Randomized Clinical Trial of Intravitreal Aflibercept Treat-and-Extend vs Fixed Dosing for Neovascular Age-Related Macular Degeneration

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Supplemental Materials

Study Design

Treatment regimen assignment was controlled via the interactive voice response system/interactive web response system specified by the Sponsor. No stratification was conducted. Due to the nature of the different dosing regimens, the 2 treatment groups did not have the same visit and treatment schedule. Patients in both treatment groups received the first intravitreal aflibercept (IVT-AFL) treatment on day 1 and 2 postbaseline visits and followed the same strict schedule in both treatment groups: primary completion at week 52 and the final visit at week 76. The schedule of all other postbaseline visits could differ between the treatment groups. The last possible IVT-AFL treatment in the treat-and-extend (T&E) group could be administered at week 76 (end of study) after completion of all protocol-specified assessments. The treatment period duration was 72 weeks in the fixed-dosing group, with a final study visit at week 76. After week 76, patients were to be returned to the standard of care.

Each visit followed a schedule of ophthalmologic assessments: best-corrected visual acuity (BCVA), optical coherence tomography, intraocular pressure, indirect ophthalmoscopy and slit lamp biomicroscopy (anterior and posterior segment assessment). Visual function of the study eye and the fellow eye was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol starting at 4 meters. Visual acuity examiners had to be certified to ensure consistent measurement of BCVA. Fundus photography and fluorescein angiography were performed at specified timepoints throughout the study.

Endpoints

Additional prespecified secondary endpoints were mean change in choroidal neovascularization (CNV) area in the study eye from baseline to week 52 and mean change in total score for National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) from baseline to week 52. All endpoints were exploratory at week 76. A post hoc analysis was performed on the number of scheduled extended treatment intervals of ≥10, ≥12, and ≥16 weeks for the T&E group by mandatory visit. Additionally, a post hoc analysis was conducted on the number of treatment interval adjustments and adjustments to the subsequent treatment interval for patients in the T&E dosing group.

Adverse events (AEs) were considered to be treatment-emergent AEs if they occurred after the first IVT-AFL dose and ≤30 days after the last dose. All AEs were coded according to the Medical Dictionary for Regulatory Activities version 23.0. An adjudication of arterial thrombotic events according to the Antiplatelet Trialists' Collaboration criteria was performed.

Inclusion/Exclusion Criteria

Two sets of inclusion/exclusion criteria were used to select patients for participation in this study. All inclusion/exclusion criteria were assessed during the screening phase, and patients must have signed informed consent forms before any of the inclusion/exclusion criteria were assessed. To be randomized into this study, a patient had to meet all of the eligibility criteria in both sets of criteria.

First set of inclusion criteria (all of the following criteria must have been met at the initial start of IVT-AFL treatment [ie, start of IVT-AFL treatment prior to this study] for a patient to be eligible for this study):

- Patients had primary subfoveal CNV lesions secondary to neovascular age-related macular degeneration (nAMD), including juxtafoveal lesions that affected the fovea, as evidenced by fluorescein angiography (FA) of the study eye within 4 weeks before the initiation of IVT-AFL treatment
- The area of CNV occupied at least 50% of the total lesion within 4 weeks before the initiation of IVT-AFL treatment

- Documented BCVA was 20/40 to 20/320 (comparable to a letter score of 73 to 25) in the study eye at the initiation of treatment (the initial BCVA of the study eye before treatment initiation must be documented as Snellen equivalent in the electronic case report form)

Second set of inclusion criteria (all of the following criteria must have been met at the time of screening for participation in this study for a patient to be eligible for this study):

- Signed written informed consent and adults aged ≥51 years
- The patient's history of IVT-AFL treatment met all of the following criteria:
    - Treatment in the study eye was initiated with 3 monthly (–1 week/+2 weeks) doses of IVT-AFL 2 mg and improvements of visual and anatomic outcomes were observed
    - Following the initiation phase of treatment, the intervals between treatments were between 6 weeks and 12 weeks (1 exception was allowed)
    - The interval between the last 2 prestudy injections was ≥8 weeks, and visual and anatomic outcomes had been stable over this interval
    - The patient received the last IVT-AFL injection in the study eye 2 months (±10 days) before the first treatment in this study
    - Total prior treatment duration with IVT-AFL (ie, from first treatment to randomization into this study) was ≥12 months
- Patient was willing, committed, and able to return for all clinic visits and complete all study-related procedures
- Women and men of reproductive potential must have agreed to a method of highly effective contraception (as defined by the Clinical Trial Facilitation Group from September 15, 2014)
    - Alternatively, women and men of reproductive potential could also use 2 acceptable methods of contraception (as defined by the Clinical Trial Facilitation Group from September 15, 2014) simultaneously
    - Contraception had to be used from the time of signing the informed consent form until 3 months after the last administration of study drug
    - Postmenopausal women must have been amenorrheic for at least 12 months in order not to be considered of childbearing potential

First set of exclusion criteria (a patient who met any of the following criteria at the initial start of IVT-AFL treatment [ie, start of IVT-AFL treatment before this study] was excluded from this study):

- Any prior or concomitant therapy with an investigational or approved agent to treat nAMD in the study eye
- 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 was:
    a) 50% or more of the total lesion area
    b) if the blood was under the fovea
    c) the blood under the fovea was ≥1 disc areas in size in the study eye
- Scar or fibrosis comprising more than 50% of the 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
- Causes of choroidal neovascularization other than age-related macular degeneration in the study eye

Second set of exclusion criteria (patient who met any of the following criteria at the time of screening for participation in this study was excluded from this study):

- Patients who currently met any of the first set of exclusion criteria except for prior treatment with IVT-AFL
- Any prior ocular (in the study eye) or systemic treatment or surgery for nAMD, except dietary supplements, vitamins, and IVT injections of aflibercept, during the time (ie, at least 12 months) between initiation of IVT-AFL treatment and randomization into this study
- Any prior treatment with anti-vascular endothelial growth factor therapy in the study eye, except for IVT injections of aflibercept, during the time (ie, at least 12 months) between initiation of IVT-AFL treatment and randomization into this study
- Prior systemic anti-vascular endothelial growth factor therapy, investigational or approved, within the last 15 months prior to randomization

- Any vitreous hemorrhage within 4 weeks before randomization in the study eye
- Active intraocular, extraocular, and periocular inflammation or infection in either eye
- Any ocular or periocular infection within 4 weeks of randomization in either eye
- Any serious AE related to IVT-AFL during prior treatment
- Any history of allergy or hypersensitivity to povidone iodine
- Known serious allergy or hypersensitivity to the fluorescein sodium for injection in angiography. Presence of any contraindications indicated in the European Union (EU) commission/locally approved label for IVT-AFL
- Hypersensitivity to the active substance IVT-AFL or to any of the excipients; active or suspected ocular or periocular infection; active severe intraocular inflammation
- Prior vitrectomy in the study eye
- History of vitreomacular traction 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
- Prior trabeculectomy or other filtration surgery in the study eye
- Uncontrolled glaucoma (defined as intraocular pressure more than 25 mmHg despite treatment with antiglaucoma medication) in the study eye
- Aphakia or pseudophakia with absence of posterior capsule (unless it occurred because of an yttrium aluminum garnet 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 interfered with visual acuity or fundus photography
- History or clinical evidence of diabetic macular edema or any retinal vascular disease other than age-related macular degeneration in either eye
- Any history of uveitis in either eye
- Presence of scleromalacia in either eye
- Pregnancy or breastfeeding (women only)
- The use of long-acting steroids, either systemically or intraocular, in the 18 months before initiating study treatment (or Iluvien [fluocinolone acetonide intravitreal implant] [Alimera Sciences, Alpharetta, GA] at any time)
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational drug, might have affected interpretation of the results of the study, or rendered the patient at high risk for treatment complications
- Previous assignment to treatment during this study
- Concomitant participation in another clinical study with investigational medicinal products
- Close affiliation with the investigational site, such as a close relative of the investigator or a dependent person (eg, employee or student of the investigational site)

The intention of the inclusion criteria for the patient's history of IVT-AFL treatment was that patients would be treated every 8 weeks, as per the approved IVT-AFL label, prior to study entry. These inclusion criteria were selected to ensure reasonable compliance with the approved IVT-AFL label, the stability of the patients entering the study, as well as some flexibility because patients were being recruited from routine clinical practice. One exception to treatment intervals being between 6 and 12 weeks was permitted to improve the feasibility of the study.

Statistical Analysis

The full analysis set included all randomized patients who received IVT-AFL treatment, had a baseline BCVA assessment, and had ≥1 postbaseline BCVA assessment. The safety analysis set included all patients who received IVT-AFL treatment under the protocol.