

# Population Analysis of wet-AMD Disease Progression and The Therapeutic Effect of Ranibizumab

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## BACKGROUND

- Late stage age-related macular degeneration (AMD) is a leading cause of vision loss in the Western world in adults aged 50 years and older. Although the neovascular form (wet-AMD) only accounts for approximately 10%–20% of cases, it is responsible for 80%–90% of the significant visual loss associated with AMD, and if left untreated it may cause legal blindness.
- Vascular endothelial growth factor A (VEGF-A), an angiogenic cytokine, has been implicated as an important factor promoting both angiogenesis and microvascular leakage for wet-AMD.
- Ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA) is a humanized monoclonal antibody antigen binding fragment (Fab) engineered to bind with high affinity and to potently inhibit all known biologically active isoforms of VEGF-A [1]. Intravitreal (ITV) administration of ranibizumab on a monthly or *pro re nata* (prn) basis is associated with significant stabilization and improvement of visual acuity (VA).

## OBJECTIVE

- The aim of this study was to develop a population-based model to describe wet-AMD disease progression and the therapeutic effect of ranibizumab.

## METHODS

### Patients and data

- VA data from 2 randomized Phase III studies were utilized in model development.

#### 1. MARINA

- Patients (N=716) were enrolled with either minimally classic or occult choroidal neovascularization (CNV). Subjects were randomized in a 1:1:1 ratio to receive 24 monthly ITV injections of 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections. In all, 233 subjects in sham group and 477 subjects in treatment group were used in model development. In the sham group, the data collected after switching to 0.5-mg ranibizumab treatment were excluded.

#### 2. PIER

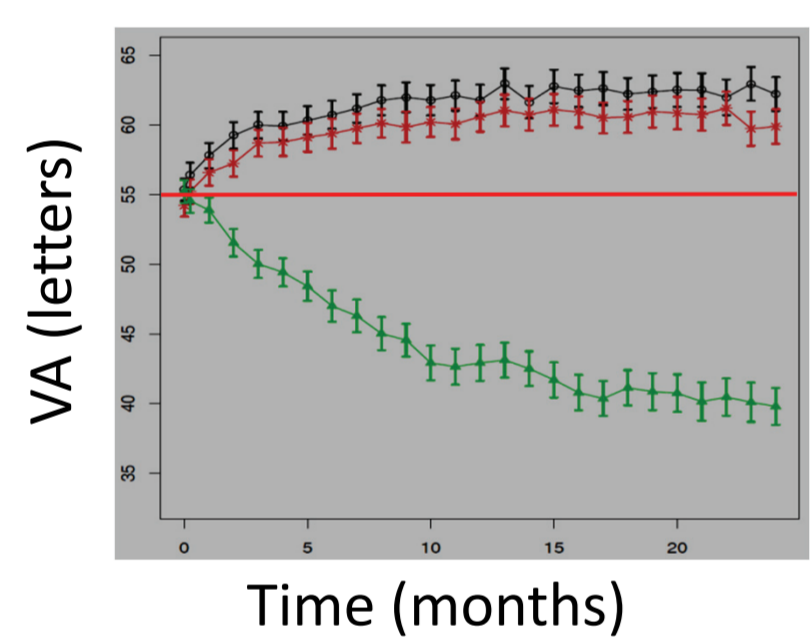
- Patients (N=184) were enrolled with predominantly or minimally classic or occult CNV. Subjects were randomized in a 1:1:1 ratio to ITV 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections. The treatment regimen included 3 monthly injections followed by quarterly injections to Month 24. A total of 62 subjects in the sham group and 120 subjects in the treatment group were used in model development. In the sham group, only 12-month data were included, as most patients switched to 0.5-mg ranibizumab treatment after Month 12.

## Disease progression model

- The natural progression of wet-AMD was modeled as a simple dynamic process (Fig.1) [2] using the data from the sham groups of the 2 trials.

$$dVA(t) / dt = VA_{prod} - VA_{deg} \cdot VA(t), \quad VA(0)$$

- Without treatment, assuming VA will approach a steady-state value, the percent decrease (Pdelta) from baseline VA was calculated using the estimated population mean value of VA(0), Vaprod, and VAdeg.



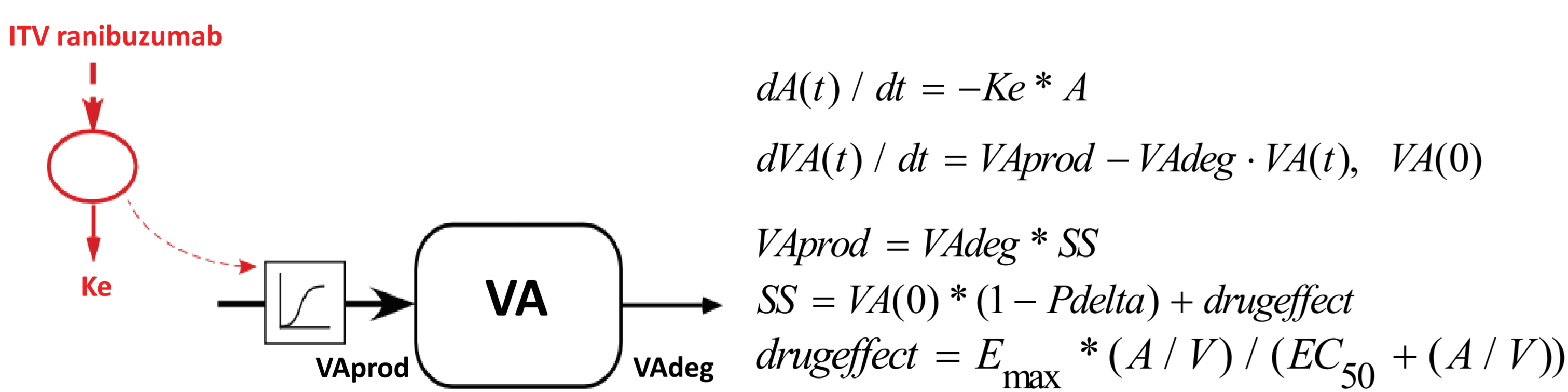
Relative decrease in VA from baseline (Pdelta) at steady state untreated value

$$Pdelta = (VA(0) - (VA_{prod} / VA_{deg})) / VA(0)$$

## Modeling of therapeutic effect

- The effect of ranibizumab was modeled separately using data from treatment arms (Fig. 1). Ranibizumab exposure in the vitreous was used directly as the driving force to alter VA profile.

### Fig. 1. Exposure response model structure for ranibizumab (PK-VA model)



$$dA(t) / dt = -Ke * A$$

$$dVA(t) / dt = VA_{prod} - VA_{deg} \cdot VA(t), \quad VA(0)$$

$$VA_{prod} = VA_{deg} * SS$$

$$SS = VA(0) * (1 - Pdelta) + drugeffect$$

$$drugeffect = E_{max} * (A / V) / (EC_{50} + (A / V))$$

A: amount of ranibizumab in the vitreous; Ke: rate of elimination of ranibizumab from the vitreous; PK: pharmacokinetics; V: volume of vitreous humor (fixed at 4 mL); VA(0): baseline VA in letters; VAprod: production rate constant of VA (generation of photoreceptor activity); VAdeg: turn-over rate constant of VA (degradation of photoreceptor activity), describing the rate of deterioration or improvement of VA in sham and treatment groups.

### The following assumptions were applied in the model for therapeutic effect:

- The use of population mean value [3] from previous population PK model to simulate the concentration–time profile of ranibizumab in the vitreous for all treated patients.
- Without treatment, VA for patients in the treated group will decrease by the same percentage (Pdelta) from their individual baseline.
- The drug concentration in the vitreous regulated the presumed steady-state untreated VA level in a concentration-dependent manner (Emax sigmoidal model). The maximum improvement in VA after ranibizumab treatment (Emax) was individualized as:

$$E_{max} = MAX_{BCVA} - VA(0) * (1 - Pdelta) \quad MAX_{BCVA} = 100 \text{ letters}$$

BCVA: best-corrected visual acuity

## DATA ANALYSIS

- To avoid unidentifiability issues, data from sham and treatment groups were fitted separately to model the disease progression process of wet-AMD and the therapeutic effect of ranibizumab.
- To better capture the initial VA benefit during the first 3 months of treatment, in the final model baseline VA value was fixed to the individual value for the treated patients.
- The estimated parameters were assumed to follow log-normal distribution. The additive residual error model was adopted.
- Maximum likelihood expectation maximization (MLEM) population module in APADT 5 was used for model development [4]. Dose and trial stratified visual predictive check (VPC) were used for model evaluation.

## RESULTS

**Table 1. Final parameter estimates for disease progression model using MARINA and PIER**

Parameter	Final Estimate (%RSE)
Evaluable subjects (n)	295
Evaluable data points	5761
VAprod (letters/day)	0.10 (12.5)
VAdeg (letters/day)	0.0037 (10.4)
TempVA0	0.761 (4.38)
VA0 (letters)*	56.8
Additive error, as SD	6.40 (0.355)
IIV_VAprod (%)	136 (14.0)
IIV_VAdeg (%)	123 (10.3)
IIV_Temp VA (0) (%)	59.8 (5.76)
IIV_VA(0) (%)*	25.9

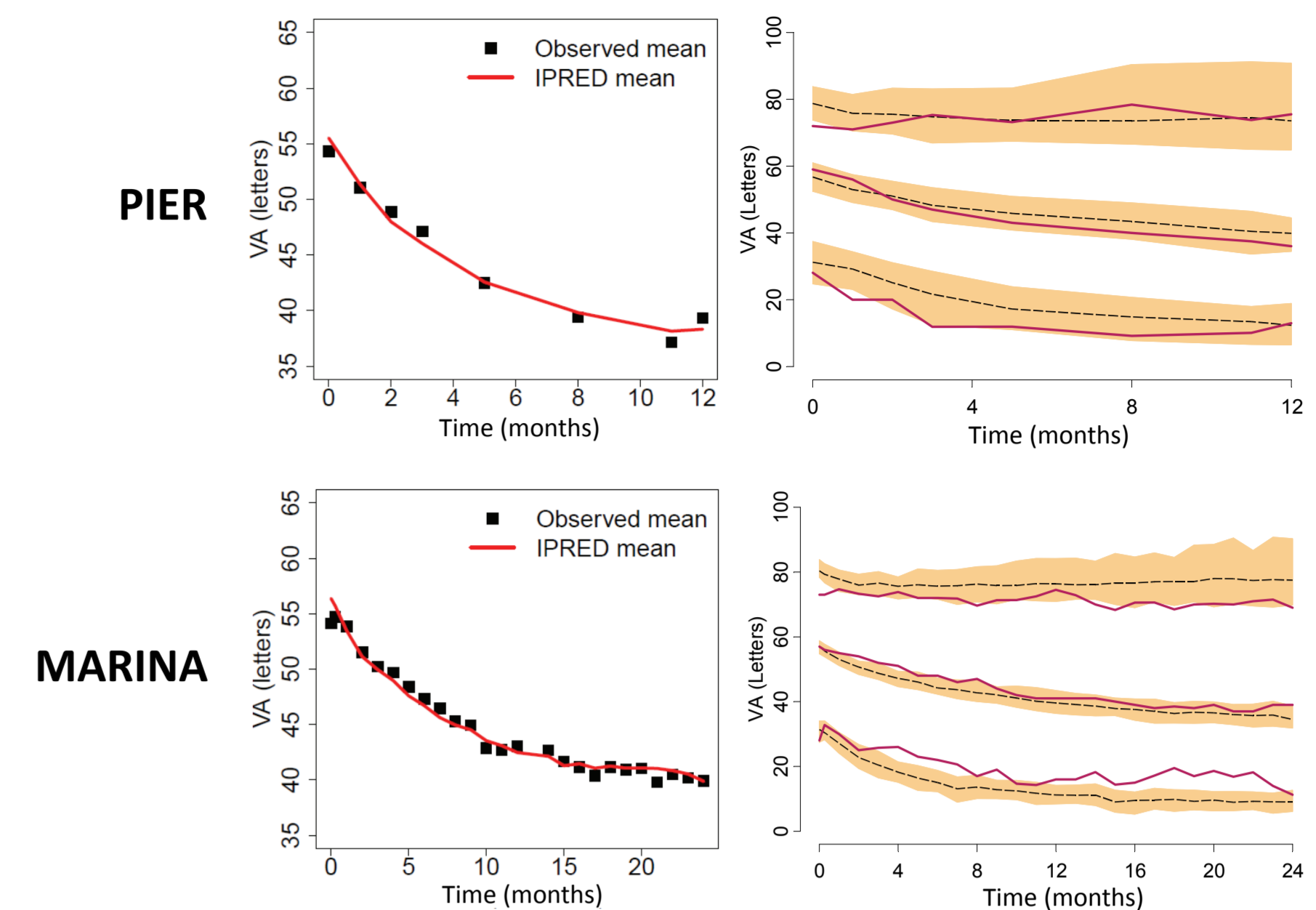
\*To improve VPC, VA0 set from 0 to 100 by 100/(1+TempVA0)  
IIV: inter-individual variability; SD: standard deviation

**Table 2. Final parameter estimates for the treatment model using PIER**

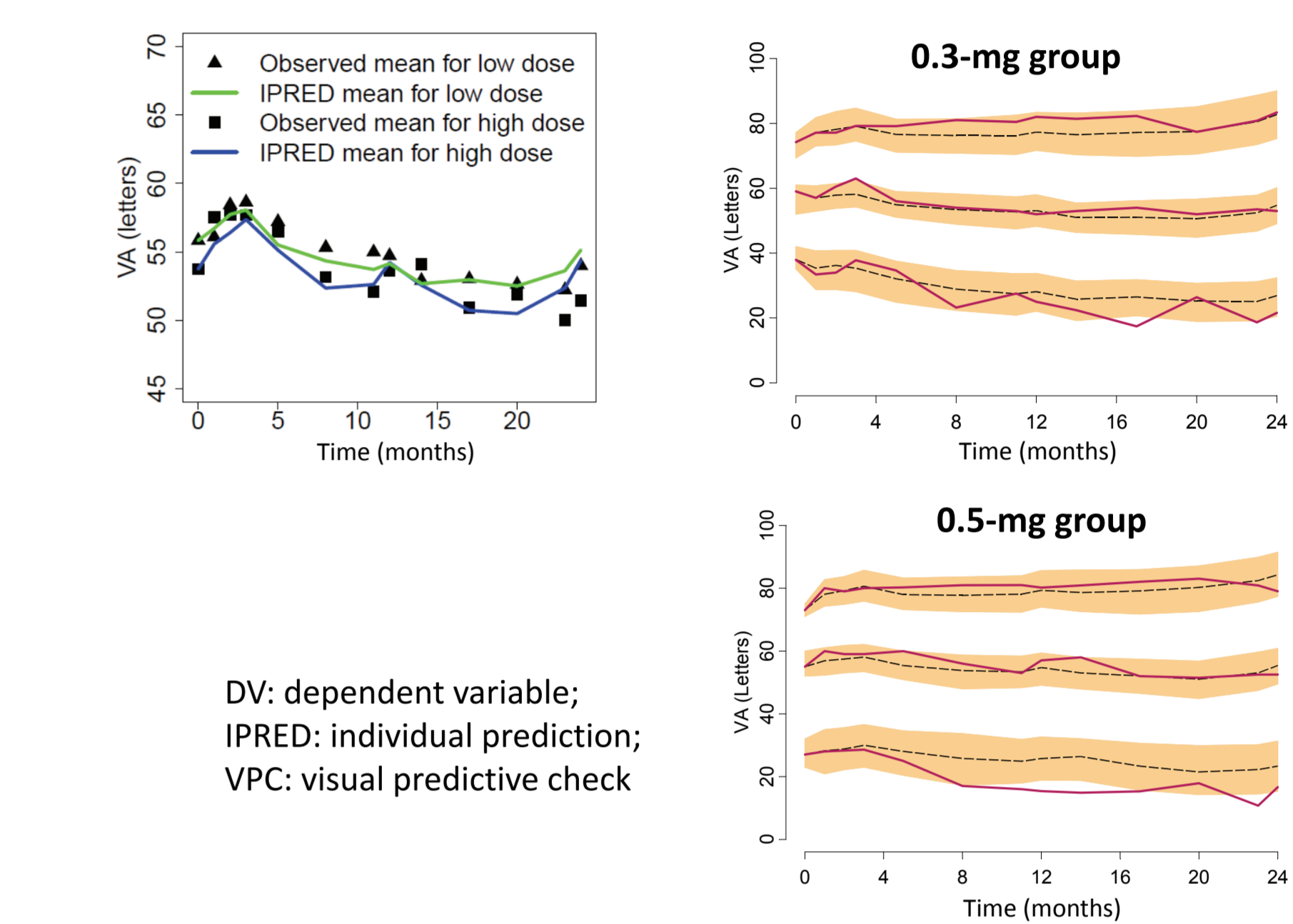
Parameter	Final Estimate (%RSE)
Evaluable subjects (n)	120
Evaluable data points	1642
TempEC <sub>50</sub> (letters/day)	6.56 (28.8)
VAdeg (letters/day)	0.00226 (11.8)
Ke (1/day)	0.08 fix
V (mL)	4.0 fix
Pdelta	0.528 fix
Emax (letters)†	74.15
EC <sub>50</sub> (mg/mL)*	0.0106
Additive error, as SD	6.91 (0.759)
IIV_TempEC <sub>50</sub> (%)	267 (29.7)
IIV_VAdeg (%)	93.7 (14.1)
IIV_Emax (letters)†	8.89
IIV_EC <sub>50</sub> (%)*	267

\*To improve VPC, EC<sub>50</sub> was set from 0 to 7.0 by 7.0/(1+TempEC<sub>50</sub>)  
†Emax=100–VA0\*(1–Pdelta); VA0: individual baseline VA  
IIV: inter-individual variability; Ke: rate of ranibizumab elimination from the vitreous; SD: standard deviation; V: volume of vitreous humor

**Fig. 2. Mean IPRED vs DV plot and VPC for disease progression model: MARINA & PIER**

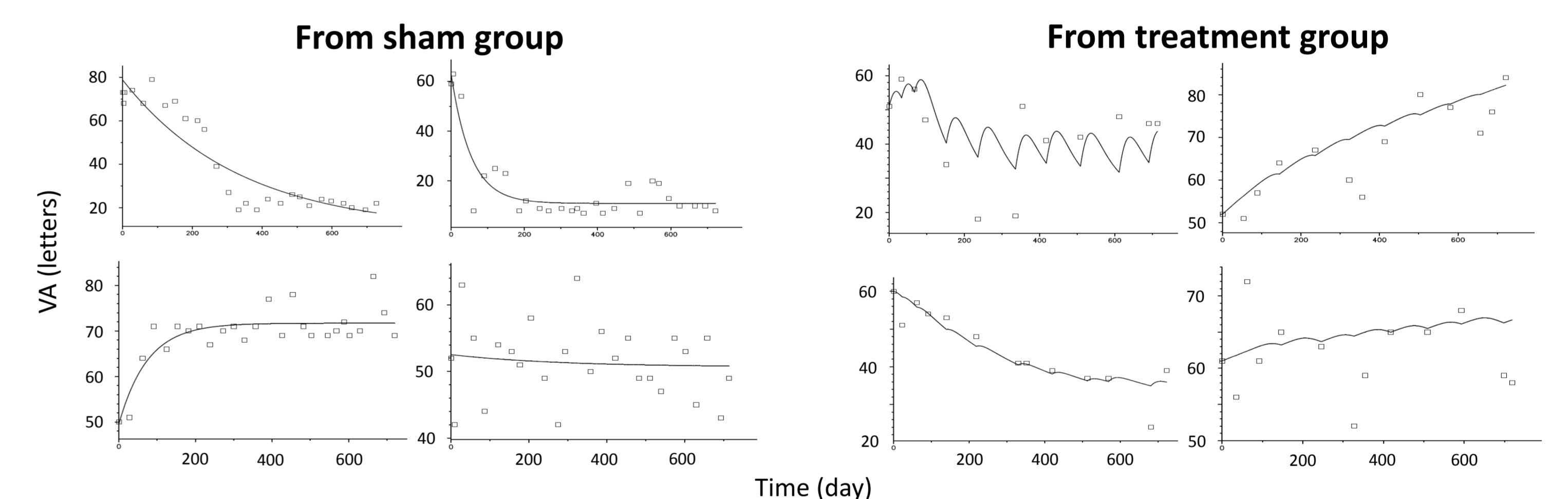


**Fig. 3. Mean-IPRED vs DV plot and VPC for treatment model: PIER 0.3-mg & 0.5-mg groups**

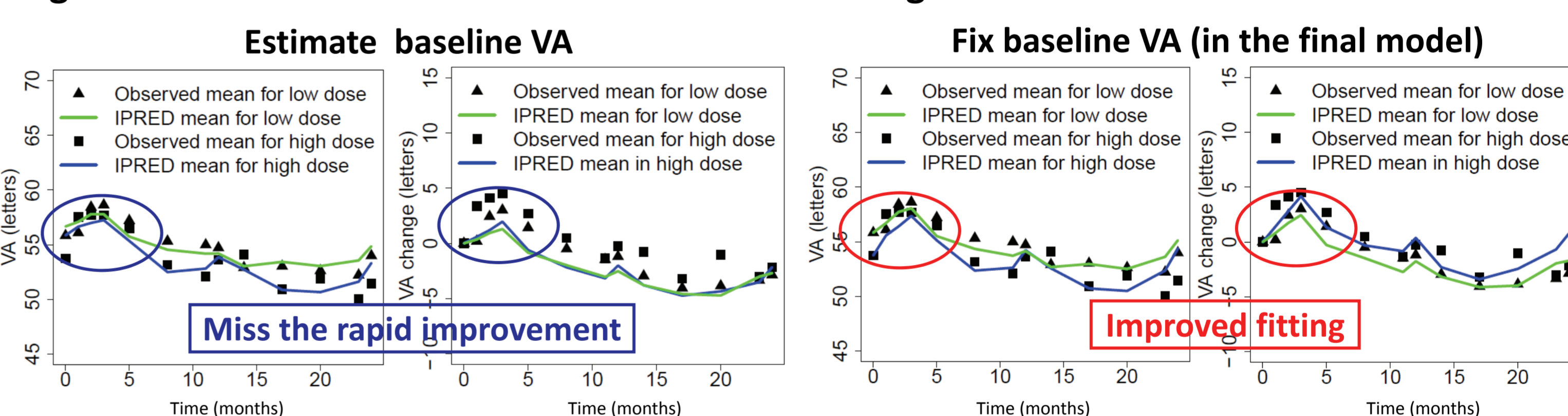


DV: dependent variable;  
IPRED: individual prediction;  
VPC: visual predictive check

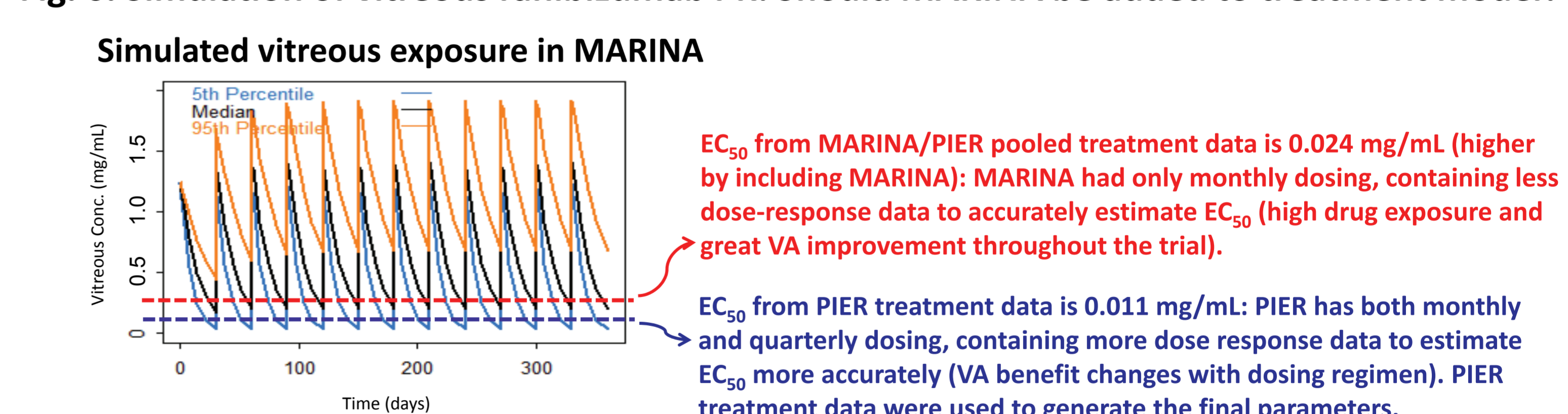
**Fig. 4. Representative fits for patients from sham and PIER treatment groups**



**Fig. 5. Mean-IPRED vs DV for PIER treatment showing the reason to fix baseline VA**



**Fig. 6. Simulation of vitreous ranibizumab PK: Should MARINA be added to treatment model?**



## CONCLUSIONS

- The VA profiles were well described by the disease progression model for patients in the sham groups, and by the drug-effect model for patients treated with ranibizumab: slight over estimate of disease progression model for MARINA sham group based on VPC.
- The mean value of Pdelta was 52.8%, indicating that the VA in untreated patients will eventually decrease by half, on average, from their baseline.
- The population mean value of EC<sub>50</sub> for the effect of ranibizumab on VA was 0.011 mg/mL, and was below the average trough concentration of ranibizumab in the vitreous following the FDA-approved 0.5-mg per eye monthly regimen (approximately 0.02 mg/mL).
- Compared with MARINA, PIER provided more informative VA data to support the analysis of ranibizumab exposure–response relationship in AMD patients.
- This model could be used to access the effects of varied dosing scenarios and PK/PD properties on the disease progression of wet-AMD.

## REFERENCES

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