Supplementary Material

A Phase I, Randomized, SAD, MAD, and PK Study of Risvodetinib in Older Adults and Parkinson's Disease

Supplementary Table 1. Safety and Tolerability Outcomes Following 1x/Day Administration of Risvodetinib (IkT-148009)

Variable	# Events in Placebo (N=25)	#Events in SAD (N=54)	#Events in MAD (N=29)
Primary Tolerability			
Tolerability	0	0	0
Primary Safety			
Treatment-related serious adverse events	0	0	0
Other Safety and Tolerability			
Any Adverse Event	12	12	12
Any Serious Adverse Event	0	0	0
Dose suspensions	0	0	0
Study drug discontinuations	0	0	0
Tolerability with no dose suspensions	0	0	0

Supplementary Table 2. Amylase and/or Lipase Elevations Above Limit of Normal in SAD/MAD Studies in elderly healthy subjects or Participants with Parkinson's treated with Risvodetinib (IkT-148009)[1]

Patient ID	Dose	Dose Duration	Timepoint	Amylase/Lipase[2]	Active?
27	37.5 mg	Single dose	0 h	112/normal	Yes
			24 h	128/normal	
28	37.5 mg	Single dose	0 h	102/normal	No
			24 h	108/normal	
			Day 4	117/normal	
			Day 7	115/normal	
33	37.5 mg	Single dose	0 h	119/normal	Yes
			24 h	139/normal	
			72 h	218/normal	
36	37.5 mg	Single dose	0 h	118/normal	No
			24 h	194/normal	
			72 h	137/normal	
			Day 7	120/normal	
42	75 mg	Single dose	0 h	88/normal	Yes
			24 h	102/normal	
			Day 4	117/normal	
			Day 7	119/normal	
44	75 mg	Single dose	0 h	136/normal	Yes
			24 h	160/normal	
			Day 7	162/normal	
47	75 mg	Single dose	0 h	102/normal	Yes
			24 h	220/150	
			Day 4	406/462	
			Day 14	128/50	
52	100 mg	Single dose	0 h	normal/44	Yes
			24 h	normal/109	
			72 h	normal/54	
74	100 mg	Single dose	0 h	187/normal	No
			24 h	234/normal	
			72 h	324/normal	
			Day 14	120/normal	
166	250 mg	Single dose	Screening	118/normal	Yes
			0 h	normal/111	
			Day 4	126/normal	
			Day 7	222/587	
			Day 14	136/83	
167	250 mg	Single dose	72 h	111/normal	Yes
			Day 7	150/normal	
174	250 mg	Single dose	72 h	116/normal	No
192	325 mg	Single dose	Screening	156/normal	No

201	325 mg	Single dose	72 h	117/normal	Yes
203	325 mg	Single dose	72 h	125/normal	Yes
112	25 mg	7-day	48 h	126/93 Normal otherwise	Yes
113	25 mg	7-day	Screening	156/138	Yes
			Day 1	82/33	
			Day 2	102/46	
			Day 3	114/73	
			Day 4	92/36	
			Day 5	117/51	
			Day 6	116/58	
			Day 8	89/29	
			Day 9	175/138	
100-004[3]	100 mg	4 wk	Baseline	161/196	
			4 wk	224/407	
			1 wk post- dose	Not Avail/67	

[1] There were no abnormal values see in 7-day dosing at 12.5 or 25 mg in healthy subjects dosed for 7-days and no abnormal values seen in mild-to-moderate Parkinson's patients treated for 7-days at 50 mg or 100 mg; [2]Amylase normal = 28-110; Lipase normal = 13-78; [3]This patient reported regular alcohol consumption the day before baseline visit and throughout their participation in the trial that remained within the inclusion criteria.

Supplementary Table 3. Comparison of Steady-State Pharmacokinetic parameters following therapeutic dosing in animal efficacy studies and human clinical studies

	Tmax (h)	Cmax (ng/mL)	AUC0-inf (ng-h/mL)	t1/2 (h)		Tmax (h)	Cmax (ng/mL)	AUC0-t (ng-h/mL)	t1/2 (h)
	Mouse					Human			
50 mg/kg/day	4	2562	19650	3.1	50 mg/day	3.6±1.4	2560±564	32100±8190	24.8±3.7
100 mg/kg/day	4	5060	37838	2.6	100 mg/day	4.4±1.7	3320±1870	45700±25000	24.6±4.7
					200 mg/day	5±1.7	5953±1122	97190±23147	23.3±3.5

Supplementary Table 4. Concomitant medications administered to Participants with Parkinson's who received once daily doses of Risvodetinib (IkT-148009)

System Organ Class Preferred Term	IKT 50 mg (N=6) n (%)	IKT 100 mg (N=5) n (%)	Pooled PBO (N=3) n (%)
Patients with any prior medications	6 (100.0)	5 (100.0)	3 (100.0)
Alimentary Tract and Metabolism	5 (83.3)	3 (60.0)	2 (66.7)
8-Tetrahydrocannabinol	1 (16.7)	0 (0.0)	0 (0.0)
Ascorbic Acid	1 (16.7)	0 (0.0)	0 (0.0)
Colecalciferol	2 (33.3)	1 (20.0)	1 (33.3)
Docusate	1 (16.7)	0 (0.0)	2 (66.7)
Ergocalciferol	0 (0.0)	1 (20.0)	0 (0.0)
Multivitamins, Plain	4 (66.7)	0 (0.0)	0 (0.0)
Omeprazole	1 (16.7)	0 (0.0)	0 (0.0)
Retinol	1 (16.7)	0 (0.0)	0 (0.0)
Sennoside A+b	0 (0.0)	1 (20.0)	0 (0.0)
Ubidecarenone	1 (16.7)	0 (0.0)	0 (0.0)
Vitamin B Complex	1 (16.7)	0 (0.0)	0 (0.0)
Antiinfectives For Systemic Use	3 (50.0)	1 (20.0)	0 (0.0)
Other Viral Vaccines	2 (33.3)	0 (0.0)	0 (0.0)
Vaccines	1 (16.7)	1 (20.0)	0 (0.0)
Blood And Blood Forming Organs	0 (0.0)	1 (20.0)	1 (33.3)
Acetylsalicylic Acid	0 (0.0)	0 (0.0)	1 (33.3)
Ferrous Sulfate	0 (0.0)	1 (20.0)	0 (0.0)
Cardiovascular System	1 (16.7)	2 (40.0)	1 (33.3)
Amlodipine	0 (0.0)	1 (20.0)	1 (33.3)
Atorvastatin	1 (16.7)	2 (40.0)	0 (0.0)
Hydrochlorothiazide	0 (0.0)	0 (0.0)	1 (33.3)
Genito Urinary System And Sex Hormones	0 (0.0)	0 (0.0)	2 (66.7)
Tamsulosin	0 (0.0)	0 (0.0)	1 (33.3)
Tolterodine	0 (0.0)	0 (0.0)	2 (66.7)
Musculo-Skeletal System	1 (16.7)	3 (60.0)	2 (66.7)
Alendronate Sodium	0 (0.0)	1 (20.0)	0 (0.0)
Baclofen	0 (0.0)	0 (0.0)	1 (33.3)
Colchicine	1 (16.7)	0 (0.0)	0 (0.0)
Diclofenac	0 (0.0)	0 (0.0)	1 (33.3)
Ibuprofen	0 (0.0)	1 (20.0)	0 (0.0)
Naproxen	0 (0.0)	1 (20.0)	0 (0.0)
Nervous System	6 (100.0)	5 (100.0)	3 (100.0)
Alprazolam	1 (16.7)	0 (0.0)	0 (0.0)
Amantadine	1 (16.7)	1 (20.0)	1 (33.3)
Amfetamine; dexamfetamine	1 (16.7)	0 (0.0)	0 (0.0)
Benzatropine	0 (0.0)	0 (0.0)	1 (33.3)
Carbidopa; levodopa	6 (100.0)	5 (100.0)	3 (100.0)
Clonazepam	1 (16.7)	0 (0.0)	1 (33.3)

System Organ Class Preferred Term	IKT 50 mg (N=6) n (%)	IKT 100 mg (N=5) n (%)	Pooled PBO (N=3) n (%)
Duloxetine	1 (16.7)	0 (0.0)	0 (0.0)
Gabapentin	1 (16.7)	1 (20.0)	1 (33.3)
Naltrexone	1 (16.7)	0 (0.0)	0 (0.0)
Pramipexole	1 (16.7)	0 (0.0)	0 (0.0)
Rasagiline	1 (16.7)	0 (0.0)	1 (33.3)
Rizatriptan	1 (16.7)	0 (0.0)	0 (0.0)
Ropinirole	1 (16.7)	1 (20.0)	0 (0.0)
Sertraline	0 (0.0)	1 (20.0)	0 (0.0)
Tramadol	0 (0.0)	0 (0.0)	1 (33.3)
Venlafaxine	1 (16.7)	1 (20.0)	0 (0.0)
Respiratory System	0 (0.0)	1 (20.0)	1 (33.3)
Cetirizine	0 (0.0)	1 (20.0)	0 (0.0)
Fluticasone Propionate; salmeterol Xinafoate	0 (0.0)	0 (0.0)	1 (33.3)
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	2 (33.3)	0 (0.0)	0 (0.0)
Fludrocortisone	1 (16.7)	0 (0.0)	0 (0.0)
Hydrocortisone	1 (16.7)	0 (0.0)	0 (0.0)
Levothyroxine	1 (16.7)	0 (0.0)	0 (0.0)