High-Dose Aflibercept
Rationale & Clinical Studies

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Take Home Messages

- Higher Dose Anti-VEGF improves anatomy / VA in historical RCTs
  - Aflibercept (Like most anti-VEGFs) has a linear PK curve
  - 8mg Aflibercept should provide two ½-lives more duration
- Variability in vitreous half-life makes standardized dosing/ clinical trial design challenging.
Disclosures

- Consultant / Clinical Trial Support from Regeneron & Competitors
Ranibizumab versus Bevacizumab for Neovascular Age-Related Macular Degeneration

The New England Journal of Medicine

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

The New England Journal of Medicine

MARINA

ANCHOR
Mean Change from Baseline (day 7)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Month</th>
<th>Mean Change in Visual Acuity (no. of letters)</th>
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<tr>
<td>0.5 mg of ranibizumab</td>
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<tr>
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<td>-6.2</td>
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<tr>
<td></td>
<td>24</td>
<td>-14.9</td>
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</tbody>
</table>
NEJM, Brown et al 2006
Figure 1. Mean change from baseline visual acuity (VA) score (letters) over time. Vertical bars represent ±1 standard error of the mean. The mean change at some visits in the first year differed slightly from those previously reported because the present analysis is based on the final data. \( P<0.001 \) for all comparisons versus verteporin photodynamic therapy (PDT) at each month. Pairwise analysis of variance models adjusting for VA score at day 0 (<45 letters vs. ≥45 letters) were used to analyze mean VA change from baseline at each monthly assessment. The last-observation-carried-forward method was used to impute missing data. All tests were 2-tailed.

Ophthalmology, Brown et al 2009
# CATT

**FLUID on OCT @ 1 Year**

Ranibizumab = 53.2%

Bevacizumab = 70.9%

## Table 2. Outcome Measures at 1 Year,

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ranibizumab Monthly (N = 284)</th>
<th>Bevacizumab Monthly (N = 265)</th>
<th>Ranibizumab as Needed (N = 285)</th>
<th>Bevacizumab as Needed (N = 271)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid on optical coherence tomography — no. (%)</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absent</td>
<td>174 (58.7)</td>
<td>186 (70.3)</td>
<td>168 (58.6)</td>
<td>170 (62.7)</td>
<td>0.197</td>
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<tr>
<td>Present</td>
<td>151 (53.2)</td>
<td>188 (70.9)</td>
<td>203 (71.2)</td>
<td>214 (79.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

NEJM, Martin et al 2011
SUPER DOSE ANTI-VEGF
(2.0 mg Ranibuzimab)
RECALCITRANT AMD

“Incomplete Responders”

- Persistent OCT or FFA activity on monthly therapy
- 50 Patients followed for 24 months
- Patients randomized to q4w vs q6w f/u with “Capped” PRN therapy
RECALCITRANT AMD

“Incomplete Responders”

- Sex = 25 male, 25 female
- Mean age = 77.3
- Prior injections = 26.8 (mean)
- Prior injections past year = 10.5 (mean)
SAVE 24 Month Anatomy

Change in Central Retinal Thickness

- Mean Change in Retinal Thickness from Baseline (μm)
- Cohort A
- Cohort B

Months:
- Loading Phase
- Variable Interval Phase
- Fixed Interval Phase
Treatment Burden Reduction

- Q6 Week arm had loss of Anatomy and VA
- 11.2 / 12.0 PRN injections required year 2
CONCLUSIONS

Will “Incomplete Responders” Respond with a higher dose?
CONCLUSIONS

Can Treatment Frequency be Reduced?
What Determines Drug Clearance?

- Axial Eye Length
- Pseudophakia
- Vitreous Syneresis
What Determines Drug Clearance?

Axial Eye Length
Psuedophakia
Vitreous Syneresis
SAVE (Super-dose Anti-VEF) Ranibizumab for Recalcitrant Age-Related Macular Degeneration

A two-year S.A.V.E. Trial: 2.0 mg Ranibizumab for Recalcitrant Neovascular AMD

Supertackle/Angle: Anti-VEGF (SAVE) Trial: 2.0 mg Intravitreal Ranibizumab for Recalcitrant Neovascular Macular Degeneration—Primary End Point

The Supertackle/Angle (SAVE) trial assessed the 2.0 mg ranibizumab 0.05 mg, a 4.6-fold higher dose than approved by the US Food and Drug Administration (FDA) and approved for the management of neovascular age-related degeneration (AMD) in 18 patients. The study results showed that the dose was safe and effective, with a statistically significant improvement in visual acuity compared to the placebo group. The primary outcome measure was the change in best-corrected visual acuity (BCVA) at month 24. The study concluded that 2.0 mg ranibizumab is well tolerated and provides a significant improvement in visual acuity in patients with neovascular AMD.

Methods: Patients with neovascular AMD were randomly assigned to receive 2.0 mg ranibizumab or placebo injections every 4 weeks for 1 year. BCVA was assessed at baseline and at 1, 3, 6, 9, 12, and 24 months. The primary outcome was the change in BCVA from baseline to month 24. Secondary outcomes included the change in central subfield thickness, choroidal thickness, and the number of injections required.

Results: A total of 18 patients completed the study. The mean age was 78 years (range 55-88), and 10 patients were male. The mean time from initial diagnosis to enrollment was 1.6 years. The mean change in BCVA from baseline to month 24 was 12.4 letters (range -1 to 26.0). The mean central subfield thickness decreased from 325.6 to 291.9 microns. The mean choroidal thickness decreased from 130.7 to 115.8 microns. The mean number of injections required was 17.2.

Conclusion: The 2.0 mg ranibizumab injections were well tolerated and provided a significant improvement in visual acuity and central subfield thickness in patients with neovascular AMD. The treatment was safe and effective, with a low number of adverse events reported.

Materials and Methods

The study was approved by the institutional review board and conducted in accordance with the tenets of the Declaration of Helsinki. All patients provided written informed consent. The study was performed at the U.S. National Institutes of Health (NIH) Clinical Center, Bethesda, Maryland, USA.
HARBOR Study Design
HARBOR will assess 2mg vs 0.5mg monthly and alternate dosing regimens

Phase III Wet AMD (N = 1100)
Randomized 1:1:1:1

- 0.5mg ranibizumab monthly
- 3 Loading Doses +0.5mg ranibizumab PRN
- 2mg ranibizumab monthly
- 3 Loading Doses +2mg ranibizumab PRN
Starting at Month 3, PRN groups were evaluated for retreatment monthly and treated if there was a \( \geq 5 \) letters decrease from previous visit \textbf{OR} any evidence of disease activity on SD-OCT.

* All groups continued same treatment schedule through Month 24.
Mean Change from Baseline in CFT by SD-O to Month 12

The last-observation-carried-forward (LOCF) method was used to impute missing data.
### Mean Change from Baseline in BCVA to Month 12

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change (Letters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg Monthly + 10.1 mg</td>
<td>12</td>
</tr>
<tr>
<td>2 mg Monthly + 9.2 mg PRN</td>
<td>10</td>
</tr>
<tr>
<td>2 mg PRN + 8.6 mg</td>
<td>8.2</td>
</tr>
<tr>
<td>0.5 mg PRN + 8.2 mg</td>
<td>8.0</td>
</tr>
</tbody>
</table>

**Mean # of Injections**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean # of Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg PRN</td>
<td>273</td>
<td>11.3</td>
</tr>
<tr>
<td>0.5 mg Monthly</td>
<td>275</td>
<td>7.7</td>
</tr>
<tr>
<td>2 mg Monthly</td>
<td>274</td>
<td>11.2</td>
</tr>
<tr>
<td>2 mg PRN</td>
<td>273</td>
<td>6.9</td>
</tr>
</tbody>
</table>

**Note:** Vertical bars are ±1 standard error of the unadjusted mean. The last observation carried forward (LOCF) method was used to impute missing data.
High-Dose Afiblercept

Rationale and Clinical Studies
Fixed dosing through year 1
modified quarterly dosing* through year 2

*During year 2, patients were evaluated every 4 weeks, and received doses at least every 12 weeks. Dosing could be as frequent as every 4 weeks.
VIEW: A 4X Increase in Aflibercept Dose Results in Significantly More Patients Achieving ≥12 Week Dosing

≥12 Weeks before 1\textsuperscript{st} Year 2 Injection

![Bar chart](chart1)

- 2q4: 72%*
- 0.5q4: 59%

*nominal $P<0.001$ vs 0.5q4

≥12 Weeks between ALL Year 2 Injections

![Bar chart](chart2)

- 2q4: 54%*
- 0.5q4: 43%

*nominal $P=0.0008$ vs 0.5q4

Observed; Full analysis set, 2Q4 n=613, 0.5Q4 n=597
Cumulative Incidence of Sustained* Dryness through Week 52

Sustained “dry” in ~50% of patients reached at week ~9 with 2 mg vs. week ~17 with 0.5 mg

*Sustained dryness = dry at two or more consecutive visits

“Dry” defined by masked reading center as absence of both cystic retinal edema and subretinal fluid on Time Domain-OCT
2 mg vs. 0.5 mg Aflibercept: Proportion of Patients without Fluid in the Center Subfield

*Nominal p<0.0001 vs 0.5q4

"Without Fluid" defined by masked reading center as absence of both cystic retinal edema and subretinal fluid on Time Domain-OCT.

Observed; Full analysis set, 2Q4 n=613, 0.5Q4 n=597
VIEW: Visual Acuity for Patients Dosed ≥12 Weeks in Year 2 with 2 mg

FAS, LOCF Pts Completing 2nd Year; 2q4 n=529;
Aqueous Humor Concentrations of Free Afibercept Over Time

- Five subjects with new-onset nAMD received intravitreal 2mg afibercept at Day 0
- Sampling of aqueous at 4 h post-dose and Days 1,3,7,14, and 28

Median Half-life of Free Afibercept in Aqueous

- Median Half-life = 11.0 days
- Mean Half-life = 9.1 days

LLOQ* = 0.078 mg/L

*LLOQ: lower limit of quantification
Do, D. Retina May 2019
Aqueous and Plasma Concentrations Vary Among Patients

Aqueous- Free Aflibercept Concentrations by Patient

LLOQ* = 0.078 mg/L

\[ T\frac{1}{2} = 3.7 \text{d} \]
\[ T\frac{1}{2} = 11 \text{d} \]

*LLOQ: Lower Limit Of Quantification
Do, D. Retina 00:1-5, 2019
In the DL-α-amino adipic acid (DL-AAA) rabbit model of chronic retinal vascular leak, the 8 mg equivalent dose of aflibercept increased duration of efficacy.

Normal rabbit fundus (FA)

8 weeks post DL-AAA (FA)

Eyes with complete leak suppression (%)

Weeks post-treatment

Regeneron data on file
Duration of Aflibercept Activity is Directly Related to Dose

* Assumes 11 d median half-life

Do, D. Retina May 2019
CLEAR-IT 2 (Phase 2 AMD): Greater Reduction in CR/LT Through Week 4 After Single Dose of 4 mg

CR/LT: Central retinal/lesion thickness manually measured on posterior pole scans with time-domain OCT included the thickness of the RPE/choriocapillaris complex  
FAS, LOCF

<table>
<thead>
<tr>
<th></th>
<th>2 mg (n=62)</th>
<th>4 mg (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>-29%</td>
<td>-42%</td>
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</tbody>
</table>
4 mg Aflibercept: Safety

- No new ocular / systemic safety signals identified in combined group of AMD patients (n=81) treated with 4 mg aflibercept
- No serious ocular AEs of intraocular inflammation
  - Only serious ocular AEs were retinal hemorrhage (1 patient) and retinal detachment (1 patient)
- In Phase 1 DME (n=5), 4 mg aflibercept was well tolerated
  - Four patients had ocular AEs, all of which were mild (including conjunctival hemorrhage in 3 patients)
High-Dose Aflibercept Phase 2 in AMD

Multi-center, randomized, single-masked
Patients with neovascular AMD (treatment naïve), N=100*
Randomized 1:1

IAI 2 mg
3 initial monthly injections

HD (8 mg)
3 initial monthly injections

Week 4:
Primary Endpoint: Safety

Week 20
Primary Endpoint: % pts without retinal fluid

Follow-up to Week 44 (End of Study)

NCT04126317
*Pharmacokinetic Substudy will include ~15 patients to be enrolled per treatment group
# High-Dose Afiblercept Phase 2 Dosing Schedule

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<thead>
<tr>
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<th>Day 1 (baseline)</th>
<th>Wk 4</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 16*</th>
<th>Wk 20</th>
<th>Wk 24</th>
<th>Wk 28</th>
<th>Wk 32</th>
<th>Wk 36</th>
<th>Wk 40</th>
<th>Wk 44</th>
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<tbody>
<tr>
<td><strong>IAI – 2 mg</strong></td>
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<td>PRN</td>
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<td><strong>HD – 8 mg</strong></td>
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*Additional treatment allowed after discussion with sponsor*
Afibercept 8 mg Clinical Studies – Current Status

• Phase 2, single-masked, study of 8 mg afibercept in neovascular AMD is currently enrolling

• Phase 3 studies in neovascular AMD and DME investigating dosing intervals of 12 weeks and longer will be initiated in 2020

VEGF = vascular endothelial growth factor
AMD = age-related macular degeneration
Take Home Messages

- Higher Dose Anti-VEGF improves anatomy /VA in historical RCTs
  - Afibercept (Like most anti-VEGFs) has a linear PK curve
  - 8mg Afibercept should provide two ½-lives more duration
- Variability in vitreous half-life makes standardized dosing/ clinical trial design challenging