Safety, Tolerability and Target Engagement Demonstrated in Phase 1 Study of LRRK2 Inhibitor DNL201 in Healthy Young and Elderly Adults

MJFF Parkinson's Disease Therapeutics Conference

October 25, 2018

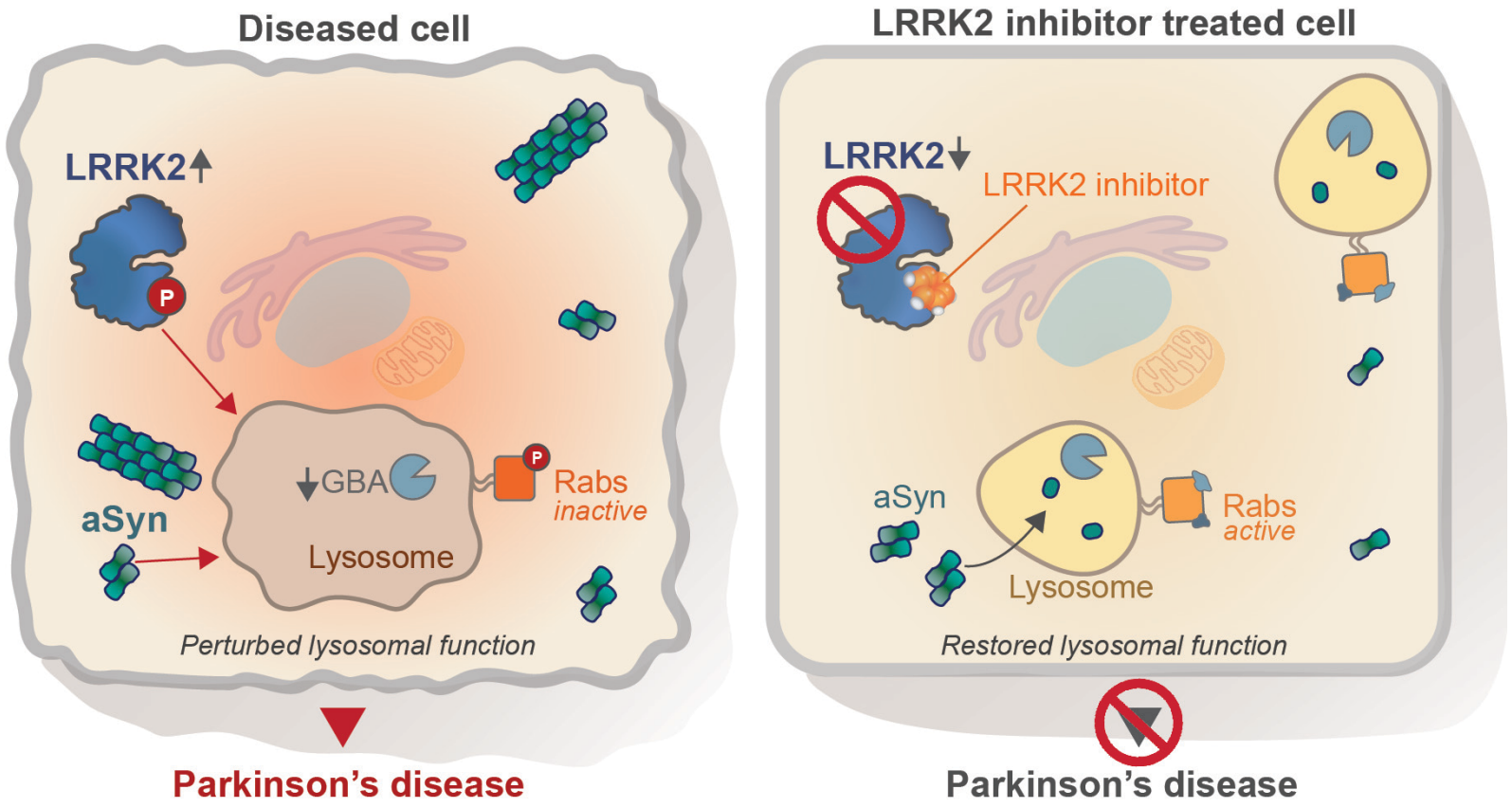
Matt Troyer MD, Denali Therapeutics

FIRST-IN-HUMAN STUDY OF LRRK2 INHIBITOR DNL201

- 122 healthy subjects, including 17 elderly subjects were studied
- Generally well tolerated at doses up to 100 mg twice daily for 10 days
- Well-behaved pharmacokinetics with robust CSF penetration
- Target and pathway engagement achieved
- Results support initiation of studies in Parkinson's disease patients with and without LRRK2 mutations

LRRK2 HYPERACTIVITY DRIVES LYSOSOMAL DYSFUNCTION AND PD

- Increased LRRK2 kinase activity impairs lysosomal function and drives PD pathogenesis
- LRRK2 inhibition can restore normal lysosomal function and reduce toxicity in PD models

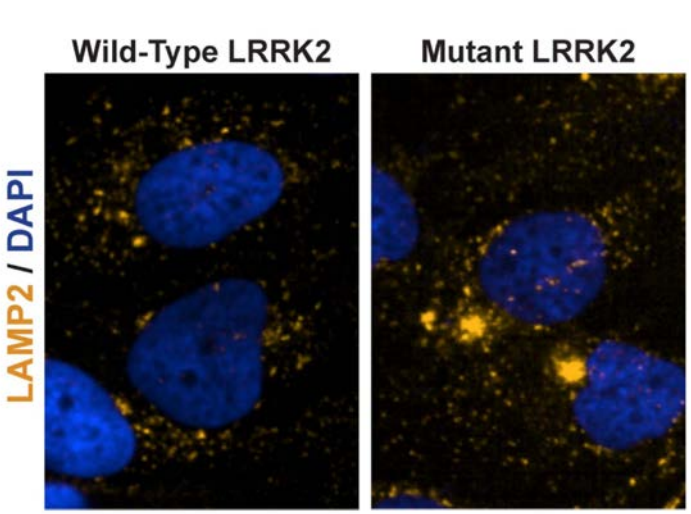


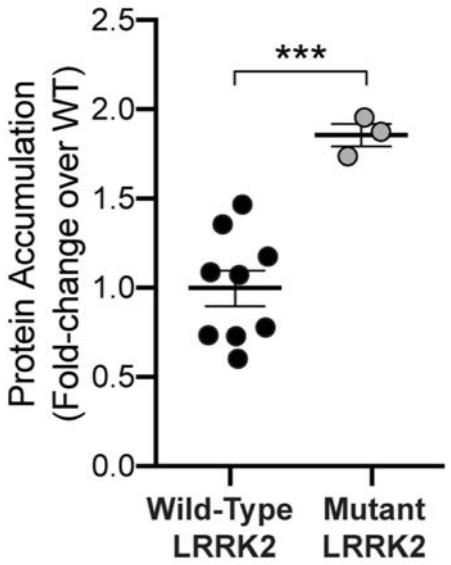
DNL201

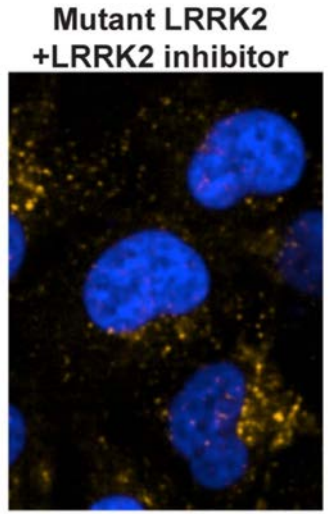
- Small molecule
- Potent and selective LRRK2 inhibitor
- Orally bioavailable
- Excellent CNS penetration

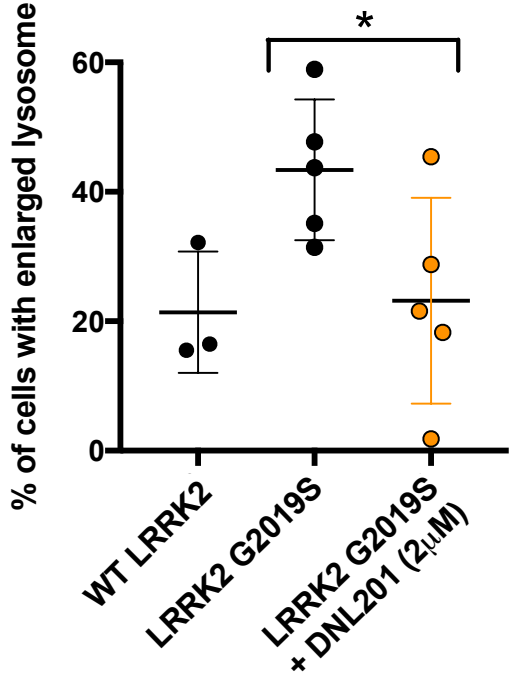
ROLE OF LRRK2 ACTIVITY IN LYSOSOMAL MORPHOLOGY AND FUNCTION

LRRK2 G2019S ALTERS LYSOSOME MORPHOLOGY AND FUNCTION IN A KINASE-DEPENDENT MANNER





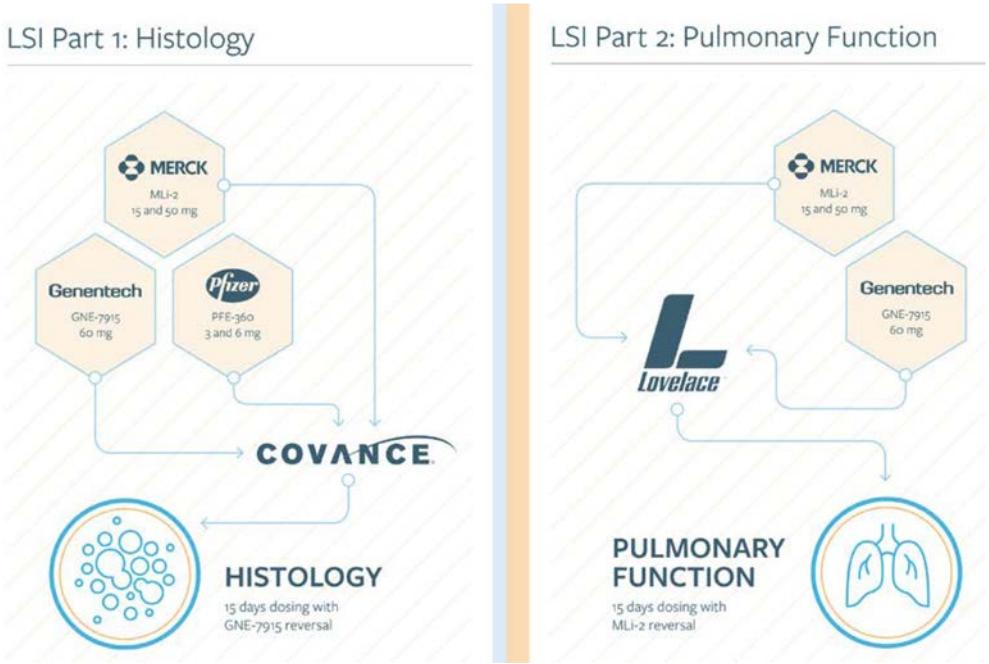


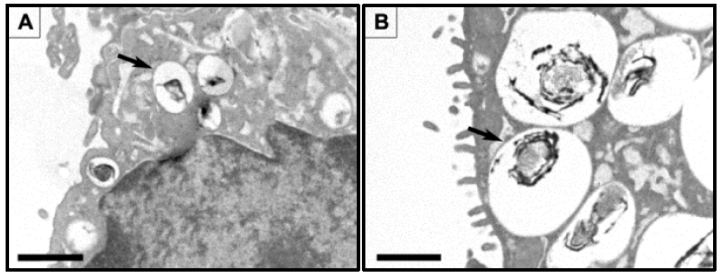


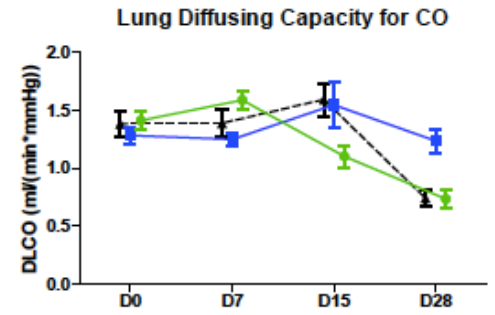
- Mutated LRRK2 (G2019S) results in coalesced, dysfunctional lysosomes (LAMP2, yellow)
- G2019S mutation results in decreased protein turnover
- LRRK2 inhibition with **DNL201** prevents abnormal lysosomal phenotype

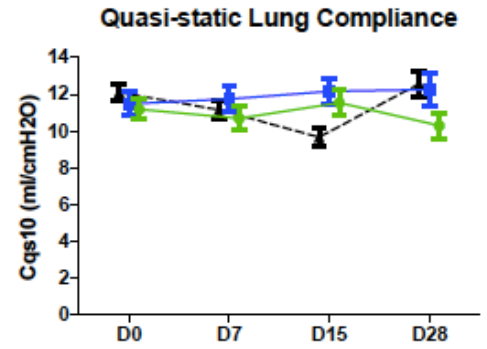
PRECLINICAL DATA SUPPORT CLINICAL STUDY OF LRRK2 INHIBITORS

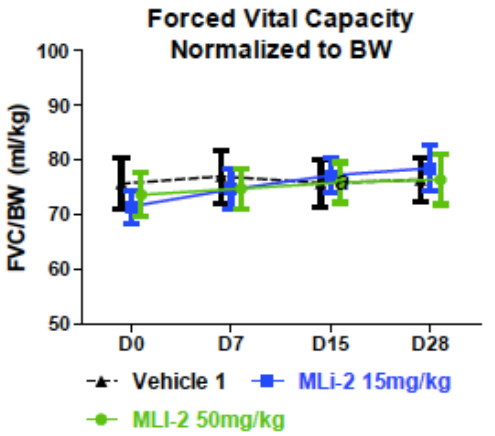
MJFF LRRK2 SAFETY INITIATIVE SUPPORTS DEVELOPMENT OF LRRK2 INHIBITORS FOR PD











DNL201 RAT AND MONKEY TOXICITY STUDIES SUPPORT HUMAN STUDY

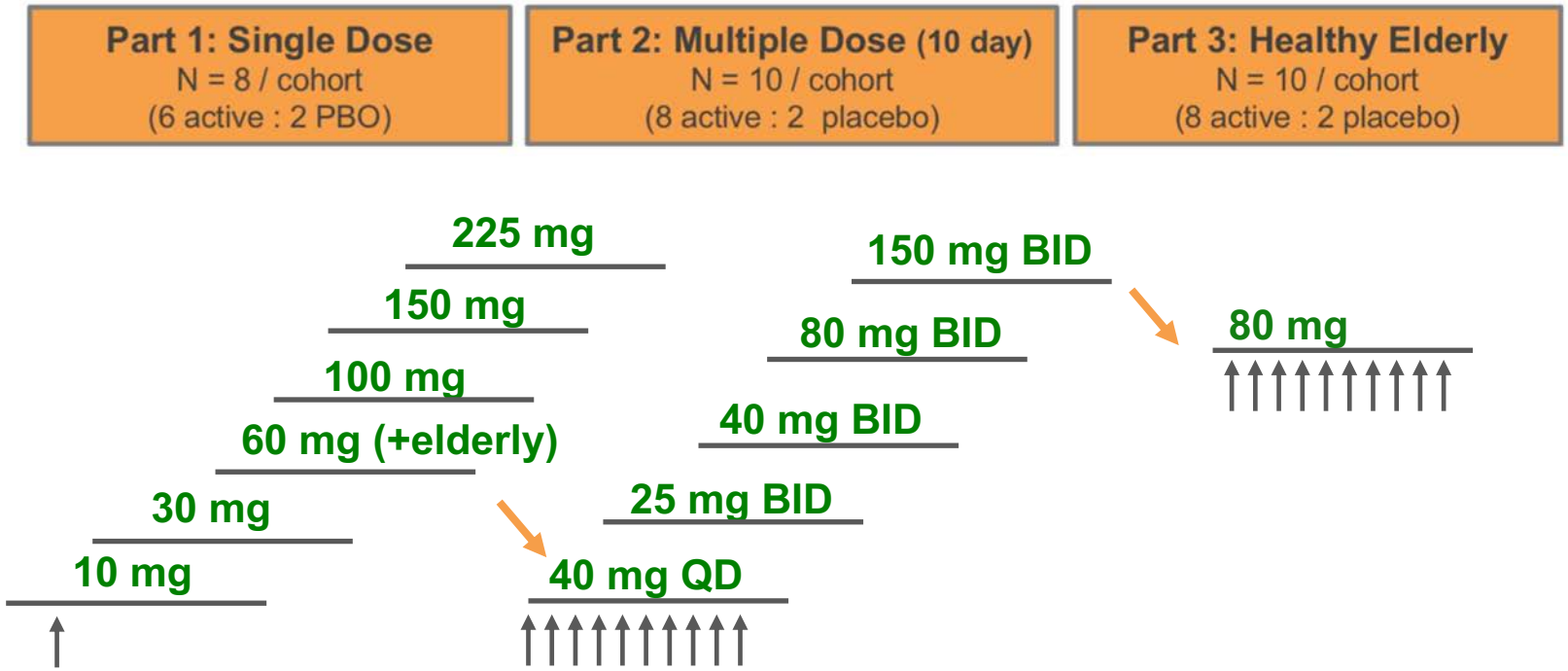
- Good tolerability in 28-day GLP toxicity studies up to high dose
  - On-target findings, non-adverse and reversible
- Initial exposure cap based on findings at high dose in rat pilot tox study
  - Cap removed after mechanism characterized in telemeterized rat study as HR, BP changes
  - Likely due to off-target phosphodiesterase inhibition
  - Findings reversible monitorable in clinic with vital signs

Oct 2018, *BioRxiv Preprint*, http://biorxiv.org/cgi/content/short/390815v1

DNL201 LRRK2 PHASE 1 HEALTHY VOLUNTEER CLINICAL TRIAL

Design	Phase 1 study in healthy volunteers • Randomized, placebo-controlled, double blind	
Study Size	**N=122** (Pt. 1=63; Pt. 2=49, Pt. 3 =10)	
Key Endpoints	**Safety:** • Pulmonary function tests • Safety labs • Vital signs • ECGs	**PK:** • Plasma • CSF • Urine

	Target engagement:
	• pS935 and pRab10 in whole blood / PBMCs
	• Exploratory endpoints
	  • CSF metabolomics, lipidomics
	  • LRRK2 in CSF exosomes	



- Safety parameters included:
  - Pulmonary: Diffusing capacity of lung for carbon monoxide (DL_{CO}); FVC, FEV_1, and FEV_1/FVC ratio
    - Pre-specified stopping rules for DL_{CO} : <80% of predicted and >20% decrease from baseline
  - Renal safety parameters included serum creatinine and urine albumin/creatine ratio

DNL201 PHASE 1 SAFETY RESULTS

ACROSS PHASE 1 STUDY

- No SAEs
- The most common Treatment Emergent Adverse Events (TEAEs), more frequent in active vs placebo subjects, were headache, dizziness, and nausea
- C_{max} related changes in pulse rate and blood pressure were observed, generally well tolerated
- No clinically meaningful changes on ECGs, physical / neurological exams, safety laboratories, renal parameters or pulmonary function
- D_{LCO} stopping criteria not met by any subject

PART 1: SINGLE ASCENDING DOSE

- Maximum tolerated single dose (MTD) was 150 mg
- All TEAEs were mild

PARTS 2 AND 3: MULTIPLE ASCENDING DOSE

- MTD was 100 mg BID in healthy young; also generally well tolerated in elderly subjects at 80 mg BID
- All TEAEs were mild except 2 subjects had moderate TEAEs
  - 1 headache (Elderly 80 mg BID); 1 atrial fibrillation (40 mg BID; unrelated to study drug based on cardiac workup)
- 3 early discontinuations related to TEAEs (2 headache, 1 atrial fibrillation, unrelated as described above)

DNL201 SINGLE ASCENDING DOSES: MOST COMMON TEAEs

	PBO (Elderly) N=2	PBO N=14	All Active[1] N=47	10 mg N=12	30 mg N=6	60 mg N=6	60 mg (Elderly) N=5	100 mg N=6	150 mg N=11	225 mg N=1
Number of subjects (%) in each dose group with at least one TEAE										
	-	3 (21%)	17 (36%)	1 (8%)	3 (50%)	1 (17%)	1 (20%)	5 (83%)	5 (46%)	1 (100%)
Number of subjects (%) with at least one report of most frequent TEAEs across single dose cohorts (≥2 reports on active treatment)										
Headache	-	-	**9 (19%)**	-	-	1 (17%)	1 (20%)	2 (33%)	4 (36%)	1 (100%)
Dizziness	-	-	**6 (13%)**	-	1 (17%)	-	1 (20%)	-	3 (27%)	1 (100%)
Procedure Reaction[2]	-	3 (21%)	5 (11%)	1 (8%)	1 (17%)	-	-	3 (50%)	-	-
Nausea	-	-	**3 (6%)**	-	-	-	-	-	2 (18%)	1 (100%)

Maximum tolerated single dose was 150 mg

- 1 subject received 225 mg and experienced nausea, dizziness, photophobia and headache 1 hour after dosing; decision was made to stop further dosing at this dose level and dose remainder of cohort 150 mg as target engagement goals met

[1] All active-dosed subjects comprise both young and elderly subjects who received DNL201
[2] Post-lumbar puncture syndrome and medical device site irritations

DNL201 MULTIPLE ASCENDING DOSES: MOST COMMON TEAEs

	PBO (Elderly) N=2	PBO N=9	All Active N=48	40 mg QD N=8	25 mg BID N=8	40 mg BID N=8	80 mg BID N=8	80 mg BID (Elderly) N=8	100 mg BID[1] N=8
Number of subjects (%) in each dose group with at least one TEAE									
	1 (50%)	5 (56%)	25 (52%)	3 (38%)	-	5 (63%)	6 (75%)	5 (63%)	6 (75%)
Number of subjects (%) with at least one report of most frequent TEAEs across multiple dose cohorts (≥2 reports on active treatment)									
Headache	1 (50%)	-	**19 (40%)**	2 (25%)	-	4 (50%)	4 (50%)	4 (50%)	5 (63%)
Dizziness	-	-	**6 (13%)**	-	-	2 (25%)	-	2 (25%)	2 (25%)
Nausea	-	-	**6 (13%)**	-	-	2 (25%)	-	2 (25%)	2 (25%)
Back/extremity pain	-	3 (33%)	3 (6%)	-	-	-	1 (13%)	1 (13%)	1 (13%)
Vomiting	-	1 (11%)	2 (4%)	-	-	1 (13%)	-	1 (13%)	-
Palpitations	-	-	2 (4%)	-	-	1 (13%)	1 (13%)	-	-

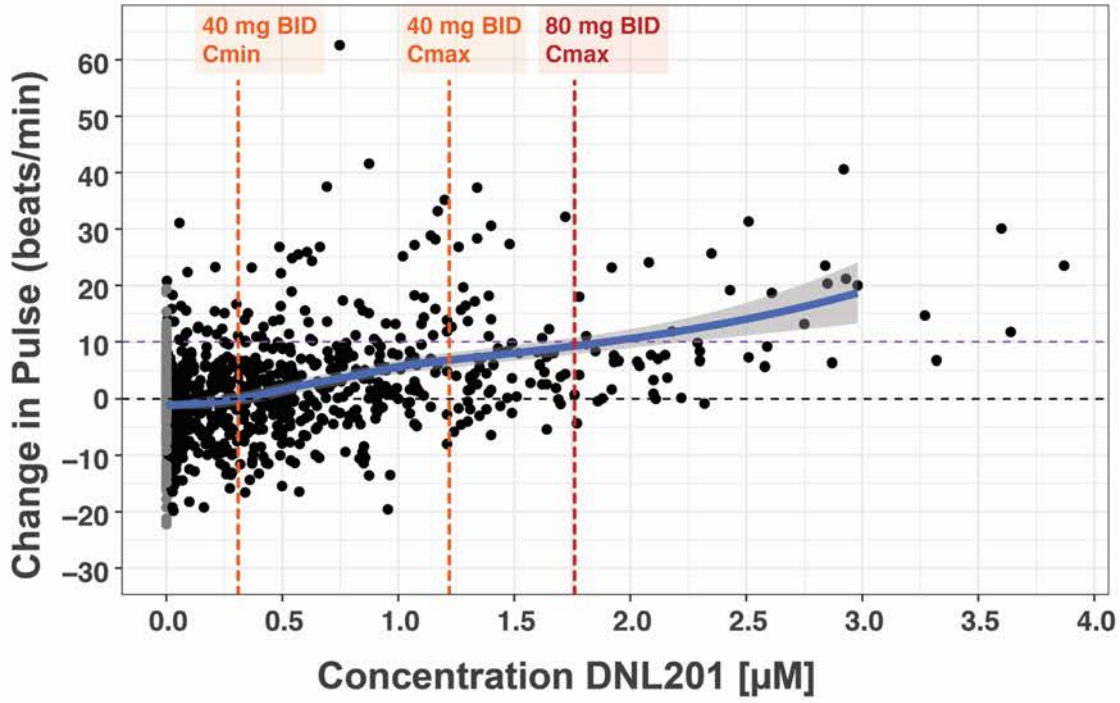
Maximum tolerated multiple dose was 100 mg BID in healthy young subjects

- 80 mg BID was studied in healthy elderly subjects and was also generally well tolerated

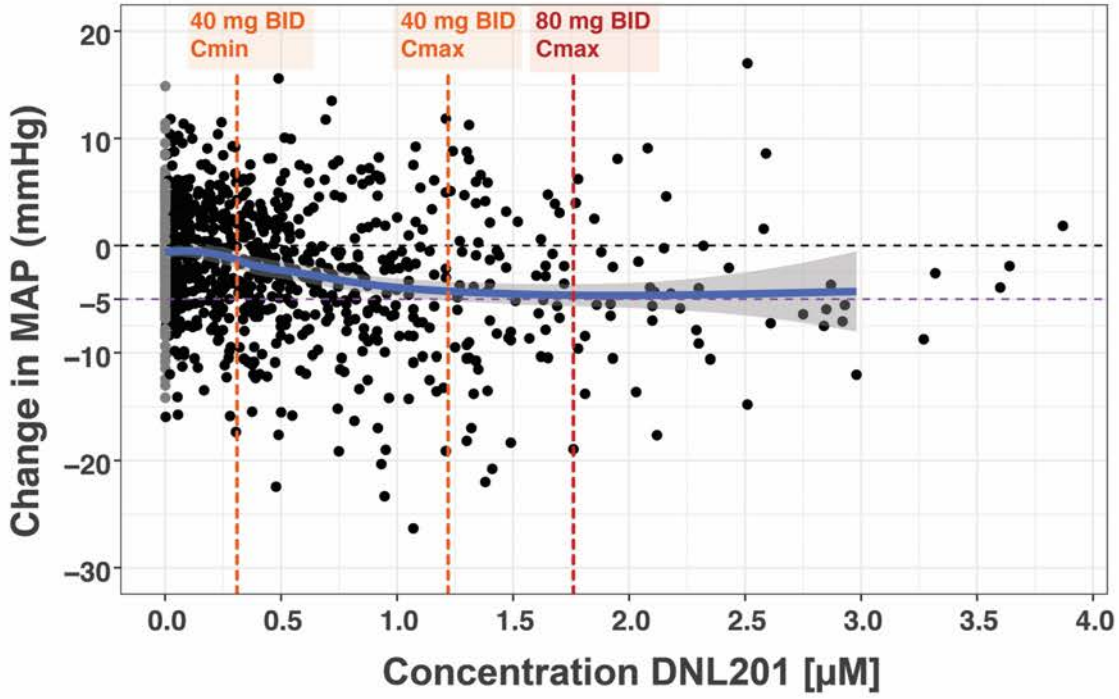
[1] In the planned 150 mg BID cohort, the dose was reduced after 150 mg dose on the morning of Day 1 due to a dizziness AE in 1 subject and asymptomatic orthostatic hypotension in a second subject. All subjects received 100 mg BID Days 2-10.

DNL201 CONCENTRATION VS. PULSE, MEAN ARTERIAL PRESSURE (MAP)

DNL201 PLASMA CONC. VS. SUPINE PULSE CHANGE FROM BASELINE



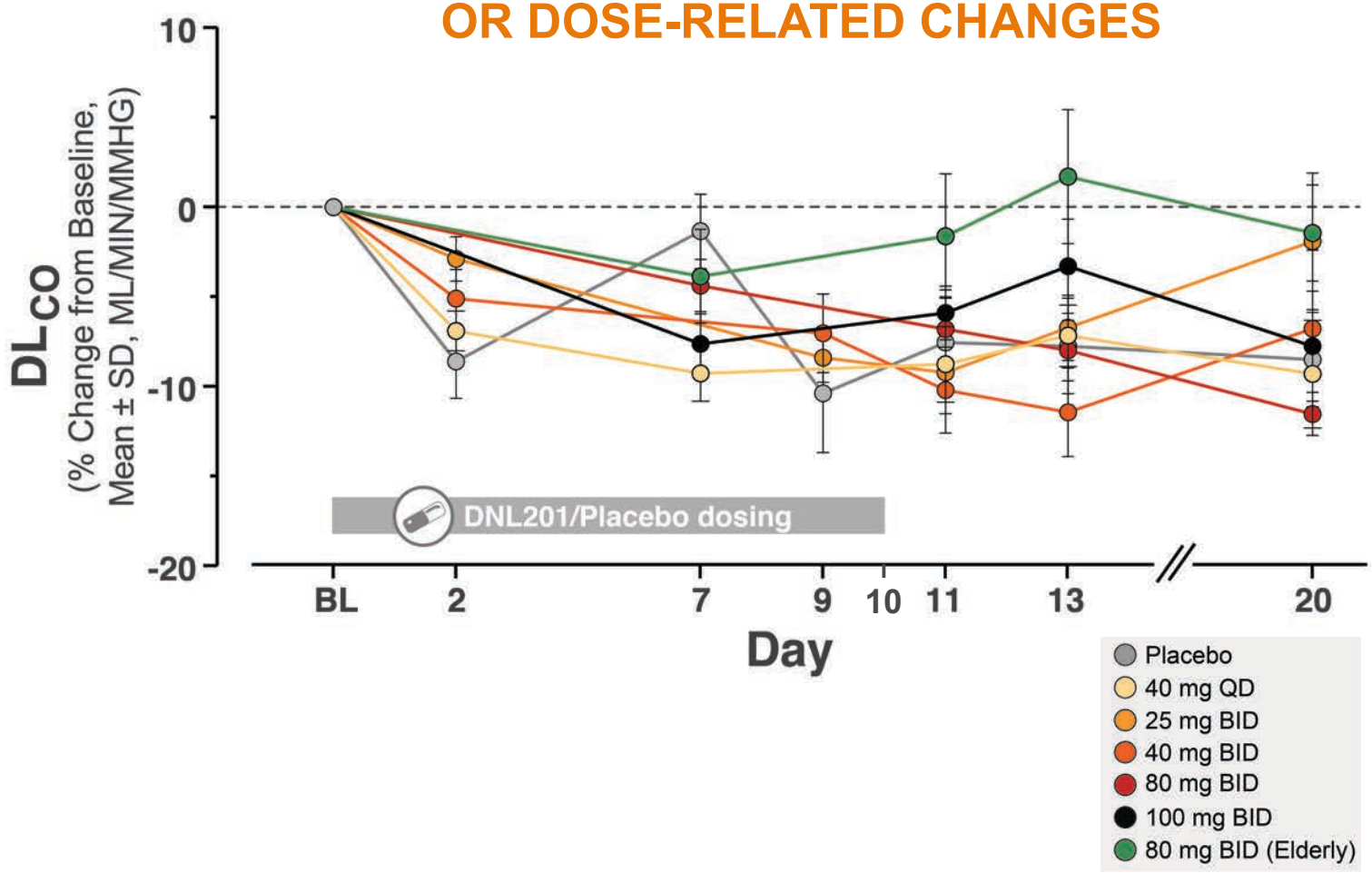
DNL201 PLASMA CONC. VS. SUPINE MAP CHANGE FROM BASELINE



- Exposure response for pulse and MAP, pooled data from all single doses and multiple doses on days 1, 8 and 10
- Mild C_{max} related changes in pulse rate and blood pressure were observed, generally asymptomatic
  - Consistent with known off-target inhibition of PDE3, PDE5 at peak concentration
- C_{max} at 80 mg BID doses associated with <10 bpm mean increases in HR and <5 mm Hg mean decreases in MAP compared to baseline

DNL201 PULMONARY SAFETY

DL_{CO}: NO CLINICALLY MEANINGFUL OR DOSE-RELATED CHANGES

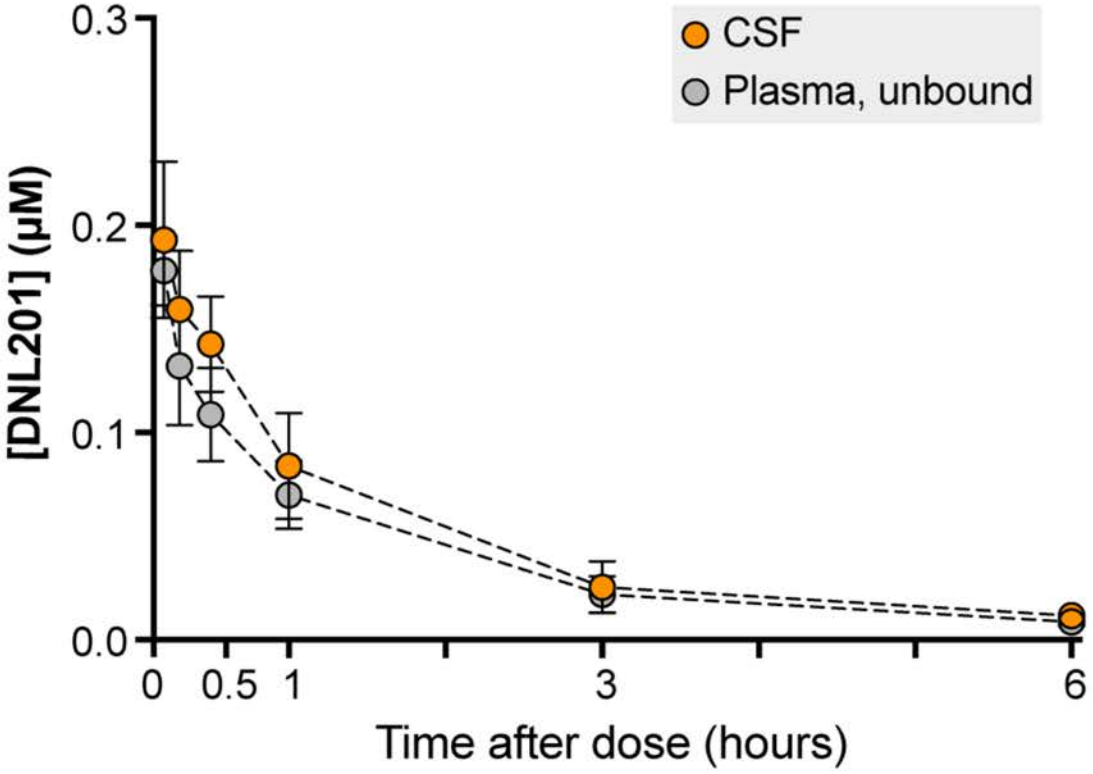


- **No clinically important changes or dose related trends in DL_{CO}, FVC, FEV_1, FEV_1/FVC ratio, or respiratory rate**
- DL_{CO} stopping criteria were not met by any subject
- 3 mild AEs related to the respiratory system
  - Cough 10 days post dose (30 yo M, 150 mg single dose), unrelated to study drug per investigator
  - Cough on days 6-8 (39 yo M, 40 mg QD), resolved spontaneously during treatment
  - Dyspnea on day 1 (64 yo F, 80 mg BID), resolved spontaneously after 4 minutes

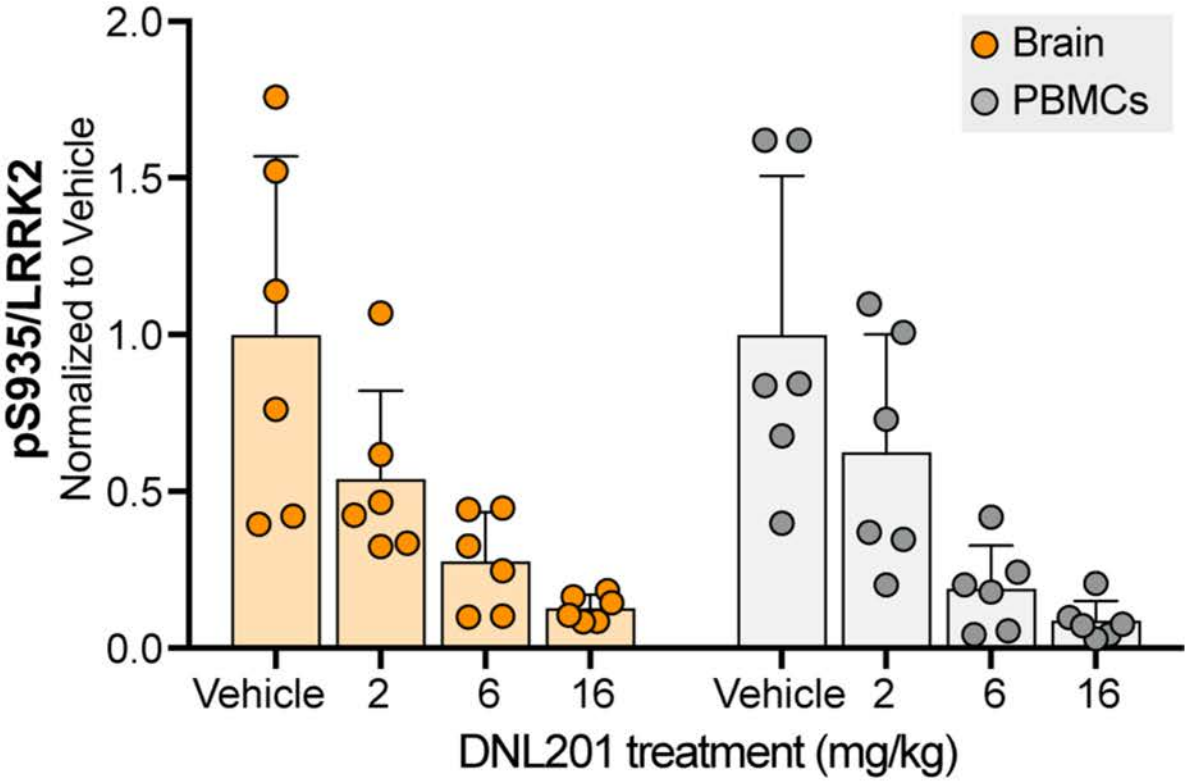
DNL201 INHIBITS BRAIN LRRK2 ACTIVITY IN CYNOMOLGUS MONKEY

LRRK2 INHIBITION IN PBMCS PREDICTS BRAIN LRRK2 INHIBITION

COMPARABLE EXPOSURE OF DNL201 IN CSF AND PLASMA



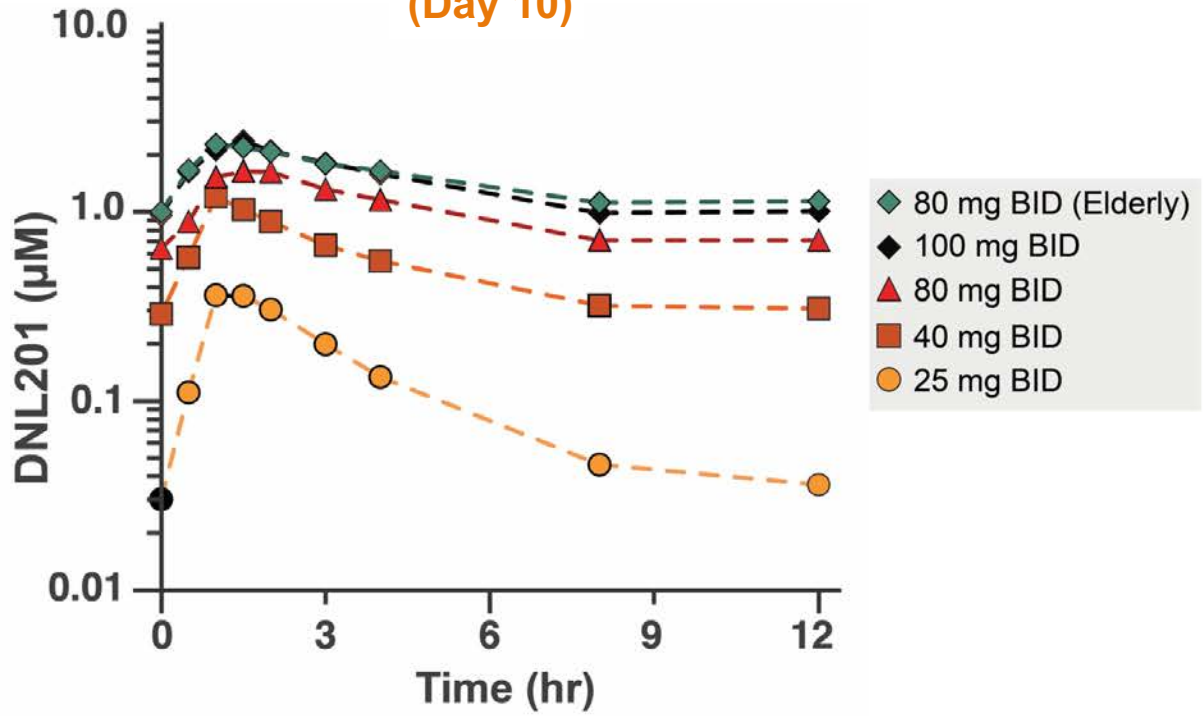
COMPARABLE INHIBITION OF LRRK2 IN BRAIN AND PBMCS



Samples collected 24 hours postdose after 28 days of dosing

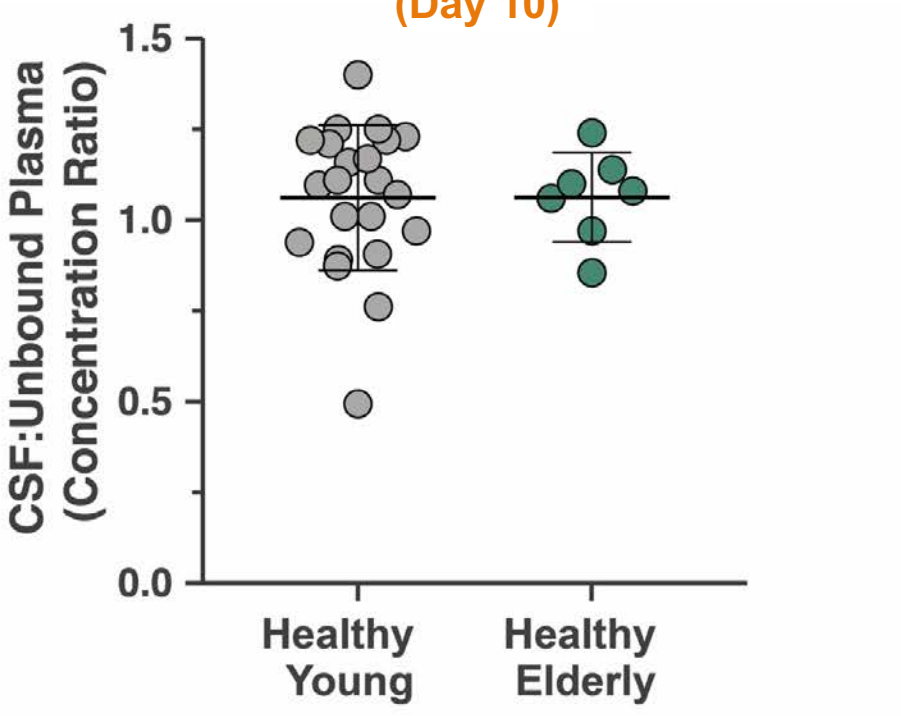
DNL201 PLASMA AND CSF PHARMACOKINETICS IN HUMAN SUBJECTS

DNL201 Plasma PK Profile (Day 10)



- PK profile supports twice daily dosing
- Terminal half life of 14-26 hours
- Low to moderate variability in C_{max} and AUC
- Steady state reached by Day 10

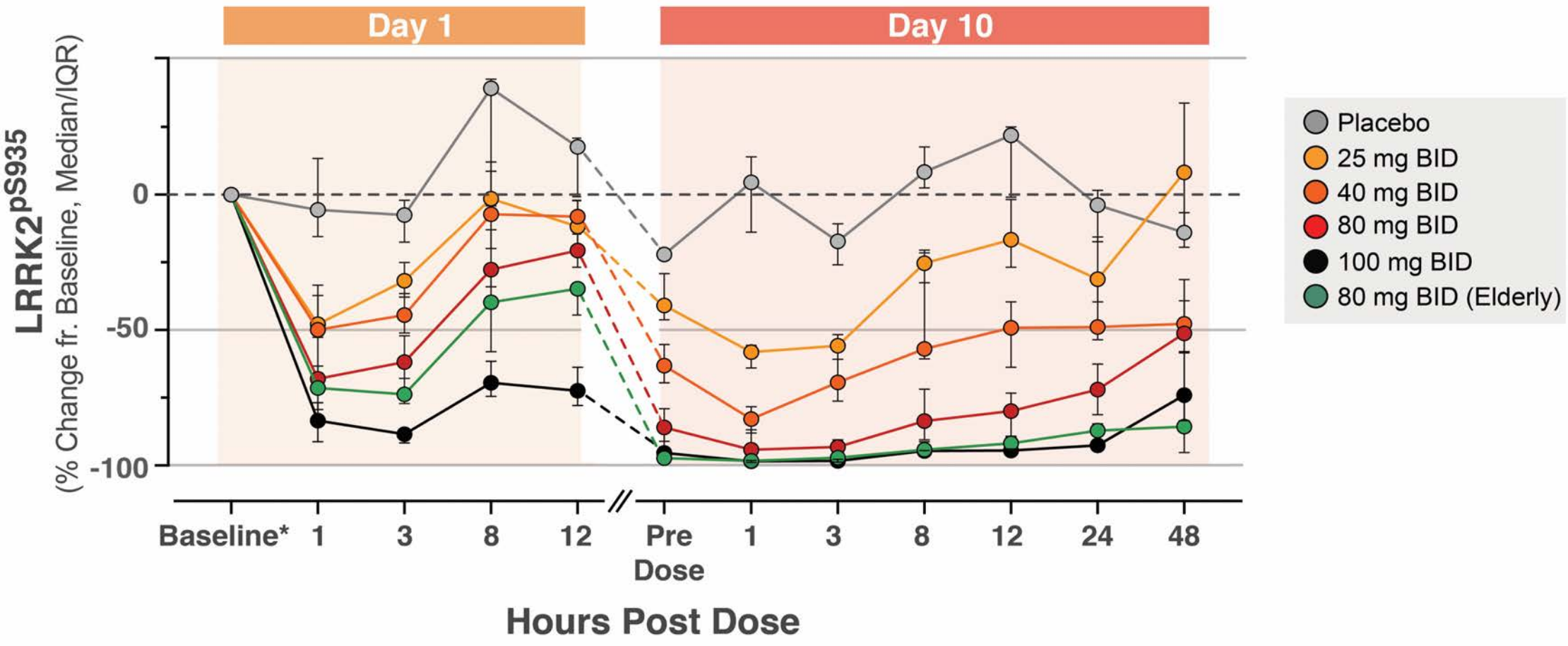
DNL201 CSF:Plasma PK Ratio (Day 10)



- Mean CSF to unbound plasma ratio of ~1.0
- Data from 25, 80 and 100 mg BID multiple dose cohorts

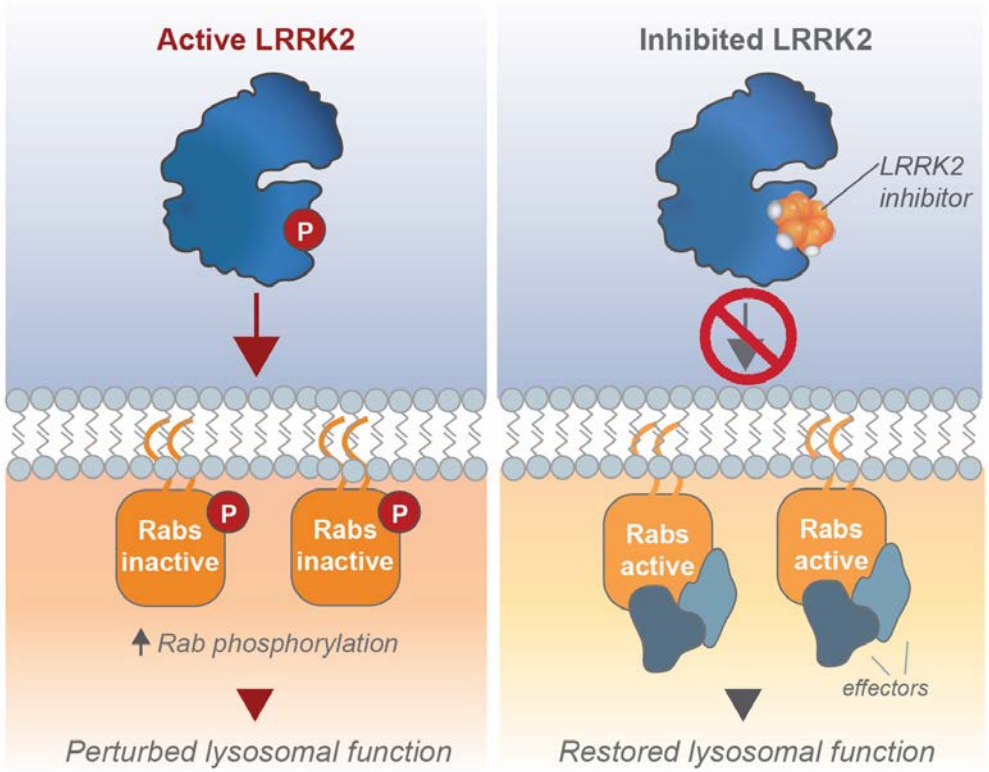
DNL201 DOSE-DEPENDENT INHIBITION OF LRRK2 IN HEALTHY SUBJECTS

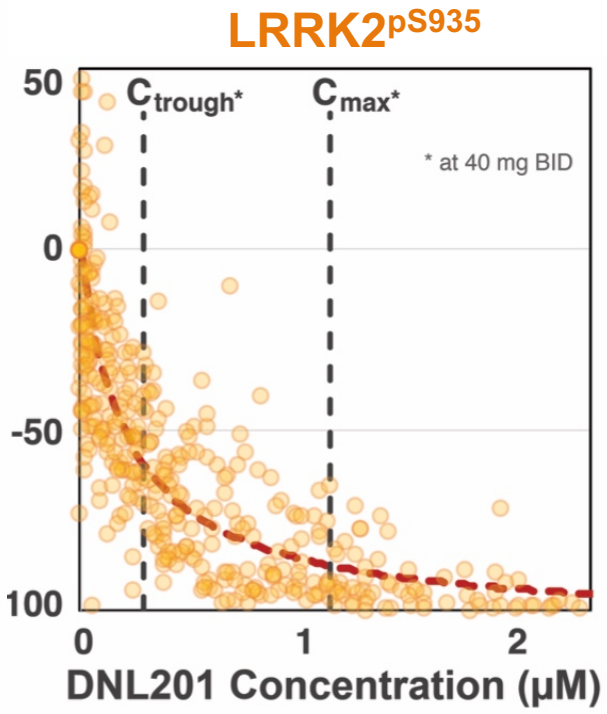
Whole Blood LRRK2^{pS935}

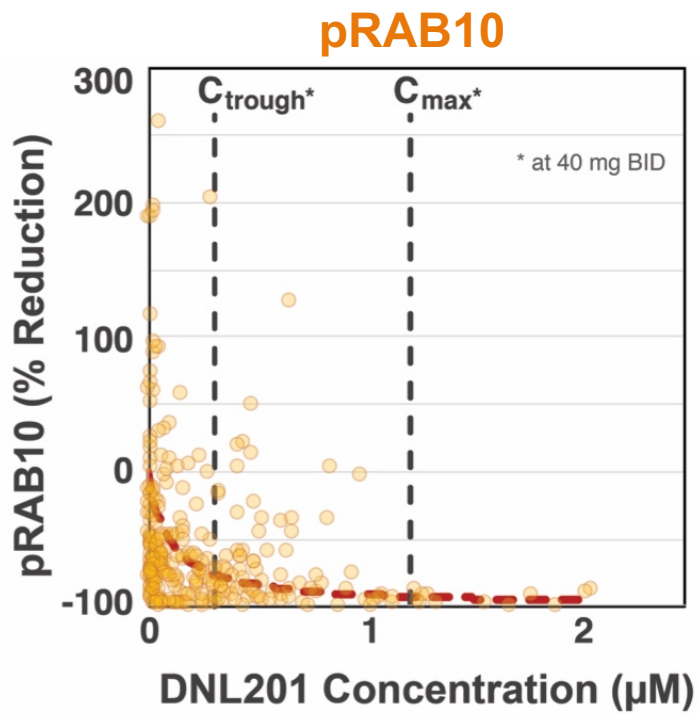


- Time course of LRRK2 pS935 inhibition after DNL201 administration every 12 hours until day 10

DNL201 EXPOSURE-RESPONSE IN HEALTHY SUBJECTS

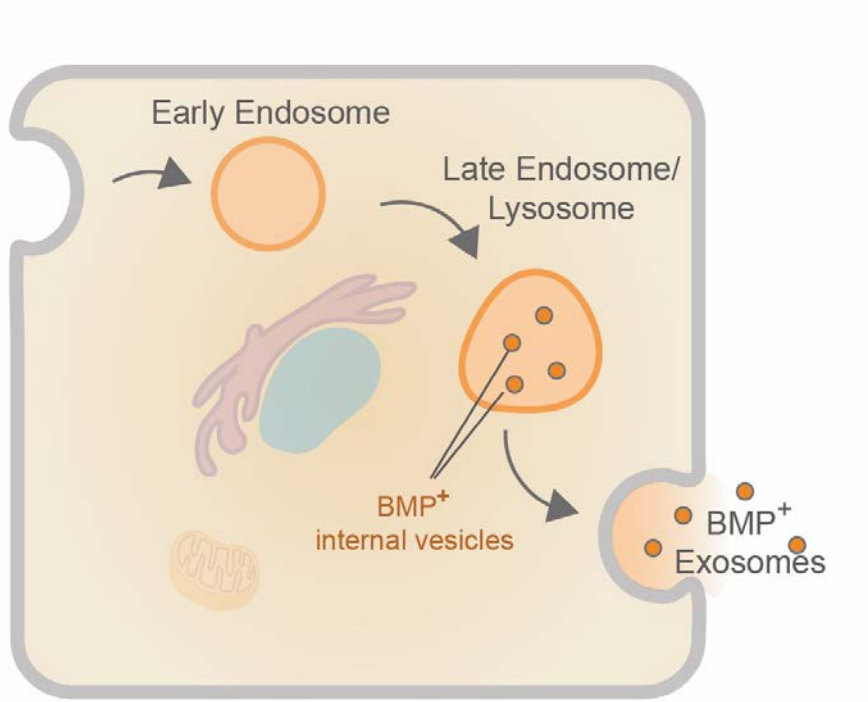




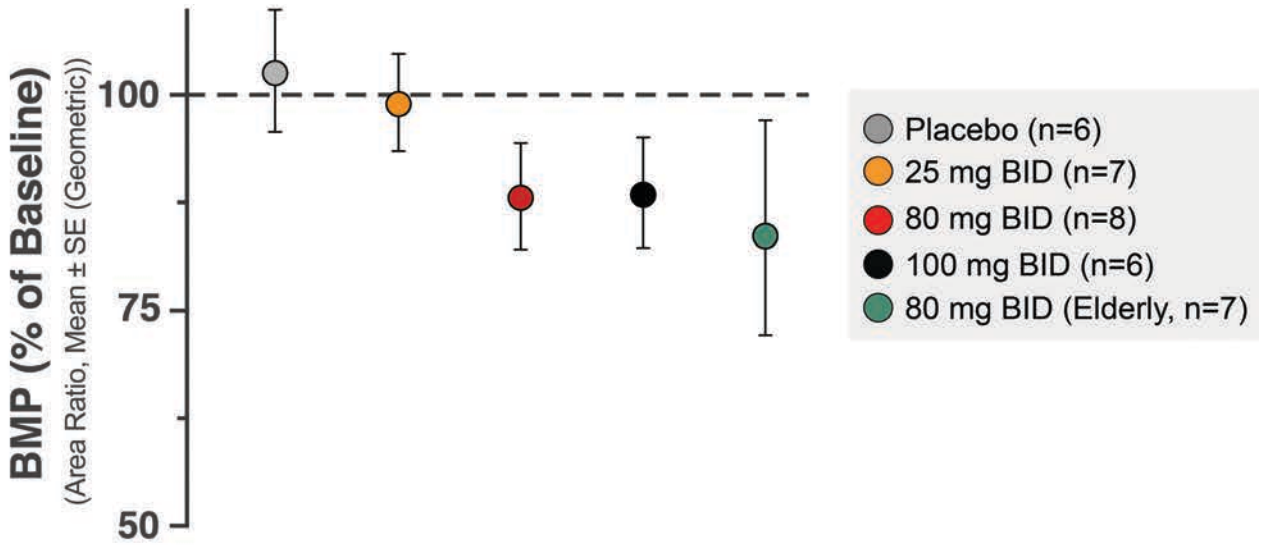


- Dose and concentration dependent LRRK2 inhibition (pS935) and pathway engagement (pRab10)
- At well-tolerated doses, >50 to 70% median inhibition observed at C_{trough} and >90% inhibition at C_{max}

LYSOSOMAL BIOMARKER BMP DECREASES IN HEALTHY SUBJECT CSF



CHANGE IN BMP Di22:6 AFTER 10 DAYS OF DNL201 DOSING



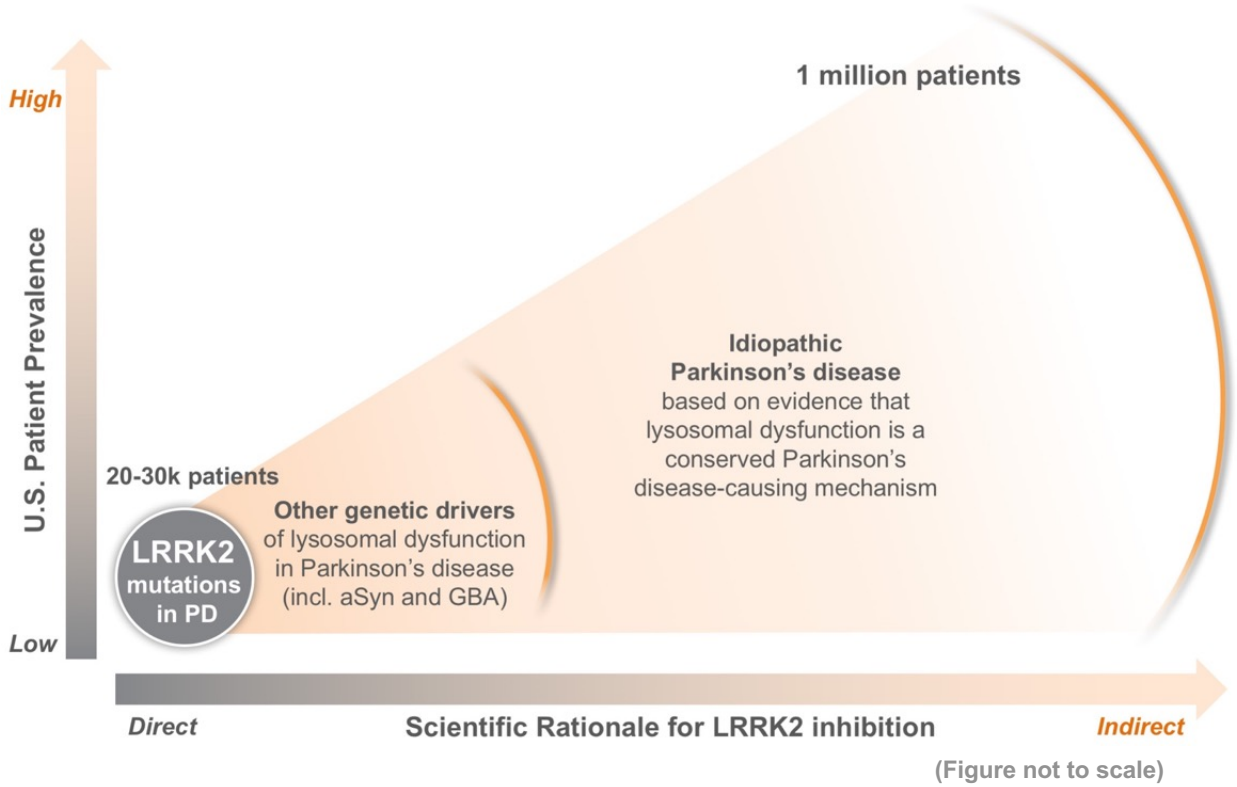
- BMP di22:6 is a lysosomal lipid; changes in BMP reflect functional change in lysosomal pathway
- Reductions in urine BMP are well-established in animals treated with structurally diverse LRRK2 inhibitors
  - **DNL201** reduced urine BMP in healthy human subjects in a dose-dependent fashion
- First evidence of CSF BMP change in humans treated with a LRRK2 inhibitor

DNL201 CLINICAL PROGRAM SUMMARY

CONCLUSIONS & NEXT STEPS

- **Phase 1 safety, target engagement, and CSF exposure goals were achieved**
  - Doses up to 100 mg BID were generally well tolerated
  - Doses up to 80 mg BID were tested in elderly subjects and generally well tolerated
  - Mild, C_{max}-related changes in HR and BP; peak concentrations in therapeutic range were well tolerated
  - At well-tolerated doses, >50 to 70% median inhibition observed at C_{trough} and >90% inhibition at C_{max}
- **The Phase 1 data support advancement of DNL201 to a Phase 1b safety and biomarker study in LRRK2-linked PD and idiopathic PD**

LRRK2 INHIBITION MAY HAVE BROAD THERAPEUTIC POTENTIAL FOR PD



EMERGING EVIDENCE LINKS LRRK2 BROADLY TO PD

- Variants in lysosomal genes are associated with PD risk
- Common variants in LRRK2 modify PD risk
- LRRK2 activity is increased is PD-relevant rodent models and in idiopathic PD

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PARKINSON'S DISEASE

LRRK2 activation in idiopathic Parkinson's disease

Roberto Di Maio[1,2,3], Eric K. Hoffman[1,2], Emily M. Rocha[1,2], Matthew T. Keeney[1,2], Laurie H. Sanders[1,2,4], Briana R. De Miranda[1,2], Alevtina Zharikov[1,2], Amber Van Laar[1,2], Antonia F. Stepan[5], Thomas A. Lanz[5], Julia K. Kofler[6], Edward A. Burton[1,2,7], Dario R. Alessi[8], Teresa G. Hastings[1,2], J. Timothy Greenamyre[1,2,7]*

Missense mutations in leucine-rich repeat kinase 2 (LRRK2) cause familial Parkinson's disease (PD). However, a potential role of wild-type LRRK2 in idiopathic PD (iPD) remains unclear. Here, we developed proximity ligation assays to assess Ser1292 phosphorylation of LRRK2 and, separately, the dissociation of 14-3-3 proteins from LRRK2. Using these proximity ligation assays, we show that wild-type LRRK2 kinase activity was selectively enhanced in substantia nigra dopamine neurons in postmortem brain tissue from patients with iPD and in two different rat models of the disease. We show that this occurred through an oxidative mechanism, resulting in phosphorylation of the LRRK2 substrate Rab10 and other downstream consequences including abnormalities in mitochondrial protein import and lysosomal function. Our study suggests that, independent of mutations, wild-type LRRK2 plays a role in iPD. LRRK2 kinase inhibitors may therefore be useful for treating patients with iPD who do not carry LRRK2 mutations.

- Lysosomal dysfunction is a central pathophysiology of PD in patients with and without known genetic drivers of PD
- Inhibition of LRRK2 may be a therapeutically beneficial approach for many forms of PD, including idiopathic PD

ACKNOWLEDGEMENTS

Denali

- Sarah Huntwork-Rodriguez
- Angela Kay
- Bradley Wong
- Romeo Maciuca
- Ella Negrou
- Janet Hurt
- Laura Harris
- Laura Kennedy
- Henry Hulter
- Sofia Mosesova
- Mark J. Dresser
- Kimberly Scearce-Levie
- Stacy Henry
- Xiang Wang
- Dolo Diaz
- Martin Larhammar
- Erica Kratz
- Carole Ho

Collaborators

- Alex King, Covance
- Harvey Wong, University of British Columbia


THANK YOU