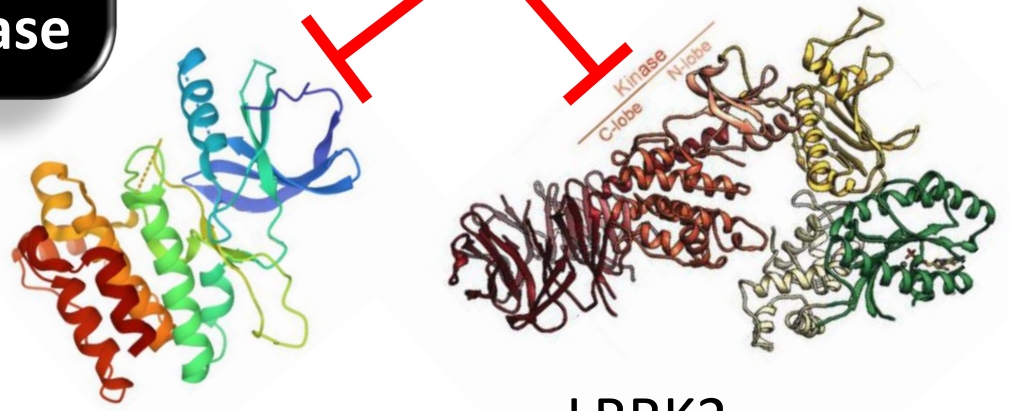
PIONEURA

Preventing neuroinflammation from overactivation of enzymes called kinases while protecting neurons in Parkinson's disease

PIO-101



MLK LRRK2

A multikinase inhibitor, orally available, brain-penetrant and well tolerated therapy in animal models that can be given on a daily basis

The Pioneura Team:
Richard Couch, CEO
Handy Gelbard, CSO
Jordan Dubow and Karl Kieburtz, Advancement/Development Team
Jesse Damsker, COO
John McCall, Med Chem Advisor

Parkinson's Disease Global Market Size Will Achieve USD 6,705 Million by 2030 growing at 11.5% CAGR – Acumen, 09/2022

Newly diagnosed patients with PD per year

Global
10 million

USA
1 million

>$655 billion
Economic costs in 2020

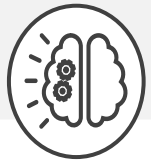
$179 billion
Medicare burden

$257 billion
Caregiver burden

>3 million DALYs*
in 2016

High diversity of Neurological Disorders, **affecting all age groups**, burden increased with age[1]

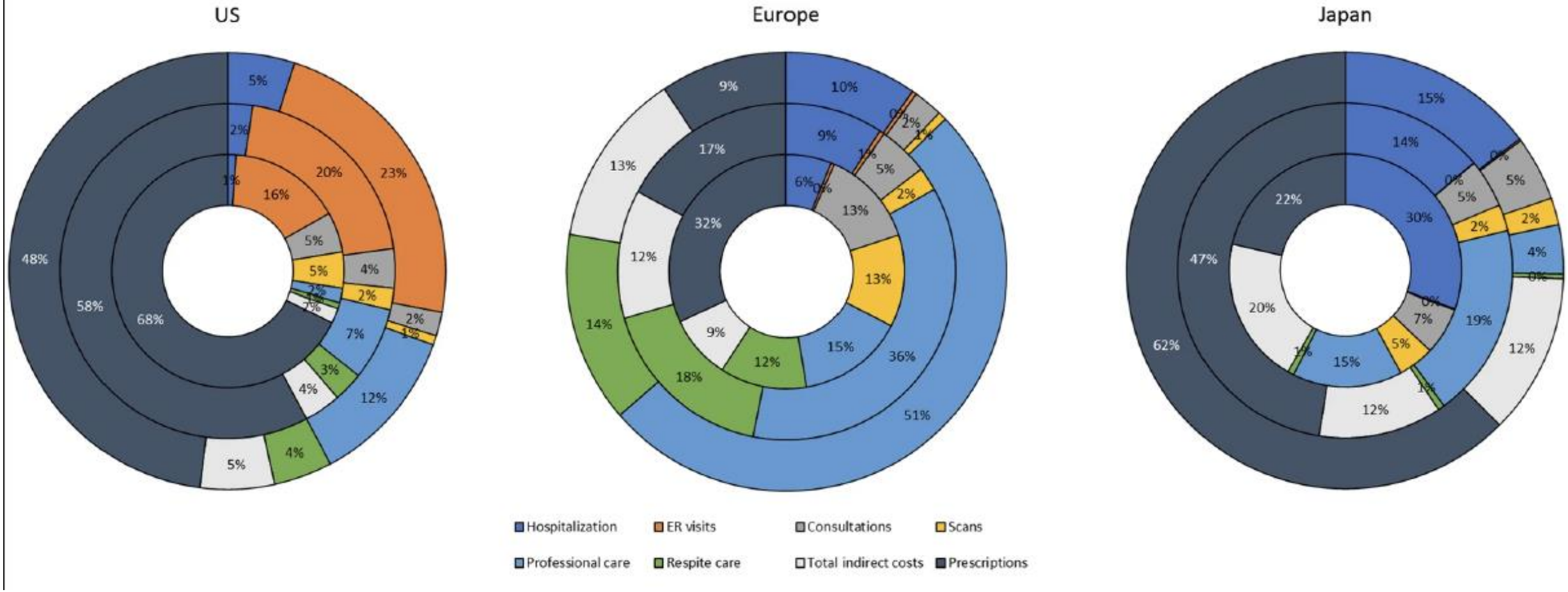
Neuroinflammation is an untreated driver of PD in current therapies.



***DALY = disability-adjusted life years**

1. The Lancet Neurology 2017 16877-897DOI: (10.1016/S1474-4422(17)30299-5)

The real-world cost of PD: Distribution of healthcare resource utilization costs/patient with PD by severity (inner ring, early PD, middle ring, intermediate PD, outer ring, advanced PD)



Chaudhuri et al., Drugs Real World Outcomes. 2024 Jan 9. doi: 10.1007/s40801-023-00410-1.

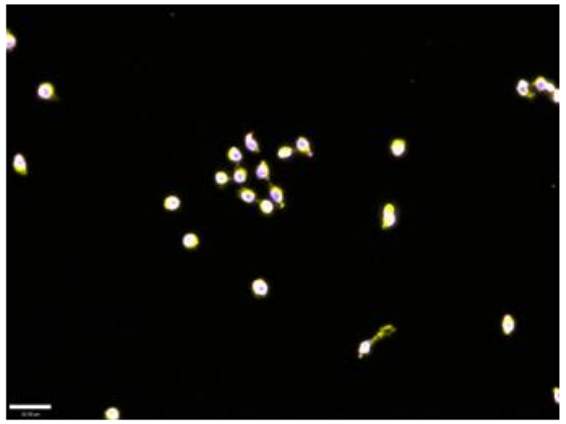
The current disease landscape for PD:

- Parkinson's disease (PD) is one of the fastest growing neurodegenerative diseases in the world.
- It is complex, multifactorial and presents in both familial and sporadic forms.
- A large number of genetic mutations (i.e., *LRRK2*, *SNCA*, *Parkin*, etc.) have been identified in people with PD, *but environmental causes may far outstrip these*.
- Ultimately all underlying causes of PD, whether genetic, environmental neurotoxicant or infectious lead to neuroinflammation and neurodegeneration of dopamine neurons
- PIO-101 markedly decreases innate inflammatory and pro-death responses in the brain by signaling through multiple kinases including MLK3 and LRRK2, **regardless of the underlying cause**; in doing so, it allows affected neurons to remain metabolically active and functional.

PIO-101 key therapeutic effects:

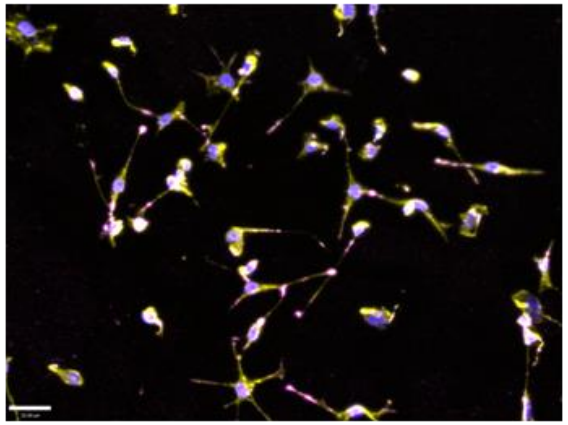
- **PIO-101 treatment leads to reduction and removal of damaged a-SYN in immune cells known as microglia.**

aSyn PFFs



Activated microglia unable to digest damaged synuclein

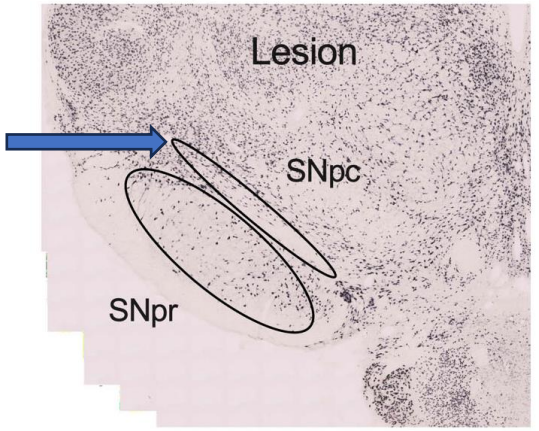
aSyn PFFs + URMC-099



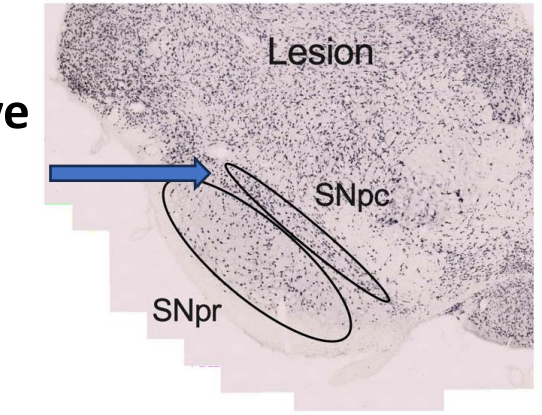
Microglia with normal morphology digesting damaged synuclein

- **PIO-101 treatment protects dopamine-producing nerve cells in the brain from the earliest stages of the disease.**

Loss of dopamine nerve cells in SNpc without PIO-101



Dopamine nerve cells protected with PIO-101



Bringing PIO-101, a new anti-neuroinflammatory drug candidate, to market for Parkinson's Disease

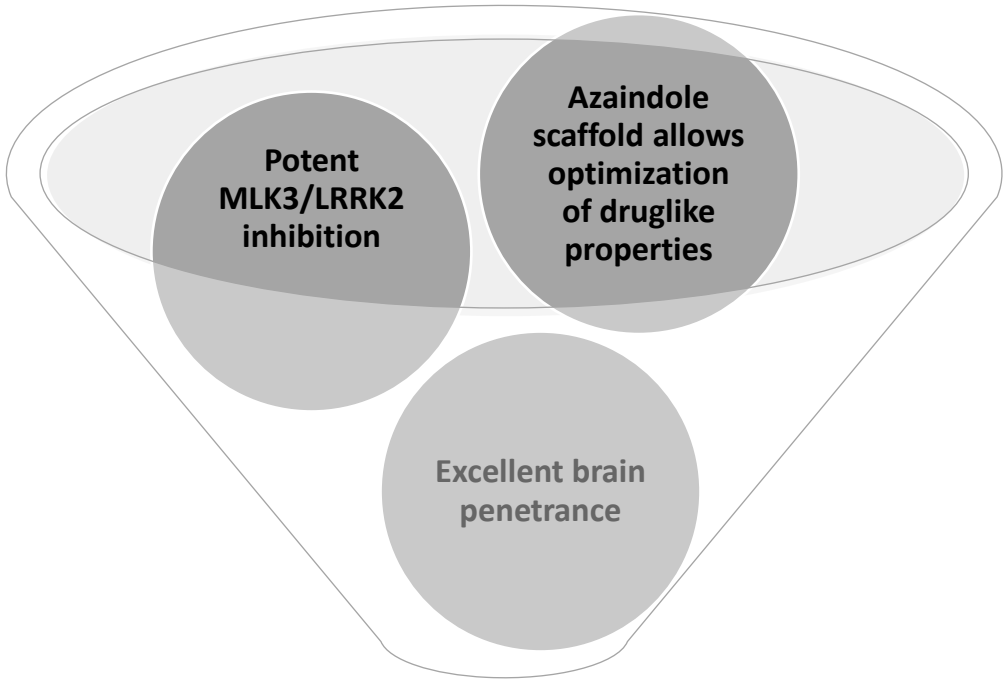
- **New composition of matter patent: acid addition salts, compositions and methods of treating therof, US 11,479,541, 10/25/2022 extends IP protection until 2042. New methods of use patent: US 11,661,409, 05/30/2023. Pioneura holds the exclusive license to all IP.**

- ***PIO-101 is the clinical candidate mono-tartrate salt. URMC-099 is the free base of PIO-101***

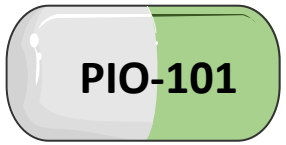
- **URMC-099 is a patented small molecule drug (US 8,877,772; 8,846,909; 10,485,800) created with >25mil NIH/Foundation funding to Gelbard, CSO of Pioneura Corp.**

- **Two key kinase targets – MLK3 and LRRK2 - dual inhibitory action to restore immune-inflammatory imbalance between microglia and neurons.**

- **Manufacturable, currently to >97% purity for PIO-101, scalable, and de-risked (for free base).**



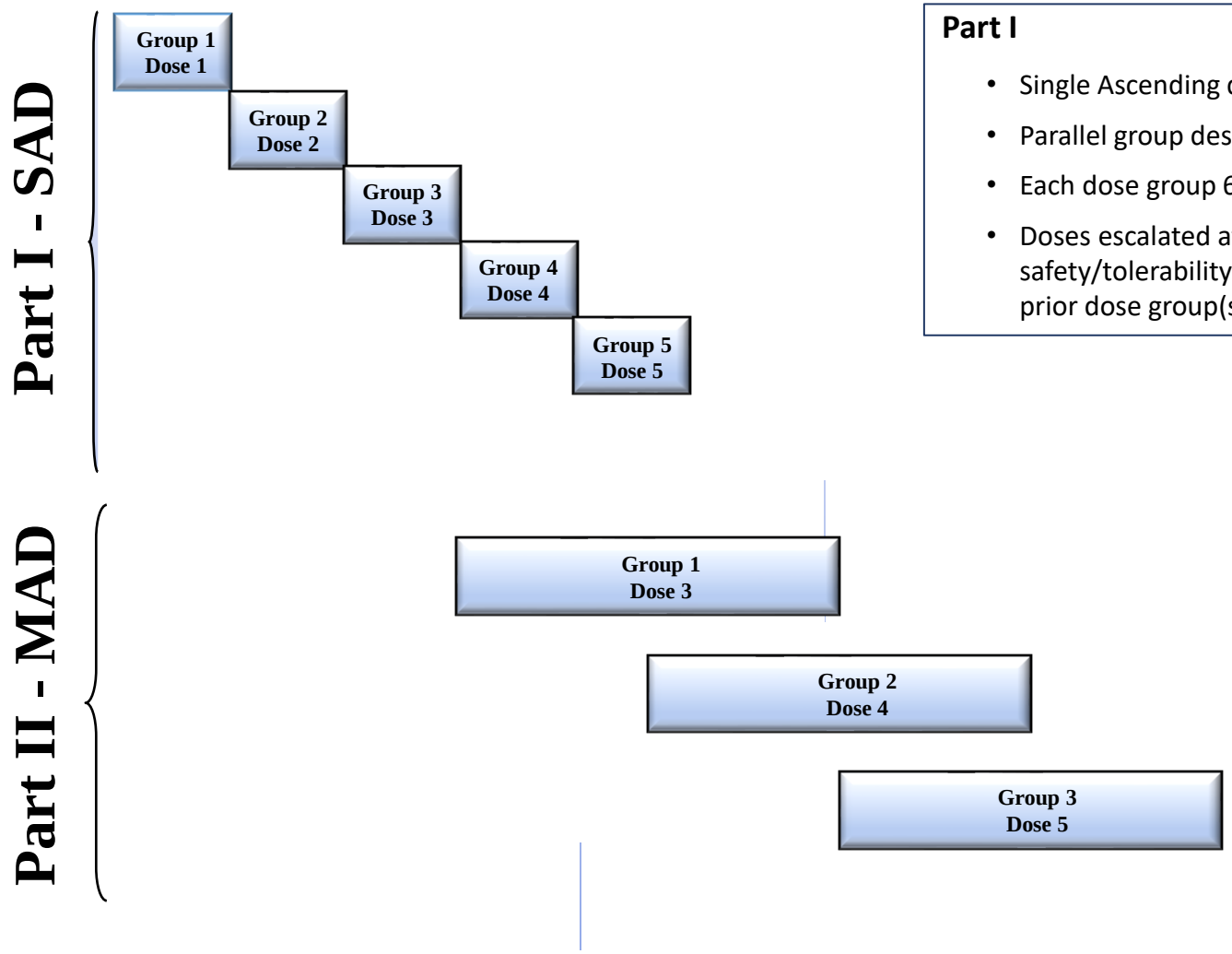
Increased oral absorption vs. URMC-099



PIO-101 Estimated Development Timeline

Task	Cost	Start	Finish	2024 01	02	03	04	2025 01	02	03	04	2026 01	02	03	04
Patent Filing	$50,000	03/01/22	03/01/23												
ADME Studies	$50,000	04/01/24	06//01/24		X										
Production of PIO-101 for preclinical and clinical studies (non-GMP, near-GMP and GMP lots)	$800,000	06/01/24	06/01/25		X	X	X	X	X						
Dose formulation analysis (including method transfer and validation)	$30,000	08/01/24	11/15/24			X	X								
Bioanalytical method transfer and validation	$91,200	09/01/24	12/15/24			X	X								
10-day DRF study in rodent species	$52,000	10/01/24	12/15/24			X	X								
10-day DRF study in non-rodent species	$106,000	10/01/24	01/01/25			X	X								
28-day GLP Tox studies in rodent species	$249,680	11/15/24	03/15/25				X	X							
28-day GLP Tox studies in non-rodent species	$359,670	11/15/24	03/15/25				X	X							
GLP Neurobehavioral Assessment in Rats	$45,500	12/15/24	03/15/25				X	X							
GLP CV Study in Dogs	$135,810	12/15/24	04/15/25				X	X	X						
GLP Respiratory Safety Study in Rats	$66,000	12/15/24	03/15/25				X	X							
FDA Pre-IND Meeting Preparation	$10,000	03/15/25	07/15/25					X	X	X					
IND Preparation, Compilation, and Submission	$50,000	05/01/25	10/01/25						X	X					
Clinical Site Contracting and Preparation of Phase 1 SAD-MAD Studies	Incl. in cost below	08/01/25	11/01/25							X	X				
Phase 1 SAD-MAD Studies	$2mil	11/01/25	08/01/26								X	X	X	X	
Chronic Toxicology Studies	$1.5mil	10/01/25	10/01/26								X	X	X	X	X

Phase 1 SAD/MAD Study: Designed to Quickly Show Safety, Target Engagement and Potentially Proof of Concept in PD Patients



Part I

- Single Ascending dose in Healthy Volunteers
- Parallel group design
- Each dose group 6:2 Active to Placebo
- Doses escalated after review of safety/tolerability and available PK data from prior dose group(s)

Part II

- Multiple Ascending for 14-28 days
- 2 cohorts in HV's for 14 days followed by 28 days of dosing in PD patient expansion cohort
- Each HV dose group 6:2 Active to Placebo
- Group 1 begins when 3 dose groups complete SAD
- Endpoints in PD patient group will include blood/CSF target engagement of LRRK2/MLK3 for biomarker studies and PD UPDRS endpoints
- Caveat: no direct ability to interrogate kinase activity in the CNS to determine PK/PD relationships

Richard Couch, CEO; Handy Gelbard, CSO and Board of Advisors:

Karl D. Kieburtz, M.D., M.P.H.
President, Clintrex, operationalize development pathways for new neurodegenerative disease therapies; long time collaborator with H. Gelbard

Jordan Dubow, M.D.
Chief Medical Officer, Clintrex

John McCall, Ph.D.
Co-founder of ReveraGen BioPharma, Advisor to NIINDS Blueprint for Neurotherapeutics; long time advisor to H. Gelbard

Jesse Damsker, Ph.D.
Chief Operating Officer, ReveraGen BioPharma, Acting COO for Pioneura

Fredric Manfredsson, Ph.D.
Associate Professor, Department of Translational Neuroscience at Barrow Neurological Institute; Collaborator with H. Gelbard.

Malú Gámez Tansey, Ph.D.
Professor of Neuroscience and Neurology, University of Florida; Collaborator with H. Gelbard

Niccolò Terrando, Ph.D.
Associate Professor of Anesthesiology, Duke University School of Medicine; Collaborator with H. Gelbard

Executive Summary

- **Immediate financial need:** Pioneura needs 3mil to initiate PIO-101 synthesis and completion of safety and toxicokinetic animal studies
- **Therapeutic Focus on Parkinson's disease:** 200+ compound library targeting mixed lineage kinase/leucine rich repeat kinase dysfunction in neuroinflammatory disease; new composition of matter and methods of use patents for formulation **extends IP protection through 2042**
- Platform Technology and Mission: Small molecule druglike compounds *with multi-target efficacy* culminating in development compound, PIO-101. **Two key kinase targets – MLK3 and LRRK2 - dual inhibitory action to restore immune-inflammatory imbalance between microglia and neurons**
- Pipeline: Demonstrated target engagement, robust patent protection through 2042
- Global partnerships: strong academic and industry collaborations
- Team: scientific and management team have a long history of successful collaborations
- Upcoming milestones: complete preclinical IND-enabling data package for PIO-101; begin planning for Phase 1 SAD/MAD study