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First-in-Human Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Ascending Doses of ARV-102, a PROTAC LRRK2 Degrader, in Healthy Participants

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Objective

- To evaluate the safety, pharmacokinetics (PK), and pharmacodynamics of ARV-102, a PROteolysis TArgeting Chimera (PROTAC) leucine-rich repeat kinase 2 (LRRK2) degrader in a phase 1, single and multiple ascending dose (SAD/MAD) study in healthy volunteers

Key Findings

- Single doses (10–200 mg) and multiple doses (10–80 mg once daily for 14 days) of ARV-102 were well tolerated in healthy volunteers, with mostly mild treatment-emergent adverse events (TEAEs) and no serious adverse events (AEs); all treatment-related AEs (TRAEs) were mild
- ARV-102 exposure metrics (area under the concentration-time curve [AUC] and maximum plasma concentration [C_{max}]) increased in a dose-dependent manner
- In cerebrospinal fluid (CSF), ARV-102 exposure increased in a dose-dependent manner, indicating brain penetration
- LRRK2 protein levels decreased from baseline in a dose-dependent manner in peripheral blood mononuclear cells (PBMCs) and CSF, indicating that ARV-102 induces LRRK2 degradation in the periphery and central nervous system (CNS)
- ARV-102 decreased phospho-Rab10^{T73} levels in PBMCs and bis(monoacylglycerol)phosphate (BMP) levels in urine, indicating modulation of lysosomal pathways downstream of LRRK2

Conclusions

- Single and multiple doses of oral ARV-102 were well tolerated in healthy participants
- The PK profile supports once-daily dosing of ARV-102
- ARV-102 demonstrated CNS penetration and achieved substantial peripheral and central LRRK2 degradation and pathway engagement in healthy participants
- A phase 1 study (EUCT 2024-516888-84-00) of ARV-102 in patients with Parkinson's disease is ongoing

References

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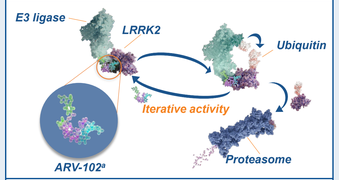
Background

- LRRK2 is a broadly expressed enzyme that plays a role in diverse cellular processes[1,2] and has been linked to neurodegeneration and pathogenesis of Parkinson's disease[3]
- LRRK2 mutations are one of the most common genetic causes of Parkinson's disease,[3] and common LRRK2 variants have been linked with idiopathic Parkinson's disease and progressive supranuclear palsy in genome-wide association studies[4–8]
- 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 consisting of a LRRK2-binding region joined by a linker to an E3 ubiquitin ligase–binding region; formation of this trimer complex induces ubiquitination and subsequent degradation of LRRK2 by the proteasome

Figure 1: Mechanism of action of ARV-102



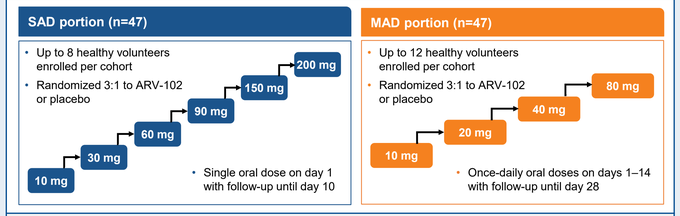
[a]General PROTAC protein degrader is shown.
LRRK2=leucine-rich repeat kinase 2; PROTAC=PROteolysis TArgeting Chimera.

- In preclinical studies comparing ARV-102 with a LRRK2 kinase inhibitor, ARV-102 showed stronger engagement of LRRK2 and its downstream pathways in the brain, greater activation of the endolysosomal pathway, and less type 2 pneumocyte enlargement and surfactant C production in primate lung[9]; collagen deposition was observed with LRRK2 inhibitor treatment, but not with LRRK2 degrader treatment in nonhuman primates (NHPs)
- In NHPs, 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 marker cathepsin B in CSF, and the lysosomal marker BMP in urine and CSF[9]

Methods

- This was a single-center, randomized, double-blind, placebo-controlled phase 1 SAD/MAD study in healthy male volunteers aged 18 to 55 years (**Figure 2**)
- ARV-102 or placebo were administered as an aqueous oral solution after a standardized breakfast
- Blood, CSF (collected via lumbar puncture), and urine were collected at prespecified times before and after dosing for evaluation of ARV-102 PK and pharmacodynamics

Figure 2: Study design



Primary objective:
- Evaluate the safety and tolerability of ARV-102

Secondary objective:
- Characterize the plasma PK of ARV-102

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

CSF=cerebrospinal fluid; MAD=multiple ascending dose; PK=pharmacokinetics; SAD=single ascending dose.

Results

Baseline characteristics

- 94 healthy adult males received ARV-102 or placebo in the SAD (n=47) or MAD (n=47) portion of the study (**Table 1**)

Safety

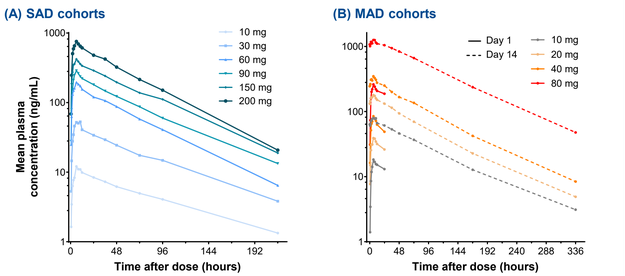
- ARV-102 was generally well tolerated at single doses ≤200 mg and multiple daily doses ≤80 mg (**Table 2**); there were no clinically meaningful or dose-related changes in vital signs, clinical laboratory values, or physical examinations
- Most TEAEs were mild, no serious TEAEs were reported, and no participants discontinued ARV-102 due to TEAEs
- All TRAEs were mild

Table 1: Demographics and baseline characteristics

Characteristic	SAD cohorts (n=47)	MAD cohorts (n=47)
Age, years, median (range)	25 (18–53)	32 (18–53)
Sex, male, n (%)	47 (100)	47 (100)
Race, n (%)		
White	41 (87)	38 (81)
Black or African American	5 (11)	1 (2)
Asian	0	4 (9)
Multiple races reported	1 (2)	4 (9)
Body weight, kg, median (range)	77.3 (55.6–103.2)	82.7 (58.9–101.5)
BMI, kg/m^2, median (range)	23.5 (18.0–31.9)	25.1 (18.5–30.7)
Baseline LRRK2 concentration in CSF, pg/mL, median (range)[a]	6.1 (2.2–19.8)	9.9 (5.0–59.6)

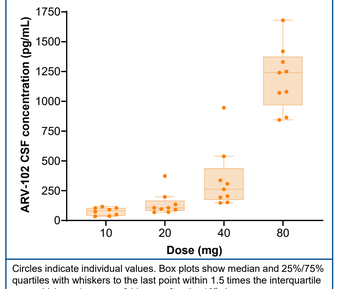
Note: Data are preliminary and were tabulated manually.
[a]Values below the LLOQ were calculated as half of the LLOQ.
BMI=body mass index; CSF=cerebrospinal fluid; LLOQ=lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; MAD=multiple ascending dose; SAD=single ascending dose.

Figure 3: ARV-102 exposure in plasma



Mean ARV-102 concentrations in plasma after (**A**) a single dose and (**B**) once-daily dosing on days 1–14.
MAD=multiple ascending dose; SAD=single ascending dose.

Figure 4: ARV-102 exposure in CSF (MAD)



Circles indicate individual values. Box plots show median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range. Values shown are 24 hours after the 13th dose.
CSF=cerebrospinal fluid; MAD=multiple ascending dose.

Please scan the QR code to view data for CSF PK and ARV-102 pharmacodynamics in the periphery and CSF from the SAD portion of this study (presented at AD/PD 2025)[10]

Table 2: TEAEs and TRAEs

AE, n (%)	SAD cohorts ARV-102 dose, mg 10 (n=6)	30 (n=6)	60 (n=6)	90 (n=6)	150 (n=6)	200 (n=5)	Total (n=35)	Placebo (n=12)	MAD cohorts ARV-102 dose, mg 10 (n=8)	20 (n=9)	40 (n=9)	80 (n=9)	Total (n=35)	Placebo (n=12)
TEAEs[a]														
Procedural pain	1 (17)	2 (33)	2 (33)	2 (33)	1 (17)	2 (40)	10 (29)	5 (42)	2 (25)	2 (22)	0	2 (22)	6 (17)	3 (25)
Post lumbar-puncture syndrome[b]	1 (17)	1 (17)	1 (17)	1 (17)	1 (17)	1 (20)	6 (17)	0	1 (13)	1 (11)	1 (11)	1 (11)	4 (11)	1 (8)
Headache	0	2 (33)	1 (17)	1 (17)	0	2 (40)	6 (17)	0	3 (38)	7 (78)	3 (33)	4 (44)	17 (49)	4 (33)
Fatigue	0	2 (33)	1 (17)	0	0	0	3 (9)	3 (25)	1 (13)	2 (22)	0	0	3 (9)	0
Lung diffusion test abnormal[c]	0	0	0	0	0	0	0	0	1 (13)	1 (11)	1 (11)	0	3 (9)	0
Nasopharyngitis	0	0	0	0	0	0	0	0	0	1 (11)	1 (11)	1 (11)	3 (9)	2 (17)
Rash	0	0	0	0	0	0	0	0	0	1 (11)	2 (22)	0	3 (9)	1 (8)
TRAE[a]														
Headache	0	2 (33)	1 (17)	1 (17)	0	2 (40)	6 (17)	0	3 (38)	5 (56)	2 (22)	4 (44)	14 (40)	4 (33)
Fatigue	0	2 (33)	1 (17)	0	0	0	3 (9)	3 (25)	1 (13)	2 (22)	0	0	3 (9)	0
Lung diffusion test abnormal[c]	0	0	0	0	0	0	0	0	1 (13)	1 (11)	1 (11)	0	3 (9)	0

Note: Data are preliminary and were tabulated manually.
[a]Reported by >2 participants who received ARV-102 in the SAD or the MAD parts of the study [b]All participants underwent lumbar puncture for CSF collection. All headaches related to lumbar puncture were recorded as post lumbar-puncture syndrome [c]3 participants had isolated mild decreased DLCO; none had clinical symptoms. High-resolution computed tomography showed no lung abnormalities. Patent foramen ovale was identified in 2 of the 3 participants. In all 3 participants, DLCO returned to baseline levels after the study.
AE=adverse event; CSF=cerebrospinal fluid; DLCO=diffusion capacity of the lungs for carbon monoxide; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; MAD=multiple ascending dose; SAD=single ascending dose; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.

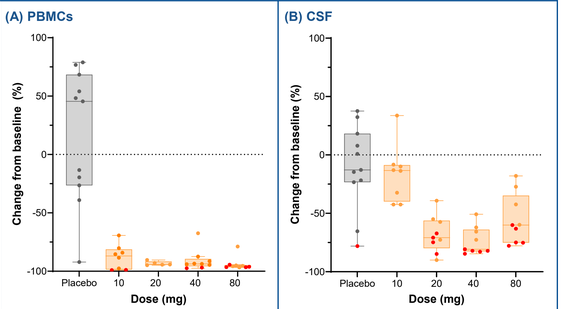
Plasma, CSF, and urine PK

- After oral administration, ARV-102 demonstrated moderate absorption with a median time to C_{max} of 6 hours and exposure metrics (AUC and C_{max}) increasing in a dose-dependent manner (**Figure 3**)
- Steady state was reached after ~10–12 days of once-daily dosing with a mean accumulation ratio of 5.7 for AUC_{tau} and 4.9 for C_{max}, followed by a mean terminal elimination half-life ranging from 64.8 to 71.5 hours
- In CSF, ARV-102 concentrations increased in a dose-dependent manner after multiple doses (**Figure 4**), supporting blood-brain barrier penetration
- Urine analysis from the SAD 90-mg cohort indicated minimal renal excretion of total ARV-102 (0.04%)

ARV-102 pharmacodynamics in the periphery and CSF (MAD portion)

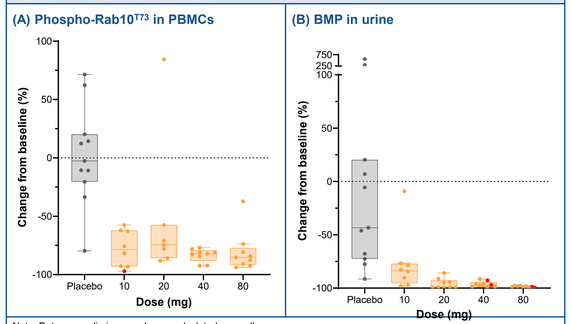
- ARV-102 induced dose-dependent reductions in peripheral and central LRRK2 protein levels, with >90% reductions from baseline in PBMCs with repeated daily doses ≥20 mg (**Figure 5A**) and >50% in CSF with repeated daily doses ≥20 mg (**Figure 5B**)
  - Many participants had post-baseline LRRK2 levels below the lower limit of quantification in PBMCs (80 mg: 4/9 participants) and CSF (80 mg: 5/9 participants), indicating that there is a floor effect in measuring the effects of ARV-102 on LRRK2 in healthy volunteers
- Median concentrations of peripheral phospho-Rab10^{T73}, a downstream marker of LRRK2 pathway engagement, were >70% lower than baseline after repeated daily doses of ARV-102 ≥10 mg (**Figure 6A**)
- ARV-102 decreased median urine concentrations of BMP, a sensitive biomarker for modulation of the lysosomal pathway downstream of LRRK2, by >90% from baseline after multiple daily doses ≥20 mg (**Figure 6B**)

Figure 5: Changes in LRRK2 protein levels in PBMCs and CSF (MAD)



Note: Data are preliminary and were calculated manually.
Changes from baseline in LRRK2 protein levels (**A**) in PBMCs 6 hours after the 14th dose and (**B**) in CSF 6 hours after the 13th or 14th dose. Circles indicate individual values. Box plots show median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range. Values below the LLOQ (shown in red) were calculated as half of the LLOQ. 4 participants (placebo, n=1; 20 mg, n=3) with baseline PBMC LRRK2 levels below the LLOQ were excluded from panel A. In panel B, 1 participant in the placebo group was excluded due to lack of baseline data.
CSF=cerebrospinal fluid; LLOQ=lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; PBMCs=peripheral blood mononuclear cells.

Figure 6: Peripheral changes in LRRK2 pathway biomarkers (MAD)



Note: Data are preliminary and were calculated manually.
Changes from baseline in (**A**) phospho-Rab10^{T73} levels in PBMCs 6 hours after the 14th dose and (**B**) BMP levels in urine obtained between 6 and 8 hours after the 14th dose of ARV-102 or placebo. Circles indicate individual values. Box plots show median and 25%/75% quartiles with whiskers to the last point within 1.5 times the interquartile range. Values below the LLOQ (shown in red) were calculated as half of the LLOQ. In panel A, 3 participants (20 mg, n=2; placebo, n=1) were excluded due to lack of baseline data.
BMP=bis(monoacylglycerol)phosphate; LLOQ= lower limit of quantification; LRRK2=leucine-rich repeat kinase 2; MAD=multiple ascending dose; PBMCs=peripheral blood mononuclear cells.