

# Supplementary Material

## Is It Possible to Conduct a Multi-Arm Multi-Stage Platform Trial in Parkinson's Disease: Lessons Learned from Other Neurodegenerative Disorders and Cancer

**Supplementary Table 1.** Examples of common pathogenic mechanisms across different neurodegenerative diseases

	MND	Progressive MS	PD	AD
Glutamate-induced excitotoxicity	✓	✓		
Oxidative stress	✓	✓	✓	✓
Mitochondrial dysfunction	✓	✓	✓	
Neuroinflammation	✓	✓	(✓)	(✓)
Protein misfolding and aggregation	✓		✓ ( $\alpha$ -synuclein)	✓ (A $\beta$ , tau)
Proteasome inhibition, protein degradation pathways			✓	✓
Apoptosis	✓	✓		✓
Impaired axonal transport	(✓)	✓	✓	(✓)
Excess iron deposition		✓	✓	
Altered neurotrophic factors			✓	✓
Neuronal loss	✓	✓	✓	✓

**Supplementary Table 2.** Inclusion criteria of phase III trials; \* with exception of MAO-B Inhibitors; ST, symptomatic treatment

<b>Intervention</b>	<b>Clinical Trial Identifier</b>	<b>Min Age</b>	<b>Max Age</b>	<b>Disease Duration</b>	<b>H&amp;Y Stage</b>	<b>Cognition (Score)</b>	<b>Depression (Score)</b>	<b>PD drugs Y/N</b>	<b>Changes to PD drugs allowed</b>	<b>Other Inclusion criteria</b>
<b>Isradipine [1]</b>	NCT02168842	30	-	< 3 years	≤ 2	MOCA (≥26)	Becks (≤ 15)	N (2 months)	Y	Time to ST > 3 months
<b>Inosine</b>	NCT02642393	30	-	< 3 years	< 3	MMSE (≥25)	-	N* (2 months)	N	ST not imminent; serum urate levels
<b>Creatine [2]</b>	NCT00449865	-	-	< 5 years	-	-	-	Y (3-24 months)	-	-
<b>Coenzyme Q10 with Vitamin E [3]</b>	NCT00740714	30	-	< 5 years	< 2.5	MMSE (≥25)	Hamilton Scale (<11)	N (3 months)	N	-
<b>Rasagiline [4]</b>	NCT00256204	30	80	< 1.5 years	< 3	MMSE (≥26)	Becks (<15)	N (3 weeks)	N	UPDRS Tremor score < 3
<b>Ganoderma</b>	NCT03594656	30	80	< 5 years	≤ 2	MMSE (>24)	-	N (2 weeks)	-	UPDRS part III 10-30 points
<b>Pramipexole [5]</b>	NCT00321854	30	75	< 2 years	≤ 2	No dementia	-	N (1 month)	N	Time to ST > 6 months
<b>Levodopa + Carbidopa [6]</b>	ISRCTN30518857	30	-	< 2 years		MMSE (>23)	Becks (≤28)	N	N	No severe resting tremor

## REFERENCES

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- [6] Verschuur CVM, Suwijn SR, Boel JA, Post B, Bloem BR, Van Hilten JJ, Van Laar T, Tissingh G, Munts AG, Deuschl G, Lang AE, Dijkgraaf MGW, De Haan RJ, De Bie RMA (2019) Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med* **380**, 315–324.