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Safety and Efficacy of an Oral Therapeutic APX3330 from ZETA-1 Phase 2 Trial in Patients with Diabetic Retinopathy

February 17, 2023
Disclosures

• Consultant: Regeneron, Alcon, Genentech, Bausch and Lomb, Ocufilure, Asclepix, Gyroscope, Apellis, Iveric
APX3330 History and Ref-1 Inhibition Mechanism

Ref-1 Involved in Key Pathways that Contribute to Diabetic Retinopathy and DME

Mechanism of Action – Ref-1 Inhibition

- Hypoxia
- Ref-1
- HIF-1α
- VEGF (Signaling Cascade)
- Inflammation
  - Ref-1
  - NF-κB
  - TNF-α
  - Chemokines
- Other Growth Factors (Signaling Cascade)
- Neovascularization

- APX3330 is a **small molecule oral drug** candidate and a first-in-class inhibitor of Ref-1 (reduction-oxidation effector factor-1)
- Novel MOA reduces **both VEGF and inflammatory cytokines to normal levels** by blocking HIF1α and NF-κB
- Extensively studied in **over 20 in-vitro and animal studies** with favorable efficacy and safety
- APX3330 previously developed by Eisai for multiple hepatic indications and later by Apexian for advanced solid tumors in **11 Phase 1 and 2 trials**
Phase 2 ZETA-1 Trial of Oral AP3330 in Subjects With Diabetic Retinopathy
Randomized, Double-Masked, Placebo-Controlled 24-Week Trial

APX3330 600mg/day (BID)

Key Inclusion – Study Eye
• ≥ 18 years of age
• DRSS 47, 53, or 61
• Noncentral DME is permitted in study eye
• ETDRS BCVA ≥ 60 Letters (20/63)

Key Exclusion – Study Eye
• OCT CST >320 μm²
  o Center involved DME allowed in fellow eye
• Anti-VEGF within past 6 months¹
• HbA1c ≥ 12.0%

Eligibility Criteria:

Primary: % subjects with ≥ 2 step improvement on DRSS (Diabetic Retinopathy Severity Scale) at week 24

Secondary:
• DRSS worsening ≥1, ≥2, ≥3*, ≥4
• DRSS improvement ≥1, ≥2, ≥3*, ≥4
• Progression to vision threatening complications
• Central subfield thickness (CST)
• Best Corrected Distance Visual Acuity (BCDVA)
• Rescue subjects
• DME fellow eye status
• Safety and tolerability

Exploratory:
• Labs / PK

*Potential Phase 3 approvable endpoints

1. By Central Reading Center
2. Center-Involved DME in Fellow Eye is Acceptable
3. Includes Systemic or IVT VEGF

Primary Endpoints

103 Subjects Enrolled (FPFV Apr 2021 to LPLV Aug 2022) Top Line Announced in Early 2023

Endpoints

ZETA-1

25 US sites
90-100 participants with moderately severe to severe NPDR or mild PDR (DRSS 47, 53, 61)

1:1

Week 0 Week 4 Week 12 Week 24

Placebo BID

NDPR = non-proliferative diabetic retinopathy
PDR = proliferative diabetic retinopathy
### Demographics

<table>
<thead>
<tr>
<th></th>
<th>APX3330 n=51</th>
<th>Placebo n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>54.3 (26-81)</td>
<td>58.3 (24-78)</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Sex: Male n (%)</strong></td>
<td>24 (47%)</td>
<td>26 (50%)</td>
</tr>
<tr>
<td><strong>Race: White n (%)</strong></td>
<td>40 (78%)</td>
<td>41 (79%)</td>
</tr>
<tr>
<td><strong>Ethnicity: Hispanic or Latino n (%)</strong></td>
<td>28 (55%)</td>
<td>23 (44%)</td>
</tr>
<tr>
<td><strong>Diabetes Status (years)</strong></td>
<td>15 (0-36)</td>
<td>16 (0-58)</td>
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<tr>
<td></td>
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<tr>
<td><strong>Systolic Blood Pressure (mmHg)</strong></td>
<td>136</td>
<td>139</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure (mmHg)</strong></td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td><strong>Heart Rate (beats/min)</strong></td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td><strong>Hemoglobin A1C (%)</strong></td>
<td>8.4</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td>31</td>
<td>31</td>
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</tbody>
</table>

### DRSS Scores

<table>
<thead>
<tr>
<th></th>
<th>APX3330 n=51</th>
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</thead>
<tbody>
<tr>
<td><strong>DRSS Score – Study Eye</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47 (Moderately severe to severe NPDR)</td>
<td>22 (43%)</td>
<td>18 (35%)</td>
</tr>
<tr>
<td>53 (Moderately severe to severe NPDR)</td>
<td>25 (49%)</td>
<td>28 (54%)</td>
</tr>
<tr>
<td>61 (Mild proliferative diabetic retinopathy)</td>
<td>4 (8%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td><strong>DRSS Score – Fellow Eye</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43 or Lower (Mild to moderate NPDR or better)</td>
<td>14 (31%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>47 (Moderately severe to severe NPDR)</td>
<td>13 (29%)</td>
<td>19 (39%)</td>
</tr>
<tr>
<td>53 (Moderately severe to severe NPDR)</td>
<td>12 (27%)</td>
<td>9 (19%)</td>
</tr>
<tr>
<td>61 (Mild proliferative diabetic retinopathy)</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>65 or Higher (Moderate to severe prolif. DR)</td>
<td>5 (11%)</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

Note: 15 fellow eyes were CST>320 microns (center-involved DME eyes)

### Key Visual Metrics

<table>
<thead>
<tr>
<th></th>
<th>APX3330 n=51</th>
<th>Placebo n=52</th>
<th>Total n=103</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCVA Study Eye Letters (mean)</strong></td>
<td>81</td>
<td>78</td>
<td>80 (20/25 Snellen)</td>
</tr>
<tr>
<td><strong>BCVA Fellow Eye Letters (mean)</strong></td>
<td>76</td>
<td>77</td>
<td>77 (20/32 Snellen)</td>
</tr>
<tr>
<td><strong>OCT CST Study Eye (µm)</strong></td>
<td>270</td>
<td>271</td>
<td>271</td>
</tr>
<tr>
<td><strong>OCT CST Fellow Eye (µm)</strong></td>
<td>292</td>
<td>286</td>
<td>289</td>
</tr>
<tr>
<td><strong>Intraretinal Fluid in the Center of SE</strong></td>
<td>Y – 21 N – 26</td>
<td>Y – 12 N – 31</td>
<td>Y – 33 N – 57</td>
</tr>
<tr>
<td><strong>Intraretinal Fluid at the Foveal Center of SE</strong></td>
<td>Y – 1 N – 20</td>
<td>Y – 1 N – 41</td>
<td>Y – 2 N – 61</td>
</tr>
<tr>
<td><strong>Intraocular Pressure in Study Eye (mmHg)</strong></td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

Source: ZETA-1 Clinical Trial
Percent of Subjects With ≥ 2-Step Improvement in DRSS From Baseline

ZETA-1 Did Not Meet the Week 24 Phase 2 Primary Endpoint (based on Anti-VEGF Precedence for DR)

Source: ZETA-1 Clinical Trial

Note: Large "N" indicates total number of participants within each arm for the mITT population. Small "n" indicates total number of evaluable eyes for each respective endpoint and arm.

Note: Images from Central Reading Center will be reviewed prior to EOP2 FDA meeting.
Clinically Meaningful Registration Endpoints in DR
Systemic Drugs Should Evaluate DRSS Change in Both Eyes; To Be Formally Confirmed at EOP2 FDA Meeting

FDA accepts improvement OR worsening (prevention of progression) in DR as endpoints

DRSS established as surrogate endpoint for DR

Recent preliminary discussions with FDA indicate binocular ≥ 3-step DRSS worsening (i.e., sum of right and left eye change in DRSS) could be acceptable for registration

➢ Distinct from historical anti-VEGF IVT endpoint precedent due to systemic delivery


Source: ZETA-1 Clinical trial
Percent of Subjects with Binocular Improvement or Worsening in DRSS at Wk 24

APX3330 Demonstrated Statistical Efficacy on the Planned Phase 3 Registration Endpoint

Percent of Subjects With Binocular Improvement or Worsening in DRSS of ≥ 1, ≥ 2, ≥ 3, and ≥ 4 Steps From Baseline (mITT-LOCF)

Source: ZETA-1 Clinical Trial; p values shown if p<0.20
% of Subjects With Binocular ≥ 3-Step Worsening in DRSS and Worsening of BCVA

APX3330 Prevented Progression of Structural Retinal Abnormalities and Reduced Worsening of Visual Function

Percent of Subjects With Worsening in DRSS of ≥3 Steps From Baseline by Visit Binocular Eyes (mITT-LOCF)

Visit

Week 12

Placebo (N=49)
APX3330 (N=46)

12% 0%
p=0.07

16% 0%
p=0.04

Week 24

n=49  n=45
n=49  n=45

Based on extrapolation from ZETA-1 and Rise/Ride extension trials¹, estimated ~25% of untreated patients may progress by ≥ 3 steps in binocular DRSS over 1 year

Percentage of Subjects with ≥ 5 Letters of BCVA Lost at Week 24 (Safety Population)

Treatment Group

Placebo (n=43)
APX3330 (n=40)

19% 5%
p=0.07

BCVA data shows function followed structure with fewer APX3330 treated subjects losing visual acuity compared to placebo at week 24

Source: ZETA-1 Clinical Trial; ¹ Sun JK, Evidence for DR Progression and Regression from Clinical Trials. Presented at NDI/FDA DR Clinical Trials Design and Endpoints Workshop, June 26, 2015.

Note: Images from Central Reading Center will be reviewed prior to EOP2 FDA meeting

Note: Large “N” indicates total number of participants within each arm for the mITT-LOCF population. Small “n” indicates total number of evaluable eyes for each respective endpoint and arm.
ZETA-1 Treatment Emergent Adverse Events
Oral APX3330 Showed a Favorable Safety Profile; Consistent with That Seen in Prior Trials

APX3330 Safety Profile:
- Limited AEs, most mild in severity
- AEs similar to or less than placebo (except for pruritis/rash)
- Few serious treatment-related AEs, all unrelated to study medication
- No ocular AEs other than expected DR progression
- No effect on clinical labs
- No adverse effects on heart, kidney, liver, CNS, GI
- No effect on vital signs (HR, BP)
- Patients continued routine medications to manage their diabetes comorbidities

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th>APX3330 (n=51)</th>
<th>Placebo (n=52)</th>
<th>Total (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs</td>
<td>91</td>
<td>120</td>
<td>211</td>
</tr>
<tr>
<td># of Subjects with AEs</td>
<td>29 (57%)</td>
<td>35 (67%)</td>
<td>64 (62%)</td>
</tr>
<tr>
<td>Treatment Related AEs</td>
<td>14 (45%)</td>
<td>17 (55%)</td>
<td>31 (30%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>3 (3%)</td>
<td>11 (9%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>Subjects Withdrawals Due to AEs</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

AEs in >5% of Subjects
- Diabetic Retinal Edema: 2 (4%) APX3330, 5 (10%) Placebo, 7 (7%)
- Diabetic Retinopathy: 1 (2%) APX3330, 6 (12%) Placebo, 7 (7%)
- Vitreous detachment: 0 (0%) APX3330, 3 (6%) Placebo, 3 (3%)
- Cataract: 3 (6%) APX3330, 1 (2%) Placebo, 4 (4%)
- Pruritus: 6 (12%) APX3330, 1 (2%) Placebo, 7 (7%)
- Rash: 3 (6%) APX3330, 1 (2%) Placebo, 4 (4%)
- COVID-19: 1 (2%) APX3330, 5 (10%) Placebo, 6 (6%)
Summary

- APX3330 first-in-class oral drug that inhibits Ref-1 which reduces VEGF and inflammatory cytokines to normal physiological levels

- Potential approvable endpoint for systemic (oral) drugs for DR treatment
  - Binocular ≥ 3-step worsening of DRSS

- Prevention of worsening is a clinically meaningful registration endpoint that was met in ZETA-1: *No subjects treated with APX3330 had a binocular ≥ 3-step DRSS worsening from baseline compared with 16% for placebo (p=0.04) after 24 weeks of treatment*

- APX3330 demonstrated favorable safety & tolerability in diabetic patients

- An EOP2 meeting with FDA is planned to advance to Phase 3 registration trials

We thank all the ZETA-1 study participants, investigators and their staff !!!