

## Context

Hereditary Haemorrhagic Telangiectasia (HHT) is a genetic disorder of the blood vessels, which affects 1 in 5,000 people. Patients with HHT suffer from unpredictable, recurrent, severe nasal bleeding which requires emergency care, nasal packing, blood transfusions, and invasive procedures. Anti-vascular endothelial growth factor (VEGF) drugs, such as bevacizumab (Avastin®), were previously shown to be effective in HHT. Concentration-effect relationship has not been described yet.

## Objectives

### To describe

- The pharmacokinetics of bevacizumab and its influence on VEGF concentrations.
- The relationship between VEGF concentrations and the reduction of epistaxis duration in HHT.

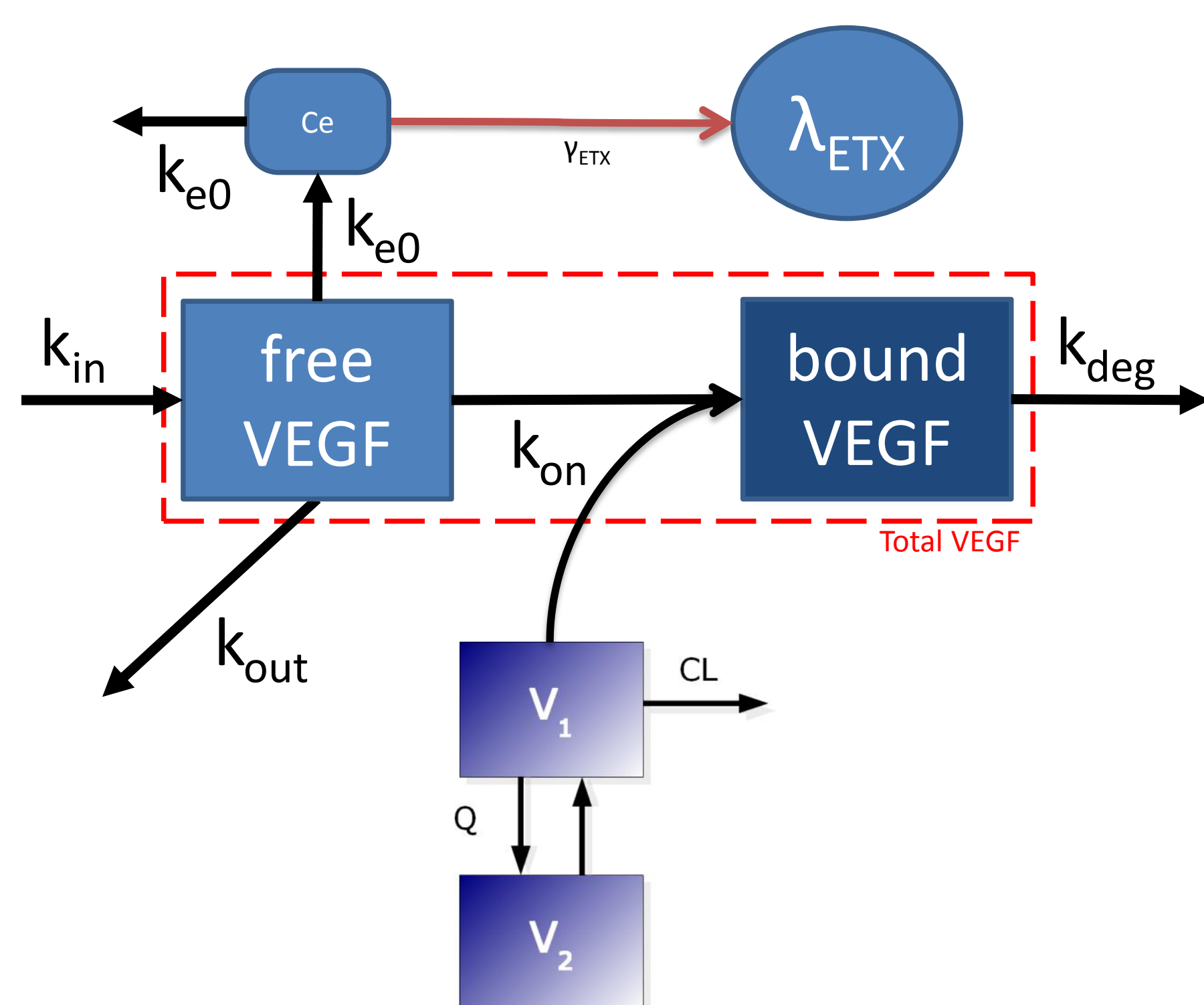
## Patients and method

- Twenty-four patients were included in a single-center, phase 2 trial. Patients had confirmed HHT, severe liver involvement, and a high cardiac index related to HHT.
- Bevacizumab was administered as infusions of 5 mg/kg, every 14 days for a total of 6 injections.
- A total of 230 and 140 blood samples were available for analysis of bevacizumab and total VEGF concentrations, respectively.
- Daily epistaxis durations were collected every day during 14 months, starting two months before initiation of treatment.

|                          | Median | Range         |
|--------------------------|--------|---------------|
| Body weight (kg)         | 58.5   | (41 - 80)     |
| BSA (m <sup>2</sup> )    | 1.66   | (1.31 - 1.91) |
| BMI (kg/m <sup>2</sup> ) | 22.6   | (15.1 - 31.6) |

Table 1: Patients characteristics - BSA: Body Surface Area, BMI: Body Mass Index.

## PK-PD model



Bevacizumab concentrations were described using a two-compartment model with first-order elimination. Concentrations of free and bound VEGF were described using a semi-mechanistic model. Free VEGF production and elimination are described by zero-order ( $k_{in}$ ) and first-order ( $k_{out}$ ) constants, respectively. Bevacizumab binds to free VEGF with a second-order constant ( $k_{on}$ ). Bevacizumab-VEGF complex is assumed to be totally eliminated with a first order constant ( $k_{deg}$ ). Free VEGF concentration was extrapolated from bound and total VEGF concentrations. In addition, free VEGF concentrations are assumed to influence (via an effect compartment  $C_e$ ) the  $\lambda_{ETX}$  parameter of the Poisson distribution of the daily epistaxis durations (categorized by 10 minutes).

## Results

- Bevacizumab concentrations were satisfactorily described by the PK model.
- Free VEGF concentrations were correctly extrapolated from total VEGF concentrations.
- No covariate influenced significantly Pk or PK-PD parameters.
- The low value of  $k_{e0}$  showed a long-lasting effect of free VEGF concentration reduction.

|                                                   | $\theta$ (% s.e.) | $\omega$ (% s.e.) |
|---------------------------------------------------|-------------------|-------------------|
| $V_1$ (L)                                         | 1.9 (4)           | 0.2 (13)          |
| $CL$ (L·day <sup>-1</sup> )                       | 0.1 (8)           | 0.4 (16)          |
| $V_2$ (L)                                         | 1.2 (9)           | 0.7 (21)          |
| $Q$ (L·day <sup>-1</sup> )                        | 0.35 (8)          |                   |
| $b_{BVZ}$                                         | 0.127 (5)         |                   |
| $k_{in}$ (nmol·day <sup>-1</sup> )                | 0.001 (21)        | 0.4 (32)          |
| $k_{out}$ (day <sup>-1</sup> )                    | 2.04 (4)          |                   |
| $k_{on}$ (nmol <sup>-1</sup> ·day <sup>-1</sup> ) | 0.007 (16)        |                   |
| $k_{deg}$ (day <sup>-1</sup> )                    | 0.14 (18)         | 0.8 (19)          |
| $k_{e0}$ (day <sup>-1</sup> )                     | 0.003 (7)         | 1.0 (12)          |
| $a_{VEGF}$                                        | 0.0375 (6)        |                   |
| $\lambda_0$                                       | 5.9 (31)          | 1.5 (14)          |
| $\gamma_{ETX}$                                    | 2.1 (2)           |                   |

Table 2: Estimates of model parameters.

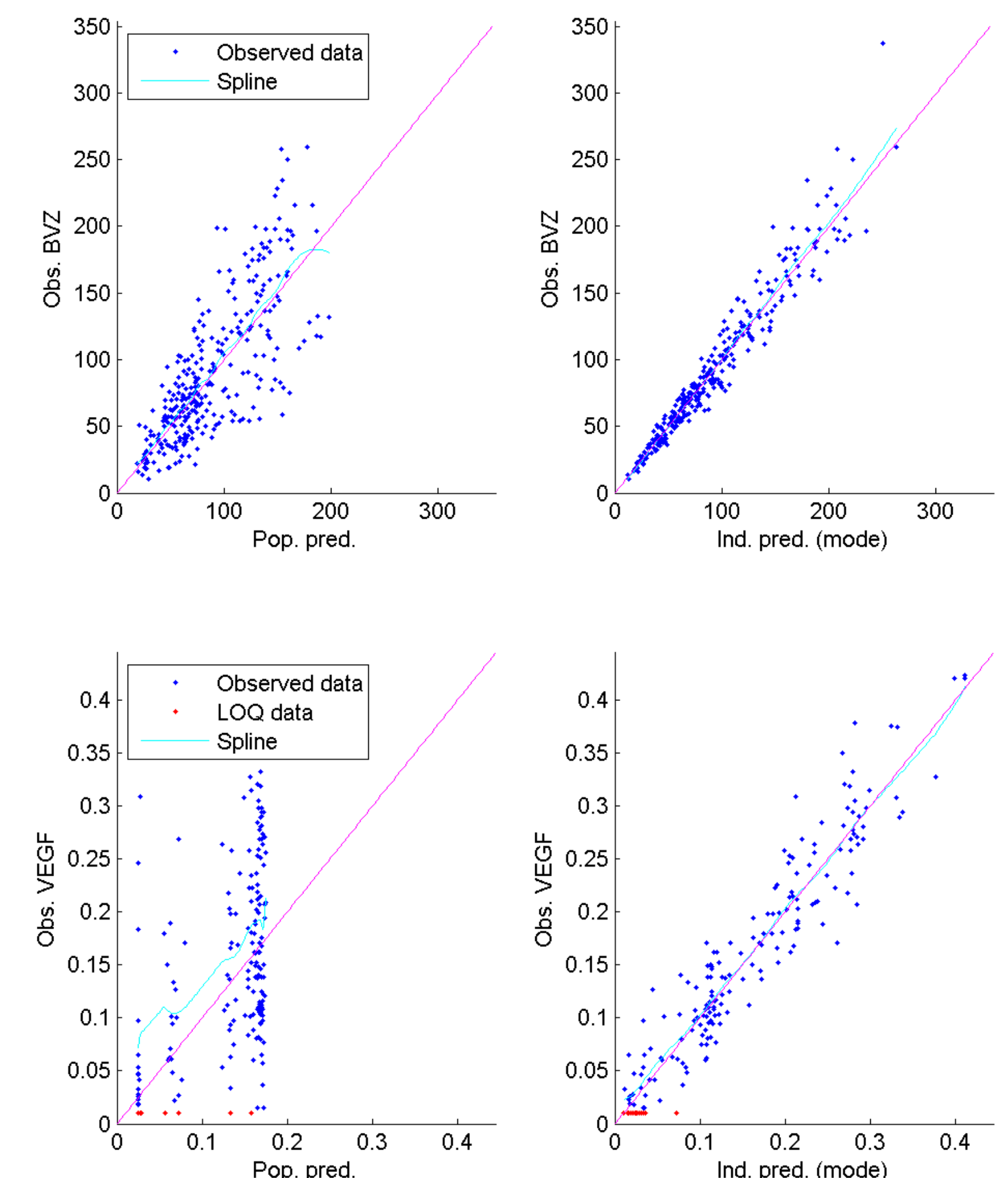
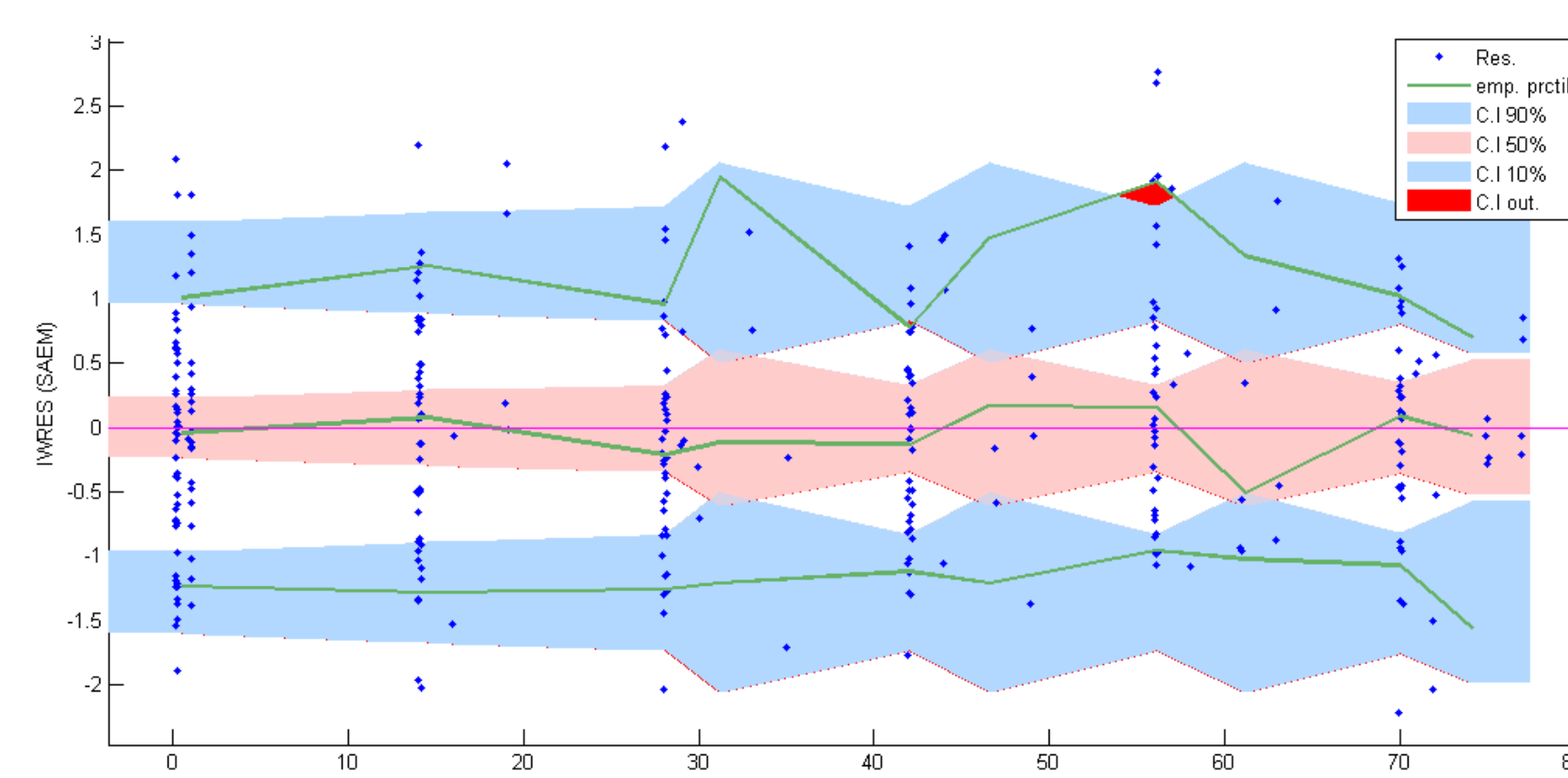


Figure 1: Population and individual model-predicted vs observed concentrations for bevacizumab, VEGF and CI, respectively.

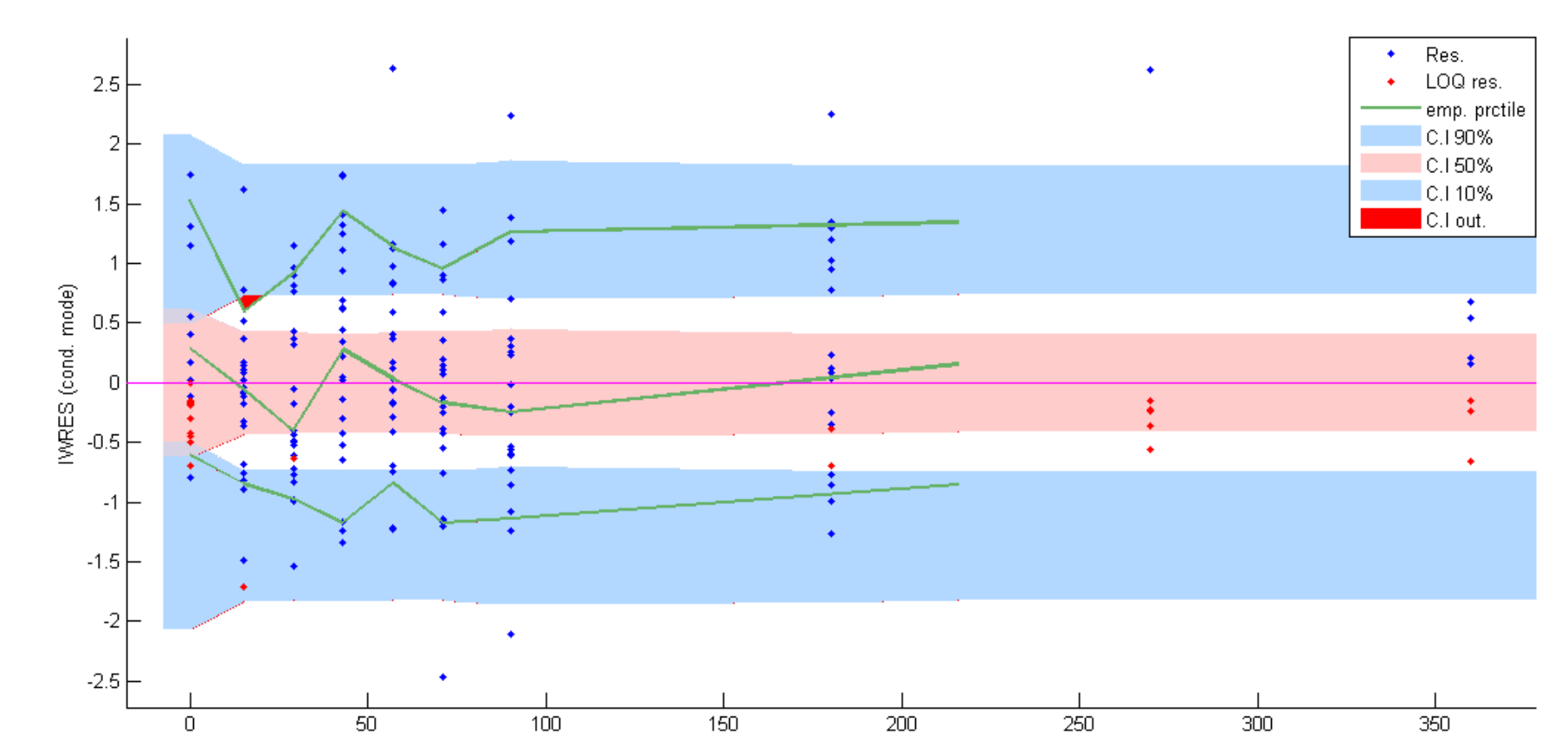


Figure 2: Individual residual distributions over time for bevacizumab concentrations (left) and total VEGF concentrations (right)

## Daily Epistaxis duration

Daily epistaxis durations were categorized by 10 minutes up to 1 hour.

The probability distribution function of the categorical duration of epistaxis ( $dETX$ ) is defined as  $P(dETX = k)$ :

$$P(dETX = k) = \frac{e^{-\lambda_{ETX}} \times \lambda_{ETX}^k}{k!}$$

where,

$$\lambda_{ETX}(t) = \lambda_0 \times \left( \frac{Ce(t)}{Ce(0)} \right)^{\gamma_{ETX}}$$

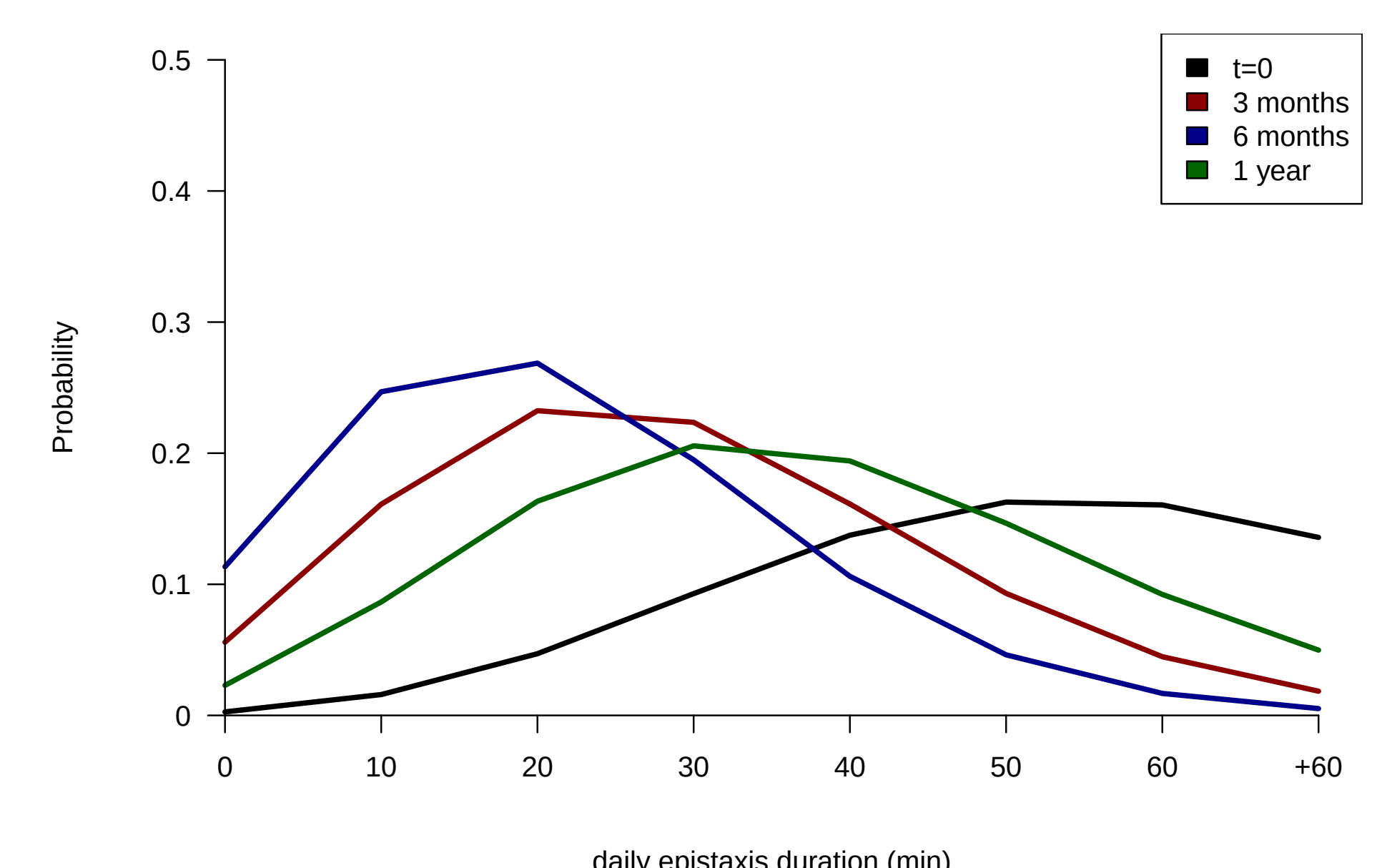
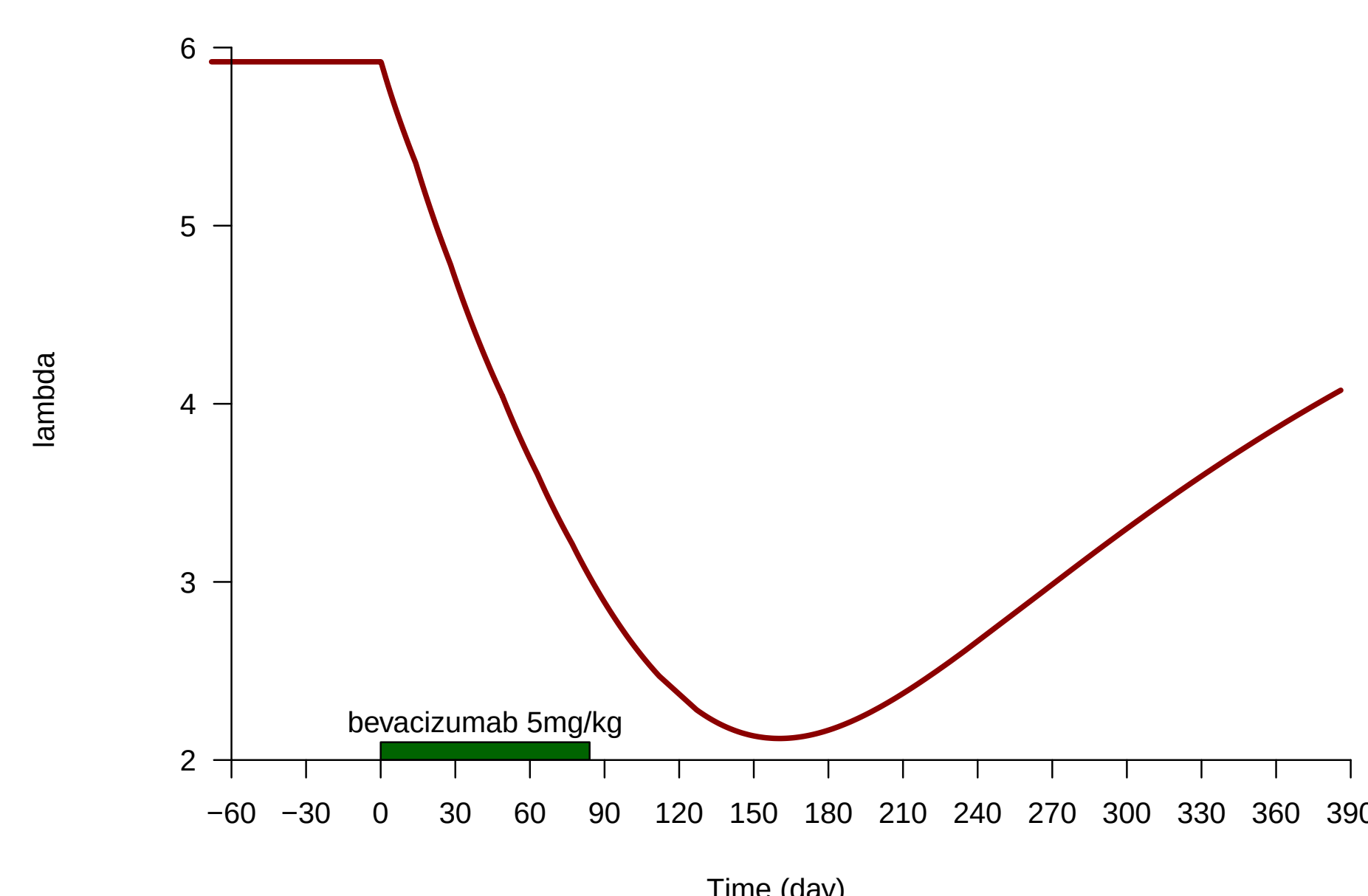


Figure 3: Left: Evolution of  $\lambda(t)$ . The free VEGF concentration reduction effect on Epistaxis duration is at its maximum 2.5 months after the end of the treatment. - Right: Poisson Density function of Epistaxis durations at different times.

## Conclusions

- Bevacizumab pharmacokinetics was satisfactorily described using a two-compartment model.
- In this preliminary study of patients with HHT, short treatment of bevacizumab was associated with
  - a reduction of free VEGF concentrations.
  - a long-lasting reduction of daily epistaxis durations.