# A mechanism-based model for the population pharmacokinetics of aflibercept in healthy subjects

H.T. Thai [1,2], C. Veyrat-Follet [2], N. Vivier [2], C. Dubruc [2], G. Sanderink [2]
E. Comets [1], F. Mentré [1]

[1] INSERM U738, University Denis Diderot Paris 7, Paris, France
[2] Global Metabolism and Pharmacokinetics Department, Sanofi-aventis, Paris, France

## Introduction

- Aflibercept, a novel antiangiogenic agent that binds to the vascular endothelial growth factor (VEGF), has been investigated for the treatment of cancer [1,2]
- Aflibercept is a fusion protein of human VEGF receptor domains and a Fc fragment, and has therefore a higher affinity for VEGF than current anti-VEGF monoclonal antibodies
- Noncompartmental analysis from phase I studies has demonstrated that aflibercept has a low volume of distribution and a dose-dependent clearance
- This population pharmacokinetic study was conducted to further understand its nonlinear pharmacokinetic properties in healthy subjects

## Objectives

- to develop a mechanism-based pharmacokinetic model for aflibercept in healthy subjects
- to characterize its nonlinear disposition and its binding to VEGF

## Methods

### Study design & blood samples

- The data were collected from two phase I, single dose studies

| Study | Description | Blood samples |
|---|---|---|
| 1 | placebo-controlled, sequential ascending dose study, 48 subjects divided in 4 groups (placebo, dose of 1, 2 or 4 mg/kg), 1h-iv infusion | predose, 1, 2, 4, 6, 8, 12, 24 h post-start of infusion on day 1, thereafter 2h post-start of infusion on days 8, 15, 22, 29, 36 and 43 |
| 2 | open-label, single-dose, crossover study (sc vs.1h-iv infusion), two groups of 20 subjects, dose of 2 mg/kg | predose, 1, 2, 4, 6, 8h post-start of administration on day 1, thereafter 2h post-start of administration on days 2, 3, 5, 8,15, 29 and 43 of each period |

- Free aflibercept and bound aflibercept (VEGF-aflibercept complex) plasma concentrations were measured in all collected samples by Elisa method (LOQ =15.6 ng/mL & 43.9 ng/mL for free and bound aflibercept, respectively)

### Data management

- 36 subjects receiving treatment from study 1 and 20 subjects receiving IV infusions at the first period from study 2 were included in the analysis
- All concentrations recorded as being below quantification limit (BQL) were taken into account in the analysis
- The concentrations of bound aflibercept were expressed as equivalent concentrations of aflibercept

### Modeling strategy

- Free aflibercept concentration-time data were first modeled alone, then bound aflibercept concentration-time data were included to develop the joint model

### Population PK analysis

- The population PK analysis was performed using MONOLIX Version 3.1 with SAEM algorithm
- Model control files were written using MLXTRAN

### Pharmacostatistical model

- Interindividual variability: exponential model
- Residual variability: additive, proportional, combined error model

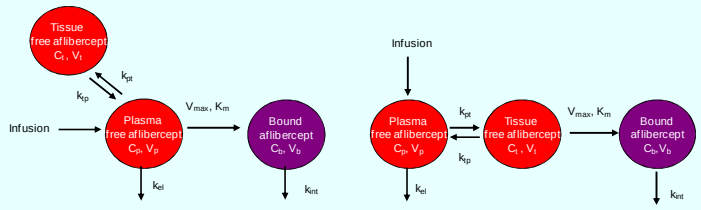
### Model selection criteria

- For nested models: log likelihood ratio test
- For non-nested models: smaller BIC

### Model evaluation

- Goodness of fit plots, SE of parameters and VPC

### Figure 1. Proposed models for free and bound aflibercept




The differential equations describing the peripheral nonlinear binding are shown below

$$\frac{dC_p}{dt} = Input - (k_{el} + k_{pt}).C_p + k_{tp}.\frac{C_t.V_t}{V_p}$$

$$\frac{dC_t}{dt} = k_{pt}.\frac{C_p.V_p}{V_t} - k_{tp}.C_t - \frac{1}{V_t}.\frac{V_{max}.C_t}{K_m + C_t}$$

$$\frac{dC_b}{dt} = \frac{1}{V_b}.\frac{V_{max}.C_t}{K_m + C_t} - k_{int}.C_b$$

Where:
$V_p$: Central volume of distribution of free aflibercept (L)
$V_t$: Peripheral volume of distribution of free aflibercept (L)
$V_b$: Volume of distribution of bound aflibercept (L)
$V_{max}$: Maximum binding capacity (mg/day)
$K_m$: Concentration of free aflibercept corresponding to half of $V_{max}$ (µg/mL)
$k_{el}$: First order elimination rate constant of free aflibercept from central compartment (day$^{-1}$)
$k_{tp}$, $k_{pt}$: First order rate constants between central and peripheral compartment (day$^{-1}$)
$k_{int}$: First order rate constant of bound aflibercept internalization (day$^{-1}$)

## Results

### Data

- 1476 concentrations from 56 subjects were available for model development
  - 732 concentrations of free aflibercept
  - 744 concentrations of bound aflibercept (BQL data=32.5%)

### Final population pharmacokinetic model

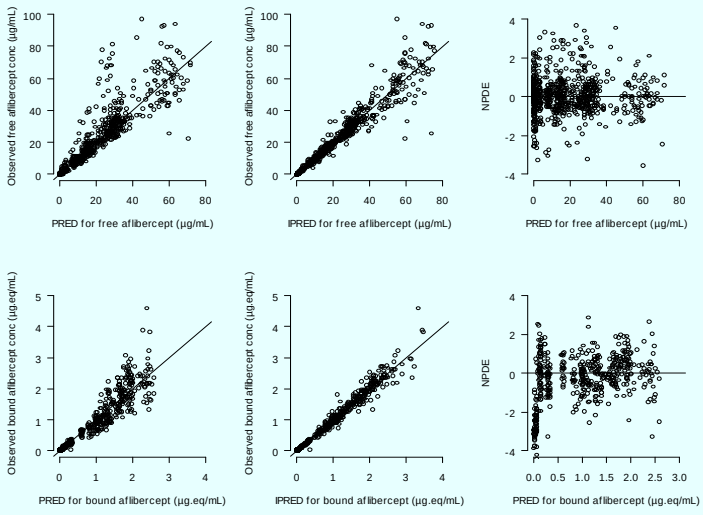
- Structural model: A three-compartment model with a Michaelis-Menten type binding to VEGF from the peripheral compartment (peripheral nonlinear binding)
  - Inspired from Michaelis-Menten approximation of TMDD model [3,4]
  - The first-order dissociation rate constant ($k_{off}$) was assumed to be negligible
  - $V_b$ was fixed to the mean value of $V_p$ due to problem of identifiability
- The clearance of bound aflibercept was found 6.4 times lower than that of free aflibercept from the central compartment (0.14 L/day and 0.88 L/day, respectively)

### Table 1. Parameter estimates for final model

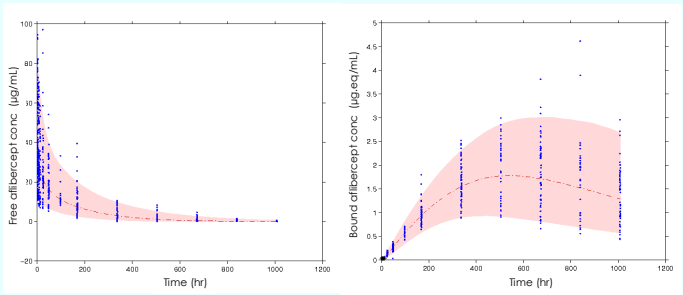
| Fixed effects | | Interindividual variability | | Residual variability | |
|---|---|---|---|---|---|
| Parameter | Estimate (CV) | ω (%) (CV) | | $\sigma_a$ (µg/mL) (CV) | $\sigma_b$(%) (CV) |
| CL (L/day) | 0.88 (4.0) | 28.0 (10) | Free | 0.05 (9.0) | 17.1(3.0) |
| $V_p$ (L) | 4.94 (4.0) | 27.3 (10) | Bound | - | 12.6 (4.0) |
| Q (L/day) | 1.39 (9.0) | 49.8 (14) | | | |
| $V_t$ (L) | 2.23 (7.0) | 39.8 (14) | | | |
| $V_b$ (L) | 4.94 (=$V_p$) | - | | | |
| $V_{max}$ (mg/day) | 0.99 (5.0) | 13.6 (17) | | | |
| $K_m$ (µg/mL) | 2.91 (11) | 45.6 (14) | | | |
| $k_{int}$ (day$^{-1}$) | 0.028 (5.0) | - | | | |

CL: Clearance of free aflibercept from central compartment (CL=$k_{el}$*$V_p$)
Q: Intercompartment clearance of free aflibercept (Q=$k_{tp}$*$V_t$=$k_{pt}$*$V_p$)

### Figure 2. Diagnostic plots




### Figure 3. Visual predictive check




## Conclusions

- The present pharmacokinetic model for aflibercept clearly characterizes the underlying mechanism of disposition of aflibercept and its nonlinear binding to VEGF
- The availability of free and bound aflibercept concentration data has an important role in defining the model structure
- This model provides an useful support for further studies in clinical development

## References

1. Chu QS. *Expert Opinion on Biological Therapy* 2009 ; 9: 263-271.
2. Holash J et al. *PNAS* 2002; 99(17): 11393-11398.
3. Gibiansky L et al. *J Pharmacokinet Pharmacodyn* 2008; 35:573-591.
4. Mager DE, Jusko WJ. *J Pharmacokinet Pharmacodyn* 2001; 28(6): 507-530.