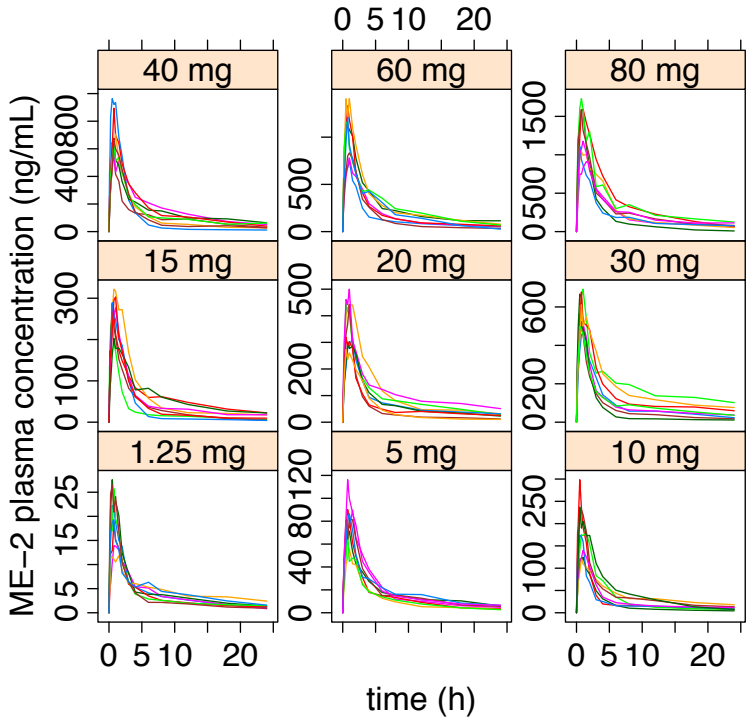
Example 3
Population PK of ME-2

- A phase IIa PoC trial of ME-2 for prevention of post-op VTEs has just been completed.
- One of your tasks is to do a pop PK analysis based on the accumulated ME-2 PK data (Phase I SD, Phase I MD & Phase IIa)
- Phase 1 single dose study in healthy volunteers described during examples 1 & 2
- Phase 1 multiple dose study in healthy volunteers
  - Parallel dose-escalation design
  - 8 subjects per dose arm
  - Placebo or ME-2 5, 10, 20, 40 or 80 mg bid (q12h) x 7 days
  - PK: plasma concentrations of parent drug
    - PK measured at 0, 0.083, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 12.1, 12.2, 12.2, 12.5, 12.8, 13, 13.5, 14, 15, 16, 18, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 168, 168, 168, 168, 169, 169, 170, 170, 171, 172, 174, 176, 180, 186 and 192 hours after the first dose.

Example 3
Population PK of ME-2

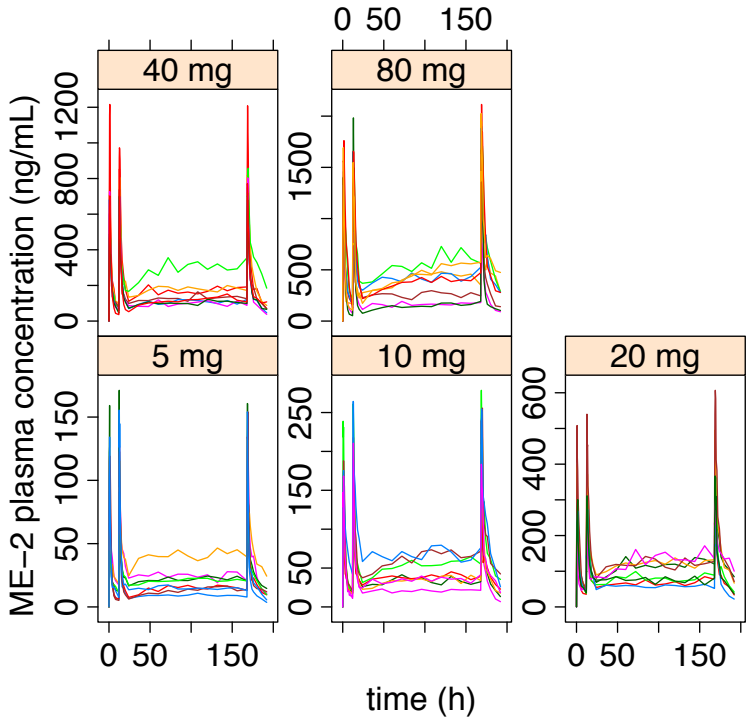
- A phase IIa PoC trial of ME-2 for prevention of post-op VTEs has just been completed.
- One of your tasks is to do a pop PK analysis based on the accumulated ME-2 PK data (Phase I SD, Phase I MD & Phase IIa)
- Phase IIa trial design:
  - Treatments
    - ME-2 20 mg bid (q12h) x 7 days
    - Enoxaparin 30 mg bid (q12h) x 7 days
  - 100 patients per treatment arm
  - Sparse ME-2 PK data (3-6 samples/patient)
    - LOQ = 10 ng/mL

Example 3



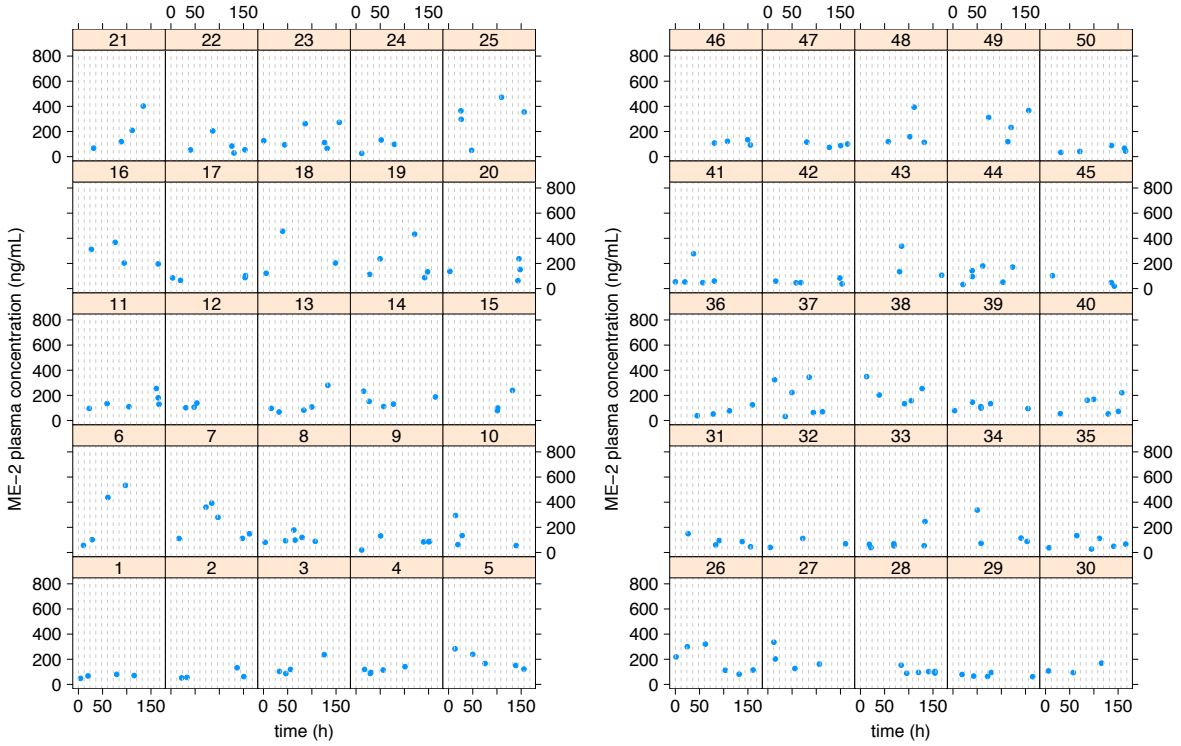
ME-2 PK data from Phase I SD trial

Example 3

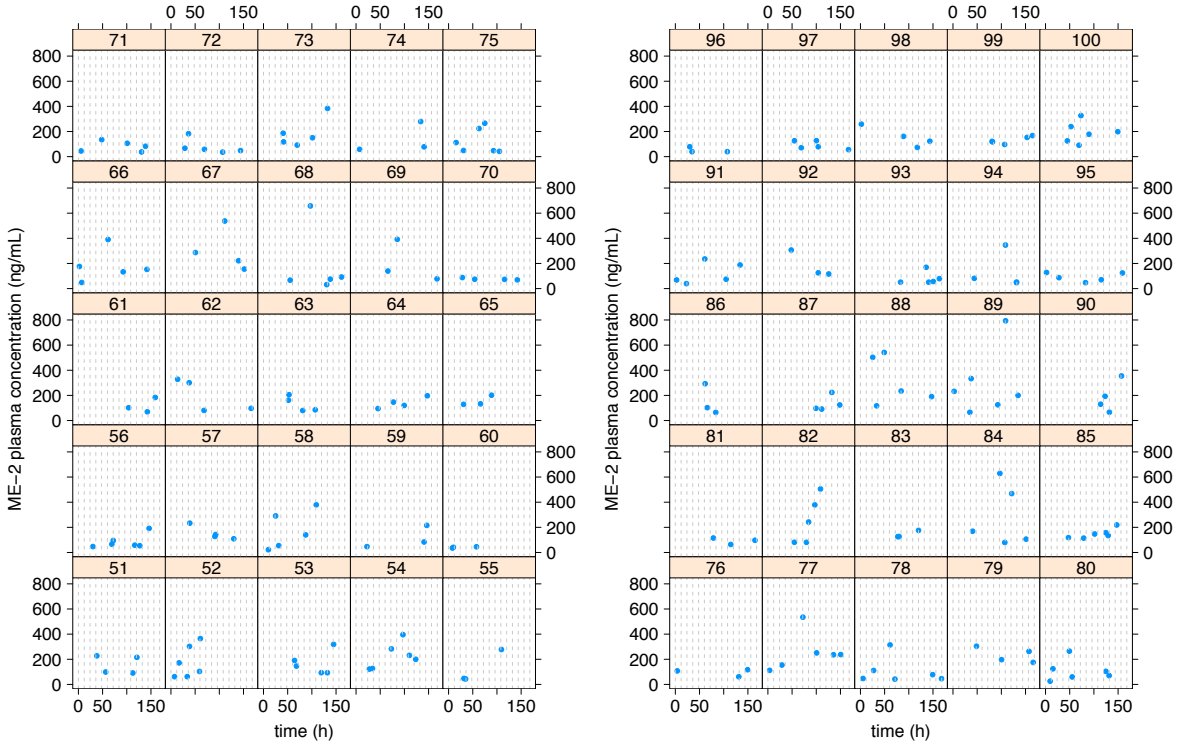


ME-2 PK data from Phase I MD trial

Example 3
ME-2 PK data from Phase IIa trial



Example 3
ME-2 PK data from Phase IIa trial



Example 3
Proposed base model

- Two compartment model with first order absorption describing ME-2 plasma concentration on the i^{th} occasion in the j^{th} subject as a function of time, dose and body weight:

$$\begin{aligned}
\log\left(c_{ij}\right) &\sim N\left(\log\left(\hat{c}_{ij}\right), \sigma^2\right) \\
\hat{c}_{ij} &= f_{2cpt}\left(t_{ij}, D_j, \tau_j, CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}\right) \\
\log\left(CL_j, Q_j, V_{1j}, V_{2j}, k_{aj}\right) & \\
&\sim N\left(\log\left(\widehat{CL}\left(\frac{bw_j}{70}\right)^{0.75}, \widehat{Q}\left(\frac{bw_j}{70}\right)^{0.75}, \widehat{V}_1\left(\frac{bw_j}{70}\right), \widehat{V}_2\left(\frac{bw_j}{70}\right), \widehat{k}_a\right), \Omega\right)
\end{aligned}$$

- Some possible weakly informative prior distributions:

$$\begin{aligned}
\widehat{CL} &\sim \text{half-}N\left(0, 20^2\right) \quad \widehat{Q} \sim \text{half-}N\left(0, 20^2\right) \quad \widehat{V}_1 \sim \text{half-}N\left(0, 100^2\right) \\
\widehat{V}_2 &\sim \text{half-}N\left(0, 1000^2\right) \quad \widehat{k}_a \sim \text{half-}N\left(0, 5^2\right) \quad \sigma \sim \text{half-Cauchy}\left(0, 5\right) \\
\Omega &= \text{diag}\left(\omega\right) P \,\text{diag}\left(\omega\right) \\
\omega_i &\sim \text{half-Cauchy}\left(0, 2\right), i \in \{1, 2, 3, 4, 5\} \quad P \sim \text{LKJCorr}\left(1\right)
\end{aligned}$$

Example 3
Files

- Data
  - ME-2 plasma concentration data in NONMEM format: data/derived/fxaNONMEMData.csv
- Stan model: model/multiDoseME2PK1.stan
- R script: script/multiDoseME2PK1.R