

VEGF Trap-Eye in Wet AMD: Update on Phase 2 Studies

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The following document summarizes the final results of a phase 2 study of investigational VEGF Trap-Eye in neovascular AMD (the CLEAR-IT 2 study and 24-month extension results of the study). This document is intended for investigators of VEGF Trap-Eye and may also be provided to healthcare professionals who make unsolicited requests for information regarding the study results.

Please note that VEGF Trap-Eye is an investigational agent and that the safety and effectiveness of VEGF Trap-Eye has not been evaluated by regulatory authorities.

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**PROVIDED TO VEGF TRAP-EYE INVESTIGATORS OR IN RESPONSE TO
AN UNSOLICITED REQUEST**

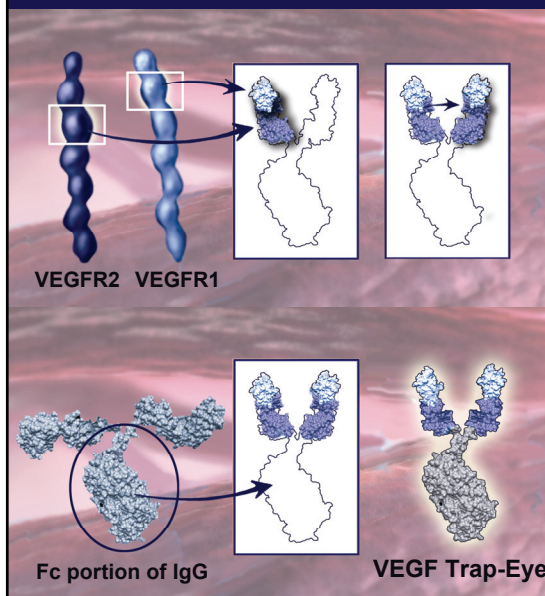
VEGF Trap-Eye in Wet AMD: CLEAR-IT 2 Extension Study Two-Year Update

A Phase 2, Randomized, Dose- and Interval-Ranging
Study of Intravitreal VEGF Trap-Eye in Patients With
Neovascular, Age-Related Macular Degeneration

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VEGF Trap-Eye: Specifically Designed to Block Members of the VEGF Family



- **Fusion protein** of key domains from human VEGF receptors 1 and 2 with human IgG Fc
- **Blocks all VEGF-A** isoforms and placental growth factor (**PlGF**)
- **High affinity** - binds VEGF-A and PlGF more tightly than native receptors
- Contains **all human** amino acid sequences
- **Penetrates** all layers of the retina (MW ~110,000)
- VEGF Trap-Eye is **specifically purified and formulated** for intravitreal injection

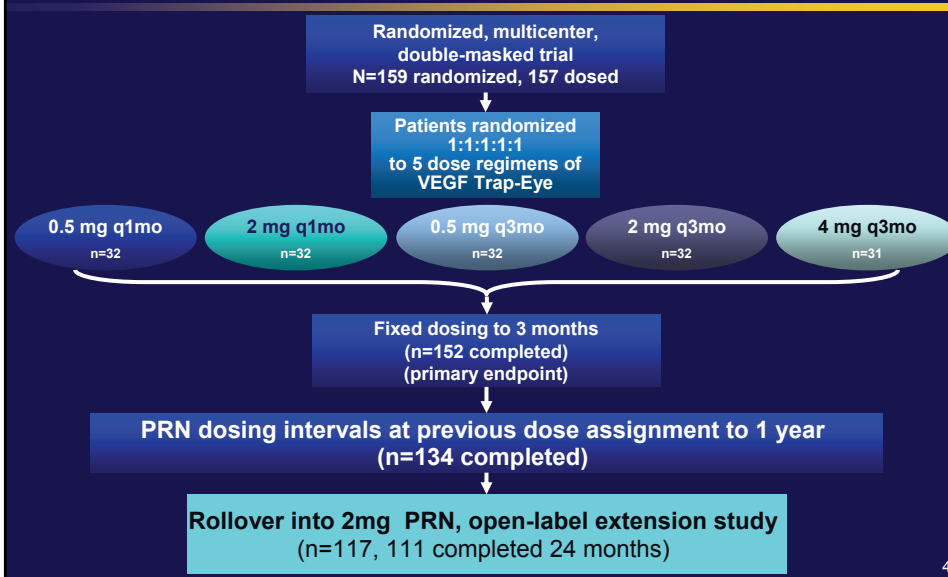
IgG=immunoglobulin G; MW=molecular weight

CLEAR-IT 2 Extension Study: Goals

- To evaluate the impact of VEGF Trap-Eye dosed on an as-needed (PRN) basis on maintenance of visual acuity gained after a 12-week fixed dosing interval
- To evaluate the long-term safety of VEGF Trap-Eye dosed on an as-needed (PRN) basis

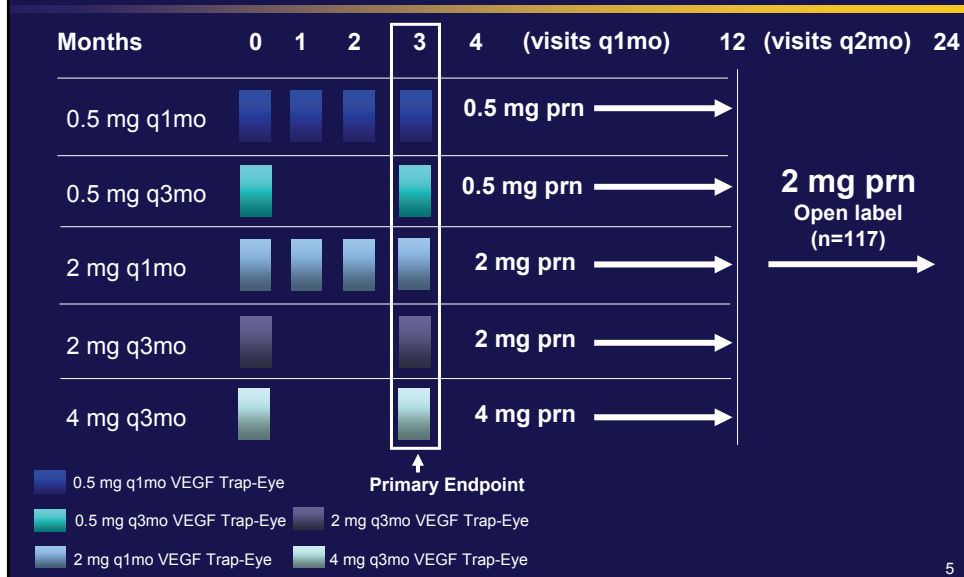
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CLEAR-IT 2 Extension Study: Design



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CLEAR-IT 2 Extension Study Schedule through 24 Months



CLEAR-IT 2 Extension Study: Baseline Characteristics

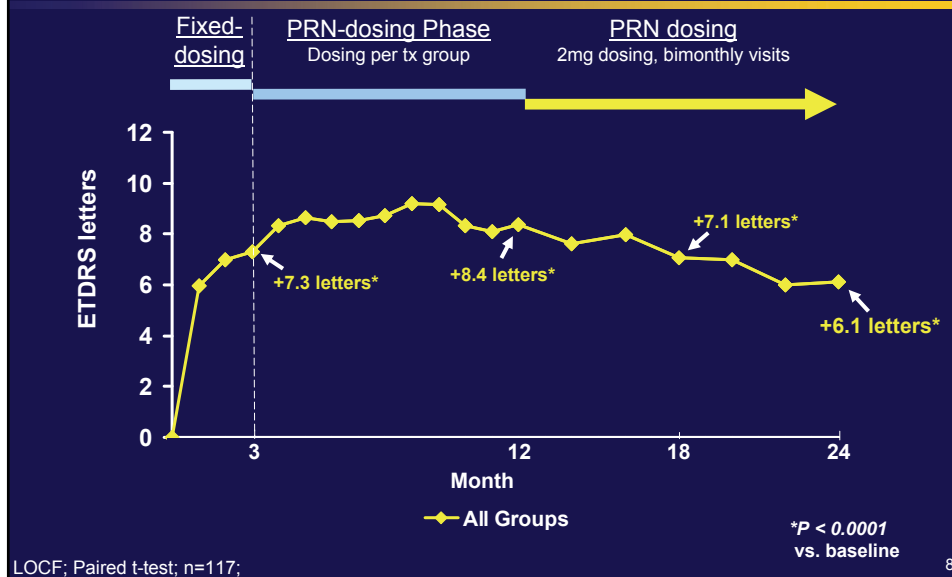
(n=117*)		Mean	Range
Age (years)		76.8	53 – 92
Gender (% M:% F)		40% : 60%	
Disease Duration (months)		4.13	0.1 – 67
Lesion Size (mean±SD) in disc areas		2.51 ± 1.93	
Lesion Type: number (%)			
Classic and Predominantly Classic		44 (38%)	
Minimally Classic		27 (23%)	
Occult Lesions		46 (39%)	
Disease Status			
Central Retinal/Lesion Thickness		450 µm	186 – 1316 µm
Foveal Thickness		326 µm	116 – 1081 µm
ETDRS BCVA (letter score)		56	27-83

*n=117 rolled into extension study; n=111 completed 24 months

Visual Acuity

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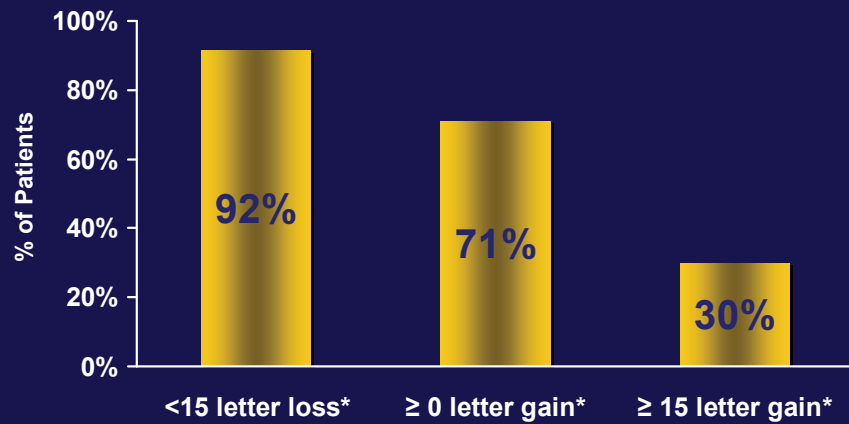
CLEAR-IT 2 Extension Study: Mean Change in Visual Acuity to 24 Months (n=117)



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CLEAR-IT 2 Extension Study: Visual Acuity at 24 Months compared to Baseline

30% of patients gained ≥ 3 lines of vision at 24 months



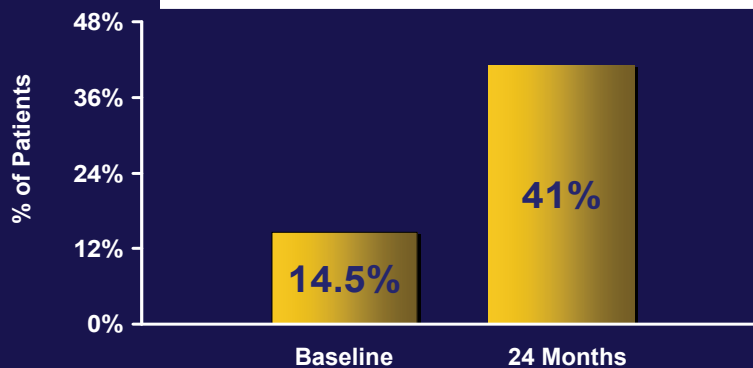
*Compared to baseline; LOCF; n=117

■ All Groups

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CLEAR-IT 2 Extension Study: Proportion of Patients w/ $\geq 20/40$ Vision at 24 Months

More patients achieved driving vision at 24 months compared to baseline



All groups combined; LOCF analysis; n=117;

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PRN Phase Injections

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Re-dosing Criteria

(starting at week 16)

- Persistent fluid on OCT
- A loss of ≥ 5 ETDRS letters with recurrent fluid on OCT
- New or persistent leak on FA
- New macular hemorrhage
- Central retinal thickness $\geq 100 \mu\text{m}$ on OCT
- New onset classic neovascularization

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CLEAR-IT 2 Extension Study:
Frequency of Re-injection over 21-month PRN Phase (n=117)

	Mean	Median	Range
Number of re-injections over 21-month PRN phase *	4.6 ± 3.4	4	0 – 16

* Over 21 months of PRN phase (after the month 3 injection through month 24)

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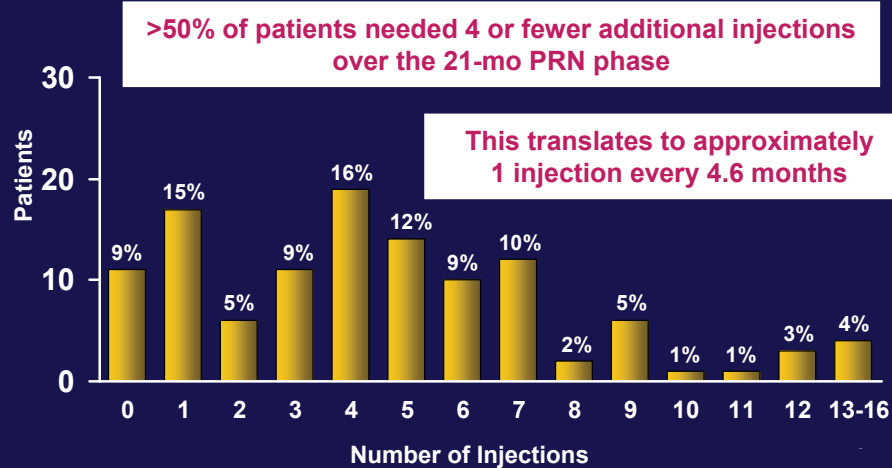
CLEAR-IT 2 Extension Study:
Timing of Re-injection over 21-month PRN Phase (n=117)

	Mean	Median	Range
Number of days to first PRN injection *	173 ± 174 (5.8 months)	112	21 – 616
Number of days between 1st and 2nd PRN injection *	99 ± 67 (3.3 months)	84	22 – 350

* Over 21 months of PRN phase (after the month 3 injection through month 24)

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CLEAR-IT 2 Extension Study: Distribution of Injections over 21-month PRN Phase (n=117)



*Number of patients receiving given number of injections over 21 months of PRN phase (after the month 3 injection through month 24); n=117

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Safety

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CLEAR-IT 2 Plus Extension Study:
Adverse Events ≥ 5% from randomization through 24 Months
Study eye and injected fellow eye (n=157)

Adverse Event	Number (N=157)	Percent (%)
Conjunctival Hemorrhage	63	40.1
Increased Intraocular pressure (post-injection)	31	19.7
Visual Acuity Reduced (patient reported)	29	18.5
Retinal Hemorrhage	28	17.8
Refraction Disorder	26	16.6
Vitreous Detachment	20	12.7
Eye Pain	20	12.7
Cataract	14	8.9
Vitreous Floaters	14	8.9
Detachment of Retinal Pigment Epithelium	14	8.9
Retinal Edema	12	7.6
Subretinal Fibrosis	12	7.6
Dry Eye	11	7.0
Blepharitis	10	6.4
Visual Disturbance	8	5.1
Eye Irritation	8	5.1
Macular Degeneration	8	5.1

CLEAR-IT 2 plus Extension:
Serious Adverse Events from randomization through 24 Months
Study eye and injected fellow eye (n=157)

Ocular Serious Adverse Events in the study eye:

- 1 case of culture-negative endophthalmitis / uveitis

Systemic Serious Adverse Events:

- 5 deaths
 - Pulmonary hypertension
 - Pancreatic carcinoma
 - Pulmonary Failure
 - Squamous cell lung cancer
 - Cerebrovascular accident
- Arterial Thromboembolic Events (ATE's):
 - 2 cerebrovascular accidents (1 fatal)
 - 2 myocardial infarction

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CLEAR-IT 2 Extension Study: Conclusions

Over a 3-month course of fixed dosing VEGF Trap-Eye established **clinically significant improvements in BCVA**

These improvements in vision were **maintained** over the course of a **21-month**, PRN dosing phase

Patients received, on average, **4.6 additional injections** over the 21-month PRN-dosing phase (after 3-month fixed dosing).
This translates to 1 dose every 4.6 months.

9% received **no additional injections** and >50% needed **4 or fewer** additional injections over 21-month PRN phase

VEGF Trap-Eye was generally well tolerated with AE's typical of those reported for other intravitreally-administered compounds

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