

**BLA 125387**

**aflibercept ophthalmic solution**

**ERRATA SHEET FOR SPONSOR'S BRIEFING DOCUMENT**

## **8. ERRATA**

Section and table numbers in this erratum refer to the original section and table numbers in the briefing book. Please add this Section 8 to the end of your briefing book.

### **8.1. Efficacy erratum**

An error in the description of the results of the sensitivity analyses (Section 4.7.1.3) was identified. The corrected text is provided.

#### **E-4.7.1.3 Sensitivity Analyses of the Primary Endpoint: VIEW 1 and VIEW 2**

Sensitivity analyses were performed on the primary endpoint in the PPS and FAS using observed values, the WOCF method, and by multiple imputation. Additional sensitivity analyses imputed “non-responder at week 52” to all drop outs and to subjects considered to be treatment failures at any time point before week 52 regardless of whether they remained in the study. A drop out was defined as any subject who prematurely discontinued the study but did not meet the criteria for treatment failure. Results of the sensitivity analyses were similar to those from the primary analysis of the PPS using the LOCF. In all instances, the upper bound of the 95.1% (VIEW 1) or 95% (VIEW 2) CI was well below the pre-specified 10% margin for noninferiority and in all but one analysis they were below 5% for all groups in both studies.

## 8.2. Safety errata

The analysis plan had specified that analyses of adverse events would be based on “treatment emergent” adverse events, defined as adverse events which started after patients had received at least one dose of study therapy and not more than 30 days after the patient’s last dose of study therapy. After submission of the briefing book, we became aware that, instead of providing tables of “Ocular Serious Treatment-Emergent Adverse Events in the Study Eye” (Table 32) and “Non-Ocular Serious Treatment-Emergent Adverse Events” (Table 35) in the briefing book, we had provided the corresponding tables of All Serious Ocular Adverse Events and All Serious Non-ocular Adverse Events. These “all” adverse events tables included both pre-treatment (i.e., prior to randomization) and post-treatment events (i.e., starting >30 days after the last dose). Although there were no meaningful differences between the “All SAE” and “Treatment Emergent SAE” tables, we have chosen to correct the briefing book. The correct tables of treatment emergent serious adverse events and the associated corrected text referring to those tables are provided below.

### **E-4.8.3.2 Serious Treatment Emergent Adverse Events in the Study Eye**

The frequency of ocular SAEs in the study eye was low and similar across treatment groups (2.3%, 55 subjects) (Table E-32). Most SAEs in the study eye were attributable to the injection procedure or progression of disease. The most commonly occurring ocular SAEs in the study eye were reduced VA (0.5% [13 subjects]), retinal hemorrhage (0.4% [9 subjects]), and endophthalmitis (0.2% [6 subjects]).

**Errata Table E-32: Ocular Serious Treatment-Emergent Adverse Events in the Study Eye (by SOC and PT) (Integrated Data) (Safety Analysis Set)**

Primary SOC Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Number of subjects with at least 1 ocular serious TEAE	19 ( 3.2%)	13 ( 2.1%)	11 ( 1.8%)	12 ( 2.0%)	36 ( 2.0%)	55 ( 2.3%)
Eye disorders	15 ( 2.5%)	10 ( 1.6%)	10 ( 1.7%)	11 ( 1.8%)	31 ( 1.7%)	46 ( 1.9%)
Angle closure glaucoma	0	1 ( 0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Cataract	1 ( 0.2%)	1 ( 0.2%)	1 ( 0.2%)	1 ( 0.2%)	3 ( 0.2%)	4 ( 0.2%)
Cataract cortical	1 ( 0.2%)	0	0	0	0	1 (<0.1%)
Cataract nuclear	0	1 ( 0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Hyphaema	1 ( 0.2%)	0	0	0	0	1 (<0.1%)
Keratitis	0	1 ( 0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Macular cyst	0	0	0	1 ( 0.2%)	1 (<0.1%)	1 (<0.1%)
Macular degeneration	0	0	0	1 ( 0.2%)	1 (<0.1%)	1 (<0.1%)
Macular hole	0	0	2 ( 0.3%)	0	2 ( 0.1%)	2 (<0.1%)
Posterior capsule opacification	2 ( 0.3%)	0	0	0	0	2 (<0.1%)
Retinal degeneration	1 ( 0.2%)	1 ( 0.2%)	0	0	1 (<0.1%)	2 (<0.1%)
Retinal detachment	1 ( 0.2%)	0	2 ( 0.3%)	0	2 ( 0.1%)	3 ( 0.1%)
Retinal hemorrhage	3 ( 0.5%)	2 ( 0.3%)	1 ( 0.2%)	3 ( 0.5%)	6 ( 0.3%)	9 ( 0.4%)
Retinal edema	1 ( 0.2%)	0	1 ( 0.2%)	0	1 (<0.1%)	2 (<0.1%)
Retinal pigment epithelial tear	1 ( 0.2%)	0	1 ( 0.2%)	2 ( 0.3%)	3 ( 0.2%)	4 ( 0.2%)
Retinal pigment epitheliopathy	0	1 ( 0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Retinal tear	1 ( 0.2%)	0	1 ( 0.2%)	0	1 (<0.1%)	2 (<0.1%)
Visual acuity reduced	3 ( 0.5%)	2 ( 0.3%)	3 ( 0.5%)	5 ( 0.8%)	10 ( 0.5%)	13 ( 0.5%)
Infections and infestations	3 ( 0.5%)	3 ( 0.5%)	0	0	3 ( 0.2%)	6 ( 0.2%)
Endophthalmitis	3 ( 0.5%)	3 ( 0.5%)	0	0	3 ( 0.2%)	6 ( 0.2%)
Injury, poisoning and proced. complicat.	1 ( 0.2%)	1 ( 0.2%)	0	0	1 (<0.1%)	2 (<0.1%)
Incorrect dose administered	1 ( 0.2%)	0	0	0	0	1 (<0.1%)
Macular scar	0	1 ( 0.2%)	0	0	1 (<0.1%)	1 (<0.1%)
Investigations	1 ( 0.2%)	0	1 ( 0.2%)	1 ( 0.2%)	2 ( 0.1%)	3 ( 0.1%)
Intraocular pressure increased	1 ( 0.2%)	0	1 ( 0.2%)	1 ( 0.2%)	2 ( 0.1%)	3 ( 0.1%)

VTE = VEGF Trap-Eye

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.

#### **E-4.8.4.1 Serious Treatment Emergent Adverse Events**

In the VIEW 1 and VIEW 2 studies, 13.8% (335) subjects had at least 1 non-ocular SAE: 13.9% (RQ4), 12.4% (2Q4), 14.5% (0.5Q4), and 14.6% (2Q8) (Table E-35).

Most non-ocular SAEs were reported in the following SOCs:

- Cardiac disorders were reported in 73 (3.0%) subjects. The most commonly occurring cardiac TEAEs were myocardial infarction (17 subjects, 0.7%), atrial fibrillation (16 subjects, 0.7%), coronary artery disease (9 subjects, 0.4%), and cardiac failure, congestive (8 subjects, 0.3%); all cardiac SAEs occurred with similar frequency across the treatment groups.
- Infections and infestations were reported in 62 (2.6%) subjects in total. The most commonly occurring TEAE in this SOC was pneumonia (in 21 subjects, 0.9%). All other TEAEs in this SOC occurred in  $\leq 0.2\%$  of subjects overall.
- Neoplasms benign, malignant and unspecified (including polyps) were reported in 58 (2.4%) subjects in total. The most commonly occurring TEAEs in this SOC were squamous cell carcinoma of skin (9 subjects, 0.4%), and breast cancer (7 subjects, 0.3%).
- Nervous system disorders were reported in 41 (1.7%) subjects in total. The most commonly occurring nervous system TEAEs were transient ischemic attack (TIA) (10 subjects, 0.4%), and CVA (8 subjects, 0.3%). The incidence of nervous system disorders was lowest in the ranibizumab treatment group; no subject in the RQ4 group had a TIA.

All non-ocular SAEs occurred with similar frequency across the treatment groups (**Error! Reference source not found.**).

**Errata Table E-35: Non-Ocular Serious Treatment-Emergent Adverse Events (by SOC)  
(Integrated Data) (Safety Analysis Set)**

Primary system organ class MedDRA Version 13.1	R 0.5 mg Q4 N=595	VTE 2.0 mg Q4 N=613	VTE 0.5 mg Q4 N=601	VTE 2.0 mg Q8 N=610	VTE total N=1824	TOTAL N=2419
Number of subjects with at least 1 non-ocular serious TEAE	83 ( 13.9%)	76 ( 12.4%)	87 ( 14.5%)	89 ( 14.6%)	252 ( 13.8%)	335 ( 13.8%)
Blood system and lymphatic disorders	0	1 ( 0.2%)	1 ( 0.2%)	2 ( 0.3%)	4 ( 0.2%)	4 ( 0.2%)
Cardiac disorders	19 ( 3.2%)	15 ( 2.4%)	17 ( 2.8%)	22 ( 3.6%)	54 ( 3.0%)	73 ( 3.0%)
Congenital, familial, and genetic disorders	0	0	0	1 ( 0.2%)	1 (<0.1%)	1 (<0.1%)
Ear and labyrinth disorders	1 ( 0.2%)	1 ( 0.2%)	2 ( 0.3%)	1 ( 0.2%)	4 ( 0.2%)	5 ( 0.2%)
Gastrointestinal disorders	5 ( 0.8%)	8 ( 1.3%)	10 ( 1.7%)	9 ( 1.5%)	27 ( 1.5%)	32 ( 1.3%)
General disorders and administration site conditions	4 ( 0.7%)	6 ( 1.0%)	3 ( 0.5%)	3 ( 0.5%)	12 ( 0.7%)	16 ( 0.7%)
Hepatobiliary disorders	3 ( 0.5%)	4 ( 0.7%)	1 ( 0.2%)	1 ( 0.2%)	6 ( 0.3%)	9 ( 0.4%)
Infections and infestations	21 ( 3.5%)	10 ( 1.6%)	11 ( 1.8%)	20 ( 3.3%)	41 ( 2.2%)	62 ( 2.6%)
Injury, poisoning, and procedural complications	7 ( 1.2%)	7 ( 1.1%)	12 ( 2.0%)	14 ( 2.3%)	33 ( 1.8%)	40 ( 1.7%)
Investigations	0	3 ( 0.5%)	0	1 ( 0.2%)	4 ( 0.2%)	4 ( 0.2%)
Metabolism and nutritional disorders	4 ( 0.7%)	3 ( 0.5%)	3 ( 0.5%)	3 ( 0.5%)	9 ( 0.5%)	13 ( 0.5%)
Musculoskeletal and connective tissue disorders	7 ( 1.2%)	4 ( 0.7%)	0	5 ( 0.8%)	9 ( 0.5%)	16 ( 0.7%)
Neoplasms benign malignant and unspecified (incl. cysts and polyps)	13 ( 2.2%)	12 ( 2.0%)	19 ( 3.2%)	14 ( 2.3%)	45 ( 2.5%)	58 ( 2.4%)
Nervous system disorders	3 ( 0.5%)	14 ( 2.3%)	15 ( 2.5%)	9 ( 1.5%)	38 ( 2.1%)	41 ( 1.7%)
Psychiatric disorders	2 ( 0.3%)	0	0	2 ( 0.3%)	2 ( 0.1%)	4 ( 0.2%)
Renal and urinary disorders	1 ( 0.2%)	1 ( 0.2%)	2 ( 0.3%)	3 ( 0.5%)	6 ( 0.3%)	7 ( 0.3%)
Reproductive system and breast disorders	0	2 ( 0.3%)	0	1 ( 0.2%)	3 ( 0.2%)	3 ( 0.1%)
Respiratory, thoracic and mediastinal disorders	5 ( 0.8%)	8 ( 1.3%)	4 ( 0.7%)	6 ( 1.0%)	18 ( 1.0%)	23 ( 1.0%)
Skin and subcutaneous tissue disorders	2 ( 0.3%)	1 ( 0.2%)	2 ( 0.3%)	1 ( 0.2%)	4 ( 0.2%)	6 ( 0.2%)
Surgical and medical procedures	2 ( 0.3%)	0	1 ( 0.2%)	1 ( 0.2%)	2 ( 0.1%)	4 ( 0.2%)
Vascular disorders	7 ( 1.2%)	4 ( 0.7%)	5 ( 0.8%)	6 ( 1.0%)	15 ( 0.8%)	22 ( 0.9%)

VTE = VEGF Trap-Eye

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events.