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

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On behalf of the RUBY Investigators

Ophthalmic Consultants of Boston
Boston, MA
Financial Disclosures
Ang-1 & Ang-2 Discovery

Tie2 is an endothelial cell-specific tyrosine kinase receptor to which two ligands bind

- **Ang1** –
  - Expressed in normal adult tissues to help maintain vascular integrity

- **Ang2** –
  - Secreted by endothelial cells
  - Required for post-natal vascular remodeling and is *only expressed under pathological conditions*
  - Expressed in endothelial cells at
    - very low levels in quiescent blood vessels
    - high levels in 'angiogenic' vessels
Effect of IVT Administration of Nesvacumab, Alone or in Combination with Aflibercept in a Retinal Vascular Development Model

Area of the superficial retinal plexus

Total vessel length superficial retinal plexus

P4 (postnatal day 4); P6 (postnatal day 6)
Ang-2 Levels Elevated in Human Vitreous
RVO > DR > AMD

Vitreous levels in newly diagnosed patients

Data courtesy of Roche US Medical Affairs
Single IVT injection of aflibercept or nesvacumab or both co-formulated
Nesvacumab/aflibercept is a co-formulated drug product consisting of the fully human mAb, REGN910, and the fusion protein, aflibercept.
Multiple-dose, double-masked, randomized, controlled study in patients with DME

Randomized 1:2:3

Key Eligibility Criteria

- Clinically significant DME with central involvement
- BCVA ETDRS letter score equivalent to 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

LD Combo
Nesvacumab (3 mg) + aflibercept (2 mg) q4 weeks (n=50)

HD Combo
Nesvacumab (6 mg) + aflibercept (2 mg) q4 weeks (n=100)

IAI
Intravitreal aflibercept injection (2 mg) q4 weeks (n=152)

Week 12

Week 36 (End of Study)
Study Design
Week 12 – Week 36

LD q8

LD Combo
Nesvacumab (3 mg) + aflibercept (2 mg) q4 weeks (n=50)

HD Combo
Nesvacumab (6 mg) + aflibercept (2 mg) q4 weeks (n=100)

IAI
Intravitreal aflibercept injection (2mg) q4 weeks (n=152)

Re-randomization at Week 12

HD q8

HD q12

IAI q8

IAI q12

IAI→HD q8

Week 36 (End of Study)

Stratification for re-randomization based on VA outcomes at week 12
LD: Low Dose; HD: High Dose
## Patients Disposition and Demographics

<table>
<thead>
<tr>
<th></th>
<th>LD (n=50)</th>
<th>HD (n=100)</th>
<th>IAI (n=152)</th>
<th>Total (N=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients completing Week 12, n (%)</td>
<td>46 (92.0%)</td>
<td>97 (97.0%)</td>
<td>148 (97.4%)</td>
<td>291 (96.4%)</td>
</tr>
<tr>
<td>Mean Age, years (SD)</td>
<td>62.1 (8.90)</td>
<td>62.4 (10.37)</td>
<td>59.5 (10.24)</td>
<td>60.9 (10.15)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>21 (42.0%)</td>
<td>49 (49.0%)</td>
<td>68 (44.7%)</td>
<td>138 (45.7%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>37 (74.0%)</td>
<td>87 (87.0%)</td>
<td>121 (79.6%)</td>
<td>245 (81.1%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>11 (22.0%)</td>
<td>8 (8.0%)</td>
<td>19 (12.5%)</td>
<td>38 (12.6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2.0%)</td>
<td>2 (2.0%)</td>
<td>4 (2.6%)</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>1 (2.0%)</td>
<td>0</td>
<td>3 (2.0%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>0</td>
<td>1 (1.0%)</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>3 (2.0%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>0</td>
<td>2 (2.0%)</td>
<td>2 (1.3%)</td>
<td>4 (1.3%)</td>
</tr>
</tbody>
</table>

SAF
LD: Low Dose; HD: High Dose
## Baseline Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LD</th>
<th>HD</th>
<th>IAI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=47)</td>
<td>(n=99)</td>
<td>(n=150)</td>
<td>(N=296)</td>
</tr>
<tr>
<td>Mean Baseline Hemoglobin A1C (SD)</td>
<td>8.5 (1.86)</td>
<td>7.8 (1.61)</td>
<td>8.1 (1.86)</td>
<td>8.0 (1.79)</td>
</tr>
<tr>
<td>Mean Diabetes Duration, years (SD)</td>
<td>17.6 (10.93)</td>
<td>17.5 (11.22)</td>
<td>15.8 (10.69)</td>
<td>16.7 (10.90)</td>
</tr>
<tr>
<td>Diabetes Type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>2 (4.3%)</td>
<td>5 (5.1%)</td>
<td>11 (7.3%)</td>
<td>18 (6.1%)</td>
</tr>
<tr>
<td>Type 2</td>
<td>45 (95.7%)</td>
<td>94 (94.9%)</td>
<td>139 (92.7%)</td>
<td>278 (93.9%)</td>
</tr>
<tr>
<td>Prior Treatment for DME/DR*, Study Eye, n %</td>
<td>27 (57.4%)</td>
<td>40 (40.4%)</td>
<td>58 (38.7%)</td>
<td>125 (42.2%)</td>
</tr>
<tr>
<td>Prior Focal or Grid Laser</td>
<td>19 (40.4%)</td>
<td>27 (27.3%)</td>
<td>36 (24.0%)</td>
<td>82 (27.7%)</td>
</tr>
<tr>
<td>Prior Intravitreal Anti-VEGF</td>
<td>12 (25.5%)</td>
<td>28 (28.3%)</td>
<td>27 (18%)</td>
<td>67 (22.6%)</td>
</tr>
<tr>
<td>Prior Intravitreal Steroids</td>
<td>4 (8.5%)</td>
<td>7 (7.1%)</td>
<td>7 (4.7%)</td>
<td>18 (6.1%)</td>
</tr>
</tbody>
</table>

FAS
*Patients could have had more than one treatment
LD: Low Dose; HD: High Dose
## Baseline Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LD (n=47)</th>
<th>HD (n=99)</th>
<th>IAI (n=150)</th>
<th>Total (N=296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ETDRS BCVA, letters (SD)</td>
<td>57.7 (11.13)</td>
<td>60.6 (11.11)</td>
<td>58.7 (10.78)</td>
<td>59.2 (10.96)</td>
</tr>
<tr>
<td>Mean CRT, um (SD)</td>
<td>484.2 (152.78)</td>
<td>497.8 (151.77)</td>
<td>520.1 (151.27)</td>
<td>507.0 (151.80)</td>
</tr>
<tr>
<td>Diabetic Retinopathy Severity Score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10, 20</td>
<td>0</td>
<td>3 (3.0%)</td>
<td>1 (0.7%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>35</td>
<td>10 (21.3%)</td>
<td>14 (14.1%)</td>
<td>17 (11.3%)</td>
<td>41 (13.9%)</td>
</tr>
<tr>
<td>43</td>
<td>10 (21.3%)</td>
<td>15 (15.2%)</td>
<td>37 (24.7%)</td>
<td>62 (20.9%)</td>
</tr>
<tr>
<td>47</td>
<td>9 (19.1%)</td>
<td>34 (34.3%)</td>
<td>46 (30.7%)</td>
<td>89 (30.1%)</td>
</tr>
<tr>
<td>53</td>
<td>13 (27.7%)</td>
<td>19 (19.2%)</td>
<td>35 (23.3%)</td>
<td>67 (22.6%)</td>
</tr>
<tr>
<td>61</td>
<td>1 (2.1%)</td>
<td>2 (2.0%)</td>
<td>4 (2.7%)</td>
<td>7 (2.4%)</td>
</tr>
<tr>
<td>65</td>
<td>1 (2.1%)</td>
<td>7 (7.1%)</td>
<td>3 (2.0%)</td>
<td>11 (3.7%)</td>
</tr>
<tr>
<td>71</td>
<td>1 (2.1%)</td>
<td>4 (4.0%)</td>
<td>5 (3.3%)</td>
<td>10 (3.4%)</td>
</tr>
<tr>
<td>75</td>
<td>1 (2.1%)</td>
<td>0</td>
<td>1 (0.7%)</td>
<td>2 (0.7%)</td>
</tr>
</tbody>
</table>

FAS, 3 patients (1 in each group) were ungradable for DRSS and are not included.
LD: Low Dose; HD: High Dose
Mean Change in Best-Corrected Visual Acuity
Baseline - Week 12

FAS, LOCF
LD: Low Dose; HD: High Dose
All p values are nominal

- LD (n=47)
- HD (n=99)
- IAI (n=150)

\[ p = 0.1368 \text{ (95\% CI: -4.84, 0.67)} \]
\[ p = 0.9716 \text{ (95\% CI: -2.10, 2.18)} \]
Mean Central Retinal Thickness
Baseline - Week 12

Absolute Change

Weeks

μm

0 4 8 12

μm

0 50 100 150 200

LD (n=47)
HD (n=99)
IAI (n=150)

P = 0.0183 (-50.83, -4.74)

FAS, LOCF
LD: Low Dose; HD: High Dose
All p values are nominal
Proportion of Patients With Complete Resolution of Fluid at the Foveal Center at Week 12

FAS, Patients with no intraretinal or subretinal fluid at the foveal center on SD-OCT, LOCF; LD: Low Dose; HD: High Dose; All p values are nominal

*p = 0.0489 compared with IAI
Proportion of Patients With Normalization of Macular Thickness (CRT ≤300 μm) at Week 12

FAS, LOCF
LD: Low Dose; HD: High Dose
All p values are nominal

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD</td>
<td>40.4%</td>
<td>47</td>
</tr>
<tr>
<td>HD</td>
<td>57.6%</td>
<td>99</td>
</tr>
<tr>
<td>IAI</td>
<td>35.3%</td>
<td>150</td>
</tr>
</tbody>
</table>

*p = 0.0006
Proportion of Patients With ≥2 Step Improvement in DRSS at Week 12

Total

FAS, LOCF
LD: Low Dose; HD: High Dose

Proportion of Patients

<table>
<thead>
<tr>
<th>DRSS ≥47</th>
<th>DRSS ≥53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>LD (n=47)</td>
<td>HD (n=99)</td>
</tr>
<tr>
<td>13.3%</td>
<td>21.3%</td>
</tr>
<tr>
<td>24.0%</td>
<td>30.2%</td>
</tr>
<tr>
<td>25.0%</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

Moderately Severe Non-Proliferative Diabetic Retinopathy or Worse

Severe Non-Proliferative Diabetic Retinopathy or Worse

Δ = 6.1%

Δ = 8.2%

Δ = 14.4%
Week 36
Study Design

Week 12 – Week 36

LD Combo
Nesvacumab (3 mg) + aflibercept (2 mg) q4 weeks (n=50)

HD Combo
Nesvacumab (6 mg) + aflibercept (2 mg) q4 weeks (n=100)

IAI
Intravitreal aflibercept injection (2 mg) q4 weeks (n=152)

Re-randomization at Week 12

LD q8
HD q8
HD q12
IAI q8
IAI q12
IAI→HD q8

Week 36 (End of Study)

Stratification for re-randomization based on VA outcomes at week 12
LD: Low Dose; HD: High Dose
## Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>LD q8</th>
<th>HD q8</th>
<th>HD q12</th>
<th>IAI q8</th>
<th>IAI q12</th>
<th>IAI → HD q8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients in the Secondary Randomization Set, n (%)</strong></td>
<td>(n=45)</td>
<td>(n=44)</td>
<td>(n=52)</td>
<td>(n=46)</td>
<td>(n=48)</td>
<td>(n=49)</td>
</tr>
<tr>
<td><strong>Number of patients completing week 36, n (%)</strong></td>
<td>44 (97.8%)</td>
<td>42 (95.5%)</td>
<td>50 (96.2%)</td>
<td>46 (100%)</td>
<td>43 (89.6%)</td>
<td>45 (91.8%)</td>
</tr>
</tbody>
</table>

**FAS - Secondary randomization set**

LD: Low Dose; HD: High Dose
## Dose Exposure Through Week 36

<table>
<thead>
<tr>
<th></th>
<th>LD q8</th>
<th>HD q8</th>
<th>HD q12</th>
<th>IAI q8</th>
<th>IAI q12</th>
<th>IAI q12</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=45)</td>
<td>(n=44)</td>
<td>(n=52)</td>
<td>(n=46)</td>
<td>(n=48)</td>
<td>(n=49)</td>
<td></td>
</tr>
<tr>
<td>Number of Planned Injections, n</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Mean Number of Injections, n (SD)</td>
<td>7.2*</td>
<td>5.9</td>
<td>5.1*</td>
<td>5.9</td>
<td>4.8</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>(0.92)</td>
<td>(0.35)</td>
<td>(0.58)</td>
<td>(0.45)</td>
<td>(0.63)</td>
<td>(0.44)</td>
</tr>
</tbody>
</table>

*~10% and 50% of patients received per protocol dosing in the LD q8 and HD q12 groups, respectively.

SAF—Secondary randomization set
LD: Low Dose; HD: High Dose
Mean Change in Best-Corrected Visual Acuity

Baseline – Week 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

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0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose

FAS - Secondary randomization set, LOCF

ETDRS Letters

0 5 10 15

0 4 8 12 16 20 24 28 32 36

Weeks

0 4 8 12 16 20 24 28 32 36

ETDRS Letters

0 5 10 15

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

LD: Low Dose; HD: High Dose
Mean Change in Central Retinal Thickness

Baseline – Week 36

Weeks

μm

LD q8 (n=45)
HD q8 (n=44)
HD q12 (n=52)
IAI q8 (n=46)
IAI q12 (n=48)
IAI to HD q8 (n=49)

*p < 0.05 vs IAI q8

FAS - Secondary randomization set, LOCF
LD: Low Dose; HD: High Dose. All p values are nominal.
Proportion of Patients with Complete Resolution of Fluid at the Foveal Center at Week 32*

![Bar chart showing proportions of patients with complete resolution of fluid at different intervals and doses.](image)

*8 or 12 weeks from the last study treatment
FAS - Secondary randomization set, OC
Per Protocol Set
LD: Low Dose; HD: High Dose
Proportion of Patients with Complete Resolution of Fluid at the Foveal Center at Week 36

Combined q8+q12 Groups

- **HD**: q8 + q12
  - n=75/83
  - 90.4%

- **IAI**: q8 + q12
  - n=57/77
  - 74.0%

* * p = 0.0044

FAS: Secondary randomization set, Patients with no intraretinal or subretinal fluid at the foveal center on SD-OCT; OC
LD: Low Dose; HD: High Dose
All p values are nominal
Patients **Maintaining** Complete Resolution of Fluid at the Foveal Center through Week 36

*Defined as reaching “No fluid at the foveal center” and maintaining that status for all subsequent study visits.*

**FAS - Secondary randomization Set, OC**

**LD: Low Dose; HD: High Dose**

All p values are nominal

---

**Combined q8+q12 Groups**

<table>
<thead>
<tr>
<th>Proportion of Patients</th>
<th>Proportion</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD q8 + q12</td>
<td>79.5%</td>
<td>n=66/83</td>
</tr>
<tr>
<td>IAI q8 + q12</td>
<td>57.1%</td>
<td>n=44/77</td>
</tr>
</tbody>
</table>

* * p = 0.0025

---

*Defined as reaching “No fluid at the foveal center” and maintaining that status for all subsequent study visits.*

FAS - Secondary randomization Set, OC

LD: Low Dose; HD: High Dose

All p values are nominal
Proportion of Patients with Normalization of Macular Thickness (CRT ≤300 μm) at Week 36

Combined q8+q12 Groups

<table>
<thead>
<tr>
<th>Proportion of Patients</th>
<th>HD q8 + q12</th>
<th>IAI q8 + q12</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>n=62/83</td>
<td>n=43/76</td>
</tr>
<tr>
<td>IAI</td>
<td>74.7%</td>
<td>56.6%</td>
</tr>
</tbody>
</table>

*p = 0.0089

FAS- Secondary randomization set; OC
LD: Low Dose; HD: High Dose
All p values are nominal
Patients **Maintaining** Normalization of Macular Thickness (CRT ≤300 µm) through Week 36

**Combined q8+q12 Groups**

- **Proportion of Patients**
  - HD q8 + q12: 66.3%
  - IAI q8 + q12: 42.1%

- **Sample Sizes**
  - HD q8 + q12: n=55/83
  - IAI q8 + q12: n=32/76

* Defined as reaching CRT≤300 and maintaining ≤300 for all subsequent study visits.
* FAS - Secondary randomization Set, OC
* LD: Low Dose; HD: High Dose
* All p values are nominal
* $p = 0.0005$
Proportion of Patients with ≥2 Step Improvement in DRSS at Week 36

<table>
<thead>
<tr>
<th></th>
<th>Combined q8+q12 Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>DRSS ≥47 (Moderately Severe Non-Proliferative Diabetic Retinopathy or Worse)</td>
</tr>
<tr>
<td></td>
<td>DRSS ≥53 (Severe Non-Proliferative Diabetic Retinopathy or Worse)</td>
</tr>
<tr>
<td>Proportion of Patients</td>
<td>34.0%</td>
</tr>
<tr>
<td>HD q8+q12 n=96</td>
<td>96</td>
</tr>
<tr>
<td>IAI q8+q12 n=94</td>
<td>94</td>
</tr>
</tbody>
</table>
Proportion of Patients with ≥3 Step Improvement in DRSS at Week 36

**Combined q8+q12 Groups**

<table>
<thead>
<tr>
<th>Proportion of Patients</th>
<th>Total</th>
<th>DRSS ≥47</th>
<th>DRSS ≥53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Moderate Severe Non-Proliferative Diabetic Retinopathy or Worse</td>
<td>Severe Non-Proliferative Diabetic Retinopathy or Worse</td>
</tr>
<tr>
<td><strong>Combined q8+q12 Groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD q8 + q12 n=96</td>
<td>11.7%</td>
<td>17.5%</td>
<td>29.0%</td>
</tr>
<tr>
<td>IAI q8 + q12 n=94</td>
<td>7.5%</td>
<td>10.7%</td>
<td>16.0%</td>
</tr>
<tr>
<td>∆ = 4.2%</td>
<td></td>
<td>∆ = 6.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Δ = 13.0%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FAS- Secondary randomization set, LOCF
LD: Low Dose; HD: High Dose
# Most Frequent Ocular Adverse Events Through Week 36

<table>
<thead>
<tr>
<th>Event</th>
<th>LD q8 (%)</th>
<th>HD q8 (%)</th>
<th>HD q12 (%)</th>
<th>IAI q8 (%)</th>
<th>IAI q12 (%)</th>
<th>HD q8 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with at least 1 AE, n (%)</td>
<td>14 (30.4%)</td>
<td>12 (27.3%)</td>
<td>19 (35.8%)</td>
<td>10 (21.3%)</td>
<td>11 (22.4%)</td>
<td>17 (34.7%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>0</td>
<td>4 (9.1%)</td>
<td>3 (5.7%)</td>
<td>1 (2.1%)</td>
<td>0</td>
<td>4 (8.2%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>4 (8.7%)</td>
<td>1 (2.3%)</td>
<td>1 (1.9%)</td>
<td>6 (12.8%)</td>
<td>2 (4.1%)</td>
<td>3 (6.1%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>1 (2.2%)</td>
<td>0</td>
<td>0</td>
<td>2 (4.3%)</td>
<td>2 (4.1%)</td>
<td>2 (4.1%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>2 (4.3%)</td>
<td>1 (2.3%)</td>
<td>2 (3.8%)</td>
<td>0</td>
<td>2 (4.1%)</td>
<td>2 (4.1%)</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>0</td>
<td>1 (2.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>1 (2.2%)</td>
<td>1 (2.3%)</td>
<td>1 (1.9%)</td>
<td>0</td>
<td>1 (2.0%)</td>
<td>2 (4.1%)</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>0</td>
<td>1 (2.3%)</td>
<td>1 (1.9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>1 (2.2%)</td>
<td>0</td>
<td>2 (3.8%)</td>
<td>1 (2.1%)</td>
<td>2 (4.1%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>0</td>
<td>1 (2.3%)</td>
<td>4 (7.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retinal exudates</td>
<td>1 (2.2%)</td>
<td>0</td>
<td>3 (5.7%)</td>
<td>0</td>
<td>2 (4.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

SAF—Secondary randomization set; >4% in any treatment group.
LD: Low Dose; HD: High Dose
<table>
<thead>
<tr>
<th></th>
<th>LD q8 (n=46)</th>
<th>HD q8 (n=44)</th>
<th>HD q12 (n=53)</th>
<th>IAI q8 (n=47)</th>
<th>IAI q12 (n=49)</th>
<th>IAI → HD q8 (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients w/ at least 1 AE, n (%)</td>
<td>3 (6.5%)</td>
<td>0</td>
<td>2 (3.8%)</td>
<td>2 (4.3%)</td>
<td>1 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1 (2.2%)</td>
<td>0</td>
<td>1 (1.9%)</td>
<td>1 (2.1%)</td>
<td>1 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1 (2.2%)</td>
<td>0</td>
<td>1 (1.9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular death</td>
<td>2 (4.3%)</td>
<td>0</td>
<td>0</td>
<td>1 (2.1%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SAF-Secondary randomization set
LD: Low Dose; HD: High Dose
Conclusions

- Ocular and systemic safety consistent with IAI monotherapy