Name of Sponsor/Company: Astellas Pharma B.V.		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: ASP8232		

SYNOPSIS

Title of Study: Phase 2, Double-masked, Randomized, Active-controlled Study to Evaluate the Efficacy and Safety of ASP8232 in Reducing Central Retinal Thickness in Patients with Diabetic Macular Edema (The VIDI-study) (ISN 8232-CL-3001)

Investigators/Coordinating Investigator: [redacted], MD, MSc

Study Center(s): This multicenter study was conducted at 21 sites in the United States.

Publication Based on the Study: None

Study Period: 1Q2015 to 3Q2016

Study Initiation Date (Date of First Enrollment): 12 Jan 2015

Study Completion Date (Date of Last Evaluation): 12 Aug 2016

Phase of Development: Phase 2

Objectives:

Primary Objective:

- To evaluate the percent change from baseline in excess central subfield thickness (CST) in the study eye as assessed by spectral domain-optical coherence tomography (SD-OCT) for ASP8232 monotherapy at 12 weeks.

Secondary Objectives

- To evaluate the percent change from baseline in excess CST in the study eye as assessed by SD-OCT for ASP8232 monotherapy compared to ASP8232 as adjunctive therapy with ranibizumab, ASP8232 monotherapy compared to ranibizumab and ASP8232 as adjunctive therapy with ranibizumab compared to ranibizumab at 12 weeks.
- To evaluate the absolute change from baseline in CST in the study eye as assessed by SD-OCT for ASP8232 monotherapy compared to ASP8232 as adjunctive therapy with ranibizumab, ASP8232 monotherapy compared to ranibizumab and ASP8232 as adjunctive therapy with ranibizumab compared to ranibizumab at 12 weeks.
- To evaluate the overall change from baseline in the early treatment diabetic retinopathy study (ETDRS) best-corrected visual acuity (BCVA) letters in the study eye at 12 weeks.
- To evaluate pharmacodynamics of ASP8232 by assessing vascular adhesion protein-1 (VAP-1) plasma concentration and inhibition of VAP-1 activity in plasma and in anterior chamber fluid and total antioxidant status (TAS) in serum.

- To evaluate the pharmacokinetics of ASP8232 in patients with diabetic macular edema (DME).
- To evaluate the safety and tolerability of ASP8232 in patients with DME.

Methodology:

This was a double-masked, randomized, parallel-group study to evaluate the efficacy of ASP8232 as a stand-alone treatment or in combination with ranibizumab.

The study consisted of 8 visits over approximately 7 months including a screening period of 7 days up to 28 days, a 12-week treatment period and a 12-week follow-up period.

Randomization was stratified by CST of the study eye (≤ or > 500 μm), which was the value at visit 1 as assessed by the central imaging reading center (CIRC).

Patients were randomized in a 1:1:1 ratio to 1 of the following 3 treatment groups:

- ASP8232 (40 mg) capsules + sham intravitreal (within the eye-ball) (IVT) injections
- ASP8232 (40 mg) capsules + ranibizumab (0.3 mg) IVT injections
- ASP8232-matched placebo capsules + ranibizumab (0.3 mg) IVT injections

All patients in all treatment groups took 1 capsule ASP8232/placebo once daily in the morning for 84 consecutive days and received an IVT (ranibizumab or sham) injection administered by an unmasked injecting ophthalmologist 3 times during the study, with 4-week intervals (visit 2, 4 and 5).

CIRC reviewed the images from the visit 1/screening and communicated the eligibility and the value of CST in both eyes to the investigator prior to randomization at visit 2. The investigator decided at randomization which eye would become the study eye (to receive IVT injections). The other eye was considered as the fellow eye (qualified when eligible or nonqualified when not eligible).

After randomization on day 1 (visit 2), all patients returned to the investigative site on day 15 (visit 3), day 29 (visit 4), day 57 (visit 5) and day 85 (visit 6, end of treatment [EoT]) as per schedule of assessment. Patients returned for a safety follow-up evaluation on day 113 (visit 7) and for the final follow-up visit on day 169 (visit 8, end of study).

Number of Patients (Planned, Enrolled and Analyzed):

The planned sample size was 23 evaluable patients per treatment group. Out of 240 patients who signed the informed consent, 96 patients were randomized as follow:

- 32 patients in the ASP8232 + sham group (that is, ASP8232 monotherapy referred to as ‘ASP8232’)
- 33 patients in the ASP8232 + ranibizumab group
- 31 patients in the placebo + ranibizumab group (that is, ranibizumab monotherapy referred to as ‘ranibizumab)

All of the 96 randomized patients were included in the safety analysis set (SAF). The full analysis set (FAS) excluded 1 patient from the ASP8232 + ranibizumab treatment group (no efficacy data after the study drug was taken were available for this patient). Additionally, all randomized patients were included in the pharmacokinetic analysis set (PKAS) and pharmacodynamic analysis set (PDAS). The per protocol set (PPS) included 87 patients.

Diagnosis and Main Criteria for Inclusion:

Institutional Review Board-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization) were obtained from the patient prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).

Patient was male or female ≥ 18 and ≤ 85 years of age.

Patient had a documented diagnosis of type 1 or type 2 diabetes mellitus and glycated hemoglobin of ≤ 12.0% at screening.

Presence of intraretinal and/or subretinal fluid at visit 1/screening in the study eye, with a CST of at least 375 μm by SD-OCT at screening (as measured by the investigator and confirmed by the CIRC) and at least 375 μm at visit 2 (as measured by the investigator).

Patient had in the eye proposed to be the study eye, an ETDRS BCVA letter score ≤ 73 (Snellen 20/40) and ≥ 24 (Snellen 20/320) at screening.

Test Product, Dose and Mode of Administration, Batch Numbers:

The study drug ASP8232 (40 mg) was provided in capsules. Patients self-administered ASP8232 (40 mg) or placebo capsules once daily for 84 days (range 80 to 88 days). The first dose was to be taken on visit 2 following the IVT injection; the last dose was to be taken on the day prior to visit 6/EoT. Capsules were preferably taken in the morning, with some fluid, with or without food. On the days of visits 3 to 6 where a pharmacokinetic sample was to be taken, patients were instructed not to take the study medication prior to the visit.

Batch numbers: [redacted]

Duration of Treatment (or Duration of Study, if applicable):

Approximately 7 months including a screening period of 7 days up to 28 days, a 12-week treatment period and a 12-week follow-up period.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Ranibizumab

The comparative drug ranibizumab (LUCENTIS®, San Francisco, CA) was administered as a 0.05 mL IVT injection. Sham or active IVT injections (0.3 mg, 0.05 mL) were to be administered by the unmasked injecting ophthalmologist 3 times at 4-weekly intervals (visit 2, visit 4 and visit 5). All patients received an anesthetic in the study eye prior to receiving either the ranibizumab or sham injection.

Batch numbers: [redacted]

Placebo and Sham IVT

The placebo for ASP8232 (with inactive ingredients) was supplied as a matching capsule for oral administration.

Batch numbers: [redacted]

The sham IVT for ranibizumab was supplied as an empty vial in order to provide a sham injection with a syringe. The sham injection was administered by pressing a needleless syringe to the surface of the eye.

Batch numbers: [redacted]

Criteria for Evaluation:

Primary Efficacy Endpoint: The primary analysis was performed on the percent change from baseline in excess CST in the study eye to visit 6/EoT (corresponding to 12 weeks).

Secondary Efficacy Endpoints: Secondary efficacy endpoints were the absolute change from baseline in CST in the study eye to each visit, percent change from baseline in excess CST in the study eye at week 2, 4 and 8 and change from baseline in ETDRS BCVA score in the study eye to each visit.

Pharmacokinetic assessments included ASP8232 concentrations in plasma and in anterior chamber aqueous humor.

Pharmacodynamic assessments included change from baseline in VAP-1 concentration and VAP-1 activity (in plasma and aqueous humor), TAS (in serum) and other exploratory biomarkers in plasma or urine.

Safety assessments included overall incidence of adverse events (AEs), laboratory variables, vital signs and electrocardiogram (ECG).

Statistical Methods:

All data processing, summarization and analyses were performed on SAS® version 9.3 or higher on UNIX.

Population for Analysis:

The SAF consisted of all patients who took at least 1 dose of study medication.

The FAS consisted of all randomized patients who received at least 1 dose of randomized study drug and who had an efficacy measurement at baseline and at postbaseline. This was the primary analysis set for the efficacy analyses.

The PPS consisted of all patients of the FAS who did not meet criteria for PPS exclusion. These criteria were to capture relevant nonadherence to the protocol.

The PKAS consisted of patients from the SAF for whom sufficient plasma concentration data were collected.

The PDAS consisted of patients from the SAF for whom sufficient pharmacodynamic measurements were collected.

Efficacy:

Primary Efficacy Endpoint:

The following null and alternative hypotheses were given for comparisons with the ASP8232 monotherapy treatment group (ASP8232 40 mg capsules + sham IVT injections):

H0: percent change from baseline in excess CST $\geq$ -10% in ASP8232 monotherapy group

H1: percent change from baseline in excess CST < -10% in ASP8232 monotherapy group

The hypothesis test was made on the upper bound of a 2-sided 80% confidence intervals (CIs) constructed using the t-distribution. If the upper bound was lower than -10% then a null hypothesis was rejected and an alternative hypothesis was accepted. Descriptive 2-sided 95% CIs were also constructed. When Visit 6/EoT data were not available, last observation carried forward (LOCF) was to be used to impute the visit 6/EoT value.

Secondary Efficacy Endpoint:

Analyses were performed using the same methods as described for the primary endpoint.

Pharmacokinetics:

Descriptive statistics were provided for plasma concentrations and aqueous humor samples of ASP8232 by time point and by treatment group for patients in the PKAS.

Pharmacodynamics:

The baseline value was the last measurement taken prior to initial study drug administration. For the patients in the PDAS, descriptive statistics were provided for soluble VAP-1 concentration, VAP-1 activity, TAS measures and percent of baseline (postbaseline value/baseline value) by treatment group and visit.

Safety:

The coding dictionary for this study was MedDRA v15.1, and was used to summarize AEs by SOC and preferred term.

Laboratory variables (i.e., hematology, biochemistry and urinalysis), vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse rate) and ECG variables were summarized using descriptive statistics for each treatment group at each visit.

Summary of Results/Conclusions:

Patient Disposition Results:

Patient disposition results can be found in [Table 1].

Demographics Results:

The overall mean age at randomization of 61.5 years was comparable across all treatment groups with 58 (60.4%) patients ≤ 64 years of age and 38 (39.6%) patients ≥ 65 years of age. The age range of patients was 30 to 82 years. The majority of patients were white (78.1%), followed by Black or African American (14.6%) [Table 2].

Efficacy Results:

ASP8232 did not achieve the primary study objective and did not demonstrate a significant change in central retinal thickness [Table 3]. Although there was a mild increase of BCVA in all treatment groups, the difference of ASP8232 monotherapy vs ranibizumab monotherapy at week 12/EoT in BCVA was statistically significant in favor of the ranibizumab monotherapy.

The results in the ranibizumab study groups (ranibizumab + ASP8232 and ranibizumab) confirmed findings in earlier ranibizumab studies by showing clinically significant improvements in both central retinal thickness and BCVA.

ASP8232 in combination with ranibizumab did not show any additional benefit over ranibizumab alone in both the primary and the secondary efficacy endpoints of the study.

Pharmacokinetic Results:

ASP8232 plasma concentrations showed wide variability across patients during the treatment period, with median concentrations ranging from [redacted].

ASP8232 was still measurable in plasma 12 weeks after the last dose, at concentrations that were [redacted] of the concentrations during the treatment period.

The aqueous humor concentrations of ASP8232 were very low in most patients and remained close to the limit of detection during the whole treatment period.

Pharmacodynamic Results:

In the ASP8232 treated-patients, VAP-1 activity in plasma was reduced to very low levels at all measured time points during the dosing period. VAP-1 inhibition from baseline values at all visits in the treatment period ranged from [redacted] The mean percent of baseline for VAP-1 activity [redacted]

No relevant changes with TAS were observed with any treatment.

VAP-1 concentrations in aqueous humor were very low and remained relatively constant during the dosing period with all treatments.

Safety Results:

Treatment with ASP8232, with ranibizumab and with the combination of these 2 (ASP8232 + ranibizumab) was generally well-tolerated in patients with DME.

The overall incidence of treatment-emergent adverse events (TEAEs) was generally comparable among the 3 treatment groups (65.6%, ASP8232; 51.5%, ASP8232 + ranibizumab; 61.3%, ranibizumab). Eye Disorders represented the SOC with the highest incidence of TEAEs. In this class, the incidence of ocular TEAEs was 25.0% for ASP8232, 39.4% for ASP8232 + ranibizumab and 38.7% for ranibizumab [Table 4].

The most commonly reported TEAEs were conjunctival hemorrhage and worsening of type 2 diabetes mellitus in 3 (9.1%) ASP8232 + ranibizumab-treated patients and diabetic retinal edema in 3 (9.4%) ASP8232-treated patients [Table 4].

Most TEAEs were mild in severity in the ASP8232 and ASP8232 + ranibizumab groups (12 [37.5%] patients and 11 [33.3%] patients, respectively). In the ranibizumab group, most TEAEs were moderate in severity (10 [32.3%] patients). A total of 5 severe TEAEs were reported during the study (3 in the ASP8232 group and 2 in the ranibizumab group).

The incidence of drug-related TEAEs was low and comparable among the 3 treatment groups (6.3% for ASP8232, 9.1% for ASP8232 + ranibizumab and 9.7% for ranibizumab). Most events were reported in the SOC Eye Disorders with 1 patient each in the ASP8232 and ASP8232 + ranibizumab groups and 2 patients in the ranibizumab group.

No patients died during the study.

The overall incidence of serious TEAEs was 3 (9.4%), 1 (3.0%) and 3 (9.7%) in the ASP8232, ASP8232 + ranibizumab, and ranibizumab groups, respectively. None of the reported serious TEAEs were considered to be related to study drug [Table 5].

There were a total of 3 TEAEs reported leading to permanent discontinuation of study drug. Two patients in the ASP8232 group discontinued: 1 due to retinal disorder (deterioration of DME, necessitating rescue therapy) and the other due to prostate cancer. One patient in the ASP8232 + ranibizumab group discontinued due to metastatic malignant melanoma. Out of these 3 TEAEs, the TEAE of retinal disorder was considered to be possibly related to study drug.

Changes in estimated glomerular filtration rate and urinary albumin to creatinine ratio did not indicate any deterioration of the kidney function.

In general, no clinically significant differences in change from baseline were found for clinical laboratory evaluations, vital signs or ECG.

Only 2 patients (1 in the ASP8232 group and 1 in the ASP8232 + ranibizumab group) had potentially clinically significant (PCS) liver enzyme values. None of the patients who met the criteria for PCS liver function values met the criteria for Hy's law.

PCS criterion for SBP was met in 2 patients in the ASP8232 group and in 4 patients in the ASP8232 + ranibizumab treatment group. PCS criterion for DBP was met in 1 patient in the ASP8232 group. There were no reports of PCS heart rate changes in the study.

Mean changes from baseline to EoT in ECG parameters were generally comparable across all treatment groups. Clinically significant ECG abnormalities were observed at visit 1/screening (4 patients; 2 with ASP8232, 1 with ASP8232 + ranibizumab and 1 with ranibizumab), baseline (3 patients; 2 with ASP8232 and 1 with ASP8232 + ranibizumab) and week 4 (1 patient with ASP8232). No clinically relevant treatment-emergent ECG abnormalities were observed in this study.

CONCLUSIONS:

Treatment with both ASP8232 and ranibizumab was generally well tolerated in patients with DME. ASP8232 did not show a change in CST and therefore did not achieve the primary study objective.

Date of Report: 09 Apr 2017

Table 1 Patient Disposition

Discontinuation Parameters	ASP8232 (n = 32)	ASP8232 + Ranibizumab (n = 33)	Ranibizumab (n = 31)	Total (n = 96)
Treatment discontinuation, n (%)				
Yes	2 (6.3)	2 (6.1)	2 (6.5)	6 (6.3)
No	30 (93.8)	31 (93.9)	29 (93.5)	90 (93.8)
Primary reason for treatment discontinuation, n (%)†				
Completed	30 (93.8)	31 (93.9)	29 (93.5)	90 (93.8)
Randomized/registered but never received/dispensed study drug	0	0	0	0
Adverse event	1 (3.0)	1 (3.1)	0	2 (2.1)
Death	0	0	0	0
Lost to follow-up	0	1 (3.0)	1 (3.2)	2 (2.1)
Protocol violation	0	0	0	0
Withdrawal by subject	0	0	1 (3.2)	1 (1.0)
Study terminated by Sponsor	0	0	0	0
Physician decision	1 (3.1)	0	0	1 (1.0)
Noncompliance with study drug	0	0	0	0
Pregnancy	0	0	0	0
Other	0	0	0	0
Study discontinuation, n (%)				
Yes	3 (9.4)	2 (6.1)	4 (12.9)	9 (9.4)
No	29 (90.6)	31 (93.9)	27 (87.1)	87 (90.6)
Primary reason for discontinuation, n (%)†				
Completed	29 (90.6)	31 (93.9)	27 (87.1)	87 (90.6)
Randomized/registered but never received/dispensed study drug	0	0	0	0
Adverse event	0	1 (3.0)	0	1 (1.0)
Death	0	0	0	0
Lost to follow-up	2 (6.3)	1 (3.0)	3 (9.7)	6 (6.3)
Withdrawal by subject	1 (3.1)	0	1 (3.2)	2 (2.1)
Study terminated by Sponsor	0	0	0	0
Physician decision	0	0	0	0
Pregnancy	0	0	0	0
Other	0	0	0	0

All randomized patients.

† Only the primary reason for discontinuation was collected.

Source: Tables 12.1.1.4 and 12.1.1.5

Table 2 Summary of Demographics and Baseline Characteristics for Patients (Safety Analysis Set)

Parameter Category/ Statistics	ASP8232 (n = 32)	ASP8232 + Ranibizumab (n = 33)	Ranibizumab (n = 31)	Total (n = 96)
Sex, n (%)				
Male	17 (53.1)	15 (45.5)	16 (51.6)	48 (50.0)
Female	15 (46.9)	18 (54.5)	15 (48.4)	48 (50.0)
Ethnicity, n (%)				
Not Hispanic or Latino	21 (65.6)	18 (54.5)	24 (77.4)	63 (65.6)
Hispanic or Latino	11 (34.4)	15 (45.5)	7 (22.6)	33 (34.4)
Race, n (%)				
White	26 (81.3)	27 (81.8)	22 (71.0)	75 (78.1)
Black or African American	4 (12.5)	5 (15.2)	5 (16.1)	14 (14.6)
Asian	1 (3.1)	0	1 (3.2)	2 (2.1)
American Indian or Alaska Native	0	0	2 (6.5)	2 (2.1)
Other	1 (3.1)	1 (3.0)	1 (3.2)	3 (3.1)
Age, years				
Mean (SD)	61.5 (8.1)	59.8 (9.2)	63.4 (8.6)	61.5 (8.7)
Median	61.5	60.0	65.0	62.0
Min - Max	47 - 82	30 - 81	45 - 78	30 - 82
Age group, n (%)				
≤ 64 years	22 (68.8)	22 (66.7)	14 (45.2)	58 (60.4)
≥ 65 years	10 (31.3)	11 (33.3)	17 (54.8)	38 (39.6)
EudraCT age category, n (%)				
≥ 18 to ≤ 64 years	22 (68.8)	22 (66.7)	14 (45.2)	58 (60.4)
≥ 65 to ≤ 84 years	10 (31.3)	11 (33.3)	17 (54.8)	38 (39.6)
≥ 85 years	0	0	0	0
Weight (kg)†				
Mean (SD)	87.66 (19.79)	92.68 (25.33)	92.42 (20.37)	90.92 (21.91)
Median	86.85	83.60	88.20	86.40
Min – Max	53.2 - 139.5	61.4 - 157.7	55.9 - 140.9	53.2 - 157.7
Height (cm)				
Mean (SD)	165.738 (9.125)	167.527 (11.311)	167.575 (8.775)	166.946 (9.763)
Median	166.820	167.640	165.100	165.550
Min – Max	146.05 - 182.88	149.86 - 190.50	152.40 - 187.96	146.05 - 190.50
BMI (kg/m^2)‡				
Mean (SD)	31.92 (6.99)	32.70 (6.80)	33.06 (7.76)	32.56 (7.13)
Median	29.40	30.50	31.10	30.60
Min – Max	21.5 - 51.1	24.5 - 54.5	21.8 - 53.3	21.5 - 54.5
Study eye, n (%)§				
Left	12 (37.5)	20 (60.6)	14 (45.2)	46 (47.9)
Right	20 (62.5)	13 (39.4)	17 (54.8)	50 (52.1)
Number of qualified eyes, n (%)¶				
1	25 (78.1)	30 (90.9)	27 (87.1)	82 (85.4)
2	7 (21.9)	3 (9.1)	4 (12.9)	14 (14.6)

Table continued on next page

Parameter Category/ Statistics	ASP8232 (n = 32)	ASP8232 + Ranibizumab (n = 33)	Ranibizumab (n = 31)	Total (n = 96)
CST stratification, n (%)††				
≤ 500µm	16 (50.0)	18 (54.5)	16 (51.6)	50 (52.1)
> 500µm	16 (50.0)	15 (45.5)	15 (48.4)	46 (47.9)
Iris color, n (%)				
Blue	7 (21.9)	5 (15.2)	6 (19.4)	18 (18.8)
Green	1 (3.1)	1 (3.0)	1 (3.2)	3 (3.1)
Brown	20 (62.5)	25 (75.8)	17 (54.8)	62 (64.6)
Hazel	4 (12.5)	2 (6.1)	6 (19.4)	12 (12.5)
Other	0	0	1 (3.2)	1 (1.0)
Smoking history, n (%)				
Never	22 (68.8)	20 (60.6)	20 (64.5)	62 (64.6)
Current	2 (6.3)	1 (3.0)	2 (6.5)	5 (5.2)
Former	8 (25.0)	12 (36.4)	9 (29.0)	29 (30.2)
Smoking duration, years				
n	10	13	11	34
Mean (SD)	21.8 (15.8)	20.5 (11.1)	18.5 (11.8)	20.2 (12.5)
Median	29.5	20.0	20.0	20.0
Min – Max	0 – 42	2 – 35	1 - 40	0 - 42

All patients who took at least 1 dose of study medication.

BMI: body mass index; CIRC: central imaging reading center; CST: central subfield thickness; Max: maximum; Min: minimum.

† Weight recorded at visit 1/screening procedures.

‡ BMI (kg/m^2) is calculated as: (weight in kg) / (height in m^2).

§ Final confirmation of study eye by investigator at visit 2/baseline.

¶ Final assessment of qualified eye by investigator.

†† CST assessment by CIRC corresponding to visit 1/screening procedures.

Source: Table 12.1.2.1.3

Table 3 Percent Change From Baseline in Excess CST in the Study Eye at Week 12/EoT, With LOCF CIRC-values (Full Analysis Set)

Visits/Statistics	ASP8232	ASP8232 + Ranibizumab	Ranibizumab
Baseline			
n	32	32	31
Mean (SD)	215.8 (117.9)	191.8 (103.9)	181.6 (105.5)
Week 12/EoT (LOCF)			
n	32	32	31
Mean (SD)	210.3 (127.4)	54.0 (105.6)	58.6 (107.5)
Percent Change From Baseline at Week 12/EoT (LOCF)			
Mean (SD)	11.4† (73.1)	-61.7 (67.8)	-75.3 (53.0)
80% CI	(-5.5, 28.3)	(-77.4, -46.0)	(-87.8, -62.8)
95% CI	(-15.0, 37.8)	(-86.1, -37.2)	(-94.8, -55.8)
P Value	0.108	< 0.001	< 0.001

All randomized patients who received at least 1 dose of randomized study drug and who had an efficacy measurement at baseline and at postbaseline.

Footnotes continued on next page

CI: confidence interval; CIRC: central imaging reading center; CST: central subfield thickness; EoT: end of treatment; LOCF: last observation carried forward.

† With ASP8232 monotherapy, the mean excess CST decreased slightly from 215.8 µm at baseline to 210.3 µm at EoT, however the mean percent change from baseline was positive (a ratio of means does not equal a mean of ratios).

Source: Tables 12.3.1.1.1.1, 12.3.1.2.1.1

Table 4 Most Common TEAEs Reported in ≥ 5% of Patients in Any Treatment Group (Safety Analysis Set)

MedDRA v15.1 System Organ Class Preferred Term	Treatment		
	ASP8232 (n = 32) n (%)	ASP8232 + ranibizumab (n = 33) n (%)	Ranibizumab (n = 31) n (%)
All Systems			
Overall†	21 (65.6)	17 (51.5)	19 (61.3)
Endocrine disorders	0	2 (6.1)	0
Hypothyroidism	0	2 (6.1)	0
Eye disorders	8 (25.0)	13 (39.4)	12 (38.7)
Conjunctival haemorrhage	0	3 (9.1)	0
Diabetic retinal oedema	3 (9.4)	1 (3.0)	2 (6.5)
Retinal aneurysm	0	0	2 (6.5)
Retinal exudates	2 (6.3)	2 (6.1)	1 (3.2)
Visual acuity reduced	0	2 (6.1)	1 (3.2)
Vitreous floaters	1 (3.1)	2 (6.1)	1 (3.2)
Vitreous haemorrhage	0	2 (6.1)	2 (6.5)
Gastrointestinal disorders	1 (3.1)	2 (6.1)	1 (3.2)
Vomiting	0	2 (6.1)	0
Metabolism and nutrition disorders	3 (9.4)	3 (9.1)	3 (9.7)
Type 2 diabetes mellitus	2 (6.3)	3 (9.1)	0

All patients who took at least 1 dose of study medication.

AE: adverse event; TEAE: treatment-emergent adverse event.

† Overall includes both ocular and systemic AEs.

Source: Table 12.6.1.2.1

Table 5 Serious† TEAEs (MedDRA v15.1) – (Safety Analysis Set)

MedDRA v15.1 System Organ Class Preferred Term	ASP8232 (n = 32)		ASP8232 + ranibizumab (n = 33)		Ranibizumab (n = 31)	
	n (%)	# E	n (%)	# E	n (%)	# E
All Systems						
Overall ‡	3 (9.4)	3	1 (3.0)	1	3 (9.7)	3
Cardiac disorders	0	0	0	0	1 (3.2)	1
Acute myocardial infarction	0	0	0	0	1 (3.2)	1
Infections and infestations	1 (3.1)	1	0	0	0	0
Osteomyelitis bacterial	1 (3.1)	1	0	0	0	0
Injury, poisoning and procedural complications	1 (3.1)	1	0	0	0	0
Eye operation complication	1 (3.1)	1	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	1 (3.2)	1
Hypoglycaemia	0	0	0	0	1 (3.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.1)	1	1 (3.0)	0	0	0
Metastatic malignant melanoma	0	0	1 (3.0)	1	0	0
Prostate cancer	1 (3.1)	1	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	1 (3.2)	1
Diabetic foot	0	0	0	0	1 (3.2)	1

All patients who took at least 1 dose of study medication.

AE: adverse event; E: event; TEAE: treatment-emergent adverse event; SAE: serious adverse event.

† Includes SAEs upgraded by the Sponsor based on review of the Sponsor's list of Always Serious terms, if any upgrade was done.

‡ Overall includes both ocular and systemic AEs.

Source: Table 12.6.1.7.1