# Population pharmacokinetics/-dynamics of the direct thrombin inhibitor dabigatran in patients undergoing hip replacement surgery

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# Introduction

Thrombin is the key regulator of blood coagulation in plasma converting fibrinogen to fibrin

Direct thrombin inhibitors are under clinical development for:

- prevention of deep vein thrombosis (DVT) in patients undergoing hip and knee arthroplasty
- and the prevention of stroke in patients with atrial fibrillation (Afib)

Dabigatran etexilate is currently in Phase II of clinical development

# Introduction

Dabigatran etexilate pharmacokinetics:

The prodrug dabigatran etexilate is orally available and is completely converted to the active drug dabigatran

AUC and $C_{max}$ of dabigatran increase in proportion with dose

Dabigatran is not metabolised by CYP 450 isoenzymes

Renal excretion of dabigatran and its glucuronide conjugate represents the main elimination pathway

The terminal elimination half life of dabigatran is about 15 hrs

# Study Objectives

The objectives of this study were :

- to evaluate the pharmacokinetics and -dynamics of dabigatran

  after oral administration of the prodrug to
  patients undergoing elective hip replacement surgery

- to identify factors predicting intersubject variability

- to provide population parameter estimates and their variability for clinical trial simulation studies

  ⇨ to support dose selection for Phase II dose range finding studies

  ⇨ to explore clinical relevance of covariate effects

# Methods

The data were obtained from the first rising dose tolerance study in orthopaedic patients (BISTRO)

4600 plasma concentrations of dabigatran were collected in 287 patients

In parallel, blood coagulation parameters were determined:

activated partial thromboplastin time, aPTT

ecarin clotting time, ECT

prothrombin time, expressed as INR

thrombin time, TT

# Methods

BISTRO: ‘ Boehringer Ingelheim Study in Thrombosis’

‘oral only’ administration of Dabigatran etexilate 4 - 6 hours after surgery

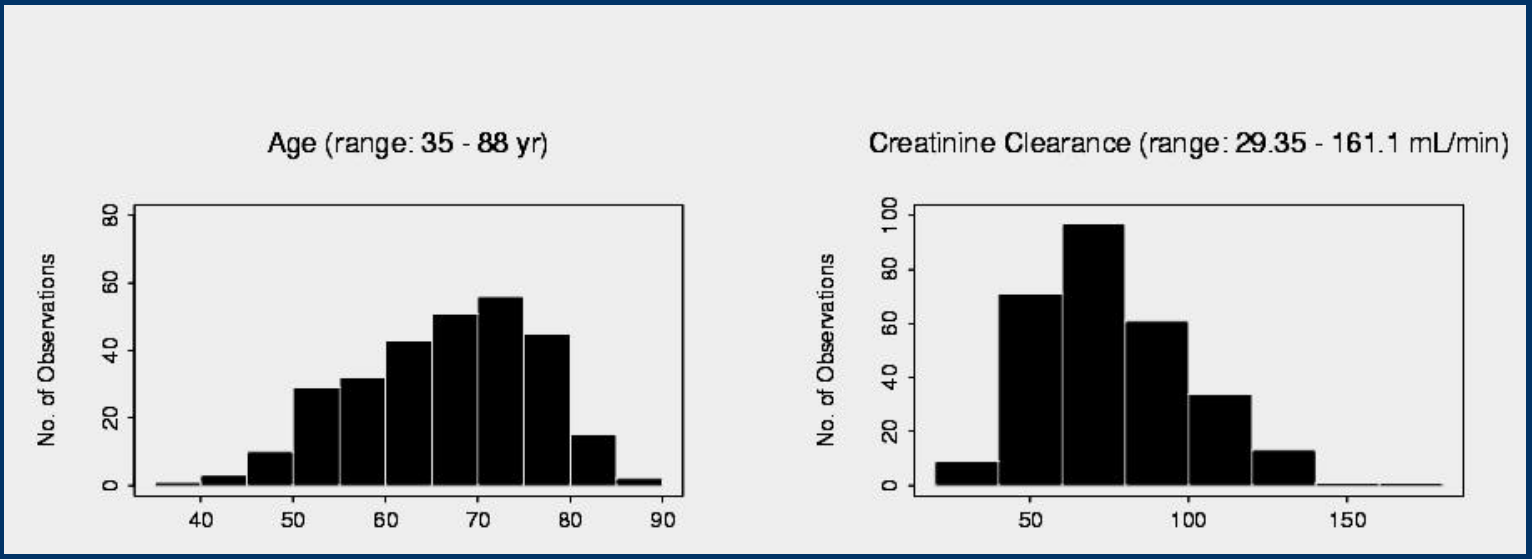
Treatment: 12.5, 25, 50, 100, 150, 200 and 300 mg BID and
150 and 300 mg QD (experimental tablet formulation)
20 - 46 patients per dose group
289 patients treated for 6 - 10 days after arthroplasty

Primary clinical endpoints:

- Major bleeding events post surgery
- Venography at the end of treatment period to detect DVT

# BISTRO I Patient Demographics

| | No. | Min | 1stQ | Median | Mean | 3rd.Q | Max | SD. |
|---|---|---|---|---|---|---|---|---|
| AGE (years) | 287 | 35 | 60 | 68 | **67** | 75 | 88 | 9.68 |
| WT (kg) | 287 | 49 | 67.5 | 76 | **78.2** | 88 | 130 | 14.91 |
| CRCL (mL/min) | 287 | 29.35 | 58.63 | 72.04 | **76.16** | 90.38 | 161.1 | 24.33 |
| GAST (pmol/L) | 287 | 10 | 10 | 24.5 | **34.6** | 34.5 | 501 | 54.77 |



# Covariates recorded and tested in BISTRO I

## Demographic characteristics

| | |
|---|---|
| • Age (years) | AGE |
| • Weight (kg) | WT |
| • Height (cm) | HGT |
| • Body mass index (kg/m$^2$) | BMI |
| • Gender | SEX |

## Comedication

| | |
|---|---|
| • CYP3A4 inhibitors | COM2 |
| • GI passage accelerators | COM3 |
| • NSAIDS | COM7 |
| • Diuretics | COM9 |
| • Paracetamol | COM10 |
| • Opioids | COM11 |
| • Others | COM12 |
| • Benzodiazepines | COM13 |

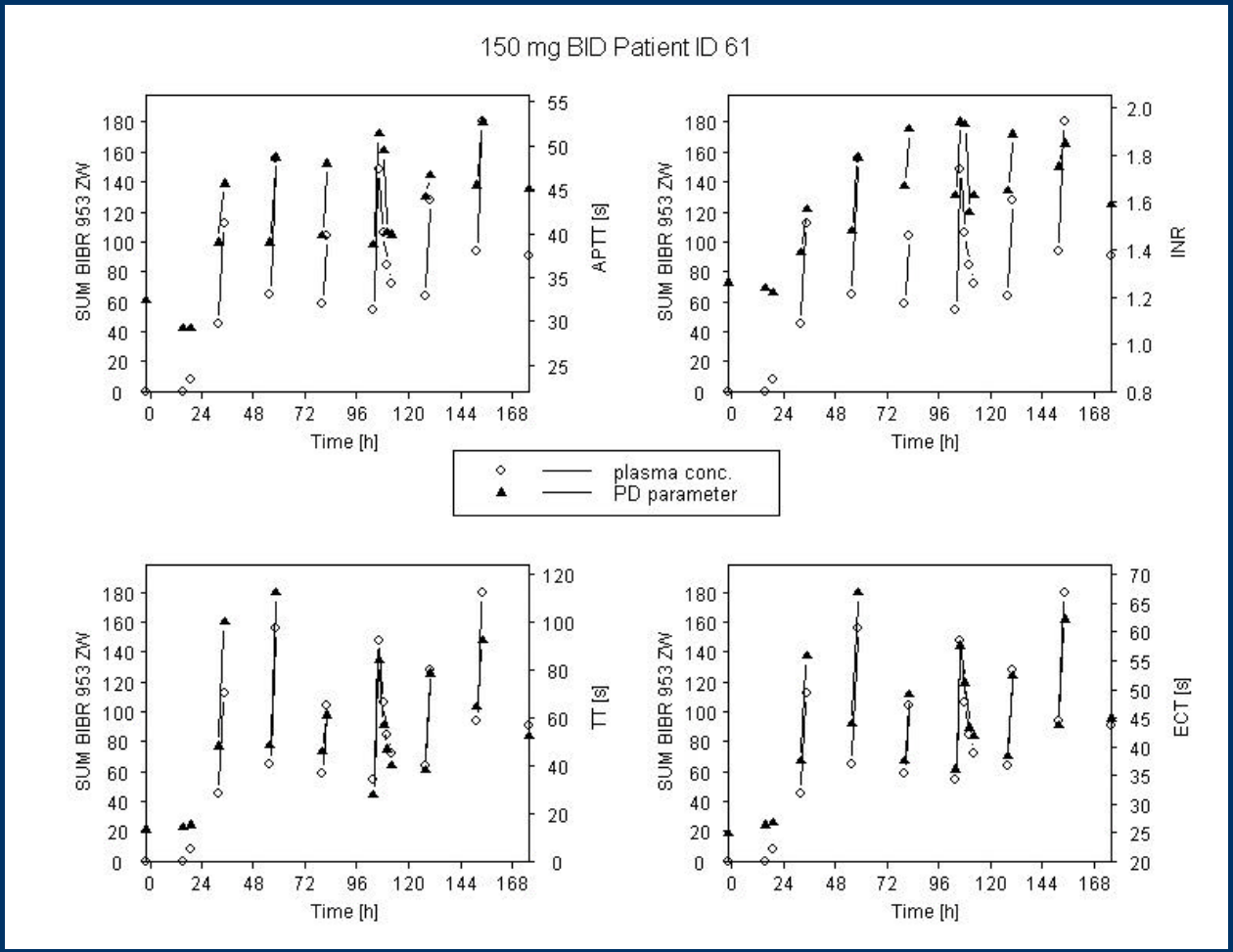
## Lab values

| | |
|---|---|
| • Serum creatinine (mg/dL) | SCR |
| • Creatinine clearance (mL/min) | CRCL |
| • Gastrin concentration | GAST |
| • Alanine transferase (U/L) | ALT |
| • Aspartate transaminase (U/L) | AST |
| • Bilirubin (mgL) | BIL |

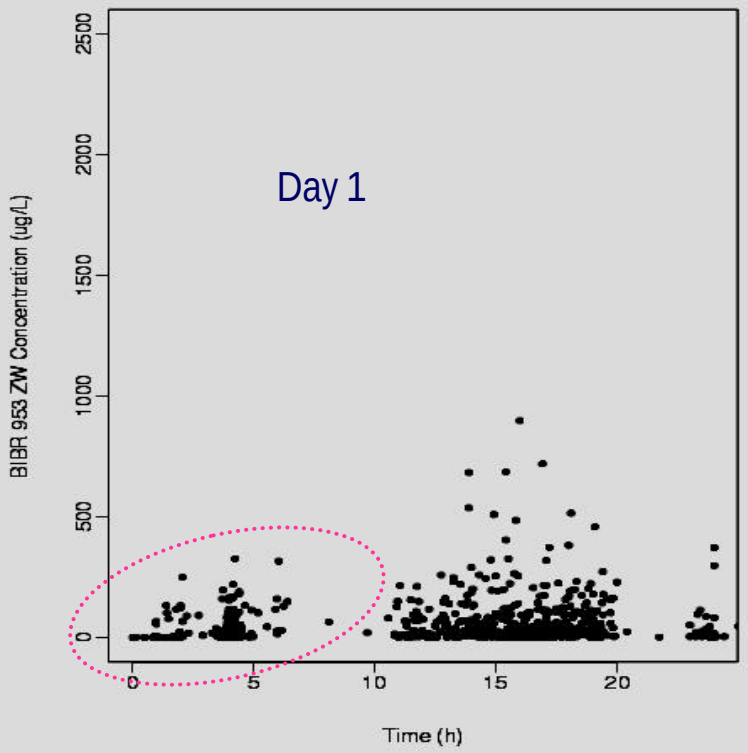
## Design variables

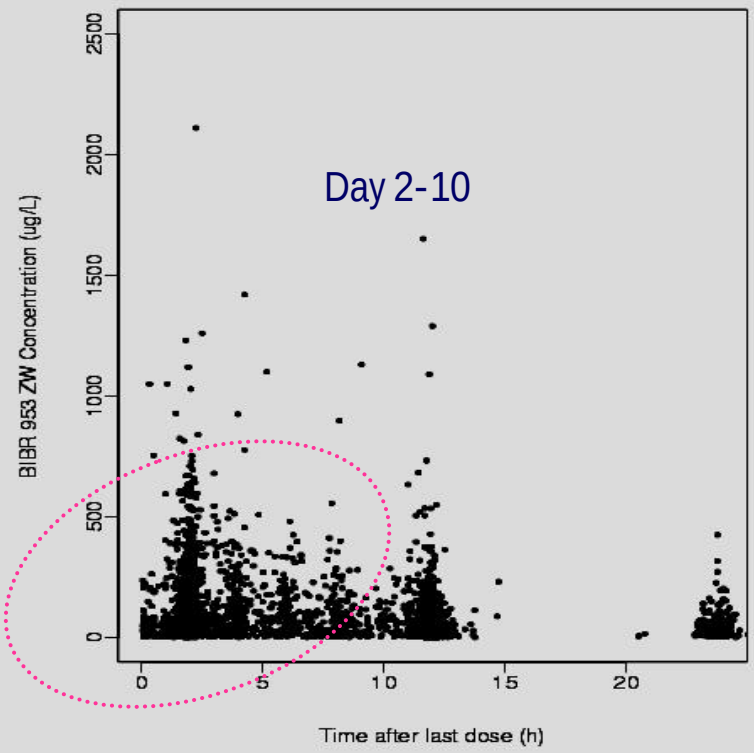
| | |
|---|---|
| • Time to first dose | TTFD |
| • Random group | RAND |
| • Fasting conditions | FAST |
| • Alcohol consumption | ASTA |
| • Smoking habits | SMOK |

# PK-Model Development - The Data



# PK-Model Development - The Data (cont.)



# PK-Model Development

Challenges:

- Absorption on day 1 (first dose on day of surgery)
- high variability within the dose groups
- different plasma concentration / time profiles within a subject during the treatment period

# PK-Model Development - Base Model

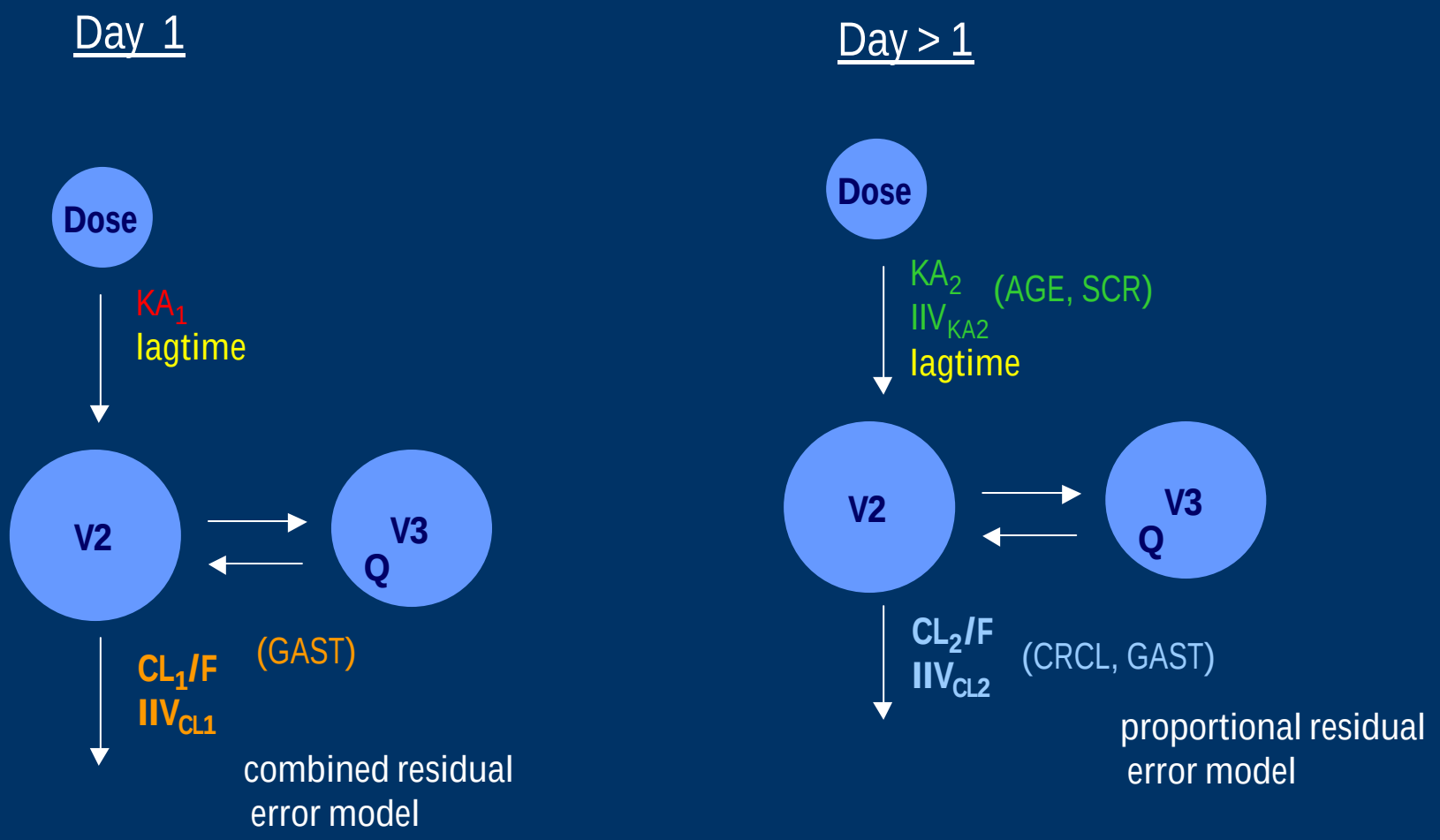
2-Comp. model, 1st order absorption, CL, V2, Q, V3, $K_A$, lagtime, residual error model IIV on CL and $K_A$

CL/F, $K_A$ } different on day1 and day > 1 ⇒ could explain the in general low concentrations on day 1

different IIV on CL/F for day 1 and day > 1
IIV on $K_A$ only for day > 1 (limited number of data points on day 1)

Different residual error models for day 1 and day > 1 ⇒ combined error model only necessary for day 1

# PK-Model Development - Final PK Model

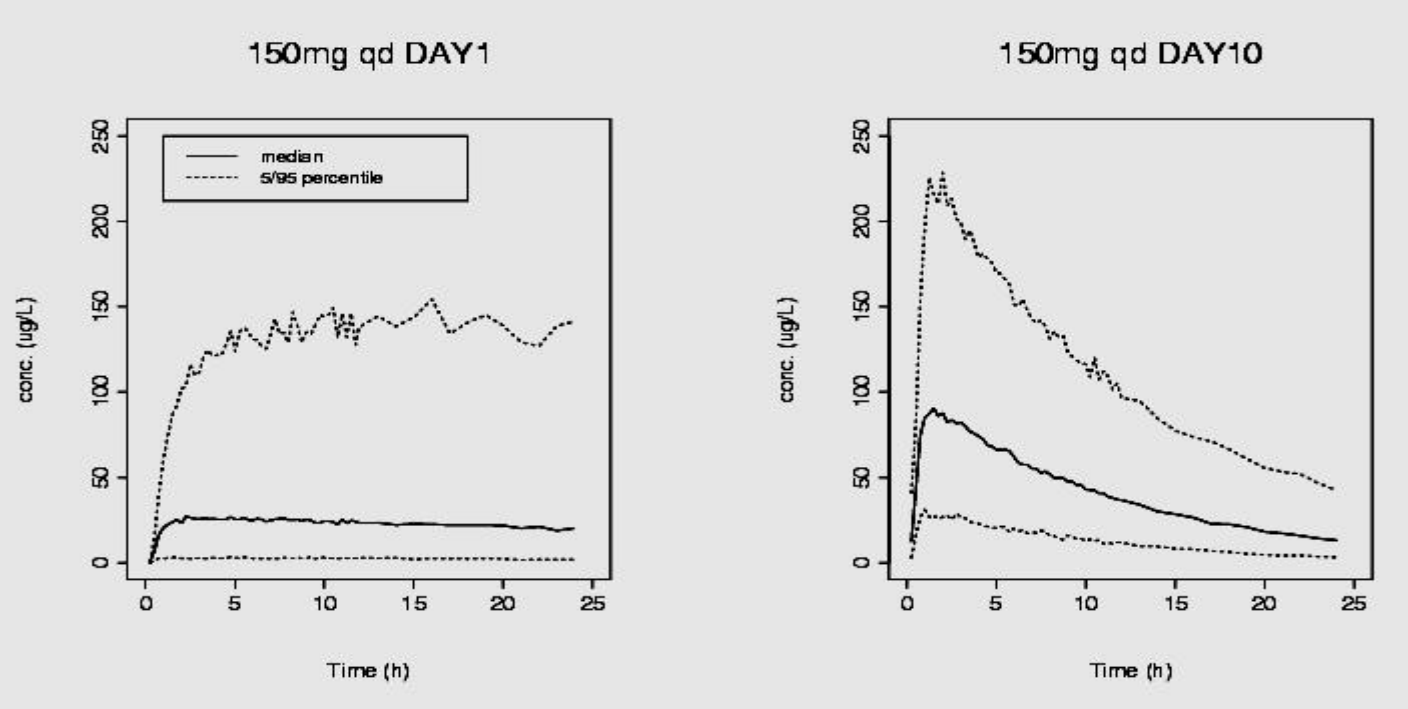


# PK-Model Development - Final Parameter Estimates

| | Unit | Parameter Estimate | SE (%) |
|---|---|---|---|
| **CL >24h** | (L/h) | 82.1 | 5.62 |
| **V2** | (L) | 30.8 | 16.72 |
| **Q** | (L/h) | 13.6 | 35.51 |
| **V3** | (L) | 136 | 41.99 |
| **Ka <24h** | ($h^{-1}$) | 0.0217 | 25.35 |
| **ALAG1** | (h) | 0.399 | 7.69 |
| **Ka >24h** | ($h^{-1}$) | 0.265 | 11.28 |
| **CL <24h** | (L/h) | 43.4 | 27.42 |
| **GAST_CL>24h** | | 0.294 | 25.92 |
| **GAST_CL <24h** | | 0.633 | 42.65 |
| **SCR_Ka >24h** | | 0.363 | 12.53 |
| **AGE_Ka >24h** | | 0.447 | 11.12 |
| | | | |
| **IIV CL >24h** | (% CV) | 46.04 | 9.29 |
| **IIV CL <24h** | (% CV) | 108.6 | 16.36 |
| **IIV Ka >24h** | (% CV) | 29.83 | 23.15 |
| | | | |
| **add. res.error <24h** | (SD) | 0.375 | 11.84 |
| **prop. Res. Error < 24h** | (% CV) | 66.9 | 2.72 |
| **prop. Res. Error >24h** | (% CV) | 36.61 | 4.85 |

# PK-Model Development

Simulated typical plasma concentration-time profiles of dabigatran on day 1 and day 10 of treatment



# Pharmacodynamic Model - ECT and aPTT

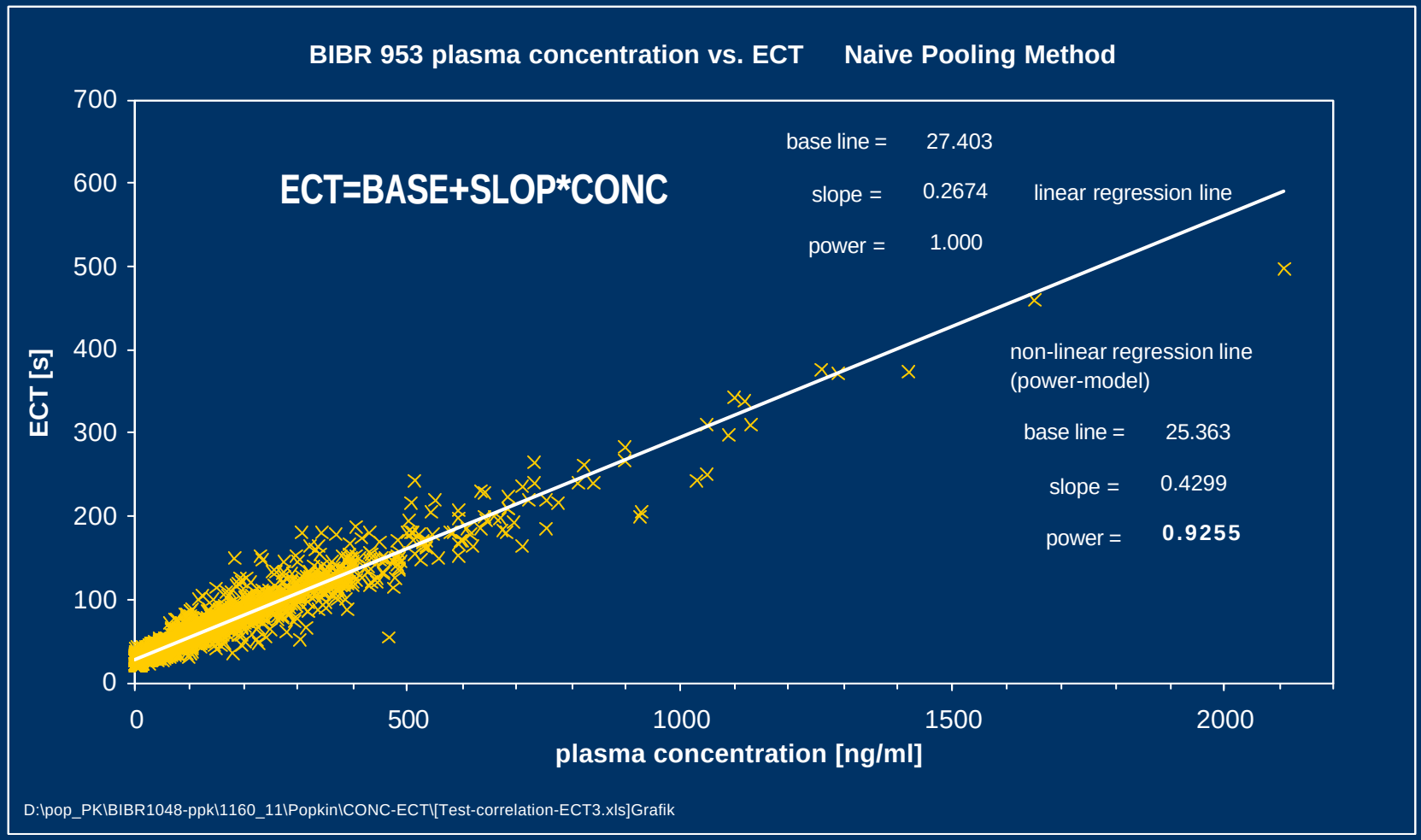
Development of Pharmacodynamic Models for

Ecarin Clotting Time

and

activated Partial Thromboplastin Time

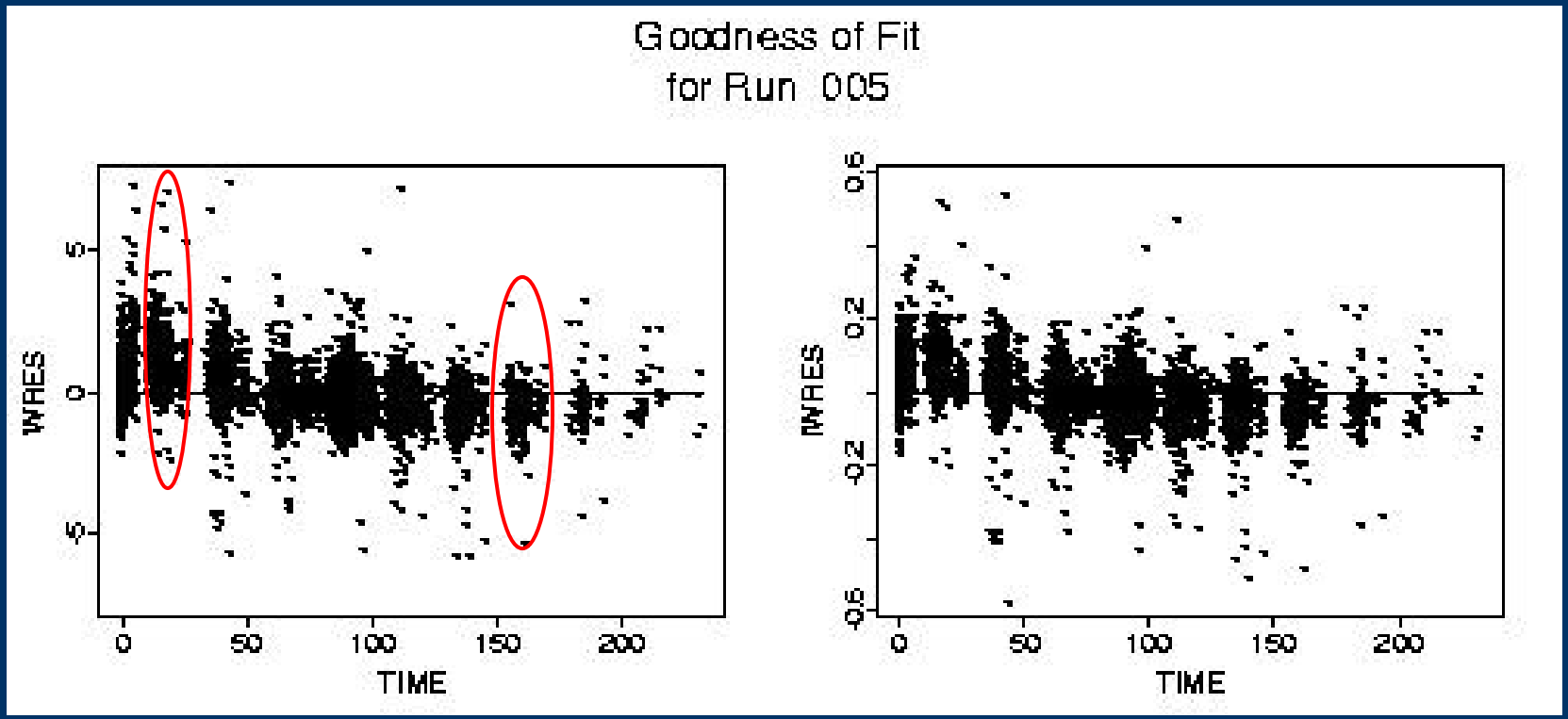
# PK/PD Correlation of Dabigatran in Patients - ECT



# Goodness of Fit plots without time effect on BASE and SLOP

ECT=BASE+SLOP*CONC

BASE & SLOP considered to be time independent parameters

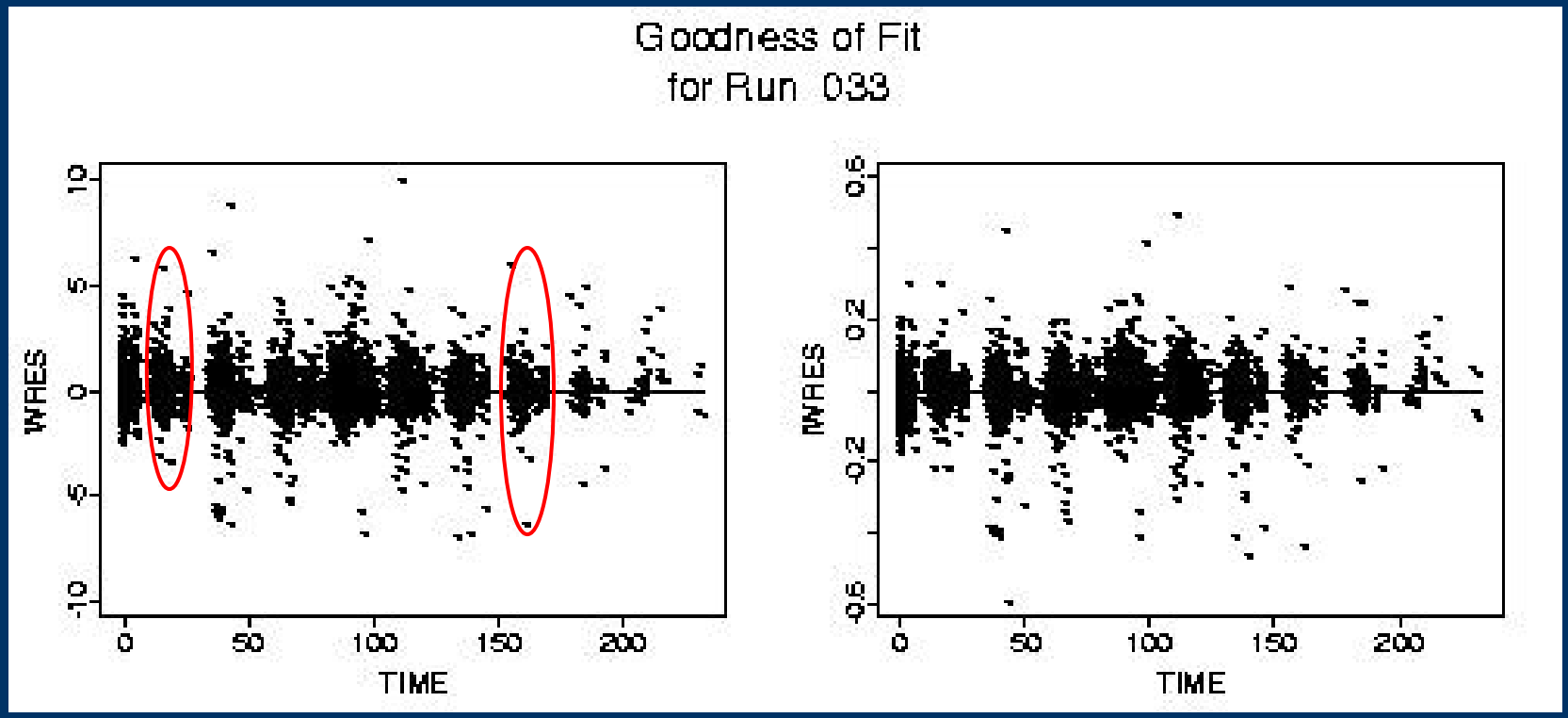


# GOF plots with SLOP and BASE changing over time

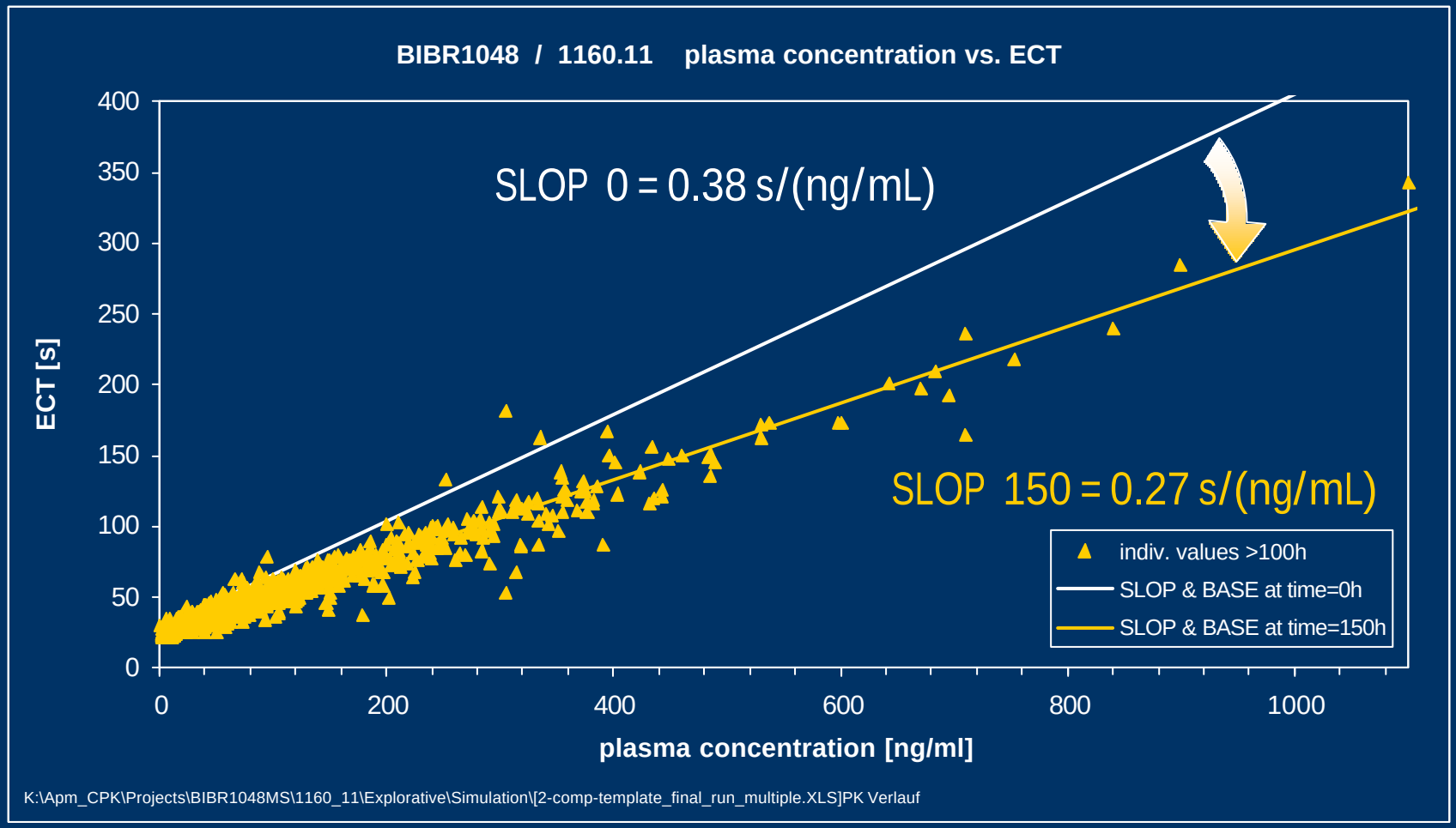
ECT=BASE+SLOP*CONC

BASE = BASO *(1-(EMBA*TIME/24)/(EB50+TIME/24))

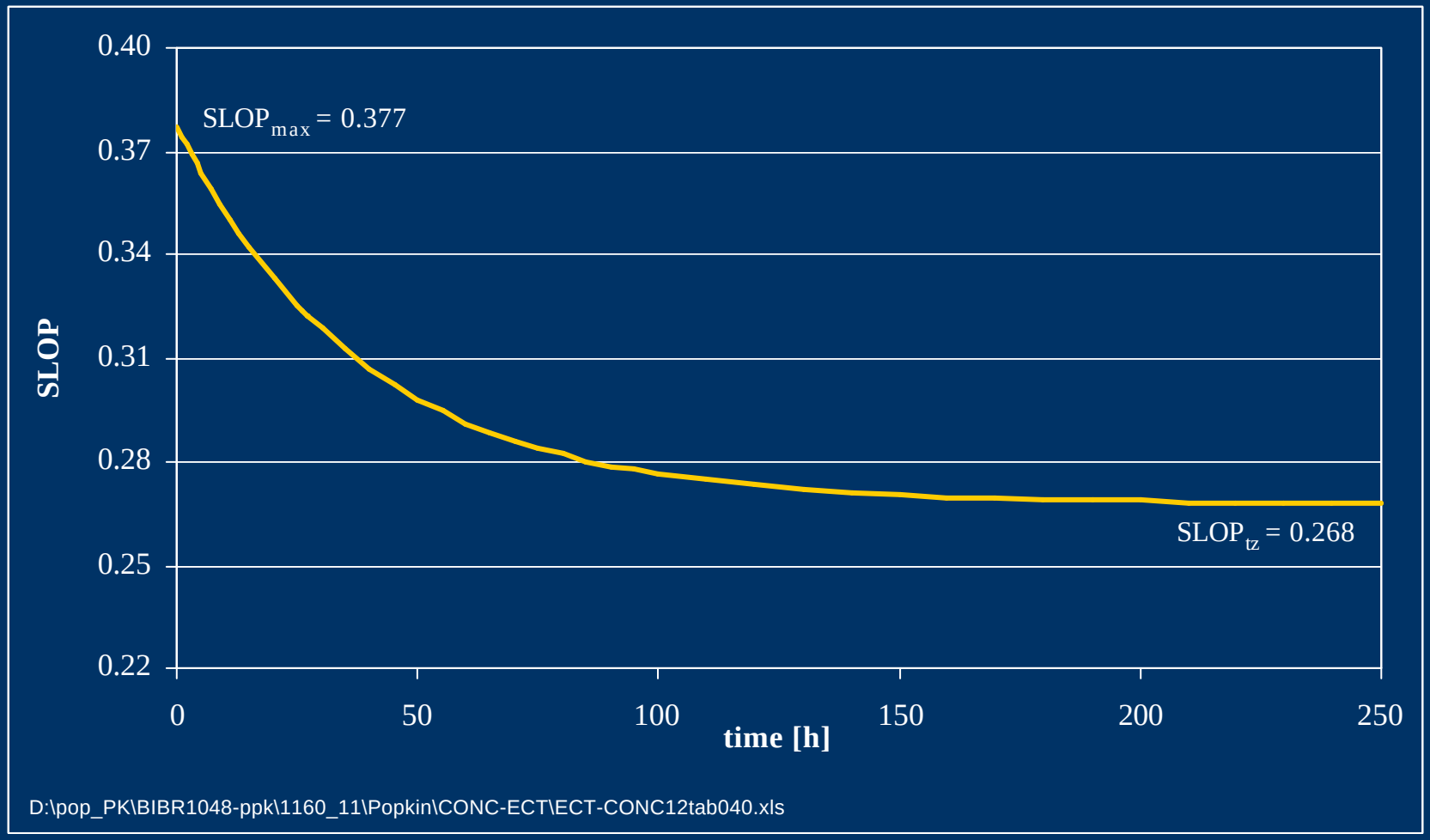
SLOP = SLOO*EXP(-KM*TIME)+SLOF*(1-EXP(-KM*TIME))



# Decrease of SLOP over Time



# Decrease of SLOP over Time



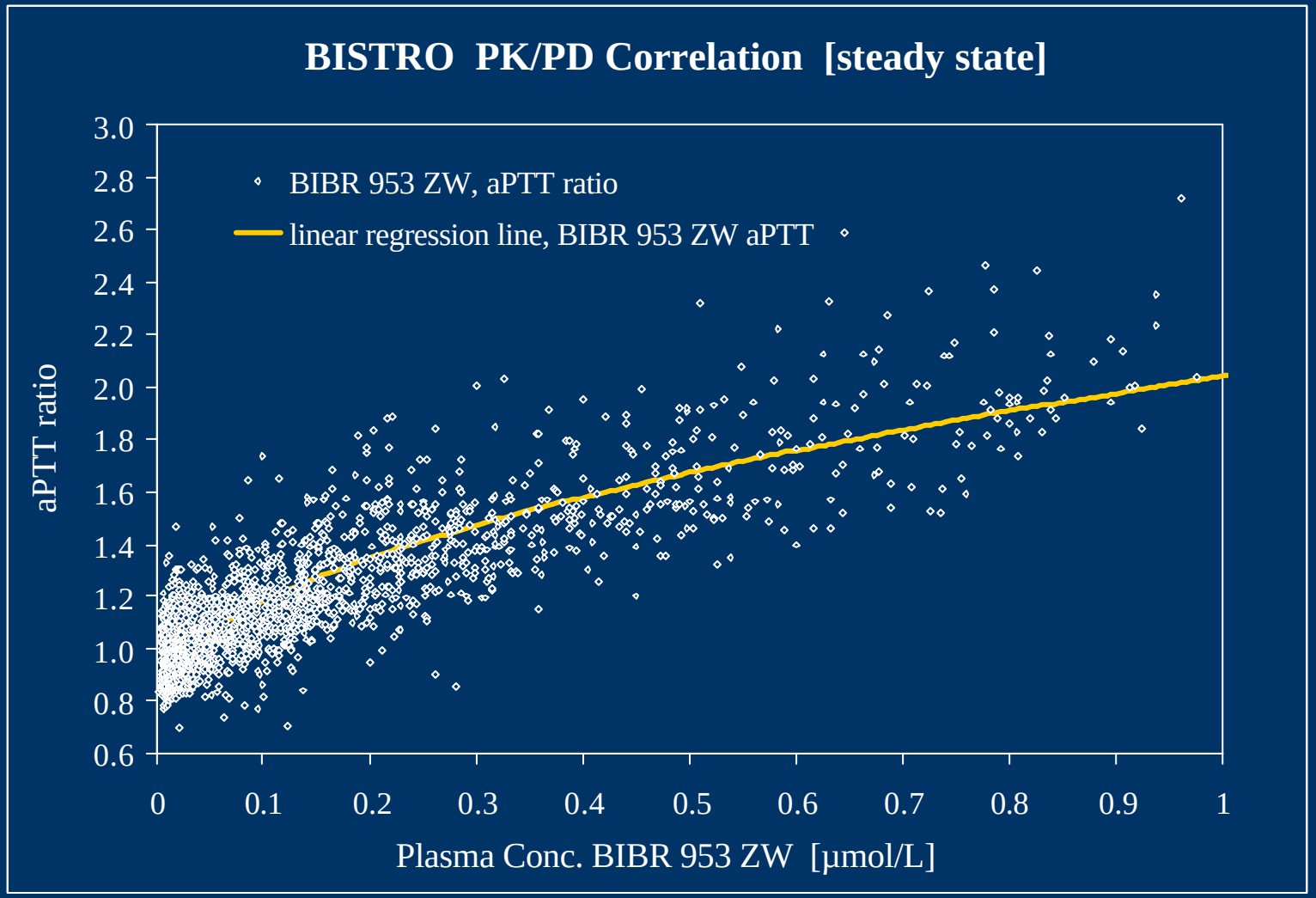
# Final Parameter Estimates ECT

| parameter | | population mean of final model | | magnitude of interindividual variability | | |
|---|---|---|---|---|---|---|
| | unit | final estimate | %RSE## | para-meter | final estimate %CV# | %RSE## |
| SLOO | [s/(ng/ml)] | 0.377 | 2.18 | SLOP | 13.7 | 13.76 |
| SLOF | [s/(ng/ml)] | 0.268 | 1.49 | | | |
| BASO | [s] | 28.0 | 0.49 | BASE | 8.2 | 8.98 |
| KM | [ ] | 0.617 | 13.55 | | | |
| EMBA | [ ] | 0.175 | 6.46 | | | |
| EB50 | [day] | 2.86 | 13.50 | | | |
| residual variability | | %CV# | | | | |
| $\sigma_1$ | | 6.63 | 6.83 | | | |

\# Estimates of variance components (ω's and σ's) were converted into standard deviations by taking their square root. These are reported as coefficients of variation (%CV) after multiplication by 100%.

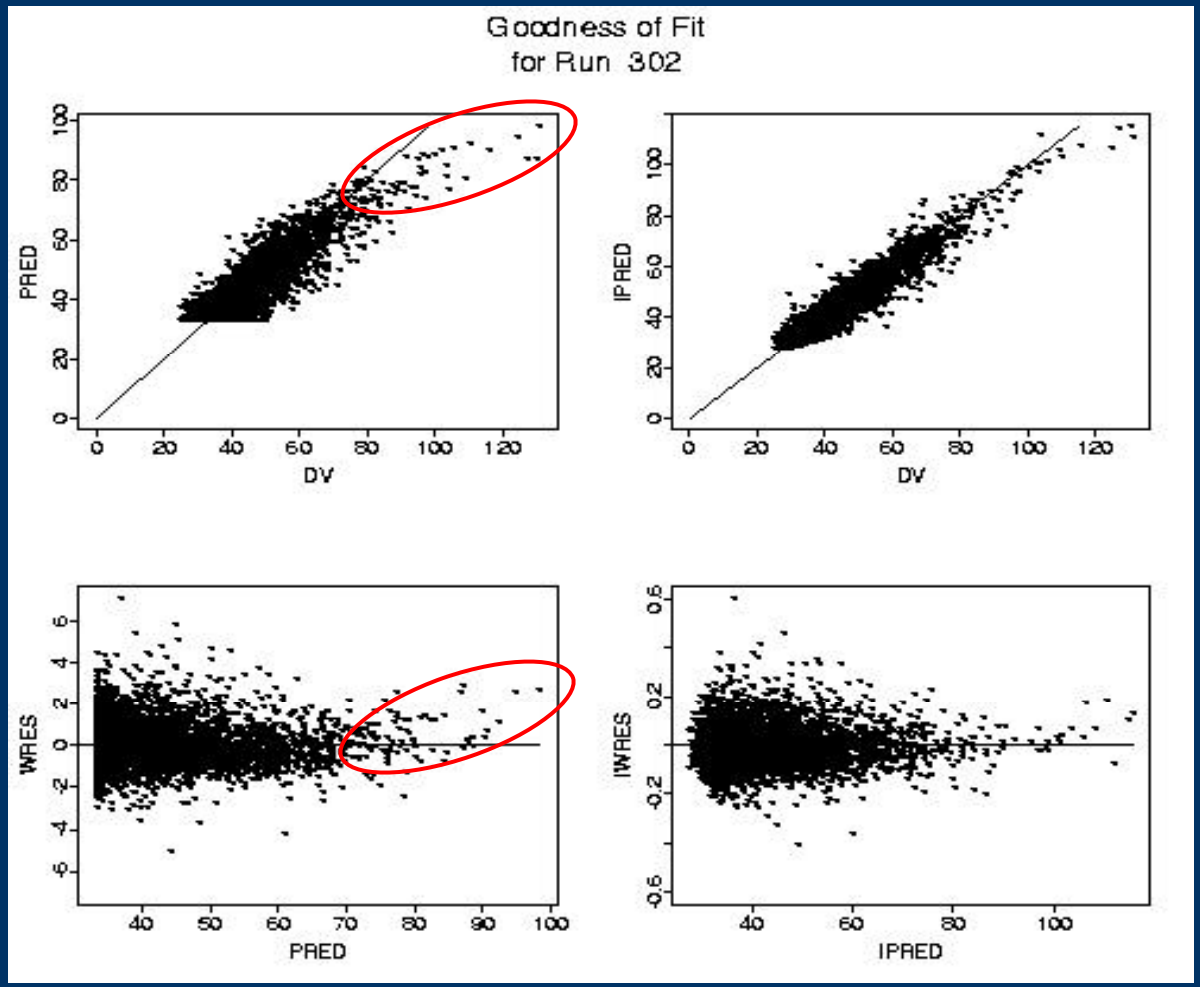
## The percent standard error of parameter estimates was calculated according to %RSE = standard error (SE)/ parameter estimate · 100%

# PK/PD Correlation in Patients - aPTT



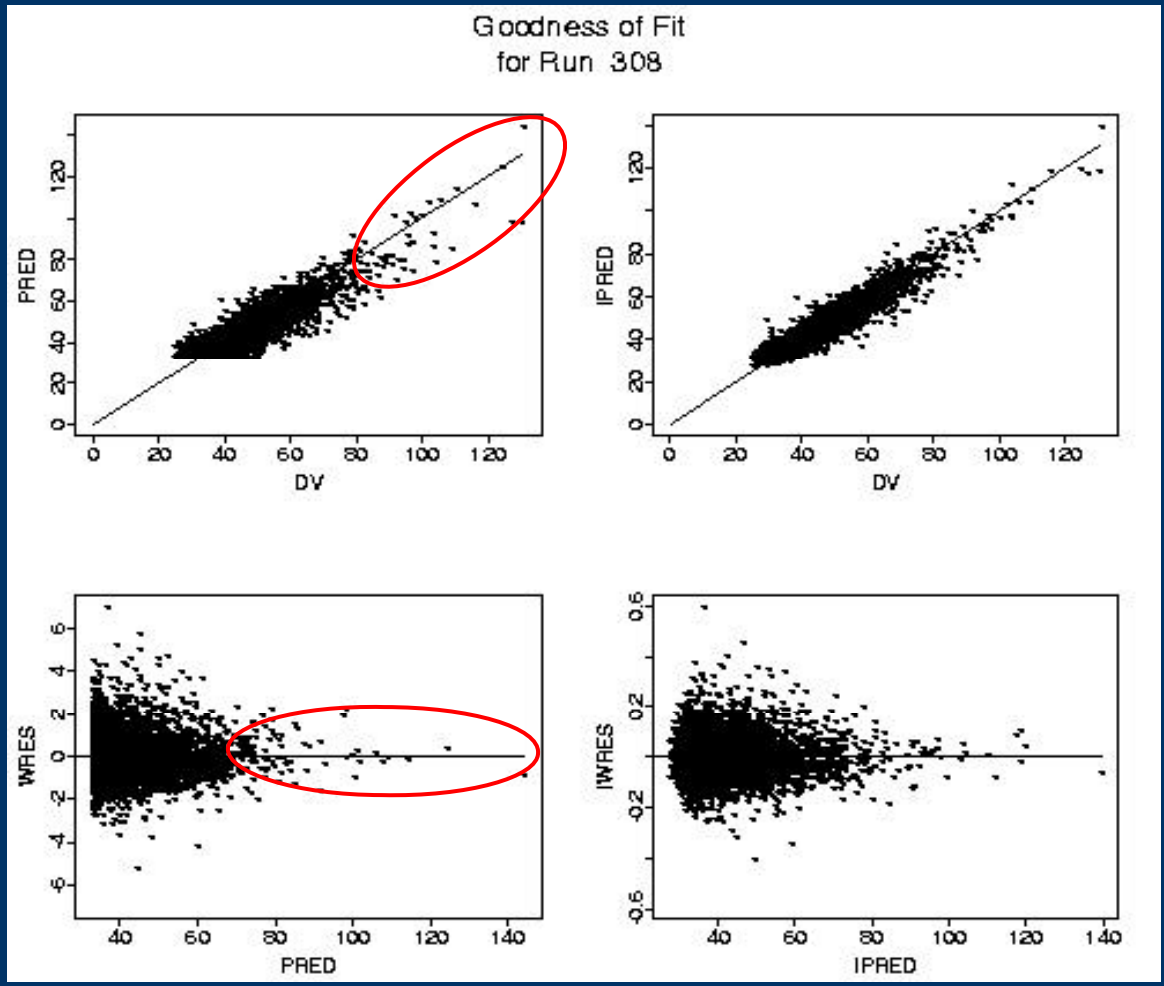
# GOF plot of an aPTT - $E_{max}$ Model

aPTT = BASE + (EMAX*CONC /(EC50+CONC))

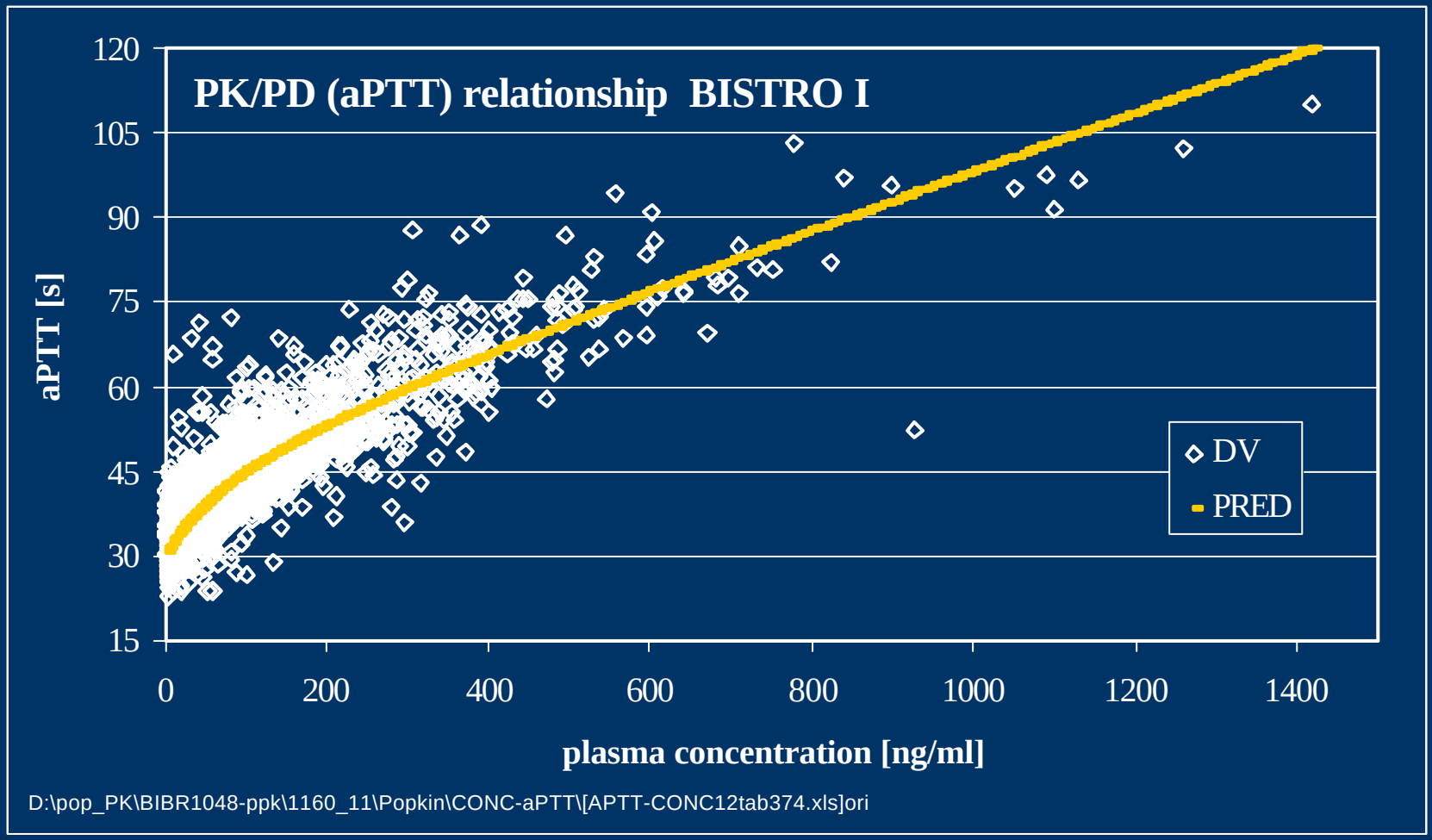


# GOF plot of aPTT $E_{max}$ model with linear term

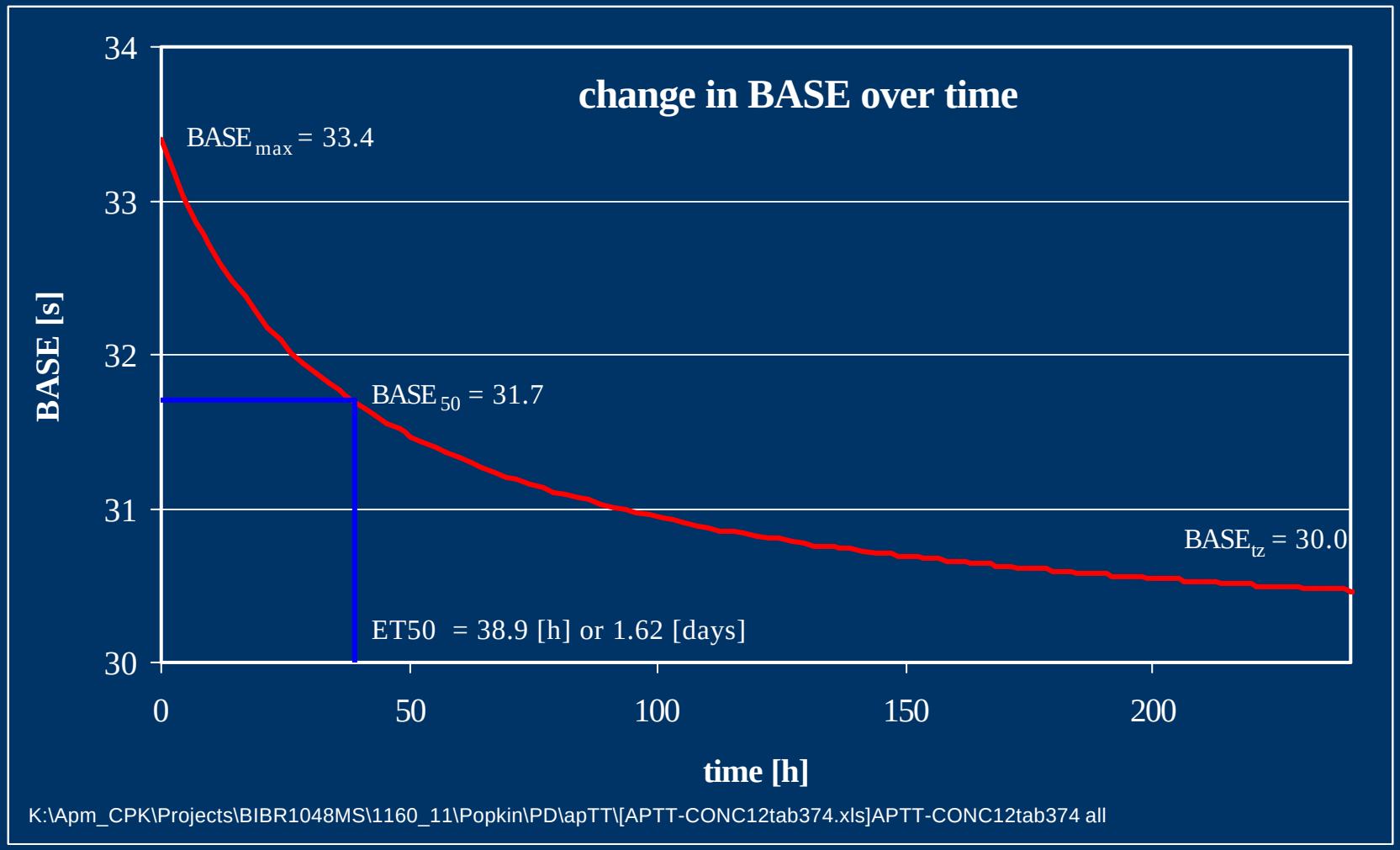
aPTT = BASE + (EMAX*CONC /(EC50+CONC)) + SLOP*CONC



# PK/aPTT Correlation in Patients - final model



# Effect of TIME on base line of aPTT



# Final Parameter Estimates aPTT

| parameter | | population mean of final model | | magnitude of interindividual variability | | |
|---|---|---|---|---|---|---|
| | unit | final estimate | %RSE## | para-meter | final estimate %CV# | %RSE## |
| EMAO | [s] | 26.9 | 12.45 | EMAX | 19.9 | 33.92 |
| BASO | [s] | 33.4 | 0.63 | BASE | 8.7 | 10.51 |
| EC50 | [ng/ml] | 94.7 | 17.11 | EC50 | 38.5 | 40.41 |
| SLOP | [s/(ng/ml)] | 0.0509 | 6.68 | SLOP | 15.2 | 45.22 |
| EMMX | [ ] | 0.463 | 12.68 | | | |
| ET50 | [day] | 1.62 | 15.99 | | | |
| EMBA | [ ] | 0.102 | 14.41 | | | |
| residual variability | | %CV# | | | | |
| $\sigma_1$ | | 7.55 | 3.53 | | | |

\# Estimates of variance components (ω's and σ's) were converted into standard deviations by taking their square root. These are reported as coefficients of variation (%CV) after multiplying them by 100%.

## The percent standard error of parameter estimates was calculated according to %RSE = standard error (SE)/ parameter estimate · 100%

# A simulation study to assess the dose-response relationship between BIBR 1048 and the Blood coagulation Parameters ECT and aPTT in patients undergoing hip replacement surgery

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Howard Lee, MD, PhD

Center for Drug Development Science

# CTS - Methods

The Simulation Platform:

- Covariate Distribution Model
- PK Model with Covariates
- PD Models for ECT and aPTT
    - Stochastic Models for PK and PD Parameter Uncertainty
    - Interindividual Variability and Residual Error
- Trial Execution Model

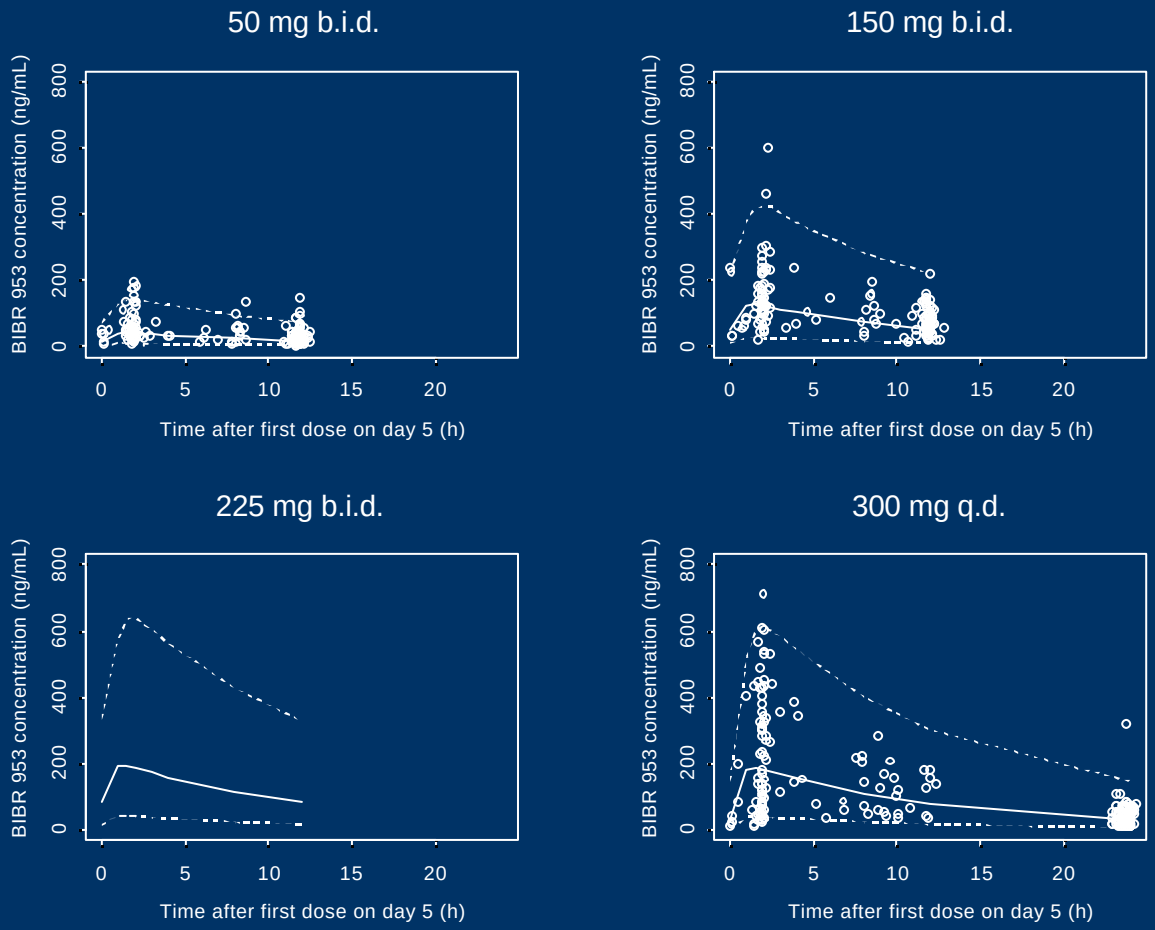
# CTS - Trial Execution Model

Simulated patients from the covariate distribution model were randomised to one of four treatment groups:

- Treatment Arm 1: 50 mg b.i.d. for 5 days
- Treatment Arm 2: 150 mg b.i.d. for 5 days
- Treatment Arm 3: 225 mg b.i.d. for 5 days
- Treatment Arm 4: 300 mg q.d. for 5 days

⇨ Treatment groups of the BISTRO II dose range finding trial

# CTS - predicted vs observed dabigatran plasma concentrations




BIBR 953 ZW concentration versus time data from 100 replicates were pooled together and the 50$^{th}$ (solid line) and 95$^{th}$ / 5$^{th}$ (dotted lines) percentiles were calculated for each dose group. Open circles represent observed data.