Neovascular Age-Related Macular Degeneration: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Wiley Chambers at 301-796-0690, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Neovascular Age-Related Macular Degeneration: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors regarding eligibility criteria, trial design considerations, and efficacy endpoints to enhance clinical trial data quality and to foster greater efficiency in development programs for drugs for the treatment of neovascular age-related macular degeneration.[2, 3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Ophthalmology in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. For biological products regulated by CBER, sponsors should contact the Office of Tissues and Advanced Therapies (OTAT).

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] Neovascular age-related macular degeneration is also known as wet age-related macular degeneration.

II. CONSIDERATIONS FOR CLINICAL TRIALS[4]

A. Trial Design

Sponsors developing drugs for the treatment of neovascular age-related macular degeneration should consider the following regarding trial design:

- FDA recommends parallel-group, randomized by patient, double-masked trials in which the investigational drug group demonstrates superiority over the control group.

- Alternatively, FDA recommends parallel-group, randomized by patient, double-masked trials in which the investigational drug group demonstrates noninferiority either to ranibizumab injection administered intravitreally every 4 weeks or to aflibercept administered intravitreally either every 4 weeks or every 8 weeks (after 3 monthly injections).

B. Comparator

Sponsors developing drugs for the treatment of neovascular age-related macular degeneration should consider the following regarding comparative clinical trials:

- Each investigational drug arm is expected to have at least one other comparative arm in which the dosing frequency, criterion for dosing adjustments, and criterion for interventions are the same.

C. Trial Population

Sponsors developing drugs for the treatment of neovascular age-related macular degeneration should consider the following regarding trial population:

- Trials should include patients older than 50 years of age from relevant demographic subsets, including both men and women and multiple racial/ethnic and eye color groups.

- Patients should have choroidal neovascularization documented by fundus photography, fluorescein angiography, or optical coherence tomography.

- For a trial designed as a superiority trial, the sponsor should enroll patients with neovascularization caused by age-related macular degeneration who have had visual loss or would be expected to develop visual loss.

[4] For clinical trials involving cellular or gene therapy products, sponsors should discuss their development programs with OTAT. For clinical trials involving gene therapy products, sponsors should also consult the guidance for industry *Human Gene Therapy for Retinal Disorders* (January 2020). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- For a trial designed as a noninferiority trial, the sponsor should enroll patients with neovascularization caused by age-related macular degeneration who have visual loss.

- Neovascular macular degeneration secondary to causes other than aging (such as presumed ocular histoplasmosis or high myopia) are considered separate indications, and sponsors should study patients with these conditions separately.

D. Efficacy Considerations

Sponsors developing drugs for the treatment of neovascular age-related macular degeneration should consider the following regarding efficacy:

- In general, safety and efficacy should be demonstrated in at least two adequate and well-controlled, multicenter trials utilizing different investigative sites.

- One eye per patient should be prespecified as the study eye for the purposes of the efficacy analysis even if both eyes are treated. Both eyes should be followed for safety.

- FDA recommends that the sponsor demonstrate one of the following:

  — A statistically significant smaller percentage of patients with a doubling of the visual angle[5] in best corrected distance visual acuity[6] at 9 months[7] or later after the start of drug administration in the investigational drug treatment group compared to the control[8] group;

  — A statistically significant larger percentage of patients with a halving of the visual angle[9] in best corrected distance visual acuity[6] at 9 months[7] or later after the start of drug administration in the investigational drug treatment group compared to the control group;

  — A statistically significant difference between groups in mean best corrected distance visual acuity[6] of 15 or more letters at 9 months[7] or later after the start of drug administration.

[5] The phrase *doubling of the visual angle* is equivalent to 15 letters or more decrease on an ETDRS visual acuity chart measured at a distance of 4 meters or longer.

[6] Best corrected distance visual acuity can be measured at 3 meters instead of 4 meters if measured using an automated threshold testing system.

[7] For cellular and gene therapy products, FDA recommends that efficacy be demonstrated at 12 months or later.

[8] Control can be the vehicle of the investigational drug or another drug.

[9] The phrase *halving of the visual angle* is equivalent to 15 letters or more improvement on an ETDRS visual acuity chart measured at a distance of 4 meters or longer.

— A two-sided, 95 percent confidence interval in which either the lower bound of the confidence interval for the difference between the investigational drug group and a ranibizumab injection group is greater than or equal to -4.5 letters or the lower bound of the two-sided, 95 percent confidence interval for the difference between the investigational drug group and an aflibercept group is greater than -4.5 letters in mean best corrected distance visual acuity[6] at 9 months[7] or later after the start of drug administration.

A decrease in the number of administrations of available effective therapies alone is not sufficient for the demonstration of efficacy.

E. Safety Considerations

Sponsors developing drugs for the treatment of neovascular age-related macular degeneration should consider the following regarding safety:

- FDA recommends that approximately 400 or more patients using the investigational drug complete treatment with a concentration of the investigational drug at least as high as proposed for marketing and with a dosing frequency at least as frequent as proposed for marketing.

- Before submission of a marketing application, the sponsor should ensure that at least 300 patients have completed at least 9 months of follow-up after the initiation of treatment.

- FDA recommends that at least one concurrently controlled safety trial be conducted for at least 2 years' duration.[10]

F. Clinical Evaluations

Sponsors developing drugs for the treatment of neovascular age-related macular degeneration should consider the following regarding clinical evaluations:

- At a minimum, FDA recommends sponsors perform the following evaluations in each eye and report separately for each eye (regardless of which eye or eyes are treated):

  — Best corrected distance visual acuity[11] at every visit.

  — Dilated seven-field fundus photographs or equivalent wide-field views at no less than 6-month intervals during the first 2 years.

[10] For clinical trials involving gene therapy products, sponsors should consult the guidance for industry *Long Term Follow-Up After Administration of Human Gene Therapy Products* (January 2020) and should discuss their development programs with OTAT.

[11] Best corrected distance visual acuity can be measured at 3 meters instead of 4 meters if measured using an automated threshold testing system.

143 — A dilated slit lamp examination of the anterior segment including the cornea,
144 conjunctiva, anterior chamber, iris, lids, and lashes. At a minimum, examinations
145 should be performed at baseline and at no less than 3-month intervals during the first
146 year and no less than every 6 months during the second year.
147
148 — Applanation tonometry at no less than 3-month intervals. If the investigational drug is
149 administered topically, dosing of the drug should be at least 30 minutes after use of
150 any anesthetic drug.
151
152 — Endothelial cell count at baseline and at the end of at least one 9-month or longer trial.
153
154 • If systemic exposure is minimal, systemic clinical and laboratory evaluations are
155 recommended at baseline and at the end of at least one 9-month or longer trial. If systemic
156 exposure is not minimal, systemic clinical and laboratory evaluations are recommended at
157 regular intervals in all clinical trials.
158
159 **G. Pediatrics**
160
161 Neovascular age-related macular degeneration rarely occurs in the pediatric population. Sponsors
162 should consider pediatric assessment waiver requests when submitting their required pediatric
163 study plans under the Pediatric Research Equity Act.[12]

[12] See section 505B(e)(1) of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 355c(e)(1)) and section 505B(a)(1)(A) of the FD&C Act (21 U.S.C. 355c(a)(1)(A)).