20068205).

Table 48 Maternal body weight gain during rat Segment II study^a

Gestation Day Interval	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
GD 6-8	10.8	6.5 (-40%)	3.1 (-71%)	-2.0 (-119%)
GD 8-10	12.5	13.3 (6%)	10.2 (-18%)	7.7 (-38%)
GD 10-12	13.2	13.3 (1%)	12.7 (-4%)	11.4 (-14%)
GD 12-14	15.2	16.1 (6%)	12.3 (-19%)	11.8 (-22%)
GD 14-16	21.2	18.0 (-15%)	18.0 (-15%)	17.2 (-19%)
GD 16-18	24.8	26.3 (-6%)	24.4 (-2%)	23.2 (-6%)
GD 18-21	36.4	36.0 (-1%)	27.9 (-23%)	20.4 (-44%)

a. Data are presented as group means with % change from control in parenthesis.

Food Consumption

The reductions in maternal body weight gain correlated with reduced food intake at the 5 and 15 mg/kg/day dose levels throughout the dosing period. Food consumption remained lower during the postdose period (GD 18-21) which likely contributed to significant reduction in body weight gain observed during this period.

Table 49 Maternal food consumption during rat PPND study^a

Gestation Day Interval	0 mg/kg/day (control)	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
GD 6-8	29	28	26	23
GD 8-10	30	29	27	26
GD 10-12	32	30	27	26
GD 12-14	33	32	28	26
GD 14-16	32	30	27	24
GD 16-18	33	32	29	27
GD 18-21	29	27	23	20

Toxicokinetics

Exposure to valbenazine and a pharmacologically active metabolite NBI-98782 increased with increase in dose level from 1 to 15 mg/kg/day. Exposures (C_{max} and AUC_{0-24}) increased in a greater than dose proportional level for valbenazine and in a dose proportional manner for NBI-98782 on GD 6 and 17. No signs of significant accumulation were noted for either valbenazine or NBI-98782.

Reviewer Comment: Valbenazine exposure (both C_{max} and AUC_{0-24}) was about ½ in pregnant females what was observed in non-pregnant females in the general toxicology studies. This is in contrast to pregnant rabbits where valbenazine exposures were greater than non-pregnant rabbits. NBI-98782 exposure was similar between pregnant and non-pregnant rats.

Table 50 Mean (\pm SE) valbenazine TK Parameters in the segment II rat study

Dose Group (mg/kg/day)	GD	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng·hr/mL)	T_{max} (hr.)
1	6	11.2 (2.41)	92.0 (50.3)	1
	17	20.5 (3.82)	133 (53.7)	1
5	6	72.2 (27.8)	537 (184)	1
	17	141 (57.8)	1000 (440)	1
15	6	350 (169)	3150 (754)	1
	17	480 (198)	4230 (1050)	1

Table 51 Mean (\pm SE) NBI-98782 TK Parameters in the segment II rat study

Valbenazine Dose Group (mg/kg/day)	GD	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	T _{max} (hr.)
1	6	28.7 (8.91)	325 (144)	3
	17	26.4 (2.61)	274 (30.3)	3
5	6	189 (20.3)	1660 (211)	3
	17	151 (16.5)	1550 (228)	1
15	6	514 (78.9)	5590 (577)	3
	17	362 (45.3)	4740 (540)	1

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations prepared on GD 6 and GD 17 were within 4.0% of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Necropsy

No valbenazine treatment-related findings were observed during gross necropsy.

Cesarean Section Data

No valbenazine treatment-related differences in gravid uterine weights, number of corpora lutea, implantation sites, or pre-/post-implantation losses were noted. All females had viable fetuses with similar mean fetal weights and sex ratios.

Reviewer Comment: These findings are in contrast to those from the rat PPND study where doses of 5 and 15 mg/kg/day resulted in increased still birth and low fetal birth weight.

Offspring

No valbenazine treatment-related external variations or malformations were observed. One fetus (No. 8 from dam B69479) at the 15 mg/kg/day maternal dose level displayed polydactyly. However, in the absence of signs of developmental toxicity in any other fetus it was judged to be incidental.

No valbenazine treatment-related soft tissue variations/malformations or skeletal variations/malformations were noted under the conditions of this study.

9.3 Embryonic Fetal Development - Rabbit

Study title: Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetic with NBI-98854 in Rabbits

Study no.: 8235046
Sponsor Reference No. 2010-TX-031
Study report location: SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location: (b) (4)
Date of study initiation: 1/17/2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Valbenazine, 08KL014D, 98.8%

Key Study Findings

- Maternal toxicity evidenced by significantly lower body weight or body weight gain was noted at the 50 and 100 mg/kg/day dose levels.
- 1 mortality on GD 17 at the 100 mg/kg/day dose level.
- Clinical signs (hypoactivity, palpebral ptosis, rapid respiration) consistent with the known pharmacology of valbenazine were noted at ≥ 50 mg/kg/day.
- 2 non-pregnant rabbits at the 100 mg/kg/day dose level.
- Significantly reduced fetal weight at the 100 mg/kg/day dose level correlated with delayed ossification consistent with developmental delay.
- No valbenazine treatment-related findings were noted on maternal necropsy or cesarean section of pregnant rabbits.
- The NOAEL for maternal toxicity based on decreased body weight gain was 20 mg/kg/day.
- The NOAEL for embryo/fetal viability, growth, and development was 50 mg/kg/day, corresponding to a C_{max} of 1530 ng/mL and an AUC_{0-24} of 6030 ng•hr/mL.

Methods

Doses: 0, 20, 50, and 100 mg/kg
Frequency of dosing: Daily
Dose volume: 5 mL/Kg
Route of administration: Oral
Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain: Rabbit/Hra:(NZW)SPF, (b) (4)
Number/Sex/Group: 20/group
Satellite groups: 5/group for TK analysis
Study design: 80 pregnant female (F0 generation) rabbits were randomly assigned to 4 groups (20 females per group). Valbenazine or vehicle were administered via oral gavage once daily from gestation day (GD) 7 through 20. The high-dose level was chosen based on signs of maternal

toxicity evidenced by clinical signs (palpebral ptosis) and reduced body weight gain observed in a prior dose range finding study at doses of 75 and 100 mg/kg/day. Although 100 mg/kg/day was judged to be a maternally toxic dose there were no dose-dependent effects on cesarean parameters, fetal weight, or fetal evaluations noted and therefore 100 mg/kg/day was chosen as the top-dose in the current study. Doses of 20 and 50 mg/kg/day were chosen as the low- and mid-dose to provide adequate exposure separation and explore any potential dose-response.

Deviation from study protocol: None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Observations and Results

Mortality

One female rabbit (F73117) at the 100 mg/kg/day dose level was found dead on GD 17. Although no necropsy findings were noted and the cause of death was not determined this mortality was considered valbenazine-related. Clinical signs in this female were consistent with those observed in the other rabbits at the 100 mg/kg/day dose level.

Clinical Signs

Valbenazine-treatment related clinical signs, consisting of hypoactivity, rapid respiration, and palpebral ptosis, were frequently observed at the 50 and 100 mg/kg/day dose levels. Less frequent clinical signs consisting of ataxia, recumbency, and constricted pupils were intermittently noted at the 50 and 100 mg/kg/day dose levels. These effects were not present prior to dosing the next day. These findings are consistent with monoamine depletion a known pharmacological action of valbenazine acting as a VMAT2 inhibitor.

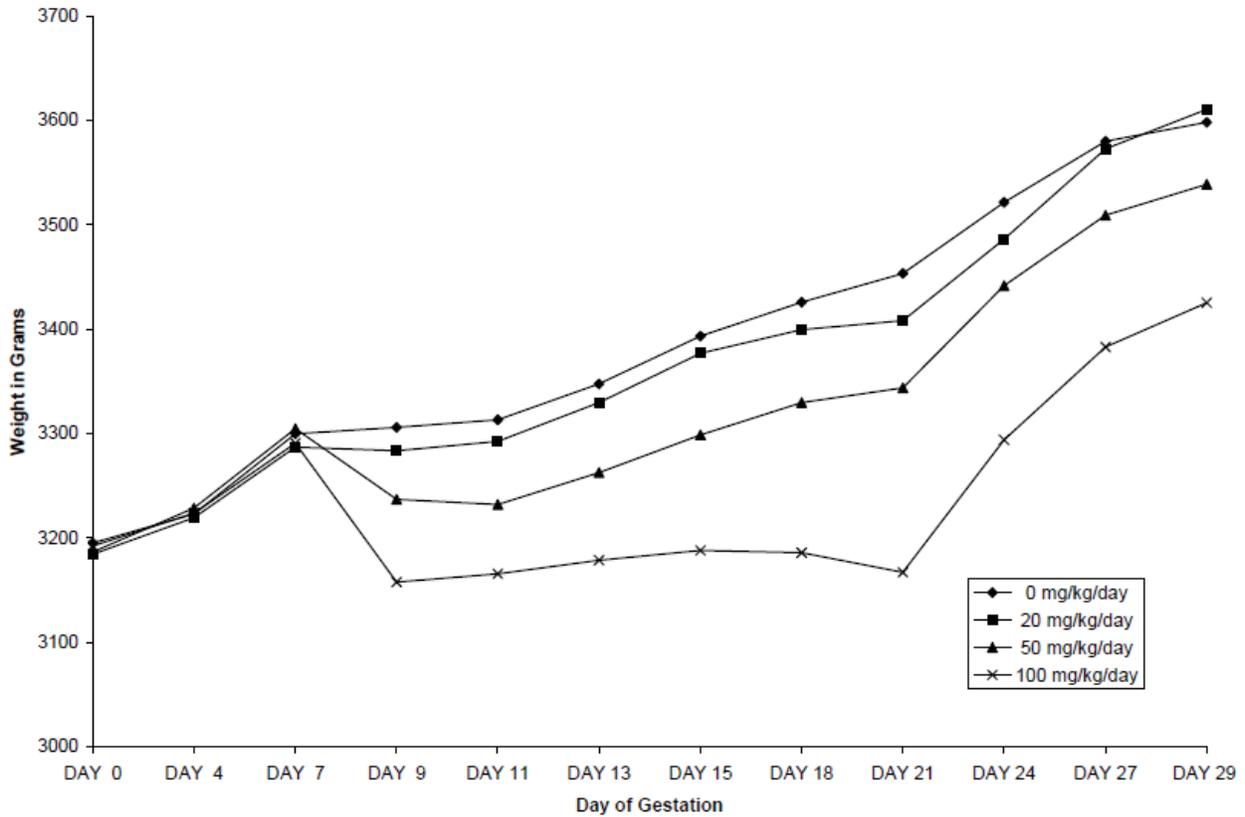
Body Weight

Maternal body weight or body weight gains were significantly reduced during gestation at the 50 and 100 mg/kg/day dose levels. Female rabbits at the 50 mg/kg/day dose level lost body weight from GD 7 to 11, however, body weight gain was similar to control throughout the rest of the dosing period although body weight was significantly reduced on GD 20 relative to control in these rabbits. Female rabbits at the 100 mg/kg/day dose level lost body weight from GD 7 to 9 and failed to gain weight throughout the remainder of the dosing period.

Reviewer Comment: The reduction in maternal body weight gain during the late gestation intervals at the 100 mg/kg/day dose level suggests potentially delayed fetal development as well as maternal toxicity. These effects are in-line with observations of

increased duration of gestation, reduced fetal weight, and still births noted in the rat PPND study.

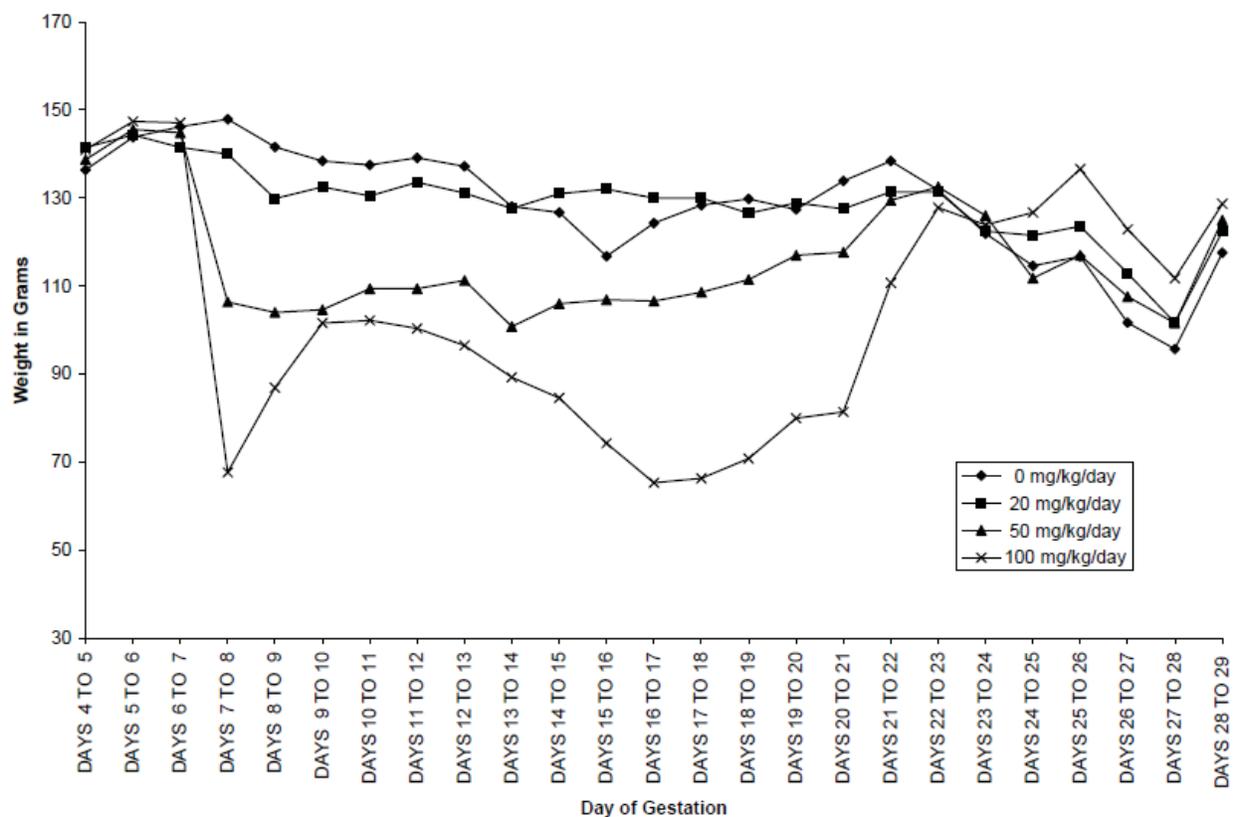
Figure 6 Mean Body weight Data from the Embryo-fetal Development Study in Rabbits



Food Consumption

The reductions in maternal body weight gain correlated with reduced food intake at the 50 and 100 mg/kg/day dose levels throughout the dosing period.

Figure 7 Mean Food Consumption Data from the Embryo-fetal Development Study in Rabbits



Toxicokinetics

Exposure to valbenazine and a pharmacologically active metabolite NBI-98782 increased with increase in dose level from 20 to 100 mg/kg/day. Exposures (C_{max} and AUC_{0-24}) increased in a greater than dose proportional level for valbenazine and in a dose proportional manner for NBI-98782 on GD 7 and 20. No signs of significant accumulation were noted for either valbenazine or NBI-98782.

Reviewer Comment: Valbenazine exposure (both C_{max} and AUC_{0-24}) was about 2 times greater in pregnant rabbits than non-pregnant rabbits in the dose range finding study. This is in contrast to pregnant rats where valbenazine exposures were less than non-pregnant rats. NBI-98782 exposure was similar between pregnant and non-pregnant rabbits.

Table 52 Mean (\pm SE) valbenazine TK Parameters in the segment II rabbit study

Dose Group (mg/kg/day)	GD	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	T _{max} (hr.)
20	7	227 (116)	781 (294)	2
	20	299 (236)	998 (306)	0.5
50	7	952 (252)	4990 (1460)	2
	20	1530 (633)	6030 (846)	0.5
100	7	2170 (812)	20500 (3330)	4
	20	3520 (1040)	32800 (10700)	4

Table 53 Mean (\pm SE) NBI-98782 TK Parameters in the segment II rabbit study

Valbenazine Dose Group (mg/kg/day)	GD	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (ng·hr/mL)	T _{max} (hr.)
20	7	61.6 (11.1)	344 (83.2)	2
	20	74.5 (14.6)	425 (55.9)	2
50	7	146 (28.3)	1140 (179)	2
	20	174 (38.2)	1320 (343)	2
100	7	270 (65.4)	2750 (585)	2
	20	310 (54.4)	3430 (493)	3

Dosing Solution Analysis

Concentration verification results indicated that all the valbenazine dose formulations prepared on GD 6 and GD 17 were within 4.0% of the target concentration. All formulations met analytical criteria and were thus suitable for use.

Necropsy

No valbenazine treatment-related findings were observed.

Cesarean Section Data

Two female rabbits (F73061 and F73106) at the 100 mg/kg/day dose level were not pregnant at cesarean section and another female (F73117) was found dead on GD 17. Of the pregnant females surviving until term, no abortions, early deliveries occurred and all fetuses were viable. No valbenazine treatment-related differences in gravid uterine weights, number of corpora lutea, implantation sites, resorptions, or pre-/post-implantation losses were noted. Necropsy of the female found dead on GD 17 revealed five apparently normally developing fetuses each on the left and right uterine horn.

Valbenazine treatment-related reductions in mean fetal weight for males (11%) and females (10%) was noted at the 100 mg/kg/day dose level when compared with fetal weight from controls.

Reviewer Comment: These findings are consistent with reduced maternal body weights observed throughout gestation. These findings are consistent with those from the rat PPND study where doses of 5 and 15 mg/kg/day resulted in increased still birth and low fetal birth weight. While these findings may be due to significantly reduced food intake observed throughout the gestation period, a direct effect of valbenazine on fetal development cannot be ruled out.

Offspring

No valbenazine treatment-related external variations/malformations or soft tissue variations/malformations were noted under the conditions of this study.

Valbenazine treatment-related skeletal variations consisted of incomplete ossification of the 5th/6th sternebrae and unossified 6th sternebrae at the 100 mg/kg/day dose level.

Reviewer Comment: These variations are consistent with fetal growth delays and may be secondary to the significant maternal toxicity noted at this dose. However, a direct effect of valbenazine on fetal development cannot be ruled out. All other skeletal variations or malformation were not considered valbenazine treatment-related as they are common findings in the rabbit or occurred in only a single fetus and were within historical control ranges.

9.4 Prenatal and Postnatal Development

Study title: Oral (Gavage) Developmental and PeriNatal/Postnatal Reproduction Toxicity Study of NBI-98854 di-Tosylate in Rats, Including a Postnatal Behavioral/Functional Evaluation.

Study no.:	20068205
Sponsor Reference No.	2014-TX-183
Study report location:	SDN 1 (eCTD 0000), 4/29/2016
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/13/2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Valbenazine, Z534FP-12-001, 99.9%

Key study findings:

F0 generation findings: Dose related adverse effects on clinical signs body weight gain, delivery and litter observations were noted in dams at the 3 and 10 mg/kg/day dose levels that increased in frequency and severity.

- Clinical signs – Consistent with VMAT2 inhibition: Ptosis, whole body tremors, piloerection, hunched posture, and dehydration, hyperpnea, red perivaginal substance, and decreased activity.
- Body weight gain: ↓ > 10% during most of the gestation period including the late gestation period suggesting a delay in fetal development. Correlated with

decreased food consumption and increased duration of gestation and decreased pup weight at the 10 mg/kg/day dose level.

- F1 generation (pre-weaning) findings: At 3 and 10 mg/kg/day dose levels, drug-related increase in number of stillborn pups and early pup mortality resulting in a decrease in the number of live born pups, live litter size, and surviving pups per litter. Decreased pup weights were also noted on PND 1 at the 10 mg/kg/day maternal dose level.
- No drug-related effects were noted in F1 generation male and female rats selected for post-weaning observations.
- Valbenazine and its metabolites NBI-98782, and NBI-136110 increased with increasing dose and were detected in milk and plasma from F1 pups on lactation day 14.
- The NOAEL for maternal toxicity was 1 mg/kg/day.
- The NOAEL for perinatal development was 1 mg/kg/day based on stillbirths and mortality early in the lactation period.
- The NOAEL for growth and reproductive development was 3 mg/kg/day, the highest maternal dose level with rats selected for postweaning observations.

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Methods

Doses: 0, 1, 3, 10 mg/kg/day
Frequency of dosing: Once Daily
Dose volume: 5 mL/kg
Route of administration: Oral Gavage
Formulation/Vehicle: 0.25% (w/v) methylcellulose in reverse osmosis deionized water
Species/Strain: Rat/Crl:CD(SD), (b) (4)
Number/Sex/Group: 22 female rats/dose
Satellite groups: 3 female rats/dose for TK analysis
Study design: 88 pregnant female (F0 generation) rats were randomly assigned to 4 groups (22 females per group). Additional 12 pregnant female rats were randomly assigned to 4 groups (3 rats/group) for TK sample collections. Valbenazine or vehicle were administered via oral gavage once daily from gestation day (GD) 7 through lactation day (LD) 20 for rats that delivered a litter, or GD 24 for rats that did not deliver a litter.

Parameters and endpoints evaluated: For *F0 generation dams*, viabilities, clinical observations, and observations of maternal behavior were recorded. Blood (1, 3, and 8 hrs. postdose) and milk (3 hrs. postdose) samples were collected from dams assigned for TK sample collections and blood was collected from pups on LD 14. For *F1 generation pups*, viabilities, clinical observations, and body weights were recorded. On LD 21 all F0 generation dams and all F1 generation pups not selected for continued evaluation, including all surviving pups at the 10 mg/kg/day maternal dose level, were sacrificed by CO2 and examined for gross lesions. 132 F1 pups (22/sex/group) were chosen for continued evaluation. No pups from the 10 mg/kg/day maternal dose level were selected for postweaning observations due to excessive early postnatal mortality. Viabilities, clinical observations, body weights, and food consumption were recorded. These pups were also evaluated for sexual maturation, sensory function by acoustic startle (PND 61), and learning and memory by M-shaped water maze tests (PND70). At PND 90 the F1 generation pups were assigned to cohabitation. Male rats

were sacrificed after completion of the cohabitation period and a gross necropsy was performed. Testes and epididymides weights were recorded. Female rats were sacrificed on GD 21, C-sectioned and a gross necropsy was performed. Each fetus was weighted and examined for any gross external alterations.

Deviations from protocol: None that were judged to have negatively impacted the quality, integrity, or conclusions of the study.

Observations and Results

F0 In-life Observations

Mortality

No valbenazine treatment-related deaths were reported among the F0 generation dams. During the lactation period 8 dams were euthanized due to no surviving pups.

Clinical signs

Valbenazine treatment-related clinical signs were noted throughout the gestation and lactation periods and increased in incidence and severity with increasing dose.

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Table 54 Clinical Signs Observed in Dams During the Rat PPND Study^a

Gestation Period				
Clinical Sign	0 mg/kg/day (control)	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
Ptosis	0/0	0/0	8/7	179/22
Whole Body Tremors	0/0	0/0	1/1	129/22
Piloerection	0/0	0/0	6/5	27/13
Hyperpnea	0/0	0/0	0/0	19/13
Hunched Posture	0/0	0/0	0/0	23/9
Red Perivaginal Substance	0/0	0/0	0/0	4/3
Decreased Activity	0/0	0/0	0/0	3/3
Dehydration	0/0	0/0	0/0	3/1
Lactation Period				
Clinical Sign	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
Ptosis	0/0	0/0	3/2	18/13
Whole Body Tremors	0/0	0/0	0/0	23/11
Piloerection	0/0	0/0	0/0	27/13
Hyperpnea	0/0	0/0	0/0	2/2
Hunched Posture	0/0	0/0	6/2	8/4
Red Perivaginal Substance	0/0	0/0	0/0	1/1
Dehydration	0/0	0/0	18/2	21/5

a. Number of observations/number of rats with observation

The majority of these clinical signs are consistent with depletion of monoamines and are considered adverse at the 10 mg/kg/day dose level.

Maternal body weight

Maternal body weight gains were significantly reduced during gestation at the 3 and 10 mg/kg/day dose levels.

Reviewer Comment: The reduction in maternal body weight gain was noted during both the early- and late-gestation intervals indicating it is unlikely due only to maternal toxicity. Moreover reductions in maternal body weight gain correlated with a reduced litter size and an increase in the number of stillborn pups at the 3 and 10 mg/kg/day dose levels, and a decrease in surviving pup weight at the 10 mg/kg/day dose level.

Therefore, this latter effect is likely indicative of both maternal- and pup-related toxicity. Although changes in maternal body weight gain were noted during the lactation period these findings were not consistent and were confounded by early postnatal loss and euthanasia of dams at the 10 mg/kg/day dose due to total litter loss.

Table 55 Maternal body weight gain during rat PPND study^a

Gestation Day Interval	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
GD 7-10	15.8	13.3 (-16%)	11.0 (-30%)	4.7 (-70%)
GD 10-12	14.0	11.8 (-16%)	11.3 (-19%)	9.2 (-34%)
GD 12-15	19.2	19.4 (+1%)	19.8 (+3%)	16.6 (-14%)
GD 15-18	40.6	38.5 (-5%)	35.4 (-13%)	32.8 (-19%)
GD 18-20	32.0	30.1 (-6%)	28.0 (-12%)	24.2 (-24%)

a. Data are presented as group means with % change from control in parenthesis.

Food consumption

The reductions in maternal body weight gain correlated with reduced food intake at the 3 and 10 mg/kg/day dose levels throughout the gestation period. In addition, although marked and consistent changes in maternal body weight gain were not noted during the lactation period, maternal food consumption was significantly reduced.

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Table 56 Maternal food consumption during rat PPND study^a

Gestation Day Interval	0 mg/kg/day (control)	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
GD 7-10	24.1	22.9 (-5%)	22.2 (-8%)	22.0 (-9%)
GD 10-12	26.4	24.4 (-8%)	22.6 (-14%)	21.6 (-18%)
GD 12-15	27.5	24.5 (-11%)	25.1 (-9%)	23.6 (-14%)
GD 15-18	28.3	27.5 (-3%)	26.6 (-6%)	23.7 (-16%)
GD 18-20	28.5	27.2 (-5%)	25.3 (-11%)	24.0 (-16%)
Lactation Day Interval	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
LD 1-4	33.1	34.9 (+5%)	27.5 (-17%)	24.2 (-27%)
LD 4-7	47.6	49.9 (+5%)	41.1 (-14%)	36.0 (-24%)
LD 7-10	60.8	60.8 (+0%)	50.2 (-17%)	37.1 (-39%)
LD 10-14	73.4	74.0 (+1%)	63.1 (-14%)	51.6 (-30%)

a. Data are presented as group means with % change from control in parenthesis.

F0 necropsy

There were no valbenazine treatment-related necropsy findings reported in the F0 generation dams.

Natural delivery and litter observations

Natural delivery observations were adversely effected by valbenazine administration at the 3 and 10 mg/kg/day dose levels. Pregnancy rate was unaffected by drug: 21, 22, 22, and 20 of the 22 mated female rats in the 0, 1, 3, and 10 mg/kg/day groups, respectively. All pregnant dams delivered litters. However, the number of dams with stillborn pups was significantly increased at the 3 and 10 mg/kg/day dose levels. In addition 8 females at the 10 mg/kg/day dose level had total litter loss during the lactation period. Moreover, although the duration of gestation was increased at the 10 mg/kg/day dose level, pup body weights on post-natal day 1 were significantly lower than control. An increase in pup body weight is expected with an increase in the duration of gestation.

Reviewer Comment: Taken together these findings indicate that valbenazine administration produces significant and adverse perinatal effects in the rat at doses of 3 and 10 mg/kg/day. It is important to note that similar valbenazine doses administered until GD 7 in the rat fertility and early embryonic development study (No. 8235039) or from GD 6-18 in the Segment II study (No. 8235041) produced no significant effects on fetal viability or fetal body weights suggesting this effect requires very late-term gestational exposure or is a fetal withdrawal phenomena.

Table 57 Natural Delivery and Litter Observations in the rat PPND study

Endpoint	0 mg/kg/day (control)	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
Duration of Gestation (Days)	22.4	22.5	22.6	23.0
Dams with Stillborn Pups (n)	4	4	14	17
Dams with total litter loss LD 1-4 (n)	0	0	0	7
Dams with total litter loss LD 5-21 (n)	0	0	0	1
Mean number of liveborn pups	11.8	12.0	9.4	8.4
Mean number of stillborn pups	0.2	0.3	2.3	3.4
Viability Index	98.8	97.4	91.7	44.4
Lactation Index	100.0	100.0	100.0	97.3
Numbers of Pups Found Dead, Euthanized, or Presumed Cannibalized (n/total live born)				
LD 1	1/247	2/265	5/206	12/169
LD 2-4	2/246	5/263	12/201	82/157
LD 5-7	0/244	0/258	0/189	1/75
LD 8-21	0/244	0/258	0/189	1/74
Mean Pup Weight/Litter (grams)				
LD 1	6.9	6.9	6.6	6.0
LD 21	42.3	44.3	46.2	41.0

Valbenazine did not adversely affect the number of pregnant dams, average implantation sites/litter, or gestation index.

F1 pups: clinical and necropsy observation

Adverse valbenazine treatment-related clinical signs were observed at the 3 and 10 mg/kg/day dose levels. At the 3 mg/kg/day dose level clinical signs consisted of cold to touch, no milk band present, absence of nursing, whole body pale, and mild to moderate dehydration (based on skin turgor). At the 10 mg/kg/day dose level clinical signs consisted of cold to touch, no milk band present, absence of nursing, whole body pale/purple/gray, mild to severe dehydration (based on skin turgor), lack of nesting, and decreased motor activity.

Table 58 Clinical Signs in the F1 generation pups during the pre-weaning period in the rat PPND study

Clinical Signs	0 mg/kg/day (control)	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
Litters Examined	21	22	22	20
Cold to Touch	0/0	1/1	39/7	209/18
No Milk Band	0/0	0/0	9/4	108/15
Whole body pale	0/0	0/0	4/2	29/3
Absence of nursing	0/0	0/0	0/0	15/3
Dehydration	0/0	0/0	17/2	29/3
Lack of nesting	0/0	0/0	0/0	13/2
Decreased activity	0/0	0/0	0/0	4/1
Tip of tale missing	0/0	0/0	0/0	5/1

No valbenazine treatment-related gross lesions were noted in pups surviving until weaning on postnatal day 21 at any dose level. Among the pups in the 10 mg/kg/day dose level that died during the lactation period (excludes still born and cannibalized pups) the majority had no milk in the stomach. The high number of pups with no milk band present during clinical observation and no milk in the stomach at necropsy in combination with the observed dehydration and low pup weight indicates that pups at this dose level were not getting sufficient nutrition. Although, this effect might be due to poor maternal care, a direct effect of valbenazine administration on the pups cannot be ruled out. In addition, the increased number of stillborn pups suggests a direct effect of valbenazine on perinatal development.

Table 59 Necropsy Observations in the rat PPND study

Necropsy Findings	0 mg/kg/day (control)	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
Found Dead	1	3	9	24
No Milk in Stomach	1	0	3	22

Toxicokinetics

No valbenazine or related metabolites were detected in plasma samples from F0 generation control dams or their pups.

On day 14 of the lactation period valbenazine and the pharmacologically active metabolites NBI-98782 and NBI-136110 were detected in the plasma of all valbenazine-treated F0 generation dams and their respective F1 generation pups.

Maternal plasma levels of valbenazine, NBI-98782, and NBI-136110 increased with increasing dose. A large enough number of time points were not collected to calculate an accurate AUC or make an accurate assessment of dose proportionality. However, the data suggest that exposures increased in a dose proportional or greater than dose proportional manner.

The t_{max} for valbenazine, NBI-98782, and NBI-136110 were 1, 3, and 3 hrs., respectively in maternal plasma. This is in line with results from the general toxicology studies conducted in rats.

Table 60 Valbenazine, NBI-98782, and NBI-136110 Maternal Plasma Concentrations on LD 14

Valbenazine Dose (mg/kg/day)	1 hr.	3 hr.	8 hr.
<u>Valbenazine Concentrations (ng/mL)</u>			
1	18.1±2.59	12.5±1.84	<LLOQ
3	41.3±15.2	38.2±9.03	12.1±4.00
10	206±28.7	130±4.73	55.0±13.1
<u>NBI-98782 Concentrations (ng/mL)</u>			
1	18.0±2.06	23.1±2.56	9.33±1.68
3	47.8±13.4	62.0±4.70	39.4±12.4
10	301±99.1	278±59.4	116±1.75
<u>NBI-136110 Concentrations (ng/mL)</u>			
1	9.39±0.864	10.8±1.34	5.05±0.285
3	20.2±6.26	29.6±6.39	17.2±5.66
10	68.9±4.92	89.1±6.08	63.2±8.79

Valbenazine, NBI-98782, and NBI-136110 were detected in milk at 3 hrs. postdose. In addition although valbenazine concentrations were below the limit of quantitation in plasma from pups, the metabolites NBI-98782 and NBI136110 were both detected.

Together these data indicate the potential for infant exposure to valbenazine or its metabolites via breast milk.

Table 61 Valbenazine, NBI-98782, and NBI-136110 Milk Concentrations on LD14 3 hrs. postdose

Valbenazine Dose (mg/kg/day)	
<u>Valbenazine Concentrations (ng/mL)</u>	
1	53.6
3	118
10	314
<u>NBI-98782 Concentrations (ng/mL)</u>	
1	106
3	265
10	797
<u>NBI-136110 Concentrations (ng/mL)</u>	
1	23.5
3	50.5
10	125

Table 62 Valbenazine, NBI-98782, and NBI-136110 Rat Pup Plasma Concentrations on LD 14

Valbenazine Dose (mg/kg/day)	1 hr.	3 hr.	8 hr.
<u>NBI-98782 Concentrations (ng/mL)</u>			
3	1.36	1.49	2.10
10	3.62	3.53	6.16
<u>NBI-136110 Concentrations (ng/mL)</u>			
10	2.08	2.35	2.77

F1 In-life Observations

Mortality

Due to extensive pup mortality at the 10 mg/kg/day dose level no F1 generation pups from this dose were selected for postweaning evaluations. All F1 generation pups from the 1 and 3 mg/kg/day dose levels selected for further evaluation, survived to the day of scheduled sacrifice.

Clinical signs

No valbenazine treatment-related adverse clinical signs were noted in F1 generation rats during the postweaning observational period at maternal doses up to 3 mg/kg/day.

All clinical observations in the F1 generation male and female rats were considered unrelated to treatment of the F0 generation dams with test article since the incidences were not dose dependent, were common observations in rodents in a laboratory setting, or occurred in rats from the control group.

Body weight

No valbenazine treatment-related effects on body weight or body weight gain were noted in F1 generation rats during the postweaning observational period at maternal doses up to 3 mg/kg/day.

Food consumption

No valbenazine treatment-related effects on food consumption were noted in F1 generation rats during the postweaning observational period at maternal doses up to 3 mg/kg/day.

Necropsy observations

No valbenazine treatment-related gross lesions were noted in the F1 generation rats at maternal doses up to 3 mg/kg/day.

No valbenazine treatment-related effects on mean terminal body weights or organ weights were noted in the F1 generation rats at maternal doses up to 3 mg/kg/day.

Sexual maturation

No valbenazine treatment-related effects on sexual maturation were noted in F1 generation rats during the postweaning observational period at maternal doses up to 3 mg/kg/day.

Behavioral evaluation

Treatment with valbenazine had no effect on learning, short-term retention, long-term retention, or response inhibition in the F1 generation male and female rats as measured by m and water maze tests.

- **Motor activity:** No valbenazine treatment-related effects on fine movements or ambulations were noted in F1 generation pups during the postweaning observational period at maternal doses up to 3 mg/kg/day.
- **Acoustic Startle:** No valbenazine treatment-related effects on reactivity to auditory stimuli or habituation were noted in F1 generation pups during the postweaning observational period at maternal doses up to 3 mg/kg/day.
- **Water maze performance:** No valbenazine treatment-related effects on learning, short-term and long-term retention, or response inhibition were noted in F1 generation pups during the postweaning observational period at maternal doses up to 3 mg/kg/day.

Mating/Fertility

No valbenazine treatment-related effects on the mating and fertility parameters or estrous cycling were noted in the F1 generation pups at maternal doses up to 3 mg/kg/day.

C-sectioning and litter observations

C-sectioning observations were based on 22, 22, and 20 pregnant F1 generation female rats in the control, 1, and 3 mg/kg/day dose groups, respectively. No valbenazine treatment-related effects on ovarian and uterine examinations were noted. The litter averages for corpora lutea, implantations, percentage of preimplantation loss, viable and nonviable embryos, and percentage of postimplantation loss were comparable among the groups.

10 Special Toxicology Studies

10.1 Photo Toxicity Study

Study Title: Neutral Red Uptake Phototoxicity Assay of NBI-98854 di-Tosylate in BALB/c 3T3 Mouse Fibroblasts

Study No.: 20072835

Sponsor Reference No.: 2015-TX-027

Testing Facility: (b) (4)

Study Design: GLP

The phototoxic potential of valbenazine was assessed by measuring the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to valbenazine at concentrations of 1.78, 3.16, 5.62, 10, 17.8, 31.6, 56.2, or 100 µg/mL in the presence or absence of ultraviolet radiation. Valbenazine was soluble at all concentrations tested. Promethazine at concentrations of 0.1, 0.316, 1, 3.16, 10, 31.6, 100, or 178 µg/mL was used as a positive control. Cells were exposed to 5 J/cm² of UVA and 22 mJ/cm² of UVB from a xenon arc solar simulator equipped with a Schott WG 320 filter.

Results:

Valbenazine was not judged to have phototoxic potential under the conditions of this assay.

Table 63 Phototoxicity Assay – BALB/c 3T3 Mouse Fibroblasts

Test Material	IC 50 (µg/mL) -UVR	IC 50 (µg/mL) +UVR	PIF	MPE	Phototoxic Potential
Valbenazine	-----	-----	*1	-0.049	Non- Phototoxic
Promethazine	-----	1.934	>85	0.470	Phototoxic

+UVR: Phototoxicity: with ultraviolet radiation exposure.

-UVR: Cytotoxicity: without ultraviolet radiation exposure.

-: IC50 not achieved.

PIF: Photoirritancy Factor The criterion for "phototoxic" is PIF > 5.

MPE: Mean Photo Effect. The criterion for "phototoxic" is MPE > 0.15.

PIF =*1: Both IC50(-UVR) and IC50(+UVR) could not be calculated (test article did not show cytotoxicity or phototoxicity), indicating a lack of phototoxic potential. In this case, a formal PIF = *1 is used to characterize the result.

11 Integrated Summary and Safety Evaluation

Valbenazine is a new molecular entity under development for the treatment of Tardive Dyskinesia (TD). Sufficient nonclinical information was submitted under NDA (b) (4) to perform a thorough nonclinical safety assessment of valbenazine. Dosage information throughout this document is expressed as valbenazine free base.

Pharmacology:

In vitro radioligand binding assays demonstrated that valbenazine binds to the rat (striatal cell membranes) and human (platelet cell membranes) Vesicular Monoamine Transporter 2 (VMAT2) with moderate affinity ($K_i = 110$ and 150 nM, respectively). In addition, valbenazine is metabolized to three pharmacologically active metabolites which display moderate to high binding affinity for human and rat VMAT2: alpha-dihydrotrabenazine (NBI-98782), M10b (NBI-679006), and M14 (NBI-136110). Of the circulating drug-related material, including valbenazine, NBI-98782 displays the highest affinity for both rat and human VMAT2 ($K_i \sim 1.0$ to 2.8 and 2.6 to 3.3 nM, respectively). NBI-98782 is likely the primary pharmacologically active moiety across all species, including humans. However, it is formed to a significantly greater extent in rats relative to dog or human. Therefore, it is estimated that NBI-98782 contributes approximately 90% of the pharmacological activity of valbenazine in the rat. However, in the dog and human it is estimated that NBI-98782, while still the principle pharmacologically active moiety, only contributes ~60% and ~80%, respectively, with valbenazine responsible for the majority of the remainder. It should be noted that NBI-98782 is also a metabolite of the FDA approved drug XENAZINE® (trabenazine, NDA 021894).

Although no in vitro functional assessments were performed, valbenazine and NBI-98782 likely act as inhibitors of VMAT2 in vivo. Valbenazine was active in several rat models sensitive to depletion of monoamines including induction of palpebral ptosis (↓ dopamine or norepinephrine), hypoactivity (↓ dopamine or norepinephrine), and prolactin secretion (↓ dopamine). It should be noted that although these models are also sensitive to blockade of certain receptors or inhibition of other transporters/enzymes, valbenazine and NBI-98782 lack affinity for these targets.

Therefore any activity in these models is likely due to inhibition of VMAT2 as opposed to, for example, dopaminergic D2 receptor antagonism. In addition valbenazine has limited potential to produce toxicity due to off-target activity, owing to its greater affinity (> 30 times) for VMAT2 versus other targets including dopaminergic (including D₂), serotonergic (including 5-HT_{2B}), adrenergic, histaminergic, muscarinic, and NMDA receptors and other monoamine transporters (DAT, NET, and SERT). Consistent with its known pharmacological activity, the potential of valbenazine to produce adverse CNS-related events (CNS depression, extrapyramidal effects, etc.) at therapeutically relevant doses is high. A single oral administration of valbenazine to rats at doses ≥ 15 mg/kg/day resulted in decreased motor activity, increased lacrimation, palpebral ptosis, slight to severe gait abnormalities (ataxia, hindlimbs/forelimbs splayed/dragging, flattened body posture), slight to severe impairment of locomotion, and very low arousal, decreased hindlimb grip strength, and depressed reflexes (miosis/abnormal pupil response, air righting). These findings indicate valbenazine treatment may result in depressed neuromuscular and sensorimotor function, as well as stimulation of the parasympathetic nervous system. Similar effects were observed in the repeat dose toxicology studies in mouse, rat, and dog.

Consistent with a lack of activity at targets other than VMAT2 including peripherally expressed VMAT1, the potential of valbenazine to produce adverse cardiovascular or respiratory system events at therapeutically relevant exposures is minimal. Valbenazine produced a minimal inhibition of hERG tail peak currents at physiologically relevant concentrations (IC₅₀ 2.0 μ M). In addition, although valbenazine produced a moderate prolongation of the QTc interval (<15 msec) in dogs, this prolongation occurred at doses ≥ 15 mg/kg/day which are at least 6 times MRHD of 80 mg/day based on mg/m². The NOEL for prolongation of the QTc interval in dogs across all studies is 12.5 mg/kg/day, which is ~ 5 times the MRHD of 80 mg/day based on mg/m². Similarly in dogs, valbenazine decreased in respiratory rate (26% to 35%) and minute volume (4% to 17%) with compensatory increases in tidal volume (23% to 32%) and an increased incidence of sighs (deep breaths) at doses ≥ 15 mg/kg/day. Although these effects are common to CNS depressants, and therefore drug related, the compensatory increase in tidal volume suggests a non-adverse effect on central respiratory centers at the doses tested. The NOAEL for respiratory effects in the beagle dog is 35 mg/kg, which is ~ 15 times the MRHD of 80 mg/day based on mg/m².

ADME:

Valbenazine is highly permeable across cell bilayers and is not a substrate for efflux transporters. However, valbenazine displayed a moderate oral bioavailability (%F 50 to 70) and volume of distribution at steady state (1 to 2 L/kg) in rats and humans. Clearance was lower in humans and dogs relative to rats resulting in a longer elimination half-life (t_{1/2}) in dogs (5.9 hrs.) and humans (16 hrs.) versus rats (1.3 hrs.). Valbenazine is highly protein bound, > 95% across species, while NBI-98782 is moderately protein bound, 48 to 76% across species. Valbenazine-related material is rapidly and widely distributed to tissues including the brain, with the most significant levels generally detected in highly perfused tissues such as the lungs, liver, kidney and spleen. In addition valbenazine-related material is highly distributed to pigmented region of the eye, particularly the uveal tract with a tissue to plasma ratio > 4000 and t_{1/2}

> 1000 hrs. A similar degree of distribution to pigmented skin was not observed. The only nonclinical study with potentially valbenazine treatment-related eye findings was the 6-month chronic rat study (study No. 8271662), in which retinal degeneration was observed. However, as these rats are albino, the relevance of this finding to accumulation of valbenazine in pigmented eye is unclear. Moreover, no valbenazine treatment-related eye findings were noted in the dog or pigmented mouse, and no phototoxicity was observed in BALB/c 3T3 mouse fibroblasts. Moreover, no eye-related toxicities were reported in the toxicology studies conducted with the FDA approved drug XENAZINE® (tetrabenazine, NDA 021894). Therefore, the clinical significance of the extensive distribution of valbenazine-related material to the eye is unclear at present.

Valbenazine is extensively metabolized in rats, dogs, and humans with little unchanged drug excreted via biliary or renal pathways. In total, more than 60 metabolites were detected in human urine and feces by radiometry or mass spectrometry. However, no single metabolite represented > 10% of the administered dose. The metabolic profile in rat and dog was similar to human, with every excretory human metabolite detected in at least one and the majority detected in both species. The structural characterization of the metabolites present in rat, dog, and human plasma and excreta suggest several metabolic clearance pathways, common to all three species. Pathway 1 is ester hydrolysis to NBI-98782 followed by mono-oxidation to NBI-679006. Pathway 2 is mono-oxidation to NBI-136110. All three of these metabolites are pharmacologically active. The primary difference in metabolism across species is related to the extent of ester hydrolysis of valbenazine to form NBI-98782, which is significantly greater in the rat than in the dog, mouse, or human. NBI-98782, NBI-679006, and NBI-136110 account for ~10%, 8%, and 13% of circulating valbenazine-related material, respectively. Exposure to all three of these metabolites was greater in rats, dogs, and mice used in the toxicity studies compared to exposures at the MRHD of 80 mg valbenazine. Therefore, the safety of these metabolites has been adequately assessed. Taken together these findings indicate the dog is the most clinically-relevant nonclinical species based on overall ADME profile.

General Toxicology:

Single dose toxicity studies were conducted with valbenazine in rats (oral gavage), and dogs (oral intubation and capsule). Repeat dose toxicity studies were conducted in mice (oral gavage) up to 91-days, rats (oral gavage) up to 6-months, and dogs (oral capsule) up to 9-months in duration.

Mice

24-day and 91-day repeat dose toxicology studies were conducted in CD-1 mice at doses of valbenazine ranging from 30 to 600 mg/kg/day and 10 to 300 mg/kg/day, respectively. Treatment-related mortality was observed at doses \geq 100 mg/kg/day. However, the majority of mice tolerated a dose of 300 mg/kg/day for 24 days, while in the subsequent study this dose resulted in significant mortality and group termination following a single administration. The reason for this significant difference in MTD is unknown but was not related to an exposure difference. Valbenazine treatment resulted in decreased activity and ptosis at doses \geq 30 mg/kg/day and hypothermia, hunched posture, lateral/sternal recumbency, labored/shallow breathing, ataxia, body rigidity,

rough/urine-stained hair coat, and dehydration at 300 mg/kg. The decreased activity noted at doses \geq 30 mg/kg/day likely was responsible for the decrease body weight gain observed in these mice. In addition, increased activity/aggressiveness was noted during the pre-dose period at doses \geq 100 mg/kg/day. This effect required 2 to 3 weeks of dosing to develop. A similar effect was noted in rats following repeated valbenazine administration. The only microscopic findings noted were lobular hyperplasia in the mammary glands of females at all dose levels. This finding is consistent with increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. Although prolactin levels were not measured in mice they were demonstrated to be increased in rats where similar effects on reproductive tissue were noted. Although no effects were noted in mammary tissue from male mice, only limited numbers of mammary tissue were present for evaluation, owing to the difficulty of obtaining mammary tissue from male mice. Therefore, a potential effect on male mammary tissue (e.g. feminization) cannot be ruled out under the conditions of this study. The NOAEL was judged to be 60 mg/kg/day based on mortality and decreased bodyweight gain observed at higher doses.

Rat

The rat is the most sensitive species to valbenazine treatment-related adverse effects. Two oral dose range-finding and 14-day, 91-day with a 42-day recovery, and 6-month with a 42-day recovery repeat-dose toxicology studies were conducted in rats. The toxicity profile across these studies was similar with the exception of retinal degeneration and late developing convulsions noted only in the 6-month chronic toxicology study. In the initial MTD studies, male rats were administered valbenazine by oral gavage at doses of 50 to 200 mg/kg or 60 to 150 mg/kg. In the first study no mortality was reported up to 200 mg/kg. However, in the second study multiple rats were sacrificed in moribund condition at doses \geq 100 mg/kg. In general valbenazine treatment resulted in dose-related CNS depression consistent with VMAT2 inhibition. Hunched posture, splayed front legs, ptosis, and tremors were noted at doses \geq 50 mg/kg and ataxia was noted at \geq 100 mg/kg. In addition a significant (up to 14%) decrease in body weight was noted 2 days postdose at all dose levels. All doses were judged to have exceeded an MTD based on the significant decrease in body weight and adverse clinical signs observed.

In all repeat dose studies in rats valbenazine treatment produced effects on multiple hematology and clinical chemistry parameters. In general these effects were considered non-adverse as they were relatively minimal in magnitude (e.g. ALT increased $<$ 2-fold), lacked microscopic correlates (e.g. no liver or muscle lesions) or were consistent with changes typically observed following stress (e.g. decreased white cell counts) or reduced food intake (e.g. decreased triglycerides). Therefore these findings will not be discussed further. In addition expanded histopathology was performed by a neuropathologist at (b) (4) on the brains of rats from the 14-day, 91-day and 6-month toxicology studies. No CNS lesions were noted at valbenazine doses up to 50 mg/kg/day for 14 days or 15 mg/kg for 6 months. In particular no lesions were noted in the pars compacta region of the substantia nigra or striatum.

In the 14-day toxicology study male and female rats were administered valbenazine at doses of 15, 25, or 50 mg/kg/day. Similar to the single dose studies valbenazine treatment resulted in a dose-related increase in CNS depression. However, male and female reproductive tissues were also affected. Mortality was observed at doses \geq 25 mg/kg/day and decreased activity and ptosis were noted at doses \geq 15 mg/kg. This decrease in activity was likely responsible for a significant and adverse (>44%) decrease in body weight gain noted at all dose levels. Microscopic findings consisted of lobuloalveolar hyperplasia in females at all dose levels and feminization of the mammary gland in males at doses \geq 25 mg/kg/day. In addition a minimal to slight decrease in bone marrow cellularity was noted at doses \geq 25 mg/kg/day and was likely secondary to the decreased food intake/bodyweight gain observed in these rats. A NOAEL was not achieved in this study based on the significant decrease in bodyweight gain observed at all dose levels. Therefore 15 mg/kg/day was the LOAEL.

In the 91-day toxicology study male and female rats were administered valbenazine at doses of 1, 3, 10, or 15 mg/kg/day. Similar to the findings noted in the shorter term studies valbenazine administration resulted in dose-related CNS depression, effects on body weight gain, and microscopic changes in reproductive tissues and bone marrow. Decreased activity and ptosis were noted at doses \geq 3 mg/kg/day. In addition, similar to what was observed following repeat dosing in mice, hyperactivity was noted prior to valbenazine administration following approximately 4 weeks of dosing and carried through the first week of recovery. These effects were observed when valbenazine levels would have been at trough and may be indicative of a rodent specific withdrawal phenomenon, although no specific studies to address this were conducted. Similar effects were not observed in dogs or humans. The postdose decrease in activity likely contributed to the decreased food consumption and body weight gain that were noted over the course of this study. However, these effects weren't as profound at 15 mg/kg/day in the current study as they were in the previous 14 day toxicology study. This is likely due to the fact that bodyweight gain was most significantly reduced during the first 3 weeks of dosing when the rats were generally hypoactive and prior to the onset of pre-dose hyperactivity noted later in the study. Microscopic findings consisted of lobuloalveolar hyperplasia in females at doses \geq 10 mg/kg/day and feminization of the mammary gland in males at 15 mg/kg/day. In addition a minimal decrease in bone marrow cellularity was noted at doses \geq 3 mg/kg/day in females and at 15 mg/kg/day in males and was likely secondary to the decreased food intake/bodyweight gain observed in these rats. A dose of 3 mg/kg/day was judged to be the NOAEL based on clinical signs leading to a significant reduction in food consumption and bodyweight gain observed at doses \geq 10 mg/kg/day.

In the 6-month toxicology study male and female rats were administered valbenazine at doses of 3, 10, or 15 mg/kg/day. Similar to the findings noted in the shorter term studies, valbenazine administration resulted in dose-related CNS depression, effects on body weight gain, and microscopic changes in reproductive tissues and bone marrow. However, in addition to these effects, **unique findings of** mortality and convulsions were observed at doses \geq 10 mg/kg/day, and retinal degeneration and angiectasis of

the adrenal cortex was observed at doses ≥ 3 mg/kg/day. **Unique CNS related adverse toxicities** consisting of myoclonic jerking and/or clonic convulsions were observed in males at doses ≥ 10 mg/kg/day and in females at 15 mg/kg/day. These convulsions tended to last less than 1 minute but occasionally exceeded this time. The timing of convulsions was not associated with t_{max} , but instead with handling of the rats (dosing, detailed clinical examinations, etc.), didn't develop until late in the dosing phase, and typically were associated with periods hyperactivity. However, unlike the pre-dose hyperactivity, convulsions were not observed following cessation of dosing during the recovery period. In addition extensive neuropathology examination revealed no associated CNS lesions. These findings indicate that the convulsions are the result of a chronic process that appears to be reversible. Decreased activity and ptosis as well as predose hyperactivity were also noted at doses ≥ 3 mg/kg/day. The postdose decrease in activity likely contributed to the decreased food consumption and body weight gain that were noted over the course of this study. In addition, unlike the previous 91-day study these effects were significant during the entire dosing phase in male rats. Female rats exhibited a similar trend as was observed in the previous study with greater reductions in body weight observed early during the dosing phase.

Microscopic findings unique to this study consisted of retinal degeneration and angiectasis of the adrenal cortex. Both of these lesions are known to occur spontaneously in aged rats. However, their presence in only the valbenazine treated groups together with an apparent dose responsiveness in incidence/severity, suggest it is treatment related. Prolactin is known to directly affect the retina and potentiate light damage (De Vera Mudry, 2013). Moreover, hyperactivity was noted in these rats prior to dosing each day and this hyperactivity occurred during the period when room lights were on. Therefore, it is possible that the observed retinal degeneration is a treatment-related exacerbation of a spontaneous background change due to hyperactivity and prolactin-induced increased sensitivity. However, a direct effect of valbenazine on the retina cannot be ruled out at this time. No retinal degeneration or eye related toxicities were observed in any of the other studies conducted with valbenazine, including the 6-month carcinogenicity assay in pigmented mice (study No. AD20XW.7G8R. (b) (4)) or the 9-month chronic toxicology study in beagle dogs (study No. 20028697) or in toxicology studies conducted with the FDA approved drug XENAZINE® (tetrabenazine, NDA 021894). Angiectasis of the adrenal cortex is likely an exacerbation of a spontaneous background change. Although non-age-related angiectasis can occur, it is typically secondary to other adrenal lesions such as inflammation, atrophy, degeneration, and neoplasia. In the absence of associated lesions this finding is likely a treatment-related exacerbation of a spontaneous background change. Similar to what was observed in the previous studies, valbenazine treatment-related histopathology findings were noted in male and female reproductive tissues at all dose levels. However, the number of tissues affected was expanded, now including the ovary (increased eosinophilic nondegenerate corpora lutea), uterus (decidual reaction), and vagina (mucification/atrophy) in females in addition to the mammary gland (lobular hyperplasia) of females and males. These findings are consistent with increased prolactin secretion resulting from dopamine depletion, a known pharmacological action of valbenazine acting as a VMAT2 inhibitor. Although prolactin was not measured in the current study, oral administration of valbenazine was previously demonstrated to significantly increase

serum prolactin levels in rats at a dose of 3 mg/kg/day (study No. 08-98854-002-PH). Lastly, decreased bone marrow cellularity was noted at doses \geq 3 mg/kg/day in males and females and was likely secondary to the decreased food intake/bodyweight gain observed in these rats. The MTD was exceeded in this study at the 10 mg/kg/day dose level based on excessive morbidity and convulsions in males and bodyweight effects in females. A NOAEL was not achieved in this study based on the retinal degeneration and clinical signs associated with decreased food consumption/bodyweight gain observed. Therefore, 3 mg/kg/day was judged to be the LOAEL.

Dog

One oral dose range-finding and 14-day with 1-week recovery, 91-day with a 28-day recovery, and 9-month with a 28-day recovery repeat-dose toxicology studies were conducted in dogs. In the initial MTD study, male and female dogs were administered valbenazine by oral intubation at doses of 50 and 80 mg/kg or oral capsule at a dose of 80 mg/kg. Three dogs were sacrificed due to convulsions at the 80 mg/kg dose level. In surviving dogs clinical signs consisting of ataxia, trembling, decreased activity, lethargy, recumbency, excessive salivation, and emesis were noted at all dose levels. A dose of 80 mg/kg exceeded an MTD based on the convulsions.

Expanded histopathology was performed by a neuropathologist at (b) (4) on the brains of dogs from the 14-day, 91-day and 9-month toxicology studies. No CNS lesions were noted at valbenazine doses up to 35/30 mg/kg/day for 14 days, 20 mg/kg/day for 91-days, or 15 mg/kg for 9 months. In particular no lesions were noted in the pars compacta region of the substantia nigra or striatum.

In the 14-day toxicology study male and female dogs were administered valbenazine at doses of 5, 15, or 35 mg/kg/day. Valbenazine administered at 35 mg/kg/day resulted in mortality and adverse CNS effects including seizure-like activity (jerky/uncoordinated movement, convulsions). In addition, trembling, ataxia, difficulty standing, head bobbing, weak pulse, and excessive salivation were noted at doses \geq 15 mg/kg/day. As a result the top dose was lowered to 30 mg/kg/day on dosing day 11 for the remainder of the study. These findings were generally observed in association with C_{max} , and increased in incidence and severity with increasing dose. With the exception of seizure-like activity, these findings are consistent with monoamine depletion. A dose of 5 mg/kg/day was judged to be the NOAEL based on clinical signs noted at 15 mg/kg/day and convulsion/mortality noted at 35 mg/kg/day.

In the 91-day toxicology study male and female dogs were administered valbenazine at doses of 2, 5, 12.5, or 20 mg/kg/day. No mortality was observed in this study. Similar to the findings noted in the shorter term studies valbenazine administration resulted in dose-related adverse CNS effects. Hypoactivity, tremors, and ataxia (i.e. wobbly gate) were noted at doses \geq 5 mg/kg/day. These findings were generally observed in association with C_{max} , increased in incidence and severity with increasing dose, and are consistent with monoamine depletion. The noted CNS depression likely was responsible for the decreased body weight gain observed in this study. This effect correlated with decreased food consumption during the early dosing phase as food was

only available during the 4 hour postdose period of hypoactivity. As a result food was not removed allowing the dogs more time to eat. This protocol change resulted in a more normalized body weight gain. Microscopic findings of minimal to mild thymic lymphoid depletion were noted in male and females at doses ≥ 12.5 mg/kg/day. Given the relatively minor nature of the finding based on severity score and the association of these findings with stress it is likely secondary to an adaptive stress response and not a direct action of valbenazine on the thymus. Other findings were considered incidental (minimal, multifocal mononuclear cell infiltrates, minimal, multifocal granulocytic infiltrates, minimal Kupffer cell hyperplasia, and mild chronic pericholangial inflammation in the liver or of unknown toxicological significance (perivascular inflammation in the oviducts, heart, and cervix. These findings were absent in the 9-month chronic toxicology study in dogs at comparable doses (up to 15 mg/kg/day). Therefore these changes are likely incidental and unrelated to valbenazine treatment. No effects on reproductive tissues were noted, in line with a lack of effect on prolactin levels noted in this study. A dose of 5 mg/kg/day was judged to be the NOAEL based on clinical signs (CNS depression, muscle tremors) and decreased body weight gain noted at doses ≥ 12.5 mg/kg/day.

In the 9-month toxicology study male and female dogs were administered valbenazine at doses of 3, 10, or 15 mg/kg/day. No mortality was observed in this study. Similar to the findings noted in the shorter term studies valbenazine administration resulted in dose-related adverse CNS effects. Hypoactivity, tremors, and ptosis were noted at doses ≥ 10 mg/kg/day. These findings were generally observed in association with C_{max} , increased in incidence and severity with increasing dose, and are consistent with monoamine depletion. The noted CNS depression likely was responsible for the decreased body weight gain observed in female dogs in this study. This effect correlated with decreased food consumption during the early dosing phase as food was only available during the 4 hour postdose period of hypoactivity. As a result food was made available prior to dosing allowing dogs time to eat. This protocol change resulted in a more normalized body weight gain. Microscopic findings of bilateral degenerative/inflammatory changes were noted in the kidney of one female dog at the 15 mg/kg/day dose level at terminal necropsy. Unilateral degenerative/inflammatory changes were noted in one male dog at the 10 mg/kg/day dose level at recovery necropsy. In both instances these changes consisted of multiple infarcts and interpreted as possibly idiosyncratic by the study pathologist. Although a direct effect of valbenazine treatment cannot be ruled out, given the limited incidence (though above historical control) and lack of dose-response in males they are unlikely to be related to valbenazine treatment. Moreover, in the female with bilateral renal findings, blood urea nitrogen (BUN) and creatinine levels were double concurrent control values and at the upper limits of the historical control data at baseline suggesting this female may have had marginally compromised renal function prior to valbenazine exposure. Importantly, these values did not increase with repeated valbenazine administration indicating renal function was not further compromised over the course of the study. No effects on reproductive tissues were noted. A dose of 3 mg/kg/day was judged to be the NOAEL based on clinical signs (CNS depression, muscle tremors) noted at doses ≥ 10 mg/kg/day.

Genetic Toxicology:

Valbenazine was not mutagenic in the in vitro bacterial reverse mutation test (Ames) or clastogenic in the in vitro mammalian chromosomal aberrations assay or in the in vivo rat bone marrow micronucleus assay.

Carcinogenicity:

Valbenazine did not induce any biologically significant increases in tumors in either rats or mice as assessed in carcinogenicity studies.

Tg.rash2 mice were treated with valbenazine by oral gavage at doses up to 75 mg/kg/day for 6 months, which is ~4.6 times the MRHD of 80 mg/day based on mg/m². The NOAEL for neoplastic and non-neoplastic lesions in male and female mice is 75 mg/kg/day. The AUC_(0-24hr) values for valbenazine at 75 mg/kg/day during week 26 were 19100 and 24900 ng·hr/mL in male and female mice, respectively, which are ~3- and 4 times the AUC_(0-24hr) values expected in humans at the MRHD of 80 mg/day (6150 ng·hr/mL). The AUC_(0-24hr) values for NBI-98782 were 1580 and 1460 ng·hr/mL in male and female mice, respectively, which are ~2 times the human AUC_(0-24hr) value for this moiety, expected at the MRHD of valbenazine of 80 mg/day (695 ng·hr/mL). The AUC_(0-24hr) values for NBI-136110 were 14100 and 11300 ng·hr/mL in male and female mice, respectively, which are ~6.5 times the human AUC_(0-24hr) value for this moiety, expected at the MRHD of valbenazine of 80 mg/day (1910 ng·hr/mL).

Sprague Dawley rats were treated with valbenazine by oral gavage at doses up to 2 mg/kg/day for 91 weeks, which is ~0.24 times the MRHD of 80 mg/day based on mg/m². The NOAEL for neoplastic and non-neoplastic lesions in male and female rats is 2 mg/kg/day. For female rats an increase in the incidence of benign and malignant neoplastic lesions of the mammary gland (fibroadenoma, adenoma, and carcinoma) was observed at 2 mg/kg/day. The increase was significant only for adenoma at the 0.05 level. Since these tumors are considered common the increased incidence was interpreted as non-significant. However, the doses used in this study are significantly below clinically relevant exposures (< 0.5 times based both on AUC and mg/m²) and therefore may not be relevant. Moreover, valbenazine has been shown to increase circulating prolactin level and therefore neoplastic lesions in the mammary gland may be of concern (Harvey, 2011). For male rats a statistically significant increase in the incidence of benign and malignant neoplastic lesions of the skin/subcutis was observed. The incidence of malignant fibrosarcoma was significantly increased at a dose of 0.5 mg/kg/day and the incidence of benign trichoepithelioma was significantly increased at a dose of 1 mg/kg/day. Only the incidence of malignant fibrosarcoma was significantly increased according to the FDA biostatistics Reviewer (Hepei Chen). Although the incidence of fibrosarcoma was higher than what is reported for Crl:CD(SD) rats it is not a rare tumor. This together with the lack of a dose response would suggest the finding is incidental and of no relevance to human risk. In addition when all benign and malignant tumors of the skin/subcutis were combined the Sponsor reported a significant increase at the 1 mg/kg/day dose level. This finding was primarily driven by increases in benign trichoepithelioma, benign keratoacanthoma, and malignant sebaceous cell carcinoma, three tumor types that should not be combined as they arise from different

cell types. Finally this increase was not judged as significant according to the FDA biostatistics Reviewer (Hepei Chen). Therefore this finding is considered incidental and of no relevance to human risk. Survival was higher for both male and female rats at the high dose level as compared to all other dose groups and vehicle control beginning at ~ week 60 through study termination. Increased survival reached statistical significance in male rats at the end of the study. The increased survival is likely related to lower mean body weight observed with no correlated evidence of adverse toxicity. In addition both male and female rats in the high dose group had fewer fatal pituitary tumors relative to the other treatment groups. The $AUC_{(0-24hr)}$ values for valbenazine at 2 mg/kg/day during week 26 were 369 and 825 ng·hr/mL in male and female rats, respectively, which are ~0.06 and 0.13 times the $AUC_{(0-24hr)}$ values expected in humans at the MRHD of 80 mg/day (6150 ng·hr/mL). The $AUC_{(0-24hr)}$ values for NBI-98782 were 641 and 794 ng·hr/mL in male and female rats, respectively, which are ~1 times the human $AUC_{(0-24hr)}$ value for this moiety, expected at the MRHD of valbenazine of 80 mg/day (695 ng·hr/mL). The $AUC_{(0-24hr)}$ values for NBI-136110 were 344 and 436 ng·hr/mL in male and female rats, respectively, which are ~0.2 times the human $AUC_{(0-24hr)}$ value for this moiety, expected at the MRHD of valbenazine of 80 mg/day (1910 ng·hr/mL).

Reproductive Toxicology

Reproductive toxicity studies conducted with valbenazine included a fertility and early embryonic development study in male and female rats, embryo-fetal development study in pregnant rats and rabbits and a pre- and post-natal development study in rats. In a rat fertility study, rats were treated orally with valbenazine at 1, 3, and 10 mg/kg/day prior to mating and through mating, for a minimum of 10-weeks (males) or through Day 7 of gestation (females). Valbenazine delayed mating in both sexes which led to lower number of pregnancies and disrupted estrous cyclicity at 10 mg/kg/day. However, valbenazine had no effects on sperm parameters (motility, count, density) or on uterine parameters (corpora lutea, number of implants, viable implants, pre-implantation loss, early resorptions and post-implantation loss) at any dose. These findings are consistent with increased prolactin levels which may inhibit reproductive function by impairing gonadal steroidogenesis. The NOAEL for male and female fertility was 3 mg/kg/day, which is ~0.36 times the MRHD of 80 mg/day based on mg/m². The NOEL for early embryonic development was 10 mg/kg/day, which is ~1 times the MRHD of 80 mg/day based on mg/m².

Valbenazine was not teratogenic in pregnant Sprague-Dawley rats administered oral doses of 1, 5, of 15 mg/kg/day from gestation days 6-17. Maternal toxicity evidenced by significantly lower body weight gain was noted at dose \geq 5 mg/kg/day. No valbenazine treatment-related findings were noted on maternal necropsy or cesarean section parameters. The NOAEL for maternal toxicity was 1 mg/kg/day based on decreased body weight gain observed at higher doses. The NOAEL for embryo/fetal viability, growth, and development was 15 mg/kg/day. The $AUC_{(0-24hr)}$ value for valbenazine at 15 mg/kg/day was 4230 ng·hr/mL, which is ~0.7 times the $AUC_{(0-24hr)}$ value expected in humans at the MRHD of 80 mg/day (6150 ng·hr/mL). The $AUC_{(0-24hr)}$ value for NBI-98782 was 4740 ng·hr/mL, which is ~7 times the human $AUC_{(0-24hr)}$ value for this moiety, expected at the MRHD of valbenazine of 80 mg/day (695 ng·hr/mL).

Valbenazine was not teratogenic in New Zealand White rabbits administered oral doses of 20, 50, or 100 mg/kg/day from gestation days 7-20. Maternal toxicity evidenced by significantly lower body weight was noted at dose \geq 50 mg/kg/day. Significantly reduced fetal weights were noted at 100 mg/kg/day, consistent with developmental delay. No valbenazine treatment-related findings were noted on maternal necropsy or cesarean section parameters. The NOAEL for maternal toxicity was 20 mg/kg/day based on decreased body weight observed at higher doses. The NOAEL for embryo/fetal viability, growth, and development was 50 mg/kg/day. The $AUC_{(0-24hr)}$ value for valbenazine at 50 mg/kg/day was 6030 ng·hr/mL, which is \sim 1 times the $AUC_{(0-24hr)}$ value expected in humans at the MRHD of 80 mg/day (6150 ng·hr/mL). The $AUC_{(0-24hr)}$ value for NBI-98782 was 1320 ng·hr/mL, which is \sim 2 times the human $AUC_{(0-24hr)}$ value for this moiety, expected at the MRHD of valbenazine of 80 mg/day (695 ng·hr/mL).

In the pre- and postnatal development study, pregnant Sprague-Dawley rats were administered oral doses of 1, 3 or 10 mg/kg/day valbenazine from gestation day 7 through lactation day 20. Maternal toxicity as evidenced by decreased activity, whole body tremors, hunched posture, and decrease in maternal body weight were noted at doses \geq 3 mg/kg/day. Pregnancy rate was unaffected by valbenazine, and all pregnant dams delivered litters. However, the number of dams with stillborn pups was significantly increased at doses \geq 3 mg/kg/day. In addition 8 females at the 10 mg/kg/day dose level had total litter loss during the lactation period. Moreover, although the duration of gestation was increased at the 10 mg/kg/day dose level, pup body weights on post-natal day 1 were significantly lower than control. An increase in pup body weight is expected with an increase in the duration of gestation. Taken together these findings indicate that valbenazine administration produces significant and adverse perinatal effects in the rat at doses of 3 and 10 mg/kg/day. There were no effects on sexual maturation, neurobehavioral or reproductive function in F1 pups. The NOAEL for maternal toxicity and perinatal development was 1 mg/kg/day based on stillbirths and mortality early in the lactation period. This dose is 0.1 times the MRHD based on mg/m². The NOAEL for pup growth and reproductive development was 3 mg/kg/day, the highest maternal dose level with rats selected for postweaning observations, which is \sim 0.4 times the MRHD based on mg/m².

Overall Conclusions and Recommendations

The primary target organ of toxicity across nonclinical species is the CNS. Clinical signs consistent with depletion of monoamines from the CNS (e.g. decreased activity, ataxia, trembling, and ptosis) were noted in rats, mice, and dogs. Rodents also exhibited increased activity prior to dosing when valbenazine levels are at trough and for a couple of days following cessation of dosing, suggestive of a potential withdrawal phenomenon, although no specific studies to address this were conducted. In addition, valbenazine administration was associated with tremors and convulsions in both rats and dogs. In rats, this seizure-like activity was late developing, requiring at least 2 months of dosing, was not associated with t_{max} , but instead with handling (dosing, detailed clinical examinations, etc.), and was not observed following dosing cessation. In addition, extensive neuropathology examinations were undertaken in these studies

and no CNS lesions were noted. Taken together these findings suggest that the convulsions are the result of chronic administration and that this process appears to be reversible. Similar effects in rats have been noted with tetrabenazine (XENAZINE®, NDA 021894), another VMAT2 inhibitor, indicating this effect may be common to this class of drugs. In dogs, tremors and wobbly gait were observed in subchronic and chronic studies at doses ≥ 5 mg/kg/day, which is ~ 2 times the MRHD of 80 mg based on mg/m². These effects were related to periods of significant tremor in proximal muscles (head, neck, shoulders) with no associated electroencephalogram abnormalities or neuropathology lesions. However, convulsions and death occurred following doses ≥ 35 mg/kg/day which is at least 15 times the MRHD on mg/m². Although the toxicological significance of these findings in dogs is unclear at present, because the current indication is an involuntary movement disorder affecting the tongue, lips, face, trunk, and extremities, they may be clinically meaningful.

In addition to the CNS, the reproductive system is a potential target of toxicity. In rats, valbenazine adversely affected male and female fertility, although this effect is likely due to changes in mating behavior and disruption of estrous cyclicity owing to hyperprolactinemia and not a direct toxic effect of valbenazine on reproductive organs. Valbenazine is likely to produce effects on reproductive tissues consistent with hyperprolactinemia in humans as well. Lastly, valbenazine administration increased the incidence of stillbirths and postnatal pup mortality at doses below the MRHD of 80 mg/day based on mg/m². In addition, valbenazine and the metabolites, NBI-98782 and NBI-136110, were detected in fetuses (gestation days 11 and 13), as well as in milk and in pups (lactation day 14) following administration to pregnant or lactating rats. These data indicate risk to benefit should be considered when administering valbenazine to pregnant or breastfeeding women as fetal and infant exposure are likely to occur.

The rat was consistently more sensitive to the effects valbenazine, and in general did not tolerate doses sufficient to generate exposures comparable to humans at the MRHD of 80 mg/day. This may be in part due to the extensive ester hydrolysis that occurs in rats relative to other species, including humans, and subsequent formation of NBI-98782 which has a significantly greater affinity (55 time) for VMAT2 than valbenazine. In general the ability to tolerate valbenazine administration was more closely aligned with exposure to NBI-98782, and therefore, this metabolite, in addition to valbenazine is shown in the table below. Furthermore, because of the increased sensitivity of the rat coupled with the finding of retinal degeneration in the 6-month general toxicology study, which is unlikely to be clinically relevant, the dog and mouse are considered the more relevant species to establish appropriate safety margins. Lastly, the majority of the toxicities associated with valbenazine administration that occurred at doses with safety margins less than 10 times are associated with CNS depression which are not of significant toxicological concern.

Table 64 Safety Margins Based on Systemic Exposure for Valbenazine and NBI-98782 at the Reviewer Determined NOAEL in the Pivotal Studies

Study	Safety Margin mg/m ²	Valbenazine		NBI-98782		Safety Margin	
		C _{max} (ng/mL)	AUC (ng•hr/mL)	C _{max} (ng/mL)	AUC (ng•hr/mL)	AUC Valbenazine	AUC NBI-98782
Human 80 mg/d	----	916	6150	39.4	695	----	----
Mouse 3-month NOAEL 60 mg/kg/d	~4	6120	25300	212	1630	~4	~2
Rat 6-month LOAEL 3 mg/kg/d	<1	392	1300	118	1020	<1	~1.5
Dog 9-month NOAEL 3 mg/kg/d	~1	1725	8825	41	407	~1	<1
Rat Seg I^a NOAEL (fertility) 3 mg/kg/day NOEL (early embryonic development) 10 mg/kg/d	<1 ~1	131 606	539 2250	83 327	775 3020	<1 <1	~1 ~4
Rat Seg II NOAEL 15 mg/kg/d	~2	480	4230	362	4740	<1	~7
Rabbit Seg II NOAEL 50 mg/kg/d	~12	1530	6030	174	1320	~1	~2
Rat Seg III^b NOAEL (perinatal devel) 1 mg/kg/d NOEL (neurobehav, reprodevel) 3 mg/kg/d	<1	21	133	26	274	<1	<1

a TK was not performed in this study. Exposures taken from 3-month rat general tox study

b TK was not performed in this study. Exposures taken from rat Seg. II study at 1 mg/kg/day

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12 Appendix/Attachments

A – References

1. De Vera Mudry MC, et al, 2013. Blinded by the Light: Retinal Phototoxicity in the Context of Safety Studies. *Toxicol. Pathology*. 41:813-825.
2. Fitzgerald P, Dinan TG, 2008. Prolactin and Dopamine: What is the Connection? A Review Article. *J. Psychopharmacology*. 22: 12-19.
3. Harvey PW, 2011. Hypothesis: Prolactin is Tumorigenic to Human Breast: Dispelling the Myth that Prolactin-Induced Mammary Tumors are Rodent-Specific. *Appl. Toxicol.* 32:1-9.

APPEARS THIS WAY ON ORIGINAL

B – Exec CAC Meeting Minutes

Executive CAC Final Study Minutes

Date of Meeting: February 14, 2017

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Abigail Jacobs, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Jane Sohn, PhD, DNNDP, Alternate Member
Aisar Atrakchi, PhD, DPP, Pharm Tox Supervisor
Darren Fegley, PhD, DPP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA 209241

Drug Name: Valbenazine (NBI-98854; INGREZZA®)

Sponsor: Neurocrine Biosciences Inc.

Background:

NDA 209241 was submitted on August 11, 2016 to pursue marketing approval of valbenazine for the treatment of tardive dyskinesia. Final study reports for a 6-month transgenic mouse and a 2-year rat carcinogenicity study were submitted with the NDA.

Mouse Carcinogenicity Study

Tg.rasH2 mice (25/sex/group) were administered valbenazine ditosylate daily by oral gavage in a vehicle of 0.25% (w/v) methylcellulose in reverse osmosis deionized water for 26 consecutive weeks. Doses of 10, 30, and 75 mg/kg/day (free base equivalent dose of administered di-tosylate salt) were used for males and females. A positive control group (urethane, 1000 mg/kg on days 1, 3, and 5 by IP injection) demonstrated sensitivity of the test system. There were no statistically significant drug-related neoplastic findings in either males or females.

Rat Carcinogenicity Study

Sprague Dawley rats (60/sex/group) were administered valbenazine ditosylate daily by oral gavage in a vehicle of 0.25% (w/v) methylcellulose in reverse osmosis deionized water for 91 consecutive weeks. Doses of 0.5, 1, and 2 mg/kg/day (free base equivalent dose of administered di-tosylate salt) were used for males and females. All male dose groups were terminated during week 91 when only 20 male rats remained in the control group. Females at the 0.5 mg/kg/day dose level were terminated early during week 91 when only 15 rats remained. All remaining female dose groups were terminated later during week 91 when only 20 rats remained in the control group. The sponsor received agreement from the division and the ECAC prior to

termination for these groups. There was a statistically significant increase in survival rates for high dose males (2 mg/kg/day) compared to controls. There were no statistically significant drug-related neoplastic findings in either males or females.

Executive CAC Conclusions:

Tg.rasH2 Mouse:

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 6-month Tg.rasH2 mouse study.

Rat:

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the rat carcinogenicity study.

Karen Davis Bruno, Ph.D.

Chair, Executive CAC

C – Carcinogenicity Studies Statistical Review and Assessment

U.S. Department of Health and Human Services
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Translational Science
 Office of Biostatistics

Statistical Review and Evaluation**CARCINOGENICITY STUDIES**

IND/NDA Number: NDA-209241
 Drug Name: NBI-98854 (b) (4)
 Indication: Treatment of Tardive Dyskinesia
 Studies: 104 Week Carcinogenicity Studies in Rats and 26 Weeks in Mice
 Applicant: Sponsor:
 Neurocrine Biosciences
 12780 El Camino Real
 San Diego, California 92130
 United States of America
 Testing Facility for Rats: (b) (4)
 Testing Facility for Mice: (b) (4)
 Documents Reviewed: Electronic submission: Submitted on December 15, 2016
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 Statistical Reviewer: Hepei Chen
 Concurring Reviewer: Karl Lin, Ph.D.
 Medical Division: Division of Psychiatry Products
 Reviewing Pharmacologist: Darren Fegley, Ph.D.
 Keywords: Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to evaluate the carcinogenic potential and determine the toxicokinetics of the test article, NBI-98854, when administered daily via oral gavage to rats for the intended duration of 104 weeks, and to mice for 26 weeks.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups and one vehicle control group. Two hundred forty Crl:CD(SD) rats of each sex were assigned randomly to the treated and control groups in equal size of 60 rats per group. The dose levels for treated groups were 0.5, 1, and 2 mg/kg/day for both male and female rats. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The rats in the vehicle control group were administered with the vehicle [0.25% (w/v) methylcellulose (4000 cPs) in reverse osmosis water], and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	60	60	Vehicle control	0	0
2	60	60	NBI-98854 low	0.5	0.5
3	60	60	NBI-98854 mid	1	1
4	60	60	NBI-98854 high	2	2

Toxicokinetic and carcinogenicity animals were checked twice daily (a.m. and p.m.) for mortality, abnormalities, and signs of pain or distress. Detailed observations were conducted for carcinogenicity animals once during the predose phase, prior to dosing on Day 1, and weekly (based on Day 1) throughout the dosing phase. Detailed observations were also collected on days of scheduled sacrifice (animals scheduled for sacrifice only). Scheduled study termination was planned for Week 104 of the dosing phase. Three early scheduled terminations occurred based on survival.

- Due to Group 1 males having reached 20 surviving animals on Day 633 of the dosing phase, all surviving males were sacrificed.
- Due to Group 2 females having reached 15 surviving animals on Day 636 of the dosing phase, all surviving females in Group 2 were sacrificed.
- Due to Group 1 females having reached 20 surviving animals on Day 641 of the dosing phase, all surviving females in Groups 1, 3, and 4 were sacrificed.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor performed the tests to compare survival with a two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response and for each treated group against vehicle control using Kaplan-Meier product-limit estimation curves, along with log-rank and Wilcoxon tests, using the LIFETEST procedure in SAS. The time to death or sacrifice (in weeks) was the dependent variable. Treatment group was included as the strata. Animals with a death or sacrifice status recorded as a planned sacrifice (interim or terminal) or an accidental death were censored in the analysis.

Sponsor's findings:

The sponsor's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (33.33%), 22 (36.67%), 23 (38.33%), and 33 (55.00%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 20 (33.33%), 15 (25.00%), 18 (30.00%), and 27 (45.00%) for female rats respectively. The sponsor reported that for males, the high dose group (2 mg/kg/day) had lower mortality than the vehicle control group (27/60 versus 40/60 in the vehicle control group), with $p=0.0216$ and $p=0.0395$ for the Log-Rank and Wilcoxon tests respectively. The dose response was also significant, with $p=0.0195$ and $p=0.0394$ for the Log-Rank and Wilcoxon tests respectively. For females, no significant findings were noted in the sponsor's report.

2.1.2. Tumor data analysis

The sponsor analyzed those tumors from tissues that were listed in the protocol to be examined. For each given tumor type, statistical analysis was performed if the incidence at least one treated group was increased by at least two occurrences over the vehicle control group. Tests to compare tumor incidence were performed with a one-sided risk for increasing incidence with dose. Tests were performed for dose response and for each treated group against vehicle control.

For tumors occurring in animals dying spontaneously or sacrificed in extremis during the study, the pathologist classified the context of observation as one of the following:

- (1) Fatal: the tumor was a factor in the demise of the animal.
- (2) Non-fatal: the tumor was not a factor in the demise of the animal.
- (3) Uncertain

Occult or non-palpable tumors were analyzed by the IARC asymptotic fixed interval based prevalence test (Peto et al., 1980). The cut off points for the interval based test were Weeks 0 to 52, 53 to 78, 79 to before terminal sacrifice, and the terminal sacrifice. Fatal and non-fatal tumors were analyzed together, with separate strata for each. There were no tumors of uncertain context. The test was implemented using PROC MULTTEST in the SAS system. In the case of sparse tables (<10 total in the strata), the exact form of the test was used for that strata. Otherwise, the asymptotic version of the test was used. Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded in the data, and were not assigned based on their week of necropsy.

Observable or palpable (superficial as in mammary or skin) tumors were analyzed using the methods previously described for analyzing survival, using the time to death or time of detection of the tumor (in weeks) as a surrogate for the tumor onset time. Comparisons between vehicle and treated groups were performed with a one-sided risk for increasing incidence with dose.

Unadjusted P-values were reported for tumors. Where applicable, site or tumor combinations were statistically analyzed if the incidence in at least one treated group was increased by at least two occurrences compared to the vehicle control group. The criteria for combination were based on the work of McConnell et al. (McConnell et al., 1986) and as indicated by the study pathologist. Incidences of multiple-organ and combined neoplastic findings, such as hemangioma, fibrosarcoma, and endometrial stromal polyp were counted by animal, not by tissue type. Due to individual values being rounded for inclusion in the report, calculation of summary statistics from these reported values may, in some cases, yield minor differences.

Adjustment for multiple testing:

Indication of a possible treatment effect was assessed on the basis of rare or common tumor type, in line with the current FDA guidelines (FDA Draft Guidance for Industry, 2001).

Sponsor's findings:

For male rats, the sponsor reported statistically significant increases for the incidence of malignant fibrosarcoma in skin/subcutis at the low dose group when compared to the vehicle control group (p-value=0.0143 and 0.0156 for Log-rank test and Wilcoxon test, respectively), for the incidence of benign trichoepithelioma in skin/subcutis at the mid dose group when compared to the vehicle control group (p-value=0.0227 and 0.0265 for Log-rank test and Wilcoxon test, respectively), and for the incidence of combined tumor including benign adenoma sebaceous, basal cell tumor, keratoacanthoma, papilloma squamous cell, trichoepithelioma, and malignant carcinoma sebaceous and carcinoma squamous cell in skin/subcutis at the mid dose group when compared to the vehicle control group (p-value=0.0290 and 0.0457 for Log-rank test and Wilcoxon test, respectively).

No other statistically significant tumor findings were noted in both male and female rats.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of rats in all four groups (Groups 1, 2, 3, and 4) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 1, 2, 3, and 4 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all four groups in male and female rats, respectively. The intercurrent mortality data of all four groups, and the results of the tests for dose response relationship and homogeneity of survivals for Groups 1, 2, 3, and 4 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (33.33%), 22 (36.67%), 23 (38.33%), and 33 (55.00%) in Groups 1, 2, 3, and 4 for male

rats, respectively, and 20 (33.33%), 15 (25.00%), 18 (30.00%), and 27 (45.00%) for female rats respectively. A statistically significant positive dose-response relationship in mortality was noted in male rats (p -value=0.0190), along with a statistically significant increase in the high dose group when compared to the vehicle control group (p -value=0.0227 and 0.0216 for the dose-response test and the log-rank test, respectively). No statistically significant findings in mortality were noted in female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across Groups 1, 2, 3, and 4, and pairwise comparisons of each of the three treated groups (Groups 2, 3, and 4) against the vehicle control group (Group 1), using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the poly-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the i -th treatment group R^*_i is defined as $R^*_i = \sum w_{ij}$ where w_{ij} is the weight for the j -th animal in the i -th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$$w_{ij} = 1 \text{ to animals dying with the tumor, and}$$
$$w_{ij} = (t_{ij} / t_{sacr})^k \text{ to animals dying without the tumor,}$$

where t_{ij} is the time of death of the j -th animal in the i -th treatment group, and t_{sacr} is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned $w_{ij} = 1$ since $t_{ij} = t_{sacr}$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the t_{sacr} should not be affected by the unplanned early terminations. The t_{sacr} should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than t_{sacr} , regardless their actual terminal sacrifice time, t_{sacr} was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k , which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of $k=3$ is suggested in the literature. Hence, this reviewer used $k=3$ for the analysis of this data.

Multiple testing adjustment:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). For dose response relationship tests, the guidance suggests the use of test levels of $\alpha=0.01$ for common

tumors and $\alpha=0.05$ for rare tumors for a submission with one two-year study in one species and one short-term study with another species, in order to keep the overall false-positive rate at the nominal level of approximately 10%. For multiple pairwise comparisons of treated group with control group, however, the guidance indicated that the corresponding multiple testing adjustment is still under development and not yet available. To be conservative, the test level of $\alpha=0.05$ was used for pairwise comparisons of treated group with control group for both rare and common tumors in this study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-k tests.

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. However, if the background information for the common or rare tumor is not available, the number of animals bearing tumors in the vehicle control group in the present study was used to determine the common or rare tumor status in the review report. That is, if the number of animals bearing tumors in the vehicle control group is 0, then this tumor is considered as the rare tumor, otherwise, if the number of animals bearing tumors in the control group is greater than or equal to 1, then this tumor is considered as the common tumor.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 2.

Table 2. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Rats

Organ name	Tumor name	0 mg	5 mg	10 mg	20 mg
		Vehicle (C) P - Trend	Low (L) P - L vs. C	Mid (M) P - M vs. C	High (H) P - H vs. C
Male-Skin/Subcutis	M-Fibrosarcoma	0/58 (26) 0.5269	5/59 (31) 0.0406 §	0/59 (27) NC	2/59 (32) 0.3001
Female Mammary Gland	B-Adenoma	1/59 (28) 0.0394 @	0/59 (27) 0.4909	0/60 (25) 0.4717	4/60 (34) 0.2437

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

§ = Statistically significant at 0.05 level in rare tumor for test of pairwise comparisons;

@ = Not statistically significant at 0.01 level in common tumor for test of dose response relationship;

NC = Not calculable.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that a statistically significant increase ($p = 0.0406$) for the incidence rates of malignant fibrosarcoma of skin/subcutis in the low dose group when comparing to the vehicle control group in male rats, if this tumor was considered to be rare. A p-value of 0.0394 was noted for the dose response relationship of the benign adenoma in mammary gland for female rats. However, this trend was not statistically significant as this tumor was considered to be common. No other

statistically significant findings were noted for male and female rats.

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3, in each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and ten hemizygous Tg.rasH2 mice of each sex were assigned randomly in size of 25 mice per group to the treated and vehicle control groups, and 10 mice to the positive control group. The dose levels for treated groups were 10, 30, and 75 mg/kg/day for both male and female mice. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The mice in the vehicle control and the positive control group were administered with the vehicle control [0.25% methylcellulose (4000 cps) in de-ionized (DI) water] and the positive control [Urethane in 0.9% NaCl (saline)], respectively, and handled for the same duration and in the same manner as the treated groups.

Table 3. Experimental Design in Mouse Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	25	25	Vehicle control	0	0
2	25	25	NBI-98854 low	10	10
3	25	25	NBI-98854 mid	30	30
4	25	25	NBI-98854 high	75	75
5	10	10	Positive control	0	0

All animals were observed twice daily at least 6 hours apart for moribundity and mortality, except as noted (see Deviations). For the Main Cohort only, cage side observations were performed daily within 2 hours after the last animal was dosed in each group. For the Main Cohort animals, detailed hands-on observations were performed on Day 1 and weekly thereafter (at the time animals were weighed). Any Main Cohort animals found dead were necropsied as soon as possible after discovery, usually within 8 hours. Moribund animals were sacrificed by CO₂ overdose and carcasses were refrigerated until necropsied, when needed. In the Main Cohort (Groups 1-4), surviving animals were sacrificed by CO₂ overdose on Day 183 or Day 184 and necropsied. Prior to sacrifice, animals were weighed to the nearest 0.1 gram. All surviving animals in the positive control (Group 5) were sacrificed by CO₂ overdose on Day 64. A complete necropsy was performed for all Main Cohort animals (Groups 1-4); in addition, animals found dead or moribund sacrificed were also evaluated for evidence of gavage error.

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor calculated the Kaplan-Meier estimates of group survival rates by sex and showed in graph. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the vehicle control and test article groups, by sex, at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pairwise comparisons of each test article group with the vehicle control group. Additionally, the positive control group was compared to the vehicle control group using the

generalized Wilcoxon test. Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 25 (100%), 23 (92%), and 24 (96%) in Groups 1, 2, 3, and 4 for male, respectively, and 25 (100%), 25 (100%), 25 (100%), and 23 (92%) for female, respectively. The sponsor reported no statistically significant findings in survival rates for male and female mice.

3.1.2. Tumor data analysis

For the vehicle and treated groups, the sponsor used Peto's mortality-prevalence method to analyze the incidence of tumors, incorporating the context (incidental, fatal, or mortality independent) in which tumors were observed without continuity correction. The following fixed intervals were used for incidental tumor analyses: Days 1 through 130, and Days 131 through and including terminal sacrifice. A minimum exposure of 130 days was considered sufficient to be included with animals surviving through scheduled termination. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis. Tumors classified as mortality-independent were analyzed with Peto's mortality independent method incorporating the day of detection. A 1-sided comparison of each test article group with the vehicle control was performed. An exact permutation test was conducted for all analyses. Findings were evaluated for statistical significance at both the 0.01 and 0.05 levels and all p values were reported.

Each diagnosed tumor type was analyzed separately and, at the discretion of the study director, analysis of combined tumor types and/or organs was performed. All metastases and invasive tumors were considered secondary and not statistically analyzed.

For the vehicle and positive control groups, because the positive control group was scheduled for early terminal sacrifice, tumor incidence in the positive control group was compared to the vehicle control group with a 1-sided Fisher's exact test at both the 0.01 and 0.05 significance levels and all p values were reported. Only the following tumors were statistically analyzed: alveolarbronchiolar adenoma, alveolar-bronchiolar carcinoma, and hemangiosarcoma in the spleen.

Sponsor's findings:

The sponsor's analysis showed that for both male and female mice, there were no statistically significant tumor findings in the treated groups when compared to the vehicle control group; while statistically significant increases in the incidence of alveolar-bronchiolar adenoma in lungs with bronchi and hemangiosarcoma in spleen were noted when comparing the positive control with the vehicle control group for both male and female rats.

3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor's analyses. Data used in this reviewer's analyses were provided by the

sponsor electronically.

For the analysis of both the survival data and the tumor data, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data, and the results of the tests for dose response relationship and homogeneity of survivals for the combined vehicle control, low, mid, and high dose groups were given in Tables 3A and 3B in the appendix for male and female mice, respectively.

Reviewer's findings:

In the reviewer's analysis, the numbers of mice surviving to their terminal necropsy were 25 (100%), 25 (100%), 23 (92%), and 24 (96%) in Groups 1, 2, 3, and 4 for male, respectively, and 25 (100%), 25 (100%), 25 (100%), and 23 (92%) for female, respectively. A statistically significant positive dose-response relationship in mortality was noted in female mice (p -value=0.0179), without any statistically significant pairwise comparisons between the vehicle control groups and the treated groups. No statistically significant findings in mortality were noted in male mice.

3.2.2. Tumor data analysis

The tumor rates and the p -values of the tested tumor types are given in Tables 4A and Table 4B in the appendix, for male and female mice, respectively.

Reviewer's findings:

The reviewer's analysis showed no statistically significant dose response relationship or pairwise comparisons in the treated groups when compared to the vehicle control group for both male and female mice. When comparing the positive control with the vehicle control group, statistically significant increases in the incidence of alveolar-bronchiolar adenoma in lungs with bronchi and hemangiosarcoma in spleen were noted for both male and female rats (all p -values < 0.0001).

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to evaluate the carcinogenic potential and determine the toxicokinetics of the test article, NBI-98854, when administered daily via oral gavage to rats for the intended duration of 104 weeks, and to mice for 26 weeks.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred forty CrI:CD(SD) rats of each sex were assigned randomly to the treated and control

groups in equal size of 60 rats per group. The dose levels for treated groups were 0.5, 1, and 2 mg/kg/day for both male and female rats.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 20 (33.33%), 22 (36.67%), 23 (38.33%), and 33 (55.00%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 20 (33.33%), 15 (25.00%), 18 (30.00%), and 27 (45.00%) for female rats respectively. A statistically significant positive dose-response relationship in mortality was noted in male rats (p -value=0.0190), along with a statistically significant increase in the high dose group when compared to the vehicle control group (p -value=0.0227 and 0.0216 for the dose-response test and the log-rank test, respectively). No statistically significant findings in mortality were noted in female rats.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that a statistically significant increase ($p = 0.0406$) for the incidence rates of malignant fibrosarcoma of skin/subcutis in the low dose group when comparing to the vehicle control group in male rats, if this tumor was considered to be rare. A p -value of 0.0394 was noted for the dose response relationship of the benign adenoma in mammary gland for female rats. However, this trend was not statistically significant as this tumor was considered to be common. No other statistically significant findings were noted for male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and ten hemizygous Tg.rasH2 mice of each sex were assigned randomly in size of 25 mice per group to the treated and vehicle control groups, and 10 mice to the positive control group. The dose levels for treated groups were 10, 30, and 75 mg/kg/day for both male and female mice.

In the reviewer's analysis, the numbers of mice surviving to their terminal necropsy were 25 (100%), 25 (100%), 23 (92%), and 24 (96%) in Groups 1, 2, 3, and 4 for male, respectively, and 25 (100%), 25 (100%), 25 (100%), and 23 (92%) for female, respectively. A statistically significant positive dose-response relationship in mortality was noted in female mice (p -value=0.0179), without any statistically significant pairwise comparisons between the vehicle control groups and the treated groups. No statistically significant findings in mortality were noted in male mice.

The reviewer's analysis showed no statistically significant dose response relationship or pairwise comparisons in the treated groups when compared to the vehicle control group for both male and female mice. When comparing the positive control with the vehicle control group, statistically significant increases in the incidence of alveolar-bronchiolar adenoma in lungs with bronchi and hemangiosarcoma in spleen were noted for both male and female rats (all p -values < 0.0001).

Hepei Chen.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, DBVI

Cc: Archival NDA 209241

Dr. Darren Fegley
Dr. Lillian Patrician

5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

Week / Type of Death	Vehicle Control		Low		Mid		High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	4	6.67	6	10.00	5	8.33	6	10.00
53 - 78	22	43.33	18	40.00	19	40.00	11	28.33
79 - 91	14	66.67	14	63.33	13	61.67	10	45.00
Terminal sacrifice	20	33.33	22	36.67	23	38.33	33	55.00
Total	60		60		60		60	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.0190*		0.6731		0.6586		0.0227*	
Homogeneity (Log-Rank)	0.1132		0.6702		0.6556		0.0216*	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level;

Table 1B: Intercurrent Mortality Rate in Female Rats

Week / Type of Death	Vehicle Control		Low		Mid		High	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	5	8.33	3	5.00	7	11.67	4	6.67
53 - 78	22	45.00	23	43.33	23	50.00	12	26.67
79 - 91	13	66.67	19	75.00	12	70.00	15	51.67
92 - 104							2	3.33
Terminal sacrifice	20	33.33	15	25.00	18	30.00	27	45.00
Total	60		60		60		60	
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High	
Dose-Response (Likelihood Ratio)	0.0534		0.4849		0.3846		0.0958	
Homogeneity (Log-Rank)	0.0480*		0.4770		0.3776		0.0909	

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level;

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	20 mg High (H) P - H vs. C
Adrenal, Cortex	B-Adenoma	1/60 (28) 0.7560	1/60 (28) NC	1/60 (28) NC	0/60 (31) 0.5254
	M-Carcinoma	0/60 (27) 0.2719	0/60 (28) NC	0/60 (28) NC	1/60 (31) 0.5345
	B-Adenoma/M-Carcinoma	1/60 (28) 0.4537	1/60 (28) NC	1/60 (28) NC	1/60 (31) 0.2718
	B-Hemangioma	0/60 (27) 0.2719	0/60 (28) NC	0/60 (28) NC	1/60 (31) 0.5345
Adrenal, Medulla	B-Pheochromocytoma	4/60 (29) 0.8509	6/60 (31) 0.4102	5/60 (29) 0.5000	2/60 (32) 0.7108
	M-Malignant Pheochromocytoma	0/60 (27) 0.6277	2/60 (29) 0.2636	1/60 (28) 0.5091	0/60 (31) NC
	B-Pheochromocytoma/ M-Malignant Pheochromocytoma	4/60 (29) 0.8875	8/60 (31) 0.2013	6/60 (30) 0.3878	2/60 (32) 0.7108
Brain	B-Granular Cell Tumor	0/60 (27) 0.2719	0/60 (28) NC	0/60 (28) NC	1/60 (31) 0.5345
	M-Glioma	0/60 (27) 0.5259	1/60 (29) 0.5179	1/60 (28) 0.5091	0/60 (31) NC
Epididymis	M-Malignant Mesothelioma	0/60 (27) 0.2719	0/60 (28) NC	0/60 (28) NC	1/60 (31) 0.5345
Femur	M-Osteosarcoma	0/60 (27) 0.5175	0/60 (28) NC	1/60 (28) 0.5091	0/59 (31) NC
Heart	M-Endocardial Schwannoma	0/60 (27) 0.2719	0/60 (28) NC	0/60 (28) NC	1/60 (31) 0.5345
Hemolympho- Reticular System	M-Histiocytic Sarcoma	1/60 (28) 0.4291	2/60 (29) 0.5134	1/60 (28) NC	2/60 (32) 0.5508
	M-Malignant Lymphoma	1/60 (28) 0.4865	1/60 (29) 0.2544	0/60 (28) 0.5000	1/60 (32) 0.2802

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	20 mg High (H) P - H vs. C
Kidney	B-Adenoma, Tubule Cell, Amp*	1/60 (28) 0.6265	3/60 (30) 0.3325	1/60 (28) NC	1/60 (31) 0.2718
	B-Adenoma, Tubule Cell, Amp*/ M-Carcinoma, Tubule C	1/60 (28) 0.6265	3/60 (30) 0.3325	1/60 (28) NC	1/60 (31) 0.2718
	B-Lipoma	0/60 (27) 0.5175	1/60 (28) 0.5091	0/60 (28) NC	0/60 (31) NC
	M-Carcinoma, Tubule Cell	0/60 (27) 0.5130	1/60 (29) 0.5179	0/60 (28) NC	0/60 (31) NC
	M-Carcinoma, Tubule Cell, A*	0/60 (27) 0.3405	1/60 (29) 0.5179	0/60 (28) NC	1/60 (31) 0.5345
	M-Carcinoma, Tubule Cell/ M-Carcinoma, Tubule Cell, A*	0/60 (27) 0.4850	2/60 (29) 0.2636	0/60 (28) NC	1/60 (31) 0.5345
	M-Liposarcoma	0/60 (27) 0.2719	0/60 (28) NC	0/60 (28) NC	1/60 (31) 0.5345
	Liver	M-Carcinoma, Hepatocellular	2/60 (28) 0.9423	0/60 (28) 0.7545	0/60 (28) 0.7545
Lung	M-Squamous Cell Carcinoma	0/60 (27) 0.2783	0/59 (28) NC	0/60 (28) NC	1/60 (32) 0.5424
Lymph Node, Mesenteric	B-Hemangioma	0/60 (27) 0.4850	2/60 (29) 0.2636	0/60 (28) NC	1/60 (31) 0.5345
Mammary Gland	B-Fibroadenoma	1/57 (26) 0.6487	0/59 (27) 0.5094	1/59 (28) 0.2642	0/57 (29) 0.5273
	M-Carcinoma	3/57 (27) 0.9169	0/59 (27) 0.8821	2/59 (29) 0.5347	0/57 (29) 0.8945
Nerve, Sciatic	B-Schwannoma	0/60 (27) 0.5175	0/60 (28) NC	1/60 (28) 0.5091	0/60 (31) NC
Pancreas	B-Adenoma, Acinar Cell	1/60 (28) 0.5815	0/60 (28) 0.5000	3/60 (29) 0.3191	0/60 (31) 0.5254
	B-Adenoma, Islet Cell	0/60 (27) 0.1642	1/60 (28) 0.5091	2/60 (28) 0.2545	2/60 (32) 0.2899
	M-Carcinoma, Islet Cell	1/60 (28) 0.7565	0/60 (28) 0.5000	0/60 (28) 0.5000	0/60 (31) 0.5254
	B-Adenoma, Islet Cell/ M-Carcinoma, Islet Cell	1/60 (28) 0.3321	1/60 (28) NC	2/60 (28) 0.5000	2/60 (32) 0.5508

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	20 mg High (H) P - H vs. C
Parathyroid	B-Adenoma	0/58 (26) 0.3415	1/57 (27) 0.5094	0/60 (28) NC	1/57 (30) 0.5357
Pituitary	B-Adenoma	35/60 (47) 0.9957	36/60 (46) 0.4265	27/60 (41) 0.7421	21/60 (41) 0.9795
	M-Carcinoma	0/60 (27) 0.5175	0/60 (28) NC	1/60 (28) 0.5091	0/60 (31) NC
	B-Adenoma/M-Carcinoma	35/60 (47) 0.9953	36/60 (46) 0.4265	28/60 (41) 0.6573	21/60 (41) 0.9795
	M-Malignant Schwannoma	0/60 (27) 0.5175	0/60 (28) NC	1/60 (28) 0.5091	0/60 (31) NC
Seminal Vesicle	M-Fibrosarcoma	0/60 (27) 0.2719	0/60 (28) NC	0/60 (28) NC	1/60 (31) 0.5345

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

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**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg	5 mg	10 mg	20 mg
		Vehicle (C) P - Trend	Low (L) P - L vs. C	Mid (M) P - M vs. C	High (H) P - H vs. C
Skin/Subcutis	B-Adenoma, Sebaceous	0/58 (26) 0.6506	2/59 (28) 0.2642	0/59 (27) NC	0/59 (30) NC
	M-Carcinoma, Sebaceous	0/58 (26) 0.5312	0/59 (27) NC	2/59 (28) 0.2642	0/59 (30) NC
	B-Adenoma, Sebaceous/ M-Carcinoma, Sebaceous	0/58 (26) 0.5885	2/59 (28) 0.2642	2/59 (28) 0.2642	0/59 (30) NC
	B-Basal Cell Tumor	0/58 (26) 0.5265	1/59 (28) 0.5185	1/59 (28) 0.5185	0/59 (30) NC
	B-Fibroma	2/58 (27) 0.8929	1/59 (28) 0.5139	1/59 (27) 0.5000	0/59 (30) 0.7801
	M-Fibrosarcoma	0/58 (26) 0.5269	5/59 (31) 0.0406 \$	0/59 (27) NC	2/59 (32) 0.3001
	B-Fibroma/M-Fibrosarcoma	2/58 (27) 0.7612	6/59 (32) 0.1892	1/59 (27) 0.5000	2/59 (32) 0.3733
	B-Hemangiopericytoma	0/58 (26) 0.5135	1/59 (28) 0.5185	0/59 (27) NC	0/59 (30) NC
	B-Keratoacanthoma	1/58 (27) 0.5828	0/59 (27) 0.5000	3/59 (28) 0.3194	0/59 (30) 0.5263
	B-Papilloma, Squamous Cell	1/58 (27) 0.8219	1/59 (28) 0.2545	0/59 (27) 0.5000	0/59 (30) 0.5263
	M-Carcinoma, Squamous Cell	1/58 (27) 0.5352	0/59 (27) 0.5000	0/59 (27) 0.5000	1/59 (31) 0.2813
	B-Keratoacanthoma/ M-Carcinoma, Squamous Cell/ B-Papilloma, Squamous Cell	3/58 (27) 0.7681	1/59 (28) 0.7084	3/59 (28) 0.3524	1/59 (31) 0.7449
	B-Lipoma	2/58 (27) 0.9425	0/59 (27) 0.7547	0/59 (27) 0.7547	0/59 (30) 0.7801
	B-Neural Crest Tumor	1/58 (27) 0.7568	0/59 (27) 0.5000	0/59 (27) 0.5000	0/59 (30) 0.5263
	B-Trichoepithelioma	0/58 (26) 0.4450	1/59 (28) 0.5185	4/59 (29) 0.0696	0/59 (30) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

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**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	20 mg High (H) P - H vs. C
Testis	B-Hemangioma	1/60 (28) 0.6455	0/60 (28) 0.5000	1/60 (28) NC	0/60 (31) 0.5254
	B-Interstitial Cell Tumor	2/60 (28) 0.9160	2/60 (29) 0.3191	1/60 (28) 0.5000	0/60 (31) 0.7791
	M-Malignant Mesothelioma	0/60 (27) 0.2719	0/60 (28) NC	0/60 (28) NC	1/60 (31) 0.5345
Thymus	B-Thymoma	1/58 (27) 0.7611	0/60 (28) 0.5091	0/59 (27) 0.5000	0/60 (31) 0.5345
Thyroid	B-Adenoma, C-Cell	8/60 (31) 0.9588	7/59 (31) 0.5000	5/60 (30) 0.7109	3/60 (32) 0.9178
	M-Carcinoma, C-Cell	1/60 (28) 0.7089	1/59 (28) NC	2/60 (28) 0.5000	0/60 (31) 0.5254
	B-Adenoma, C-Cell/ M-Carcinoma, C-Cell	9/60 (31) 0.9691	7/59 (31) 0.6138	7/60 (31) 0.6138	3/60 (32) 0.9532
	B-Adenoma, Follicular Cell	4/60 (30) 0.9013	1/59 (28) 0.8014	6/60 (30) 0.3653	0/60 (31) 0.9475
	M-Carcinoma, Follicular Cell	1/60 (28) 0.5259	0/59 (28) 0.5000	0/60 (28) 0.5000	1/60 (31) 0.2718
	B-Adenoma, Follicular Cell/ M-Carcinoma, Follicular Cell	5/60 (30) 0.8651	1/59 (28) 0.8867	6/60 (30) 0.5000	1/60 (31) 0.9097
Zymbal Gland	M-Carcinoma	0/60 (27) 0.5175	0/60 (28) NC	1/60 (28) 0.5091	0/60 (31) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

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Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	20 mg High (H) P - H vs. C
Adrenal, Cortex	B-Adenoma	1/60 (28) 0.2521	0/60 (27) 0.4909	1/60 (25) 0.7257	2/60 (33) 0.5624
	M-Carcinoma	0/60 (28) 0.5089	0/60 (27) NC	1/60 (25) 0.4717	0/60 (32) NC
	B-Adenoma/M-Carcinoma	1/60 (28) 0.2545	0/60 (27) 0.4909	2/60 (25) 0.4568	2/60 (33) 0.5624
Adrenal, Medulla	B-Pheochromocytoma	0/59 (27) 0.0827	0/60 (27) NC	0/59 (24) NC	2/59 (32) 0.2899
	M-Malignant Pheochromocytoma	1/59 (27) 0.7545	0/60 (27) 0.5000	0/59 (24) 0.4706	0/59 (32) 0.5424
	B-Pheochromocytoma/ M-Malignant Pheochromocytoma	1/59 (27) 0.2432	0/60 (27) 0.5000	0/59 (24) 0.4706	2/59 (32) 0.5645
Brain	B-Mixed Glioma	0/60 (28) 0.5133	0/60 (27) NC	1/60 (26) 0.4815	0/60 (32) NC
	M-Glioma	1/60 (28) 0.7500	0/60 (27) 0.4909	0/60 (25) 0.4717	0/60 (32) 0.5333
	B-Mixed Glioma/M-Glioma	1/60 (28) 0.6503	0/60 (27) 0.4909	1/60 (26) 0.7358	0/60 (32) 0.5333
	M-Malignant Oligodendroglio*	0/60 (28) 0.5089	0/60 (27) NC	1/60 (25) 0.4717	0/60 (32) NC
Cervix	B-Polyp, Stromal	0/60 (28) 0.0834	0/60 (27) NC	0/60 (25) NC	2/60 (33) 0.2885
	M-Sarcoma, Stromal	1/60 (28) 0.7500	0/60 (27) 0.4909	0/60 (25) 0.4717	0/60 (32) 0.5333
	B-Polyp, Stromal/ M-Sarcoma, Stromal	1/60 (28) 0.2460	0/60 (27) 0.4909	0/60 (25) 0.4717	2/60 (33) 0.5624
Clitoral Gland	M-Carcinoma	1/60 (28) 0.7500	0/60 (27) 0.4909	0/60 (25) 0.4717	0/60 (32) 0.5333
Hemolympho- Reticular System	M-Histiocytic Sarcoma	0/60 (28) 0.5089	1/60 (27) 0.4909	0/60 (25) NC	0/60 (32) NC
	M-Malignant Lymphoma	1/60 (29) 0.8077	2/60 (28) 0.4866	1/60 (25) 0.7163	0/60 (32) 0.5246

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	20 mg High (H) P - H vs. C
Kidney	B-Adenoma, Tubule Cell, Amp*	1/60 (28) 0.7591	1/60 (28) NC	1/60 (26) 0.7358	0/60 (32) 0.5333
	M-Carcinoma, Tubule Cell, Amp*	1/60 (28) 0.4706	2/60 (28) 0.5000	0/60 (25) 0.4717	2/60 (34) 0.5736
	B-Adenoma, Tubule Cell, Amp/ M-Carcinoma, Tubule Cell Amp*	1/60 (28) 0.4573	2/60 (28) 0.5000	1/60 (26) 0.7358	2/60 (34) 0.5736
	B-Lipoma	0/60 (28) 0.2920	0/60 (27) NC	0/60 (25) NC	1/60 (33) 0.5410
Liver	B-Adenoma, Hepatocellular	0/60 (28) 0.5089	0/60 (27) NC	1/60 (25) 0.4717	0/60 (32) NC
Mammary Gland	B-Adenoma	1/59 (28) 0.0394*	0/59 (27) 0.4909	0/60 (25) 0.4717	4/60 (34) 0.2437
	M-Carcinoma	17/59 (36) 0.3157	23/59 (40) 0.2528	19/60 (35) 0.3604	24/60 (43) 0.2964
	B-Adenoma/M-Carcinoma	18/59 (36) 0.2689	23/59 (40) 0.3357	19/60 (35) 0.4508	26/60 (44) 0.2785
	B-Fibroadenoma	21/59 (38) 0.1913	23/59 (37) 0.3551	23/60 (35) 0.2510	29/60 (44) 0.2241
Ovary	B-Granulosa Theca Cell Tumor	0/60 (28) 0.5089	1/60 (27) 0.4909	0/60 (25) NC	0/59 (32) NC
	B-Hemangioma	0/60 (28) 0.6460	2/60 (28) 0.2455	0/60 (25) NC	0/59 (32) NC
	M-Sertoli Cell Tumor, Malig*	0/60 (28) 0.5044	1/60 (28) 0.5000	0/60 (25) NC	0/59 (32) NC
Pancreas	B-Adenoma, Acinar Cell	0/60 (28) 0.5044	1/60 (28) 0.5000	0/60 (25) NC	0/59 (32) NC
	B-Adenoma, Islet Cell	1/60 (28) 0.6485	0/60 (27) 0.4909	1/60 (25) 0.7257	0/59 (32) 0.5333
	M-Carcinoma, Islet Cell	0/60 (28) 0.5089	1/60 (27) 0.4909	0/60 (25) NC	0/59 (32) NC
	B-Adenoma, Islet Cell/ M-Carcinoma, Islet Cell	1/60 (28) 0.7605	1/60 (27) 0.7455	1/60 (25) 0.7257	0/59 (32) 0.5333

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	5 mg Low (L) P - L vs. C	10 mg Mid (M) P - M vs. C	20 mg High (H) P - H vs. C
Pituitary	B-Adenoma	47/59 (54) 0.8117	52/60 (56) 0.7428	51/60 (54) 0.1599	43/60 (52) 0.6380
	M-Carcinoma	1/59 (27) 0.5068	0/60 (27) 0.5000	1/60 (25) 0.7353	1/60 (33) 0.2983
	B-Adenoma/M-Carcinoma	48/59 (54) 0.8647	52/60 (56) 0.3480	52/60 (54) 0.1351	44/60 (53) 0.7239
Skin/Subcutis	B-Keratocanthoma	0/60 (28) 0.5044	1/59 (28) 0.5000	0/60 (25) NC	0/60 (32) NC
	B-Papilloma, Squamous Cell	1/60 (28) 0.7500	0/59 (27) 0.4909	0/60 (25) 0.4717	0/60 (32) 0.5333
	B-Keratocanthoma/ B-Papilloma, Squamous Cell	1/60 (28) 0.8164	1/59 (28) NC	0/60 (25) 0.4717	0/60 (32) 0.5333
	M-Carcinoma, Trichoepitheli*	1/60 (29) 0.7434	0/59 (27) 0.4821	0/60 (25) 0.4630	0/60 (32) 0.5246
	M-Fibrosarcoma	1/60 (28) 0.4991	0/59 (27) 0.4909	1/60 (25) 0.7257	1/60 (33) 0.2885
	M-Sarcoma	1/60 (28) 0.7500	0/59 (27) 0.4909	0/60 (25) 0.4717	0/60 (32) 0.5333
Spleen	M-Sarcoma	0/60 (28) 0.5044	1/60 (28) 0.5000	0/60 (25) NC	0/60 (32) NC
Thoracic Cavity	B-Hibernoma	0/60 (28) 0.2920	0/60 (27) NC	0/60 (25) NC	1/60 (33) 0.5410
Thyroid	B-Adenoma, C-Cell	2/60 (29) 0.1984	5/60 (30) 0.2260	2/59 (25) 0.6360	6/60 (35) 0.1983
	B-Adenoma, Follicular Cell	1/60 (28) 0.8142	2/60 (28) 0.5000	1/59 (25) 0.7257	0/60 (32) 0.5333
	M-Carcinoma, Follicular Cell	1/60 (29) 0.7434	0/60 (27) 0.4821	0/59 (25) 0.4630	0/60 (32) 0.5246
	B-Adenoma, Follicular Cell/ M-Carcinoma, Follicular	2/60 (29) 0.9119	2/60 (28) 0.6809	1/59 (25) 0.4435	0/60 (32) 0.7781
Urinary Bladder	B-Papilloma, Transitional C*	0/60 (28) 0.2857	0/60 (27) NC	0/60 (25) NC	1/59 (32) 0.5333
Uterus	B-Polyp, Endometrial Stromal	0/60 (28) 0.1265	2/60 (28) 0.2455	2/60 (25) 0.2177	3/60 (33) 0.1516

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg	5 mg	10 mg	20 mg
		Vehicle (C) P - Trend	Low (L) P - L vs. C	Mid (M) P - M vs. C	High (H) P - H vs. C
Vagina	B-Fibroma	1/60 (28) 0.7500	0/60 (27) 0.4909	0/60 (25) 0.4717	0/60 (32) 0.5333
	B-Papilloma, Squamous Cell	0/60 (28) 0.2920	0/60 (27) NC	0/60 (25) NC	1/60 (33) 0.5410
	M-Sarcoma	0/60 (28) 0.5089	0/60 (27) NC	1/60 (25) 0.4717	0/60 (32) NC
	M-Schwannoma, Malignant	1/60 (29) 0.7434	0/60 (27) 0.4821	0/60 (25) 0.4630	0/60 (32) 0.5246
Zymbal Gland	M-Carcinoma	1/60 (28) 0.6503	0/60 (27) 0.4909	1/60 (26) 0.7358	0/60 (32) 0.5333

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

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Table 3A: Intercurrent Mortality Rate in Male Mice

Week / Type of Death	Vehicle Control		Low		Mid		High		Positive Control	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
14 - 27					2	8.00	1	4.00		
Planned intermittent sacrifice									10	
Terminal sacrifice	25	100.00	25	100.00	23	92.00	24	96.00		
Total	25		25		25		25			
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High			
Dose-Response (Likelihood Ratio)	0.3511		NC		0.0935		0.2390			
Homogeneity (Log-Rank)	0.2814		NC		0.1531		0.3173			

#All Cum. % Cumulative Percentage except for Terminal sacrifice; NC = Not calculable.

Table 3B: Intercurrent Mortality Rate in Female Mice

Week / Type of Death	Vehicle Control		Low		Mid		High		Positive Control	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
14 - 27							2	8.00		
Planned intermittent sacrifice									10	
Terminal sacrifice	25	100.00	25	100.00	25	100.00	23	92.00		
Total	25		25		25		25			
Test	All Dose Groups		Vehicle Control vs. Low		Vehicle Control vs. Mid		Vehicle Control vs. High			
Dose-Response (Likelihood Ratio)	0.0179*		NC		NC		0.0935			
Homogeneity (Log-Rank)	0.1058		NC		NC		0.1531			

#All Cum. % Cumulative Percentage except for Terminal sacrifice; NC = Not calculable.
* = Significant at 5% level;

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Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Vehicle (VC)	Low (L)	Mid (M)	High (H)	Positive (PC)
		0 mg P - Trend	10 mg P - L vs. VC	30 mg P - M vs. VC	75 mg P - H vs. VC	0 mg P - PC vs. VC
Harderian Glands	Carcinoma	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC	
Lungs With Bronchi	Alveolar-Bronchiolar Adenoma	1/25 (25) 0.2682	1/25 (25) NC	3/25 (24) 0.2890	2/25 (25) 0.5000	10/10 (10) 0.0000#
Spleen	Hemangiosarcoma	1/25 (25) 0.6455	2/25 (25) 0.5000	0/25 (24) 1.0000	1/25 (25) NC	7/10 (7) 0.0000#
Stomach	Papilloma	0/25 (25) 0.2525	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0.5000	
Testes	Hemangiosarcoma	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC	
Thyroid Glands	Follicular Cell Adenoma	1/25 (25) 0.7475	0/25 (25) 1.0000	1/25 (24) 0.7449	0/25 (25) 1.0000	
Whole body	Hemangiosarcoma	1/24 (25) 0.7353	3/22 (25) 0.3046	0/24 (25) 1.0000	1/24 (25) NC	7/0 (10) 0.0000#

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

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Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

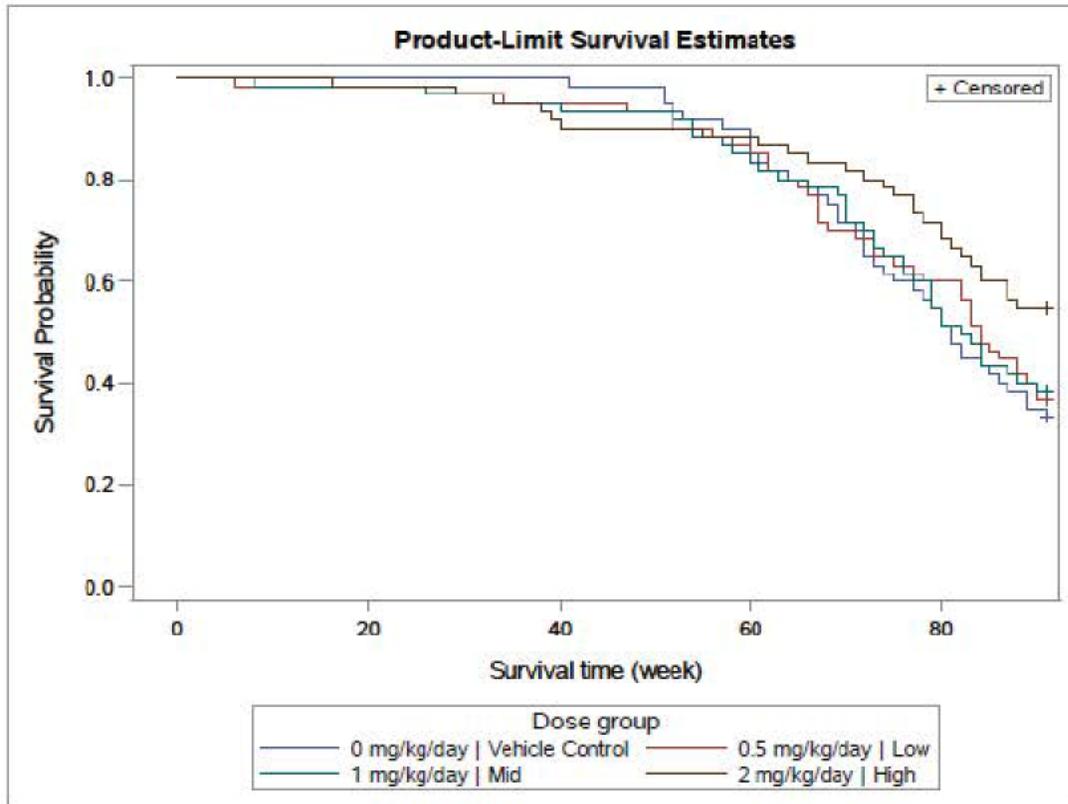
Organ name	Tumor name	Vehicle (VC)	Low (L)	Mid (M)	High (H)	Positive (PC)
		0 mg P - Trend	10 mg P - L vs. VC	30 mg P - M vs. VC	75 mg P - H vs. VC	0 mg P - PC vs. VC
Cavity, Nasal	Adenocarcinoma	0/25 (25)	0/25 (25)	0/25 (25)	1/25 (24)	
		0.2424	NC	NC	0.4898	
Harderian Glands	Adenoma	0/25 (25)	1/25 (25)	1/25 (25)	0/25 (24)	
		0.6186	0.5000	0.5000	NC	
	Carcinoma	0/25 (25)	2/25 (25)	0/25 (25)	0/25 (24)	
		0.8093	0.2449	NC	NC	
	Adenoma/Carcinoma	0/25 (25)	3/25 (25)	1/25 (25)	0/25 (24)	
		0.7847	0.1173	0.5000	NC	
Lungs With Bronchi	Alveolar-Bronchiolar Adenoma	3/25 (25)	0/25 (25)	1/25 (25)	1/25 (24)	10/10 (10)
		0.7242	1.0000	0.9451	0.9403	0.0000#
Multicentric	Sarcoma	0/25 (25)	0/25 (25)	1/25 (25)	0/25 (24)	0/10 (1)
		0.4949	NC	0.5000	NC	NC
Ovaries	Hemangiosarcoma	1/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	
		1.0000	1.0000	1.0000	1.0000	
Spleen	Hemangiosarcoma	1/25 (25)	0/25 (25)	2/25 (25)	0/25 (24)	5/10 (5)
		0.6798	1.0000	0.5000	1.0000	0.0000#
Whole body	Hemangiosarcoma	2/23 (25)	0/25 (25)	2/23 (25)	0/24 (25)	5/0 (10)
		0.8239	1.0000	NC	1.0000	0.0001#

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;

NC = Not calculable.

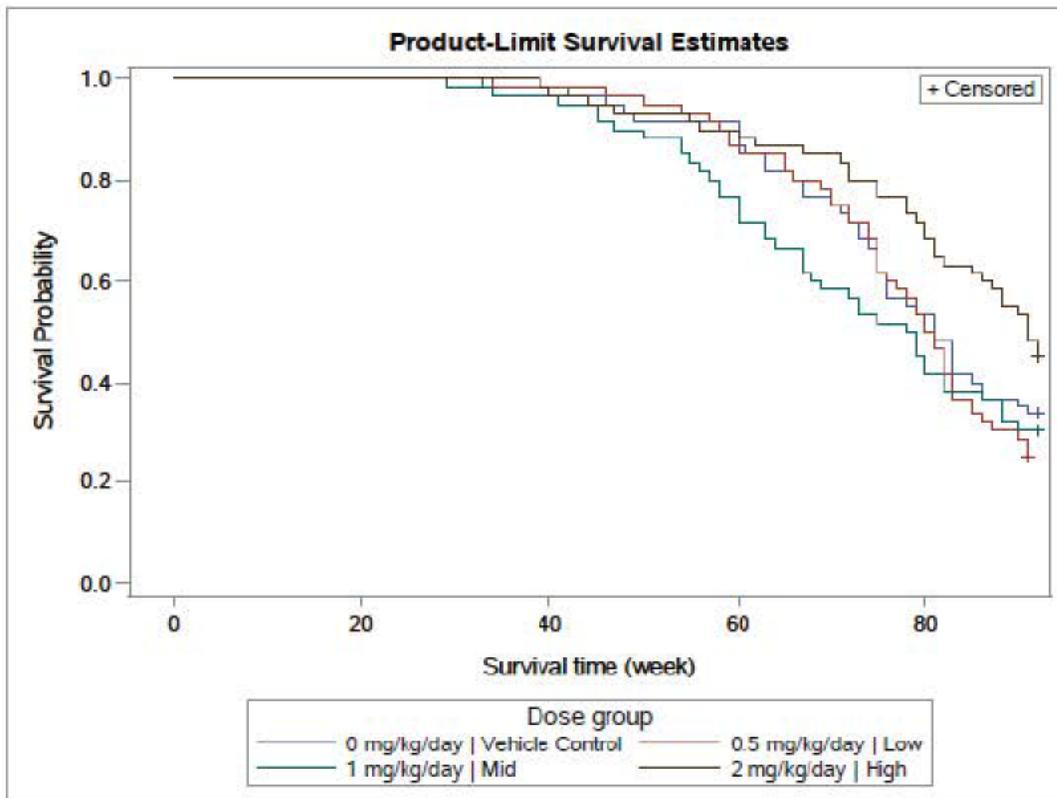
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Figure 1A: Kaplan-Meier Survival Functions for Male Rats



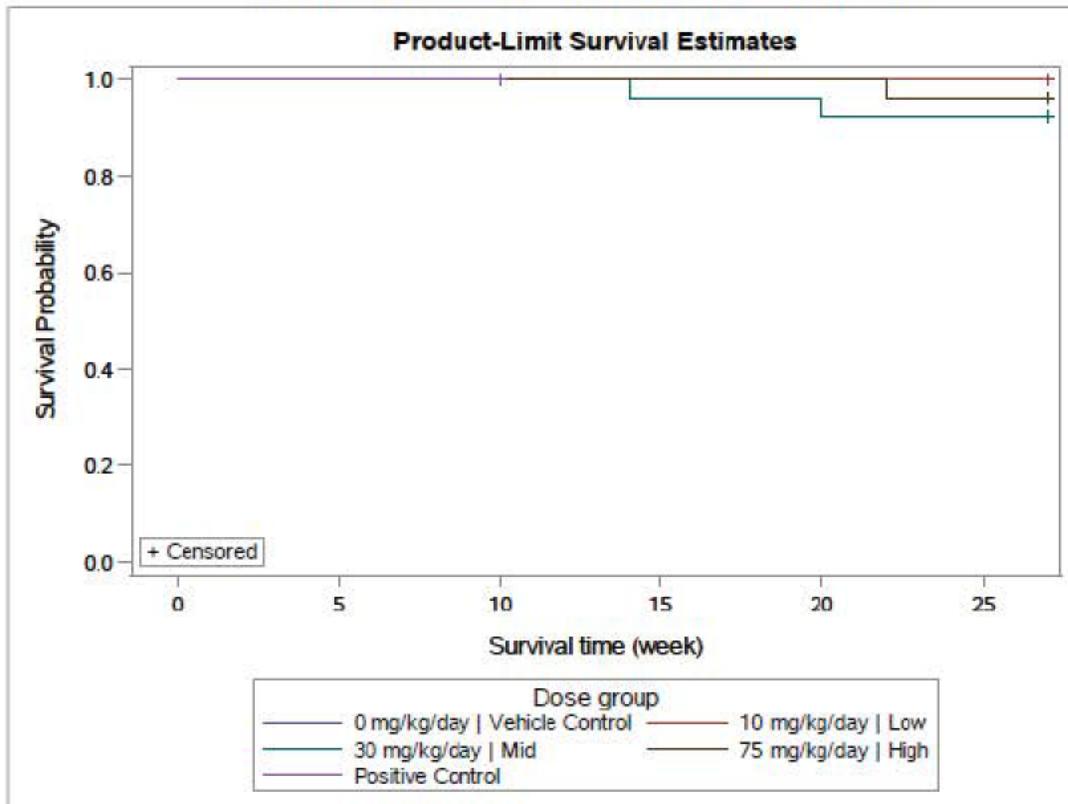
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Figure 1B: Kaplan-Meier Survival Functions for Female Rats



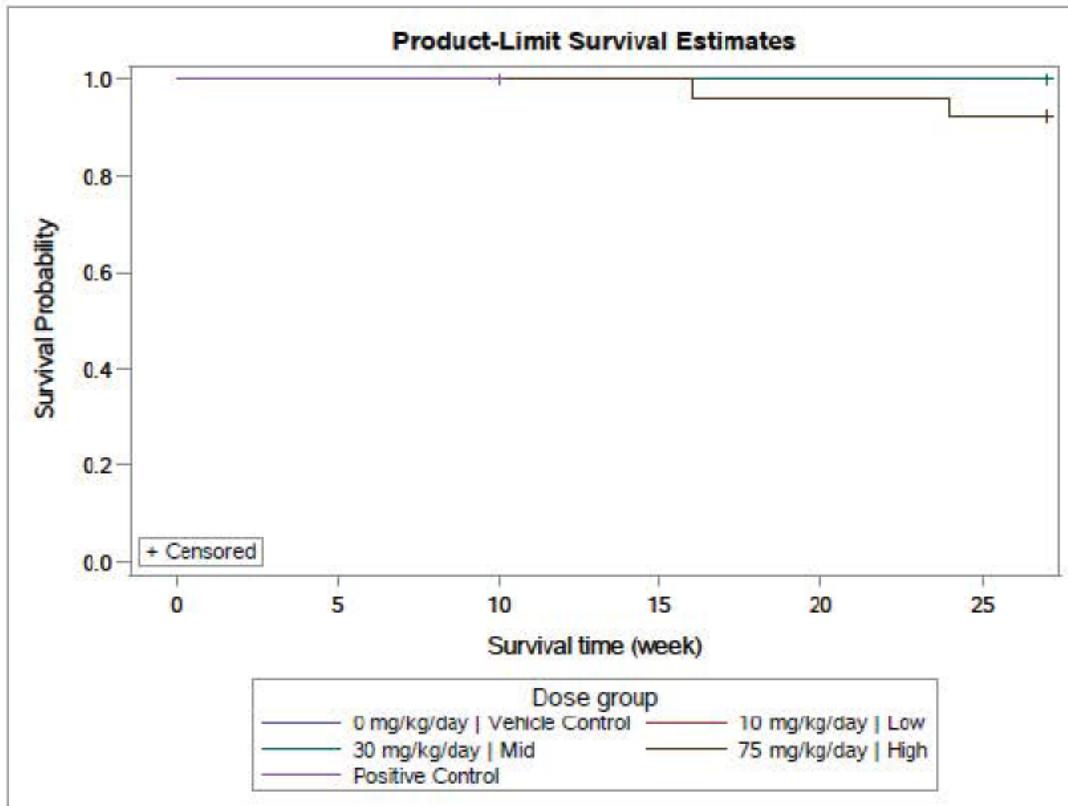
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Figure 2A: Kaplan-Meier Survival Functions for Male Mice



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Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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6. References

- Bailer, A.J, Portier, C.J. (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
- Bieler, G.S. and Williams, R.L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
- Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). May 2001.
- Haseman, J. (1983). "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.
- Lin KK (2000) Carcinogenicity Studies of Pharmaceuticals. In: *Encyclopedia of Biopharmaceutical Statistics*, ed. Shein-Chung Chow, Marcel Dekker, New York.
- Lin K.K. and Rahman A.M. (1998). "Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics*, 8(1), 1-15.
- Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J. Wahrendorf. (1980) "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426.
- Rahman, A.M., and Lin, K.K. (2008), "A Comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.
- Rahman, A.M., and Lin, K.K. (2009), "Design and Analysis of Chronic Carcinogenicity Studies of Pharmaceuticals in Rodents", in "Design and Analysis of Clinical Trials with Time-to-Event Endpoints", K.E Peace, Editor, Chapman & Hall/CRC, Taylor & Francis Group, LLC, Boca Raton, FL, London, and New York.

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