

# First Clinical Trials of ARV-102, a PROTAC LRRK2 Degradar: Characterization of Pathway Engagement in Healthy Volunteers and Patients With Parkinson's Disease

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## Objectives

- To assess downstream effects of leucine-rich repeat kinase 2 (LRRK2) degradation by ARV-102, a potent PROteolysis TArgeting Chimera (PROTAC), in healthy volunteers
- To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics of single doses of ARV-102 in an ongoing phase 1 study in patients with Parkinson's disease

## Key Findings

- Proteomic analyses of cerebrospinal fluid (CSF) from healthy volunteers treated with ARV-102 80 mg daily for 14 days showed significant reductions from baseline in lysosomal pathway markers (cathepsin H [CTSH], GPNMB, and granulin [GRN]) and microglial markers (C1QTNF1, ENTPD1, TMEM106A and CD68) known to be associated with LRRK2 Parkinson's disease
- Levels of CD68 in CSF decreased in a dose-dependent manner, consistent with observed reductions in CSF LRRK2 concentrations
- In a phase 1 study in 19 patients with Parkinson's disease, single doses of ARV-102 50 mg or 200 mg were well tolerated; treatment-related adverse events (TRAEs) of headache, diarrhea, and nausea were mild; no serious AEs occurred
- ARV-102 exposure metrics (area under the concentration-time curve [AUC] and maximum plasma concentration [ $C_{max}$ ]) increased in a dose-dependent manner in plasma and in CSF, indicating brain penetration
- Median LRRK2 protein levels in peripheral blood mononuclear cells (PBMCs) decreased by 86% from baseline with the 50-mg dose and by 97% with the 200-mg dose

## Conclusions

- In healthy volunteers, ARV-102 decreased CSF levels of lysosomal pathway and microglial markers that are known to be elevated in patients with Parkinson's disease with LRRK2 variants
- ARV-102 demonstrated consistent safety and PK in patients with Parkinson's disease and healthy volunteers, with dose-dependent peripheral LRRK2 degradation
- Evaluation of multiple doses of ARV-102 in patients with Parkinson's disease, including assessment of LRRK2 and downstream pathway engagement, is ongoing

## References

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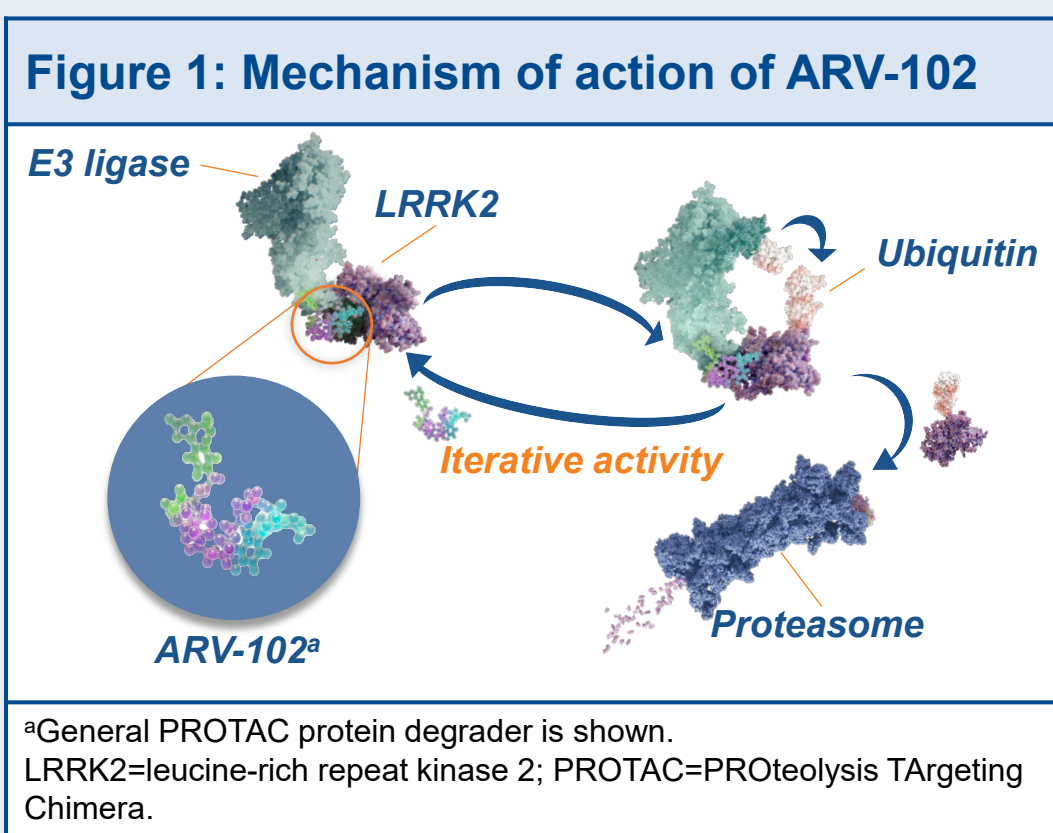
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## Background

- LRRK2 is a broadly expressed multidomain enzyme that plays a role in diverse cellular processes, including endolysosomal pathway regulation and autophagy<sup>1,2</sup>
- LRRK2 modulates clinical features of Parkinson's disease, and mutations are a cause of late-onset disease<sup>3–8</sup>
- ARV-102 is an oral, brain-penetrant PROTAC LRRK2 degrader that harnesses the ubiquitin-proteasome system to induce degradation of LRRK2 (**Figure 1**)
  - ARV-102 is a bifunctional molecule with LRRK2- and E3 ubiquitin ligase-binding regions that form a trimer complex to induce ubiquitination and subsequent degradation of LRRK2 by the proteasome
- Preclinical studies showed that ARV-102 induces stronger engagement of LRRK2 and its downstream pathways in the brain, greater activation of the endolysosomal pathways, and increased tau reduction compared with a LRRK2 kinase inhibitor<sup>9</sup>
- In non-human primates, oral ARV-102 reduced LRRK2 levels in CSF and “deep-brain” regions and induced reductions in LRRK2 pathway biomarkers, including the microglial marker ionized calcium binding adaptor molecule 1 and the lysosomal markers cathepsin B and bis(monoacylglycerol)phosphate in CSF<sup>9</sup>



- In a phase 1, single- and multiple-ascending dose study in healthy volunteers, oral ARV-102 was well tolerated, demonstrated central nervous system penetration with a PK profile supportive of once-daily dosing, and achieved peripheral and central LRRK2 degradation and downstream pathway engagement (see poster 904)<sup>10</sup>

## Methods

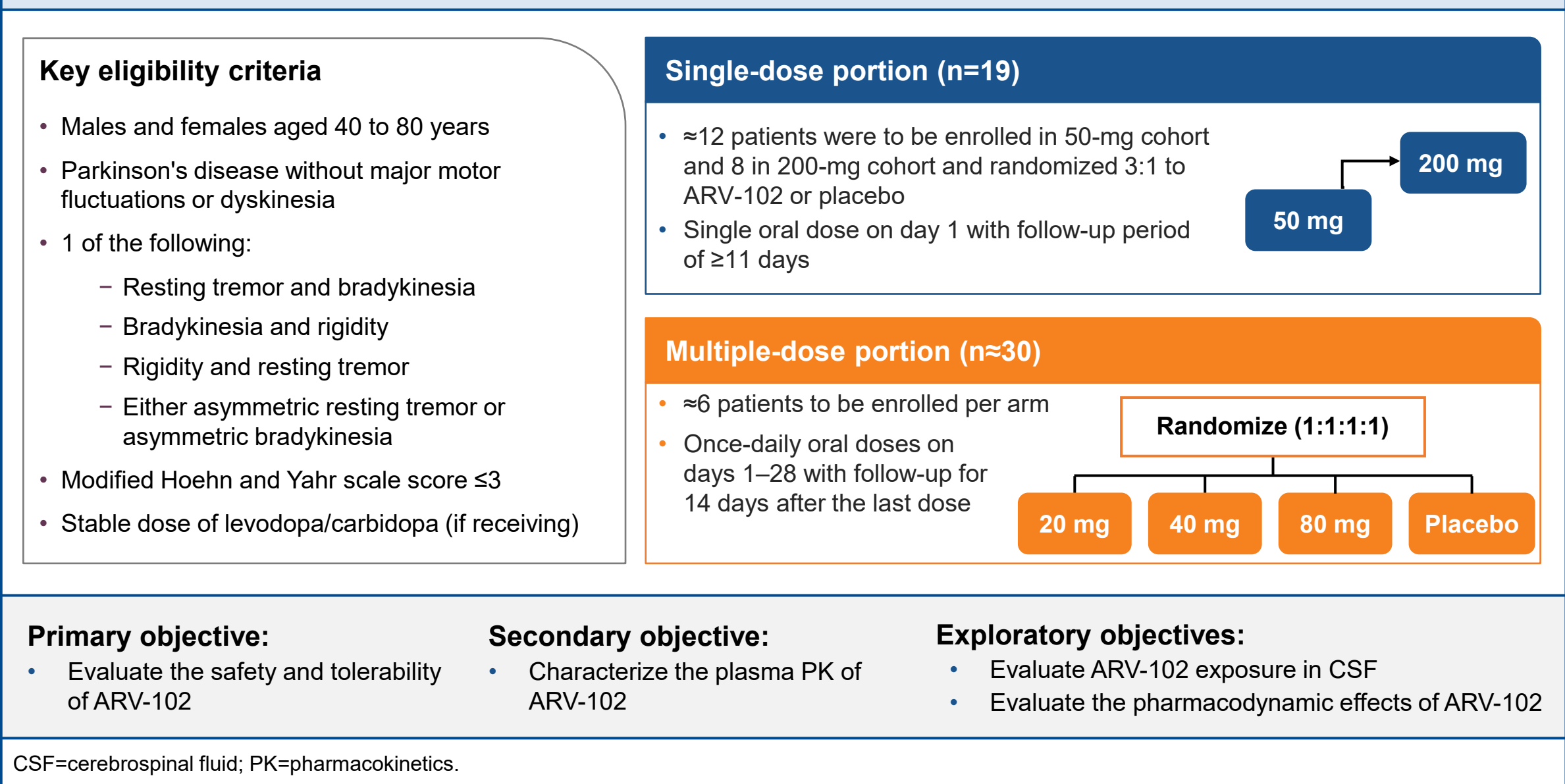
### Proteomic analyses of CSF from healthy volunteers

- To assess ARV-102-induced changes in LRRK2-associated proteins, unbiased proteomic analyses utilizing the SomaScan platform were conducted on CSF samples from participants who received ARV-102 or placebo once daily (QD) for 14 days in the phase 1 healthy volunteer study

### Phase 1 study in patients with Parkinson's disease

- A single-center, double-blind, randomized, phase 1 study is evaluating ARV-102 in patients with Parkinson's disease (**Figure 2**)
- Results of the single-dose portion of the study as of September 9, 2025 are reported here

**Figure 2: Phase 1 study in patients with Parkinson's disease (EUCT 2024-516888-84-00)**

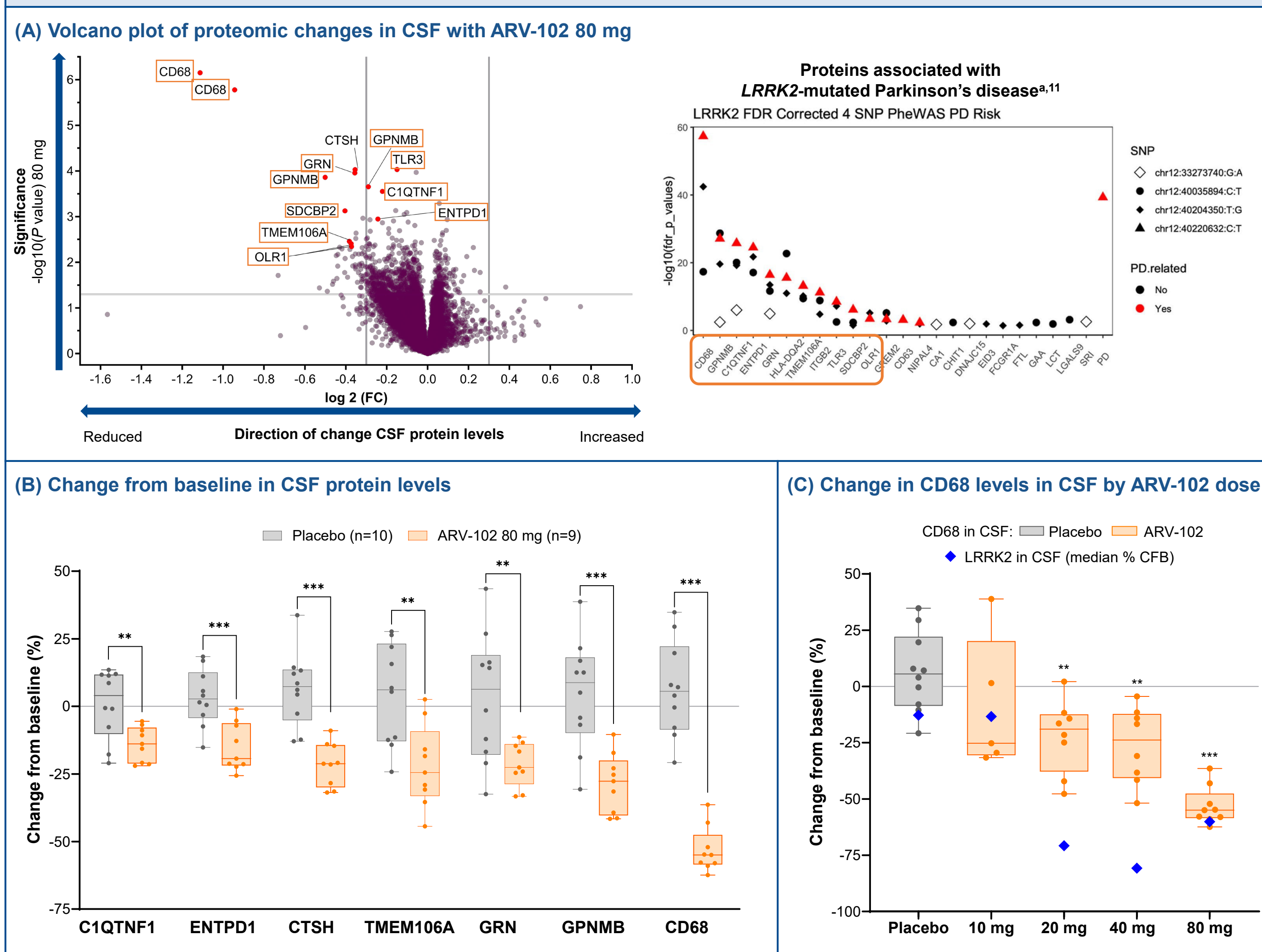


## Results

### HEALTHY VOLUNTEERS: CSF proteomics

- ARV-102 80 mg QD for 14 days significantly decreased CSF levels of lysosomal pathway markers (median % change from baseline: CTSH, -21.2%; GPNMB, -27.7%; GRN, -22.6%) and microglial markers (C1QTNF1, -13.9%; ENTPD1, -19.3%; TMEM106A, -24.5%; CD68, -55.0%; **Figure 3A-B**), which are elevated in patients with Parkinson's disease harboring LRRK2 variants<sup>11</sup>
- CD68 levels in CSF decreased in a dose-dependent manner, consistent with observed reductions in CSF LRRK2 concentrations (**Figure 3C**)

**Figure 3: CSF proteomics in healthy volunteers**



## PATIENTS WITH PARKINSON'S DISEASE: Phase 1 study (single-dose portion)

### Baseline characteristics

- 19 patients with Parkinson's disease received a single dose of ARV-102 50 mg (n=9) or 200 mg (n=6) or placebo (n=4; **Table 1**)

| Table 1: Demographics and baseline characteristics |                     |                      |                  |
|--|---------------------|----------------------|------------------|
| Characteristic                                     | ARV-102 50 mg (n=9) | ARV-102 200 mg (n=6) | Placebo (n=4)    |
| Age, years, median (range)                         | 67 (50–79)          | 67 (59–79)           | 62 (55–70)       |
| Sex, n (%)   |                     |                      |                  |
| Male   | 7 (78)              | 5 (83)               | 3 (75)           |
| Female   | 2 (22)              | 1 (17)               | 1 (25)           |
| Race, n (%)  |                     |                      |                  |
| White  | 9 (100)             | 6 (100)              | 4 (100)          |
| Body weight, kg, median (range)                    | 84.4 (73.2–100.1)   | 79.6 (61.6–98.7)     | 74.6 (68.2–86.3) |
| BMI, kg/m <sup>2</sup> , median (range)            | 26.8 (21.1–30.9)    | 25.0 (22.9–28.3)     | 24.7 (23.1–27.3) |
| Hoehn and Yahr score, mean (range)                 | 1.7 (1–3)           | 1.7 (1–3)            | 2.3 (1–3)        |
| MMSE score, mean (range)                           | 29.2 (27–30)        | 28.7 (27–30)         | 28.0 (26–30)     |

Note: Data are preliminary and were calculated manually. BMI=body mass index; MMSE=Mini Mental State Examination.

### Safety and tolerability

- Single doses of ARV-102 were well tolerated at both dose levels (**Table 2**)
- All TRAEs were mild; no serious adverse events occurred

| Table 2: TEAEs and TRAEs                   |             |              |              |         |
|--|-------------|--------------|--------------|---------|
| AE, n (%)                                  | ARV-102     |              |              | Placebo |
|  | 50 mg (n=9) | 200 mg (n=6) | Total (n=15) | (n=4)   |
| <b>TEAEs<sup>a</sup></b>                   |             |              |              |         |
| Headache                                   | 1 (11)      | 1 (17)       | 2 (13)       | 0       |
| Post-lumbar puncture syndrome <sup>b</sup> | 1 (11)      | 1 (17)       | 2 (13)       | 2 (50)  |
| Catheter site bruise                       | 1 (11)      | 1 (17)       | 2 (13)       | 0       |
| Puncture site pain                         | 1 (11)      | 0            | 1 (7)        | 1 (25)  |
| <b>TRAEs</b>                               |             |              |              |         |
| Headache                                   | 1 (11)      | 1 (17)       | 2 (13)       | 0       |
| Nausea                                     | 1 (11)      | 0            | 1 (7)        | 0       |
| Diarrhea                                   | 1 (11)      | 0            | 1 (7)        | 0       |

Note: Data are preliminary and were tabulated manually.

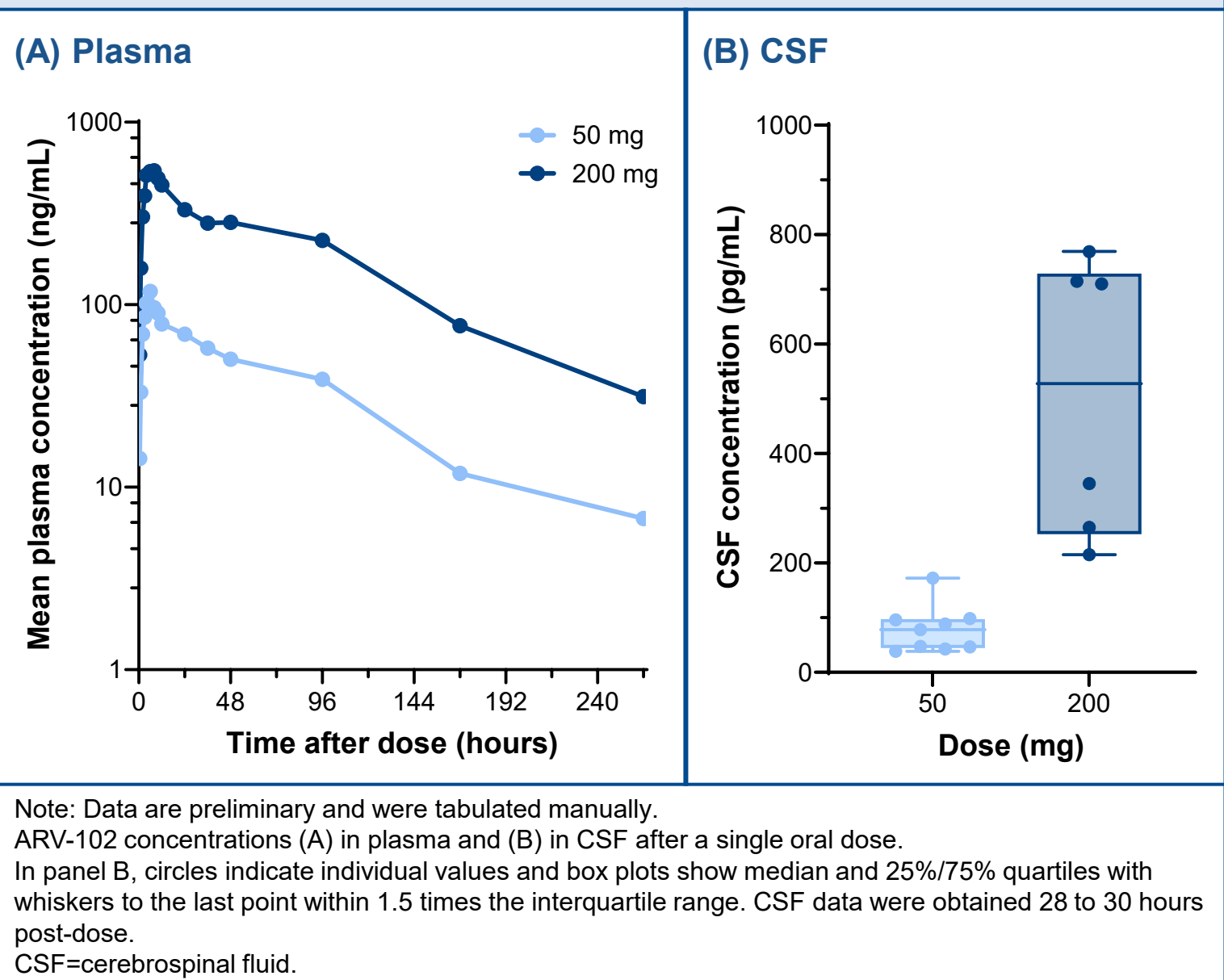
<sup>a</sup>Events reported by  $\geq 2$  patients who received a single dose of ARV-102. <sup>b</sup>All patients underwent lumbar puncture for CSF collection. All headaches related to lumbar puncture were recorded as post-lumbar puncture syndrome.

CSF=cerebrospinal fluid; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.

### PK in plasma and CSF

- ARV-102 exposure ( $AUC_{inf}$  and  $C_{max}$ ) increased in a dose-dependent manner in plasma and in CSF (**Figure 4**)

**Figure 4: ARV-102 exposure in plasma and CSF**



### LRRK2 in PBMCs

- Median LRRK2 protein levels in PBMCs decreased by 86% from baseline following a single 50-mg dose of ARV-102 and by 97% after a 200-mg dose (**Figure 5**)

**Figure 5: Change from baseline in LRRK2 levels in PBMCs**

