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Intravitreal Nesvacumab+Aflibercept in Diabetic Macular Edema: The Phase 2 RUBY Trial

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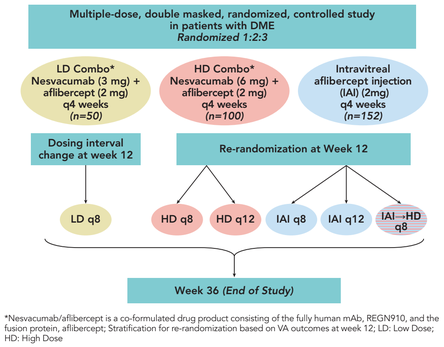
OBJECTIVE

- To evaluate if a combination of intravitreal nesvacumab+aflibercept offered additional benefit over monotherapy with intravitreal aflibercept injection (IAI) in patients with diabetic macular edema (DME).

METHODS

Figure 1. Study Design



*Nesvacumab/aflibercept is a co-formulated drug product consisting of the fully human mAb, REGN910, and the fusion protein, aflibercept; Stratification for re-randomization based on VA outcomes at week 12; LD: Low Dose; HD: High Dose

KEY ELIGIBILITY CRITERIA

- Clinically significant DME with central involvement
- Best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 73 to 24 (Snellen equivalent of approximately 20/40 to 20/320)
- Intravitreal anti-VEGF ≥ 3 months from screening
- Panretinal laser photocoagulation or macular laser photocoagulation ≥ 3 months from screening
- Intraocular or periocular corticosteroids in the study eye ≥ 4 months from screening

STUDY ENDPOINTS

Primary endpoint

- Change from baseline in BCVA at week 12 through 36 as measured by the ETDRS letter score.

Secondary endpoints

- Change from baseline in central subfield retinal thickness (CST) between week 12 and 36 as measured by spectral domain-optical coherence tomography (SD-OCT)
- Proportion of patients with a ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score from baseline at weeks 12 and 36

Additional endpoint

- Proportion of patients with complete resolution of fluid at the foveal center at week 12 and 36

STATISTICS

- All data were analyzed descriptively with no adjustment for multiplicity.
- All p-values are nominal. All *p*-values are vs IAI at week 12 and IAI q8 at week 36.

RESULTS

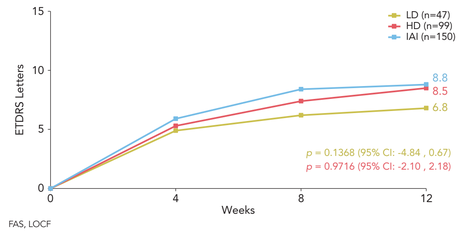
OUTCOMES FROM BASELINE THROUGH WEEK 12

Table 1. Patient Disposition and Demographics

	LD (n=50)	HD (n=100)	IAI (n=152)	Total (N=302)
Patients completing week 12, n (%)	46 (92.0%)	97 (97.0%)	148 (97.4%)	291 (96.4%)
Mean age, years (SD)	62.1 (8.9)	62.4 (10.4)	59.5 (10.2)	60.9 (10.2)
Female, n (%)	21 (42.0%)	49 (49.0%)	68 (44.7%)	138 (45.7%)
Race, n (%)				
White	37 (74.0%)	87 (87.0%)	121 (79.6%)	245 (81.1%)
Black or African American	11 (22.0%)	8 (8.0%)	19 (12.5%)	38 (12.6%)
Other	2 (4.0%)	5 (5.0%)	12 (7.9%)	19 (6.3%)

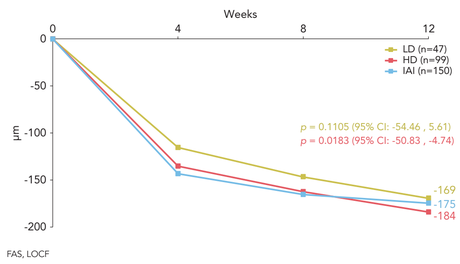
SAF

Figure 2. Mean BCVA Gains



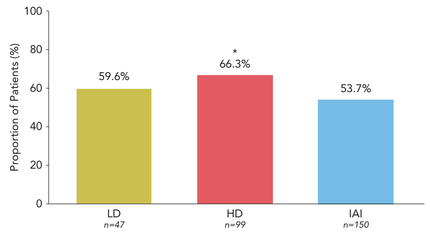
FAS, LOCF

Figure 3. Mean CST Reductions



FAS, LOCF

Figure 4. Complete Resolution of Fluid at the Foveal Center at Week 12



*p=0.0489; FAS, Patients with no intraretinal or subretinal fluid at the foveal center on SD-OCT; LOCF

Table 2. Baseline Disease Characteristics

	LD (n=47)	HD (n=99)	IAI (n=150)	Total (N=296)
Hemoglobin A1c, % (SD)	8.5 (1.86)	7.8 (1.61)	8.1 (1.86)	8.0 (1.79)
Diabetes Duration, years (SD)	17.6 (10.93)	17.5 (11.22)	15.8 (10.69)	16.7 (10.90)
Type 1 diabetes, n (%)	2 (4.3%)	5 (5.1%)	11 (7.3%)	18 (6.1%)
Type 2 diabetes, n (%)	45 (95.7%)	94 (94.9%)	139 (92.7%)	278 (93.9%)
Prior Treatment*, n %	27 (57.4%)	40 (40.4%)	58 (38.7%)	125 (42.2%)
Focal or Grid Laser	19 (40.4%)	27 (27.3%)	36 (24.0%)	82 (27.7%)
Anti-VEGF Agents	12 (25.5%)	28 (28.3%)	27 (18%)	67 (22.6%)
Intravitreal Steroids	4 (8.5%)	7 (7.1%)	7 (4.7%)	18 (6.1%)
ETDRS BCVA, letters (SD)	57.7 (11.13)	60.6 (11.11)	58.7 (10.78)	59.2 (10.96)
CST, µm (SD)	484.2 (152.78)	497.8 (151.77)	520.1 (151.27)	507.0 (151.80)
DRSS Score, n (%)				
10, 20	0	3 (3.0%)	1 (0.7%)	4 (1.4%)
35	10 (21.3%)	14 (14.1%)	17 (11.3%)	41 (13.9%)
43	10 (21.3%)	15 (15.2%)	37 (24.7%)	62 (20.9%)
47	9 (19.1%)	34 (34.3%)	46 (30.7%)	89 (30.1%)
53	13 (27.7%)	19 (19.2%)	35 (23.3%)	67 (22.6%)
61	1 (2.1%)	2 (2.0%)	4 (2.7%)	7 (2.4%)
65	1 (2.1%)	7 (7.1%)	3 (2.0%)	11 (3.7%)
71	1 (2.1%)	4 (4.0%)	5 (3.3%)	10 (3.4%)
75	1 (2.1%)	0	1 (0.7%)	2 (0.7%)

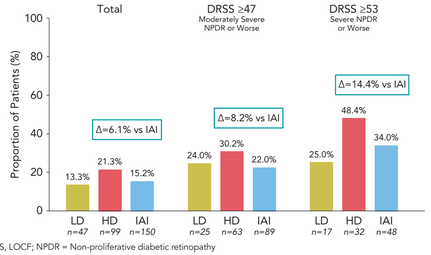
FAS, 3 patients (1 in each group) were ungradable for DRSS and are not included; *Prior treatment for DME. Patients could have had more than one treatment

Table 3. Normalization of CST (≤300 µm) at Week 12

	LD (n=47)	HD (n=99)	IAI (n=150)
Proportion of patients	40.4%	57.6%*	35.3%

Post hoc, FAS, LOCF; *P = 0.0006

Figure 5. ≥2-Step Improvement in DRSS Score at Week 12



FAS, LOCF; NPDR = Non-proliferative diabetic retinopathy

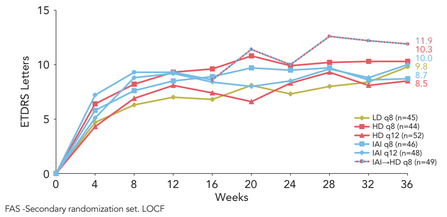
OUTCOMES FROM BASELINE THROUGH WEEK 36

Table 4. Patient Disposition and Drug Exposure

Secondary Randomization Set, n (%)	LD q8 (n=45)	HD q8 (n=44)	HD q12 (n=52)	IAI q8 (n=46)	IAI q12 (n=48)	IAI→HD q8 (n=49)
Patients completing week 36, n (%)	44 (97.8)	42 (95.5)	50 (96.2)	46 (100)	43 (89.6)	45 (91.8)
Number of Planned Injections, n	6	6	5	6	5	6
Mean Number of Injections, n (SD)	7.2* (0.9)	5.9 (0.4)	5.1* (0.6)	5.9 (0.5)	4.8 (0.6)	5.8 (0.4)

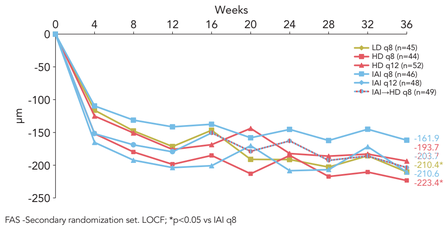
FAS -Secondary randomization set; *~10% and 50% of patients received per protocol dosing in the LD q8 and HD q12 groups, respectively.

Figure 6. Mean BCVA Gains



FAS -Secondary randomization set. LOCF

Figure 7. Mean CST Reductions



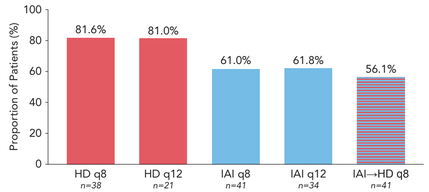
FAS -Secondary randomization set. LOCF; *p<0.05 vs IAI q8

Table 5. Complete Resolution of Fluid at the Foveal Center and Normalization of CST (≤300 µm) at Week 36

	Resolution of Fluid		Normalization of CST	
	HD q8+q12 (n=83)	IAI q8+q12 (n=77)	HD q8+q12 (n=83)	IAI q8+q12 (n=76)
Proportion of patients	90.4%*	74.0%	74.7**	56.6%

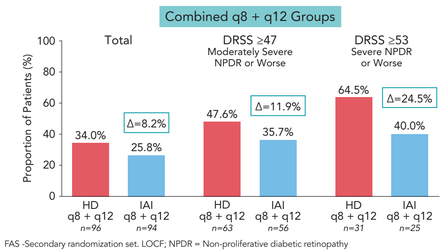
Post hoc, FAS -Secondary randomization set, Patients with no intraretinal or subretinal fluid at the foveal center on SD=-OCT; OC; *P = 0.0044; **P = 0.0089

Figure 8. Complete Resolution of Fluid at the Foveal Center at Week 32*



*8 or 12 weeks from the last study treatment; FAS -Secondary randomization set, OC. Per Protocol Set

Figure 9. ≥2-Step Improvement in DRSS at Week 36



FAS -Secondary randomization set. LOCF; NPDR = Non-proliferative diabetic retinopathy

SAFETY THROUGH WEEK 36

Table 7. Most Frequent Ocular Adverse Events

	LD q8 (n=46)	HD q8 (n=44)	HD q12 (n=53)	IAI q8 (n=47)	IAI q12 (n=49)	IAI→HD q8 (n=49)
Patients with ≥1 AE, n (%)	14 (30.4)	12 (27.3)	19 (35.8)	10 (21.3)	11 (22.4)	17 (34.7)
Vitreous detachment	0	4 (9.1)	3 (5.7)	1 (2.1)	0	4 (8.2)
Conjunctival hemorrhage	4 (8.7)	1 (2.3)	1 (1.9)	6 (12.8)	2 (4.1)	3 (6.1)
Cataract	1 (2.2)	0	0	2 (4.3)	2 (4.1)	2 (4.1)
Eye pain	2 (4.3)	1 (2.3)	2 (3.8)	0	2 (4.1)	2 (4.1)
Punctate keratitis	0	1 (2.3)	0	0	0	2 (4.1)
Visual acuity reduced	1 (2.2)	1 (2.3)	1 (1.9)	0	1 (2.0)	2 (4.1)
Vitreous hemorrhage	0	1 (2.3)	1 (1.9)	0	0	2 (4.1)
Vitreous floaters	1 (2.2)	0	2 (3.8)	1 (2.1)	2 (4.1)	1 (2.0)
Dry eye	0	1 (2.3)	4 (7.5)	0	0	0
Retinal exudates	1 (2.2)	0	3 (5.7)	0	2 (4.1)	0

SAF-Secondary randomization set; >4% in any treatment group

Table 8. APTC-Defined Arterial Thromboembolic Events

	LD q8 (n=46)	HD q8 (n=44)	HD q12 (n=53)	IAI q8 (n=47)	IAI q12 (n=49)	IAI→HD q8 (n=49)
Patients with ≥1 AE, n (%)	3 (6.5)	0	2 (3.8)	2 (4.3)	1 (2.0)	0
Non-fatal MI	1 (2.2)	0	1 (1.9)	1 (2.1)	1 (2.0)	0
Non-fatal Stroke	1 (2.2)	0	1 (1.9)	0	0	0
Vascular Death	2 (4.3)	0	0	1 (2.1)	0	0

SAF-Secondary randomization set; APTC = Anti-Platelet Trialists' Collaboration; MI = myocardial infarction

CONCLUSIONS

- BCVA gains were similar with the combination therapy versus IAI alone
- High dose combination was superior to IAI in the reduction of CRT and the proportion of patients with complete resolution of fluid
- Greater proportion of patients treated with high dose combination had ≥2-step improvement in DRSS score compared to those treated with IAI
- Ocular and systemic safety was consistent with IAI

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