Poster: 0240

First-in-Human Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of ARV-102, a PROTAC LRRK2 Degrader, in Healthy Volunteers

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Objective

- To characterize the safety and pharmacokinetics (PK) of the PROteolysis TArgeting Chimera (PROTAC) leucine-rich repeat kinase 2 (LRRK2) degrader, ARV-102, and evaluate the effect of ARV-102 on target and pathway engagement biomarkers in healthy volunteers

Key Findings

- ARV-102, an orally bioavailable PROTAC LRRK2 degrader, was well tolerated at single doses in healthy volunteers
- The PK profile of ARV-102 supports once-daily dosing
- Single and multiple doses of ARV-102 demonstrated substantial reductions in peripheral LRRK2 protein levels, indicating that ARV-102 induces LRRK2 degradation
- LRRK2 pathway engagement was observed after single doses of ARV-102
- Dose-dependent increases in ARV-102 exposure in cerebrospinal fluid (CSF) after single and multiple doses indicate brain penetration
- Single and multiple doses of ARV-102 demonstrated substantial LRRK2 reductions in CSF

Conclusions

- ARV-102, an oral, brain-penetrant, well-tolerated PROTAC LRRK2 degrader, demonstrated LRRK2 and downstream pathway engagement in healthy volunteers
- These results support continued investigation of ARV-102 in neurodegenerative diseases associated with LRRK2 dysfunction
  - A phase 1 study of ARV-102 in patients with Parkinson's disease (PD) has been initiated (EUCT 2024-516888-84-00)

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Disclosure
Lars Smits, Sandra Korsten, and Philip Kremer are employees of the Center for Human Drug Research. Yuanyuan Zhang, Caroline Woodward, Sergey Aksenov, Ana Luiza Costa Zaninotto, Charles Donnelly, Thomas Storz, Yetty Folami, Christine Lubeski, Margit MacDougall, Kaela Kelly, Adam Hendricson, and Angela Cacace are employees and shareholders of Arvinas Inc.

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Background

LRRK2 in Parkinson's Disease and Progressive Supranuclear Palsy

- Mutations in the *LRRK2* gene are one of the most common genetic causes of PD; variants have also been observed in idiopathic cases[1]
- Increased LRRK2 expression and activity contribute to neurodegeneration and pathogenesis of PD,[1] making it a rational therapeutic target
- Progressive supranuclear palsy (PSP) is characterized by tauopathy (accumulation of abnormal forms of the microtubule-associated protein tau)[2]
- Preclinical data indicate that *LRRK2* mutations are associated with tau pathology resembling PSP[2]
- Genetic variations in *LRRK2* are associated with PSP progression, highlighting the potential importance of LRRK2 in tauopathies[2]
- No approved disease-modifying therapies exist for patients with PD or PSP

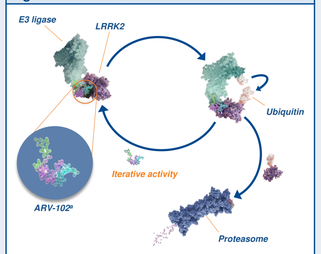
Differentiated Mechanism of Action: ARV-102

- ARV-102 is a potent, selective, oral PROTAC LRRK2 degrader (**Figure 1**)
- PROTAC protein degraders harness the ubiquitin-proteasome system to trigger the degradation of disease-causing proteins
  - PROTACs are bifunctional small molecules consisting of a target protein–binding region and an E3 ubiquitin ligase–binding region joined by a linker
  - PROTACs form a trimer complex that induces ubiquitination and subsequent proteasomal degradation of the target protein

ARV-102 in Preclinical Studies[3]

- In preclinical studies of ARV-102 vs a LRRK2 kinase inhibitor, ARV-102 showed stronger LRRK2 and downstream pathway engagement in the brain; increased lysosome activity; and less type 2 pneumocyte enlargement, less surfactant C, and no collagen deposition to date in primate lung
- Oral ARV-102 reduced LRRK2 levels in "deep brain" regions and in CSF of nonhuman primates (**Figure 2**)
- In addition, ARV-102 induced reductions in LRRK2 pathway biomarkers ionized calcium binding adaptor molecule 1 (IBA1) and cathepsin B in CSF and in the lysosomal marker bis(monoacylglycerol)phosphate (BMP) in urine and CSF

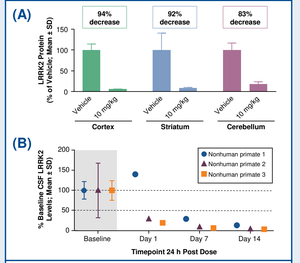
Figure 1: ARV-102 mechanism of action



Please scan this QR code with your smartphone app to view a video showing how PROTAC protein degraders work

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

Figure 2: ARV-102 reduced LRRK2 levels in brain (A) and CSF (B) of nonhuman primates[3]

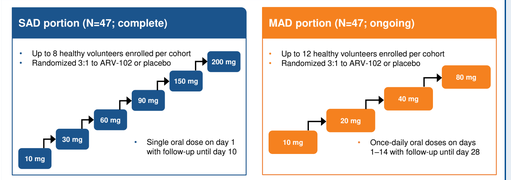


LRRK2 quantified in nonhuman primate brain by MSD ELISA and in CSF by SIMOA. LLOQ for the LRRK2 CSF assay was 0.5 pg/mL.
CSF=cerebrospinal fluid; LLOQ=lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; MSD ELISA=meso-scale discovery enzyme-linked immunosorbent assay; SIMOA=single-molecule array.

Methods

- This was a single-center, randomized, double-blind, placebo-controlled study (**Figure 3**)
- The primary objective was to evaluate the safety and tolerability of ARV-102
- The secondary objective was to characterize the plasma PK of ARV-102
- Exploratory objectives were to evaluate the exposure of ARV-102 in CSF and urine and to assess the effects of ARV-102 on target engagement and pathway engagement biomarkers

Figure 3: Phase 1 SAD/MAD ARV-102 study in healthy volunteers



Data cutoff date for this analysis was March 13, 2025. This analysis was conducted prior to formal database lock.
MAD=multiple ascending doses; SAD=single ascending doses.

Results

Baseline Characteristics

- Baseline characteristics of healthy male volunteers enrolled in the single ascending doses (SAD) portion of the study are shown in **Table 1**
- The multiple ascending doses (MAD) portion of the study has enrolled 47 healthy male volunteers (10 mg cohort: n=11; 20 mg cohort: n=12; 40 mg cohort: n=12; 80 mg cohort: n=12)
  - Preliminary safety, PK, and pharmacodynamic data for the MAD portion are reported

Table 1: Baseline characteristics of participants in the SAD portion

Characteristic	Total (N=47)
Male, n (%)	47 (100)
Age, median (range), years	25 (18–53)
Race, n (%)	
White	41 (87.2)
Black or African American	5 (10.6)
Multiple	1 (2.1)
Weight, median (range), kg	77.25 (55.60–103.20)
Baseline LRRK2 concentration in CSF, median (range), pg/mL	6.1 (4.4–19.8)

CSF=cerebrospinal fluid; LRRK2=leucine-rich repeat kinase 2; SAD=single ascending doses.

Safety

- Treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) for the SAD portion are shown in **Table 2**
- Single oral doses of ARV-102 were well tolerated in healthy volunteers; most TEAEs were mild
- No serious adverse events were reported in the SAD or MAD portions

Table 2: TEAEs and TRAEs reported in the SAD portion

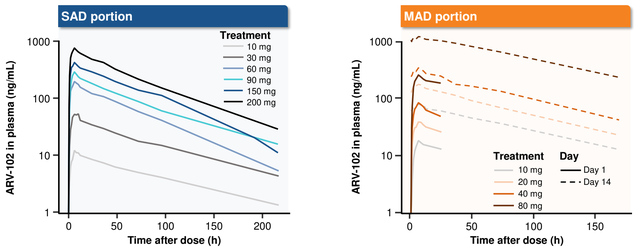
	ARV-102							
TEAE, n (%)[a]	10 mg (n=6)	30 mg (n=6)	60 mg (n=6)	90 mg (n=6)	150 mg (n=6)	200 mg (n=5)	Total (n=35)	Placebo (n=12)
Procedural pain	1 (16.7)	2 (33.3)	2 (33.3)	2 (33.3)	1 (16.7)	2 (40.0)	10 (28.6)	5 (41.7)
Post lumbar puncture syndrome[b]	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (20.0)	6 (17.1)	0
Headache	0	2 (33.3)	1 (16.7)	1 (16.7)	0	2 (40.0)	6 (17.1)	0
Fatigue	0	2 (33.3)	1 (16.7)	0	0	0	3 (8.6)	3 (25.0)
TRAE, n (%)[a]								
Headache	0	2 (33.3)	1 (16.7)	1 (16.7)	0	2 (40.0)	6 (17.1)	0
Fatigue	0	2 (33.3)	1 (16.7)	0	0	0	3 (8.6)	3 (25.0)

[a]Reported in ≥2 participants across the SAD portion of the study (N=47).
[b]Lumbar puncture was used for CSF collection.
CSF=cerebrospinal fluid; SAD=single ascending doses; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.

ARV-102 PK and PD

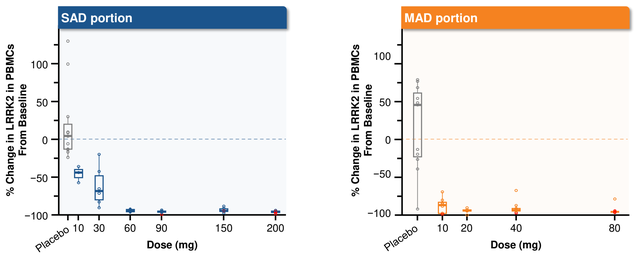
- ARV-102 displayed the predicted absorption rate after oral administration (**Figure 4**)
  - Median time to reach the maximum plasma concentration was 6 hours
- Area under the concentration-time curve from time 0 to 24 hours and maximum plasma concentration increased in a dose-dependent manner
  - The accumulation ratio was ~5-fold at steady state, and the median terminal elimination half-life was 73 hours
- ARV-102 induced reductions in LRRK2 levels in peripheral blood mononuclear cells (PBMCs) (**Figure 5**)
  - At single doses ≥60 mg and repeated doses ≥20 mg, >90% reduction in LRRK2 levels was observed
- ARV-102 at single doses ≥30 mg induced >50% decreases in peripheral phospho-Rab10^{T73} (**Figure 6**)
  - Rab10, a GTPase involved in the lysosomal stress response, is a LRRK2 substrate and biomarker for downstream LRRK2 pathway engagement[4–9]
- ARV-102 at single doses ≥30 mg resulted in >90% decreases in BMP in urine (**Figure 7**)
  - BMP is a lysosomal lipid and a sensitive biomarker for the LRRK2 lysosome pathway in urine[10–13]
- ARV-102 exposure in CSF increased in a dose-dependent manner after single and multiple doses, indicating brain penetration (**Figure 8**)
- ARV-102 induced dose-dependent reductions in LRRK2 levels in CSF, with >50% LRRK2 reduction at single doses ≥60 mg and repeated doses ≥20 mg (**Figure 9**)

Figure 4: Mean ARV-102 exposure in plasma



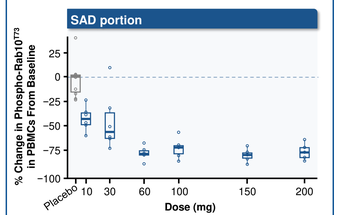
ARV-102 exposure measured by mass spectrometry.
MAD=multiple ascending doses; SAD=single ascending doses.

Figure 5: Changes in LRRK2 protein from baseline in PBMCs



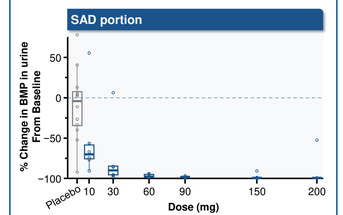
LRRK2 protein in PBMCs measured by MSD ELISA. Circles indicate individual values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times the IQR. Values at 24 hours after a single dose and 6 hours after 13th and 14th doses are shown. Values below LLOQ (shown in red) were calculated as half of LLOQ. Individuals who received single 10-mg doses with outlying low baseline values were excluded. Participants who received placebo across cohorts in the respective portions (SAD or MAD) were pooled.
IQR=interquartile range; LLOQ=lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; MAD=multiple ascending doses; MSD ELISA=meso-scale discovery enzyme-linked immunosorbent assay; PBMC=peripheral blood mononuclear cells; SAD=single ascending doses.

Figure 6: Changes in phospho-Rab10^{T73} levels from baseline in PBMCs



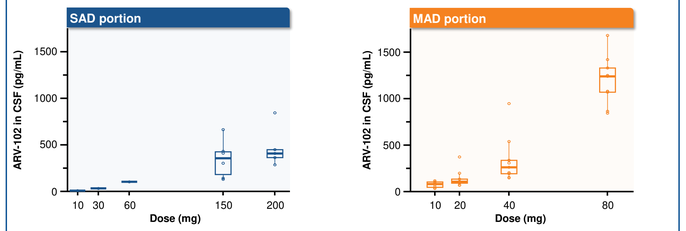
Phospho-Rab10 measured by AS/MS. Circles indicate individual values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times the IQR. Values at 24 hours after a single dose are shown. Values below LLOQ were calculated as half of LLOQ. Participants who received placebo across cohorts were pooled.
AS/MS=affinity selection/mass spectrometry; IQR=interquartile range; LLOQ=lower limit of quantification; PBMC=peripheral blood mononuclear cells.

Figure 7: Changes in BMP levels from baseline in urine



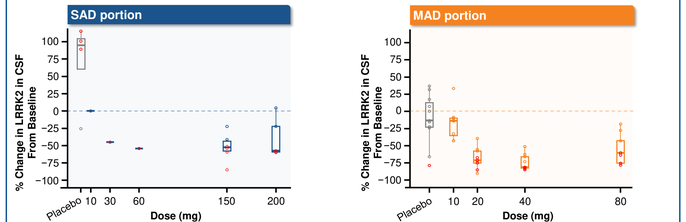
BMP measured by UPLC-MS/MS analysis. Circles indicate individual values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times the IQR. Values at 24 hours after a single dose are shown. Values below LLOQ were calculated as half of LLOQ. Participants who received placebo across cohorts were pooled.
BMP=bis(monoacylglycero)phosphate; IQR=interquartile range; LLOQ=lower limit of quantification; UPLC-MS/MS=ultra-performance liquid chromatography tandem mass spectrometry

Figure 8: ARV-102 exposure in CSF



ARV-102 exposure measured by mass spectrometry. Circles indicate individual values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times the IQR. Values shown are 24 hours post-dose.
CSF=cerebrospinal fluid; IQR=interquartile range; LLOQ=lower limit of quantification. LRRK2=leucine-rich repeat kinase 2; MAD=multiple ascending doses; SAD=single ascending doses; SISCAPA=stable isotope standards and capture by anti-peptide antibodies.

Figure 9: Changes in LRRK2 protein levels in CSF



LRRK2 detected by SISCAPA. Circles indicate individual values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times the IQR. Values below LLOQ (~5 pg/mL; shown in red) were calculated as half of LLOQ. Participants who received placebo across cohorts in the respective portions (SAD or MAD) were pooled. Values shown are 24 hours post-dose.
CSF=cerebrospinal fluid; IQR=interquartile range; LLOQ=lower limit of quantification. LRRK2=leucine-rich repeat kinase 2; MAD=multiple ascending doses; SAD=single ascending doses; SISCAPA=stable isotope standards and capture by anti-peptide antibodies.