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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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Conflicts of interest:

Lars Smits is an employee of the Center for Human Drug Research

This study is sponsored by Arvinas Inc.

LRRK2 in Parkinson's Disease and Progressive Supranuclear Palsy

Parkinson's Disease

- 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

No approved disease-modifying therapies exist for patients with PD or PSP

Progressive Supranuclear Palsy

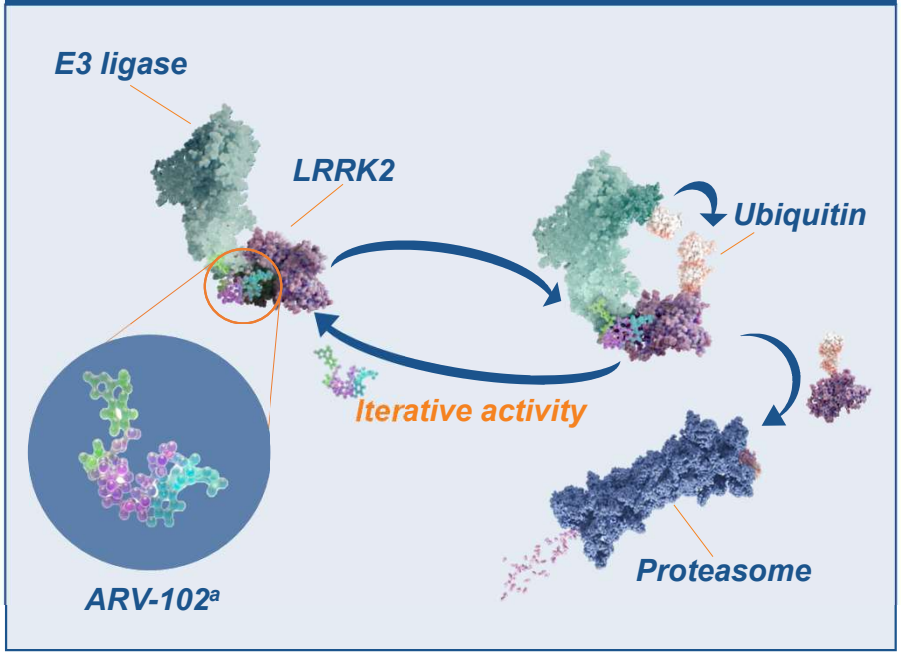
- PSP is characterized by tauopathy (accumulation of abnormal forms of the microtubule-associated protein tau)[2]
- Preclinical data indicate that LRRK2 mutations are associated with tau pathology resembling PSP[2]
- Genetic variations in LRRK2 are associated with PSP progression, highlighting the potential importance of LRRK2 in tauopathies[2]

1. Kluss et al. Biochem Soc Trans. 2019;47:651-61. 2. Herbst et al. Clin Sci 2022;136:1071-1079.
LRRK2=leucine-rich repeat kinase 2; PD=Parkinson's disease; PSP=progressive supranuclear palsy

Differentiated Mechanism of Action: ARV-102

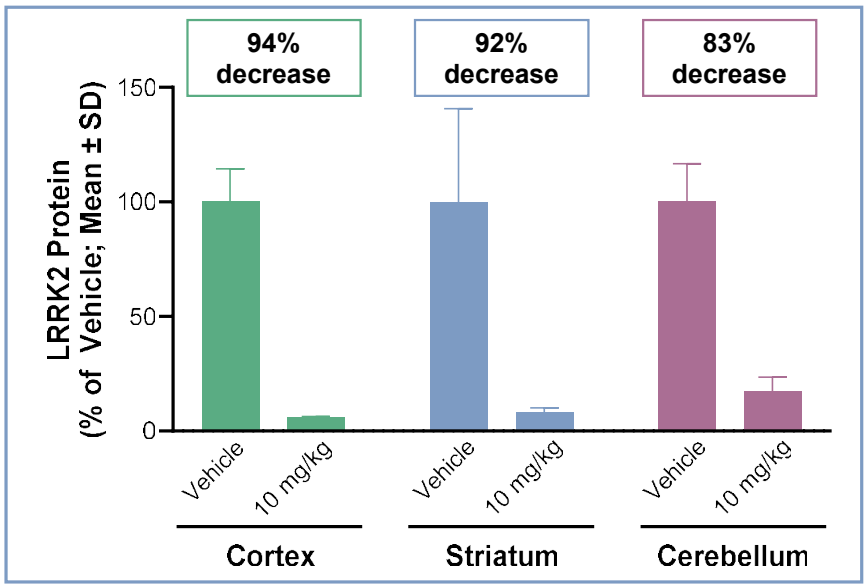
- PROteolysis TArgeting Chimera (PROTAC) protein degraders harness the ubiquitin-proteasome system to trigger the degradation of disease-causing proteins
  - PROTACs are bifunctional small molecules consisting of a target protein–binding region and an E3 ubiquitin ligase–binding region joined by a linker
  - PROTACs form a trimer complex that induces ubiquitination and subsequent proteasomal degradation of the target protein
- In preclinical studies of ARV-102 vs a LRRK2 kinase inhibitor, ARV-102 showed[1]:
  - Stronger LRRK2 and downstream pathway engagement in the brain
  - Increased lysosome activity
  - Less type 2 pneumocyte enlargement, less surfactant C, and no collagen deposition to date in primate lung

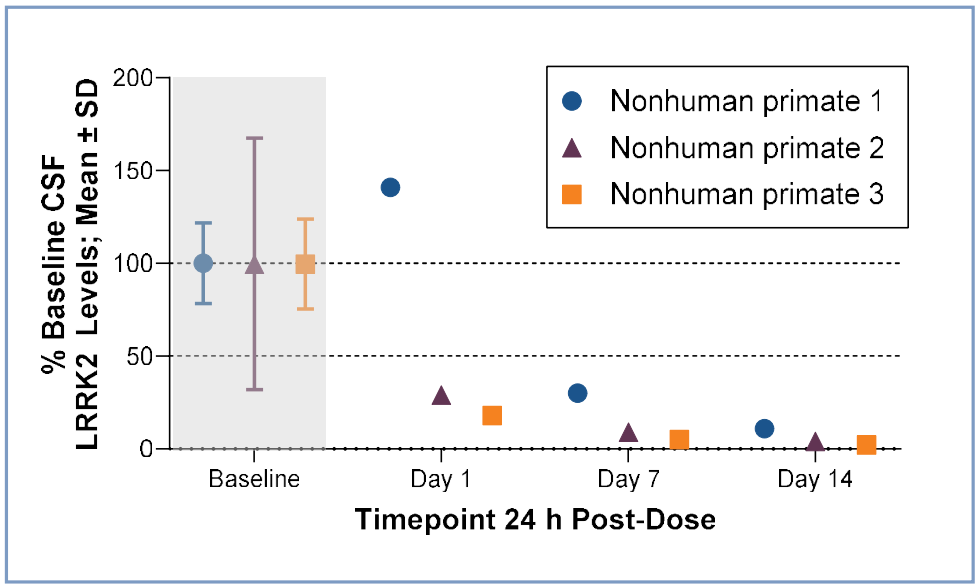
ARV-102 is a potent, selective, oral PROTAC LRRK2 degrader



1.Cacace. 2024 Parkinson's Disease Therapeutics Conference.
[a]General PROTAC protein degrader is shown.
LRRK2=leucine-rich repeat kinase 2; PROTAC=PROteolysis TArgeting Chimera

ARV-102 in Non-Human Primate Studies[1]





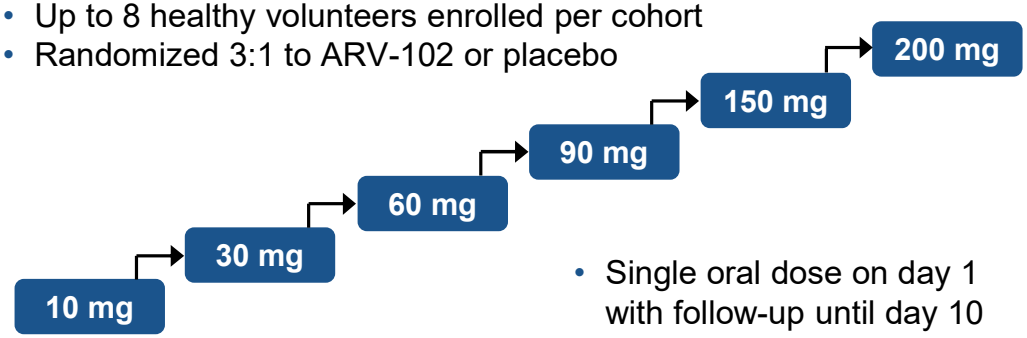
- Oral ARV-102 reduced LRRK2 levels in “deep brain” regions and in CSF
- In addition, ARV-102 induced reductions in LRRK2 pathway biomarkers, IBA1 and cathepsin B, in CSF and in the lysosomal marker BMP in urine and CSF

1.Cacace. 2024 Parkinson’s Disease Therapeutics Conference.
LRRK2 quantified in non-human primate brain by MSD ELISA and in CSF by SIMOA. LLOQ for the LRRK2 CSF assay was 0.5 pg/mL.
BMP=bis(monoacylglycerol)phosphate; CSF=cerebrospinal fluid; IBA1=ionized calcium-binding adapter molecule 1; LLOQ=lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; MSD ELISA=meso-scale discovery enzyme-linked immunosorbent assay; SIMOA=single-molecule array

Phase 1 SAD/MAD ARV-102 Study in Healthy Volunteers

SAD portion (N=47; complete)

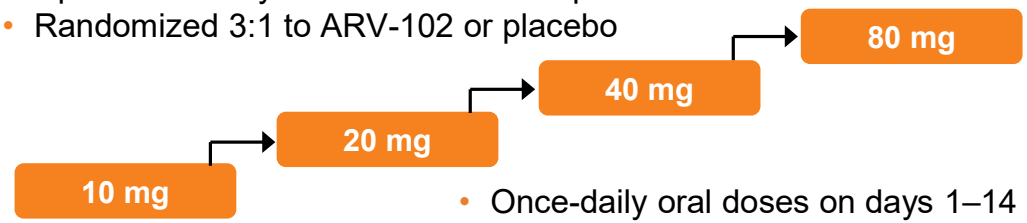
- Up to 8 healthy volunteers enrolled per cohort
- Randomized 3:1 to ARV-102 or placebo



- Single oral dose on day 1 with follow-up until day 10

MAD portion (N=47; ongoing)

- Up to 12 healthy volunteers enrolled per cohort
- Randomized 3:1 to ARV-102 or placebo



- Once-daily oral doses on days 1–14 with follow-up until day 28

- This was a single-center, randomized, double-blind, placebo-controlled study

Primary objective:

- Evaluate the safety and tolerability of ARV-102

Secondary objective:

- Characterize the plasma PK of ARV-102

Exploratory objectives:

- Evaluate the exposure of ARV-102 in CSF
- Evaluate the exposure of ARV-102 in urine
- Evaluate the effects of ARV-102 on target engagement and pathway engagement biomarkers

Data cutoff date for this analysis[a]:

- March 13, 2025

[a]This analysis was conducted prior to formal database lock.
CSF=cerebrospinal fluid; MAD=multiple ascending doses; PK=pharmacokinetics; SAD=single ascending doses

Baseline Characteristics

SAD portion

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

MAD portion

- 47 healthy male volunteers have been enrolled in the MAD portion of the study:
  - 10 mg cohort: n=11
  - 20 mg cohort: n=12
  - 40 mg cohort: n=12
  - 80 mg cohort: n=12
- Preliminary safety, PK, and PD data for the MAD portion are reported

CSF=cerebrospinal fluid; LRRK2=leucine-rich repeat kinase 2; MAD=multiple ascending doses; PD=pharmacodynamics; PK=pharmacokinetics; SAD=single ascending doses

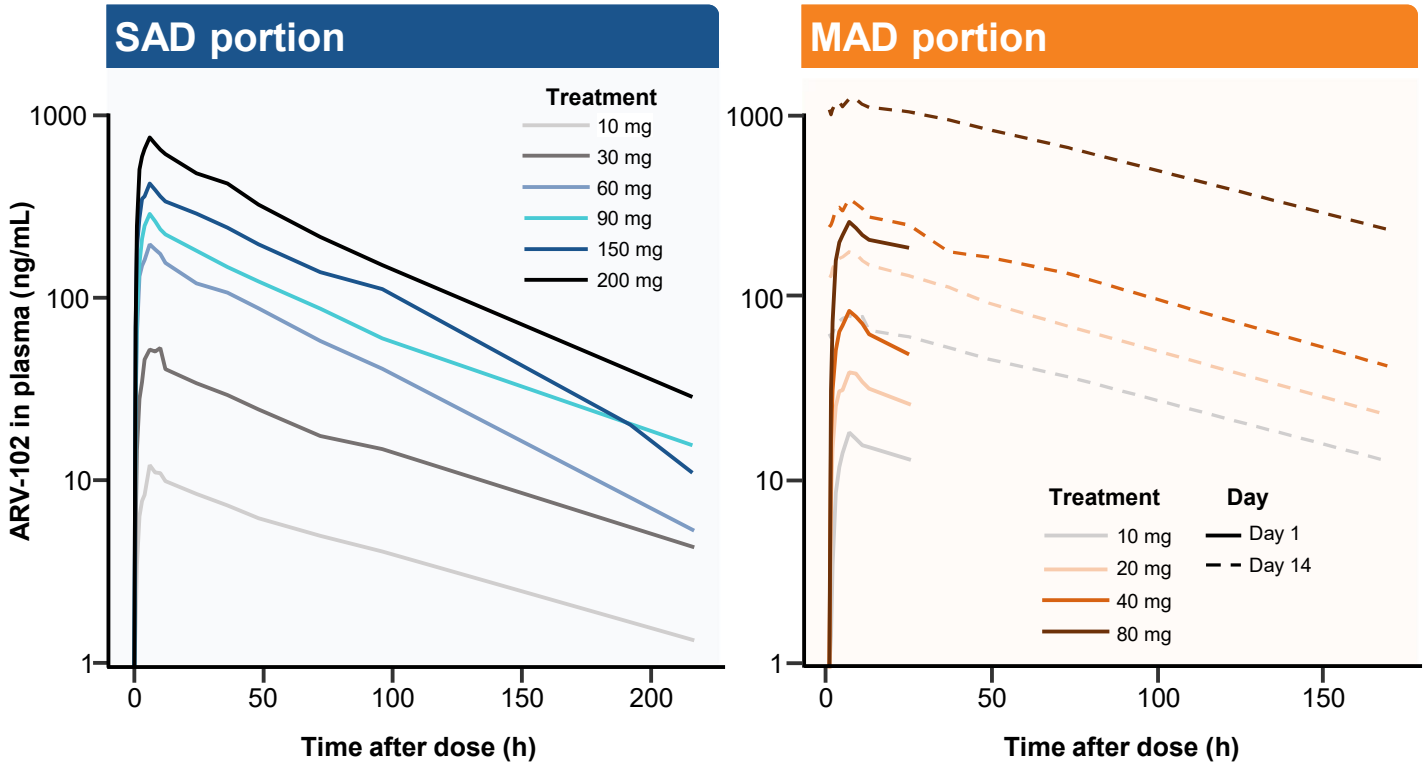
Safety

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)

- Single oral doses of ARV-102 were well tolerated in healthy volunteers; most TEAEs were mild
- No serious adverse events reported were reported in the SAD or MAD portions

[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; MAD=multiple ascending doses; SAD=single ascending doses; TEAE=treatment-emergent adverse event; treatment-related adverse event

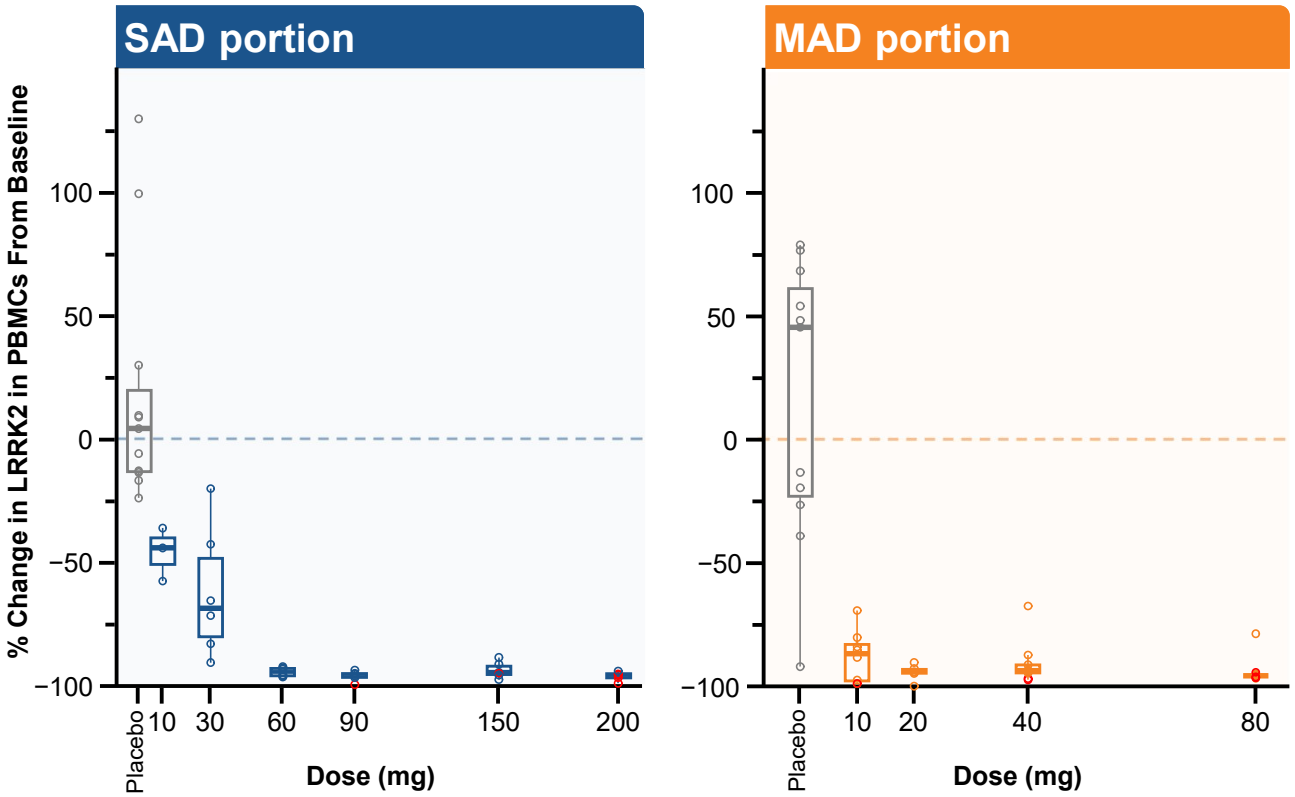
Mean ARV-102 Exposure in Plasma



- ARV-102 displayed the predicted absorption rate after oral administration
  - Median T_{max} was 6 h
- $AUC_{0\text{-}24}$ and C_{max} increased in a dose-dependent manner
  - The accumulation ratio was ~5-fold at steady state
  - Median terminal $t_{1/2}$ was 73 h

ARV-102 exposure measured by mass spectrometry.
$AUC_{0\text{-}24}$=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum plasma concentration; MAD=multiple ascending doses; PK=pharmacokinetics; SAD=single ascending doses; T_{max}=time to reach C_{max}; $t_{1/2}$=terminal elimination half-life

Changes in LRRK2 Protein Levels From Baseline in PBMCs

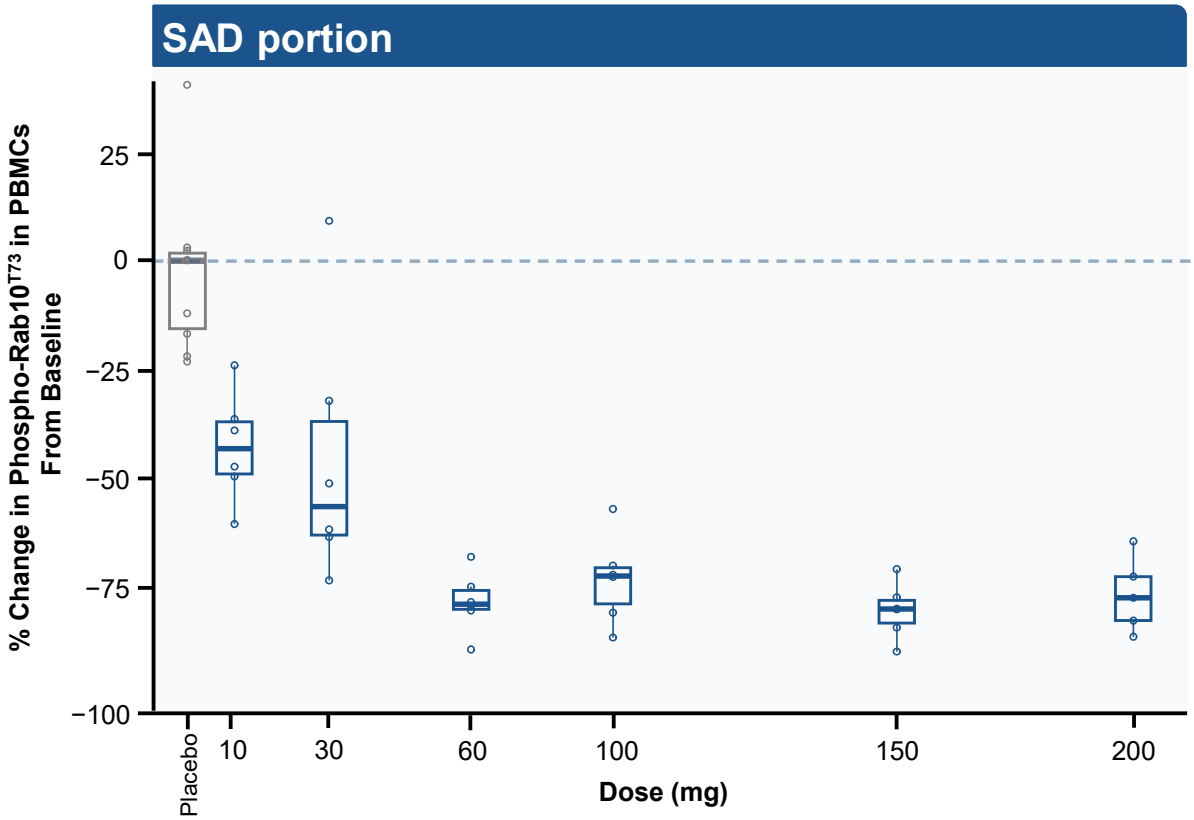


- ARV-102 induced reductions in LRRK2 levels in PBMCs
- At single doses ≥60 mg and repeated doses ≥20 mg, >90% reduction in LRRK2 levels was observed

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-hour post-single dose and 6-hours post 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 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

Changes in Phospho-Rab10^{T73} Levels From Baseline in PBMCs



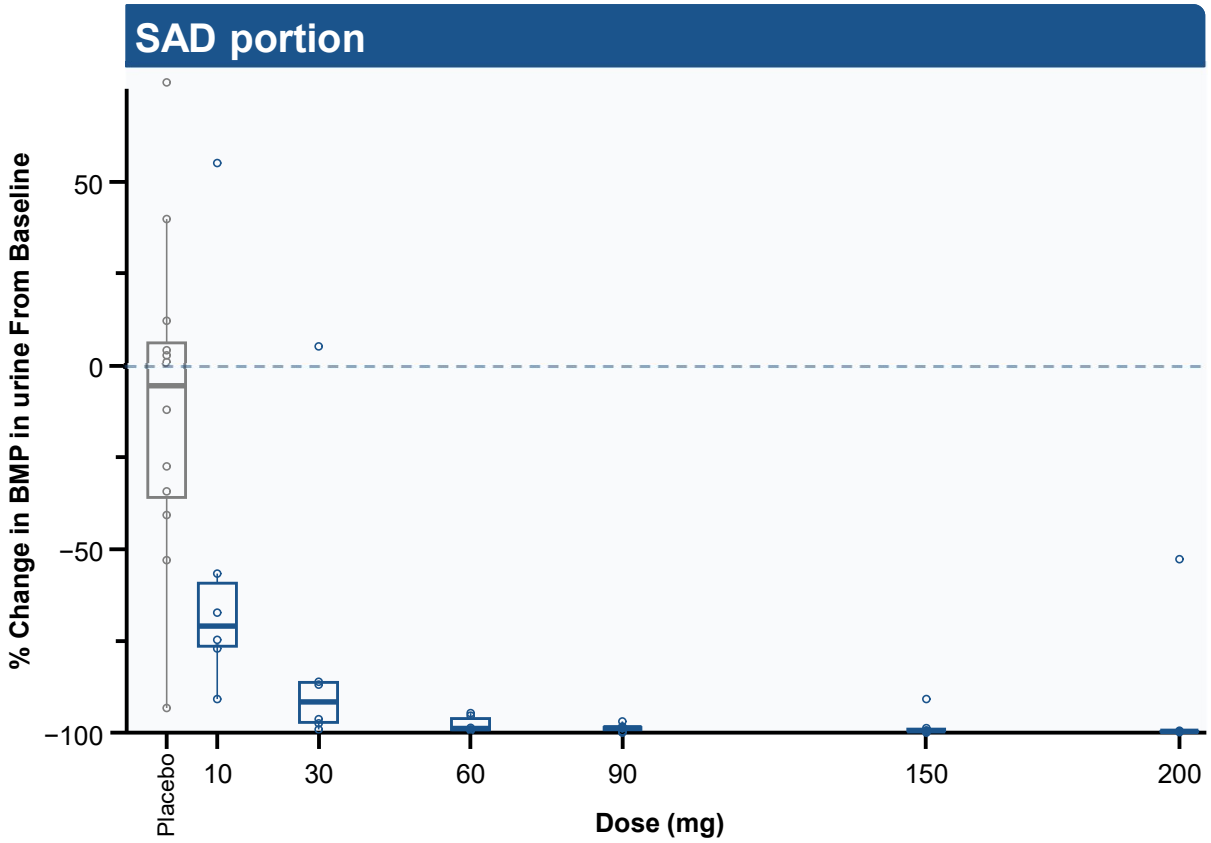
- Rab10, a GTPase involved in the lysosomal stress response, is a LRRK2 substrate and biomarker for downstream LRRK2 pathway engagement[1–6]
- ARV-102 at single doses ≥30 mg induced >50% decreases in peripheral phospho-Rab10^{T73}

1. Steger et al. Elife. 2016;5:e12813. 2. Dzamko et al. J Park Dis. 2013;3:145–52. 3. Perera et al. Sci Rep. 2016;6:31391. 4. Wang et al. Sci Rep. 2021;11:12900. 5. Jennings et al. Sci Transl Med. 2022;14:eabj2658. 6. Jennings et al. Mov Disord. 2023;38:386–98.

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-hour post-single dose are shown. Values below LLOQ were calculated as half of LLOQ. Participants who received placebo across cohorts in SAD were pooled.

AS/MS=affinity selection/mass spectrometry; IQR=interquartile range; LLOQ=lower limit of quantification; PBMC=peripheral blood mononuclear cells

Changes in BMP Levels From Baseline in Urine

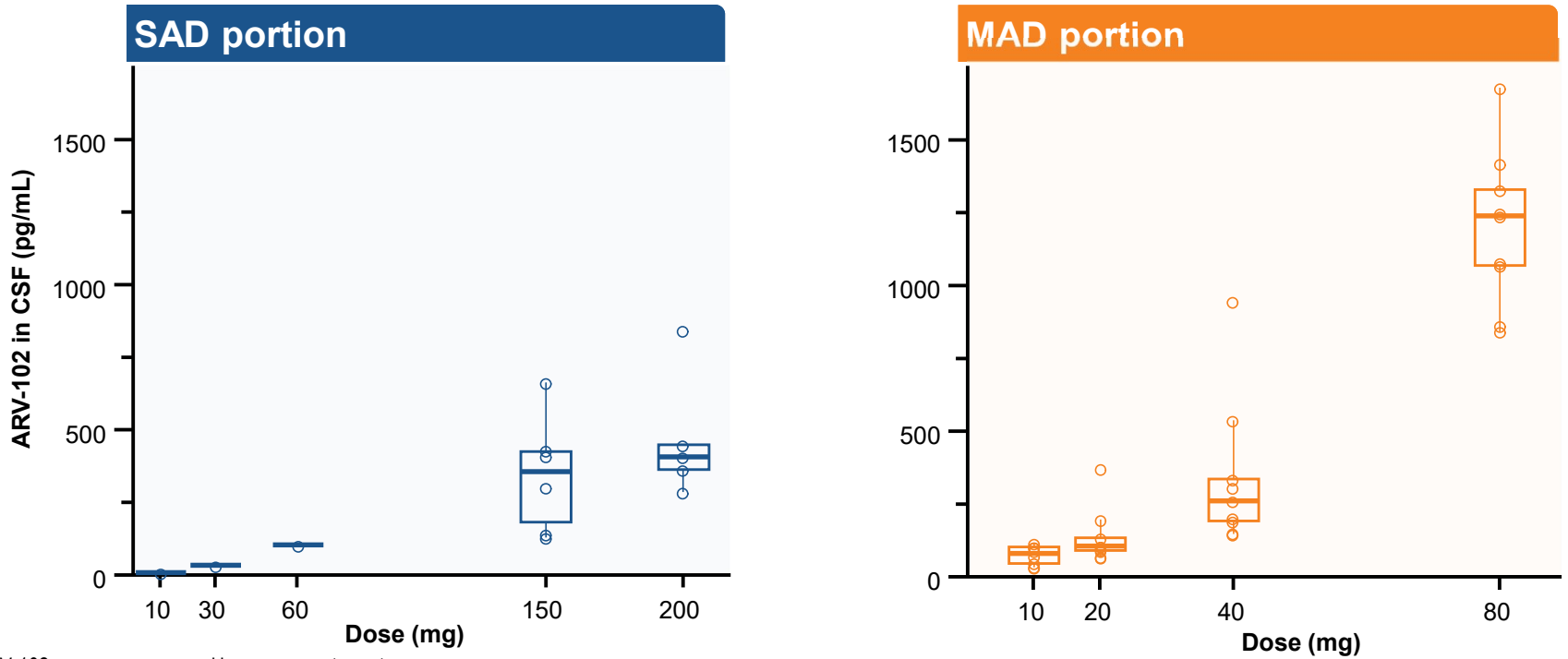


- BMP is a lysosomal lipid and a sensitive biomarker for the LRRK2 lysosome pathway in urine[1–4]
- ARV-102 at single doses ≥30 mg resulted in >90% decreases in BMP in urine

1. Schmitz and Müller. J Lipid Res. 1991;32:1539–70. 2. Gallala and Sandhoff. Neurochem Res. 2011;36:1594–600. 3. Showalter et al. Int J Mol Sci. 2020;21:8067. 4. Alcalay et al. Mov Disord. 2020;35:134–41.
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-hour post-single dose are shown. Values below LLOQ were calculated as half of LLOQ. Participants who received placebo across cohorts in SAD were pooled.
BMP=bis(monoacylglycerol)phosphate; IQR=interquartile range; LLOQ=lower limit of quantification; UPLC-MS/MS =ultra-performance liquid chromatography tandem mass spectrometry

ARV-102 Exposure in CSF

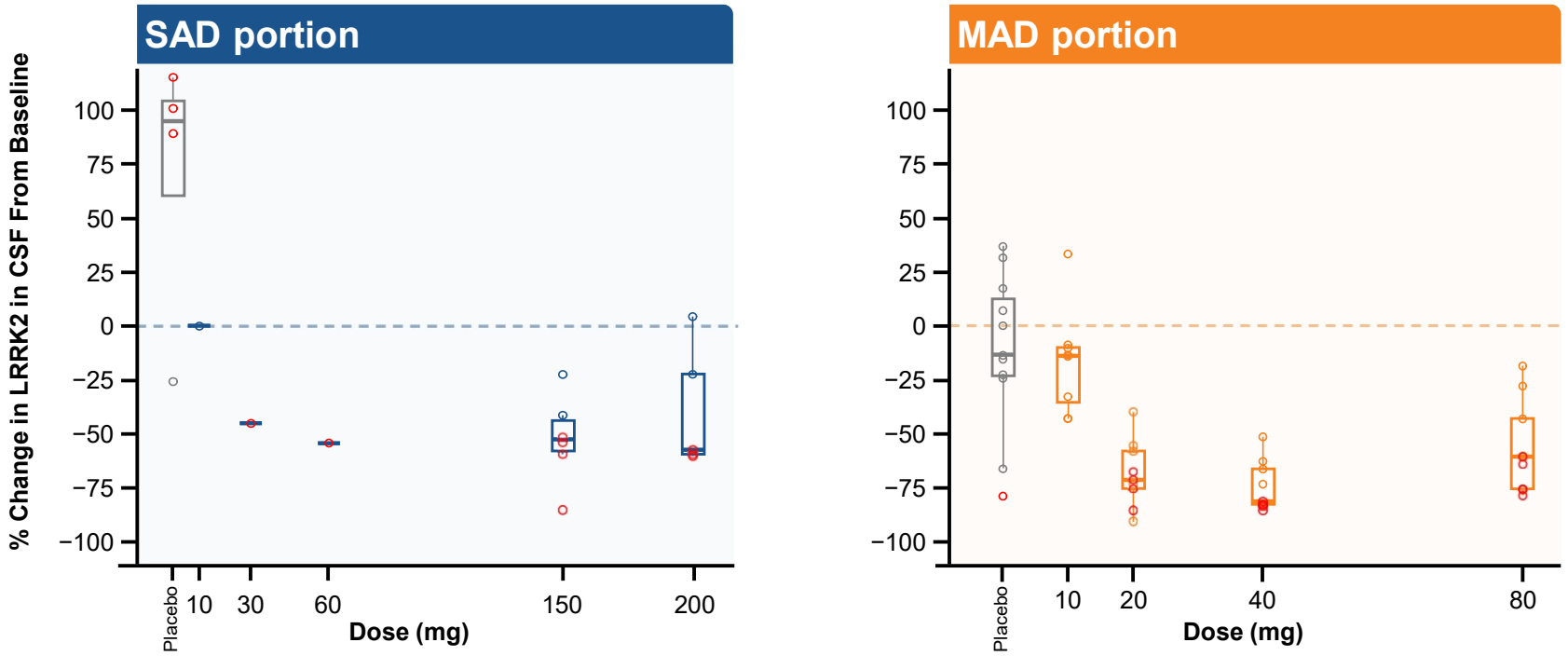
ARV-102 exposure in CSF increased in a dose-dependent manner after single and multiple doses, indicating brain penetration



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; MAD=multiple ascending doses; SAD=single ascending doses

Changes in LRRK2 Protein Levels From Baseline in CSF

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



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 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

Conclusions

- 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 CSF after single and multiple doses indicate brain penetration
- Single and multiple doses of ARV-102 demonstrated substantial LRRK2 reductions in CSF
- 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 has been initiated (EUCT 2024-516888-84-00)

ARV-102, an oral, brain-penetrant, well-tolerated PROTAC LRRK2 degrader, demonstrated LRRK2 and downstream pathway engagement in healthy volunteers

CSF=cerebrospinal fluid; LRRK2=leucine-rich repeat kinase 2; PK=pharmacokinetics

Acknowledgments

- We thank the volunteers who participated in this study, as well as the researchers, and coordinators who contributed to this study
- This study is sponsored by Arvinas Inc.

PROTAC Mechanism of Action

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

PROTAC=PROteolysis TArgeting Chimera