First Clinical Trials of ARV-102, a PROTAC LRRK2 Degrader: **Characterization of Pathway Engagement in Healthy Volunteers** and Patients With Parkinson's Disease

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Objectives

- To assess downstream effects of leucine-rich repeat kinase 2 (LRRK2) degradation by ARV-102, a potent PROteolysis TArgeting Chimera (PROTAC), in healthy volunteers
- To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics of single doses of ARV-102 in an ongoing phase 1 study in patients with Parkinson's disease

Key Findings

- Proteomic analyses of cerebrospinal fluid (CSF) from healthy volunteers treated with ARV-102 80 mg daily for 14 days showed significant reductions from baseline in lysosomal pathway markers (cathepsin H [CTSH], GPNMB, and granulin [GRN]) and microglial markers (C1QTNF1, ENTPD1, TMEM106A and CD68) known to be associated with LRRK2 Parkinson's disease
- Levels of CD68 in CSF decreased in a dose-dependent manner, consistent with observed reductions in CSF LRRK2 concentrations
- In a phase 1 study in 19 patients with Parkinson's disease, single doses of ARV-102 50 mg or 200 mg were well tolerated; treatment-related adverse events (TRAEs) of headache, diarrhea, and nausea were mild; no serious AEs occurred
- ARV-102 exposure metrics (area under the concentration-time curve [AUC] and maximum plasma concentration [C_{max}]) increased in a dosedependent manner in plasma and in CSF, indicating brain penetration
- Median LRRK2 protein levels in peripheral blood mononuclear cells (PBMCs) decreased by 86% from baseline with the 50-mg dose and by 97% with the 200-mg dose

Conclusions

- In healthy volunteers, ARV-102 decreased CSF levels of lysosomal pathway and microglial markers that are known to be elevated in patients with Parkinson's disease with LRRK2 variants
- ARV-102 demonstrated consistent safety and PK in patients with Parkinson's disease and healthy volunteers, with dose-dependent peripheral LRRK2 degradation
- Evaluation of multiple doses of ARV-102 in patients with Parkinson's disease, including assessment of LRRK2 and downstream pathway engagement, is ongoing

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Acknowledgments: This study was sponsored by Arvinas Operations, Inc. Medical writing support was provided by Lela Creutz, PhD and funded by Arvinas Operations, Inc.

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International Congress of Parkinson's Disease and Movement Disorders (MDS)

Background

Results

- LRRK2 is a broadly expressed multidomain enzyme that plays a role in diverse cellular processes, including endolysosomal pathway regulation and autophagy^{1,2}
- LRRK2 modulates clinical features of Parkinson's disease, and mutations are a cause of late-onset disease^{3–8}
- ARV-102 is an oral, brain-penetrant PROTAC LRRK2 degrader that harnesses the ubiquitin-proteasome system to induce degradation of LRRK2 (Figure 1)
- ARV-102 is a bifunctional molecule with LRRK2and E3 ubiquitin ligase-binding regions that form a trimer complex to induce ubiquitination and subsequent degradation of LRRK2 by the proteasome

HEALTHY VOLUNTEERS: CSF proteomics

Figure 3: CSF proteomics in healthy volunteers

(B) Change from baseline in CSF protein levels

(A) Volcano plot of proteomic changes in CSF with ARV-102 80 mg

-1.6 -1.4 -1.2 -1.0 -0.8 -0.6 -0.4 -0.2 0.0 0.2 0.4 0.6 0.8 1.0

log 2 (FC)

Direction of change CSF protein levels

Placebo (n=10) ARV-102 80 mg (n=9)

TMEM106A

harboring LRRK2 variants¹¹

concentrations (Figure 3C)

- Preclinical studies showed that ARV-102 induces stronger engagement of LRRK2 and its downstream pathways in the brain, greater activation of the endolysosomal pathways, and increased tau reduction compared with a LRRK2 kinase inhibitor9
- In non-human primates, oral ARV-102 reduced LRRK2 levels in CSF and "deep-brain" regions and induced reductions in LRRK2 pathway biomarkers, including the microglial marker ionized calcium binding adaptor molecule 1 and the lysosomal markers cathepsin B and bis(monoacylglycerol)phosphate in CSF9

ARV-102 80 mg QD for 14 days significantly decreased CSF levels of lysosomal pathway markers (median % change

19.3%; TMEM106A, -24.5%; CD68, -55.0%; Figure 3A-B), which are elevated in patients with Parkinson's disease

CD68 levels in CSF decreased in a dose-dependent manner, consistent with observed reductions in CSF LRRK2

from baseline: CTSH, -21.2%; GPNMB, -27.7%; GRN, -22.6%) and microglial markers (C1QTNF1, -13.9%; ENTPD1, -

 In a phase 1, single- and multiple-ascending dose study in healthy volunteers, oral ARV-102 was well tolerated, demonstrated central nervous system penetration with a PK profile supportive of once-daily dosing, and achieved peripheral and central LRRK2 degradation and downstream pathway engagement (see poster 904)¹⁰

Methods

chr12:33273740:G:A

chr12:40035894:C:T chr12:40204350:T:G

▲ chr12:40220632:C:T

Ubiquitin

Figure 1: Mechanism of action of ARV-102

LRRK2=leucine-rich repeat kinase 2; PROTAC=PROteolysis TArgeting

Proteins associated with LRRK2-mutated Parkinson's disease^{a,11}

(C) Change in CD68 levels in CSF by ARV-102 dose

CD68 in CSF: Placebo ARV-102

◆ LRRK2 in CSF (median % CFB)

Placebo 10 mg 20 mg 40 mg 80 mg

LRRK2 FDR Corrected 4 SNP PheWAS PD Risk

E3 ligase

ARV-102^a

^aGeneral PROTAC protein degrader is shown.

Proteomic analyses of CSF from healthy volunteers

 To assess ARV-102-induced changes in LRRK2-associated proteins, unbiased proteomic analyses utilizing the SomaScan platform were conducted on CSF samples from participants who received ARV-102 or placebo once daily (QD) for 14 days in the phase 1 healthy volunteer study

Phase 1 study in patients with Parkinson's disease

- A single-center, double-blind, randomized, phase 1 study is evaluating ARV-102 in patients with Parkinson's disease (Figure 2)
- Results of the single-dose portion of the study as of September 9, 2025 are reported here

Baseline characteristics

Figure 2: Phase 1 study in patients with Parkinson's disease (EUCT 2024-516888-84-00) Key eligibility criteria

Males and females aged 40 to 80 years

fluctuations or dyskinesia

- Parkinson's disease without major motor
 - Single oral dose on day 1 with follow-up period of ≥11 days
- 1 of the following:
 - Resting tremor and bradykinesia
 - Bradykinesia and rigidity Rigidity and resting tremore
 - Either asymmetric resting tremor or asymmetric bradykinesia
- Modified Hoehn and Yahr scale score ≤3
- Stable dose of levodopa/carbidopa (if receiving)

Multiple-dose portion (n≈30) ≈6 patients to be enrolled per arm **Randomize (1:1:1:1)** Once-daily oral doses on days 1-28 with follow-up for 14 days after the last dose

Primary objective: Evaluate the safety and tolerability

of ARV-102

28.0 (26–30)

Secondary objective: Characterize the plasma PK of

Evaluate ARV-102 exposure in CSF

Single-dose portion (n=19)

ARV-102 or placebo

≈12 patients were to be enrolled in 50-mg cohort

and 8 in 200-mg cohort and randomized 3:1 to

Exploratory objectives:

Evaluate the pharmacodynamic effects of ARV-102

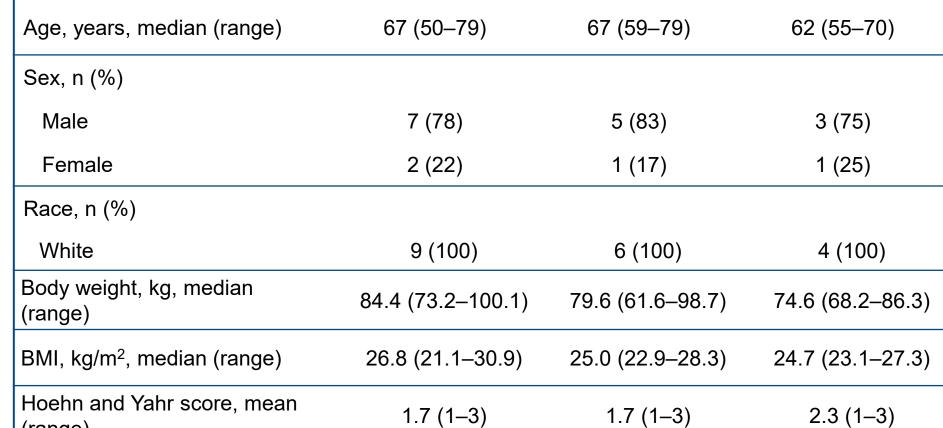
→ 200 mg

CSF=cerebrospinal fluid; PK=pharmacokinetics

PATIENTS WITH PARKINSON'S DISEASE: Phase 1 study (single-dose portion)

 19 patients with Parkinson's disease received a single dose of ARV-102 50 mg (n=9) or 200 mg (n=6) or placebo (n=4; **Table 1**)

Table 1: Demographics and baseline characteristics ARV-102 200 mg ARV-102 50 mg Placebo Characteristic 67 (50–79) 67 (59–79)



28.7 (27-30)

Note: Data are preliminary and were calculated manually. BMI=body mass index; MMSE=Mini Mental State Examination

Safety and tolerability

MMSE score, mean (range)

Single doses of ARV-102 were well tolerated at both dose levels (**Table 2**)

29.2 (27–30)

All TRAEs were mild; no serious adverse events occurred

Table 2: TEAEs and TDAEs

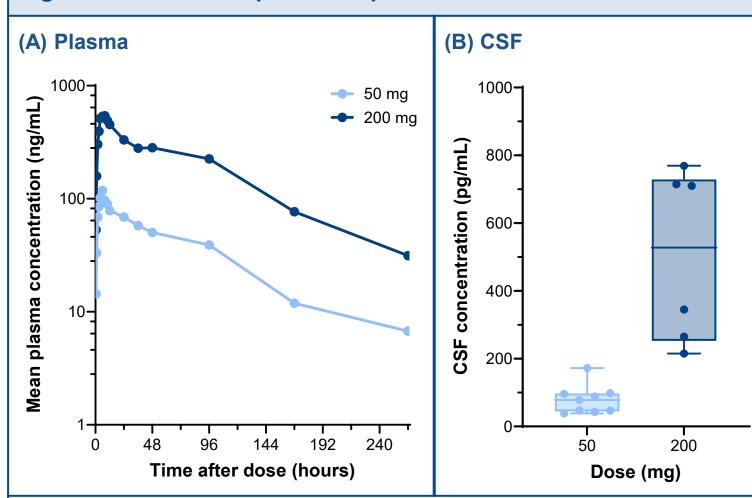
AE, n (%)	ARV-102			Placebo
	50 mg (n=9)	200 mg (n=6)	Total (n=15)	(n=4)
TEAEs ^a				
Headache	1 (11)	1 (17)	2 (13)	0
Post-lumbar puncture syndrome ^b	1 (11)	1 (17)	2 (13)	2 (50)
Catheter site bruise	1 (11)	1 (17)	2 (13)	0
Puncture site pain	1 (11)	0	1 (7)	1 (25)
TRAEs				
Headache	1 (11)	1 (17)	2 (13)	0
Nausea	1 (11)	0	1 (7)	0
Diarrhea	1 (11)	0	1 (7)	0

Note: Data are preliminary and were tabulated manually ^aEvents reported by ≥2 patients who received a single dose of ARV-102. ^bAll patients underwent lumbar puncture for CSF collection. All headaches related to lumbar puncture were recorded as post-lumbar puncture syndrome. CSF=cerebrospinal fluid; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.

PK in plasma and CSF

 ARV-102 exposure (AUC_{inf} and C_{max}) increased in a dosedependent manner in plasma and in CSF (Figure 4)

Figure 4: ARV-102 exposure in plasma and CSF



Note: Data are preliminary and were tabulated manually.

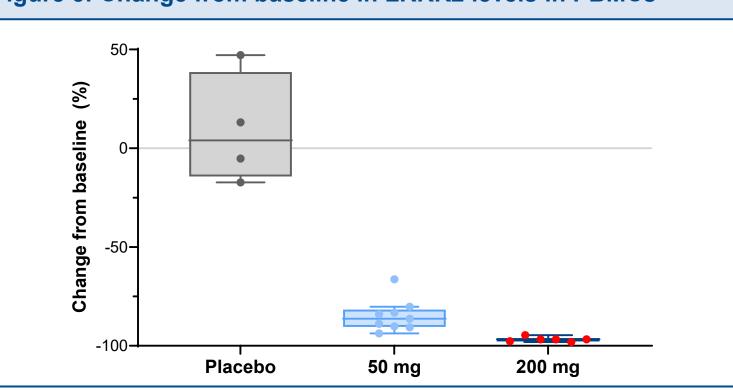
ARV-102 concentrations (A) in plasma and (B) in CSF after a single oral dose In panel B, circles indicate individual values and box plots show median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range. CSF data were obtained 28 to 30 hours

LRRK2 in PBMCs

CSF=cerebrospinal fluid

 Median LRRK2 protein levels in PBMCs decreased by 86% from baseline following a single 50-mg dose of ARV-102 and by 97% after a 200-mg dose (Figure 5)

Figure 5: Change from baseline in LRRK2 levels in PBMCs



Note: Data are preliminary and were calculated manually Change from baseline in LRRK2 protein levels in PBMCs obtained 24 hours after a single dose. Circles indicate individual patient values. Box plots show median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range. Values below the LLOQ (shown in red) are plotted as

LLOQ=lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; PBMCs=peripheral blood mononuclear cells.

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.

Honolulu, HI, USA; October 5–9, 2025

In panels B and C, the asterisks reflect P values (**P<0.01; ***P<0.001) calculated using unpaired t-tests vs placebo. Circles indicate individual values. Box plots show median and 25%/75% guartiles with whiskers to the last point within 1.5 times the interguartile range. C1QTNF1=complement 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; 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.