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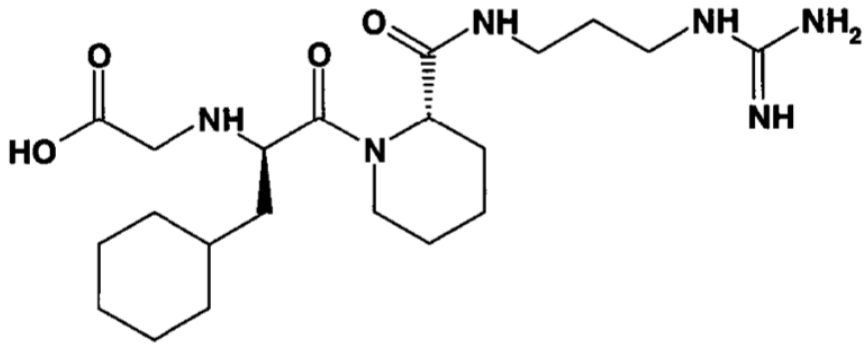
Phase I SAD Study Design of Inogatran, An Anticoagulant

Preclinical Background

- Anticoagulant designed to prevent MI
- IV formulation
- Thrombin inhibitor
- PK/PD Data
  - $t^{1/2}$ = 50 min
  - V = 0.3 L/kg
  - CL = 300 mL/min
  - $IC_{50(APTT)}$ = 1.2 µM (in vitro)
- PK extrapolated from dog, rat, and monkey
- PD from *in vitro*



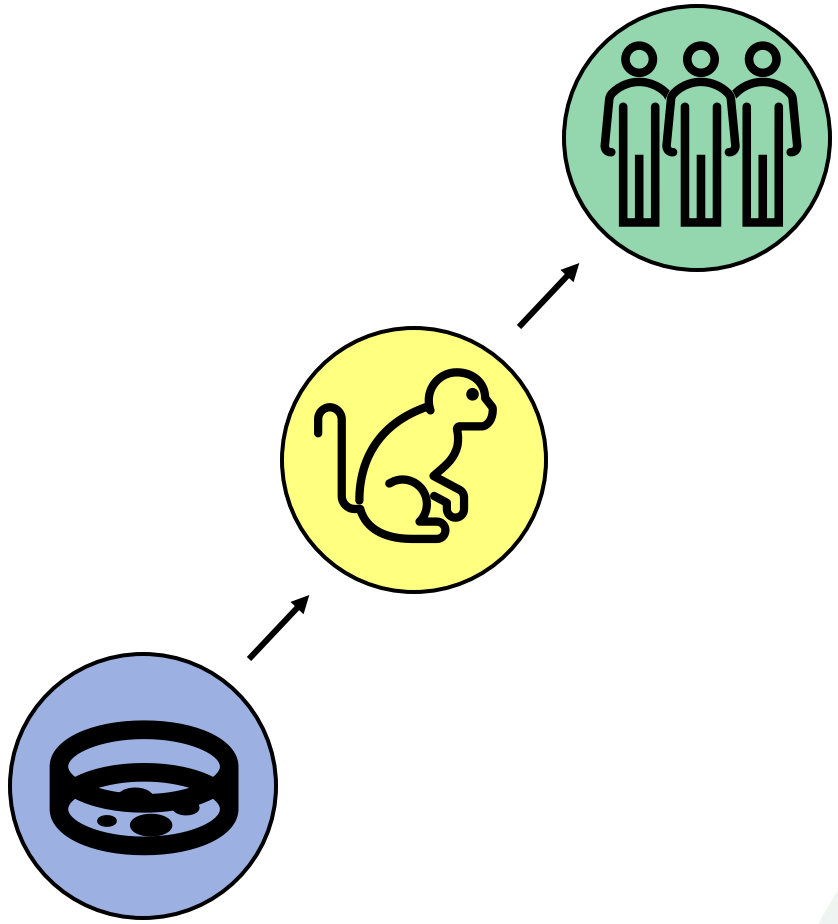
Inogatran

Objectives

- PK information:
  - Concentration-time profile
  - In vivo PK parameters: CL, half-life, C_{max}, T_{max}, AUC, V_d
- PD information:
  - Confirm Concentration-APTT relationship found in vitro.
- Other outcomes:
  - Adverse events
  - Vital signs (blood pressure, ECG, heart rate etc.)

Study Design

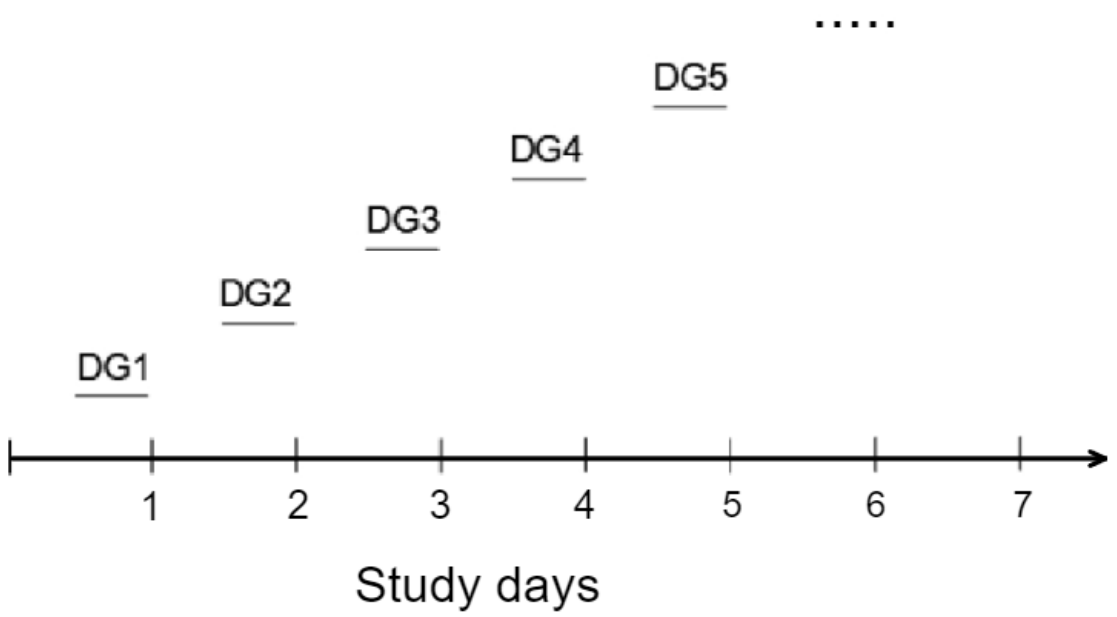
- Parallel, randomized, placebo-controlled, double-blind
- **Study population:** healthy male volunteers (18-50 yr)
- **Study arms:** 6 participants per arm
  - Inogatran: 4
  - Placebo: 2
- At least 30 participants (minimum 5 arms) but could increase based on clinical results



Dose Escalation Scheme

- **Starting dose** = 0.5 mg
- **The following doses** = 1, 2, 3, 4 mg...

- The dosing stops when APTT has approached 190 s. It is possible to stop the dosing earlier if significant AE emerge.



The sampling process

- Sampling times: 0.5, 1, 2, 5, 15, 30, 60, 90, 110 min

- Conducted calculations:
  - $C_f = C_i * e^{-k*t}$
  - 0.5 mg / 21 L = 0.0238 mg/L = Ci
  - 0.005 mg/L = 0.0238 mg/L * $e^{-0.014*t}$
  - t=111.5 min
- Minimum measurable conc. 0.005 mg/l
  - Cl = 300 ml/min
  - V = 0.3 L/kg x 70 kg = 21 L
  - 50 min = $t^{1/2}$
  - K = 0.01386 min^{-1}

Analytical Method

- PK analysis
  - Measure concentration in the blood sample, draw the mean concentration-time curve.
  - Get Cmax, Tmax, AUC from the curve.
  - V_d = Dose/C_{max}
  - CL = Dose/AUC
  - $t_{1/2}$ = ln(2) * V/CL
- PD analysis
  - Explore concentration-APTT relationship, calculate in vivo $IC_{50(APTT)}$.
- Safety analysis
  - The number of subjects experiencing treatment-emergent adverse events (TEAEs) and number of TEAEs will be summarized by treatment using frequency counts.

Questions?