Study 003: Extension of Study 002, carbidopa-levodopa in neovascular AMD

Study Design: Prospective, open-label, fixed dose

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Protocol Version 1

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Overview of extension study: If a patient completes Study 002 without significant problems, and wishes to continue carbidopa-levodopa therapy, he or she may be enrolled in protocol 003, a 9-month extension. Visits will occur monthly and will have the same monitoring at each visit as in protocol 002. Anti-VEGF injections will be administered according to the standard of care, as in protocol 002, with the same criteria for injections. Measurements and procedures at each visit will be the same as in protocol 002. This will allow evaluation of the safety of carbidopa-levodopa over an entire year of treatment.

Objectives:

1. To determine whether L-DOPA-carbidopa supplementation can improve visual function, within 12 months, in patients with choroidal neovascular AMD (nAMD), by testing best-corrected visual acuity (BCVA).
2. To determine whether L-DOPA-carbidopa supplementation in daily doses, approximating those used in Parkinson's disease, is well tolerated for 12 months in our target group of patients with nAMD in one eye.
3. To determine whether L-DOPA-carbidopa supplementation can improve the anatomic findings on optical coherence tomography (OCT), within a total of 12 months, in the eye of patients with nAMD.
4. To determine whether L-DOPA-carbidopa supplementation can improve the anatomic findings on OCT, within 12 months, in the eye without nAMD.
5. To evaluate the effect of carbidopa-levodopa on anti-VEGF injections.

Inclusion Criteria:

- Completion of Protocol 002: Dose ranging study of carbidopa-levodopa.
- A diagnosis of AMD with choroidal neovascularization (CNV) in one eye.
- Normal or Dry AMD of any grade in the fellow eye.
- Age 50-85 years.
- Willingness to maintain AREDS vitamin Supplements throughout the study or remain off these supplements for the duration of the study, if not taking them prior to the study.
- Written informed consent at visit 1.

Exclusion criteria:

- Any current use of L-DOPA containing medication or dopamine agonist medication, or any planned use of any of these agents, except for study medication, during the study.
- Concurrent use of monoamine oxidase (MAO) inhibitors.
- Any eye condition, disease, or history of trauma in either eye, which can impair vision, except cataract or cataract surgery.
- BCVA worse than 20/60 in the better eye.
- nAMD in the fellow eye.
- Neurologic conditions which can impair vision.
- Parkinson's disease.
- Significant orthostatic hypotension, defined as a drop in systolic blood pressure, immediately upon changing from the supine to standing position, of >19 mmHg, or a symptomatic drop in systolic blood pressure, immediately upon changing from the supine to standing position.
- Significant ECG abnormalities, as judged by the Investigator.
- Estimated glomerular filtration rate (eGFR) < 20 ml/min.
- Liver enzymes >3 X the upper limit of normal.
- $HbA_1C > 9.0$.
- Any other significant lab abnormalities, as judged by the Investigator.
- Women of childbearing potential.
- Known retinal hemorrhage.
- Subjects who are not fluent in English.

Treatments:

Patients will receive open label carbidopa-levodopa 25-100 mg one tablet TID, in the morning, with supper and at bedtime for 9 months, or two tablets TID, in the morning, with supper and at bedtime for 9 months (300-600 mg of levodopa daily). This is the regimen the patient was taking at the end of protocol 002. If the patient was able to complete protocol 002 without a serious adverse event, but had bothersome symptoms in protocol 002, he or she will receive the intermediate dose (carbidopa-levodopa 25-100, 1 tablet TID) in the extension. Each patient will be evaluated at monthly (25-35 day) intervals and in conjunction be evaluated by the referring Retina Specialist who will assess whether the patient requires an anti-VEGF injection, based on clinical practice standard of care.

What are the risks of taking carbidopa-levodopa?

- Body as a whole: chest pain, feeling weak and fatigued.
- Cardiovascular: irregular heartbeat, low blood pressure, low blood pressure immediately upon standing, high blood pressure, fainting, vein inflammation and palpitations.
- Gastrointestinal: dark saliva, ulcers, loss of appetite, nausea, vomiting, diarrhea, constipation, heartburn, dry mouth, altered taste and gastrointestinal bleeding.
- Hematologic: anemia, low white blood cells, low platelets.
- Hypersensitivity: skin rash, itching, face or throat swelling.
- Musculoskeletal: back pain, shoulder pain, muscle pain.
- Nervous system/Psychiatric: delusions, hallucinations, confusion, agitation, dizziness,
- sleepiness, abnormal dreams, insomnia, abnormal sensations, headache, depression, abnormal movements, mental difficulties, urge to gamble, increased sexual desire, problems with impulse control.
- Respiratory: shortness of breath, upper respiratory infection.

- Skin: Rash, increased sweating, hair loss, dark sweat.
- Urogenital: urinary tract infection, urinary frequency, dark urine.

Dealing with Adverse Events:

Study Participants will be asked about any adverse events at each visit, and asked to tell the study doctor or study staff right away if they have any side effects, or if they have any other problems with their health or the way they feel during the study, regardless of whether or not they think these problems are related to the study drug. The answers will be recorded in the source documents. For minor and easily tolerated events, the participants will continue in the study, unless they request to be withdrawn from the study. For serious or poorly tolerated events, the patient will be withdrawn from the study. Appropriate medical care will be instituted for any serious adverse events.

Number of subjects: 52 completed

Duration: Up to 9 months of treatment.

Measurements and Activities:

- Written informed consent at Visit 1.
- Ophthalmic history and comprehensive eye examination; including visual acuity, with current refraction, using an EDTRS chart, in each of both eyes separately, and ophthalmoscopic examination, and SD-OCT.
- Repeat assessment of visual acuity using an EDTRS chart, ophthalmoscopic examination, and SD-OCT at monthly visits.
- Subjective Vision Questionnaire at monthly visits.
- Demographics obtained at Baseline in Study 002 or Study 001.

- Medical History, Vital Signs and Physical Examination at Baseline in Study 002 or Study 001.
- ECG, CBC, Chem 20 and HbA_1C at Baseline in Study 002 or Study 001.
- Dispense study medication at monthly visits.
- Pill count at monthly visits
- Non-directed assessment of adverse events at each visit, including classification as to severity, seriousness and body system.
- Concomitant medications at each visit.
- If a patient had the baseline evaluation in Study 001, that will be used as the baseline evaluation for this study. If the patient entered directly into Study 002, that will be used as the baseline evaluation for this study.

Criteria for repeat anti-VEGF injections:

This will be based on monthly evaluation of: BCVA (decrease of 5 letters from previous visit); increased macular thickness (compared to normal and previous visit as measured by SD-OCT; new blood (hemorrhage) on direct retinal examination; or subjective decrease in vision. If any of these criteria are met, or if, in the opinion of the Retina Specialist, the patient requires anti-VEGF therapy, the patient will have an anti-VEGF injection administered. If none of these criteria are met at monthly visits with patient agreement, an anti-VEGF injection will not be performed, and the patient will be reevaluated.

Result sharing with subjects:

After the conclusion of the study, patients will be notified of the results, regarding safety, tolerability and vision-related outcomes.

Table 1A of Study 003 Activities by Visit

	Visit 5 Extension	Visit 6	Visit 7	Visit 8	Visit 9
	25-35 Days	25-35 Days	25-35 Days	25-35 Days	25-35 Days
Informed Consent	X				
Concomitant Medications	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X
Vital Signs	X	X	X	X	X
Subjective Vision Test	X	X	X	X	X
Retinal Exam	X	X	X	X	X
BCVA (ETDRS Protocol)	X	X	X	X	X
SD-OCT Scan	X	X	X	X	X
Dispense Medication	X	X	X	X	X
Pill Count	X	X	X	X	X

Table 1B of Study 003 Activities by Visit

	Visit 10	Visit 11	Visit 12	Visit 13
	25-35 Days	25-35 Days	25-35 Days	25-35 Days
Concomitant Medications	X	X	X	X
Adverse Event Assessment	X	X	X	X
Vital Signs	X	X	X	X
Subjective Vision Test	X	X	X	X
Retinal Exam	X	X	X	X
BCVA (ETDRS Protocol)	X	X	X	X
SD-OCT Scan	X	X	X	X
Dispense Medication	X	X	X	
Pill Count	X	X	X	X