Non-Linear Population Pharmacokinetic Model for Otamixaban in Male Healthy Subjects
Anne PACCALY1, Heiner SPETH2, Bradford K JENSEN3, Jochen MAAS2
Science & Medical Affairs Sanofi-Aventis, 1Bridgewater NJ, 2Frankfurt Germany

OBJECTIVES
Otamixaban (OTAM) is a direct Factor Xa inhibitor for the intravenous treatment of arterial thrombosis. Healthy subjects (Phase 1) showed a more than dose-proportional plasma exposure with increasing doses over a 100-fold dosage range. This phenomenon could be possibly related to a partial saturation of the biliary elimination and/or metabolism of OTAM, while renal excretion is maintained. This work describes the elaboration of a population pharmacokinetic model with Michaelis-Menten elimination that accounts for the non-linear pharmacokinetics of otamixaban in healthy subjects.

METHODS
OTAM was administered intravenously to healthy male subjects (8 per dose group, 4 dose groups) as a bolus or 24-h infusions (0.7 to 200 μg/kg/h) with or without a bolus dose (40 or 140 μg OTAM). OTAM plasma concentrations were measured at 13 to 23 pre-defined sampling times by LC/MS/MS. Nonlinear mixed effects model analysis was performed using NONMEM/PLUS programs to fit a Michaelis-Menten model. NONMEM and S-PLUS estimation procedures were subsequently used throughout the model building process. Two- and three-compartment models with proportional error, using ADV1/TRANS4 and ADV3/TRANS4, respectively, were built and converted into differential equations (ADV4). A DDES block was added that accounted for a dual elimination process with a saturable (Michaelis-Menten) (CLS) and a non-saturable (CLR) component. Final model selection was based on the minimal value of objective function (MVOF) and on the goodness of fit derived from the model parameter values and diagnostic plots.

RESULTS
A three-compartment model with proportional error and dual elimination was retained. This model proved to be superior to a two-compartment model as indicated by the difference in objective function ∆OF=1140. The dual elimination process with a saturable (Michaelis-Menten) component improved the three-compartment model fit (∆OF=233). The model (CV%) values for the main parameters were V=13.2 (6.1%), CLs=16.2 (12%), CLs=22.9 (15.9%), CLR=8.9 (5.7%), Vhs=372 (29.5)% and Km=934 (82%).

CONCLUSIONS
This approach illustrates the integration of a plausible pharmacokinetic mechanism into the population pharmacokinetic model of otamixaban, namely a partial saturation of the biliary elimination and/or metabolism, as an attempt to better understand and describe the time course of the plasma concentrations with increasing doses in healthy subjects. A three compartment non-linear PK model with dual elimination showed an improved OF. A less complex model might however be suitable and is preferred for future drug development.

INTRODUCTION
• Otamixaban (OTAM) is a direct Factor Xa inhibitor for the intravenous treatment of arterial thrombosis.
• Healthy subjects showed a non-dose-proportional plasma exposure over a 100-fold range of IV infusions given with or without a bolus dose (Fig. 6).

The non-dose proportional plasma exposure of OTAM was manifested by an increase in AUC(0-144) and a 30% decrease in C1 and C10 while (1/2 terminal) unchanged. This model was executed unchanged in subjects (~16-25% of the dose) and as metabolites in feces (up to 75% of the dose). Partial saturation of the biliary process and/or metabolism could be a possible underlying mechanism of the non-linear pharmacokinetic exposure of OTAM.

ELIMINATION / EXCRETION

TWO-DEPARTMENT MODEL

THREE-DEPARTMENT MODEL

10-25% Dose

k1, k2, k3

k1, k2, k3

75% Dose

Elaboration of a Population Pharmacokinetic (POPPhk) model for OTAM using rich sampling data. The following criteria will be evaluated:
- The model (two- vs. three-compartment model) should adequately describe therapeutically relevant individual plasma concentration-time profiles.
- The non-dose proportional plasma exposure over the investigated dosage range (10-144 mg/kg) at least at baseline and the intended therapeutic dosage range, i.e. 35 to 175 μg/kg/h of OTAM.

OBJECTIVES
Otamixaban Plasma Concentration-time Profiles with the Nonlinear PK Models - Linear Scale

TABLE 1: Two- (2CP) and three (3CP) Compartment Population PK Model Parameters - NONLIN (μg/mL) values

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>LINEAR</th>
<th>NON LINEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (L)</td>
<td>47 (14)</td>
<td>112 (49)</td>
</tr>
<tr>
<td>V2 (L)</td>
<td>10 (1)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>V3 (L)</td>
<td>41 (18)</td>
<td>109 (47)</td>
</tr>
<tr>
<td>CLs (L/h)</td>
<td>12 (5)</td>
<td>35 (16)</td>
</tr>
<tr>
<td>CLR (L/h)</td>
<td>22 (10)</td>
<td>51 (24)</td>
</tr>
<tr>
<td>WC5 (L)</td>
<td>25 (11)</td>
<td>62 (28)</td>
</tr>
<tr>
<td>MVF (%)</td>
<td>79 (33)</td>
<td>118 (51)</td>
</tr>
</tbody>
</table>

RESULTS Cont’d

Fig.6: AUC0-7 and Cmax vs. Dose (Mean ± SD, n=6)

Fig.7: Individual (IPRE) and Population (PRED) Predicted vs. Observed (OBS) Dose Response

Fig.8: Residuals (RESS) and Weighted Residuals (WRESS) vs. (PRED) Dose

Fig.9: Relationships – PRED vs. OBS

Table 2: Simulation (Subjects, Mean (CV (μg/mL))

<table>
<thead>
<tr>
<th>MODEL</th>
<th>2CP</th>
<th>3CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1</td>
<td>21 (12)</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Y2</td>
<td>109 (45)</td>
<td>109 (45)</td>
</tr>
<tr>
<td>N1</td>
<td>28 (14)</td>
<td>28 (14)</td>
</tr>
<tr>
<td>N2</td>
<td>34 (17)</td>
<td>34 (17)</td>
</tr>
<tr>
<td>N3</td>
<td>42 (19)</td>
<td>42 (19)</td>
</tr>
<tr>
<td>N4</td>
<td>50 (21)</td>
<td>50 (21)</td>
</tr>
<tr>
<td>N5</td>
<td>58 (23)</td>
<td>58 (23)</td>
</tr>
</tbody>
</table>

Fig.10: Simulation (Subjects, Mean (CV (μg/mL))

REFERENCES
3. Spokos H, Beigel D and Weker W - Paplin Linux Cluster at Sanofi-Aventis

MATERIALS
Rich OTAM plasma concentration-time data were collected in healthy male subjects from two male group rising dose studies (6 subjects per dose group, 13 dose groups) after:
- 0.4 to 185 μg/kg/h of OTAM with or without a bolus dose (Fig. 1 and 2).
- 24-h infusions of 55 to 142 μg/kg/h of OTAM (Fig. 3).

OTAM plasma concentrations were measured by LC/MS/MS with a Lower Limit of Quantitation (LLLOQ) of 1 μg/mL.

Population characteristics were age (18-40 years), body weight (54.9-124 kg), height (158-162 cm), Body Mass Index (BMI) (21.8-32.6), and creatinine clearance (Cre) (75-132.5 ml/min).

NONMEM (GlobalMax Corporation) for NONLinear Mixed Effects Model analysis installed on a customized Paplin Linux Cluster environment.

METHODS
In parallel development of the two- (2CP) and three-compartment (3CP) base models, the mixed additive/proportional error model was reduced to a proportional error model

V = IPRED/1.051R

First order (FO) and First Order Conditional Estimation (FOCE) methods were used.

The non-dose proportional plasma exposure is expressed in this model as a partially saturable clearance, where Cls is the linear (non-saturable) clearance and Clss is the saturable clearance that follows the Michaelis-Menten equation

\[ \frac{V}{\text{Vmax}} \times \frac{S}{\text{C50}} \]

Stepwise model building:

2CP and 3CP NONMEM models were built using the ADV1/TRANS4 and ADV2/TRANS4 commands, respectively, with initial parameter estimates from 2CP and 3CP models (WINNONLIN, Pharsight Corporation).

Control files commands were converted into differential equations (ADV4) and the model parameters were verified that described the mass transfer for the central compartment by addition of the terms

\[ -\text{A(1)} \times K_{10} - \frac{\text{A(1)} \times K_{M}}{1 + \text{Cl}_{S}/\text{C50}} \]

where CP=A(1)/S1, KM=ClS/V1, and C50 is the concentration at 50% of Vmax (μg/mL).

Criteria for the final base model selection were:

- Reasonable parameter estimates of THETA and ETA and minimal value of objective function (MVOF).
- Goodness of fit (GOE), including IPRE and PRED vs. OBS, IND and POP Weighted RES vs IPRE and PRED, IND and POP Weighted RES vs. Time, Histograms/Box plots THETA and ETA, Scatter plots CONV, PRED, IPRE vs. Time.
- Stability of the final 2CP and 3CP model parameter estimates (FO) was verified by nonparametric bootstrap analysis (execution of 298 new data samples).

Simulation of plasma concentration-time profiles after high and low doses of OTAM were performed for 5 subjects using the four models.

The more complex three-compartment non-linear pharmacokinetic model with partially saturable elimination showed the lowest MVOF, but did not yet fully describe the non-linear plasma exposure of OTAM.

Fig.11: 24-h Infusions were stopped after 9 and 12 hours in less subjects

Fig.12: 2CP and 3CP NONMEM models were built using the ADV1/TRANS4 and ADV2/TRANS4 commands, respectively, with initial parameter estimates from 2CP and 3CP models (WINNONLIN, Pharsight Corporation).

A three compartment base model with saturable Michaelis-Menten elimination (non-linear model) was retained based on the minimal value of objective function (MVOF), however, this model did not yet fully describe the more dose-proportional plasma exposure of OTAM.

Therefore, less complex two- or three-compartment models might be preferred for future drug development. Further development and improvement of the NONMEM model is ongoing.

Conclusion

- Two- and three-compartment population PK base models were developed to describe OTAM plasma concentrations in healthy male subjects.
- The non-linear pharmacokinetics of OTAM was integrated in these models as a Michaelis-Menten elimination process.
- A three compartment base model with saturable Michaelis-Menten elimination (non-linear model) was retained based on the minimal value of objective function (MVOF). However, this model did not yet fully describe the more dose-proportional plasma exposure of OTAM.

- Therefore, less complex two- or three-compartment models might be preferred for future drug development. Further development and improvement of the NONMEM model is ongoing.