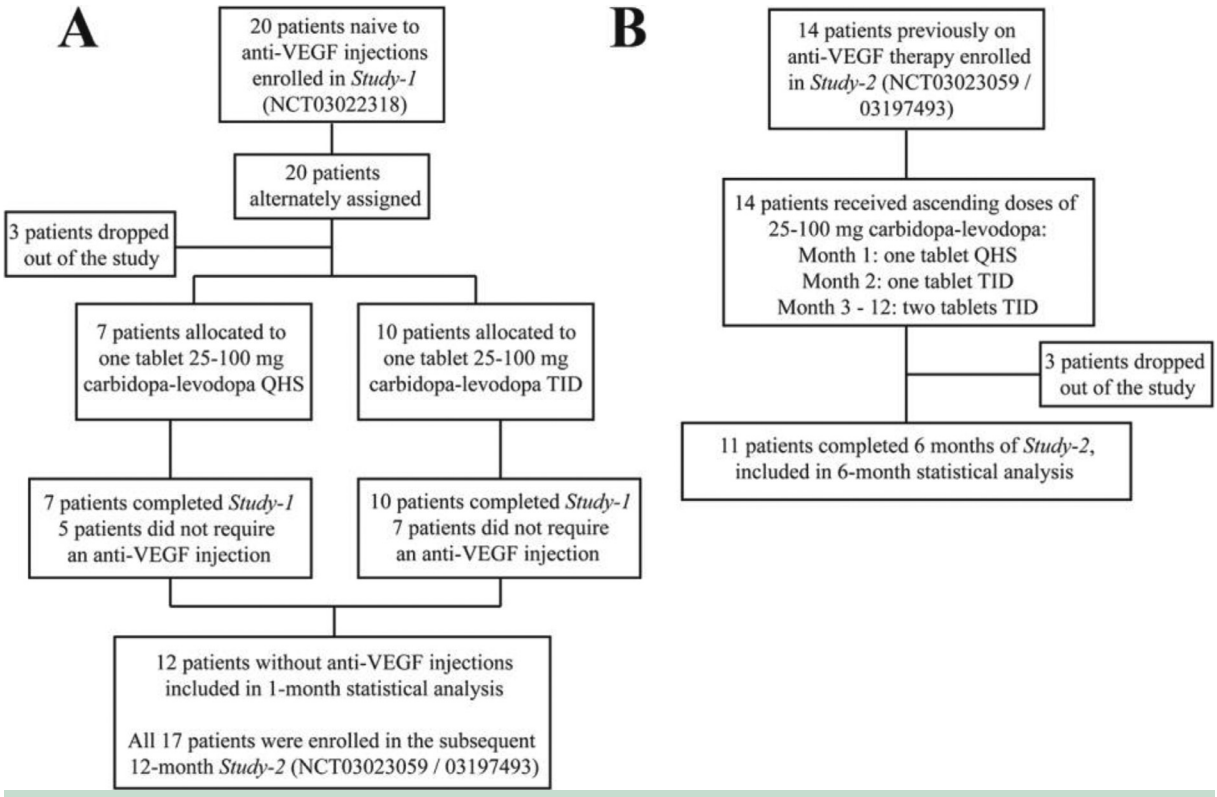

Supplementary Figure Clinical trial flowchart. These studies were proof-of-concept, Phase 2 trials that investigated the efficacy, safety, and tolerability of levodopa in patients with newly diagnosed neovascular age-related macular degeneration and naïve to anti-vascular endothelial growth factor (VEGF) therapy **(A)**. Of the 20 patients enrolled, 3 patients discontinued the trial due to personal reasons, and 5 patients required anti-VEGF injections. The patients in Cohort 1 were evaluated for 1 month (Study-1) and enrolled subsequently in Study-2. Patients with neovascular age-related macular degeneration who had been receiving anti-VEGF therapy for at least 3 months **(B)** prior to Study-2 enrollment (Cohort 2) were evaluated for the same parameters. Of the 14 patients in Cohort 2, 3 discontinued the study due to reasons unrelated to the study drug.

Supplementary Table 1 Baseline Characteristics of the Patients in Cohort 1 that Completed Study-1 and Completed 6 Months of the Subsequent Study-2

Patient Number	Sex	Age, Years	Race	AREDS Vitamins	No. of Letters as Measure of BCVA	Required anti-VEGF injection by Month-1
002-4 (001-1)	Female	78	White	X	54	
002-6 (001-2)	Male	79	White		51	
002-7 (001-3)	Female	63	White	X	48	
002-8 (001-4)*	Male	79	White		54	
002-12 (001-5)†	Female	87	White	X	38	
002-14 (001-6)	Male	80	White	X	56	
002-16 (001-7)	Female	73	White		24	X
002-17 (001-8)	Female	75	White	X	53	
002-18 (001-10)	Female	71	White	X	42	X
002-19 (001-11)	Male	58	White		54	
002-20 (001-12)	Male	81	White		41	
002-21 (001-13)	Male	77	White	X	7	
002-23 (001-14)	Male	73	White	X	43	X
002-27 (001-16)	Female	73	White		36	
002-28 (001-18)	Female	78	White		29	
002-30 (001-19)‡	Female	83	White		43	X
002-31 (001-20)	Male	75	White		39	X

AREDS = Age-related Eye Disease Study; BCVA = best-corrected visual acuity, measured with the use of the Early Treatment Diabetic Retinopathy Study protocol at 7 m; a score of 40 letters is a Snellen equivalent of 20/40; VEGF = vascular endothelial growth factor.

Race was determined by the investigators. Two patients were excluded from statistical analysis

*due to missing follow-up visits (month 4-9) or ‡due to intraocular lens displacement in the study eye. While the age for enrollment in these studies was 50-85 years; †1 patient was enrolled at the age of 87.The mean baseline age of Cohort 1 (75 years) was consistent with the general population's expected age of onset. X denotes patients taking these supplements.

Supplementary Table 2 Baseline Characteristics of the Patients in Cohort 2.

Patient Number	Sex	Age, Years	Race	AREDS Vitamins	No. of Letters as Measure of BCVA	Anti-VEGF injections/month Prior to Study-2
002-1	Female	67	White		34	0.86
002-3	Male	67	White		45	0.69
002-5	Female	77	White	X	47	0.98
002-9	Male	82	White	X	23	0.83
002-10	Female	74	White		29	1.1
002-11	Male	77	White		20	0.58
002-13	Female	68	White	X	37	1.0
002-22	Female	70	White		34	0.95
002-24	Male	83	White	X	44	1.1
002-25	Female	85	White	X	33	0.87
002-29	Female	74	White		51	0.59

AREDS = Age-Related Eye Disease Study; an X denotes patients taking these supplements; BCVA = best-corrected visual acuity, measured with the use of the Early Treatment Diabetic Retinopathy Study protocol at 7 m; a score of 40 letters is a Snellen equivalent of 20/40; VEGF = vascular endothelial growth factor.

Race was determined by the investigators. Rate of anti-VEGF injections prior to *Study-2* enrollment was determined based on the patient's previous intravitreal injection frequency. The mean baseline age of Cohort 2 (75 years) was consistent with the general population's expected age of onset.

Supplementary Table 3 Inclusion and Exclusion Criteria for Both Study-1 and Study-2

Eligibility Criteria
Inclusion criteria
50-85 years of age
Willingness and ability to provide informed consent
Clinical diagnosis of AMD with choroidal neovascularization in one eye
Healthy or dry AMD of any grade in the fellow eye
Maintain AREDS vitamin supplements or
Remain off AREDS vitamin supplements if not taking them prior
Exclusion criteria
Use of other levodopa containing medication
Use of dopamine receptor agonist medication
Concurrent use of monoamine oxidase inhibitors
Any other eye condition, disease, or history of trauma, which can impair vision (except cataract or cataract surgery)
Best-corrected visual acuity worse than 20/60
Neovascular AMD in the fellow eye
Neurologic conditions which can impair vision
Parkinson's disease
Orthostatic hypertension or significant ECG abnormalities
Estimated glomerular filtration rate >20 mL/min
Liver enzymes >3× upper limit of normal
Hemoglobin A1C >9.0
Additional significant lab abnormalities
Women of childbearing potential
Known retinal hemorrhage
Not fluent in English

AMD = Age-related Macular Degeneration; AREDS = Age-Related Eye Disease Study; ECG = electrocardiogram

The age for enrollment in these studies was 50-85 years, one patient was enrolled at the age of 87. This participant had been recently diagnosed with neovascular AMD and was naïve to anti-vascular endothelial growth factor injections, which were scarce; due to these reasons we

Supplementary Table 4 Adverse Events in Study-1 and Study-2

Total Adverse Events at 6 Months	n
Ocular SAEs caused by the study drug	0
Ocular SAEs not caused by the study drug	
Intraocular lens displacement	1
Systemic SAEs (nonocular) caused by the study drug	0
Systemic SAEs (nonocular) not caused by the study drug	
Pelvic fracture	1
Partial knee replacement	1
Ovarian cancer recurrence	1
Ocular AEs	
Blurred vision	1
Systemic AEs (nonocular)	
Increased atrial fibrillation	1
Nausea	2
Abdominal pain	1
Chest pain due to torn chest muscle*	1
Gas	1
Back spasms	1
Restless legs	2
Urinary tract infection	2
Pneumonia	1
Sinus infection	1

AE = adverse event; SAE = serious adverse event.

*One patient withdrew from the study due to the reported adverse event If a patient had significant symptoms consistent with side effects associated with levodopa, the dose was reduced to 1 tablet 3 times a day (TID). Of the 28 patients on a regimen of 2 tablets TID, 5 patients tolerated only 1 tablet TID and 1 patient only tolerated 1 tablet at bedtime for the remainder of the study. All drug-related adverse events improved with dose reduction.

All data are n.