APPENDIX 2: Eligibility Criteria

Inclusion Criteria

- Men and women ≥50 years of age.
- Active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye
- CNV must be at least 50% of total lesion size
- ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye.
- Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
- Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the informed consent form.
- Signed informed consent form

Exclusion Criteria:

- Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
- Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
- Prior treatment with anti-VEGF agents as follows:
    - Prior treatment with anti VEGF therapy in the study eye is not allowed.
    - Prior treatment with anti VEGF therapy in the fellow eye with an investigational agent (not FDA approved, e.g. bevacizumab) is allowed up to 3 months prior to first dose in the study, and such treatment will not be allowed during the study. Prior treatment with an FDA/Health Canada approved anti VEGF therapy in the fellow eye is allowed.

- Prior systemic anti VEGF therapy, investigational or FDA/Health Canada approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study.

- Total lesion size > 12 disc areas (30.5 mm^2), including blood, scars and neovascularization) as assessed by FA in the study eye.
- Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
- Scar or fibrosis, making up > 50% of total lesion in the study eye.
- Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
- History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
- Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
- History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye.
- Prior vitrectomy in the study eye.
- History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
- Any history of macular hole of stage 2 and above in the study eye.
- Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.
- Prior trabeculectomy or other filtration surgery in the study eye.
- Uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication) in the study eye.

- Active intraocular inflammation in either eye.
- Active ocular or periocular infection in either eye.
- Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye.
- Any history of uveitis in either eye.
- Presence or history of scleromalacia in either eye.
- Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye.
- Previous therapeutic radiation in the region of the study eye.
- History of corneal transplant or corneal dystrophy in the study eye.
- Significant media opacities, including cataract, in the study eye that might interfere with visual acuity, assessment of safety, or fundus photography.
- Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 96 week study period.
- Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications.
- Participation as a patient in any clinical study within the 12 weeks prior to Day 1.
- Any systemic or ocular treatment with an investigational agent in the past 12 weeks prior to Day 1.
- The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1.
- Any history of allergy to povidone iodine.

- Known serious allergy to the fluorescein sodium for injection in angiography.
- Presence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®; Genentech Inc., South San Francisco, CA).
- Females who are pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening); IUD; Depo-Provera® (Pfizer, Inc. New York); Norplant® System (Pfizer, Inc. New York) implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly.

APPENDIX 3: Summary of Statistical Analysis

The primary endpoint analysis was chosen to preserve constancy with the ranibizumab pivotal trials[7,8] and was non-inferiority of the intravitreal aflibercept treatment regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 ETDRS letters, per protocol data). Prespecified secondary efficacy variables compared baseline and 52-week data regarding: mean change in BCVA; gaining ≥15 letters; change in total National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) score; and change in CNV area on FA. Anatomic measures included retinal thickness and persistent fluid as assessed by OCT. Mean change in BCVA was also assessed in data pooled between the studies.

The full analysis set (FAS) included all randomized patients who received any study medication and had a baseline and at least one post-baseline BCVA assessment. The per protocol set (PPS) includes all patients in the FAS who:

1. Received at least 9 doses of study drug and attended at least 9 scheduled visits during the first year;
2. Had not missed two consecutive injections before administration of the 9th injection (per patient); and
3. Did not have major protocol violations.

Sham injections were counted as doses administered for the purpose of defining the PPS. The PPS included patients who discontinued the study because of treatment failure, without a major protocol deviation, at any time during the first 52 weeks (even if they met points 1 and 2 above). These patients were considered non-responders for the primary endpoint analysis.

A non-inferiority margin of 10% was chosen to preserve ~61% of the ranibizumab effect for prevention of moderate vision loss (loss of <15 letters) demonstrated in MARINA study,[7] using the two confidence interval approach. The non-inferiority for the primary endpoint was assessed by a pre-specified hierarchical testing sequence to control the overall type I error with the sequence of intravitreal aflibercept 2q4, 0.5q4, and then 2q8 as compared with ranibizumab. If all intravitreal aflibercept groups demonstrated non-inferiority to ranibizumab for the primary endpoint, additional comparisons to ranibizumab were prespecified regarding the secondary endpoints, also using a hierarchical testing sequence in which each secondary endpoint was tested for superiority of intravitreal aflibercept over ranibizumab. For the primary endpoint

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