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ARV-102, a PROTAC LRRK2 Degrader, Modulates Pathways Associated With Parkinson's Disease and Progressive Supranuclear Palsy: Proteomic Analyses of CSF From Non-human Primates and Healthy Volunteers

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Objectives

- To quantify baseline levels of leucine-rich repeat kinase 2 (LRRK2) in cerebrospinal fluid (CSF) of non-human primates (NHPs) and evaluate relationships between baseline LRRK2 and key biomarkers of endolysosomal and neuroinflammatory pathways in CSF
- To describe the kinetics of central degradation of LRRK2 induced by ARV-102, an oral PROteolysis TArgeting Chimera (PROTAC) LRRK2 degrader, in NHPs
- To evaluate effects of LRRK2 degradation and CSF biomarker changes in NHPs selected for elevated CSF LRRK2, to better reflect higher CSF LRRK2 levels reported in Parkinson's disease[1]
- To test if CSF changes in LRRK2-linked pathway markers in NHPs translate to biomarker changes observed in ARV-102-treated healthy volunteers (HVs) in a first-in-human phase 1 clinical study

Key Findings

- Baseline CSF LRRK2 concentrations varied proportionally with baseline CSF levels of downstream biomarkers of endolysosomal and neuroinflammatory pathways
- Oral dosing of ARV-102 induced measurable reductions in CSF LRRK2 levels in NHPs as early as ~8 hours after the first dose; mean decreases were >85% of baseline by the seventh day of once-daily (QD) dosing with progressive recovery to baseline levels after dosing cessation
- Proteomic analysis of NHP CSF showed decreases in endolysosomal (cathepsin B and GPNMB) and neuroinflammatory (IBA1) markers that paralleled reductions in CSF LRRK2 levels
- In NHPs prescreened for elevated baseline LRRK2 in CSF (mean >35 pg/mL), QD dosing of a PROTAC LRRK2 degrader induced saturating (>90%) and reversible degradation of LRRK2 in CSF that was proportional to drug concentrations in CSF
  - After 14 QD doses, significant reductions in CSF levels of pathway biomarkers were observed in proteomic analyses and orthogonal immunoassays
- HVs treated with ARV-102 80 mg QD for 14 days in a phase 1 clinical study had significant reductions from baseline in CSF levels of lysosomal and microglial markers known to be associated with LRRK2 Parkinson's disease

Conclusions

- PROTAC LRRK2 degraders induced rapid, robust, and reversible reductions in CSF LRRK2 levels in NHPs, including in those with elevated baseline CSF LRRK2 representative of Parkinson's disease
- Baseline levels of disease-relevant pathway markers in CSF were consistent with baseline CSF LRRK2 levels and decreased following PROTAC-induced degradation of LRRK2
- Proteomic analysis of CSF from ARV-102-treated HVs confirmed that changes in key LRRK2-sensitive pathway markers observed in NHPs translate to humans
- ARV-102 demonstrated significant reductions in CSF LRRK2 and disease pathway biomarkers, supporting further investigation in clinical trials for progressive supranuclear palsy and Parkinson's disease

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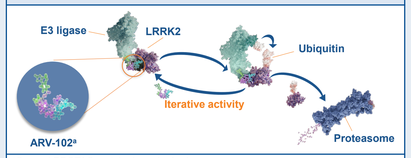
Background

- LRRK2 is a broadly expressed multidomain enzyme that is involved in diverse cellular processes, including endolysosomal, autophagy, and neuroinflammatory pathways[2,3]
- LRRK2 modulates clinical features of Parkinson's disease, and *LRRK2* mutations are a cause of late-onset disease[4–9]
- ARV-102 is an oral, brain-penetrant PROTAC LRRK2 degrader that harnesses the ubiquitin-proteasome system to induce degradation of LRRK2 (**Figure 1**)[10]
  - ARV-102 is a bifunctional molecule with LRRK2- and E3 ubiquitin ligase–binding regions that forms a trimer complex to induce ubiquitination and subsequent degradation of LRRK2 by the proteasome

Figure 1: Mechanism of action of ARV-102



[a]General PROTAC protein degrader is shown.
LRRK2=leucine-rich repeat kinase 2; PROTAC=PROteolysis TArgeting Chimera.

- Preclinical studies showed that ARV-102 induces stronger engagement of LRRK2 and its downstream pathways in the brain, greater activation of endolysosomal pathways, and increased tau reduction compared with a LRRK2 kinase inhibitor[10]
- In NHPs, oral ARV-102 reduced LRRK2 levels in CSF and "deep-brain" regions and induced reductions in LRRK2 pathway biomarkers, including the microglial marker IBA1 and the lysosomal markers cathepsin B and bis(monoacylglycerol)phosphate in CSF[10]
- In a phase 1, single- and multiple-ascending dose study in HVs, oral ARV-102 was well tolerated, demonstrated central nervous system penetration with a pharmacokinetic profile supportive of QD dosing, and achieved peripheral and central LRRK2 degradation and downstream pathway engagement[11,12]

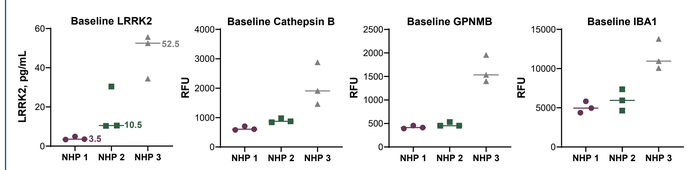
Results

LRRK2 and pathway biomarkers in the CSF of NHPs and effects of ARV-102

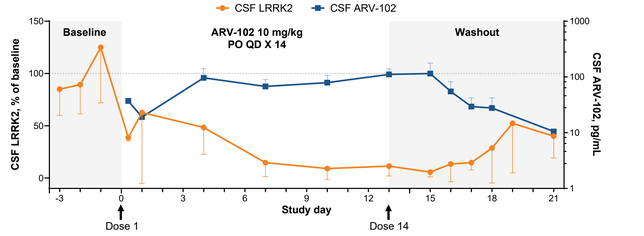
- Among 3 randomly selected NHPs, median LRRK2 concentrations in CSF at baseline ranged from 3.5 to 52.5 pg/mL and varied proportionally with baseline CSF levels of downstream markers of endolysosomal (GPNMB and cathepsin B) and neuroinflammatory (IBA1) pathways, most notably in NHP #3, which had the highest baseline LRRK2 levels (**Figure 2A**)
- Oral dosing of ARV-102 10 mg/kg QD for 14 days decreased mean CSF LRRK2 levels as early as 8 hours after the first dose, with LRRK2 levels progressively decreasing in parallel with increasing CSF compound levels (**Figure 2B**)
- Mean CSF LRRK2 degradation exceeded 85% of baseline by the seventh day of dosing and LRRK2 concentrations returned toward baseline levels after the last dose (**Figure 2B**)
- CSF proteomics showed decreases in endolysosomal and neuroinflammatory pathway markers that paralleled changes in CSF LRRK2 levels in all 3 NHPs at day 1 and day 14 (**Figure 2C**)

Figure 2: CSF LRRK2 degradation and pathway markers in NHPs dosed with ARV-102

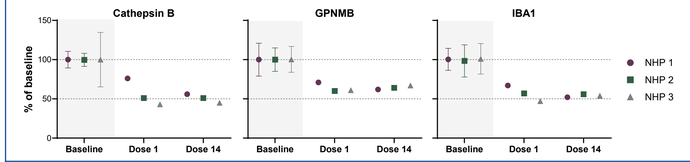
(A) Baseline LRRK2 levels correlate with baseline levels of lysosomal and microglial markers in CSF



(B) Time-dependent changes in CSF LRRK2 and ARV-102 levels



(C) Reductions in pathway markers in CSF

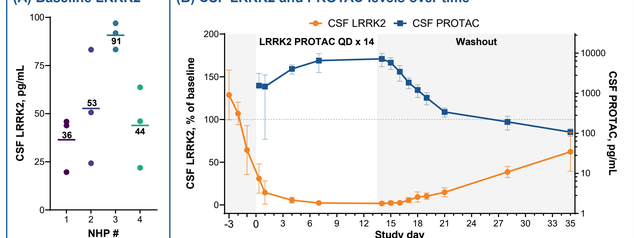


NHPs (n=3) were orally dosed with ARV-102 10 mg/kg QD for 14 days. CSF samples were obtained by spinal port before treatment (baseline) and periodically during the 14-day dosing and washout periods. LRRK2 levels in CSF were measured by single-molecule array (SIMOA). Levels of downstream pathway markers in CSF were assayed by aptamer-based proteomic analyses (7K SomaScan). In panel A, horizontal lines show median values. In panels B and C, values are mean ± SD.
CSF=cerebrospinal fluid; GPNMB=glycoprotein non-metastatic melanoma protein B; IBA1=ionized calcium-binding adaptor molecule 1; LRRK2=leucine-rich repeat kinase 2; NHP=non-human primate; PO=orally administered; RFU=raw fluorescence units; QD=once daily.

Effects of a PROTAC LRRK2 degrader in NHPs with elevated CSF LRRK2 at baseline

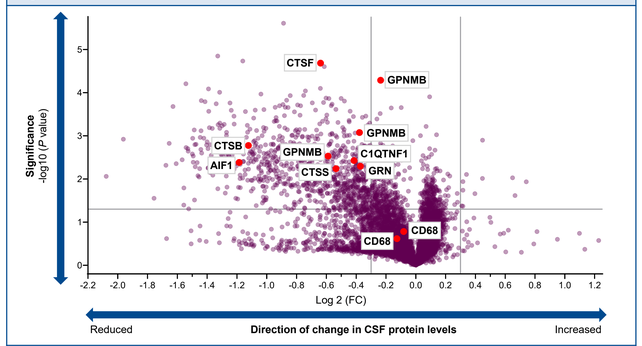
- To evaluate the effects of LRRK2 degradation in an NHP population potentially more reflective of LRRK2 Parkinson's disease,[1] animals were prescreened for elevated baseline LRRK2 concentrations in CSF (>35 pg/mL)
- Among 4 NHPs with mean CSF LRRK2 concentrations >35 pg/mL at baseline (**Figure 3A**), 14 QD oral doses of a novel tool PROTAC LRRK2 degrader induced saturating (>90%) and reversible degradation of LRRK2 in CSF that was proportional to CSF drug concentrations (**Figure 3B**)
- Proteomic analyses showed significant reductions in downstream markers of endolysosomal (GPNMB, -33%; CTSB, -54%; CTSF, -36%; CTSS, -31%; C1QTNF1, -25%) and neuroinflammatory (IBA1, -56%) pathways after 14 QD doses of a PROTAC LRRK2 degrader (**Figure 4**)
- Direct immunoassays confirmed reductions in pathway biomarkers (IBA1, -68.0%; CD68, -53.3%; GPNMB, -43.5%) that paralleled both the proteomics results and reductions in CSF LRRK2 levels (**Figure 5**)

Figure 3: CSF LRRK2 degradation in NHPs with elevated baseline levels, using a novel tool PROTAC LRRK2 degrader



NHPs (n=4) with elevated levels of LRRK2 in CSF (mean >35 pg/mL; shown in panel A) were dosed with a PROTAC LRRK2 degrader QD for 14 days. CSF samples were obtained by spinal port before treatment (baseline) and periodically during the 14-day dosing and washout periods. LRRK2 levels in CSF were measured by single-molecule array (SIMOA). In panel A, dots are individual measurements based on longitudinal pre-dose sampling and horizontal lines are means. In panel B, values plotted are mean ± SD.
CSF=cerebrospinal fluid; LRRK2=leucine-rich repeat kinase 2; NHP=non-human primate; PROTAC=PROteolysis TArgeting Chimera; QD=once daily.

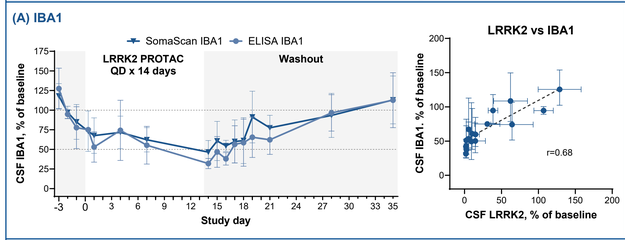
Figure 4: Proteomic changes in NHPs with elevated CSF LRRK2 at baseline



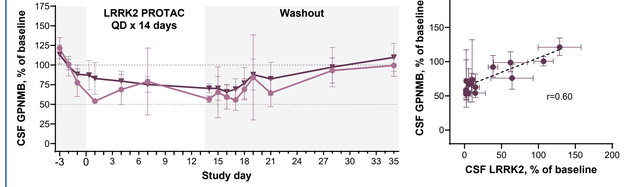
NHPs with elevated baseline CSF LRRK2 (mean >35 pg/mL; n=4) were treated with a PROTAC LRRK2 degrader for 14 days. Proteomic analyses of CSF obtained after the 14th QD dose were performed using 7K SomaScan.
AIF1=allograft inflammatory factor 1 (IBA1); C1QTNF1= complement C1q tumor necrosis factor-related protein 1; CD68=cluster of differentiation 68; CSF=cerebrospinal fluid; CTSB=cathepsin B; CTSF=cathepsin F; CTSS=cathepsin S; FC=fold change; GRN=granulin; GPNMB= glycoprotein non-metastatic melanoma protein B; LRRK2=leucine-rich repeat kinase 2; NHP=non-human primate; PROTAC=PROteolysis TArgeting Chimera.

Figure 5: Time-dependent reductions in CSF downstream pathway markers following PROTAC treatment (confirmed with orthogonal immunoassay)

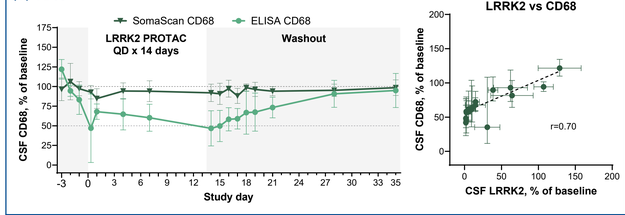
(A) IBA1



(B) GPNMB



(C) CD68

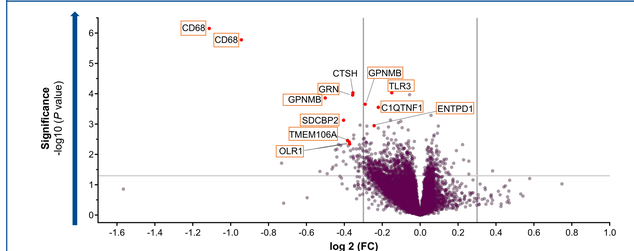


Direct immunoassays were run on CSF samples to orthogonally confirm proteomics results in a quantitative manner. Values plotted are mean (SD) change in analyte expressed as percent of baseline.
CD68=cluster of differentiation 68; CSF=cerebrospinal fluid; ELISA=enzyme-linked immunosorbent assay; GPNMB=glycoprotein non-metastatic melanoma protein B; IBA1=ionized calcium-binding adaptor molecule 1; LRRK2=leucine-rich repeat kinase 2; PROTAC=PROteolysis TArgeting Chimera; QD=once daily.

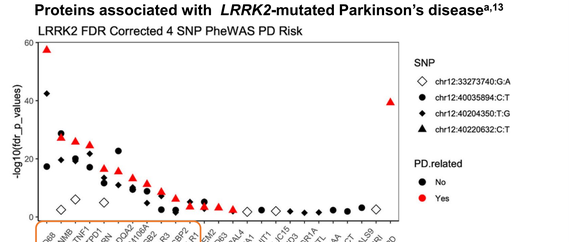
CSF proteomics in HVs (phase 1 clinical study)[12]

- To assess ARV-102-induced changes in LRRK2-associated proteins in healthy adult humans, CSF samples from HVs who received ARV-102 in a phase 1 study were analyzed utilizing the SomaScan platform[12]
- Oral administration of ARV-102 80 mg QD for 14 days significantly decreased CSF levels of lysosomal pathway markers (eg, CTSH, GPNMB, and GRN) and microglial markers (eg, C1QTNF1, ENTPD1, TMEM106A, and CD68), which are elevated in patients with Parkinson's disease harboring LRRK2 variants (**Figure 6**)[13]
  - Median % changes from baseline in lysosomal markers were -21.2% for CTSH, -27.7% for GPNMB, and -22.6% for GRN
  - For microglial markers, median % changes from baseline were -13.9% for C1QTNF1, -19.3% for ENTPD1, -24.5% for TMEM106A, and -55.0% for CD68

Figure 6: Proteomic changes in CSF of HVs who received ARV-102 80 mg for 14 days in a phase 1 study[12]



Proteins associated with *LRRK2*-mutated Parkinson's disease[a,13]



[a]Figure adapted from Phillips et al. (2023). Proteome-wide association studies of LRRK2 variants identify novel causal and druggable proteins for Parkinson's disease. npj Parkinson's Disease. DOI: 10.1038/s41531-023-00555-4. Licensed under CC BY 4.0.
C1QTNF1=compment C1q tumor necrosis factor-related protein 1; CD68=cluster of differentiation 68; CFB=change from baseline; CSF=cerebrospinal fluid; CTSH=cathepsin H; ENTPD1=ectonucleoside triphosphate diphosphohydrolase 1; FC=fold change; GRN=granulin precursor; GPNMB=glycoprotein non-metastatic melanoma protein B; HVs=healthy volunteers; LRRK2=leucine-rich repeat kinase 2; OLR1=oxidized low-density lipoprotein receptor 1; SDCBP2=syndecan binding protein 2; TLR3=Toll-like receptor 3; TMEM106A=transmembrane protein 106A.

References

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