Table 1 Selected candidate drugs targeting specific molecular pathways currently being investigated for disease-modification in Parkinson's disease. Abbreviations α -syn /α -synuclein; alpha-synuclein, AAV9; Adeno-associated virus vector 9, ADAS-cog; Alzheimer's Disease Assessment Scale-cognitive subscale, ATP; adenosine triphosphate, c-Abl; Abelson tyrosine kinase, CGIC; Clinician's Global Impression of Change, CNS; central nervous system, CSF; cerebrospinal fluid, GCase; Glucocerebrosidase, LRRK-2; Leucine-rich repeat kinase 2, MADRS-2;Montgomery Asberg Depression Rating Scale, MDS-UPDRS; Movement Disorders Society-Unified Parkinson Disease Rating Scale, NMSS; Non-Motor Symptoms Scale, SNCA; Alpha Synuclein gene, PD.

Molecular target	**Mechanism of action**	**Drug(s)**	**Efficacy in Preclinical models**	**Evidence supporting target engagement in PwP**	**Recruitment selection strategy/Primary outcomes**	**Current status**
Alpha-Synuclein -Potential therapies to reduce alpha-synuclein toxicity encompass those targeting protein synthesis and misfolding, fibril formation and aggregation, and cell-to-cell transmission as well as the enhancement of astrocytic actions. Reducing alpha -synuclein synthesis using antisense oligonucleotides and siRNAs are about to enter the early stages of human PD studies.	Inhibition of α-synuclein aggregation (stabilizing small molecule blockers)	anle138b	Efficacy in α -syn transgenic mice	Not yet available	Not yet available/ Safety & tolerability	Ongoing Phase 1 trial; NCT04208152
		NPT200-11	Efficacy in α -syn transgenic mice	Not yet available	Not yet available/ Safety & tolerability	Phase 1 trial Completed; NCT02606682
		Squalamine	Efficacy in cell lines, C.elegans	Does not access CNS	Not applicable	No longer being considered for PD disease modification
	Inhibition of α-synuclein aggregation (autophagy-cAbl inhibitors)	Nilotinib	Efficacy in α -syn transgenic mice	Levels of alpha-synuclein, Dopamine metabolites in CSF	PD patients on stable Dopaminergic treatment/ Safety & tolerability	Phase 2 trial Completed; NCT02954978
				Nilotinib levels and dopamine metabolites in CSF	PD patients on stable Dopaminergic treatment/ Safety & tolerability	Cohort 1 of phase 2 trial Completed concluding poor CSF penetration NCT03205488

		K-0706	Not available	CSF penetrant	PD patients not receiving dopaminergic therapy/ MDS-UPDRS Parts 2 and 3	Ongoing Phase 2 trial; NCT03655236
		ikt-148009	Efficacy in α -syn transgenic mice	Not available	Idiopathic PD Modified Hoehn and Yahr stage ≤ 2, Prior use of dopaminergic therapy for 30 or more days/ Safety, tolerability & Pharmacokinetic profile	Phase 1 trial in set-up; NCT04350177
	Anti-α-synuclein antibody	PRX002	Efficacy in α -syn transgenic mice	CSF antibody concentrations, lowering of free α -synuclein in CSF.	Early PD who are untreated or treated with monoamine oxidase B (MAO-B) inhibitors since baseline/ MDS-UPDRS Sum of Parts I, II, and III	Ongoing Phase 2 trial; NCT03100149
		BIIB054	Efficacy in α -syn transgenic mice	DATSCAN imaging Neuromelanin imaging CSF concentration of Ab, alpha-synuclein, neurodegenerative biomarkers.	PD patients not on medication for at least 12 weeks prior and not expected to require PD treatment for at least 6 months/ MDS-UPDRS Sum of Parts I, II, and III	Ongoing Phase 2 trial; NCT03318523
		PD01A Active alpha synuclein immunisation	Efficacy in α -syn transgenic mice	CSF PD01A specific antibody production, CSF alpha synuclein levels.	Not available	Phase 2 trial in set up.
	Reducing α-synuclein production	Antisense oligonucleotides (ASO)	Efficacy in α -syn transgenic mice	Not available	Not available	Not available

		Small interfering RNAs (siRNAs)	Efficacy in α -syn transgenic rat and mice, toxin treated rats, wild-type NHP.	Not available	Not available	Not available
	Reducing SNCA expression	β2 agonists	Efficacy in β2AR-deficient mice	Not available	Not available	Not available
LRRK2 -Dominantly inherited mutations in the Leucine-rich repeat kinase 2 (LRRK2) locus cause familial PD while polymorphisms close to the gene increase the risk of sporadic PD.	LRRK2 inhibitors (promoting autophagy)	DNL201 and DNL151	Efficacy in animal models of LRRK2	CSF levels of drug, LRRK2 pS935 in peripheral blood	Not available/ Safety & tolerability Safety & tolerability	Completed Phase 1 trial; NCT03710707, Ongoing Phase 1 trial; NCT04056689
	Antisense oligonucleotide for LRRK2 inhibition	BIIB094 (intrathecal)	Efficacy in α -syn transgenic mice	Pharmacokinetic study	PD patients with or without LRRK2 mutation/ Safety & tolerability	Ongoing Phase 1 trial; NCT03976349
Glucocerebrosidase (Lysosomal function) -Lysosomal dysfunction may occur in PD as a primary trigger, but also as a secondary process following alpha synuclein pathology. Correcting lysosomal dysfunction has therefore been explored as a therapeutic approach.	Modulator of GCase activity	Ambroxol -acts as a chaperone of the lysosomal enzyme β-glucocerebrosidase (GCase)	Efficacy in a-syn transgenic mice	CSF levels, GCase activity	PD patients with GBA (+ & -)/ ADAS-cog & CGIC Glucocerebrosidase and ambroxol levels in blood and CSF	Ongoing Phase 2 trial; NCT02914366 Completed Phase 2 trial; NCT02941822
		LTI-291	Not available	CSF levels of drug and glycosphingolipids FDG PET Functional MRI	Not available	Ongoing Phase 1 trial; EudraCT2017-004086-27
	Substrate reduction	Venglustat	Efficacy in α -syn pathological models of PD (with and without GBA mutations)	CSF levels of drug and glucosylceramide	GBA-associated PD/ MDS-UPDRS Part II and III scores	Ongoing Phase 2 trial; NCT02906020

	GCase gene therapy	PR001 (Intra-cisternal injection)	Efficacy in α -syn transgenic mice & murine models of synucleinopathy	CSF and serum levels of GCase and glycosphingolipids	Moderate to severe Parkinson's disease with at least 1 pathogenic GBA1 mutation/ Safety & tolerability, Change in immunogenicity of AAV9 & GCase in blood & CSF	Ongoing Phase 1 trial; NCT04127578

Table 2 Selected candidate drugs with specific neuronal rescue targets currently being investigated for disease-modification in Parkinson's disease. Abbreviations CGIC; Clinician's Global Impression of Change, CNS; central nervous system, CSF; cerebrospinal fluid, MADRS-2; Montgomery Asberg Depression Rating Scale, MDS-UPDRS; Movement Disorders Society-Unified Parkinson Disease Rating Scale, NMSS; Non-Motor Symptoms Scale.

Molecular target	**Mechanism of action**	**Drug(s)**	**Efficacy in Preclinical models**	**Evidence supporting target engagement in PwP**	**Recruitment selection strategy/Primary outcomes**	**Current status**
Neuroinflammation -Non-steroidal anti-inflammatory drugs (NSAIDs) have been explored for their potential neuroprotective effect. Although one retrospective study comparing	Inhibition of microglial activation	Minocycline	Efficacy in MPTP mouse model	Clinical measures only	PD patients on stable dopaminergic treatment/ time to initiation of symptomatic pharmaceutical treatment	Negative Phase 2 trial; NCT00063193
	Altered T-cell lineage	Sargramostim	Efficacy in MPTP mouse model	Improved regulatory T cell function	PD symptoms of at least 3 years/ Safety & tolerability	Completed & ongoing Phase 1 trials; NCT01882010 NCT03790670

patients taking more than two anti-inflammatory doses per week for at least 1 month found a reduced risk of PD compared with controls, subsequent meta-analyses have failed to support this assertion.					Safety & tolerability	
	Enzyme myeloperoxidase (MPO) inhibition	AZD3241	Efficacy in MPTP mouse model, alpha-synuclein MSA model.	Microglial PET imaging	Untreated PD Safety & tolerability Pharmacokinetics PET binding ([11C] PBR28 to TSPO)	Ongoing Phase 2 trials; NCT01603069 NCT01457807 NCT01527695
	NLR family pyrin domain containing 3" (NLRP3) inflammasome inhibition	Inzomelid	Efficacy in MPTP mouse model	Measurement of blood NLRP3 inhibition (results pending)	Healthy Volunteers/ Safety & tolerability, Pharmacokinetics & Pharmacodynamics	Completed (results pending) Phase 1 trial; NCT04015076
	3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) inhibition	Simvastatin	Efficacy in MPTP mouse model	Clinical measures only	PD, Hoehn & Yahr stage $\leq$ 3.0 in the ON medication state/ MDS-UPDRS part III (OFF)	Ongoing phase 2 trial; NCT02787590
	Inhibition of nucleic acid synthesis, reduced	Azathioprine	None in PD models	Microglial PET imaging	Early PD predicted to progress rapidly/	Phase 2 trial in set up.

	lymphocyte proliferation			CSF neuroinflammatory profile	MDS-UPDRS part III (OFF)	EudraCT Number: 2018-003089-14
Mitochondrial function -Abnormalities in a number of genes involved in normal mitochondrial function can lead to premature nigrostriatal cell death and parkinsonism.	Improved mitochondrial biogenesis	Pioglitazone	Efficacy in Cox10/DAT-cre mice and MPTP NHP.	Clinical measures, Blood and urine biomarkers	Early Parkinson's disease on a stable regimen/ MDS-UPDRS Sum of Parts I, II, and III	Negative phase 2 trial; NCT01280123
	Increased urate, (antioxidant)	Inosine	Efficacy in MPTP and 6-OHDA mouse models	Measurement of serum urate	Idiopathic PD Modified Hoehn and Yahr stage ≤ 2.5/ MDS-UPDRS Sum of Parts I, II, and III Safety & tolerability	Negative phase 3 trial; NCT02642393 NCT00833690
	Improved mitochondrial function	Ursodeoxycholic acid	Efficacy on mitochondrial function in parkin/ LRRK2 cells	ATP levels using ^{31}P MR spectroscopy	Idiopathic PD, Hoehn and Yahr stage ≤ 2.5/ Safety & tolerability 7 Tesla Magnetic Resonance Spectroscopy (ATP concentration)	Ongoing Phase 2 trials; NCT03840005 NCT02967250
Calcium	L-type calcium channel blocker	Isradipine	Efficacy in MPTP and 6-OHDA mouse models	Clinical measures only	Untreated PD Hoehn and Yahr stage ≤ 2.0/ MDS-	Negative phase 3 trial; NCT02168842

-The use of dihydropyrine calcium channel blockers for hypertension has been associated with a reduced risk of PD, although this is not a consistent finding and may be confounded by the use of beta blockers and/or smoking use.					UPDRS Sum of Parts I, II, and III	
Iron	Iron chelation	Deferiprone	Efficacy in α -syn transgenic mice	Reduced iron levels in substantia nigra on MRI	Untreated PD patients/ MDS-UPDRS MDS-UPDRS Part 3	Ongoing Phase 2 trials; NCT02655315, NCT02728843
Insulin resistance	GLP-1 receptor agonists (reduced insulin resistance, reduced inflammation and alpha-synuclein aggregation)	Exenatide NLY01	Protective in dopaminergic toxin and alpha synuclein based models.	Measures of insulin resistance in serum, CSF and neuronal derived exosomes, DATSCAN uptake	PD, Hoehn and Yahr stage ≤ 2.5/ MDS-UPDRS Part 3 MDS-UPDRS Part 2 +3	Ongoing Phase 3 trials; NCT04232969 Ongoing Phase 2; NCT04154072
		Liraglutide	Efficacy in MPTP mouse model	Measurement of insulin resistance	PD at least 2 years/ MDS-UPDRS Part 3,	Ongoing Phase 2 trial; NCT02953665

					NMSS& MADRS-2	
		Lixisenatide	Efficacy in MPTP mouse model	Clinical measures only	PD Hoehn and Yahr stage ≤ 3.0/ MDS-UPDRS Part 3	Ongoing Phase 2 trial; NCT03439943
		Semaglutide	Efficacy in MPTP mouse model	DATSCAN uptake	Early PD/ MDS-UPDRS Part 3 OFF medication	Ongoing Phase 2 trial; NCT03659682