

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

Kyle Fraser¹, Luuk van de Bult^{2,3}, Lars Smits^{2,3}, Sandra Korsten^{2,3}, Caroline Ngaara-Woodward¹, John Corradi¹, Sergey Aksenov¹, Xiaolong Luo¹, Miri Alon¹, Ana Luiza Costa Zaninotto¹, Christine Lubeski¹, Margit MacDougall¹, Cheryl J Fitzer-Attas¹, Ilaria Conti¹, Mark Forrest Gordon¹, Philip Kremer^{2,3}

¹Arvinas Operations, Inc., New Haven, Connecticut, USA; ²Centre for Human Drug Research (CHDR), Leiden, the Netherlands; ³Leiden University Medical Center (LUMC), Leiden, the Netherlands

Objective

- To evaluate the effects of ARV-102, a PROTAC LRRK2 degrader, on exploratory measures of oculomotor function and CSF biomarkers in a phase 1 study in participants with Parkinson’s disease (EudraCT 2024-516888-84-00)

Key Findings

- After 28 days of ARV-102 treatment, there was a dose-related trend toward improvement in amplitude of saccadic hypometria (ASH) compared with placebo, without an observed effect on oculomotor measures of alertness
- Exploratory CSF proteomic analyses showed decreases in biomarkers associated with endolysosomal function and neuroinflammation (eg, CD68 and GPNMB) and increases in biomarkers of synaptic integrity and axonal guidance (eg, NPTX2 and CBLN4)
- The magnitude of CSF LRRK2 reductions (Figure 2) correlated with changes in CSF pathway biomarkers and oculomotor function (ASH)

Conclusions

- This small phase 1 study demonstrated preliminary findings of changes in oculomotor function and CSF pathway biomarkers following CSF LRRK2 degradation in participants with Parkinson’s disease, supporting PROTAC-induced LRRK2 degradation as a potential therapeutic approach

Acknowledgments

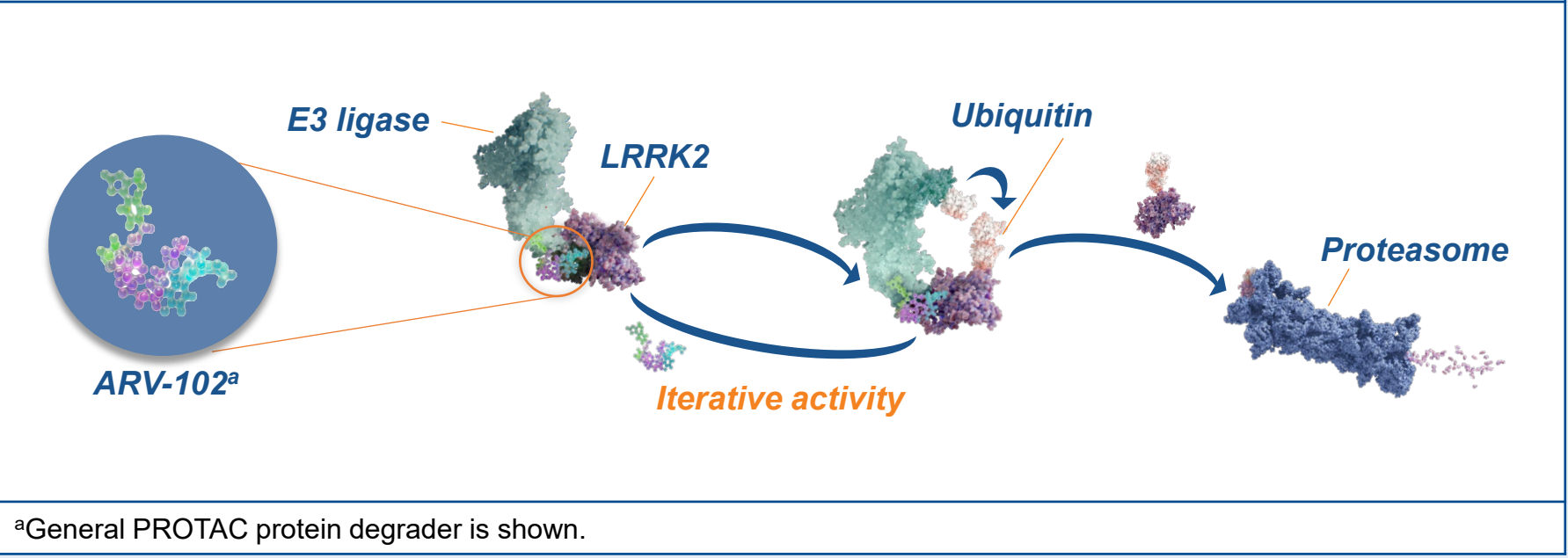
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Contact: Kyle Fraser, kyle.fraser@arvinas.com

Background

- LRRK2 mutations are a common genetic cause of Parkinson’s disease, and LRRK2 variants are also associated with idiopathic disease¹⁻³
- Increased LRRK2 expression and activity contribute to neurodegeneration, supporting LRRK2 as a therapeutic target¹
- ARV-102 is an oral, brain-penetrant PROTAC LRRK2 degrader that induces ubiquitination of LRRK2 driving its proteasomal degradation (**Figure 1**)
- In preclinical studies, ARV-102^{4,5}:
 - Demonstrated >50-fold greater potency than LRRK2 kinase inhibitors for LRRK2 target and lysosomal pRAB pathway engagement in mouse brain
 - Increased lysosome number and enhanced lysosomal function in vitro
 - Reduced pathologic oligomeric tau in vitro and in vivo
- In nonhuman primates, ARV-102 distributed throughout the evaluated brain regions, including cortex, striatum, cerebellum, and into CSF, where it induced LRRK2 degradation^{4,5}

Figure 1: Mechanism of action of ARV-102



Results

Participant characteristics

- 24 participants with Parkinson’s disease were randomized to receive multiple doses of ARV-102 or placebo (**Table 1**)
- All randomized participants received the assigned treatment and completed the study

Table 1: Demographics and baseline characteristics				
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, male, n (%)	5 (83)	6 (100)	5 (83)	4 (67)
Race, White, n (%)	6 (100)	6 (100)	6 (100)	6 (100)
BMI, kg/m ² , median (range)	24.9 (22.6–29.1)	27.0 (22.8–29.4)	24.9 (22.2–32.0)	30.1 (23.5–31.8)
Nonmodified Hoehn & Yahr stage, n (%)				
1: Unilateral involvement only	3 (50)	4 (67)	2 (33)	3 (50)
2: Bilateral involvement, no balance impairment	3 (50)	2 (33)	4 (67)	1 (17)
3: Mild to moderate involvement	0	0	0	2 (33)
Years from diagnosis, median (range)	7.8 (2.0–15.2)	2.3 (0.3–9.1)	7.8 (3.2–9.3)	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 ^b	2 (33)	1(17)	0	0
MDS-UPDRS score, median (range)				
Total sum score	26 (9–46)	35 (15–61)	50 (27–63)	39 (23–54)
Part 1 (nonmotor aspects of experiences of daily living)	6 (3–7)	6 (0–10)	7 (2–13)	6 (2–16)
Part 2 (motor aspects of experiences of daily living)	4 (0–10)	6 (2–15)	11 (3–14)	5 (2–11)
Part 3 (motor examination)	13 (4–29)	21 (10–51)	30 (21–47)	29 (16–34)

^aParticipants may have received ≥1 medication class for Parkinson’s disease.
^bIncluded adamantane derivatives, monoamine oxidase B inhibitors and other dopaminergic agents (entacapone).

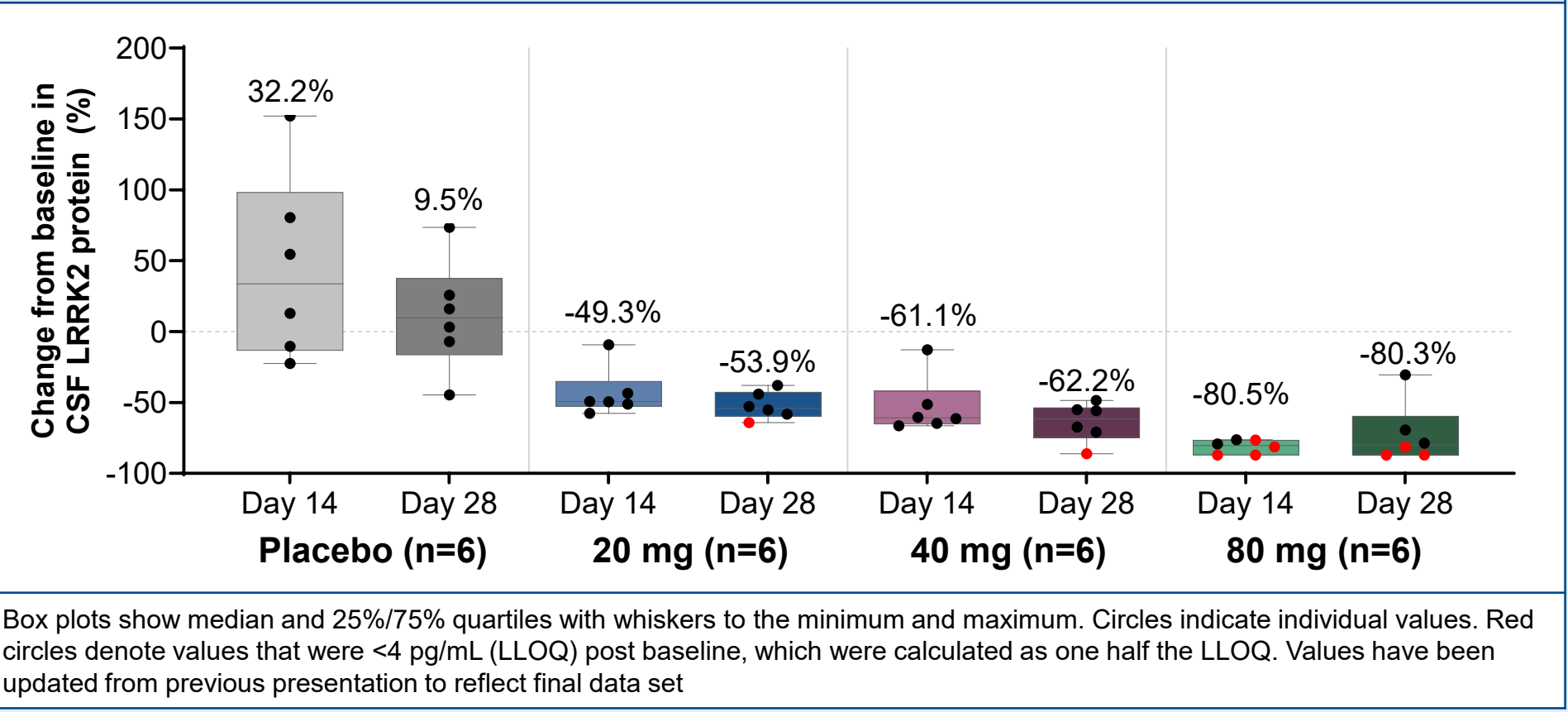
Abbreviations: ASH=amplitude of saccadic hypometria; BMI=body mass index; C1QTNF1=complement C1q tumor necrosis factor-related protein 1; CBLN4=cerebellin 4 precursor; CD68=cluster of differentiation 68; CNS=central nervous system; CSF=cerebrospinal fluid; CTSH=cathepsin H; DDI=dopa decarboxylase inhibitor; ENTPD1=ectonucleoside triphosphate diphosphohydrolase 1; FC=fold change; GPNMB=glycoprotein nonmetastatic melanoma protein B; GRN=granulin precursor; HLA-DQA2=major histocompatibility complex, class II, DQ alpha 2; IQR=interquartile range; LLOQ=lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; LSM=least squares mean; MDS-UPDRS=Movement Disorder Society–Unified Parkinson’s Disease Rating Scale; NPTX2=neuronal pentraxin 2; pRAB=phosphorylated Rab GTPase; PROTAC=PRoteolysis TArgeting Chimera; QD=once daily; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TLR3=toll-like receptor 3; TMEM106A=transmembrane protein 106A; TRAE=treatment-related adverse event.

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- In phase 1 studies in healthy participants and participants with Parkinson’s disease, ARV-102⁶⁻⁸:
 - Was generally well tolerated; all TEAEs and TRAEs were mild in severity, with no SAEs, discontinuations, or deaths reported
 - Demonstrated a favorable pharmacokinetic profile and CNS penetration
 - Achieved peripheral and central target and pathway engagement, with central LRRK2 reductions of approximately 50% or greater after multiple doses in participants with Parkinson’s disease (**Figure 2**)
- Here, we report exploratory oculomotor, MDS-UPDRS, and CSF proteomic findings from the phase 1 study of ARV-102 in participants with Parkinson’s disease

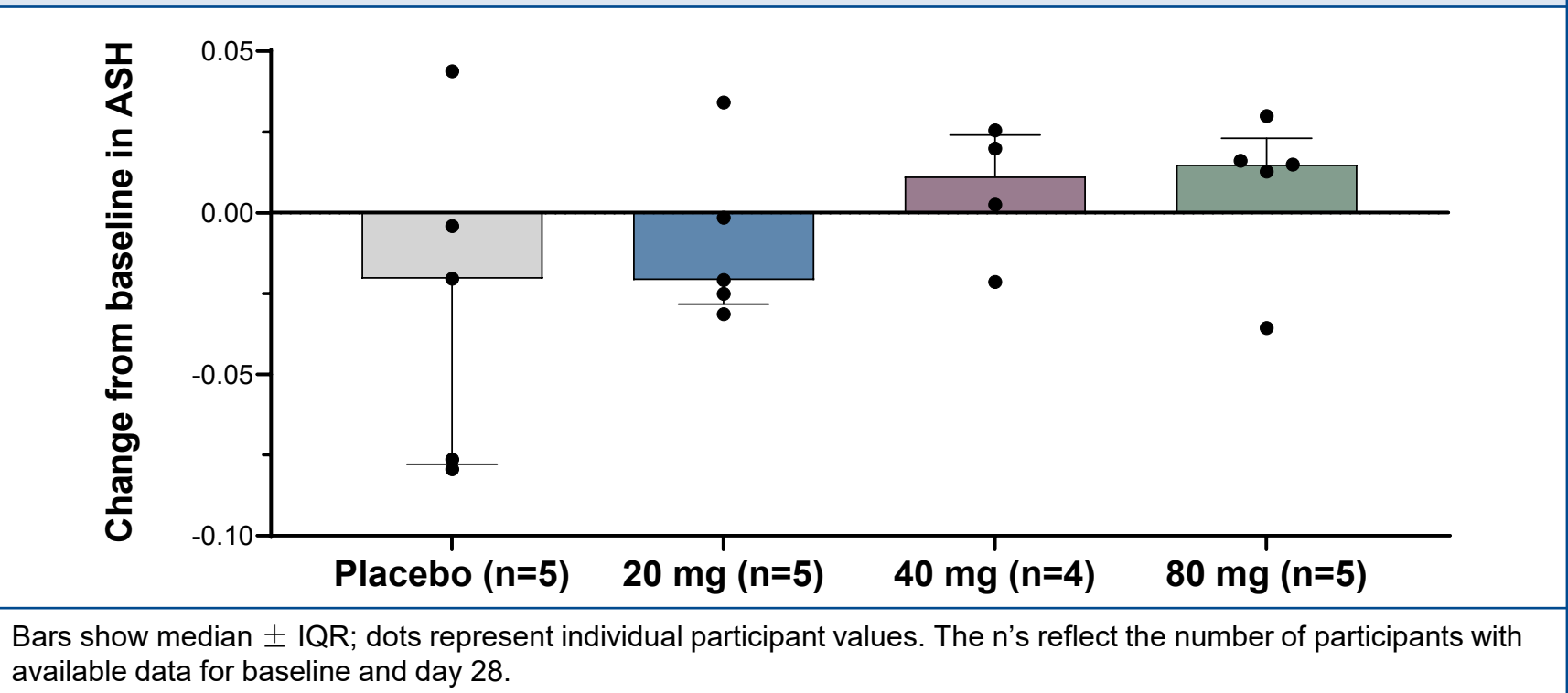
Figure 2: Change from baseline in CSF LRRK2 protein levels in participants with Parkinson’s disease following multiple doses of ARV-102⁸



Oculomotor function

- In the placebo group, ASH decreased from baseline to day 28 (**Figure 4**) at a level consistent with published natural history findings¹²
- In contrast, dose-related increases in ASH, reflecting less severe hypometria, were observed after 28 days of ARV-102 treatment (**Figure 4**)
- No notable changes were observed in oculomotor measures of alertness (data not shown)

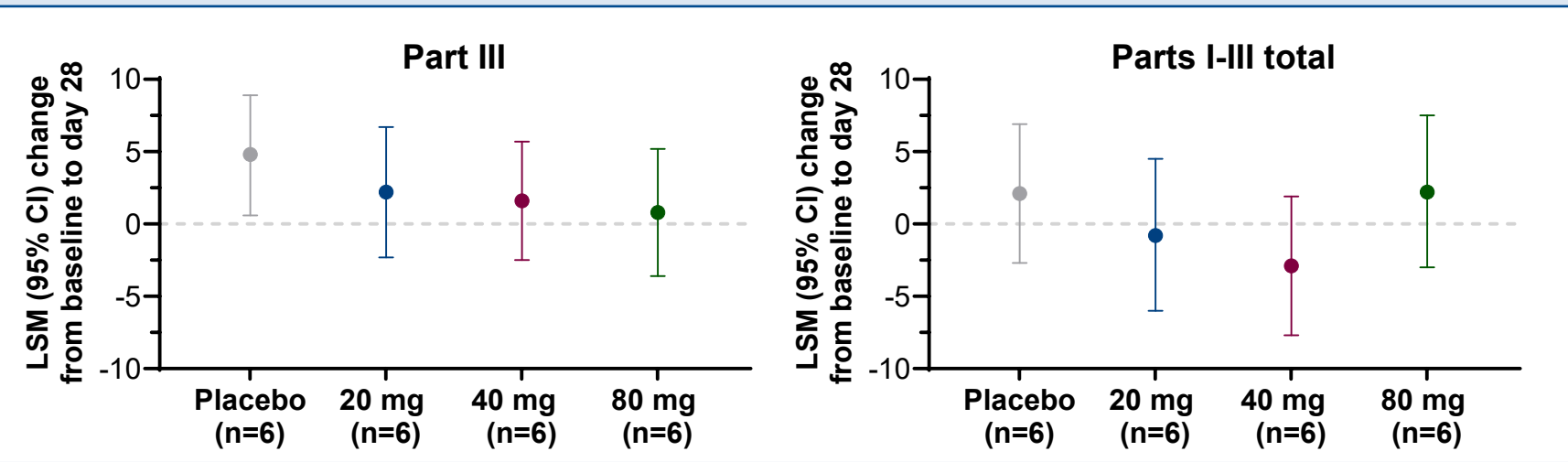
Figure 4: Change in ASH following 28 days of treatment



MDS-UPDRS

- No consistent changes from baseline in MDS-UPDRS scores were observed following 28 days of treatment with ARV-102 vs placebo (**Fig. 5**)

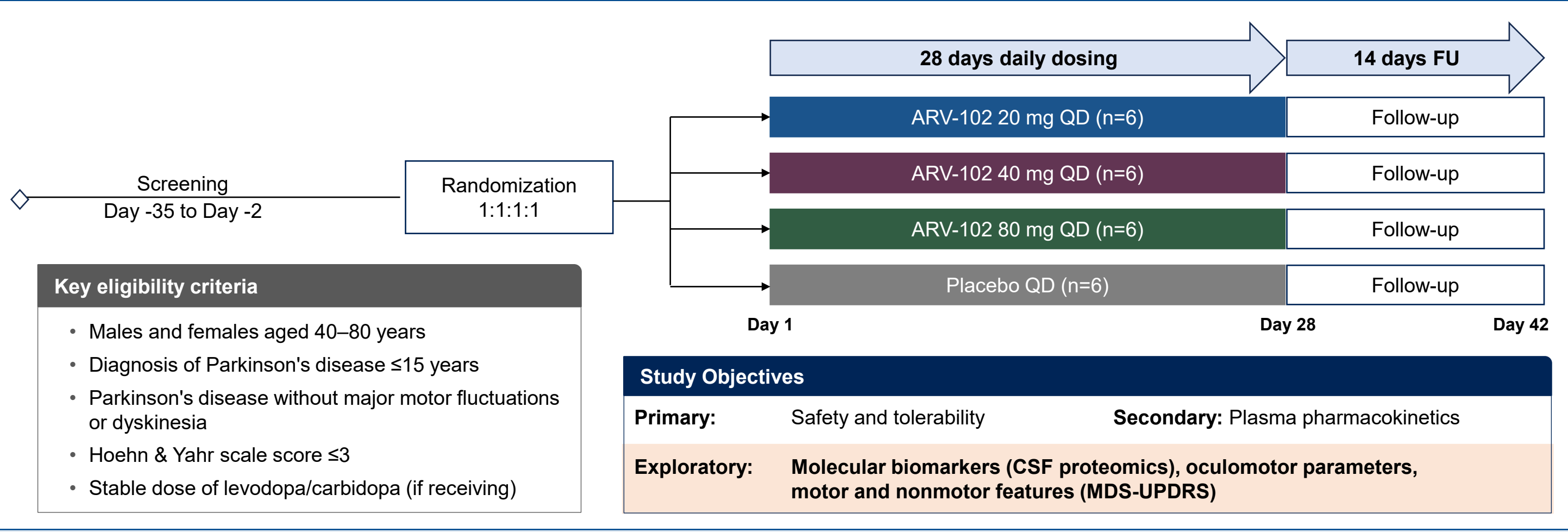
Figure 5: Change in MDS-UPDRS scores



Methods

- In the multiple-dose portion of a single-center, double-blind, phase 1 study, participants with Parkinson’s disease were randomized to receive 20, 40, or 80 mg of ARV-102, or placebo QD for 28 days (**Figure 3**)
- Oculomotor function was assessed on day -1 and 28 using the NeuraLight software-based platform^{9,10}
 - Amplitude of saccadic hypometria (ASH) was selected as the oculomotor parameter for evaluating treatment effects between groups, given its relevance as a functional biomarker of basal ganglia output in Parkinson’s disease^{11,12}
 - Oculomotor alertness was assessed to determine whether changes in ASH were attributable to changes in alertness
- MDS-UPDRS Parts I–III were administered on days -1 and 28 to assess motor and nonmotor features of Parkinson’s disease¹³
- CSF proteomic profiles were analyzed using the SomaScan 11K platform (SomaLogic)

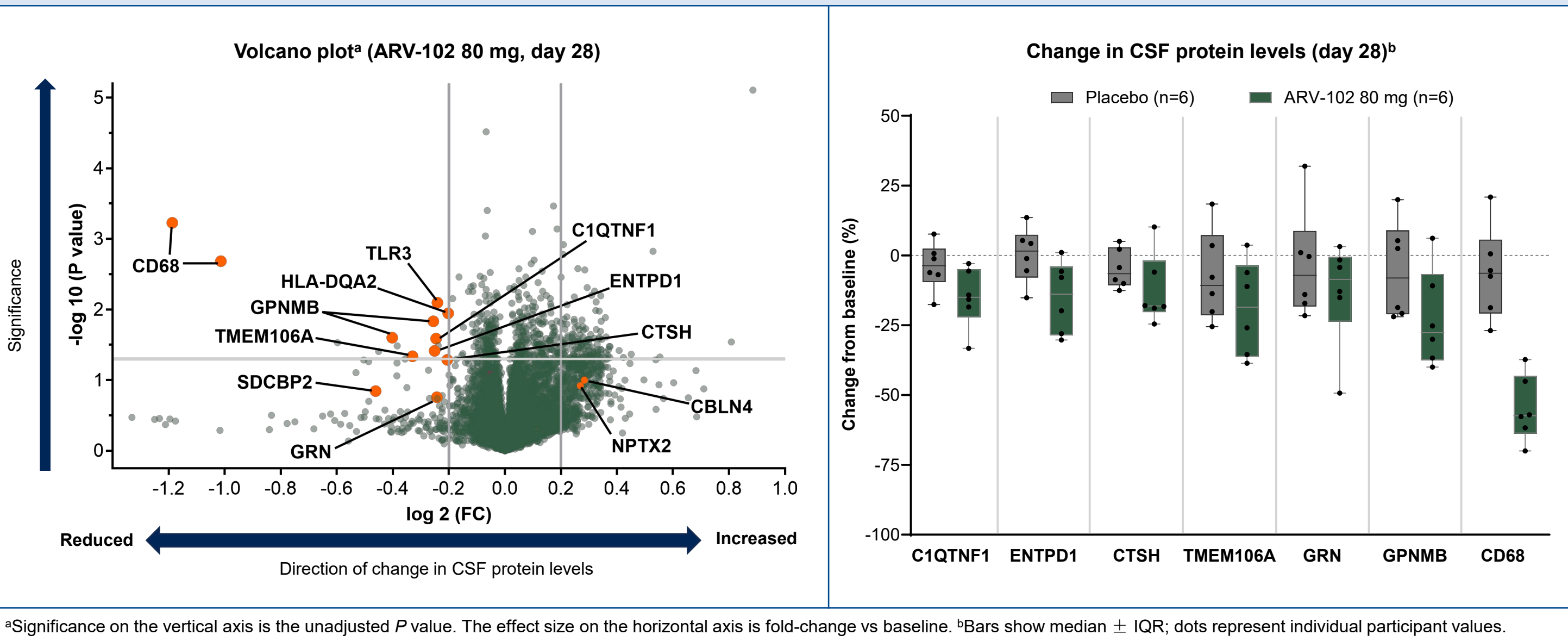
Figure 3: Multiple-dose portion of phase 1 study in participants with Parkinson’s disease (EudraCT 2024-516888-84-00)



CSF Proteomics

- ARV-102 treatment (80 mg QD for 28 days) was associated with decreases from baseline in CSF biomarkers of endolysosomal function and neuroinflammation (eg, CD68, GPNMB) and increases in markers of synaptic integrity and axonal guidance (NPTX2, CBLN4; **Figure 6**)^{7,8}

Figure 6: CSF proteomics in the 80-mg QD ARV-102 group^{7,8}



Correlations between changes in CSF LRRK2, oculomotor function, and CSF biomarkers

- Exploratory correlation analyses indicated that the magnitude of reductions in CSF LRRK2 protein levels with ARV-102 (**Figure 2**; all dose groups combined) from baseline to day 28 correlated with the magnitude of changes in ASH (*r* = -0.58) and pathway biomarkers of endolysosomal, neuroinflammatory, and synaptic function in the CSF (**Figure 7**)

Figure 7: Correlations between reduction in CSF LRRK2, oculomotor function and CSF biomarkers

