Phase 1 Study of BT-267, a Potent, Selective, Brain-Penetrant, and Oral Small Molecule Inhibitor of LRRK2

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[1]Brenig Therapeutics

Disclosures

This study is sponsored by BRENIG THERAPEUTICS.

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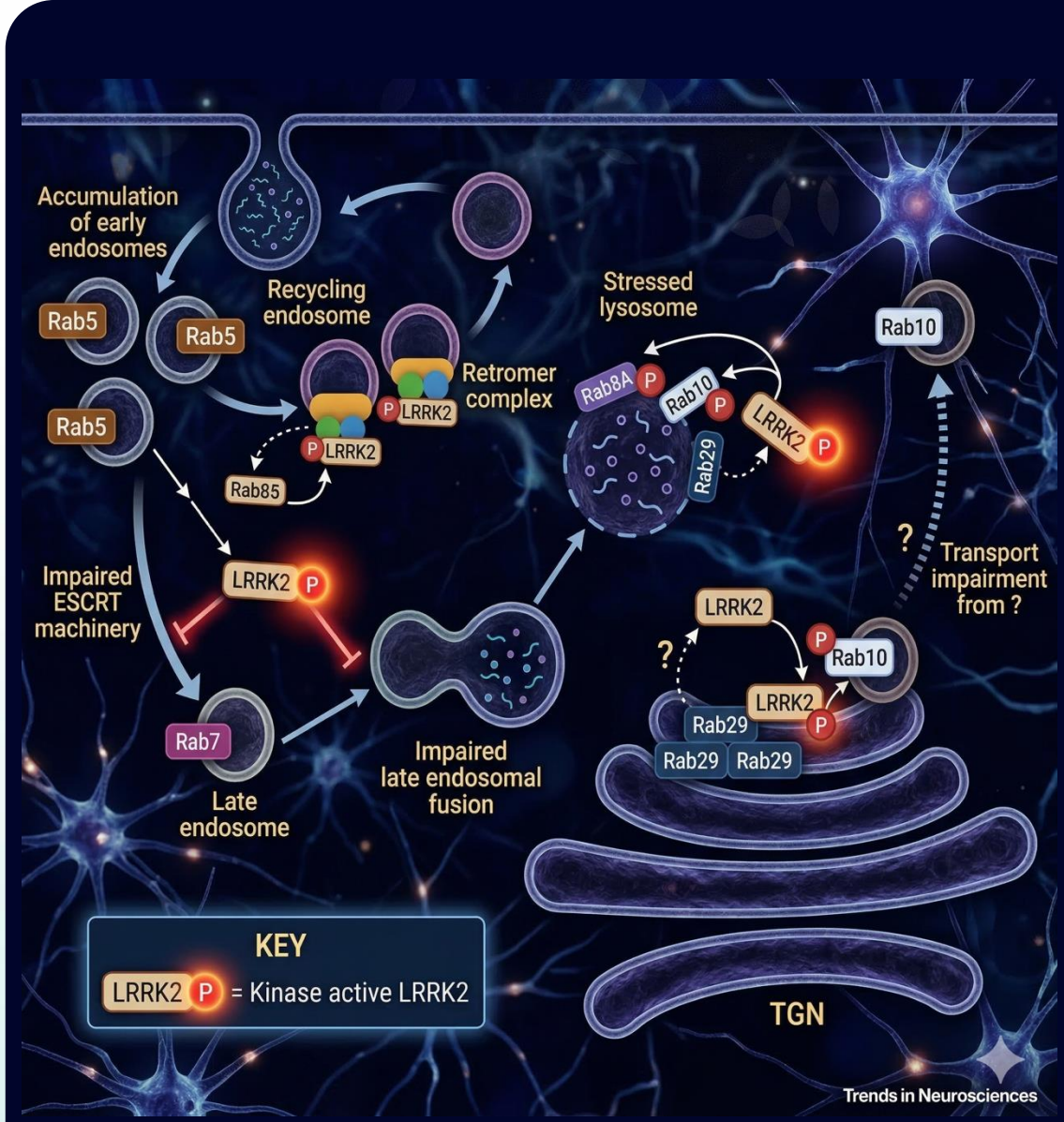
Brenig Therapeutics/ Dam T, Dokukina K, Remeeva E, Kazey V, Karapetian R, Pushechnikov A, Mathias A, Marvasty I, McGill M, Savchuk N, Dukes I, Hilt D					X		X	

LRRK2 in the Pathophysiology of PD

- Genetic studies highlight multiple lysosomal function related genes in PD
- Lysosomal dysfunction is central to the pathogenesis of PD [1, 2, 3]
- LRRK2 activity is increased in PD and negatively regulates lysosomal function [2, 4]
- LRRK2 inhibition rescues lysosomal function and normalizes protein processing [5, 6]
- Human LRRK2 loss of function variants do not have functional consequences and support safety of targeting LRRK2 [4]



Adapted from Rocha et al. Trends Neurosci 2022

1. Wallings, et al. Trends Neurosci 2019
2. Dehay B, et al. Mov Disord 2013
3. Rocha E, et al. Trends Neurosci 2022
4. DiMaio, et al. Sci Transl Med 2018
5. Khan NL, et al. Brain 2005
6. West AB, et al. Human Mol Gen 2007

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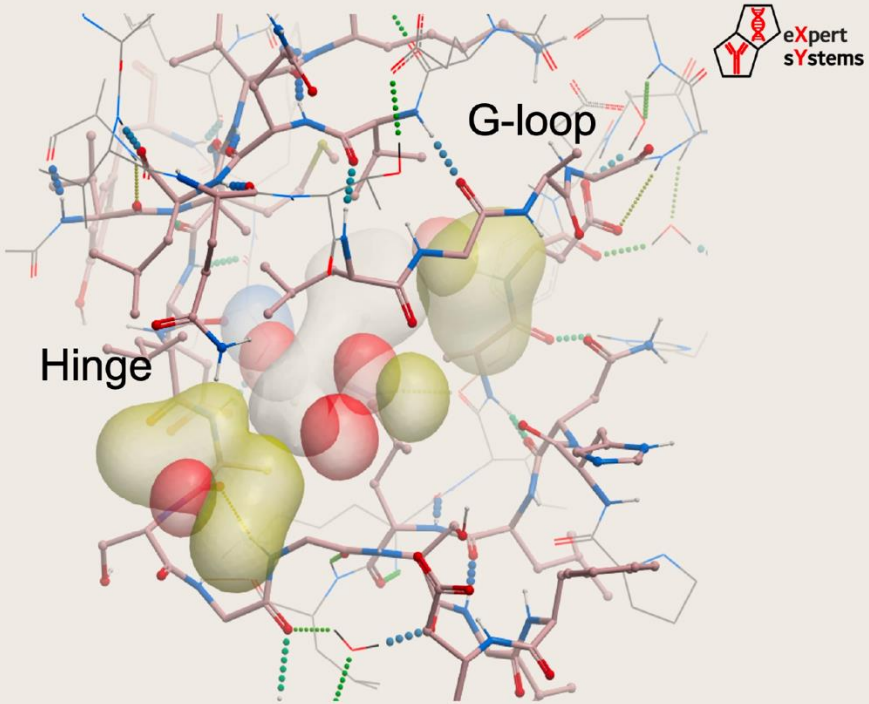
Optimized for CNS penetration and Selectivity to LRRK2 [WT] and [G2019S] vs Other Kinases in the Kinome

Multiparameter Optimization of Physicochemical Properties for Differential Biodistribution:

- Optimized potency for more brain penetration
- Maximized C_{max} for kinetic control of faster brain permeability
- Prioritized molecules with a balance between lipophilicity and polar surface area to maximize differential distribution to brain while keeping unbound fraction in plasma at a minimum

Reduced polar surface area and added small functional groups to displace unfavorable water molecules



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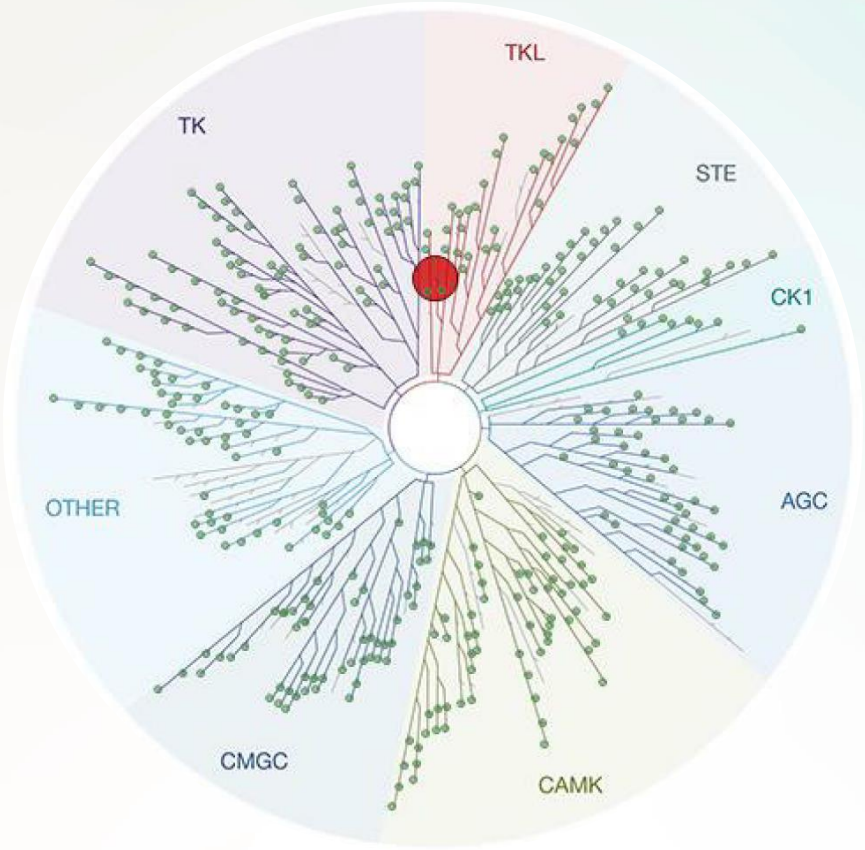
BT-267 Kinase Selectivity and Safety

Most selective kinase inhibitor potentially contributes to clean safety profile



Selectivity:

>500x selectivity against other kinases

1000x selectivity against other targets from the safety panel

Safety:

Well-tolerated in rodent + NHP 3-month GLP Toxicology

Highest dose is NOAEL, providing wide therapeutic window

Dose dependent decrease in urine BMP at all doses

References: Company, internal data

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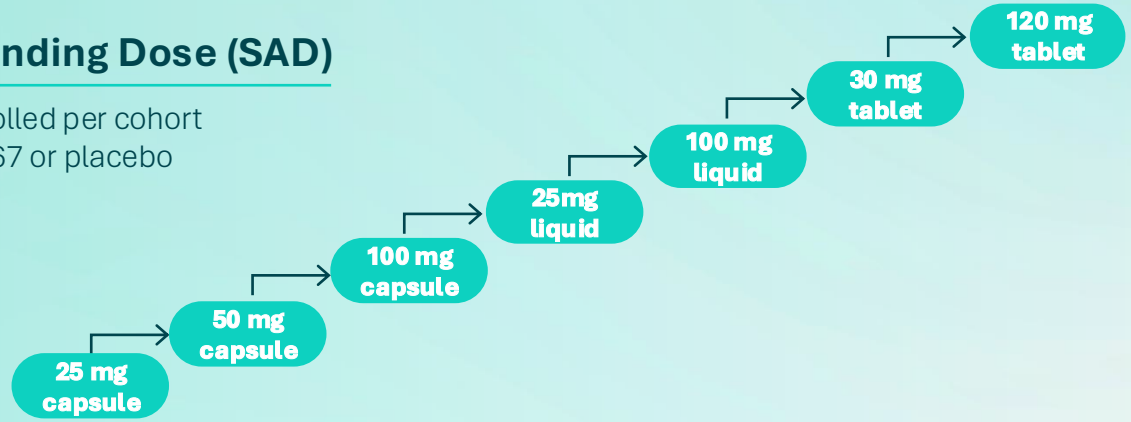
BT-267 Phase 1 SAD/MAD in Healthy Volunteers

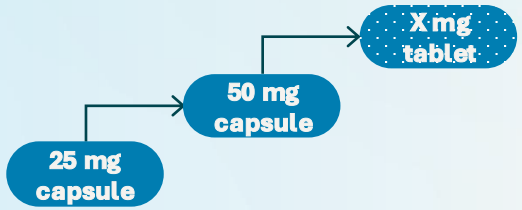
Part A: Single Ascending Dose (SAD)

- 8 healthy volunteers enrolled per cohort
- Randomized 3:1 to BT-267 or placebo
- Single oral dose on day 1
- Follow-up until day 8



Part B: Multiple Ascending Dose (MAD)

- 8 healthy volunteers enrolled per cohort
- Randomized 3:1 to BT-267 or placebo
- Once-daily dosing on days 1-10
- Follow-up until day 17



Single-center, randomized, double-blind, placebo-controlled study

Primary objective:

- Safety and tolerability of BT-267

Secondary objective:

- Plasma PK of BT-267

Exploratory objectives:

- Exposure of BT-267 in CSF
- Effects of BT-267 on target engagement and pathway engagement biomarkers

CSF= cerebrospinal fluid; MAD= multiple ascending dose; PK= pharmacokinetics; SAD= single ascending dose

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BT-267 Phase 1 Baseline Characteristics

- Total of 71 participants dosed as of data cut-off of March 6, 2026
- 55 participants received at least 1 dose of BT-267 and 16 participants received placebo
- All dosed participants completed the study

Baseline Characteristics	SAD n=55	MAD n=16
Gender, n (%)		
Male	29 (53%)	13 (81%)
Female	26 (47%)	3 (19%)
Median age (range), years	27.0 (19.0-45.0)	31.5 (22.0-55.0)
Race, n (%)		
White	35 (64%)	10 (63%)
Asian	16 (29%)	5 (31%)
American Indian or Alaska Native	3 (5.5%)	1 (6.3%)
Other	1 (1.8%)	0
Median weight (range), kg	71.0 (52.3-95.8)	71.5 (59.7-98.0)
Median BMI (range), kg/m^2	24.6 (18.5-30.0)	24.6 (20.7-29.6)

BMI= body mass index

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BT-267 Phase 1 Safety Data

- BT-267 was well tolerated following a single dose up to 120 mg and multiple doses of up to 50 mg QD
- No treatment discontinuations, SAEs, or deaths
- Most TEAEs were mild in severity and deemed not related to drug by Investigator
- Headache, nausea, venipuncture-related, and presyncope were the TEAEs reported by ≥ 2 participants
- No clinically relevant changes in vital signs, physical exam, labs, and electrocardiograms

	SAD								MAD		
n(%)	25 mg capsule n=7	50 mg capsule n=8	100 mg capsule n=8	25 mg liquid n=8	100 mg liquid n=8	30 mg tablet n=8	120 mg tablet n=8	**Overall n=55**	25 mg capsule n=8	50 mg capsule n=8	**Overall n=16**
Any TEAE	3 (43)	5 (63)	1 (13)	1 (13)	3 (38)	3 (43)	0	**16 (29)**	3 (38)	5 (63)	**8 (50.0)**
Headache	1 (13)	1 (13)	0	0	1 (13)	0	0	**3 (5)**	1 (13)	1 (13)	**2 (13)**
Nausea	0	1 (13)	1 (13)	0	1 (13)	0	0	**3 (5)**	0	1 (13)	**1 (6)**
Venipuncture*	1 (13)	1 (13)	0	0	0	1 (13)	0	**3 (5)**	0	1 (13)	**1 (6)**
Presyncope	0	1 (13)	0	0	1 (13)	0	0	**2 (4)**	0	0	**0**

SAEs= serious adverse events; TEAEs= treatment emergent adverse events
*venipuncture-related TEAEs include catheter site hematoma, vessel puncture phlebitis, vessel puncture thrombosis

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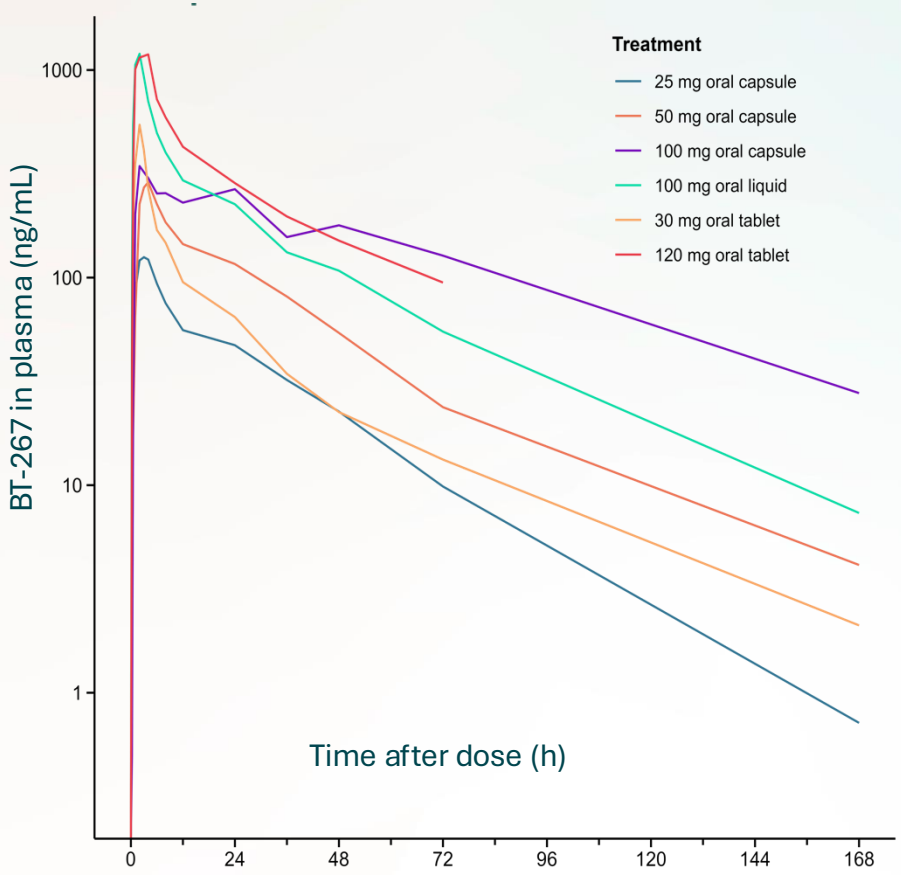
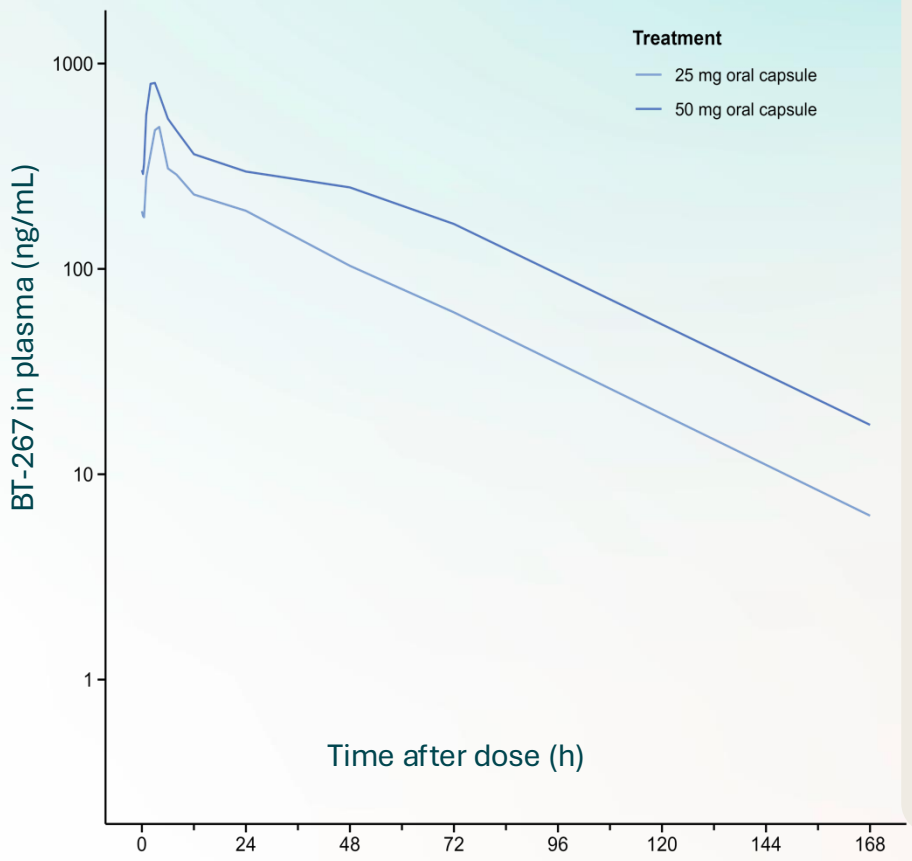
BT-267 Mean Exposure in Plasma

Amorphous drug product shows dose-dependent concentrations and supports once daily dosing

SAD



MAD



- BT-267 was rapidly absorbed and achieved **maximal concentrations within 2-4 hours** after dosing
- At near equivalent doses, amorphous drug product (tablet) outperformed the crystalline drug product (capsule**); amorphous drug product will be used in clinical development**
- BT-267 exhibited a **half-life between 18-29 hours,** supporting once daily dosing

Additional cohorts exploring formulation, effect of food have been completed; only data pertinent to understanding PK and PD are shown.
N= 6 per cohort received active drug

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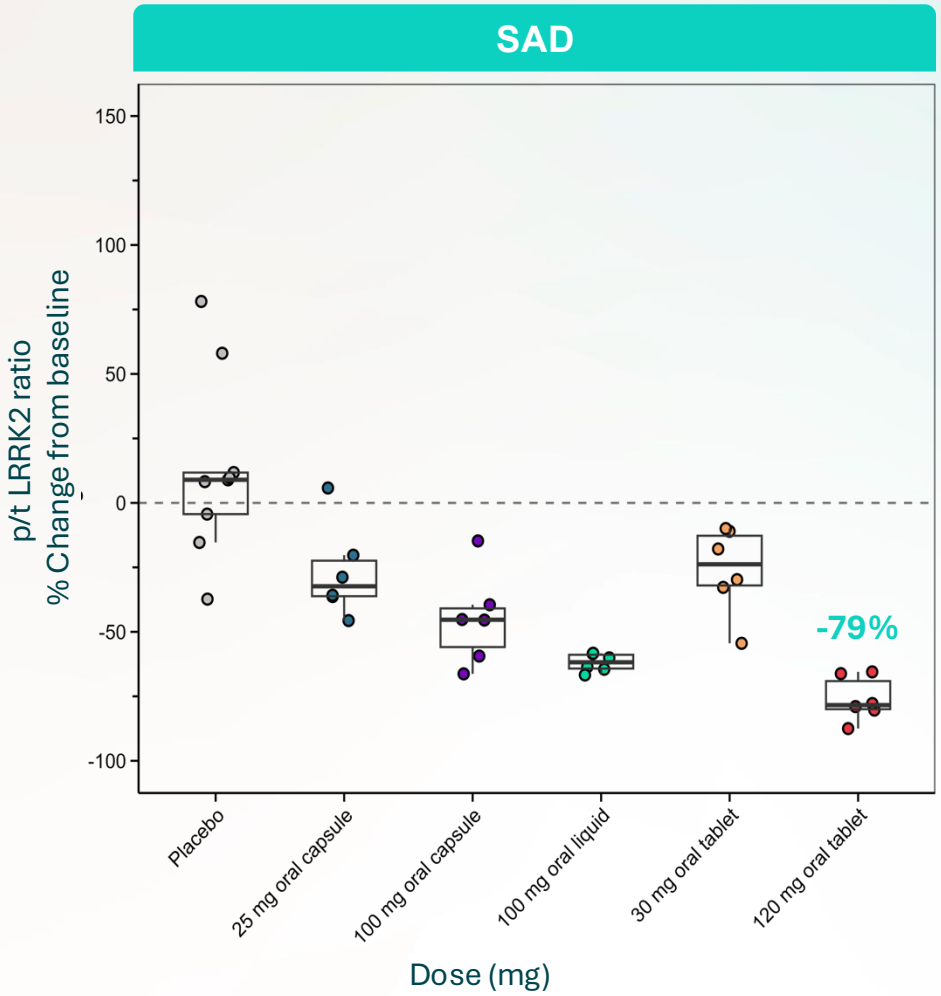
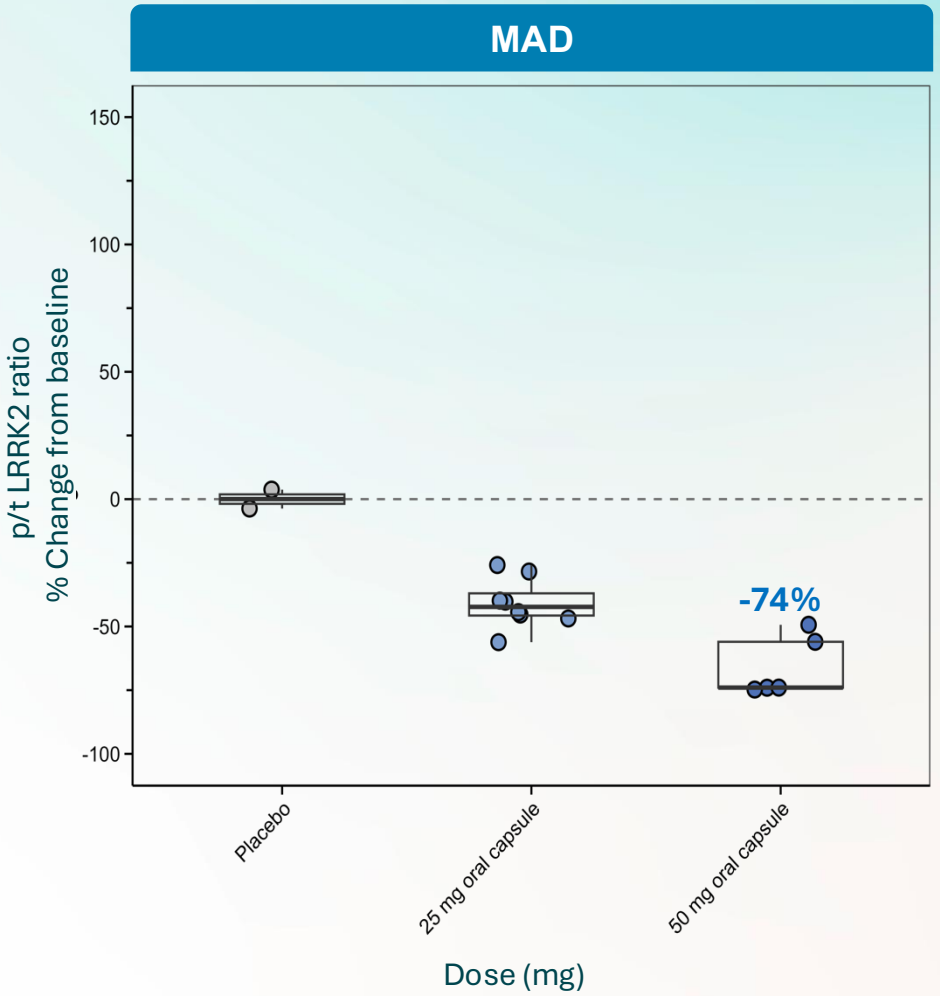
BT-267 Inhibits LRRK2 Protein Levels in PBMCs

Dose dependent reduction in p/t LRRK2 demonstrates target engagement





- BT-267 induced **reductions in LRRK2 protein levels** in PBMCs upon single- and-multiple dosing
- **At single doses of 120 mg and multiple doses of 50 mg, >70% reduction** in LRRK2 was observed

Phosphorylated/total LRRK2 ratio in PBMCs at 8 hours post-dose measured by MSD. Boxplots show the median (25th and 75th percentile) with whiskers within 1.5 times the IQR. Participants who received Placebo across cohorts in SAD or MAD were pooled. Additional cohorts exploring formulation, effect of food have been completed; only data pertinent to understanding PK and PD are shown.

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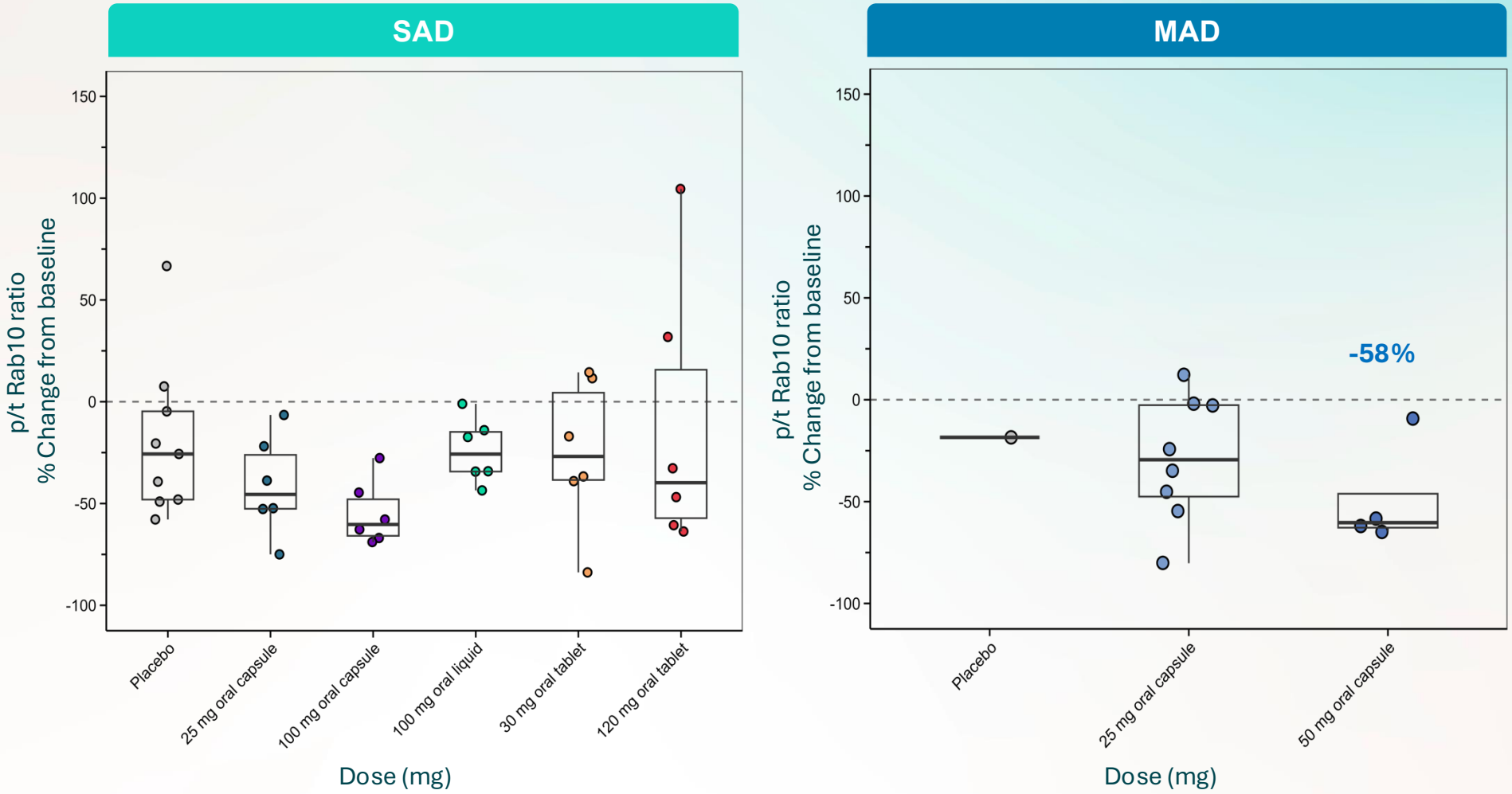
BT-267 Inhibits Rab10 Levels in PBMCs

p/t Rab10 reduction after multiple dosing supports LRRK2 pathway engagement



- BT-267 induced **reductions in Rab10 levels** in PBMCs upon multiple dosing
- At **multiple doses of 50 mg, >50% reduction in Rab10** was observed

Phosphorylated/total Rab10 ratio in PBMCs at 8 hours post-dose measured by MSD. Boxplots show the median (25th and 75th percentile) with whiskers within 1.5 times the IQR. Participants who received Placebo across cohorts in SAD or MAD were pooled. Additional cohorts exploring formulation, effect of food have been completed; only data pertinent to understanding PK and PD are shown.

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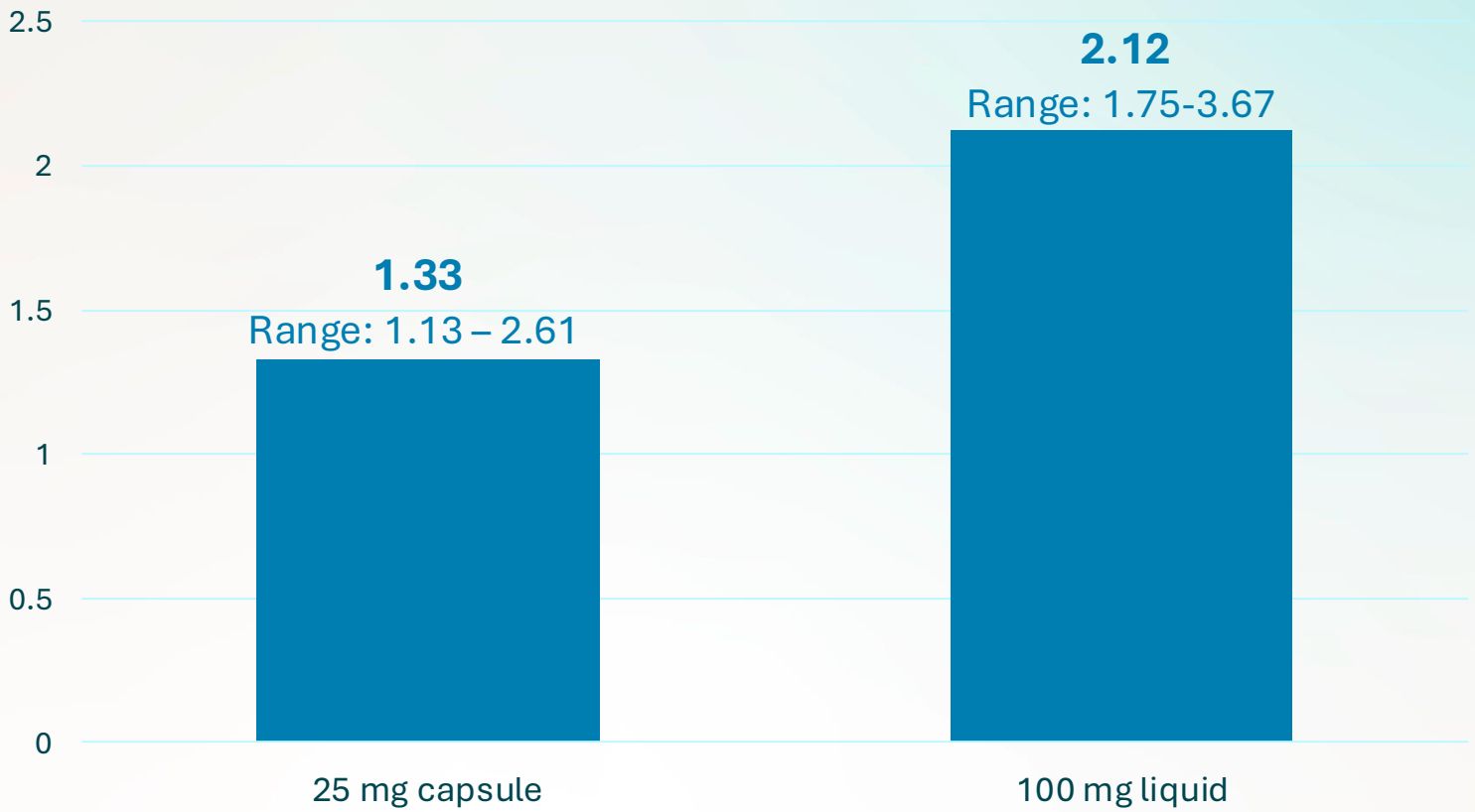
BT-267 Median CSF/Plasma Unbound Ratio



- BT-267 showed **excellent brain penetrance**
- **Increasing doses resulted in increased CSF exposure** as evidence by CSF/plasma unbound ratios >1 at 25 mg and **>2 at doses of 100 mg**

*CSF/unbound plasma ratio calculated using a plasma protein binding > 99%

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BT-267 Interim Phase 1a, Healthy Volunteer, Summary

- BT-267, an orally available LRRK2 inhibitor, **demonstrates a strong safety profile**, and has been well tolerated at single and multiple doses in healthy volunteers
- PK profile of BT-267 supports **once daily dosing**
- BT-267 **demonstrate inhibitions in peripheral LRRK2 protein levels approaching 80%** and **peripheral Rab10 >50%**
- Increased BT-267 plasma **concentrations lead to increased CSF exposure**
- **CSF/plasma unbound ratios exceed 2.0** at doses of 100 mg and demonstrate preferential brain distribution
- **Wide therapeutic window** and biomarker range will inform dose selection to optimize benefit-risk
- Strong biologic rationale for LRRK2 inhibition and Phase 1a interim data support **advancing BT-267 to a Phase1b PD study** and planning for a **Phase 2 trial**

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Thank You

Sincere gratitude to study participants, patients, families and collaborators who make this work possible.