OPTCEUTICS
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Higher doses can mean longer duration of action

- Aflibercept (Eylea®) is administered less frequently to patients than either ranibizumab (Lucentis®) or bevacizumab (Avastin®). More aflibercept molecules are in each dose than either ranibizumab or bevacizumab.
- The eye comprises two compartments and clearance of biologics is from the vitreous cavity to the anterior cavity. As the number of molecules increases in a dose, it takes a bit longer for half of the molecules to clear (modest increase in $t_{1/2}$). A larger dose also allows more half-lives to pass before a sub-therapeutic concentration is reached and the subsequent dose is required. This is known as extending the 'therapeutic tail' which can be estimated from $t_{1/2}$.
- Dose escalation studies are important during all drug development programs and can be useful for developing bio-betters.

The ease for dose escalation studies using the PK-Eye™

Because the eye is two compartments, the more molecules that are added to the vitreous cavity, the longer it will take until there is a sub-therapeutic dose remaining.

Aflibercept can be administered every other month because there is more aflibercept per dose (on a molar basis) than both ranibizumab and bevacizumab.

Drug	Dose (mg)	MWt Drug (kDa)	Dose ratio*	Dose frequency
ranibizumab	**0.5**	**50**	**1**	**once/month**
bevacizumab	**1.25**	**150**	**0.8**	**once/month**
aflibercept	**2.0**	**110**	**1.8**	**once/ 2 months**

*Molar ratio to ranibizumab

Human intravitreal injections are usually 50 µL. Volumes are much smaller in animals. Increasing the injection volume to increase dose is IMPOSSIBLE because of injury to the eye, so dose escalation studies require tedious and inexact reformulation.

Dose escalation studies in the PK-Eye™ are easy. All that is required is to increase the injected volume. The increased injection volume in the PK-Eye™ is small relative to the total vitreous volume (4.2 mL), so there is no effect on the simulated vitreous.

Bevacizumab (mg)	Volume (µL)	Half-life (days)
1.25	50	10.1 ± 0.7
2.5	100	15.4 ± 0.7
5.0	200	18.3 ± 1.1

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