LBA 22

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 dose-dependent 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

References

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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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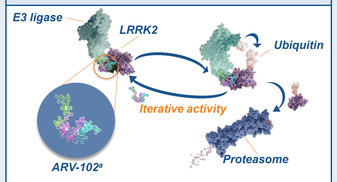
International Congress of Parkinson's Disease and Movement Disorders (MDS)
Honolulu, HI, USA; October 5–9, 2025

Background

- 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 LRRK2- and E3 ubiquitin ligase–binding regions that form a trimer complex to induce ubiquitination and subsequent degradation of LRRK2 by the proteasome
- 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 inhibitor[9]
- 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 CSF[9]

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.

- 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

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

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
- Parkinson's disease without major motor fluctuations or dyskinesia
- 1 of the following:
  - Resting tremor and bradykinesia
  - Bradykinesia and rigidity
  - Rigidity and resting tremor
  - Either asymmetric resting tremor or asymmetric bradykinesia
- Modified Hoehn and Yahr scale score ≤3
- Stable dose of levodopa/carbidopa (if receiving)

Single-dose portion (n=19)

- ≈12 patients were to be enrolled in 50-mg cohort and 8 in 200-mg cohort and randomized 3:1 to ARV-102 or placebo
- Single oral dose on day 1 with follow-up period of ≥11 days

50 mg → 200 mg

Multiple-dose portion (n≈30)

- ≈6 patients to be enrolled per arm
- Once-daily oral doses on days 1–28 with follow-up for 14 days after the last dose

Randomize (1:1:1:1): 20 mg | 40 mg | 80 mg | Placebo

Primary objective:
- Evaluate the safety and tolerability of ARV-102

Secondary objective:
- Characterize the plasma PK of ARV-102

Exploratory objectives:
- Evaluate ARV-102 exposure in CSF
- Evaluate the pharmacodynamic effects of ARV-102

CSF=cerebrospinal fluid; PK=pharmacokinetics.

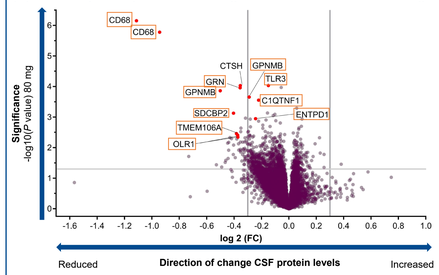
Results

HEALTHY VOLUNTEERS: CSF proteomics

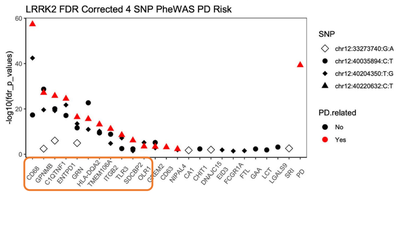
- ARV-102 80 mg QD for 14 days significantly decreased CSF levels of lysosomal pathway markers (median % change from baseline: CTSH, -21.2%; GPNMB, -27.7%; GRN, -22.6%) and microglial markers (C1QTNF1, -13.9%; ENTPD1, -19.3%; TMEM106A, -24.5%; CD68, -55.0%; **Figure 3A-B**), which are elevated in patients with Parkinson's disease harboring LRRK2 variants[11]
- CD68 levels in CSF decreased in a dose-dependent manner, consistent with observed reductions in CSF LRRK2 concentrations (**Figure 3C**)

Figure 3: CSF proteomics in healthy volunteers

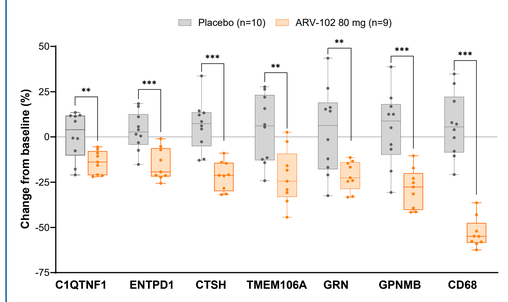
(A) Volcano plot of proteomic changes in CSF with ARV-102 80 mg



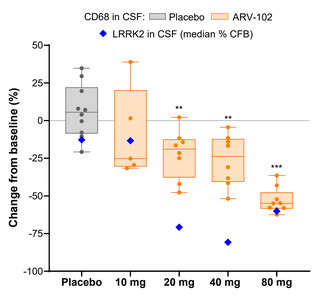
Proteins associated with *LRRK2*-mutated Parkinson's disease[a,11]



(B) Change from baseline in CSF protein levels



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



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

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

Baseline characteristics

- 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

Characteristic	ARV-102 50 mg (n=9)	ARV-102 200 mg (n=6)	Placebo (n=4)
Age, years, median (range)	67 (50–79)	67 (59–79)	62 (55–70)
Sex, n (%)			
Male	7 (78)	5 (83)	3 (75)
Female	2 (22)	1 (17)	1 (25)
Race, n (%)			
White	9 (100)	6 (100)	4 (100)
Body weight, kg, median (range)	84.4 (73.2–100.1)	79.6 (61.6–98.7)	74.6 (68.2–86.3)
BMI, kg/m^2, median (range)	26.8 (21.1–30.9)	25.0 (22.9–28.3)	24.7 (23.1–27.3)
Hoehn and Yahr score, mean (range)	1.7 (1–3)	1.7 (1–3)	2.3 (1–3)
MMSE score, mean (range)	29.2 (27–30)	28.7 (27–30)	28.0 (26–30)

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

Safety and tolerability

- Single doses of ARV-102 were well tolerated at both dose levels (**Table 2**)
- All TRAEs were mild; no serious adverse events occurred

Table 2: TEAEs and TRAEs

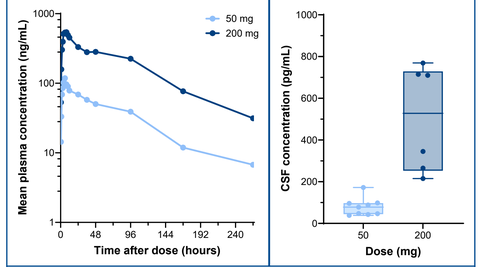
AE, n (%)	ARV-102 50 mg (n=9)	ARV-102 200 mg (n=6)	ARV-102 Total (n=15)	Placebo (n=4)
TEAEs[a]				
Headache	1 (11)	1 (17)	2 (13)	0
Post-lumbar puncture syndrome[b]	1 (11)	1 (17)	2 (13)	2 (50)
Catheter site bruise	1 (11)	1 (17)	2 (13)	0
Puncture site pain	1 (11)	0	1 (7)	1 (25)
TRAEs				
Headache	1 (11)	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.
[a]Events reported by ≥2 patients who received a single dose of ARV-102. [b]All 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 dose-dependent manner in plasma and in CSF (**Figure 4**)

Figure 4: ARV-102 exposure in plasma and CSF

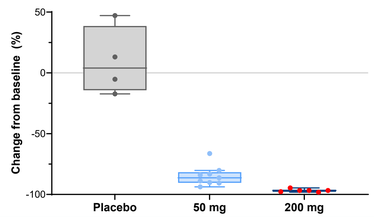


Note: Data are preliminary and were tabulated manually.
ARV-102 concentrations (A) in plasma and (B) in CSF after a single oral dose.
In panel B, circles indicate individual values and box plots show median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range.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

LRRK2 in PBMCs

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