NEURALIS

Neurovarix

Investigator's Brochure Summary

Phase 2 Clinical Development Program

Disease-Modifying Therapy for Early-Stage Parkinson's Disease

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Executive Summary

FIRST-IN-CLASS	Selective NLRP3 inflammasome inhibitor targeting neuroinflammation in Parkinson's Disease
FAST TRACK	FDA Fast Track Designation granted December 2022
PHASE 2 READY	Phase 1 completed with favorable safety and target engagement
ORAL, QD	50 mg once-daily capsule with confirmed CNS penetration

Neurovarix (NVX-247) is a novel, orally bioavailable small molecule that selectively inhibits the NLRP3 inflammasome pathway in microglial cells. By crossing the blood-brain barrier and blocking neuroinflammation-mediated neurodegeneration, NVX-247 represents a potential first-in-class disease-modifying therapy for Parkinson's Disease.

Phase 1 clinical trials demonstrated favorable pharmacokinetics with confirmed CNS penetration, robust target engagement (42% reduction in CSF IL-1beta), and a well-characterized safety profile. The 50 mg once-daily dose has been selected for Phase 2 development based on optimal efficacy-safety balance.

Proposed Indication: Treatment of early-stage Parkinson's Disease (Hoehn and Yahr Stage 1-2) to slow disease progression and reduce motor symptom deterioration

Target Population

Adults aged 50-75 years with a diagnosis of idiopathic Parkinson's Disease (Hoehn and Yahr Stage 1-2) within the past 3 years, currently on stable dopaminergic therapy, with evidence of elevated neuroinflammatory biomarkers (CSF IL-1beta greater than 2.5 pg/mL).

Drug Description

Property	Specification
Generic Name	Neurovarix (NVX-247)
Chemical Class	Sulfonamide derivative
Chemical Name	N-[4-(methylsulfonyl)phenyl]-3-(4-morpholinylmethyl)-1H-pyrazole-5-carboxamide
Molecular Formula	C16H20N4O4S
Molecular Weight	364.42 g/mol
Molecular Target	NLRP3 inflammasome (NACHT domain)
Formulation	50 mg hard gelatin capsule
Administration	Once daily, oral

Table 1. Drug Product Specifications

Mechanism of Action

NVX-247 binds directly to the NACHT domain of NLRP3 with high affinity (KD = 5.2 nM), preventing ATP-dependent oligomerization and subsequent ASC recruitment. This selective inhibition blocks the inflammasome activation cascade through the following steps:

1. NVX-247 binds to the NLRP3 NACHT domain in its inactive state
2. Binding prevents conformational change required for NLRP3 activation
3. Blocks ATP-dependent NLRP3 oligomerization
4. Prevents ASC recruitment and ASC speck formation
5. Inhibits procaspase-1 activation
6. Blocks cleavage and release of IL-1beta and IL-18
7. Reduces pyroptotic cell death

In Vitro Pharmacology

Parameter	Value	Assay System
NLRP3 IC50	8.5 nM	Human THP-1 monocytes
ASC speck IC50	12 nM	Human THP-1 monocytes
IL-1beta release IC50	15 nM	LPS+ATP-stimulated human PBMCs
IL-18 release IC50	18 nM	LPS+ATP-stimulated human PBMCs
NLRP3 binding KD	5.2 nM	Direct binding assay

Table 2. In Vitro Pharmacology Summary

Selectivity Profile

Target	IC50 (nM)	Selectivity vs NLRP3
NLRP3	8.5	Reference

NLRP1	>10,000	>1,000-fold
NLRC4	>10,000	>1,000-fold
AIM2	>10,000	>1,000-fold
NLRP6	>10,000	>1,000-fold
NF-kB pathway	No inhibition	Selective for inflammasome

Table 3. NVX-247 Selectivity Profile

Blood-Brain Barrier Penetration

Species	Brain:Plasma Ratio	CSF:Plasma Ratio	Notes
Mouse	0.42	Not measured	Crosses via passive diffusion
Rat	0.38	Not measured	Not P-gp substrate
Cynomolgus Monkey	0.35	0.15	Confirmed CNS penetration
Human (Phase 1)	Not measured	0.12-0.18	CSF levels above target threshold

Table 4. Blood-Brain Barrier Penetration Across Species

Preclinical Development

Animal Efficacy Studies

NVX-247 demonstrated consistent neuroprotective effects across multiple preclinical models of Parkinson's Disease. Four key studies are summarized below:

Study 1: MPTP Mouse Model of PD

Parameter	Result
Design	C57BL/6 mice treated with MPTP (4 x 20 mg/kg), then NVX-247 (10, 30, or 50 mg/kg QD) or vehicle for 4 weeks
Alpha-synuclein aggregation	40% reduction in substantia nigra (50 mg/kg dose)
Dopaminergic neurons	35% preservation vs vehicle control
Microglial activation	Dose-dependent reduction (Iba-1 staining)
Rotarod performance	30% improvement vs vehicle (p<0.01)
Brain IL-1beta levels	45% reduction at 50 mg/kg dose

Study 2: A53T Alpha-Synuclein Transgenic Mouse Model

Parameter	Result
Design	A53T alpha-synuclein transgenic mice, NVX-247 (25 or 50 mg/kg QD) vs vehicle for 12 weeks
Motor symptom onset	Delayed by 3.2 weeks (50 mg/kg)
Pathology burden	28% reduction in alpha-synuclein pathology
Inflammatory markers	Reduced IL-1beta, TNF-alpha, IL-6
Survival	Median survival extended by 4 weeks at 50 mg/kg

Study 3: 6-OHDA Rat Model

Parameter	Result
Design	Unilateral 6-OHDA lesion in rats, NVX-247 (20 or 40 mg/kg QD) vs vehicle for 6 weeks
Rotational behavior	42% reduction in amphetamine-induced rotation (40 mg/kg)
Striatal dopamine	30% preservation vs vehicle
Microglial activation	Reduced in substantia nigra
Forelimb use	Improved in cylinder test

Study 4: Non-Human Primate MPTP Model

Parameter	Result
Design	Cynomolgus monkeys, chronic low-dose MPTP, then NVX-247 (5 or 10 mg/kg QD) vs vehicle for 16 weeks

Parkinsonian score	25% improvement (10 mg/kg)
CSF IL-1beta	55% reduction at 10 mg/kg
PET imaging	Reduced microglial activation (18F-DPA714)
DAT density	Maintained dopamine transporter density (DAT-SPECT)

Table 5-8. Preclinical Efficacy Studies Summary

Toxicology Studies

Repeat-Dose Toxicity - Rats (Sprague-Dawley)

Parameter	Result
Duration	3-month GLP study
Doses	0, 25, 75, 150 mg/kg/day
NOAEL	75 mg/kg/day
Findings at 150 mg/kg/day	Reversible hepatocellular hypertrophy; ALT/AST 2-3x ULN (reversible within 4 weeks); no histopathological liver damage
Safety margin	Approximately 25x at human 50 mg dose (based on AUC)

Repeat-Dose Toxicity - Monkeys (Cynomolgus)

Parameter	Result
Duration	6-month GLP study
Doses	0, 10, 30, 60 mg/kg/day
NOAEL	30 mg/kg/day
Findings at 60 mg/kg/day	Mild, reversible ALT/AST elevations (1.5-2x ULN); no hepatic histopathology; mild WBC decrease (within normal range)
Safety margin	Approximately 40x at human 50 mg dose (based on AUC)

Table 9-10. Repeat-Dose Toxicology Summary

Additional Toxicology Studies

Study Type	Result
Genotoxicity - Ames test	Negative (non-mutagenic)
Genotoxicity - Chromosomal aberration	Negative
Genotoxicity - In vivo micronucleus	Negative
Fertility (rats)	No effect on male or female fertility up to 100 mg/kg/day
Embryo-fetal development (rats)	No teratogenicity up to 75 mg/kg/day
Pre/postnatal development (rats)	No adverse effects on F1 generation up to 75 mg/kg/day
Immunotoxicity	No immunosuppression; selective inflammasome inhibition without broad immune suppression
Carcinogenicity	Not yet conducted (planned for Phase 3 support)

Table 11. Additional Toxicology Studies

Animal Pharmacokinetics

Parameter	Mouse	Rat	Monkey
Oral bioavailability	65%	58%	52%
Half-life (hours)	3.8	4.2	6.5

Brain:plasma ratio	0.42	0.38	0.35
CSF:plasma ratio	Not measured	Not measured	0.15
PK linearity	Linear	Dose-proportional 25-150 mg/kg	Dose-proportional 10-60 mg/kg

Table 12. Animal Pharmacokinetics Summary

Phase 1 Clinical Development

Study Design

Study	Design	Population	Doses
SAD	Randomized, double-blind, placebo-controlled	Healthy volunteers (n=64; 8 cohorts)	5, 10, 25, 50, 100, 200, 300, 400 mg (6 active:2 placebo per cohort)
MAD	Randomized, double-blind, placebo-controlled	Healthy volunteers (n=40; 4 cohorts)	25, 50, 75, 100 mg QD x 14 days (8 active:2 placebo per cohort)

Table 13. Phase 1 Study Designs

Demographics

Parameter	SAD + MAD Combined (N=104)
Total subjects	104 (78 active, 26 placebo)
Age (years)	22-64 (mean 38)
Sex	58% male, 42% female
Race	72% White, 15% Black, 8% Asian, 5% Other
BMI (kg/m2)	19-30 (mean 24.8)

Table 14. Phase 1 Demographics

Single-Dose Pharmacokinetics (SAD Study)

Dose (mg)	Cmax (ng/mL)	Tmax (h)	AUC0-inf (ng.h/mL)	t1/2 (h)
5	42 +/- 12	2.0	285 +/- 78	6.2
10	88 +/- 24	2.0	615 +/- 145	6.5
25	245 +/- 68	2.5	1,680 +/- 385	6.8
50	515 +/- 125	2.5	3,550 +/- 720	7.2
100	1,085 +/- 245	2.0	7,420 +/- 1,450	7.5
200	2,280 +/- 485	3.0	15,800 +/- 2,950	8.0
300	3,520 +/- 725	3.0	24,500 +/- 4,200	8.2
400	4,680 +/- 890	3.5	32,800 +/- 5,500	8.5

Table 15. Single-Dose Pharmacokinetics

Key PK findings: Dose-proportional PK from 5-200 mg; slightly less than dose-proportional from 200-400 mg (suggesting saturation at very high doses); low inter-subject variability (CV% 20-30%).

Multiple-Dose Pharmacokinetics (MAD Study, Day 14)

Dose (mg QD)	Cmax,ss (ng/mL)	AUC0-24,ss (ng.h/mL)	Cmin,ss (ng/mL)	Accumulation
25	285 +/- 62	2,150 +/- 450	38 +/- 12	1.28x
50	625 +/- 135	4,680 +/- 890	82 +/- 24	1.32x

75	985 +/- 215	7,350 +/- 1,350	128 +/- 35	1.35x
100	1,350 +/- 285	10,200 +/- 1,850	185 +/- 48	1.38x

Table 16. Multiple-Dose Pharmacokinetics at Steady State

Steady-state achieved by Day 7. Minimal accumulation (1.3-1.4x, consistent with half-life). Dose-proportional at steady state. Food effect: moderate-fat meal increased AUC by 35% and delayed Tmax to 4h (can be taken with food).

PK Summary

Parameter	Value
Absorption	Tmax 2-3 hours; moderate oral bioavailability (estimated 55%)
Distribution	Vd/F approximately 130 L; plasma protein binding 88-92%
Metabolism	Extensive hepatic via CYP3A4 (75%); minor CYP2C9 (15%); glucuronidation (10%)
Elimination	Half-life 6-8 hours; fecal (65%), renal (30%); primarily as metabolites

Table 17. Human Pharmacokinetics Summary

Target Engagement (Pharmacodynamics)

A CSF biomarker substudy (n=16 healthy volunteers, 50 mg QD x 14 days) demonstrated robust CNS target engagement:

CSF Biomarker	Change from Baseline	p-value
IL-1beta	-42%	0.008
IL-18	-38%	0.012
NVX-247 concentration	75-110 ng/mL	Above 60 ng/mL target threshold

Table 18. CNS Target Engagement at 50 mg QD x 14 days

PK/PD Relationship: Plasma EC50 for 50% IL-1beta inhibition approximately 280 ng/mL. CSF concentration for target engagement (>70% inflammasome inhibition): >60 ng/mL. The 50 mg dose provides steady-state CSF levels of 75-110 ng/mL, well above target.

Safety Summary

NVX-247 was generally well-tolerated across all Phase 1 studies. No serious adverse events, deaths, or discontinuations due to adverse events were reported. The maximum tolerated dose was not reached (highest tested: 400 mg single dose, 100 mg QD x 14 days).

Parameter	NVX-247 (n=78)	Placebo (n=26)
Total exposure	456 patient-days	—
Any TEAE	67%	54%
Treatment-related TEAE	35%	23%
Serious adverse events	0%	0%
Deaths	0	0
Discontinuation due to AE	0%	0%
Grade 3 or higher AE	0%	0%

Table 19. Overall Safety Summary

Most Common Adverse Events

Adverse Event	NVX-247 (n=78)	Placebo (n=26)
Headache	14 (18%)	4 (15%)
Nausea	9 (12%)	2 (8%)
Dizziness	7 (9%)	2 (8%)
Fatigue	6 (8%)	1 (4%)
Increased ALT	6 (8%)	0 (0%)
Diarrhea	5 (6%)	1 (4%)

Table 20. Adverse Events Occurring in 5% or More of NVX-247 Group

Most adverse events were mild (Grade 1: 85%) and transient. Headache, nausea, dizziness, and fatigue showed no clear dose relationship and occurred at similar rates to placebo.

Hepatic Safety Signal

Key Finding: Dose-dependent ALT elevations observed at doses of 100 mg and above

Dose Level	Incidence of ALT >1.5x ULN
Less than 100 mg (SAD or MAD)	1/64 (1.6%)
100 mg QD x 14 days	3/8 (38%)
200 mg or higher single dose	2/16 (12.5%)
Overall at 100 mg or higher	5/24 (21%)
50 mg QD x 14 days (proposed Phase 2 dose)	0/8 (0%)

Table 21. Incidence of ALT Elevations by Dose

Characteristics of Hepatic Signal:

- Onset: Days 7-14 of repeated dosing
- Pattern: Hepatocellular (ALT predominant)
- Severity: All Grade 1 (1.5-2.4x ULN); peak ALT 72-138 U/L
- AST: Mildly elevated (1.2-1.6x ULN) in 3/5 subjects
- Bilirubin: Normal in all subjects (no Hy's Law cases)
- Symptoms: None (asymptomatic transaminitis)
- Resolution: 2-4 weeks after drug discontinuation (100% reversible)

Risk Mitigation for Phase 2: Selected dose (50 mg QD) had 0/8 subjects with ALT elevation in Phase 1. Safety margin is 2-fold below dose associated with ALT elevations. Monitoring: LFTs at baseline, Week 4, 12, 24, 52. Stopping rule: Discontinue if ALT/AST >3x ULN, or if Hy's Law criteria met.

Other Laboratory and Safety Findings

Parameter	Finding
Hematology	Transient neutrophil decrease (5-15%) at doses of 200 mg or higher; all values remained within normal range
Other chemistry	No clinically significant changes in electrolytes, renal function, or glucose
Vital signs	No clinically significant changes
ECG	No QTc prolongation (mean change -1.2 ms at 50 mg); no arrhythmias
Infections	2 URTIs (mild, resolved); no serious infections; no evidence of immunosuppression

Table 22. Other Safety Findings

Dose Selection for Phase 2

Selected Dose: 50 mg once daily

Criterion	Evidence at 50 mg Dose
Target Engagement	CSF concentrations (75-110 ng/mL) exceed target threshold (60 ng/mL)
Biomarker Response	42% reduction in CSF IL-1beta (p=0.008)
Exposure Match	Human AUC (4,680 ng.h/mL) comparable to efficacious NHP dose (10 mg/kg; AUC approximately 5,000 ng.h/mL)
PD Effect	Maintains continuous NLRP3 inhibition throughout dosing interval
Safety Margin	25-40x below NOAEL from toxicology studies
Hepatic Safety	0% ALT elevations at 50 mg in Phase 1 MAD (vs 38% at 100 mg)
PK Profile	Once-daily feasible (t1/2 7.2h); minimal accumulation (1.32x)
Variability	Low inter-subject variability (CV <30%)

Table 23. Dose Selection Rationale Summary

Drug Interactions and Metabolism

Metabolism

Pathway	Contribution	Notes
CYP3A4	75%	Primary metabolic pathway
CYP2C9	15%	Minor contribution
UGT1A9 (glucuronidation)	10%	Non-CYP metabolism

Metabolites: M1 (N-desethyl-NVX-247, 25% of parent, inactive), M2 (hydroxyl-NVX-247, 15%, weak activity), M3 (glucuronide, 18%, inactive). No active metabolites with significant contribution to efficacy.

Drug-Drug Interactions

NVX-247 is a CYP3A4 substrate. In vitro studies showed no inhibition or induction of CYP enzymes and no transporter interactions at therapeutic concentrations.

Interacting Drug Class	Predicted Effect	Recommendation
Strong CYP3A4 inhibitors (ketoconazole, ritonavir)	4-5x increase in NVX-247 AUC	Avoid; if unavoidable, reduce to 25 mg QD
Moderate CYP3A4 inhibitors (erythromycin, diltiazem)	1.6-1.8x increase in AUC	Monitor; consider dose reduction
Strong CYP3A4 inducers (rifampin, carbamazepine)	60-75% decrease in AUC	Avoid (may reduce efficacy)
Levodopa/carbidopa	No interaction	No dose adjustment needed
MAO-B inhibitors	No interaction	No dose adjustment needed
Dopamine agonists	No interaction	No dose adjustment needed

Table 24. Drug-Drug Interaction Summary

Special Populations

Population	PK Change	Recommendation
Mild hepatic impairment (Child-Pugh A)	1.4x AUC increase	Consider 35 mg dose
Moderate hepatic impairment (Child-Pugh B)	2.2x AUC increase	Reduce to 25 mg
Severe hepatic impairment (Child-Pugh C)	Not studied	Contraindicated
Mild-moderate renal impairment	1.3x AUC increase	No adjustment; monitor
Severe renal impairment/ESRD	Not studied	Avoid use
Elderly (65-75 years)	1.35x AUC increase	No adjustment needed

Table 25. Special Populations Dosing

Regulatory Status

Milestone	Status	Date
IND Filing	Active (IND 123456)	March 2022
Fast Track Designation	GRANTED	December 2022
Pre-IND Meeting	Completed; FDA supportive of approach	October 2021
End-of-Phase 1 Meeting	Completed; Phase 2 design agreed	June 2023
Phase 2 Initiation	Planned	Q1 2024
Orphan Drug Designation	Not applicable (PD prevalence >200,000)	—
Breakthrough Therapy Designation	Planned application (pending Phase 2 data)	—

Table 26. Regulatory Milestones

Key FDA Agreements from End-of-Phase 1 Meeting

- Primary endpoint accepted: MDS-UPDRS Part III change from baseline at Week 52
- Trial duration: 52 weeks (minimum for disease modification signal)
- Biomarker strategy: CSF IL-1beta enrichment supported
- Dose: 50 mg QD justified based on safety and PK/PD data
- Hepatic monitoring plan: LFTs at specified intervals agreed
- Clinically meaningful difference: 3.25 points or greater on MDS-UPDRS Part III recommended

Proposed Phase 2 Trial Design

Parameter	Specification
Design	Randomized, double-blind, placebo-controlled, parallel-group
Population	Adults 50-75 years with early PD (Hoehn and Yahr Stage 1-2), diagnosed within 3 years
Biomarker Enrichment	CSF IL-1beta >2.5 pg/mL (selects for active neuroinflammation; approximately 60% of early PD patients)
Background Therapy	Stable dopaminergic therapy (levodopa, MAO-B inhibitors, dopamine agonists permitted)
Intervention	NVX-247 50 mg QD vs. placebo (added to standard of care)
Randomization	1:1 (NVX-247 : placebo)
Primary Endpoint	Change from baseline in MDS-UPDRS Part III at Week 52
Sample Size	Approximately 150 patients (75 per arm)
Duration	52 weeks treatment + 4 weeks follow-up

Table 27. Phase 2 Trial Design Summary

Primary Endpoint Rationale

MDS-UPDRS Part III (Motor Examination) is the FDA-accepted primary endpoint for PD trials. It is validated, reliable, and clinically meaningful. Early PD patients on stable therapy show progression of 1.5-3 points per year. Minimum

clinically important difference: 3.25 points. Assessment will be performed in the 'ON' state at Week 52.

Key Secondary Endpoints

- MDS-UPDRS Parts I, II, IV (non-motor symptoms, ADLs, motor complications)
- Hoehn and Yahr stage progression
- Clinical Global Impression of Change (CGI-C)
- PDQ-39 (Parkinson's Disease Questionnaire - quality of life)
- Montreal Cognitive Assessment (MoCA)
- Time to initiation or increase of PD medication
- CSF IL-1beta change from baseline (proof-of-mechanism)
- Exploratory biomarkers: CSF IL-18, alpha-synuclein, tau, neurofilament light chain

Expected Effect Size

Parameter	Value
Expected progression (placebo)	+2.5 points over 52 weeks
Expected treatment effect	35% reduction in progression
Predicted NVX-247 arm	+1.6 points over 52 weeks
Treatment difference	0.9 points (conservative estimate)
Statistical assumptions	SD approximately 3.5 points; power 80%; alpha 0.05 (two-sided)

Table 28. Expected Effect Size and Statistical Assumptions

Disease Background and Rationale

Parkinson's Disease Epidemiology

Parameter	Value
Global prevalence	Approximately 10 million people worldwide
US incidence	60,000 new cases diagnosed annually
Age-related prevalence	<1% under 60 years; 1-2% over 60; 3-4% over 80
Sex ratio	1.5:1 male to female
Economic burden (US)	$52 billion annually (direct and indirect costs)
Early-stage (H&Y; 1-2) prevalence	Approximately 3.6 million patients worldwide

Table 29. Parkinson's Disease Epidemiology

Unmet Medical Need

No disease-modifying therapy exists for Parkinson's Disease. All approved therapies are symptomatic and do not slow the underlying neurodegeneration. Patients inevitably progress despite treatment. The early disease stage represents the optimal therapeutic window before extensive neuronal loss occurs.

Current therapies and their limitations:

- Levodopa/carbidopa: Gold standard for symptoms; causes motor complications long-term; does not modify disease
- Dopamine agonists: Less efficacious; impulse control disorders; does not modify disease
- MAO-B inhibitors: Modest benefit; no proven disease modification
- COMT inhibitors: Adjunct only; does not modify disease

NLRP3 Inflammasome as Therapeutic Target

Multiple lines of evidence support targeting NLRP3-mediated neuroinflammation in PD:

- Post-mortem studies: Elevated NLRP3, ASC, caspase-1, IL-1beta in PD brain tissue
- PET imaging: Microglial activation correlates with disease severity and progression
- CSF biomarkers: IL-1beta levels correlate with disease severity (r=0.52) and progression rate
- Genetic evidence: LRRK2 regulates NLRP3; NLRP3 and IL1B polymorphisms associated with PD risk
- Mechanistic: Alpha-synuclein activates NLRP3; IL-1beta promotes synuclein aggregation (feedforward loop)
- Preclinical: NLRP3 knockout mice show reduced PD pathology in multiple models

Competitive Landscape

All currently approved PD therapies are symptomatic only. No disease-modifying therapy has been approved. Multiple investigational approaches have failed or are in development:

Approach	Status	Challenges
Antioxidants (Vitamin E, CoQ10)	Failed Phase 3	No benefit on progression

Anti-apoptotic (minocycline)	Failed Phase 3	No slowing of progression
Calcium channel blockers (isradipine)	Failed Phase 3 (STEADY-PD III)	No benefit
GLP-1 agonists (exenatide)	Phase 2/3 ongoing	Limited CNS penetration; GI side effects
Anti-alpha-synuclein antibodies	Phase 2/3 ongoing	IV infusion; targets extracellular only
LRRK2 inhibitors	Phase 1/2	Limited to LRRK2 carriers (1-2%); pulmonary toxicity
NLRP3 inhibitors (NVX-247)	Phase 2 initiating	FIRST-IN-CLASS for PD

Table 30. Competitive Landscape

NVX-247 Differentiation

- First selective NLRP3 inhibitor in PD clinical development
- Oral, once-daily (vs IV infusions for antibody approaches)
- Confirmed CNS penetration (vs peripheral-acting GLP-1 agonists)
- Biomarker-guided patient selection (precision medicine)
- Rapid target engagement (biomarker changes in 2 weeks)
- Favorable safety profile (selective, no immunosuppression)
- Breaks pathological neuroinflammation-synucleinopathy cycle

Risk-Benefit Assessment

Potential Benefits

- Disease modification: Potential 30-40% slowing of motor symptom progression
- Functional independence: Delayed disability and reduced need for medication increases
- Quality of life: Maintained activities of daily living and reduced caregiver burden
- Cognitive benefit: Potential slowing of neuroinflammation-related cognitive decline
- First-in-class: No disease-modifying therapies currently available for PD
- Long-term impact: Potential delay of H&Y; Stage 3 (major disability) by 1-3 years

Known Risks

- Hepatotoxicity: Mild, reversible ALT elevations at doses of 100 mg and above (0% at 50 mg)
- GI effects: Nausea (12%), diarrhea (6%) - mild and transient
- CNS effects: Headache (18%), dizziness (9%) - comparable to placebo
- Theoretical: Infection risk (no signal in Phase 1; will be monitored)

Risk Mitigation Strategy

- Dose selected (50 mg) below hepatotoxicity threshold
- Frequent LFT monitoring (baseline, Weeks 4, 12, 24, 52)
- Clear stopping rules (ALT/AST >3x ULN or Hy's Law criteria)
- Infection surveillance throughout trial
- Independent Data Safety Monitoring Board

CONCLUSION: Risk-benefit profile is FAVORABLE for Phase 2 trial in early PD patients. Potential benefit (disease modification) outweighs known risks (mild, reversible hepatotoxicity with monitoring). Rigorous safety monitoring plan ensures patient safety. FDA has agreed that the risk-benefit is acceptable for further investigation (Fast Track designation granted).

Development Timeline

Phase	Timeline	Status
Phase 1 (SAD/MAD)	2022-2023	COMPLETED
Phase 2 (Proof-of-Concept)	2024-2025	INITIATING
Phase 2b (Dose-Ranging)	2025-2026	Planned (if Phase 2a positive)
Phase 3 (Pivotal)	2026-2029	Planned
NDA Submission	2030	Projected
Potential Approval	2031	Projected

Table 31. Projected Development Timeline

Manufacturing and Formulation

Drug Substance

Property	Specification
Chemical name	N-[4-(methylsulfonyl)phenyl]-3-(4-morpholinylmethyl)-1H-pyrazole-5-carboxamide
Molecular formula	C16H20N4O4S
Molecular weight	364.42 g/mol
Appearance	White to off-white crystalline powder
Melting point	178-182 degrees C
Solubility (water, pH 7.4)	0.08 mg/mL (slightly soluble)
pKa	8.2 (pyrazole NH)
log P	2.1 (moderate lipophilicity)
Polymorphic form	Form I (thermodynamically stable)
Purity specification	98.5% or greater by HPLC

Table 32. Drug Substance Properties

Drug Product Formulation

Component	Amount per Capsule	Function
NVX-247	50 mg	Active ingredient
Microcrystalline cellulose	90 mg	Filler/diluent
Lactose monohydrate	50 mg	Filler
Croscarmellose sodium	10 mg	Disintegrant
Magnesium stearate	2 mg	Lubricant
Colloidal silicon dioxide	2 mg	Glidant
Total fill weight	204 mg	—

Table 33. Drug Product Formulation

Capsule: Size 1 hard gelatin, white opaque body and cap, printed 'NVX 50' in black ink. Packaging: HDPE bottles, 30 capsules, child-resistant closure, silica gel desiccant. Storage: 20-25 degrees C (68-77 degrees F); excursions permitted to 15-30 degrees C. Stability: 24 months at 25 degrees C/60% RH (ongoing); stable under accelerated conditions.

Contact Information

Neuralis Therapeutics, Inc.

Clinical Development Operations

Medical Information: medinfo@neuralis-therapeutics.com

Clinical Operations: clinops@neuralis-therapeutics.com
Regulatory Affairs: regulatory@neuralis-therapeutics.com

24-Hour Safety Hotline: 1-800-555-DRUG

For additional information, please refer to the full Investigator's Brochure (NVX-IB-2024-001)