A population modelling framework to support early clinical development of BI-1206, a monoclonal antibody inhibiting FcγRIIB

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Aim

The aim of this work is to develop an interim population pharmacokinetic (PK), FcγRIIB receptor occupancy (RO), and platelet model to quantitatively characterize BI-1206 pharmacology and identify sources of variability, integrating data from ongoing clinical trials.

The goal is to support dose optimization and study design across diverse clinical settings.

Conclusions

A modelling framework has been successfully developed to characterize the impact of BI-1206 on pharmacodynamic (RO) and safety (platelets) markers, further supporting a drug-induced reversible binding of circulating platelets rather than cytotoxicity.

The model represents an important tool to guide dose selection and study design for upcoming clinical trials.

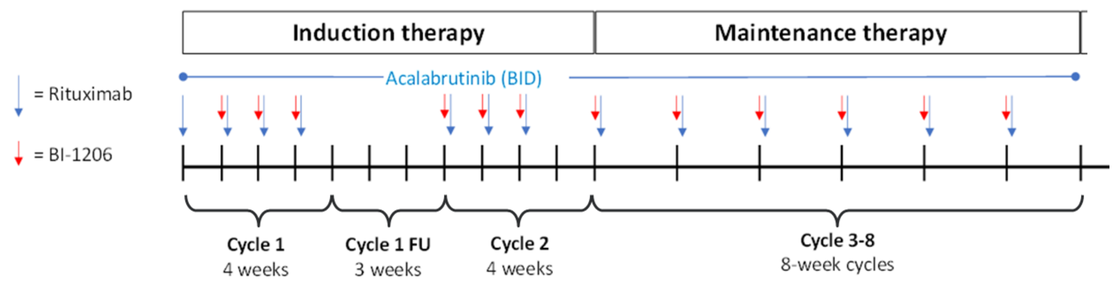
Background

BI-1206 is a fully **human monoclonal antibody** that antagonizes the only Fcγ inhibitory receptor (**FcγRIIB**), a regulator of antibody driven immune responses [1].

By blocking this pathway, BI 1206 is designed to ultimately **influence therapeutic antibody activity and immune effector responses** of established immunotherapies [2-3].

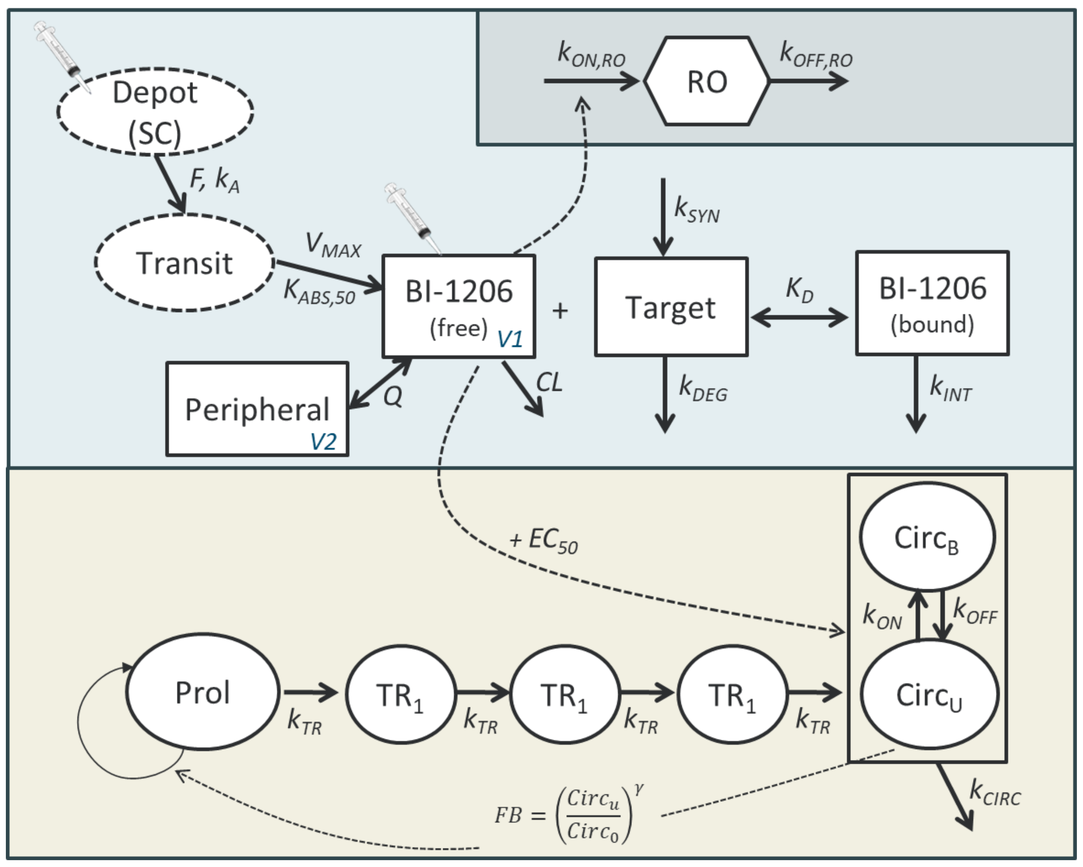
Data and methods

- 17-BI-1206-02: indolent B-cell non-Hodgkin **lymphoma** in combination with rituximab +/- acalabrutinib (n=55)
  - BI-1206 dosing: 30–200 mg (IV) & 150–300 mg (SC)



- 18-BI-1206-03: advanced **solid** tumors in combination with pembrolizumab (n = 54)
  - BI-1206 dosing : 0.5–2 mg/kg and 70 mg (IV) and 150–300 mg (SC). Once or twice per 21-day cycle, depending on the cohort

- **Sequential and integrative modelling** in NONMEM 7.5
  - (i) PK model for IV and SC
  - (ii) FcγRIIB RO (only available for solid tumors)
  - (iii) Platelet model using individual estimated PK parameters and observed baseline (B2 method)



Results

- Final model is represented and described in Figure 1
  - Differences across studies identified at the target binding (K_D) and platelet mean transit time (MTT)
  - Mixture model implemented at platelet binding level, identifying a population (p=0.09) with high drug sensitivity
- Good overall model performance (Figure 2)

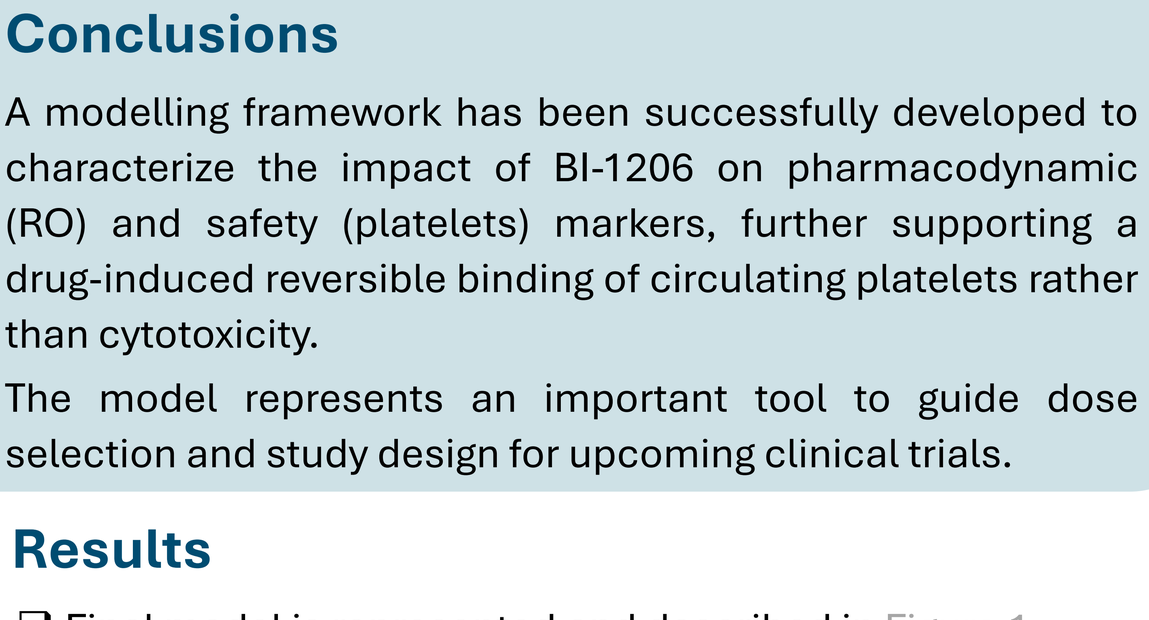


Figure 2: Prediction-corrected visual predictive checks (VPC) Colored areas are the 95% confidence intervals around the 5th, 50th and 95th predicted percentiles. Black lines and dots represent the corresponding observed percentiles and observations. Note 90th prediction interval for the % of PK data below the limit of quantification (BLQ) (panel A, bottom).

- Model predicted increased incidence of grade 3-4 thrombocytopenia with decreasing platelet counts at baseline (Figure 3 and 4)

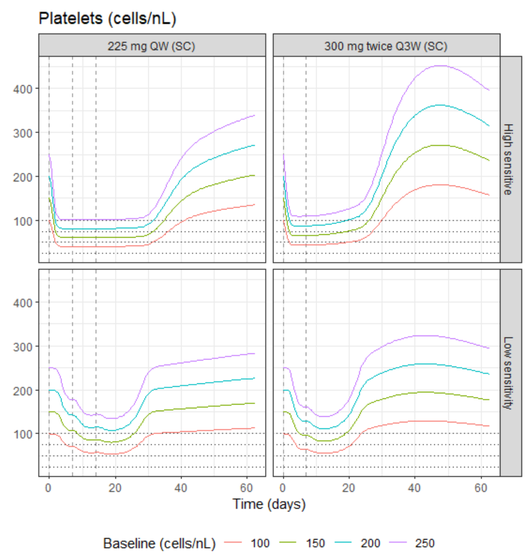


Figure 3: Platelet count time course for the high and low sensitive population at different baseline values

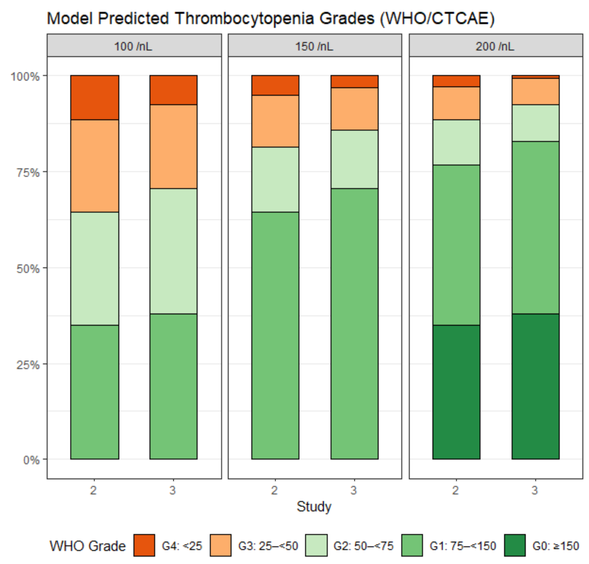


Figure 4: Model predicted thrombocytopenia grades at Cycle 1 for 225 mg QW (02 study) and 300 mg twice (03 study) at different baseline cut-offs (n=500)

Figure 1 Schematic representation of the final BI-1206 model. Pharmacokinetics described by (i) a two-compartment model (V_1/ V_2, central and peripheral volumes; Q, intercompartmental clearance) (ii) with subcutaneous (SC) absorption via a depot and a transit compartment (F, bioavailability; k_A, absorption rate constant; V_{MAX} and $K_{ABS,50}$, nonlinear absorption parameters), (iii) linear clearance (CL) and (iv) target-mediated drug disposition captured through reversible binding (k_D), target turnover (k_{SYN}/k_{DEG} synthesis and degradation rate constants), and internalization of the drug complex (k_{INT}). Receptor occupancy (RO) driven by a slow dissociation model ($k_{ON,RO}$/$k_{OFF,RO}$, association and dissociation rate constants). Platelet dynamics described with a (i) proliferative compartment (Prol), (ii) a series of maturation transit compartments (TR, transit rate constant k_{TR}), and (iii) circulating unbound ($CIRC_U$) and bound ($CIRC_B$) platelets governed by an association and dissociation rate constant (K_{ON}/K_{OFF}). A feedback (FB) mechanism regulates proliferation as a function of circulating platelets (γ, feedback exponent). Drug effects on platelet binding modeled using a non-linear effect (EC_{50}, half-maximal effect concentration).

References

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