CLEARSIDE BIOMEDICAL

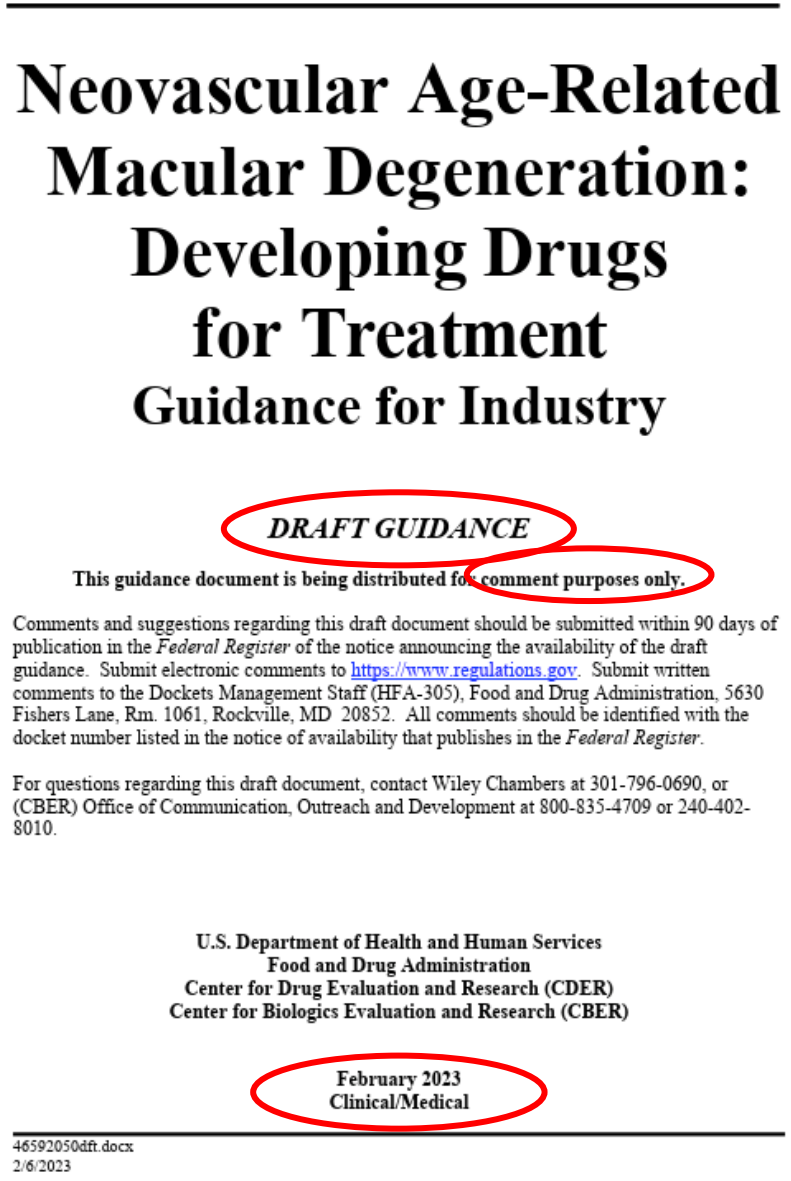
Victor Chong, MD, MBA

CMO, EVP, Head of R&D

Forward-Looking Statements

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. The words “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target” or the negative of these terms and other similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Clearside Biomedical, Inc.’s views as of the date of this presentation about future events and are subject to risks, uncertainties, assumptions, and changes in circumstances that may cause Clearside’s actual results, performance, or achievements to differ significantly from those expressed or implied in any forward-looking statement. Although Clearside believes that the expectations reflected in the forward-looking statements are reasonable, new risks and uncertainties may emerge from time to time, and Clearside cannot guarantee future events, results, performance, or achievements. Some of the key factors that could cause actual results to differ from Clearside’s expectations include its plans to develop and potentially commercialize its product candidates; adverse differences between preliminary or interim data and final data; Clearside’s planned clinical trials and preclinical studies for its product candidates; the timing of and Clearside’s ability to obtain and maintain regulatory approvals for its product candidates; the extent of clinical trials potentially required for Clearside’s product candidates; the clinical utility and market acceptance of Clearside’s product candidates; Clearside’s commercialization, marketing and manufacturing capabilities and strategy; Clearside’s intellectual property position; Clearside's ability to expand its pipeline; developments and projections relating to Clearside's competitors and its industry; the impact of government laws and regulations; the timing, design and anticipated results of Clearside's preclinical studies and clinical trials and the risk that the results of Clearside's preclinical studies and clinical trials may not be predictive of future results in connection with future studies or clinical trials and may not support further development and marketing approval; findings from investigational review boards at clinical trial sites and publication review bodies; Clearside's estimates regarding future revenue, expenses, capital requirements and need for additional financing; and Clearside’s ability to identify additional product candidates with significant commercial potential that are consistent with its commercial objectives. For further information regarding these risks, uncertainties and other factors you should read the “Risk Factors” section of Clearside’s Annual Report on Form 10-K for the year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission (SEC) on March 12, 2024, Clearside’s Quarterly Report on Form 10-Q filed with the SEC on November 12, 2024, and Clearside's subsequent filings with the SEC. Clearside expressly disclaims any obligation to update or revise the information herein, including the forward-looking statements, except as required by law. This presentation also contains estimates and other statistical data made by independent parties and by Clearside relating to market size and growth and other data about its industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of Clearside’s future performance and the future performance of the markets in which Clearside operates are necessarily subject to a high degree of uncertainty and risk.

February 2023 FDA Draft Guidance on wAMD Development



Neovascular Age-Related Macular Degeneration: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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)

February 2023
Clinical/Medical

46592050dft.docx
2/6/2023

Feb 2023
DRAFT guidance
For comment purposes only

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.

DRAFT guidance not finalized
Can use an alternative approach

Contains Nonbinding Recommendations

Draft — Not for Implementation

Confusion 1: Superiority over control group

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).

Superiority

OR

Non-inferiority

Is it ethical to perform a superiority trial to no treatment or under treatment when there is a good standard of care?

Confusion 2: Comparator in non-inferiority vs superiority design

- 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.

Non-inferiority

Superiority

Focusing on Non-inferiority trial

Contains Nonbinding Recommendations
Draft — Not for Implementation

Visual loss
20/32

- 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.

Two adequate trials

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.

Non-inferiority study – 4.5 letters margin to ranibizumab or aflibercept

Contains Nonbinding Recommendations

Draft — Not for Implementation

— 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.

Safety considerations

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]

Clinical Evaluations

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.

Clinical Evaluations

- A dilated slit lamp examination of the anterior segment including the cornea, conjunctiva, anterior chamber, iris, lids, and lashes. At a minimum, examinations should be performed at baseline and at no less than 3-month intervals during the first year and no less than every 6 months during the second year.

- Applanation tonometry at no less than 3-month intervals. If the investigational drug is administered topically, dosing of the drug should be at least 30 minutes after use of any anesthetic drug.

- Endothelial cell count at baseline and at the end of at least one 9-month or longer trial.

- If systemic exposure is minimal, systemic clinical and laboratory evaluations are recommended at baseline and at the end of at least one 9-month or longer trial. If systemic exposure is not minimal, systemic clinical and laboratory evaluations are recommended at regular intervals in all clinical trials.

- 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.

Why rescue with anti-VEGF could be a problem?

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

CLEARSIDE BIOMEDICAL

Thank you