Study 002: Dose ranging study of carbidopa-levodopa

Study Design: Prospective, open-label, escalating dose

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Objectives:

1. To determine whether L-DOPA-carbidopa supplementation can improve visual function, within 30-90 days, in patients with neovascular AMD (nAMD), by evaluating best-corrected visual acuity (BCVA).
2. To determine whether L-DOPA-carbidopa supplementation can improve the anatomic findings on optical coherence tomography (OCT), within 30-90 days, in patients with nAMD.
3. To evaluate the relative benefits of carbidopa-levodopa 25-100 mg, one tablet QHS, one tablet TID, and two tablets TID.
4. To determine whether L-DOPA-carbidopa supplementation in escalating daily doses is well tolerated in our target group of patients with nAMD in one eye.
5. To evaluate the effect of carbidopa-levodopa on anti-VEGF injections.

Inclusion criteria

- A diagnosis of AMD with choroidal neovascularization (CNV) in one eye.
    - Not previously treated with anti-VEGF injections; or
    - On anti-VEGF injections for at least 3 months, and meets criteria for a repeat injection; or
    - Patients, who have completed Study 001, may enter this trial at the point of initiation of the month of treatment with the dose of carbidopa-levodopa, that they received in Study 001.
- 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 baseline.

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 fellow 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 QHS for one month, followed by one tablet TID, in the morning, with supper and at bedtime for one month, followed by two tablets TID, in the morning, with supper and at bedtime for one month (100-600 mg of levodopa daily). This is the equivalent of very low to moderate doses of carbidopa-levodopa in patients with Parkinson's disease (daily dose of levodopa 200-800 mg). Patients entering this study after completing Study 001 will receive one month of the dose that he or she received in Study 001, and one month each of any doses higher than the dose that he or she received in Study 001.

Examples:

1. If the patient received carbidopa-levodopa 25-100 mg once daily in Study 001, he or she will receive one month of treatment with each of the 3 daily doses of carbidopa-levodopa.
2. If the patient received carbidopa-levodopa 25-100 mg TID in Study 001, he or she will receive one month of carbidopa-levodopa 25-100 mg TID, followed by one month of carbidopa-levodopa 25-100 mg, 2 tablets TID.

Each patient will receive an injection of anti-VEGF medication on the day carbidopa-levodopa dosing begins in this study. 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 (SAEs).

Number of subjects: 52 completed

Recruiting: In order to enhance recruiting, ophthalmology technicians in the offices of the Retina Specialists will be asked to identify patients who meet the criteria for the study and bring them to the attention of the Retina Specialist, who will decide whether or not to refer the patient. If the patient is referred and meets the criteria for the study, the technician will be paid $25.

Duration: Up to 105 days of treatment.

Measurements and Activities:

- Written informed consent at Baseline.
- Ophthalmic history and comprehensive eye examination; including visual acuity, wearing any prescription lenses, using an EDTRS chart, in both eyes prior to randomization, and ophthalmoscopic examination, and OCT.
- Repeat assessment of visual acuity using an EDTRS chart, ophthalmoscopic examination, and OCT at monthly visits.
- Subjective Vision Questionnaire at monthly visits.
- Demographics at Baseline.
- Medical History, Vital Signs and Physical Examination at Baseline.
- ECG, CBC, Chem 20 and HbA_1C at Baseline.
- Dispense study medication at visits, 1,2 and 3.
- 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.

Criteria for repeat anti-VEGF injections:

This will be based on monthly evaluation of: BCVA (decrease of 5 letters from previous visit); increased central macular thickness (compared to normal and previous visit as measured by 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 intraocular injection. If none of these criteria are met at visits 2, 3 or 4, with patient agreement, anti-VEGF injection will not be done, and the patient will be reevaluated in 1 month.

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 of Study Activities by Visit

	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4
		25-35 Days	25-35 Days	25-35 Days
Informed Consent	X			X
Demographics	X			
Medical History	X			
Concomitant Medications	X	X	X	X
Adverse Event Assessment	X	X	X	X
Physical and Vital Signs	X			
Vital Signs		X	X	X
ECG	X			
CBC, Chem 20, HbA_1C	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	X
Pill Count		X	X	X