

Supplementary Material

Parkinson's Disease Drug Development Since 1999: A Story of Repurposing and Relative Success

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Supplementary Table 1. Collective reasons for trial exclusions

Reason for exclusion	Number of trials excluded
Non-pharmacological intervention	720
Observational study	392
Diagnostic trial	51
Ineligible population	50
Duplicate	13
Risk factor/association study	4
Economic analysis	2

Supplementary Table 2. Data provenance by database

Database	Number of trials
Clinicaltrials.gov	251 (70.3%)
EUDRACT	51 (14.3%)
UMIN-CTR	29 (8.1%)
Other registries	26 (7.3%)

Supplementary Table 3. Trial location by country

Trial location	Number of trials
Exclusively in Europe	116 (32.5%)
Exclusively in the USA	91 (25.5%)
Exclusively in others	79 (22.1%)
Both in the USA and Europe and others	25 (7.0%)
Both in the USA and others	14 (3.9%)
Not specified	14 (3.9%)
Both in Europe and others	10 (2.8%)
Both in the USA and Europe	7 (2.0%)

Supplementary Table 4. Trial funding

Funder	Number of trials with original compounds	Number of trials repurposing compounds	Total number of trials
Exclusively industry-funded	146 (76.4%)	56 (32.6%)	202 (56.6%)
Combinations	14 (7.3%)	30 (17.4%)	44 (12.3%)
University-funded	7 (3.7%)	30 (17.4%)	37 (10.4%)
NIH-funded	17 (8.9%)	18 (10.5%)	35 (10.0%)
Hospital-funded	6 (3.1%)	28 (16.3%)	34 (9.8%)
Others	1 (0.5%)	4 (2.3%)	5 (1.4%)

Supplementary Table 5. Trials at 5-year intervals

Year of registration	Phase 1	Phase 1/2	Phase 2	Phase 3	Phase 4	Unknown phase	Total
1999-2004	0	1	15	6	3	1	26
2005-2009	4	0	29	36	21	2	92
2010-2014	22	0	28	24	10	2	86
2015-2019	36	10	63	19	19	6	153
Total	62	11	135	85	53	11	351

Supplementary Table 6. Parkinson's disease population by trial phase

Trial phase	Healthy subjects	All stages	Early PD	Early PD, late onset	Early-to-moderate PD	Early-to-advanced PD	Moderate-to-advanced PD	Moderate-to-late PD	Moderate PD	Advanced PD	Advanced-to-late PD	Late PD	Total
1	31	4	1	-	5	4	1	1	2	7	1	5	62
1/2	-	-	1	-	3	2	1	-	-	2	2	-	11
2	-	21	20	1	10	23	11	3	4	29	8	5	135
3	-	12	16	-	5	9	4	3	-	27	7	2	85
4	-	11	5	-	3	13	1	-	-	15	4	1	53
Unknown	-	3	1	-	-	1	1	-	-	4	1	-	11
Total	31	51	45	1	26	52	18	6	6		23	13	351

PD, Parkinson's disease.

Note: We defined advanced Parkinson's disease as one of: on/off phenomena or motor fluctuations. We defined late-stage Parkinson's disease as the presence of one of: dementia, being non-autonomous, or orthostatic hypotension.

Supplementary Table 7. Approval according to compound originality

Compound type	Compound approved by EMA?	
	No	Yes
Original compound	44	12
Repurposed compound	43	2
	Compound approved by FDA?	
	No	Yes
Original compound	44	12
Repurposed compound	42	3

Supplementary Table 8. Complete clinical overview of phase 1 trials

Primary trial aim	Number of trials	Number of repurposing trials	ATC anatomical category	ATC therapeutic category	ATC chemical category	Compounds	Mechanism of action	Trial ID
Dementia associated with PD	2	1	Antineoplastic and immunomodulating agents (1)	Antineoplastic agents (1)	Protein kinase inhibitors (1)	Nilotinib (1)	Tyrosine kinase inhibitor	NCT02281474
			<i>No ATC (1)</i>	<i>No ATC (1)</i>	<i>No ATC (1)</i>	ENT-01 (1)	Alpha-synuclein inhibitor	NCT03938922
Depression associated with PD	1	1	Musculo-skeletal system (1)	Muscle relaxants (1)	Other muscle relaxants, peripherally acting agents (1)	Botulinum neurotoxin type A (1)	Acetylcholinesterase inhibitor	NCT03069911
Disease modifying	11	5	Alimentary tract and metabolism (1)	Bile and liver therapy (1)	Bile acids and derivatives (1)	Ursodeoxycholic Acid (1)	Apoptosis inhibitor	NCT02967250
			Antineoplastic and immunomodulating agents (1)	Immunostimulants (1)	Colony stimulating factors (1)	Sargramostim (1)	Hematopoietic growth factor	NCT03790670
			Blood and blood forming organs (1)	Antianemic preparations (1)	Other antianemic preparations (1)	Erythropoietin (1)	Growth factor	NCT01010802
			Various (1)	All other therapeutic products (1)	Antidotes (1)	N-acetylcysteine (1)	Antioxidant	NCT03104725
			<i>No ATC (7)</i>	<i>No ATC (7)</i>	<i>No ATC (7)</i>	K0706 (1)	Tyrosine kinase inhibitor	NCT02970019

						AFFITOPE® PD03A (1)	Alpha-synuclein-mimicking peptide	NCT02267434
						DNL201 (1)	LRRK2 Kinase Inhibitor	NCT03710707
						KM-819 (1)	Apoptosis inhibitor	NCT03022799
						Lu AF82422 (1)	Alpha-synuclein inhibitor	NCT03611569
						Cu(II)ATSM (1)	Copper-containing synthetic small molecule	NCT03204929
						DNL104 (1)	Serine threonine kinase inhibitor	NTR6257
Dyskinesia	1	1	No ATC (1)	No ATC (1)	No ATC (1)	Preladenant (1)	Selective adenosine A2A receptor antagonist	NCT00845000
Early stage PD	1	0	No ATC (1)	No ATC (1)	No ATC (1)	KDT-3594 (1)	Dopaminergic agonist	NCT03068481
Motor fluctuations	28	1	Nervous system (27)	Antiparkinsonian drugs (27)	Dopa and dopa derivatives (6)	Levodopa (2)	Dopamine precursor	NCT02812394; NTR5435
						Levodopa-Carbidopa (2)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	NCT01484990; NCT03419806

						Levodopa- Carbidopa- Entacapone (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor + COMT inhibitor	NCT02448914
						Melevodopa- Carbidopa (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	EUCTR2006- 004112-51
					Dopamine agonists (3)	Apomorphine (1)	Dopaminergic agonist	NCT03822364
						Rotigotine (2)	Dopaminergic agonist	NCT03589066; NCT03733561
					Other dopaminergic agents (18)	Opicapone (18)	COMT inhibitor	NCT01515891; NCT01519284; NCT01520727; NCT01520987; NCT01532115; NCT01532128; NCT01532141; NCT01533077; NCT01533116; NCT01536366; NCT02071823; NCT02092168; NCT02305277; NCT02305316; NCT03116308; NCT03119194; NCT03496870; NCT03820037

			No ATC (1)	No ATC (1)	No ATC (1)	Lu AE04621 (1)	Dopaminergic agonist	NCT02649608	
Orthostatic hypotension	2	2	Cardiovascular system (2)	Cardiac therapy (2)	Adrenergic and dopaminergic agents (2)	Droxidopa (2*)	Norepinephrine precursor	NCT00547911; NCT02897063	
						Midodrine (1*)	Vasopressor/antihypotensive agent	NCT02897063	
Parkinsonism	15	9	Nervous system (5)	Antiparkinsonian drugs (3)	Dopa and dopa derivatives (1)	Levodopa-Carbidopa-ODM-104 (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor + COMT inhibitor	NCT03140956	
					Dopamine agonists (2)	Ropinirole (2)	Dopaminergic agonist	NCT01371682; NCT01435915	
				Psychoanalitics (2)	Anticholinesterases (1)	Donepezil (1)	Acetylcholinesterase inhibitor	NCT03599726	
					Centrally acting sympathomimetics (1)	Modafinil (1)	Dopamine reuptake inhibitor	NCT03083132	
			Genito-urinary system and sex hormones (1)	Gynecological antiinfectives and antiseptics (1)	Other antiinfectives and antiseptics (1)	Inosine (1)	Urate precursor	JPRN-UMIN000009062	
			No ATC (9)	No ATC (9)	No ATC (9)		PF-06649751 (1)	Dopaminergic agonist	NCT02373072
							PBF-509 (2)	Selective adenosine A2A receptor antagonist	NCT01691924; NCT02111330

						Trans-resveratrol (6)	Natural polyphenolic	NCT03091543; NCT03091868; NCT03093389; NCT03095092; NCT03095105; NCT03097211
Psychosis associated with PD	1	1	<i>No ATC (1)</i>	<i>No ATC (1)</i>	<i>No ATC (1)</i>	Saracatinib (1)	Tyrosine kinase inhibitor	NCT03661125

*Indicates multiple compounds were tested within one trial. Abbreviations: ATC, Anatomical Therapeutic Chemical classification system; CNS, central nervous system; COMT, catechol-O-methyltransferase; GABA, gamma-aminobutyric acid; GLP-1, Glucagon-like peptide-1; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; HPPD, Hydroxyphenylpyruvate dioxygenase; LRRK2, Leucine-rich repeat kinase 2; MAO-B, monoamine oxidase B; NDRI, norepinephrine–dopamine reuptake inhibitor; NMDA, N-methyl-D-aspartate; PD, Parkinson’s disease; SNRI, Serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

Supplementary Table 9. Complete clinical overview of phase 2 trials

Primary trial aim	Number of trials	Number of repurposing trials	ATC anatomical category	ATC therapeutic category	ATC chemical category	Compounds	Mechanism of action	Trial ID	
Dementia associated with PD	7	5	Cardiovascular system (1)	Agents acting on the renin–angiotensin system (1)	Angiotensin II receptor blockers (ARBs) (1)	Candesartan (1)	Angiotensin Receptor Blocker	EUCTR2016-000679-25	
			Nervous system (3)	Other nervous system drugs (1)	Drugs used in nicotine dependence (1)	Nicotine (1)	Nicotinic Acetylcholine Receptor Agonist	JPRN-UMIN000016664	
						Psychoanaleptics (2)	Anticholinesterases (1)	Donepezil (1)	Acetylcholinesterase inhibitor
			No ATC (3)	No ATC (3)	No ATC (3)		Other anti-dementia drugs (1)	Memantine (1)	NMDA receptor antagonist
						GRF6021 (1)	Human plasma protein fraction	NCT03713957	
						Insulin (1)	Insulin	NCT02064166	
			Safinamide (1)	MAO-B inhibitor	PER-094-10				
Depression associated with PD	5	5	Nervous system (4)	Antiparkinsonian drugs (1)	Dopa and dopa derivatives (1)	Levodopa (1)	Dopamine precursor	IRCT2014092119243N1	
				Psychoanaleptics (3)	Other antidepressants (2*)	Duloxetine (2*)	SNRI	JPRN-UMIN000016893; JPRN-UMIN000015559	
						Selective serotonin reuptake inhibitors (2*)	Paroxetine (2*)	SSRI	JPRN-UMIN000015559; NCT00062738
							Escitalopram (1)	SSRI	JPRN-UMIN000015559

					Non-selective monoamine reuptake inhibitors (1)	Nortriptyline (1)	Tricyclic antidepressant	NCT00062738
						Istradefylline (1)	Selective adenosine A2A receptor antagonist	JPRN-UMIN000022021
Disease modifying	11	9	Antiinfectives for systemic use (1)	Antibacterials for systemic use (1)	Tetracyclines (1)	Minocycline (1*)	Antibiotic	NCT00063193
			Antineoplastic and immunomodulating agents (1)	Antineoplastic agents (1)	Protein kinase inhibitors (1)	Nilotinib (1)	Tyrosine kinase inhibitor	NCT02954978
			Various (3*)	All other therapeutic products (3*)	Iron chelating agents (2)	Deferiprone (2)	Iron Chelator	EUCTR2008-006842-25; NCT02655315
					Antidotes (1)	N-acetylcysteine (1)	Antioxidant	NCT02212678
			Genito-urinary system and sex hormones (1)	Gynecological antiinfectives and antiseptics (1)	Other antiinfectives and antiseptics (1)	Inosine (1)	Urate precursor	NCT00833690
			No ATC (6)	No ATC (6)	No ATC (6)	Creatine (1*)	Mitochondrial energy supplier	NCT00063193
						Ambroxol (1)	Alpha-synuclein inhibitor	NCT02941822
						GPI 1485 (1)	Immunophilin compound	NCT00076492
						GM1 Ganglioside (1)	Neurotrophic	NCT00037830
						Paliroden (1)	Neurotrophic	EUCTR2004-001330-16
Ubiquinol (1)	Antioxidant	NCT03061513						

Dyskinesia	18	14	Cardiovascular system (1)	Lipid modifying agents (1)	HMG CoA reductase inhibitors (1)	Simvastatin (1)	Statin	EUCTR2009-011736-35
			Nervous system (6)	Antiparkinsonian drugs (4*)	Adamantane derivatives (4*)	Amantadine (4*)	NMDA receptor antagonist	JPRN-UMIN00000780; NCT01538329; NCT01190553; JPRN-UMIN000010596
				Antiepileptics (2)	Other antiepileptics (2)	Levetiracetam (2)	Antiepileptic	NCT00160576; NCT00076674
				Psychoanalitics (1)	Other anti-dementia drugs (1*)	Memantine (1*)	NMDA receptor antagonist	JPRN-UMIN000010596
			No ATC (11)	No ATC (11)	No ATC (11)	Etoprozine (1)	Serotonin receptor agonist	EUCTR2009-015928-28
						Foliglurax (1)	Metabotropic glutamate receptor 4 modulator	NCT03331848
						IRL790 (1)	Dopaminergic agonist	NCT03368170
						Mavoglurant (3)	Metabotropic glutamate receptor 5 antagonist	NCT01385592; NCT01491529; EUCTR2010-019418-25
						Preladenant (1)	Selective adenosine A2A receptor antagonist	PER-037-03
						Pridopidine (1)	Dopidine	NCT03922711
						Sarizotan (1)	Dopaminergic and serotonin agonist	NCT00314288

						Talampanel (2)	AMPA receptor antagonist	NCT00108667; NCT00004576		
Early stage PD	15	7	Alimentary tract and metabolism (2)	Drugs used in diabetes (2)	GLP-1 Analogues (2)	Lixisenatide (1)	GLP-1 receptor agonist	NCT03439943		
						Semaglutide (1)	GLP-1 receptor agonist	NCT03659682		
			Cardiovascular system (3)	Beta blocking agents (1)	Alpha and beta blocking agents (1)	Carvedilol (1)	Beta-adrenergic blocking agent	NCT03775096		
						Calcium channel blockers (1)	Dihydropyridine derivatives (1)	Isradipine (1)	Calcium channel blocker	NCT00909545
								Lipid modifying agents (1)	HMG CoA reductase inhibitors (1)	Lovastatin (1)
			Nervous system (1)	Antiepileptics (1)	Other antiepileptics (1)	Zonisamide (1)	Antiepileptic	NCT01766128		
			No ATC (9)	No ATC (9)	No ATC (9)	Aplindore (1)	Dopaminergic agonist	NCT00809302		
						G-CSF (1)	Anti-inflammatory and antiapoptotic	NCT01227681		
						GM608 (1)	Neurotrophic	NCT01850381		
						K0706 (1)	Tyrosine kinase inhibitor	NCT03655236		
						KDT-3594 (1)	Dopaminergic agonist	NCT03845387		
						Paliroden (2)	Neurotrophic	NCT00220272; NCT00228150		
						PF-06649751 (1)	Dopaminergic agonist	NCT02847650		
Tesofensine (1)	Triple reuptake inhibitor	NCT00148486								

Falling	4	4	Cardiovascular system (2)	Cardiac therapy (2)	Adrenergic and dopaminergic agents (2)	Droxidopa (2)	Norepinephrine precursor	NCT02812147; NCT03567447
			Nervous system (2)	Other nervous system drugs (1)	Drugs used in nicotine dependence (1)	Varenicline (1)	Acetylcholinesterase inhibitor	NCT01341080
				Psychoanaleptics (1)	Anticholinesterases (1)	Rivastigmine (1)	Acetylcholinesterase inhibitor	ISRCTN19880883
Fatigue	1	1	Cardiovascular system (1)	Cardiac therapy (1)	Adrenergic and dopaminergic agents (1)	Droxidopa (1)	Norepinephrine precursor	NCT03446807
Motor fluctuations	22	6	Alimentary tract and metabolism (1)	Other alimentary tract and metabolism products (1)	Various alimentary tract and metabolism products (1)	Nitisinone (1)	HPPD inhibitor	EUCTR2009-013670-41
			Cardiovascular system (1)	Diuretics (1)	Sulfonamides (1)	Bumetanide (1)	Diuretic	NCT03899324
			Nervous system (10)	Antiparkinsonian drugs (9)	Dopa and dopa derivatives (4)	Levodopa-Carbidopa (3*)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	NCT02763137; NCT03576638; NCT00562198
					Dopamine agonists (4*)	Apomorphine (2)	Dopaminergic agonist	NCT03187301; NCT03292016
						Ropinirole (2*)	Dopaminergic agonist	NCT00460148; JPRN-UMIN000003601
					Other dopaminergic agents (1*)	Entacapone (1*)	COMT inhibitor	JPRN-UMIN000003601
						Opicapone (1)	COMT inhibitor	EUCTR2008-003869-72
			Other nervous system drugs (1)	Drugs used in nicotine dependence (1)	Nicotine (1)	Nicotinic Acetylcholine Receptor Agonist	EUCTR2008-001336-13	

			Genito-urinary system and sex hormones (1)	Gynecological antiinfectives and antiseptics (1)	Other antiinfectives and antiseptics (1)	Inosine (1)	Urate precursor	JPRN-UMIN000020527
			<i>No ATC (9)</i>	<i>No ATC (9)</i>	<i>No ATC (9)</i>	BTRX-246040 (1)	Opioid receptor antagonist	NCT03608371
						Foliglurax (1)	Metabotropic glutamate receptor 4 modulator	NCT03162874
						Nebicapone (1)	COMT inhibitor	NCT03103399
						PF-06649751 (1)	Dopaminergic agonist	NCT02687542
						Preladenant (2)	Selective adenosine A2A receptor antagonist	EUCTR2005-005146-39; PER-091-03
						Safinamide (1)	MAO-B inhibitor	EUCTR2008-002769-30
						Tesofensine (1)	Triple reuptake inhibitor	NCT00148512
						Istradefylline (1)	Selective adenosine A2A receptor antagonist	NCT00455507
Neuro-psychiatric	6	6	Nervous system (5)	Antiepileptics (1)	Other antiepileptics (1)	Gabapentin (1)	Antiepileptic	EUCTR2011-005839-91
				Other nervous system drugs (1)	Drugs used in alcohol dependence (1)	Nalmefene (1)	Opioid receptor modulator	NCT02934919
				Psychoanaleptics (1)	Anticholinesterases (1)	Donepezil (1)	Acetylcholinesterase inhibitor	JPRN-UMIN000010778

				Psycholeptics (2)	Anxiolytics - Azaspirodecane dione derivatives (1)	Buspirone (1)	Serotonin receptor agonist	NCT02803749
					Other antipsychotics (1)	Pimavanserin (1)	Serotonin blocker	NCT03947216
			No ATC (1)	No ATC (1)	No ATC (1)	Safinamide (1)	MAO-B inhibitor	EUCTR2010-020109-34
Orthostatic hypotension	1	0	No ATC (1)	No ATC (1)	No ATC (1)	Amprelosetine (1)	Norepinephrine reuptake inhibitor	NCT02705755
Other	4	3	Alimentary tract and metabolism (1)	Antiemetics and anti-nauseants (1)	Other antiemetics (1)	Nabilone (1)	Cannabinoid	NCT03769896
			Musculo-skeletal system (1)	Drugs for treatment of bone diseases (1)	Other drugs affecting bone structure and mineralization (1)	Denosumab (1)	Calcium regulator	JPRN-UMIN000025056
			Nervous system (2)	Antiparkinsonian drugs (1)	Dopamine agonists (1*)	Pramipexole	Dopaminergic agonist	NCT00096720
					Dopa and dopa derivatives (1*)	Levodopa (1)	Dopamine precursor	NCT00096720
Antiepileptics (1)	Other antiepileptics (1)	Cannabidiol (1)	Cannabinoid	NCT03639064				
Parkinsonism	28	16	Alimentary tract and metabolism (2)	Drugs used in diabetes (1)	GLP-1 Analogues (1)	Liraglutide (1)	GLP-1 receptor agonist	NCT02953665
				Antiemetics and anti-nauseants (1)	Other antiemetics (1*)	Aprepitant (1*)	Antiemetic	NCT03683225
			Antineoplastic and immunomodulating agents (1)	Antineoplastic agents (1)	Protein kinase inhibitors (1)	Nilotinib (1)	Tyrosine kinase inhibitor	NCT03205488

Musculo-skeletal system (4*)	Antigout preparations (1*)	Preparations inhibiting uric acid production (1*)	Febuxostat (1)	Xanthine oxidase inhibitor	JPRN-UMIN000030930
	Muscle relaxants (3)	Other muscle relaxants, peripherally acting agents (3)	Botulinum toxin (3)	Acetylcholinesterase inhibitor	NCT02419313; NCT02427646; NCT03301272
Genito-urinary system and sex hormones (1*)	Gynecological antiinfectives and antiseptics (1*)	Other antiinfectives and antiseptics (1*)	Inosine (1)	Urate precursor	JPRN-UMIN000030930
Nervous system (13)	Analgesics (1)	Ergot alkaloids (1)	Lisuride (1)	Dopaminergic and serotonin agonist	NCT00089622
			Levodopa (1)	Dopamine precursor	EUCTR2010-020769-25
	Antiparkinsonian drugs (6*)	Dopamine agonists (5*)	Pramipexole (2*)	Dopaminergic agonist	NCT03683225; JPRN-UMIN000002163
			Ropinirole (2*)	Dopaminergic agonist	JPRN-UMIN000002163; NCT00434304
			Rotigotine (2)	Dopaminergic agonist	NCT00001931; EUCTR2013-000827-15
			Selegiline (1*)	MAO-B inhibitor	JPRN-UMIN000022533
	Antiepileptics (3*)	Other antiepileptics (3*)	Zonisamide (1)	MAO-B inhibitor	JPRN-UMIN000022533
			Cannabidiol (1)	Cannabinoid	NCT03582137
			Selegiline (1*)	MAO-B inhibitor	JPRN-UMIN000022533
			Zonisamide (2*)	Antiepileptic	JPRN-UMIN000022533; JPRN-UMIN000010371

				Other nervous system drugs (1)	Drugs used in nicotine dependence (1)	Nicotine (1)	Nicotinic Acetylcholine Receptor Agonist	NCT03865121
				Psychoanaleptics (3)	Anticholinesterases (2*)	Donepezil (2*)	Acetylcholinesterase inhibitor	NCT02857244; JPRN-UMIN000003080
					Other antidepressants (2*)	Duloxetine (2*)	SNRI	JPRN-UMIN000016734; NCT02857244
					Centrally acting sympathomimetics (1*)	Modafinil (1*)	Dopamine reuptake inhibitor	NCT02857244
				Psycholeptics (1)	Benzodiazepine related drugs (1)	Zolpidem (1)	GABA-A receptor positive allosteric modulator	NCT03621046
			Genito-urinary system and sex hormones (1*)	Gynecological antiinfectives and antiseptics (1*)	Other antiinfectives and antiseptics (1*)	Inosine (1*)	Urate precursor	JPRN-UMIN000030930
			<i>No ATC (8)</i>	<i>No ATC (8)</i>	<i>No ATC (8)</i>	PF-06412652 (1)	Dopaminergic agonist	NCT03665454
						Safinamide (1)	MAO-B inhibitor	NCT01264861
						CVXL-0107 (1)	Glutamate release inhibitor	NCT02641054
						Eliprodil (1)	NMDA receptor antagonist	NCT00001929
						Fipamezole (1)	Adrenergic agonist	NCT00040209
						Fursultiamine (1)	Thiamine	JPRN-UMIN000025703
						Mucuna pruriens (1)	Dopamine precursor	PACTR201611001882367

						Zuranolone (1)	GABA-A receptor positive allosteric modulator	NCT03000569
Psychosis associated with PD	4	2	Nervous system (3)	Antiparkinsonian drugs (1)	Dopamine agonists (1)	Aripiprazole (1)	Dopaminergic and serotonin agonist	JPRN-UMIN000007711
				Psycholeptics (2)	Antipsychotics - Butyrophenone derivatives (1)	Melperone (1)	Atypical antipsychotic	EUCTR2007-000307-15
					Other antipsychotics (1)	Pimavanserin (1)	Serotonin blocker	NCT00087542
			No ATC (1)	No ATC (1)	No ATC (1)	SEP-363856 (1)	Serotonin receptor agonist	NCT02969369
Sleep disorders	8	5	Nervous system (4)	Antiparkinsonian drugs (1)	Monoamine oxidase B inhibitors (1)	Rasagiline (1)	MAO-B inhibitor	EUCTR2008-002145-22
				Other nervous system drugs (1)	Other nervous system drugs (1)	Sodium Oxybate (1)	CNS depressant	NCT00641186
				Psychoanalitics (1)	Centrally acting sympathomimetics (1)	Modafinil (1)	Psychostimulant	JPRN-UMIN000019676
				Psycholeptics (1*)	Melatonin receptor agonists (1*)	Melatonin (1*)	Hormone for sleep-wake cycle	NCT02789592
				Antiepileptics (1*)	Benzodiazepine derivatives (1*)	Clonazepam (1*)	Benzodiazepine	NCT02789592
			No ATC (4)	No ATC (4)	No ATC (4)	BEN-2001 (1)	Histamine receptor antagonist	NCT03194217
						Solriamfetol (1)	NDRI	NCT03037203

						THN102 (1)	Glial connexin inhibitor	NCT03624920
						Tiprolisant (1)	Histamine inverse agonist	EUCTR2007-003512-57

*Indicates multiple compounds were tested within one trial. Abbreviations: ATC, Anatomical Therapeutic Chemical classification system; CNS, central nervous system; COMT, catechol-O-methyltransferase; GABA, gamma-aminobutyric acid; GLP-1, Glucagon-like peptide-1; HMG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HPPD, Hydroxyphenylpyruvate dioxygenase; LRRK2, Leucine-rich repeat kinase 2; MAO-B, monoamine oxidase B; NDRI, norepinephrine-dopamine reuptake inhibitor; NMDA, N-methyl-D-aspartate; PD, Parkinson's disease; SNRI, Serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

Supplementary Table 10. Complete clinical overview of phase 3 trials

Treatment indication	Number of trials	Number of repurposing trials	ATC anatomical category	ATC therapeutic category	ATC chemical category	Compounds	Mechanism of action	Trial ID
Dementia associated with PD	2	2	Nervous system (2)	Psychoanaleptics (2)	Anticholinesterases (1)	Donepezil (1)	Cholinesterase inhibitor	JPRN-UMIN000009958
					Other anti-dementia drugs (1)	Memantine (1)	NMDA receptor antagonist	NCT03858270
Depression associated with PD	2	2	Nervous system (3*)	Psychoanaleptics (3*)	Non-selective monoamine reuptake inhibitors (1*)	Nortriptyline (1*)	Tricyclic antidepressant	NCT03652870
					Other antidepressants (1*)	Venlafaxine (1*)	SNRI	NCT00086190
					Selective serotonin reuptake inhibitors (2*)	Escitalopram (1*)	SSRI	NCT03652870
						Paroxetine (1*)	SSRI	NCT00086190
Disease modifying	1	0	No ATC (1)	No ATC (1)	No ATC (1)	CEP-1347 (1)	Apoptosis inhibitor	NCT00040404
Dyskinesia	8	2	Nervous system (5)	Antiparkinsonian drugs (3)	Dopa and dopa derivatives (1*)	Levodopa (1)	Dopamine precursor	EUCTR2010-019396-29
					Dopamine agonists (2*)	Ropinirole (1)	Dopaminergic agonist	NCT00363727
						Pramipexole (1)	Dopaminergic agonist	EUCTR2010-019396-29

					Adamantane derivatives (1)	Amantadine (1)	NMDA receptor antagonist	NCT02136914
				Antiepileptics (1)	Other antiepileptics (1)	Levetiracetam (1)	Antiepileptic	EUCTR2005-002208-40
				Psycholeptics (1)	Anxiolytics - Azaspirodecane dione derivatives (1)	Buspirone (1)	Serotonin agonist	NCT02617017
			<i>No ATC (3)</i>	<i>No ATC (3)</i>	<i>No ATC (3)</i>	Istradefylline (1)	Selective adenosine A2A receptor antagonist	JPRN-UMIN000024536
						Safinamide (2)	MAO-B inhibitor	NCT03881371; NCT03987750
			Early stage PD	9	2	Cardiovascular system (1)	Calcium channel blockers (1)	Dihydropyridine derivatives (1)
Nervous system (2)	Analgesics (1)	Ergot alkaloids (1)				Lisuride (1)	Dopamine and serotonin agonist	EUCTR2006-003732-30
	Antiparkinsonian drugs (2)	Dopa and dopa derivatives (1)				Levodopa (1)	Dopamine precursor	ISRCTN30518857
<i>No ATC (5)</i>	<i>No ATC (5)</i>	<i>No ATC (5)</i>				P2B001 (Pramipexole-Rasagiline) (1)	Dopaminergic agonist + MAO-B inhibitor	NCT03329508
						Pardoprunox (1)	Dopaminergic agonist	NCT00335166
						Sumanriole (3)	Dopaminergic agonist	PER-024-03; NCT00058838; NCT00036218

Falling	1	1	Genito-urinary system and sex hormones (1)	Urologicals (1)	Drugs for urinary frequency and incontinence (1)	Solifenacin (1)	Acetylcholinesterase inhibitor	NCT03149809
Motor fluctuations	27	4	Nervous system (18)	Antiparkinsonian drugs (18)	Dopa and dopa derivatives (1)	Levodopa-Carbidopa (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	NCT00660387
					Dopamine agonists (15)	Apomorphine (4)	Dopaminergic agonist	NCT00142545; NCT02469090; EUCTR2013-000980-10; NCT00145171
						Pramipexole (2)	Dopaminergic agonist	NCT01191944; NCT00466167
						Piribedil (1)	Dopaminergic agonist	EUCTR2005-002010-38
						Ropinirole (5)	Dopaminergic agonist	NCT00381472; NCT01154166; NCT00823836; NCT00331149; NCT01154166
						Rotigotine (3)	Dopaminergic agonist	NCT00244387; NCT00522379; PER-044-10
					Monoamine oxidase B inhibitors (1)	Rasagiline (1)	MAO-B inhibitor	NCT01736891
					Other dopaminergic agents (1)	Opicapone (1)	COMT inhibitor	CTRI/2011/07/001859

			<i>No ATC (9)</i>	<i>No ATC (9)</i>	<i>No ATC (9)</i>	Istradefylline (2)	Selective adenosine A2A receptor antagonist	NCT01968031; NCT00955526
						Preladenant (2)	Selective adenosine A2A receptor antagonist	NCT01227265; NCT01155466
						Safinamide (1)	MAO-B inhibitor	EUCTR2006-005860-14
						SLV308 (2)	Dopamine and Serotonin Agonist	PER-034-07; PER-070-07
						Sumanitrole (1)	Dopaminergic agonist	NCT00036205
						Tozadenant (1)	Selective adenosine A2A receptor antagonist	EUCTR2016-003961-25
Neuro-psychiatric	4	4	Nervous system (2)	Antiparkinsonian drugs (2)	Dopamine agonists (2)	Apomorphine (1)	Dopaminergic agonist	EUCTR2008-006045-10
			Various (1)	All other therapeutic products (1)	Antidotes (1)	N-acetylcysteine (1)	Antioxidant	NCT03146130
			<i>No ATC (1)</i>	<i>No ATC (1)</i>	<i>No ATC (1)</i>	NeuroEpo (Erythropoietin with low sialic acid) (1)	Growth factor	RPCEC00000233
Other	5	5	Alimentary tract and metabolism (1)	Antiemetics and anti-nauseants (1)	Other antiemetics (1)	Nabilone (1)	Cannabinoid	NCT03773796

			Musco-skeletal system (1)	Drugs for treatment of bone diseases (1)	Bisphosphonates (1*)	Zoledronic acid (1*)	Bisphosphonate	JPRN-UMIN000033285
			Nervous system (3)	Analgesics (1*)	Natural opium alkaloids (1*)	Oxycodone (1)	Opioid	NCT02601586
				Antiparkinsonian drugs (2*)	Dopa and dopa derivatives (1)	Levodopa (1)	Dopamine precursor	NCT02601586
					Monoamine oxidase B inhibitors (1)	Rasagiline (1)	MAO-B inhibitor	EUCTR2008-005085-30
			Psychoanaleptics (1)	Other antidepressants (1)	Duloxetine (1)	SNRI	EUCTR2010-018650-12	
			<i>No ATC (1*)</i>	<i>No ATC (1*)</i>	<i>No ATC (1*)</i>	Minodronic Acid Hydrate (1*)	Bisphosphonate	JPRN-UMIN000033285
Parkinsonism	22	6	Cardiovascular system (1)	Beta blocking agents (1)	Beta blocking agents, non-selective (1)	Propranolol (1)	Beta-Adrenergic Blocking Agent	EUCTR2016-004629-18
			Musculo-skeletal system (1)	Muscle relaxants (1)	Other muscle relaxants, peripherally acting agents (1)	Botulinum toxin (1)	Acetylcholinesterase Inhibitor	NCT00909883
			Nervous system (15)	Antiparkinsonian drugs (12)	Dopa and dopa derivatives (2)	Levodopa (1)	Dopamine precursor	NCT03462043
						Levodopa-Carbidopa (1)	Peripheral dopa decarboxylase inhibitor	NCT01096186
					Dopamine agonists (10)	Ropinirole (4)	Dopaminergic agonist	NCT00465452; NCT01929317; NCT00275275; NCT00650104

						Pramipexole (6)	Dopaminergic agonist	NCT00240409; NCT02172573; NCT00560508; NCT02177357; EUCTR2007-004234-16; NCT00274131
				Psychoanaleptics (3)	Centrally acting sympathomimetics (1)	Methylphenidate (1)	NDRI	EUCTR2008-005801-20
					Other anti-dementia drugs (2)	Memantine (2)	NMDA receptor antagonist	IRCT20190207042651N1; EUCTR2008-008210-38
Psychosis associated with PD	2	1	Nervous system (1)	Psychoanaleptics (1)	Anticholinesterases (1)	Donepezil (1)	Cholinesterase inhibitor	JPRN-UMIN000005403
				Psycholeptics (1)	Other antipsychotics (1)	Pimavanserin (1)	Serotonin blocker	NCT01174004
Sleep disorders	2	2	Nervous system (1)	Antiparkinsonian drugs (1)	Monoamine oxidase B inhibitors (1)	Rasagiline (1)	MAO-B inhibitor	EUCTR2010-023756-82
			No ATC (1)	No ATC (1)	No ATC (1)	Tiprolisant (1)	Histamine inverse agonist	EUCTR2009-013885-14

*Indicates multiple compounds were tested within one trial. Abbreviations: ATC, Anatomical Therapeutic Chemical classification system; CNS, central nervous system; COMT, catechol-O-methyltransferase; GABA, gamma-aminobutyric acid; GLP-1, Glucagon-like peptide-1; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; HPPD, Hydroxyphenylpyruvate dioxygenase; LRRK2, Leucine-rich repeat kinase 2; MAO-B, monoamine oxidase B; NDRI, norepinephrine–dopamine reuptake inhibitor; NMDA, N-methyl-D-aspartate; PD, Parkinson’s disease; SNRI, Serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

Supplementary Table 11. Complete clinical overview of phase 4 trials

Treatment indication	Number of trials	Number of repurposing trials	ATC anatomical category	ATC therapeutic category	ATC chemical category	Compounds	Mechanism of action	Trial ID
Dementia associated with PD	2	2	Nervous system (2)	Psychoanaleptics (2)	Anticholinesterases (2)	Donepezil (1)	Acetylcholinesterase inhibitor	NCT00030979
						Rivastigmine (1)	Acetylcholinesterase inhibitor	NCT03840837
Depression associated with PD	4	4	Nervous system (4)	Antiparkinsonian drugs (1)	Monoamine oxidase B inhibitors (1)	Rasagiline (1)	MAO-B inhibitor	EUCTR2009-011144-19
				Psychoanaleptics (3)	Centrally acting sympathomimetics (1)	Atomoxetine (1)	Norepinephrine reuptake inhibitor	NCT00304161
					Other antidepressants (2)	Agomelatine (1)	Serotonin blocker	NCT03977441
						Duloxetine (1)	SNRI	EUCTR2006-006043-32
Dyskinesia	5	3	Musculo-skeletal system (1)	Muscle relaxants (1)	Other muscle relaxants, peripherally acting agents (1)	Botulinum neurotoxin type A (1)	Acetylcholinesterase inhibitor	NCT00477802
			Nervous system (4)	Antiparkinsonian drugs (3)	Adamantane derivatives (2)	Amantadine (2)	NMDA receptor antagonist	EUCTR2009-016143-19; EUCTR2006-006684-22

					Dopa and dopa derivatives (1)	Levodopa-Carbidopa (1)	Acetylcholinesterase inhibitor	NCT00888186
				Antiepileptics (1)	Other antiepileptics (1)	Zonisamide (1)	Antiepilepticum	NCT03034538
Early stage PD	3	0	Nervous system (3)	Antiparkinsonian drugs (2)	Dopamine agonists (2)	Pramipexole (2)	Dopaminergic agonist	NCT00321854; NCT02231905
					Other dopaminergic agents (1)	Entacapone (1*)	COMT inhibitor	NCT00906828
						Tolcapone (1*)	COMT inhibitor	NCT00906828
Fatigue	1	1	Cardiovascular system (1)	Cardiac therapy (1)	Adrenergic and dopaminergic agents (1)	Droxidopa (1)	Norepinephrine precursor	NCT03034564
Motor fluctuations	10	1	Nervous system (8)	Antiparkinsonian drugs (8)	Dopa and dopa derivatives (2)	Levodopa-Benserazide (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	NCT02769793
						Levodopa-Carbidopa-Entacapone (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor + COMT inhibitor	EUCTR2006-000680-28
					Dopamine agonists (5)	Apomorphine (1)	Dopaminergic agonist	NCT01770145
						Pramipexole (1)	Dopaminergic agonist	NCT03521635

						Ropinirole (3)	Dopaminergic agonist	NCT00485069; NCT00986245; NCT01494532
					Other dopaminergic agents (1)	Entacapone (1)	COMT inhibitor	EUCTR2004-002643-27
			No ATC (1)	No ATC (1)	No ATC (1)	Safinamide (1)	MAO-B inhibitor	NCT03843944
Neuro-psychiatric	8	5	Cardiovascular system (1)	Cardiac therapy (1)	Adrenergic and dopaminergic agents (1)	Droxidopa (1)	Norepinephrine precursor	NCT03115827
			Nervous system (7)	Antiparkinsonian drugs (6)	Dopa and dopa derivatives (3)	Levodopa-Benserazide (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	EUCTR2007-002800-16
						Levodopa-Carbidopa (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	EUCTR2015-002631-17
						Levodopa-Carbidopa-Entacapone (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor + COMT inhibitor	EUCTR2006-002408-32
						Dopamine agonists (1)	Pramipexole (1*)	Dopaminergic agonist
			Ropinirole (1*)	Dopaminergic agonist	ISRCTN39374171			

					Monoamine oxidase B inhibitors (2)	Rasagiline (2)	MAO-B inhibitor	EUCTR2007-004400-12; NCT01385735
				Other nervous system drugs (1)	Drugs used in alcohol dependence (1)	Naltrexone (1)	Opioid receptor antagonist	NCT01052831
Orthostatic hypotension	1	1	Cardiovascular system (1)	Cardiac therapy (1)	Adrenergic and dopaminergic agents (1)	Droxidopa (1)	Norepinephrine precursor	NCT03229174
Other	5	5	Genito-urinary system and sex hormones (1)	Urologicals (1)	Drugs for urinary frequency and incontinence (1)	Mirabegron (1)	Adrenergic agonist	NCT03412513
			Musculo-skeletal system (1)	Drugs for treatment of bone diseases (1)	Bisphosphonates (1)	Zoledronic Acid (1)	Bisphosphonate	NCT03924414
			Nervous system (2)	Antiparkinsonian drugs (1)	Dopamine agonists (1)	Apomorphine (1)	Dopaminergic agonist	EUCTR2006-005318-11
				Psychoanaleptics (1)	Anticholinesterases (1)	Rivastigmine (1)	Acetylcholinesterase inhibitor	NCT01856738
<i>No ATC (1)</i>	<i>No ATC (1)</i>	<i>No ATC (1)</i>	Safinamide (1)	MAO-B inhibitor	NCT03841604			
Parkinsonism	10	2	Musculo-skeletal system (1)	Muscle relaxants (1)	Other muscle relaxants, peripherally acting agents (1)	Botulinum neurotoxin type A (1)	Acetylcholinesterase inhibitor	IRCT20100127003217N11

			Nervous system (8)	Antiparkinsonian drugs (7)	Dopa and dopa derivatives (2)	Levodopa-Benserazide (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	NCT02741947
						Levodopa-Carbidopa-Entacapone (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor + COMT inhibitor	EUCTR2005-001032-72
					Dopamine agonists (3)	Pramipexole (2*)	Dopaminergic agonist	NCT00402233; NCT00144300
						Ropinirole (2*)	Dopaminergic agonist	NCT00144300; NCT01485172
					Monoamine oxidase B inhibitors (1)	Rasagiline (1)	MAO-B inhibitor	EUCTR2007-007397-28
					Other dopaminergic agents (1)	Tolcapone (1)	COMT inhibitor	EUCTR2009-017416-33
				Psychoanaleptics (1)	Anticholinesterases (1)	Donepezil (1)	Acetylcholinesterase inhibitor	NCT03011476
			No ATC (1)	No ATC (1)	No ATC (1)	Istradefylline (1)	Selective adenosine A2A receptor antagonist	JPRN-UMIN000020288
Psychosis associated with PD	1	1	Nervous system (1)	Psycholeptics (1)	Antipsychotics - Diazepines, oxazepines, thiazepines and oxepines (1)	Quetiapine (1)	Atypical antipsychotic	NCT00043849

Sleep disorders	3	3	Nervous system (3)	Antiparkinsonian drugs (2)	Dopamine agonists (2)	Apomorphine (1)	Dopaminergic agonist	NCT02940912
						Cabergoline (1)	Dopaminergic agonist	NCT00174239
				Psycholeptics (1)	Other hypnotics and sedatives (1)	Suvorexant (1)	Orexin antagonist	NCT02729714

*Indicates multiple compounds were tested within one trial. Abbreviations: ATC, Anatomical Therapeutic Chemical classification system; CNS, central nervous system; COMT, catechol-O-methyltransferase; GABA, gamma-aminobutyric acid; GLP-1, Glucagon-like peptide-1; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; HPPD, Hydroxyphenylpyruvate dioxygenase; LRRK2, Leucine-rich repeat kinase 2; MAO-B, monoamine oxidase B; NDRI, norepinephrine–dopamine reuptake inhibitor; NMDA, N-methyl-D-aspartate; PD, Parkinson’s disease; SNRI, Serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

Supplementary Table 12. Complete clinical overview of ongoing trials

Phase	Primary trial aim	Number of trials	Number of trials repurposing compounds	ATC anatomical category	ATC therapeutic category	ATC chemical category	Compounds	Mechanism of action	Trial ID		
1	Motor fluctuations	3	0	Nervous system (3)	Antiparkinsonian drugs (3)	Dopa and dopa derivatives (1)	Levodopa-Carbidopa (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	NCT03419806		
						Dopamine agonists (1)	Opicapone (1)	COMT inhibitor	NCT03820037		
						Other dopaminergic agents (1)	Rotigotine (1)	Dopaminergic agonist	NCT03733561		
	Parkinsonism	2	2	Nervous system (2)	Psycholeptics (2)	Anticholinesterases (1)	Donepezil (1)	Acetylcholinesterase inhibitor	NCT03599726		
						Centrally acting sympathomimetics (1)	Modafinil (1)	Dopamine reuptake inhibitor	NCT03083132		
	Disease modifying	7	4	Alimentary tract and metabolism (1)	Bile and liver therapy (1)	Bile acids and derivatives (1)	Ursodeoxycholic acid (1)	Apoptosis Inhibitor	NCT02967250		
						Antineoplastic and immunomodulating agents (1)	Immunostimulants (1)	Colony stimulating factors (1)	Sargramostim (1)	Hematopoietic growth factor	NCT03790670
						Various (1)	All other therapeutic products (1)	Antidotes (1)	N-acetylcysteine (1)	Antioxidant	NCT03104725
No ATC (5)						No ATC (5)	No ATC (5)	Cu(II)ATSM (1)	Copper-containing synthetic small molecule	NCT03204929	

							DNL201 (1)	LRRK2 Kinase Inhibitor	NCT03710707
							K0706 (1)	Tyrosine kinase inhibitor	NCT02970019
							Lu AF82422 (1)	Alpha-synuclein inhibitor	NCT03611569
	Dementia associated with PD	1	0	No ATC (1)	No ATC (1)	No ATC (1)	ENT-01	Alpha-synuclein inhibitor	NCT03938922
	Orthostatic hypotension	1	1	Cardiovascular system (1*)	Cardiac therapy (1*)	Adrenergic and dopaminergic agents (1*)	Midodrine (1)	Vasopressor/antihypotensive agent	NCT02897063
							Droxidopa (1)	Norepinephrine precursor	NCT02897063
	Psychosis associated with PD	1	1	No ATC (1)	No ATC (1)	No ATC (1)	Saracatinib (1)	Tyrosine kinase inhibitor	NCT03661125
1/2	Motor fluctuations	3	1	Nervous system (2)	Antiparkinsonian drugs (2)	Dopa and dopa derivatives (1)	Levodopa (1)	Dopamine precursor	NTR7054
						Dopamine agonists (1)	Ropinirole (1)	Dopaminergic agonist	NCT03250117
				Alimentary tract and metabolism (1)	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents (1)	Antibiotics (1)	Rifaximin (1)	Antibiotic	NCT03575195
	Parkinsonism	2	1	Antiinfectives for systemic use (1)	Antibacterials for systemic use (1)	Macrolides (1)	Clarithromycin (1)	GABA-A receptor negative allosteric modulator	NCT03440112
				No ATC (1)	No ATC (1)	No ATC (1)	IPT803	Dopamine and endorphin agonist	NCT03407378
	Early stage PD	1	1	Alimentary tract and metabolism (1)	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents (1)	Antibiotics (1)	Rifaximin (1)	Antibiotic	NCT03958708
	Falling	1	1	No ATC (1)	No ATC (1)	No ATC (1)	Terazosin (1)	Alpha-1 blocker	NCT03905811

	Sleep disorders	1	1	Nervous system (1)	Antiepileptics (1)	Other antiepileptics (1)	Cannabidiol (1)	Cannabinoid	RBR-5fwhf7	
2	Motor fluctuations	5	3	Nervous system (2)	Antiparkinsonian drugs (1)	Dopa and dopa derivatives (1)	Levodopa-Carbidopa (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	NCT03576638	
					Other nervous system drugs (1)	Drugs used in nicotine dependence (1)	Nicotine (1)	Nicotinic Acetylcholine Receptor Agonist	EUCTR2008-001336-13	
				Cardiovascular system (1)	Diuretics (1)	Sulfonamides (1)	Bumetanide (1)	Diuretic	NCT03899324	
				Genito-urinary system and sex hormones (1)	Gynecological antiinfectives and antiseptics (1)	Other antiinfectives and antiseptics (1)	Inosine (1)	Urate precursor	JPRN-UMIN000020527	
				No ATC (1)	No ATC (1)	No ATC (1)	Foliglurax (1)	Metabotropic glutamate receptor 4 modulator	NCT03162874	
	Parkinsonism	11	9	Nervous system (6)	Antiparkinsonian drugs (2*)	Dopamine agonists (1*)	Pramipexole (1*)	Dopaminergic agonist	NCT03683225	
						Monoamine oxidase B inhibitors (1*)	Selegiline (1*)	MAO-B inhibitor	JPRN-UMIN000022533	
					Antiepileptics (3*)	Other antiepileptics (3*)	Zonisamide (2*)	Antiepileptic	JPRN-UMIN000022533; JPRN-UMIN000010371	
							Cannabidiol (1)	Cannabinoid	NCT03582137	
					Psycholeptics (1)	Benzodiazepine derivatives (1)	Zolpidem (1)	GABA-A receptor positive allosteric modulator	NCT03621046	
					Alimentary tract and metabolism (2*)	Drugs used in diabetes (2*)	Other antiemetics (1*)	Aprepitant (1*)	Antiemetic	NCT03683225
							GLP-1 Analogues (1)	Liraglutide (1)	GLP-1 receptor agonist	NCT02953665

				Antineoplastic and immunomodulating agents (1)	Antineoplastic agents (1)	Protein kinase inhibitors (1)	Nilotinib (1)	Tyrosine kinase inhibitor	NCT03205488		
				Musculo-skeletal system (2)	Muscle relaxants (1)	Other muscle relaxants, peripherally acting agents (1)	Botulinum toxin (1)	Acetylcholinesterase inhibitor	NCT02427646		
					Antigout preparations (1*)	Preparations inhibiting uric acid production (1*)	Febuxostat (1*)	Xanthine oxidase inhibitor	JPRN-UMIN000030930		
				Genito-urinary system and sex hormones (1)	Gynecological antiinfectives and antiseptics (1)	Other antiinfectives and antiseptics (1)	Inosine (1*)	Urate precursor	JPRN-UMIN000030930		
				No ATC (1)	No ATC (1)	No ATC (1)	Mucuna pruriens (1)	Dopamine precursor	PACTR201611001882367		
	Dyskinesia	4	3	Nervous system (2)	Antiparkinsonian drugs (2)	Adamantane derivatives (2)	Amantadine (2)	NMDA receptor antagonist	NCT01538329; NCT01190553		
						Cardiovascular system (1)	Lipid modifying agents (1)	HMG CoA reductase inhibitors (1)	Simvastatin (1)	Statin	EUCTR2009-011736-35
						No ATC (1)	No ATC (1)	No ATC (1)	Pridopidine (1)	Dopidine	NCT03922711
	Early stage PD	7	5	Alimentary tract and metabolism (2)	Drugs used in diabetes (2)	GLP-1 analogues (2)	Lixisenatide (1)	GLP-1 receptor agonist	NCT03439943		
									Semaglutide (1)	GLP-1 receptor agonist	NCT03659682
						Cardiovascular system (2)	Beta blocking agents (1)	Alpha and beta blocking agents (1)	Carvedilol (1)	Beta-adrenergic blocking agent	NCT03775096
							Lipid modifying agents (1)	HMG CoA reductase inhibitors (1)	Lovastatin (1)	Statin	NCT03242499
						Nervous system (1)	Antiepileptics (1)	Other antiepileptics (1)	Zonisamide (1)	Antiepileptic	NCT01766128
			No ATC (2)	No ATC (2)	No ATC (2)	KDT-3594 (1)	Dopaminergic agonist	NCT03845387			

							K0706 (1)	Tyrosine kinase inhibitor	NCT03655236
Disease modifying	4	3	Various (2)	All other therapeutic products (2)	Iron chelating agents (2)	Deferiprone (2)	Iron chelator	EUCTR2008-006842-25; NCT02655315	
			Antineoplastic and immunomodulating agents (1)	Antineoplastic agents (1)	Protein kinase inhibitors (1)	Nilotinib (1)	Tyrosine kinase inhibitor	NCT02954978	
			No ATC (1)	No ATC (1)	No ATC (1)	Paliroden (1)	Neurotrophic	EUCTR2004-001330-16	
Sleep disorders	4	2	Nervous system (2)	Antiparkinsonian drugs (1)	Monoamine oxidase B inhibitors (1)	Rasagiline (1)	MAO-B inhibitor	EUCTR2008-002145-22	
				Psycholeptics (1*)	Melatonin receptor agonists (1*)	Melatonin (1*)	Hormone for sleep-wake cycle	NCT02789592	
				Antiepileptics (1*)	Benzodiazepine derivatives (1*)	Clonazepam (1*)	Benzodiazepine	NCT02789592	
			No ATC (2)	No ATC (2)	No ATC (2)	THN102 (1)	Glial connexin inhibitor	NCT03624920	
						Tiprolisant (1)	Histamine inverse agonist	EUCTR2007-003512-57	
Falling	3	3	Cardiovascular system (2)	Cardiac therapy (2)	Adrenergic and dopaminergic agents (2)	Droxidopa (2)	Norepinephrine precursor	NCT02812147; NCT03567447	
			Nervous system (1)	Other nervous system drugs (1)	Drugs used in nicotine dependence (1)	Varenicline (1)	Acetylcholinesterase inhibitor	NCT01341080	
Dementia associated with PD	2	1	Nervous system (1)	Other nervous system drugs (1)	Drugs used in nicotine dependence (1)	Nicotine (1)	Nicotinic Acetylcholine Receptor Agonist	JPRN-UMIN000016664	
			No ATC (1)	No ATC (1)	No ATC (1)	GRF6021 (1)	Human plasma protein fraction	NCT03713957	
Neuro-psychiatric	2	2	Nervous system (1)	Psycholeptics (1)	Other antipsychotics (1)	Pimavanserin (1)	Serotonin blocker	NCT03947216	

				No ATC (1)	No ATC (1)	No ATC (1)	Safinamide (1)	MAO-B inhibitor	EUCTR2010-020109-34
	Other	2	2	Alimentary tract and metabolism (2)	Antiemetics and anti-nauseants (1)	Other antiemetics (1)	Nabilone (1)	Cannabinoid	NCT03769896
				Nervous system (1)	Antiepileptics (1)	Other antiepileptics (1)	Cannabidiol (1)	Cannabinoid	NCT03639064
	Fatigue	1	1	Cardiovascular system (1)	Cardiac therapy (1)	Adrenergic and dopaminergic agents (1)	Droxidopa (1)	Norepinephrine precursor	NCT03446807
	Psychosis associated with PD	1	0	No ATC (1)	No ATC (1)	No ATC (1)	SEP-363856 (1)	Serotonin receptor agonist	NCT02969369
3	Dyskinesia	4	1	Nervous system (2)	Antiparkinsonian drugs (1*)	Dopa and dopa derivatives (1*)	Levodopa (1*)	Dopamine precursor	EUCTR2010-019396-29
						Dopamine agonists (1*)	Pramipexole (1*)	Dopaminergic agonist	EUCTR2010-019396-29
					Psycholeptics (1)	Anxiolytics - Azaspirodecanedione derivatives (1)	Buspirone (1)	Serotonin receptor agonist	NCT02617017
					No ATC (2)	No ATC (2)	No ATC (2)	Safinamide (2)	MAO-B inhibitor
	Parkinsonism	3	3	Nervous system (2)	Psychoanaleptics (2)	Other anti-dementia drugs (1)	Memantine (1)	NMDA receptor antagonist	EUCTR2008-008210-38
						Centrally acting sympathomimetics (1)	Methylphenidate (1)	NDRI	EUCTR2008-005801-20
				Cardiovascular system (1)	Beta blocking agents (1)	Beta blocking agents, non-selective (1)	Propranolol (1)	Beta-Adrenergic Blocking Agent	EUCTR2016-004629-18

Early stage PD	3	2	Nervous system (2)	Analgesics (1)	Ergot alkaloids (1)	Lisuride (1)	Dopaminergic and serotonin agonist	EUCTR2006-003732-30
				Antiparkinsonian drugs (1)	Dopamine agonists (1)	Pramipexole (1*)	Dopaminergic agonist	NCT03329508
			Cardiovascular system (1)	Calcium channel blockers (1)	Dihydropyridine derivatives (1)	Isradipine (1)	Calcium channel blocker	NCT02168842
			No ATC (1)	No ATC (1)	No ATC (1)	Rasagiline (1*)	MAO-B inhibitor	NCT03329508
Neuro-psychiatric	4	4	Nervous system (2)	Antiparkinsonian drugs (2)	Dopamine agonists (2)	Apomorphine (1)	Dopaminergic agonist	EUCTR2008-006045-10
						Rotigotine (1)	Dopaminergic agonist	NCT02786667
			Various (1)	All other therapeutic products (1)	Antidotes (1)	N-acetylcysteine (1)	Antioxidant	NCT03146130
			No ATC (1)	No ATC (1)	No ATC (1)	NeuroEPO (1)	Growth factor	RPCEC00000233
Other	3	3	Alimentary tract and metabolism (1)	Antiemetics and anti-nauseants (1)	Other antiemetics (1)	Nabilone (1)	Cannabinoid	NCT03773796
			Musculo-skeletal system (1)	Drugs for treatment of bone diseases (1)	Bisphosphonates (1*)	Zoledronic acid (1)	Bisphosphonate	JPRN-UMIN000033285
			Nervous system (2*)	Analgesics (1*)	Natural opium alkaloids (1*)	Oxycodone (1*)	Opioid	NCT02601586
				Antiparkinsonian drugs (1*)	Dopa and dopa derivatives (1)	Levodopa (1*)	Dopamine precursor	NCT02601586
			No ATC (1*)	No ATC (1*)	No ATC (1*)	Minodronic Acid Hydrate (1)	Bisphosphonate	JPRN-UMIN000033285
Dementia associated with PD	1	1	Nervous system (1)	Psychoanaleptics (1)	Other anti-dementia drugs (1)	Memantine (1)	NMDA receptor antagonist	NCT03858270
	1	1	Nervous system (1*)	Psychoanaleptics (1*)	Non-selective monoamine	Nortriptyline (1*)	Tricyclic antidepressant	NCT03652870

	Depression associated with PD					reuptake inhibitors (1*)	Escitalopram (1*)	SSRI	NCT03652870
	Falling	1	1	Genito-urinary system and sex hormones (1)	Urologicals (1)	Drugs for urinary frequency and incontinence (1)	Solifenacin (1)	Acetylcholinesterase inhibitor	NCT03149809
	Sleep disorders	1	1	No ATC (1)	No ATC (1)	No ATC (1)	Tiprolisant (1)	Histamine inverse agonist	EUCTR2009-013885-14
4	Motor fluctuations	3	0	Nervous system (2)	Antiparkinsonian drugs (2)	Dopa and dopa derivatives (1)	Levodopa-Benserazide (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	NCT02769793
						Dopamine agonists (1)	Pramipexole (1)	Dopaminergic agonist	NCT03521635
				No ATC (1)	No ATC (1)	No ATC (1)	Safinamide (1)	MAO-B inhibitor	NCT03843944
	Dyskinesia	2	1	Nervous system (2)	Antiparkinsonian drugs (2)	Adamantane derivatives (2)	Amantadine (2)	NMDA receptor antagonist	EUCTR2009-016143-19; EUCTR2006-006684-22
	Parkinsonism	3	2	Nervous system (2)	Psychoanaleptics (1)	Anticholinesterases (1)	Donepezil (1)	Acetylcholinesterase inhibitor	NCT03011476
					Antiparkinsonian drugs (1)	Monoamine oxidase B inhibitors (1)	Rasagiline (1)	MAO-B inhibitor	EUCTR2007-007397-28
				Musculo-skeletal system (1)	Muscle relaxants (1)	Other muscle relaxants, peripherally acting agents (1)	Botulinum toxin (1)	Acetylcholinesterase inhibitor	IRCT20100127003217 N11
	Other	4	4	Genito-urinary system and sex hormones (1)	Urologicals (1)	Drugs for urinary frequency and incontinence (1)	Mirabegron (1)	Adrenergic agonist	NCT03412513
Musculo-skeletal system (1)				Drugs for treatment of bone diseases (1)	Bisphosphonates (1)	Zoledronic acid (1)	Bisphosphonate	NCT03924414	

				Nervous system (1)	Antiparkinsonian drugs (1)	Dopamine agonists (1)	Apomorphine (1)	Dopaminergic agonist	EUCTR2006-005318-11
				No ATC (1)	No ATC (1)	No ATC (1)	Safinamide (1)	MAO-B inhibitor	NCT03841604
	Neuropsychiatric	4	1	Nervous system (4)	Antiparkinsonian drugs (4)	Monoamine oxidase B inhibitors (2)	Rasagiline (2)	MAO-B inhibitor	EUCTR2007-004400-12; NCT01385735
						Dopa and dopa derivatives (2)	Levodopa-Benserazide (1)	Dopamine precursor + Peripheral dopa decarboxylase inhibitor	EUCTR2007-002800-16
								Levodopa-Carbidopa-Entacapone (1)	Dopamine Precursor + Peripheral Dopa Decarboxylase Inhibitor + COMT inhibitor
	Dementia associated with PD	1	1	Nervous system (1)	Psychoanaleptics (1)	Anticholinesterases (1)	Rivastigmine (1)	Acetylcholinesterase inhibitor	NCT03840837
	Depression associated with PD	1	1	Nervous system (1)	Psychoanaleptics (1)	Other antidepressants (1)	Agomelatine (1)	Serotonin blocker	NCT03977441
	Orthostatic hypotension	1	1	Cardiovascular system (1)	Cardiac therapy (1)	Adrenergic and dopaminergic agents (1)	Droxidopa (1)	Norepinephrine precursor	NCT03229174
Sleep disorders	1	1	Nervous system (1)	Psycholeptics (1)	Other hypnotics and sedatives (1)	Suvorexant (1)	Orexin antagonist	NCT02729714	
Not specified	Depression associated with PD	1	1	Nervous system (1)	Psychoanaleptics (1)	Centrally acting sympathomimetics (1)	Methylphenidate (1)	NDRI	NTR1115
	Parkinsonism	1	0	No ATC (1)	No ATC (1)	No ATC (1)	Istradefylline (1)	Selective adenosine A2A receptor antagonist	JPRN-UMIN000026492
	Other	1	0	Nervous system (1)	Antiparkinsonian drugs (1)	Dopamine agonists (1)	Apomorphine (1)	Dopaminergic agonist	NCT03693872

	Sleep disorders	1	1	Nervous system (1)	Antiparkinsonian drugs (1)	Dopa and dopa derivatives (1)	Levodopa-Carbidopa-Entacapone (1)	Dopamine Precursor + Peripheral Dopa Decarboxylase Inhibitor + COMT inhibitor	NCT02452606
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*Indicates multiple compounds were tested within one trial. Abbreviations: ATC, Anatomical Therapeutic Chemical classification system; CNS, central nervous system; COMT, catechol-O-methyltransferase; GABA, gamma-aminobutyric acid; GLP-1, Glucagon-like peptide-1; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; HPPD, Hydroxyphenylpyruvate dioxygenase; LRRK2, Leucine-rich repeat kinase 2; MAO-B, monoamine oxidase B; NDRI, norepinephrine–dopamine reuptake inhibitor; NMDA, N-methyl-D-aspartate; PD, Parkinson’s disease; SNRI, Serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

Supplementary Table 13. Biomarkers used as endpoints in phase 2 and phase 3 trials

Biomarker	Number of phase 2 trials	Number of phase 3 trials	Total
<i>Biochemical biomarkers</i>			
CSF alpha-synuclein	2	0	2
CSF dopamine markers	3	0	3
CSF drug concentration	6	0	6
CSF other	1	0	1
CSF target engagement	5	0	5
Other wet endpoint	1	0	1
Plasma alpha-synuclein	2	0	2
Plasma bioavailability	0	1	1
Plasma dopamine markers	1	0	1
Plasma drug concentration	18	2	20
Plasma inflammatory markers	3	0	3
Plasma metabolites	2	0	2
Plasma neuroprotective markers	1	0	1
Plasma other	3	0	3
Plasma target engagement	7	1	8
Potential surrogate radiological and biological biomarkers	1	0	1
Urine drug concentration	1	0	1
<i>Imaging biomarkers</i>			
DAT-SPECT	8	0	8
DTI	1	0	1
fMRI connectivity	2	0	2
MRI degeneration	1	1	2
MRI target engagement	1	0	1
MRS mitochondria	1	0	1
PET cerebral metabolism	0	1	1
PET dopamine	3	1	4
PET protective effect	0	1	1
PET serotonin	0	1	1
Polysomnograph	1	0	1

Abbreviations: CSF, cerebrospinal fluid; DAT-SPECT, dopamine transporter - single-photon emission computed tomography, DTI, diffusion tensor imaging; MRI, magnetic resonance imaging; fMRI, functional MRI; MRS, magnetic resonance spectroscopy; PET, positron emission tomography

Supplementary Table 14. Repurposed compounds and their original regulatory indication

Repurposed compound	Original regulatory indication	Currently investigated for
Agomelatine	Major depressive episodes in adults	Depression associated with PD
Amantadine	Prophylaxis and treatment of infection caused by influenza A virus	Dyskinesia
Ambroxol	Multiple pulmonary conditions	Disease modifying
Apomorphine	Relieve anxiety and craving in alcoholics, an emetic, erectile dysfunction	Motor fluctuations Sleep disorders Other neuropsychiatric Other
Aripiprazole	Schizophrenia and bipolar I disorder	Psychosis associated with PD
Atomoxetine	Treatment of Attention Deficit Hyperactivity Disorder	Depression associated with PD
Botulinum neurotoxin type A	Blepharospasm, spasmodic torticollis, spasticity of upper limbs, sialorrhea	Parkinsonism Dyskinesia Depression associated with PD
Bumetanide	Treatment of autism spectrum disorder	Motor fluctuations
Buspirone	Treatment of anxiety disorders	Dyskinesia Other neuropsychiatric
Cabergoline	Prevention or suppression of lactation post-partum, Hyperprolactinemia	Sleep disorders
Candesartan	Hypertension, Heart failure	Dementia associated with PD
Cannabidiol	Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome	Sleep disorders Parkinsonism Other
Carvedilol	Hypertension, Angina pectoris, Heart Failure	Early stage PD, disease modifying
Clarithromycin	Respiratory tract infections, Skin and soft tissue infections	Parkinsonism
Clonazepam	Epilepsy	Sleep disorders
Clozapine	Schizophrenic patients resistant or intolerant to other antipsychotics	Psychosis associated with PD
Creatine	Improving muscle strength	Disease modifying
Cu(II)ATSM	Orphan drug status for ALS	Disease modifying

Deferiprone	Treatment of iron overload in patients with thalassemia major	Disease modifying
Denosumab	Osteoporosis	Other
Donepezil	Symptomatic treatment of mild to moderate Alzheimer disease	Parkinsonism Dementia associated with PD Psychosis associated with PD Other neuropsychiatric
Droxidopa	Hypotension, including neurogenic orthostatic hypotension	Orthostatic hypotension Fatigue Falling Other neuropsychiatric
Duloxetine	Depressive disorder, Diabetic peripheral neuropathic pain, Generalized anxiety disorder	Depression associated with PD Other Parkinsonism
Erythropoietin	Anemia	Disease modifying
Escitalopram	Major depressive episodes, Anxiety disorders, Obsessive-compulsive disorder	Depression associated with PD
Febuxostat	Chronic hyperuricemia with urate deposition	Parkinsonism
Fursultiamine	Treatment of thiamine deficiency	Parkinsonism
G-CSF	Neutropenia, Mobilisation of peripheral blood progenitor cells	Early stage PD, disease modifying
Gabapentin	Epilepsy, Peripheral neuropathic pain	Other neuropsychiatric
Inosine	Elevating uric acid levels	Disease modifying Motor fluctuations Parkinsonism
Insulin	Diabetes mellitus	Dementia associated with PD
Isradipine	Hypertension	Early stage PD, disease modifying
Istradefylline	Dyskinesia (FDA and Japan)	Depression associated with PD
Levetiracetam	Epilepsy	Dyskinesia
Levodopa standard formulation	Treatment of symptoms of Parkinson's disease	Depression associated with PD Other

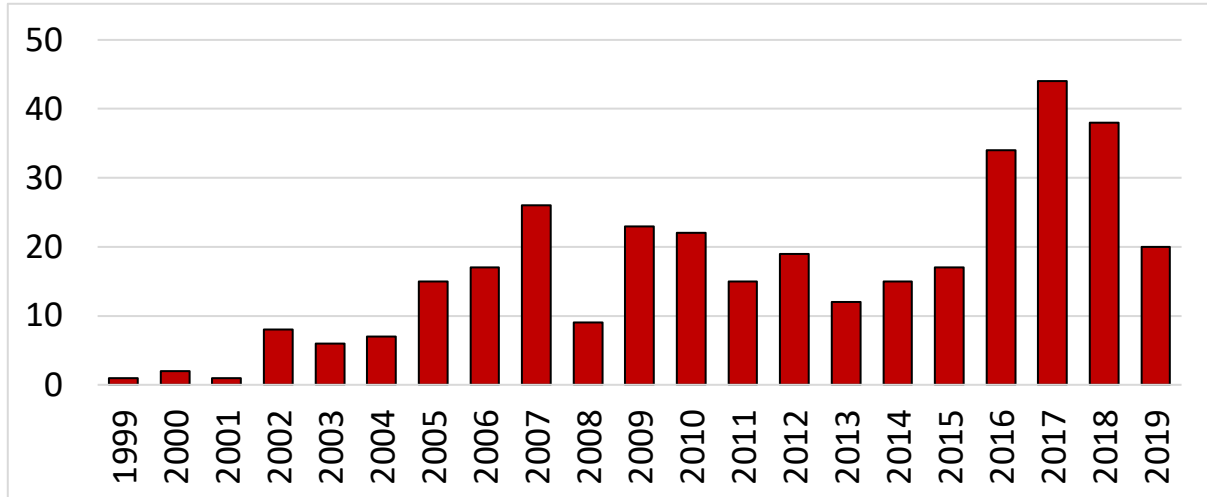
Levodopa-Carbidopa intestinal infusion	Advanced idiopathic Parkinson's disease with severe motor fluctuations and not responding to oral treatment	Other neuropsychiatric
Levodopa-Carbidopa standard formulation	Advanced idiopathic Parkinson's disease with severe motor fluctuations	Other neuropsychiatric
Levodopa-Carbidopa-Entacapone standard formulation	Advanced idiopathic Parkinson's disease with severe motor fluctuations not stabilized by levodopa with decarboxylase inhibitor	Other neuropsychiatric Sleep disorders
Liraglutide	Diabetes mellitus type 2, Obesity	Parkinsonism
Lisuride transdermal patch	Restless legs syndrome	Early stage PD, symptomatic Parkinsonism
Lixisenatide	Diabetes mellitus type 2	Early stage PD, disease modifying
Lovastatin	Dyslipidemia, prevention of cardiovascular disease	Early stage PD, disease modifying
Mavoglurant	EMA orphan designation for Fragile X syndrome	Dyskinesia
Melatonin PR	Insomnia	Sleep disorders
Melperone	Schizophrenia	Psychosis associated with PD
Memantine	Symptomatic treatment of mild to moderate Alzheimer disease	Dementia associated with PD Dyskinesia Parkinsonism
Methylphenidate	Attention deficit hyperactivity disorder (ADHD), narcolepsy	Depression associated with PD Parkinsonism
Midodrine	Symptomatic orthostatic hypotension	Orthostatic hypotension
Minocycline	Treatment of multiple bacterial infections	Disease modifying
Minodronic Acid Hydrate	Osteoporosis	Other
Mirabegron	Urgency incontinence	Other
Modafinil	Narcolepsy	Parkinsonism Sleep disorders
N-acetylcysteine	Paracetamol overdose, Kidney disease, Hemorrhagic cystitis	Disease modifying Other neuropsychiatric
Nabilone	Anti-emetic	Other
Nalmefene	Alcohol dependence	Other neuropsychiatric
Naltrexone	Alcohol dependence	Other neuropsychiatric
NeuroEpo	Anemia	Other neuropsychiatric
Nicotine	Nicotine addiction	Dementia associated with PD Motor fluctuations Parkinsonism

Nilotinib	Chronic myeloid leukemia	Dementia associated with PD Disease modifying Parkinsonism
Nitisinone	Hereditary tyrosinemia type 1	Motor fluctuations
Nortriptyline	Depression	Depression associated with PD
Oxycodone	Pain	Other
Paroxetine	Depression, Obsessive-compulsive disorder, Anxiety disorders, Post-traumatic stress disorder	Depression associated with PD
Pimavanserin	Schizophrenia and other psychotic disorders	Other neuropsychiatric
Pramipexole	Monotherapy for Parkinson's disease or as add-on to levodopa inducing motor fluctuations	Other neuropsychiatric
Propranolol	Cardiovascular disorders, Migraine, Tremor simplex	Parkinsonism
Quetiapine	Psychosis, Bipolar disorder	Psychosis associated with PD
Rasagiline	Monotherapy for Parkinson's disease or as add-on to levodopa inducing motor fluctuations	Depression associated with PD Other Sleep disorders
Rifaximin	Prophylaxis of hepatic encephalopathy	Early stage PD, disease modifying Motor fluctuations
Rivastigmine	Symptomatic treatment of mild to moderate Alzheimer disease	Dementia associated with PD Falling Other
Ropinirole	Monotherapy for Parkinson's disease to postpone necessity for levodopa treatment	Other neuropsychiatric
Rotigotine	Monotherapy for Parkinson's disease or as add-on to levodopa inducing motor fluctuations	Other neuropsychiatric
Safinamide	Add-on therapy to levodopa inducing motor fluctuations	Other neuropsychiatric Other
Saracatinib	Orphan drug status for idiopathic pulmonary fibrosis	Psychosis associated with PD
Sargramostim	Myeloid reconstitution after bone marrow transplantation, Neutropenia	Disease modifying
Sarizotan	Rett syndrome	Dyskinesia
Semaglutide	Diabetes mellitus type 2	Early stage PD, disease modifying
Simvastatin	Hypercholesterolemia	Dyskinesia

Sodium Oxybate	Narcolepsy	Sleep disorders
Solifenacin	Overactive bladder	Falling
Solriamfetol	Narcolepsy, Sleep apnea	Sleep disorders
Suvorexant	Insomnia	Sleep disorders
Talampanel	Orphan designation for ALS	Dyskinesia
Terazosin	Symptoms of an enlarged prostate, Hypertension	Falling
Tiprolisant	Narcolepsy	Sleep disorders
Trans-resveratrol	Spinocerebellar ataxia	Parkinsonism
Ubiquinol	Primary coenzyme Q10 deficiency syndrome	Disease modifying
Ursodeoxycholic Acid	Bile and liver therapy	Disease modifying
Varenicline	Nicotine addiction	Falling
Venlafaxine	Major depressive episodes	Depression associated with PD
Zoledronic Acid	Bone diseases	Other
Zolpidem	Sleep disorders	Parkinsonism
Zonisamide	Epilepsy	Disease modifying Dyskinesia Early stage PD, disease modifying Parkinsonism

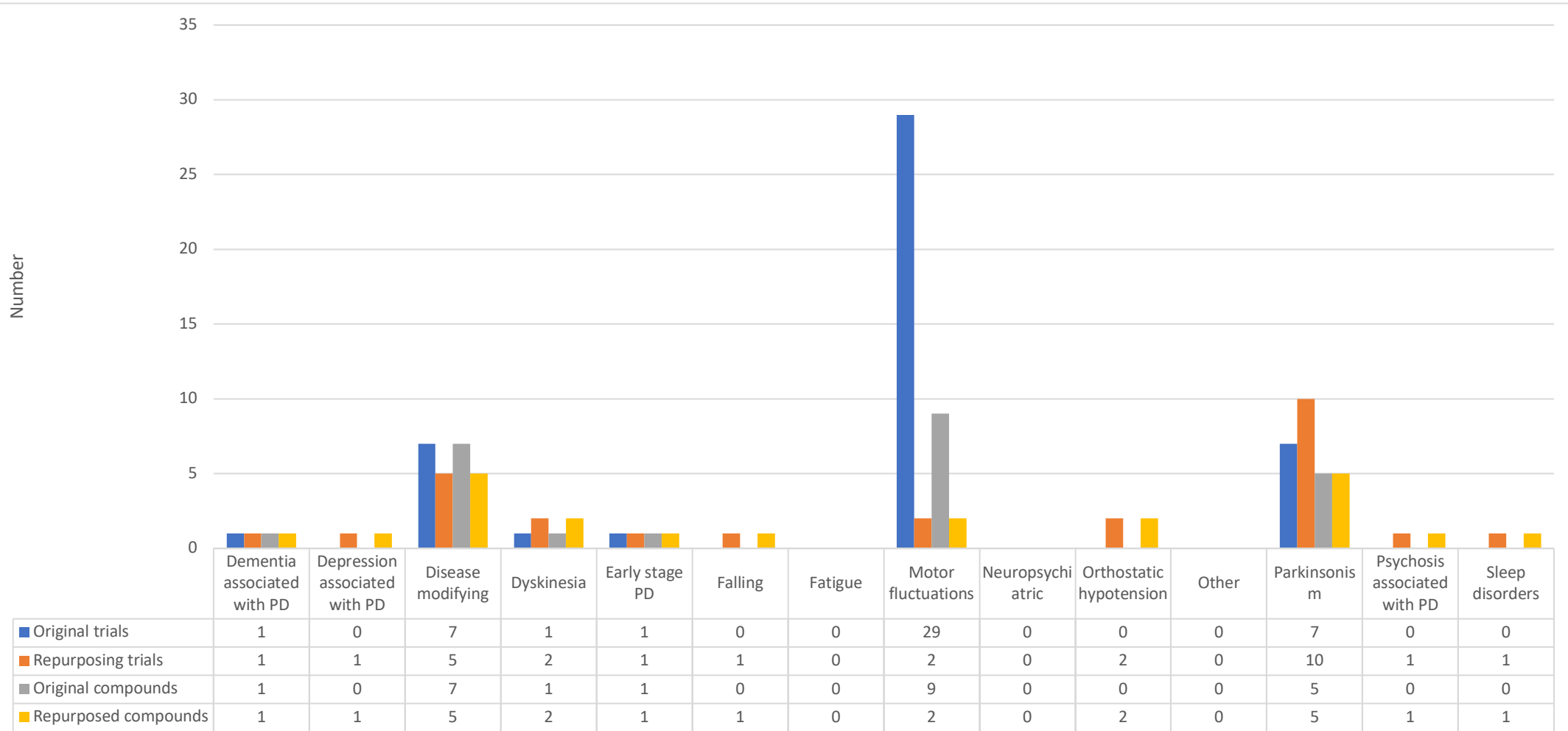
Supplementary Figures

Supplementary Figure 1. Number of registered trials per year



Note: The number of registered trials for 2019 is incomplete as we only included trials registered until September 2019. The number of registered trials for recent years may also be incomplete as a result of retrospective registration.

Supplementary Figure 2. Overview of phase 1/2 trials



Supplementary Figure 3. Overview of phase 4 trials

