



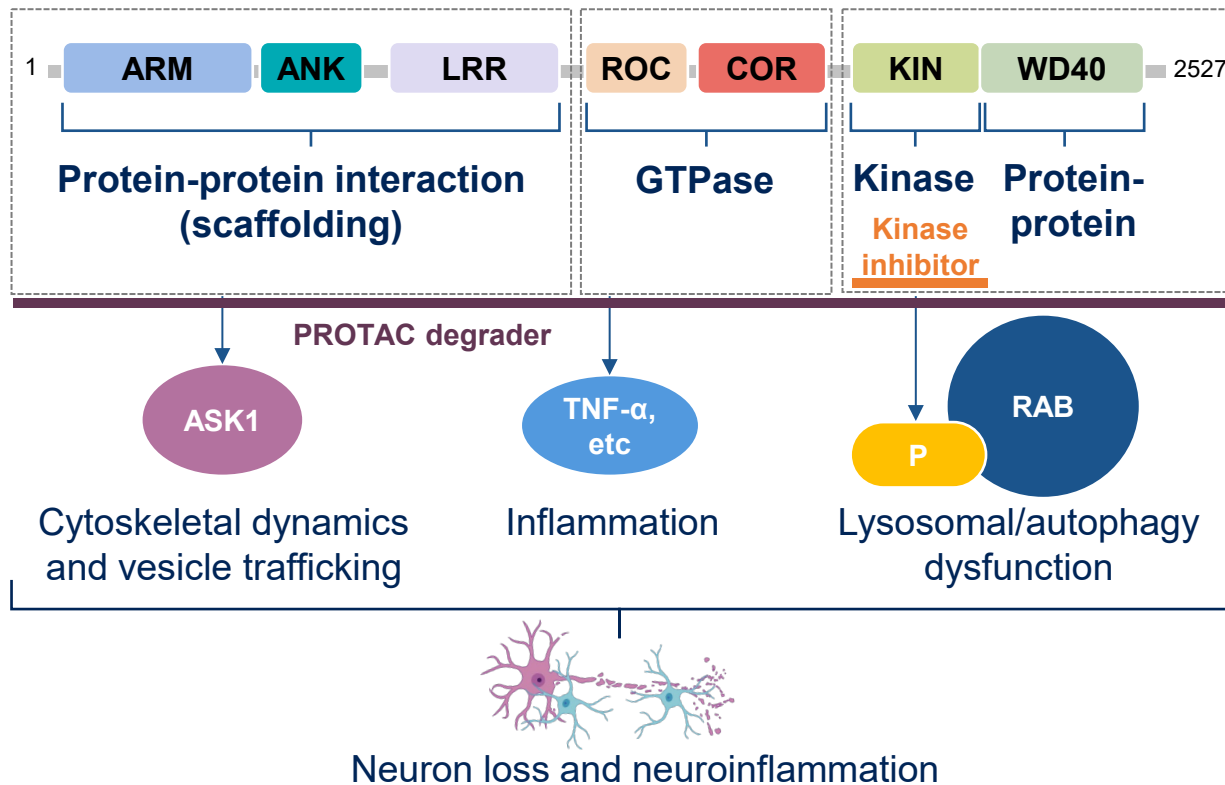
Phase 1 Study of ARV-102, a PROTAC LRRK2 Degradar, in Parkinson's Disease: Oculomotor and Biomarker Data

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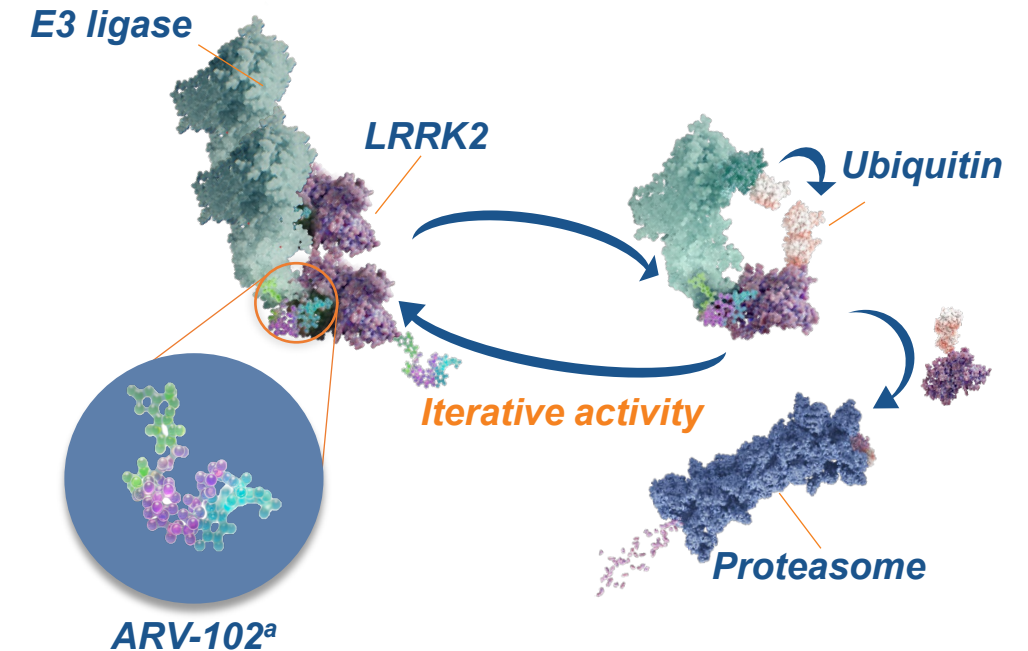
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Targeting LRRK2 in Parkinson's Disease

LRRK2 is implicated in endolysosomal dysfunction, neuroinflammation, and synaptic alterations in Parkinson's disease¹⁻³



ARV-102 is an oral, brain-penetrant PROTAC LRRK2 degrader

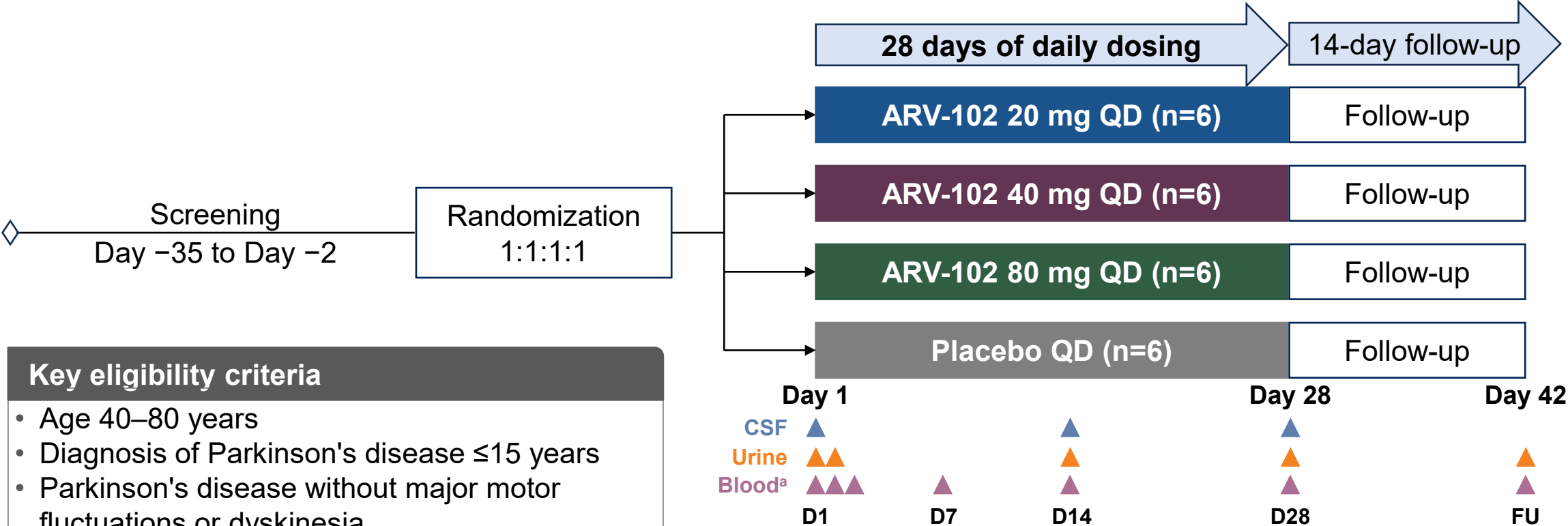


ANK=ankyrin; ARM=armadillo; ASK1=apoptosis signal-regulating kinase 1; COR=C-terminal of ROC; KIN=kinase; LRR=leucine-rich repeat; LRRK2=leucine-rich repeat kinase 2; PROTAC=proteolysis-targeting chimera; ROC=Ras of complex proteins; SNP=single-nucleotide polymorphism; TNF-α=tumor necrosis factor α.

^aA general PROTAC protein degrader is shown.

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.

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



Key eligibility criteria

- Age 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

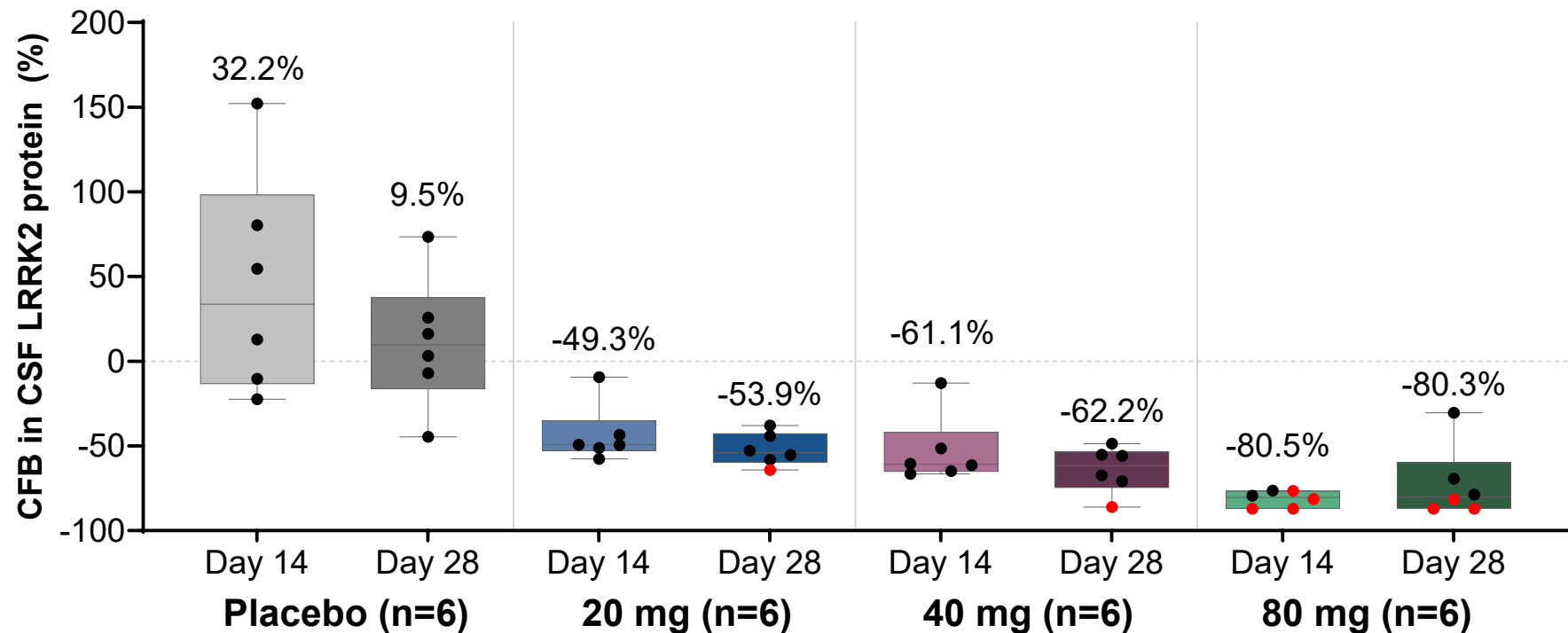
Exploratory: Molecular biomarkers (CSF proteomics), oculomotor parameters, motor and nonmotor features (MDS-UPDRS)

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^aPeripheral blood mononuclear cells and whole blood.

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

CFB in CSF LRRK2 Protein in Participants With Parkinson's Disease After Multiple Doses of ARV-102¹



Exploratory analyses showed median LRRK2 reductions of ~50% or greater with ARV-102 doses of 20 mg QD or higher

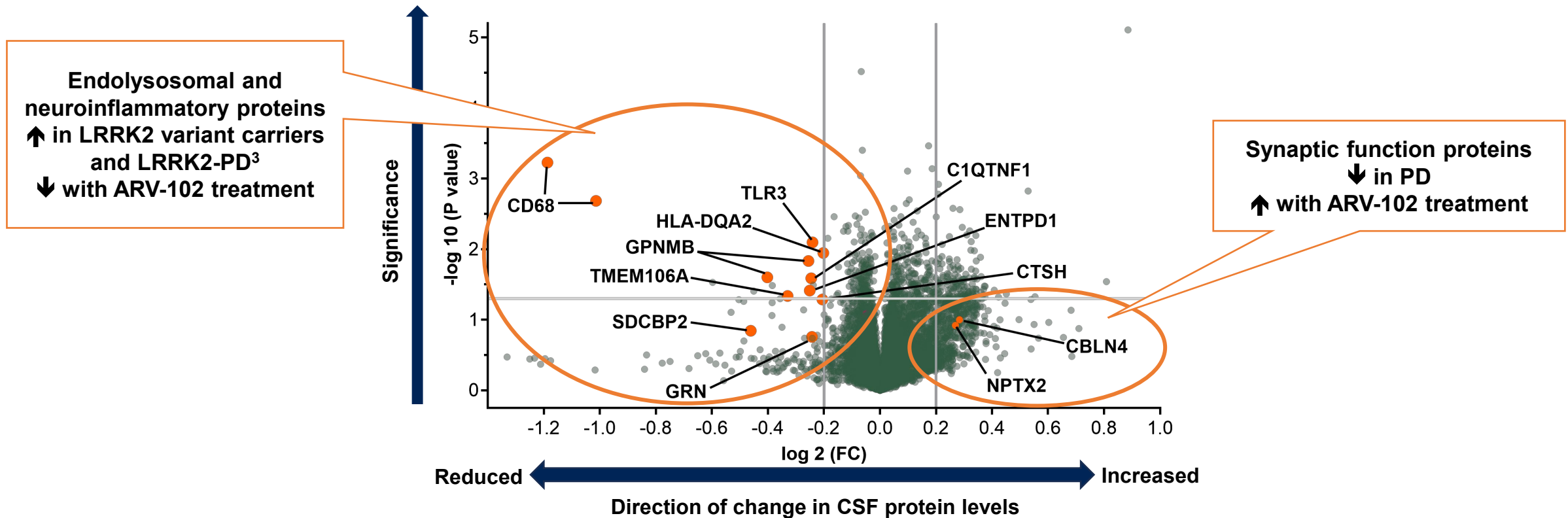
Box plots show medians and 25th and 75th percentiles; whiskers indicate minimum and maximum values. Circles indicate individual participant values. Red circles indicate postbaseline values less than 4 pg/mL (LLOQ), calculated as one-half the LLOQ. Orange circles indicate values below the LLOQ but above the LLD (2 pg/mL); reported values were used to calculate CFB.

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.

¹Van de Bult L, et al. International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD) 2026.

CSF Proteomics in the 80-mg QD ARV-102 Group^{1,2}

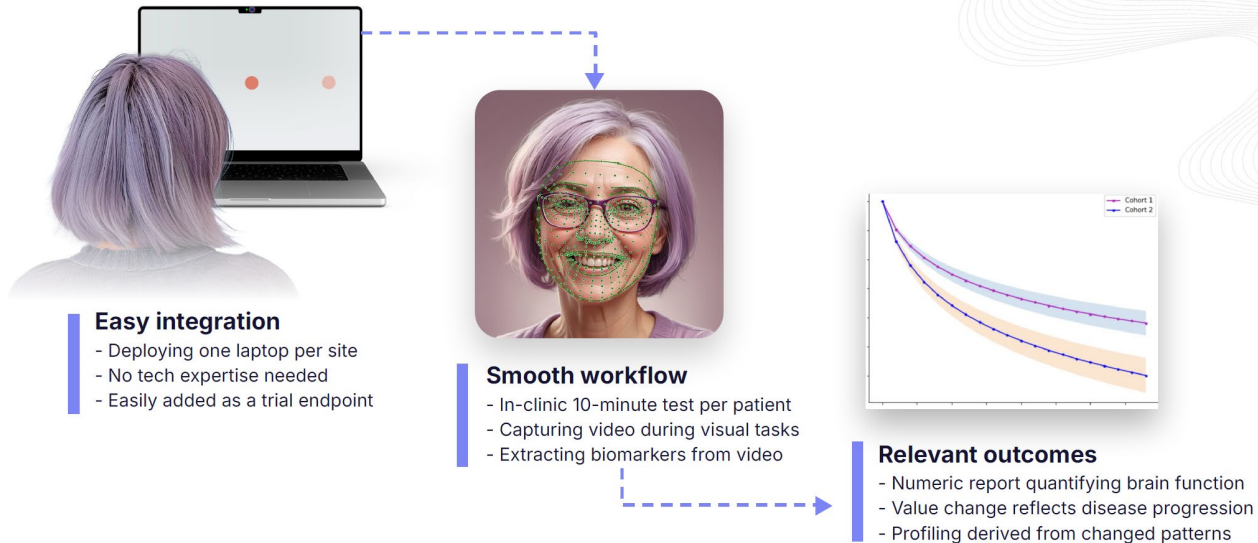
- ARV-102 decreased CSF biomarkers of endolysosomal function and neuroinflammation (eg, CD68, GPNMB) and increases in markers of synaptic integrity and axonal guidance (NPTX2, CBLN4)



C1QTNF1=complement C1q tumor necrosis factor-related protein 1; CBLN4=cerebellin 4 precursor; CD68=cluster of differentiation 68; CSF=cerebrospinal fluid; CTSH=cathepsin H; ENTPD1=ectonucleoside triphosphate diphosphohydrolase 1; GPNMB=glycoprotein nonmetastatic melanoma protein B; GRN=granulin precursor; HLA-DQA2=major histocompatibility complex, class II, DQ alpha 2; LRRK2=leucine-rich repeat kinase 2; NPTX2=neuronal pentraxin 2; QD=once daily; TLR3=toll-like receptor 3; TMEM106A=transmembrane protein 106A.

1. Smits L, et al. International Congress of Parkinson's Disease and Movement Disorders (MDS) 2025; Poster #904. 2. Van de Bult L, et al. International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD) 2026. 3. Phillips, B. et al. NPJ Parkinsons Dis. 2023 Jul 8;9(1):107.

Change in Oculomotor Function: Amplitude of Saccadic Hypometria (ASH)



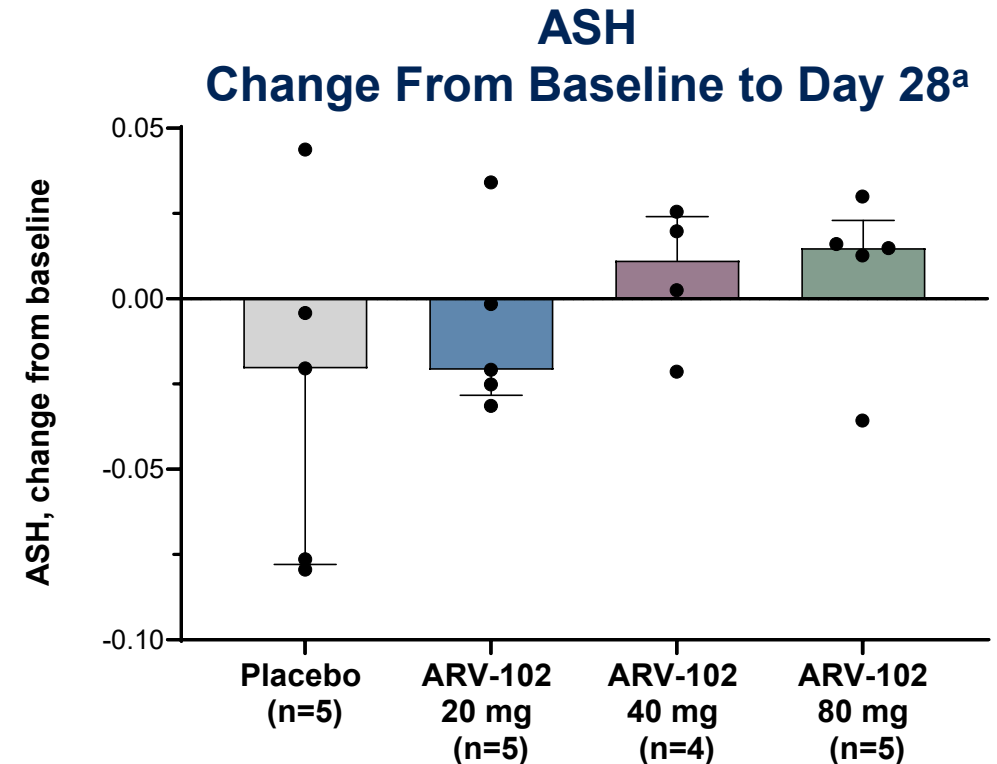
NeuraLight

- ASH is a measure of basal ganglia–cortical motor circuit function that can be assessed using eye-tracking tests in clinical studies¹
- ASH is reduced in individuals with Parkinson disease and generally decreases with disease severity²

ASH=amplitude of saccadic hypometria; IQR=interquartile range.

^aBars show medians $\pm$ IQRs; dots represent individual participant values.

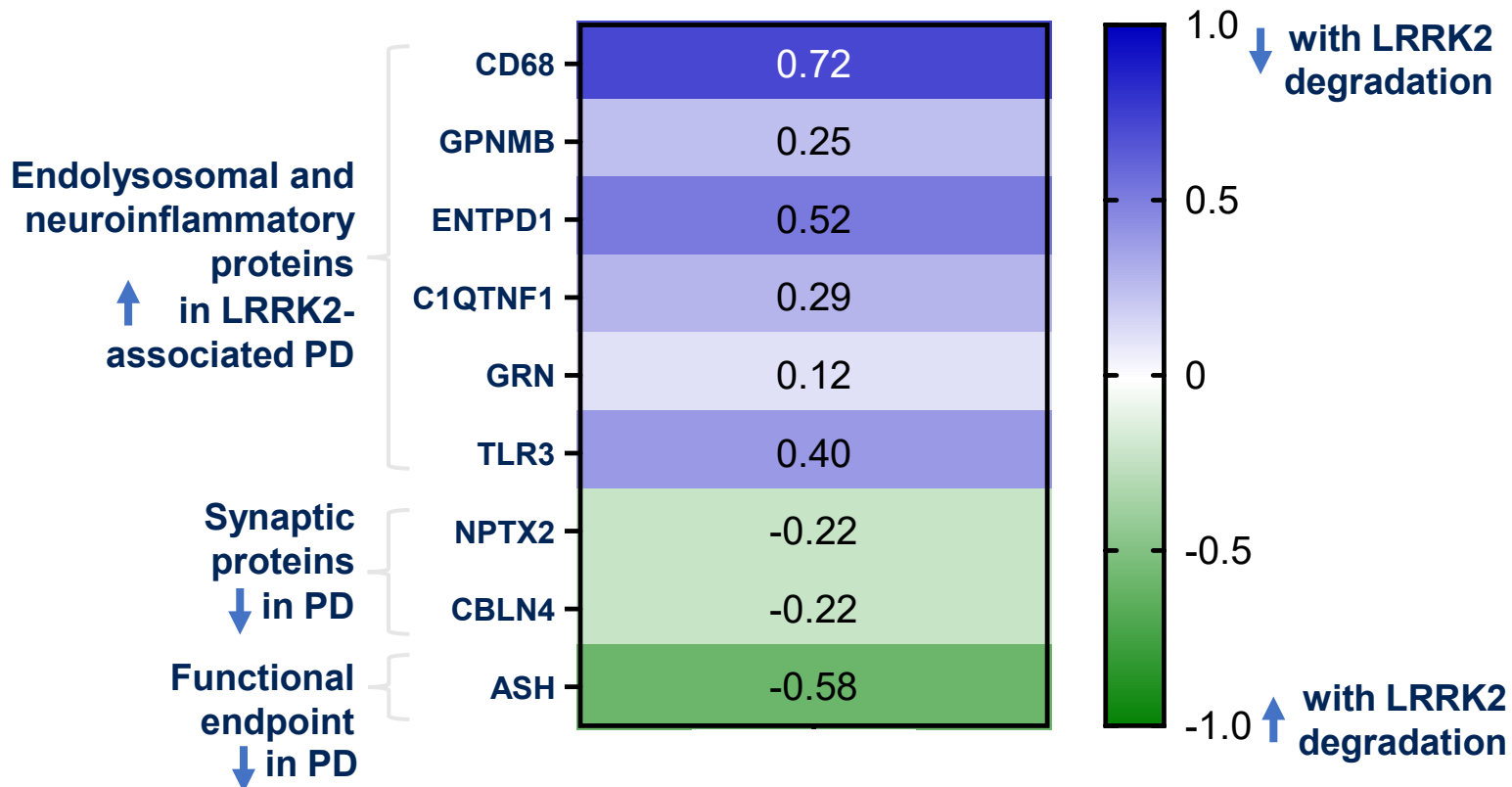
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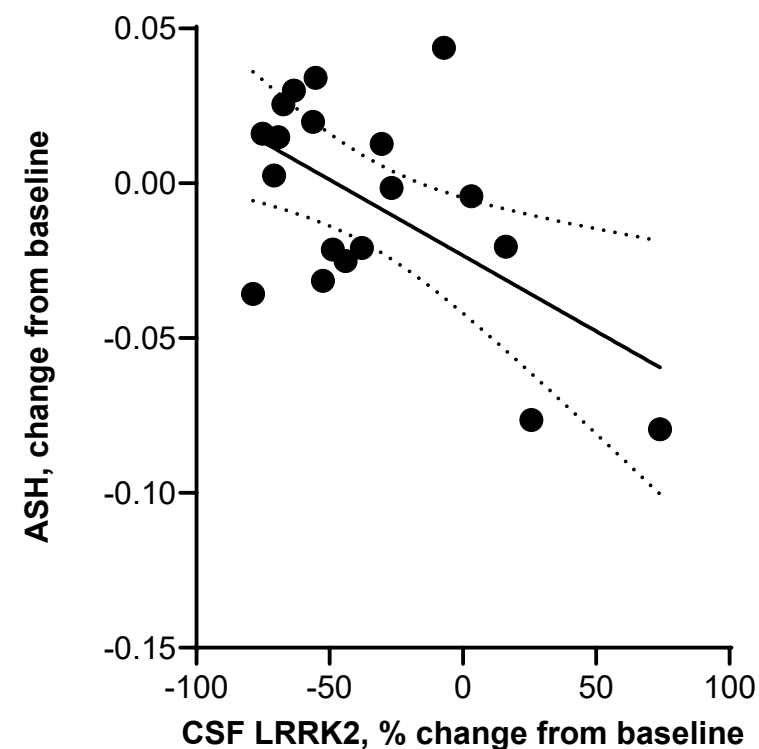
Correlations Between Reduction in CSF LRRK2, Oculomotor Function and CSF Biomarkers

7

Heat map of Pearson correlation coefficients



Change in ASH vs change in CSF LRRK2 (Day 28)



Heat map shows Pearson correlation coefficients.

ASH=amplitude of saccadic hypometria; C1QTNF1=complement C1q tumor necrosis factor-related protein 1; CBLN4=cerebellin 4 precursor; CD68=cluster of differentiation 68; CSF=cerebrospinal fluid; ENTPD1=ectonucleoside triphosphate diphosphohydrolase 1; GPNMB=glycoprotein nonmetastatic melanoma protein B; GRN=granulin precursor; LRRK2=leucine-rich repeat kinase 2; NPTX2=neuronal pentraxin 2; PD=Parkinson's disease; TLR3=toll-like receptor 3.

Conclusions

- In this small phase 1 study in participants with Parkinson's disease, ARV-102:
 - Was well tolerated, with dose-dependent plasma and CSF exposure¹⁻³
 - Induced robust peripheral target and pathway engagement¹⁻³
 - Decreased CSF LRRK2 dose dependently
- Preliminary data indicate that CSF LRRK2 degradation is correlated with:
 - Reductions in endolysosomal and neuroinflammatory proteins
 - Increases in proteins associated with synaptic integrity and axonal guidance
 - Changes in oculomotor function

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

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. 3. Van de Bult L, et al. Oral presentation at International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders (AD/PD) 2026.