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Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ARV-102, a PROTAC LRRK2 Degrader, in Participants With Parkinson's Disease

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Conflicts of interest:

Luuk van de Bult is an employee of the Center for Human Drug Research

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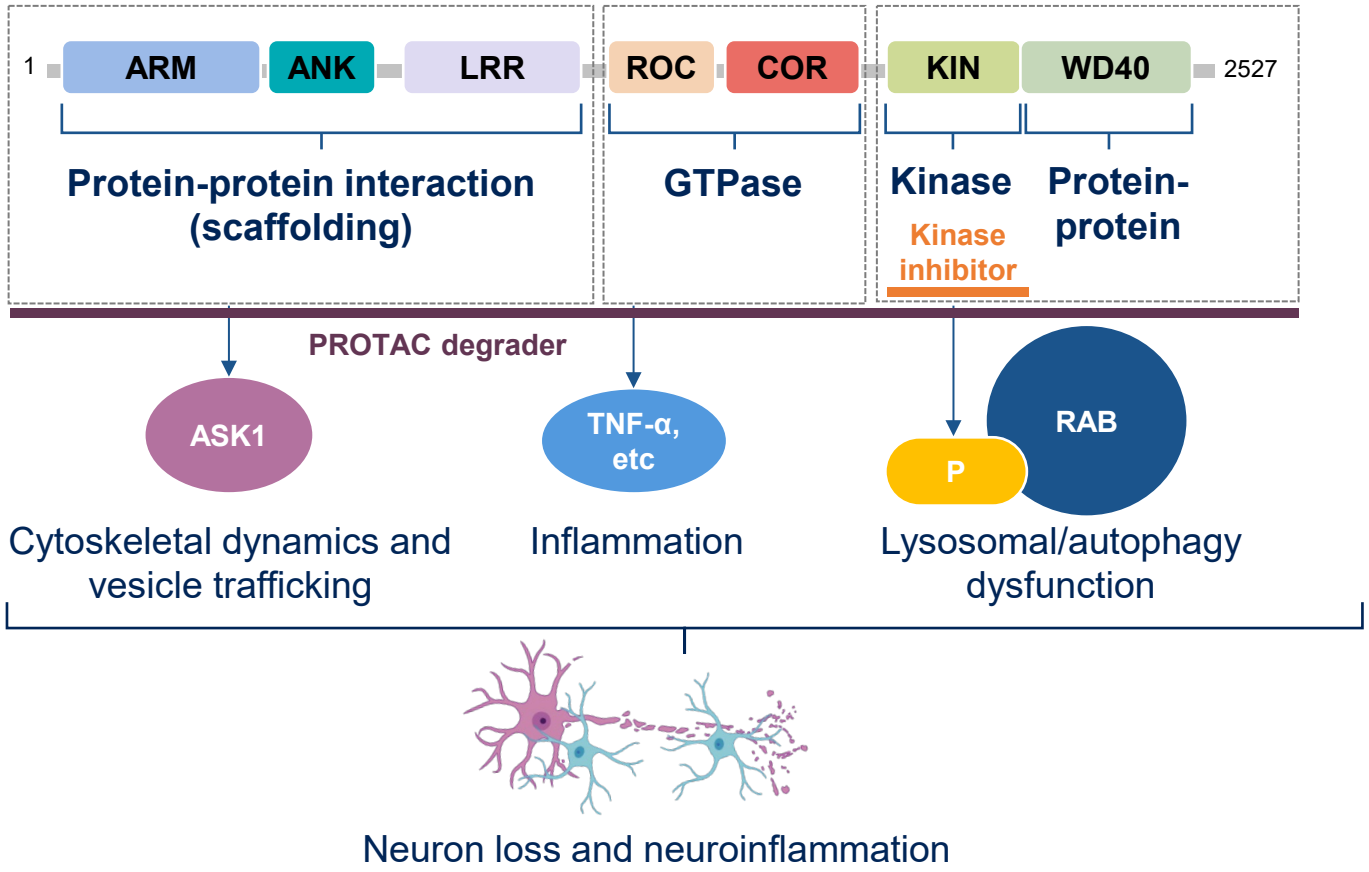
Targeting LRRK2 in Neurodegenerative Diseases (Parkinson's Disease and Progressive Supranuclear Palsy)

- Parkinson's disease:
  - LRRK2 mutations are a common genetic cause of Parkinson's disease; variants have also been observed in idiopathic case[1-3]
  - Increased LRRK2 expression and activity contribute to neurodegeneration and pathogenesis of Parkinson's disease,[1] making it a rational therapeutic target
- PSP (tauopathy):
  - LRRK2 SNPs and variants are associated with tau pathology resembling PSP[4]
  - Increased LRRK2 expression is associated with PSP progression, highlighting the potential importance of LRRK2 in tauopathies[4]

LRRK2 is a large multidomain scaffolding kinase[1-3]

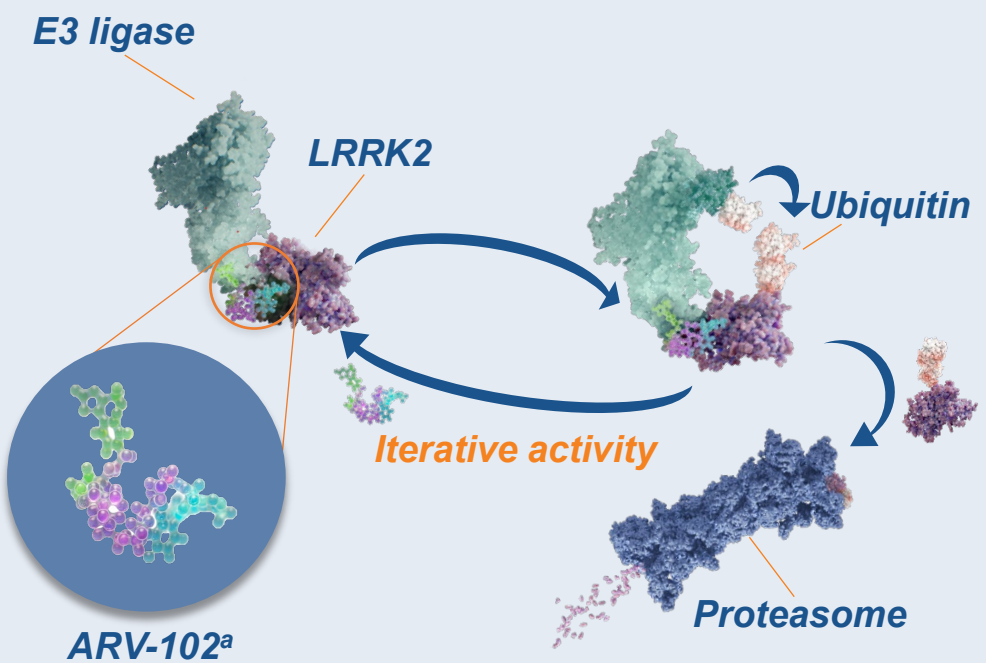


ARM=armadillo; ANK=ankyrin; ASK1=apoptosis signal-regulating kinase 1; COR=C-terminal of ROC; KIN=kinase; LRR=leucine-rich repeat; LRRK2=leucine-rich repeat kinase 2; PSP=progressive supranuclear palsy; ROC=Ras of complex; SNP=single nucleotide polymorphism; TNF-α=tumor necrosis factor α.

1. Rocha EM, et al. Trends Neurosci. 2022;45(3):224-36. 2. Kluss JH, et al. Biochem Soc Trans. 2019;47(2):651-661. 3. Di Fonzo A, et al Lancet. 2005;365(9457):412-5. 4. Jabbari E, et al. Lancet Neurol. 2021;20(2):107-116.

Differentiated Mechanism of Action: ARV-102

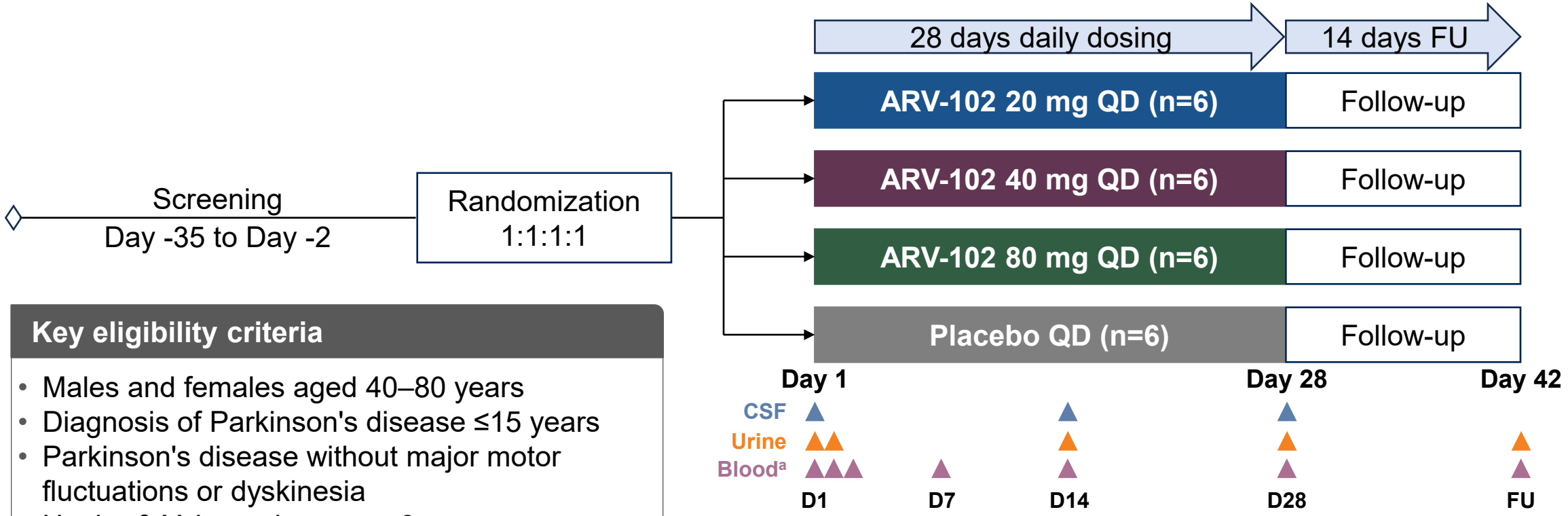
ARV-102 is a potent, selective, PROTAC LRRK2 degrader



- ARV-102 is an oral, brain-penetrant PROTAC LRRK2 degrader that induces ubiquitination of LRRK2 driving its subsequent proteasomal degradation
- In preclinical studies comparing ARV-102 to a LRRK2 kinase inhibitor, ARV-102:
  - Showed >50-fold greater potency for LRRK2 target and lysosomal pRAB pathway engagement in mouse brain
  - Enhanced lysosome number and function in vitro
  - Induced reduction of pathologic oligomeric tau in vitro and in vivo
- In NHPs, ARV-102 distributed across all brain regions evaluated (ie, cortex, striatum, cerebellum, CSF) where it induced LRRK2 degradation
- In healthy volunteers, ARV-102 was well tolerated and demonstrated CNS penetration and peripheral and central target and pathway engagement[1,2]

[a]General PROTAC protein degrader is shown.
CNS=central nervous system; CSF=cerebrospinal fluid; LRRK2=leucine-rich repeat kinase 2; NHP=non-human primates; pRAB=phosphorylated Rab GTPase; PROTAC=PROteolysis TArgeting Chimera.
1. Smits L, et al. Oral presentation at International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD) 2025. 2. Smits L, et al. Poster presented at the International Congress of Parkinson's Disease and Movement Disorders (MDS) 2025; Poster #904.

Single-Center, Double-blind, Phase 1 Study of ARV-102 in Participants With Parkinson's Disease



Key eligibility criteria

- Males and females aged 40–80 years
- Diagnosis of Parkinson's disease ≤15 years
- Parkinson's disease without major motor fluctuations or dyskinesia
- Hoehn & Yahr scale score ≤3
- Stable dose of levodopa/carbidopa (if receiving)

Study Objectives

Primary:	Safety and tolerability
Secondary:	Plasma PK
Exploratory:	ARV-102 exposure in CSF Pharmacodynamic effects of ARV-102

EUCT number: 2024-516888-84-00

[a]Peripheral blood mononuclear cells and whole blood.

CSF=cerebrospinal fluid; D=day; FU=follow-up; PK=pharmacokinetics; QD=once daily.

Baseline Characteristics of Participants Enrolled in the Multiple-Dose Portion of the Phase 1 Study

Characteristic	ARV-102 20 mg (n=6)	ARV-102 40 mg (n=6)	ARV-102 80 mg (n=6)	Placebo (n=6)
Age, years, median (range)	60 (53–68)	60 (51–77)	65 (53–75)	67 (54–69)
Sex, n (%)				
Male	5 (83)	6 (100)	5 (83)	4 (67)
Female	1 (17)	0	1 (17)	2 (33)
Race, n (%)				
White	6 (100)	6 (100)	6 (100)	6 (100)
Nonmodified Hoehn & Yahr, n (%)				
Unilateral involvement only	3 (50)	4 (67)	2 (33)	3 (50)
Bilateral involvement, no balance impairment	3 (50)	2 (33)	4(67)	1 (17)
Mild to moderate involvement	0	0	0	2 (33)
Years from diagnosis, median (range)	7.7 (2.0–15.2)	2.3 (0.3–9.1)	7.7 (3.0–9.0)	3.8 (2.1–15.2)
Concomitant medications for Parkinson's disease,[a] n (%)				
Levodopa/DDI	6 (100)	5 (83)	6 (100)	6 (100)
Dopamine agonist	2 (33)	4 (67)	2 (33)	3 (50)
Other	2 (33)	1(17)	0	1 (17)

[a]Participants may have received ≥1 medication class for Parkinson's disease.
BMI=body mass index; DDI=dopa decarboxylase inhibitor.

Safety and Tolerability

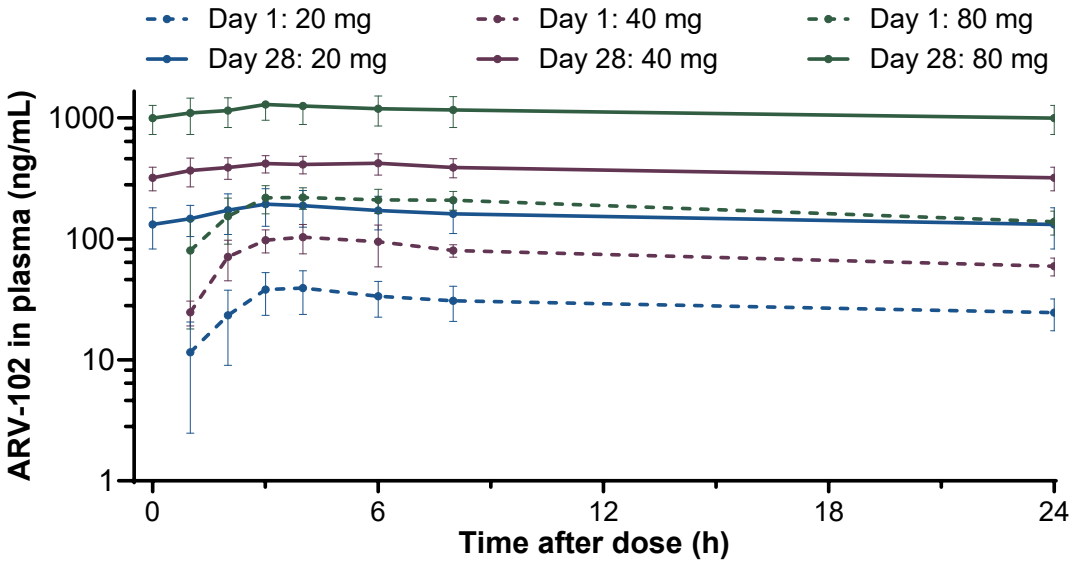
Event, n (%)	ARV-102 20 mg (n=6)	ARV-102 40 mg (n=6)	ARV-102 80 mg (n=6)	ARV-102 Total (n=18)	Placebo (n=6)
TEAEs reported by ≥3 participants					
Any TEAE	5 (83)	5 (83)	6 (100)	16 (89)	6 (100)
Headache	3 (50)	0	2 (33)	5 (28)	4 (67)
Myalgia	0	1 (17)	3 (50)	4 (22)	2 (33)
Fatigue	1 (17)	1 (17)	1 (17)	3 (17)	2 (33)
Post-lumbar puncture syndrome[a]	2 (33)	1 (17)	0	3 (17)	1 (17)
TRAEs reported by ≥2 participants					
Any TRAE	3 (50)	3 (50)	4 (67)	10 (56)	2 (33)
Headache	3 (50)	0	2 (33)	5 (28)	1 (17)

- Multiple oral doses of ARV-102 (20, 40, or 80 mg QD for 28 days) were well tolerated in participants with Parkinson's disease
- All TEAEs and TRAEs were mild in severity, with no SAEs, discontinuations, or deaths reported
- No respiratory symptoms or clinically significant changes in lung function were observed during the 28 days of treatment or follow-up

[a]All participants underwent lumbar puncture for CSF collection. All headaches related to lumbar puncture were recorded as post-lumbar puncture syndrome.
CSF=cerebrospinal fluid; QD=once daily; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.

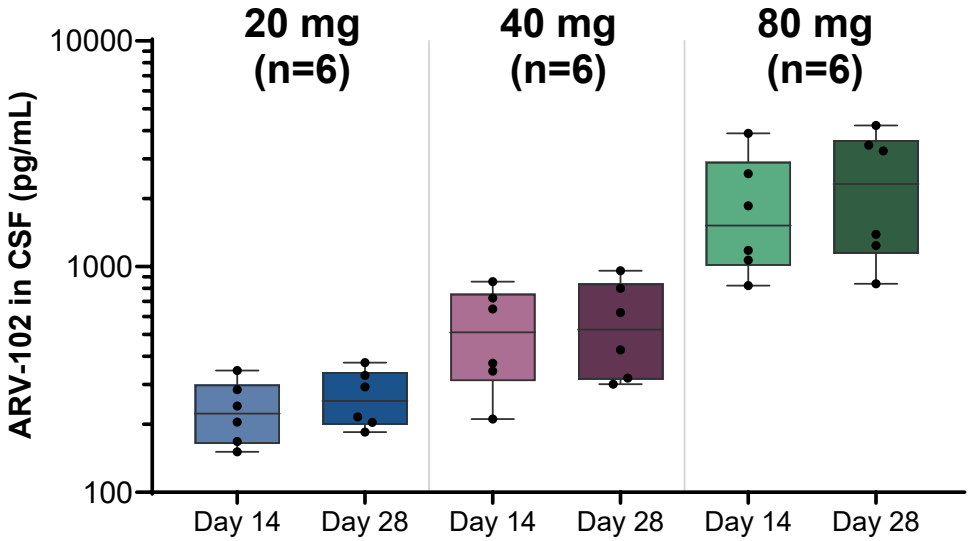
Multiple Dose PK of ARV-102 in Participants With Parkinson's Disease

ARV-102 in Plasma



- ARV-102 displayed moderate absorption (median T_{max} ≈5 h)
- Exposure increased in a dose-dependent manner with accumulation ratio of ~5-fold
- Mean $t_{1/2}$ was 68 h, with steady state reached by day 14
- There were no meaningful differences in PK disposition when compared with healthy participants[1]

ARV-102 in CSF



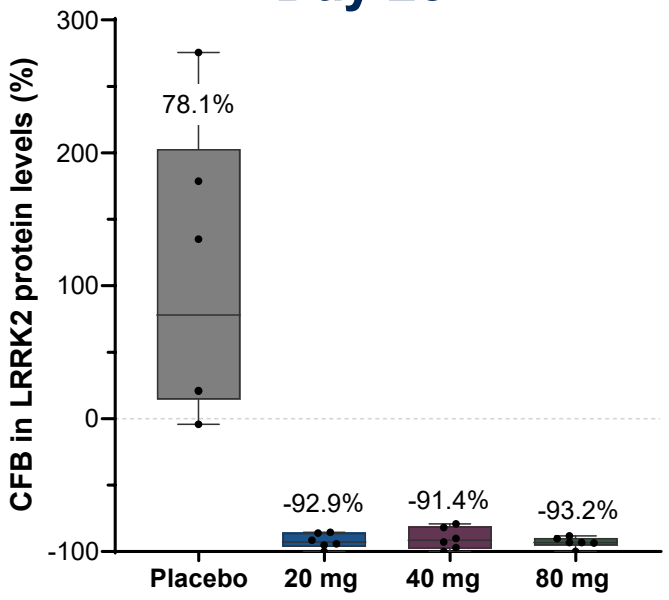
- ARV-102 concentrations in CSF increased with dose, indicating brain penetration
- Comparable concentrations in CSF on days 14 and 28 suggest steady state is attained by day 14

Lower limit of quantification was 0.25 ng/mL.
PK=pharmacokinetics; $t_{1/2}$=terminal elimination half-life; T_{max}=time to C_{max}.
1. Smits L, et al. Oral presentation at International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD) 2025.

Peripheral Pharmacodynamic Biomarkers

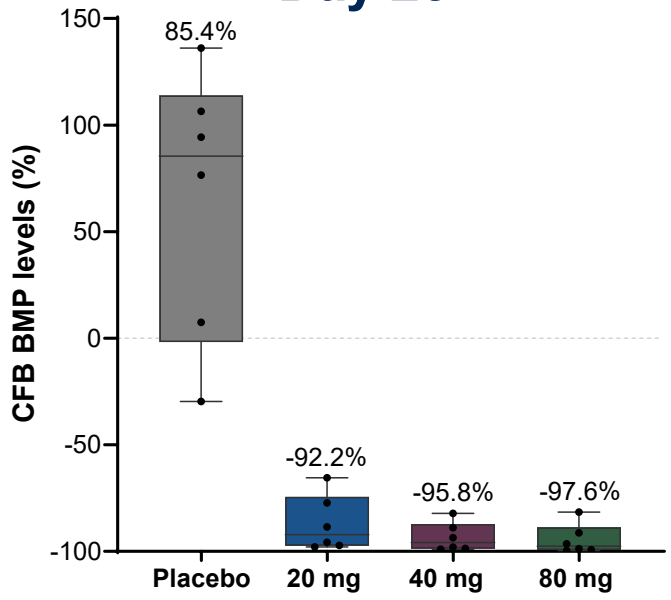
PBMC LRRK2

Day 28

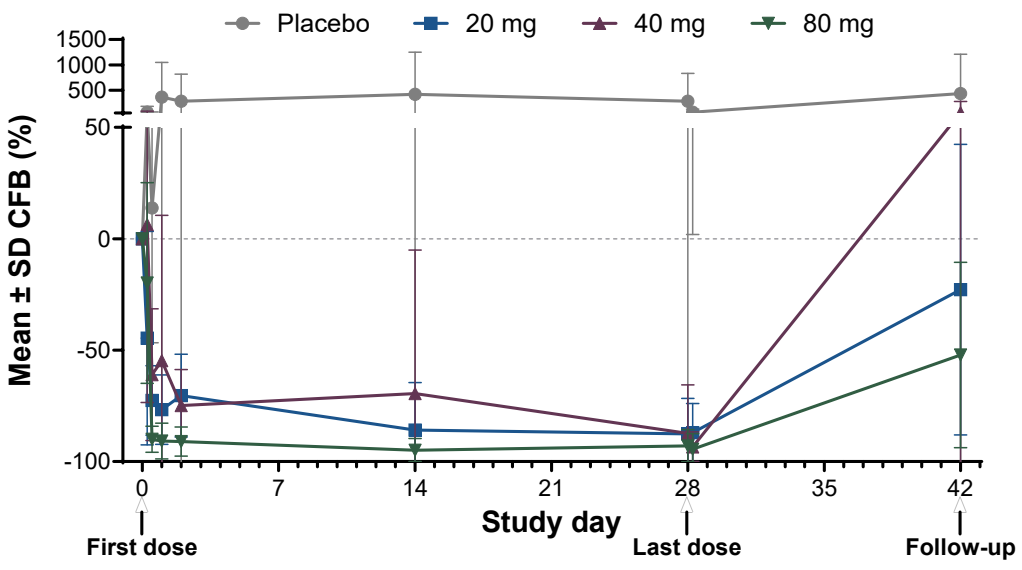


Urine BMP

Day 28



Time course



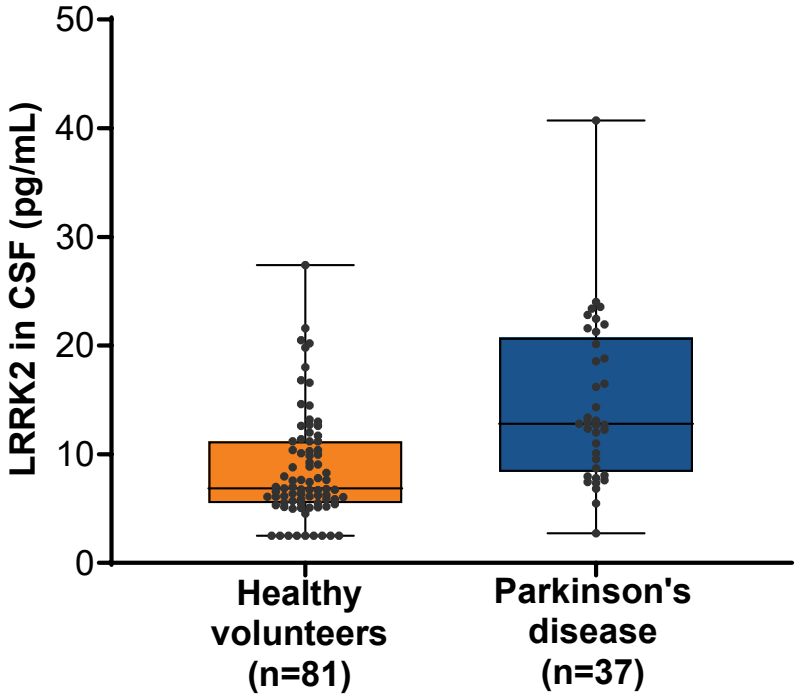
- Robust reductions of LRRK2 levels in PBMCs and BMP levels in urine were observed following multiple doses of ARV-102 treatment, with BMP levels returning towards baseline after 2 weeks of follow-up
- Peripheral pharmacodynamic biomarker results in participants with Parkinson's disease were consistent with those observed in the study of ARV-102 in healthy volunteers[1,2]

BMP=bis(monoacylglycerol)phosphate; LRRK2=leucine-rich repeat kinase 2; PBMC=peripheral blood mononuclear cell.

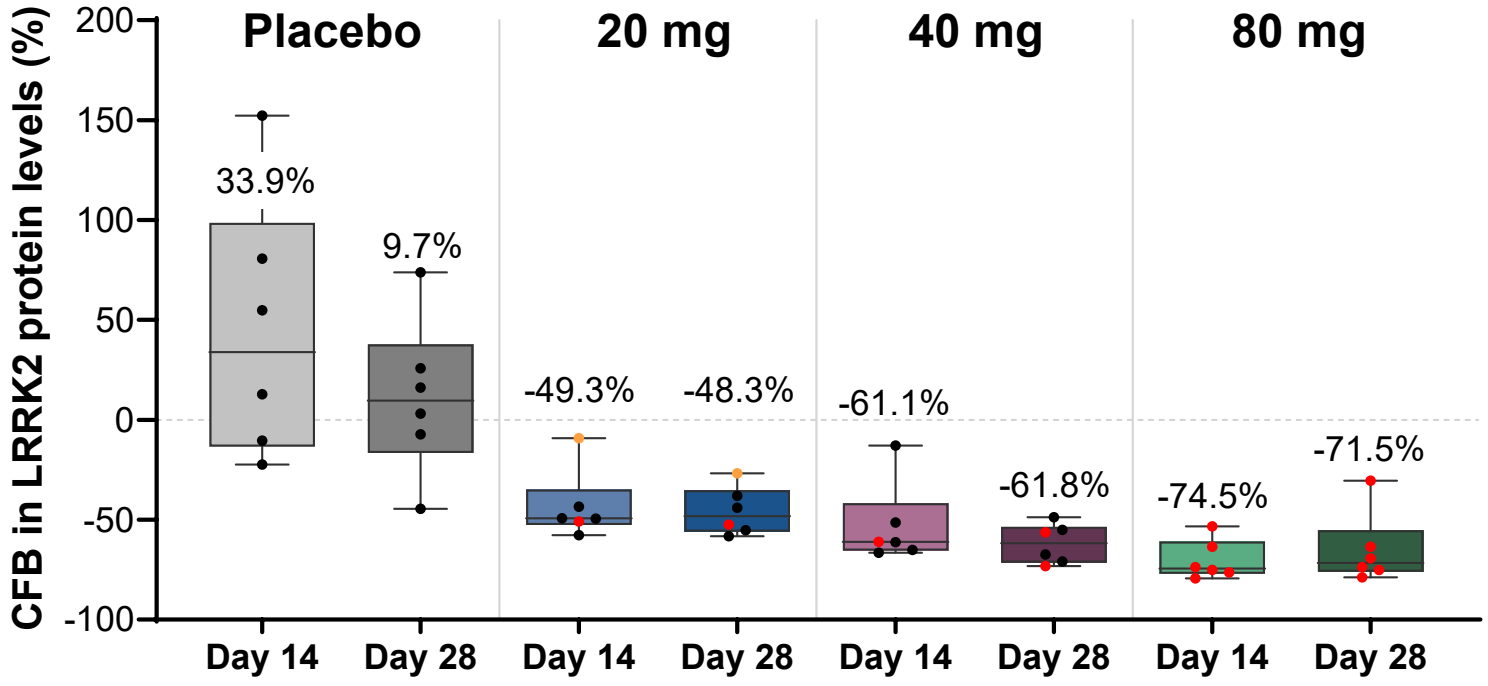
1. Smits L, et al. Oral presentation at International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD) 2025. 2. Smits L, et al. Poster presented at the International Congress of Parkinson's Disease and Movement Disorders (MDS) 2025; Poster #904.

LRRK2 Protein Levels in CSF With ARV-102 Treatment

Baseline LRRK2 in CSF[a]



Change in participants with Parkinsons disease[b]



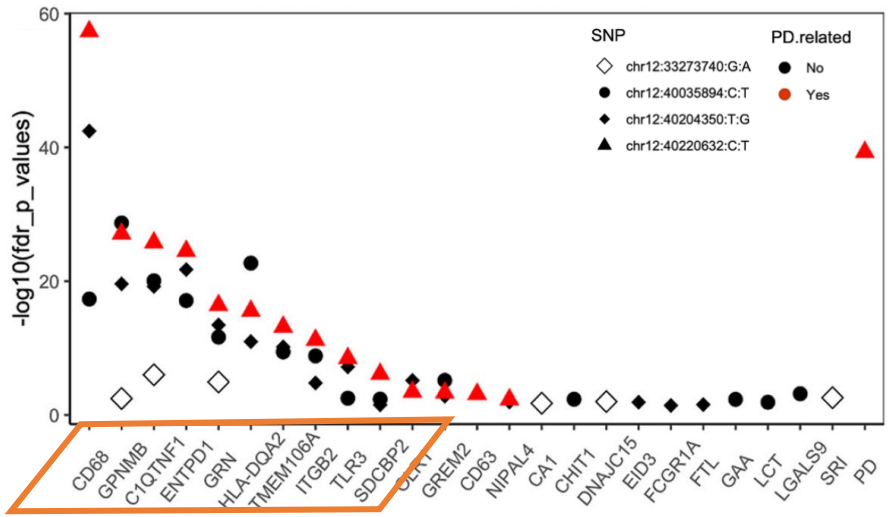
- Baseline levels of LRRK2 in CSF were higher in participants with Parkinson's disease than in healthy volunteers
- Median LRRK2 reductions of ~50% or greater were achieved in participants with Parkinson's disease starting at daily ARV-102 doses of 20 mg

Box plots show median and 25%/75% quartiles with whiskers to the minimum and maximum values. Circles indicate individual participant values.
CFB=change from baseline; CSF=cerebrospinal fluid; LLD=lower limit of detection; LLOQ=lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; QD=once daily.
[a]Plot shows baseline total LRRK2 levels in CSF from all participants in the single- and multiple-dose arms of the phase 1 studies in healthy volunteers and participants with Parkinson's disease.
[b]Red circles denote values that were <4 pg/mL (LLOQ) post baseline, which were calculated using one half of the LLOQ. Orange circles denote values that were below the LLOQ, but above the LLD (2 pg/mL); reported values were used to calculate CFB for these data points.

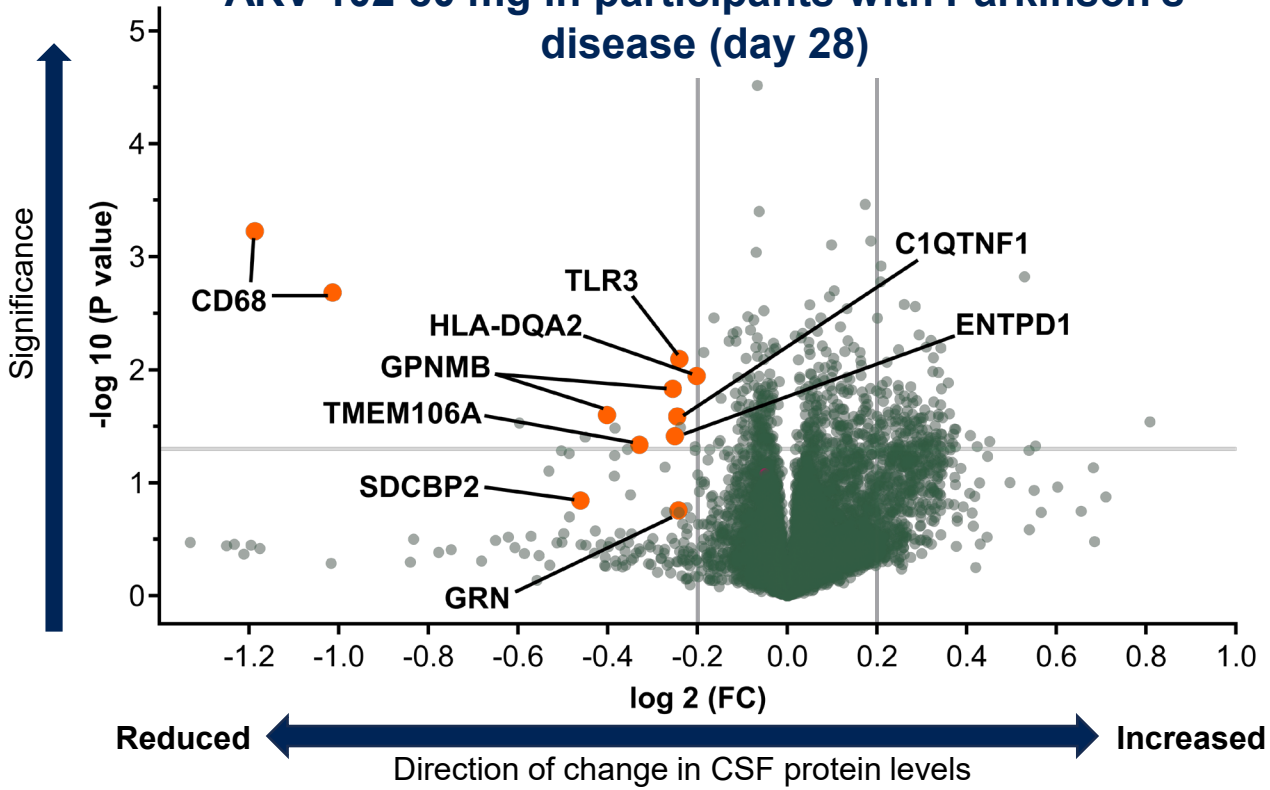
CSF Proteomics

- Multi-cohort CSF proteomics analysis identified lysosomal and microglial proteins associated with LRRK2 variants[1] that are also reduced with ARV-102 treatment in healthy volunteers[2]
- A prespecified panel of these proteins were evaluated in this study of ARV-102 in participants with Parkinson's disease; aggregate protein reductions in this panel were observed with LRRK2 degradation (*P*=0.024)[a]

Proteins associated with *LRRK2* variants in Parkinson's disease[b, 1]



ARV-102 80 mg in participants with Parkinson's disease (day 28)



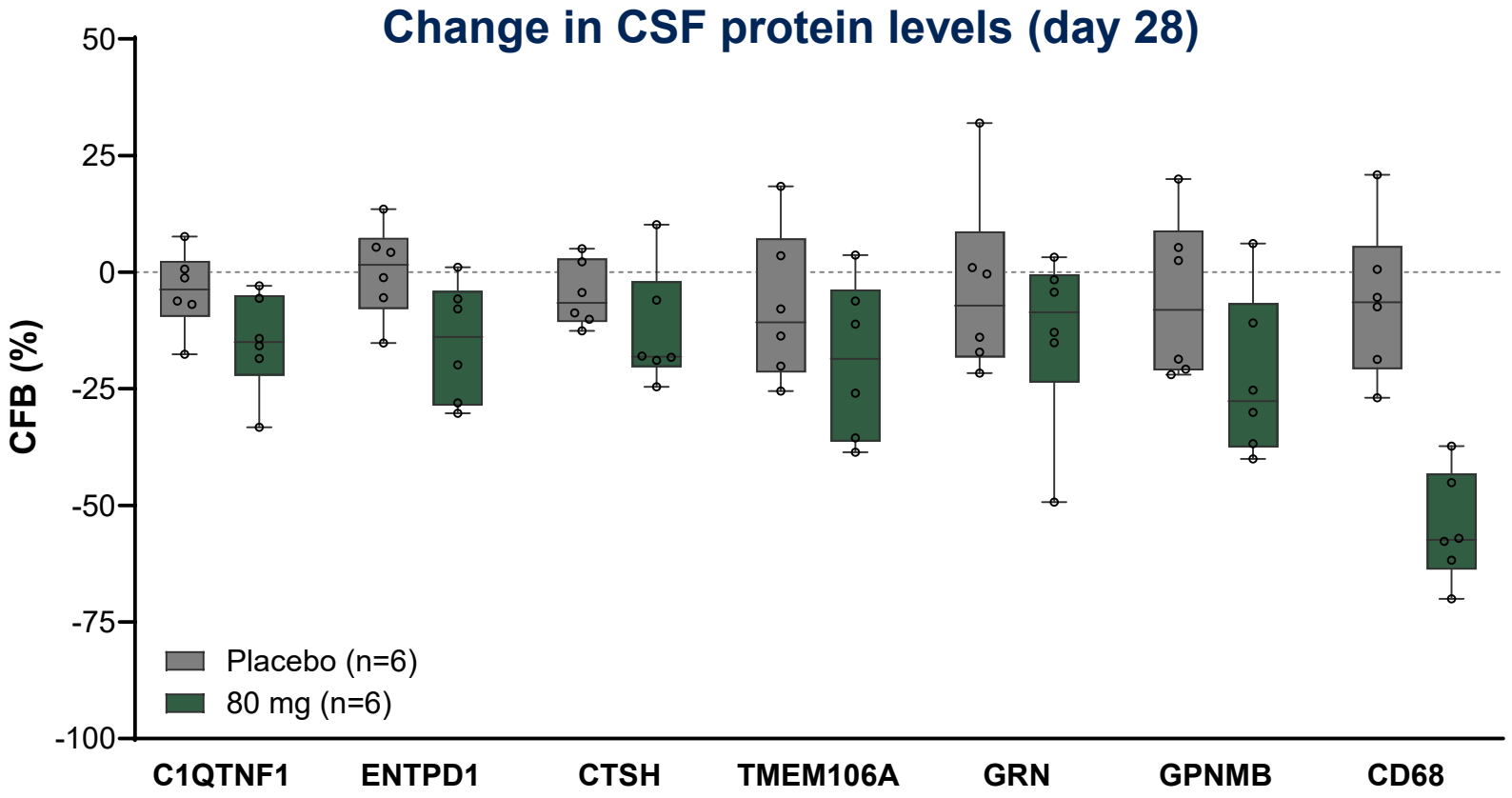
C1QTNF1=complement C1q tumor necrosis factor-related protein 1; CD68=cluster of differentiation 68; CSF=cerebrospinal fluid; ENTPD1=ectonucleoside triphosphate diphosphohydrolase 1; FC=fold change; GRN=granulin precursor; GPNMB=glycoprotein non-metastatic melanoma protein B; HLA-DQA2=major histocompatibility complex, class II, DQ alpha 2; ITGB2=integrin subunit beta 2; LRRK2=leucine-rich repeat kinase 2; PheWAS=protein phenome-wide association studies; PPMI=Parkinson's Progression Markers Initiative; SDCBP2=syndecan binding protein 2; TLR3=Toll-like receptor 3; TMEM106A=transmembrane protein 106A.

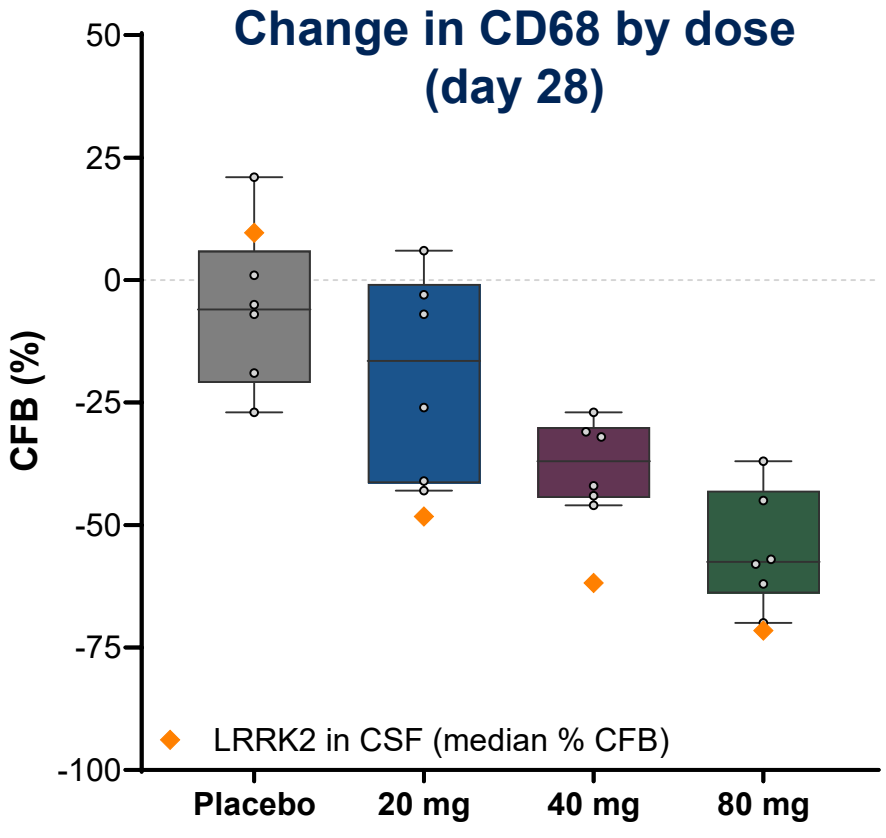
[a]Global O'Brien's statistical test was utilized to evaluate aggregate change in top 10 proteins related to LRRK2 variants. [b]Figure adapted from Phillips et al. (2023). NPJ Parkinson's Disease. DOI: 10.1038/s41531-023-00555-4. Licensed under CC BY 4.0.

1. Phillips B, et al. NPJ Parkinsons Dis. 2023;9(1):107. 2. Smits L, et al. Poster presented at the International Congress of Parkinson's Disease and Movement Disorders (MDS) 2025; Poster #LBA 22.

CSF Protein Levels With ARV-102 Treatment

- ARV-102 at 80 mg QD led to consistent reductions from baseline across the predefined panel of CSF proteins
- Dose-dependent reductions in CD68 were observed





C1QTNF1=complement C1q tumor necrosis factor-related protein 1; CD68=cluster of differentiation 68; CFB=change from baseline; CTSH=cathepsin H; CSF=cerebrospinal fluid; ENTPD1=ectonucleoside triphosphate diphosphohydrolase 1; GRN=granulin precursor; GPNMB=glycoprotein non-metastatic melanoma protein B; LRRK2=leucine-rich repeat kinase 2; QD=once daily; TMEM106A=transmembrane protein 106A.

Conclusions

- Once daily oral administration of ARV-102 for 28 days was well tolerated in this Parkinson's disease population
- ARV-102 displayed a favorable PK profile with efficient CNS penetration
- ARV-102 achieved substantial reductions in peripheral LRRK2 levels and downstream pathway engagement
- ARV-102 treatment led to dose-dependent reduction of LRRK2 levels in CSF, with ~50% or greater degradation observed at all doses tested
- Endolysosomal and neuroinflammatory pathway proteins that are elevated in LRRK2-related Parkinson's disease[1] were reduced with ARV-102
- These data support further clinical development of ARV-102 in neurodegenerative diseases, such as Parkinson's disease and PSP

CSF=cerebrospinal fluid; CNS=central nervous system; LRRK2=leucine-rich repeat kinase 2; PK=pharmacokinetics; PSP=progressive supranuclear palsy.

1. Phillips B, et al. NPJ Parkinsons Dis. 2023;9(1):107.

Acknowledgments

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- This study is sponsored by Arvinas Operations, Inc.