Pop PK/PD analysis of roginolisib in healthy participants using the basophil activation test to determine the PI3Kδ occupancy.

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Introduction

- **Roginolisib**: A highly selective, oral allosteric modulator of PI3Kδ that blocks the activity of PI3Kδ-dependent signalling, in both tumor cells and Tregs [1].
- **Activation of basophils (CD63⁺)** is PI3Kδ-dependent, which makes CD63⁺ a potential **surrogate** to characterise the **inhibitory effect of roginolisib** on PI3Kδ in tumor cells.

Objective

- Development of **a population PK/PD** (PK/PD) for **roginolisib in HV** understand influence of food, sex and alpha1-acid glycoprotein (AAG) binding on clearance exposure in HV and predicting patient studies.
- Discuss appropriate **data transformation** to describe the drug effect on **CD63⁺** basophils

Methods

Data for model development

- **Phase I** cross-over FDI study of roginolisib in **HV** (N = 32) [2].
  - Two single dose incl. 7 days washout.
  - PK data: N = 960 up to 7 days post-dose.
  - CD63⁺ data: N = 503 up to 7 days post-dose.
  - **Time varying AAG data.**

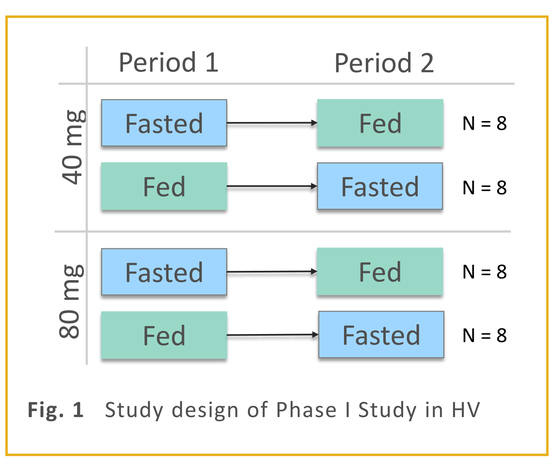

Fig. 1 Study design of Phase I Study in HV

Data for projection

- **Phase II** study of roginolisib in **patients** [3].
  - Daily dosing 40 mg or 80 mg, **No AAG** data.

PK/PD model development

- Non-linear mixed-effects modeling and simulation were conducted with **NONMEM** 7.6.0 [4].
  Post-processing was performed in **R:** 4.5.0 [5] facilitated by **Rstudio:** 2025.05.0-496 [6].

Modeling CD63⁺ data – The need of logit transformation

- Normal scale:
  - $0 \leq CD63^{+} \leq 100\ \%$

$\varepsilon \not\sim N(0, \sigma^2)$

$$logit(p) = \ln\left(\frac{p}{1-p}\right) \qquad p = \frac{CD63^{+}\ (\%)}{100}$$

- Logit scale:
  - $-\infty \leq logit(CD63^{+}) \leq \infty$

$\varepsilon \sim N(0, \sigma^2)$

Logit transformation – model implementation

```
TVBASE      = THETA(1)/100                ; initial on normal scale divided to put between 0-1
TVBASELOGIT = LOG(TVBASE/(1 - TVBASE))    ; logit - transformation, values between -∞,∞
BASELOGIT   = TVBASELOGIT + ETA(1)        ; IIV additive
BASE        = 100 / (1 + EXP(-BASELOGIT)) ; back-transform to normal scale, values between 0 - 100


$ERROR
CONC = A(2)/S2  ; model predicted concentration on normal scale
EFF = SLOPE * CONC ** POWER ; exponential (quasi-linear) effect model (POWER fixed to 1)
LOGITCD63 = BASELOGIT - EFF ; effect on logit scale to ensure values stay between 0 - 1

SD1 = THETA(5) ; add error on logit scale as standard deviation
W = SQRT(SD1*SD1)


; predicted percentage CD63+ cells
Y = 100 / (1 + EXP(-(IPRED + W * EPS(1)))) ; back-transform to normal scale values between 0 - 100
```

Results

Model structure

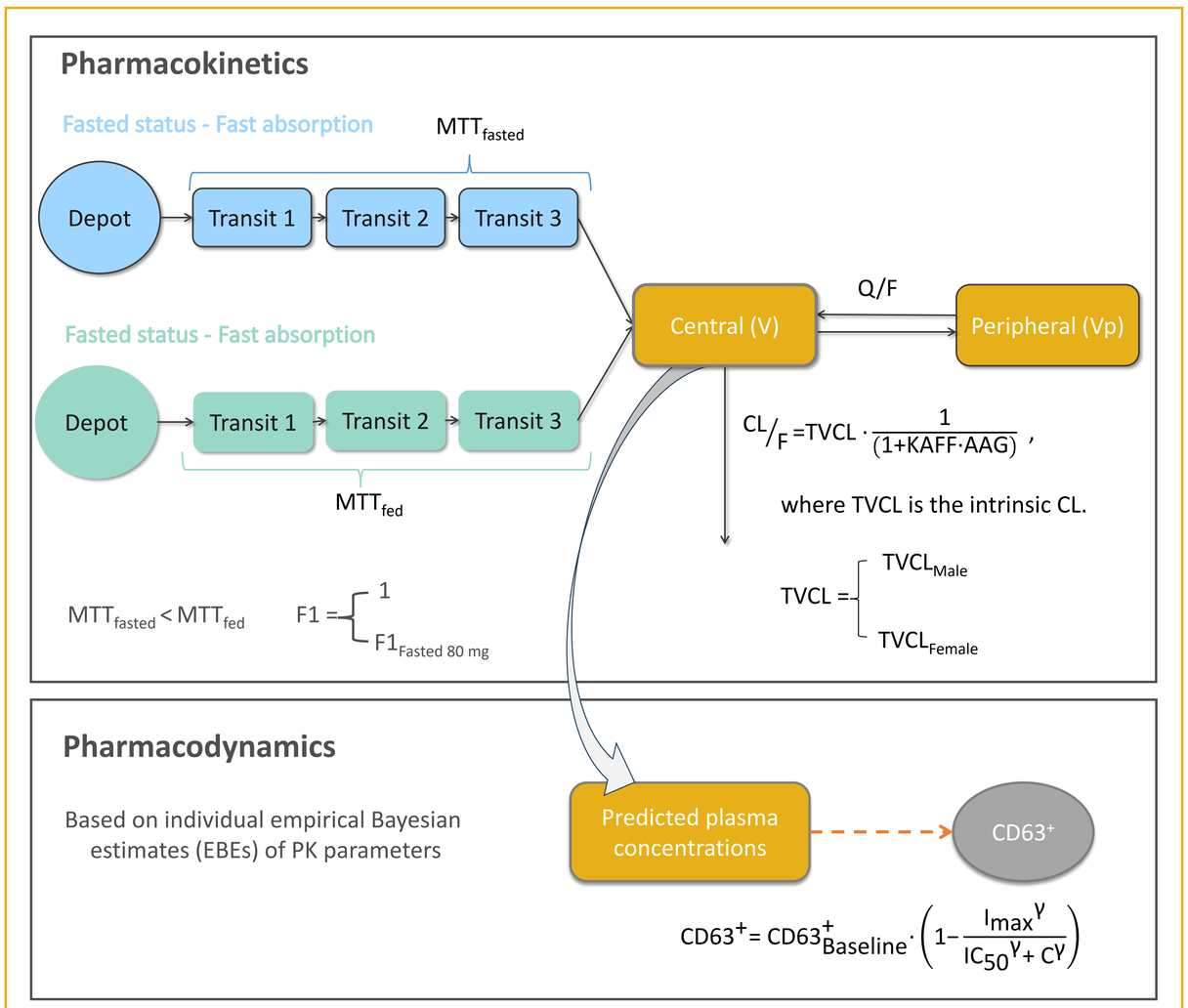

Fig. 2 Schematic representation of the sequential PK/PD model. MTT: Mean transition time, CL: Clearance, Q: Inter-compartmental CL, V: Volume, F1: Bio-avialability, I_{max}: Maximum inhibitory effect, IC_{50}: Concentration at half-maximal effect, CD63⁺: Percentage of activated basophil cells.

- All parameters were estimated with **good precision** (<30% RSE).
- **The intrinsic clearance for women** was estimated to be **36% higher** compared to men.
- **Doubling the AAG** results in a **34% reduction of CL/F**.

Model evaluation - PK/PD model

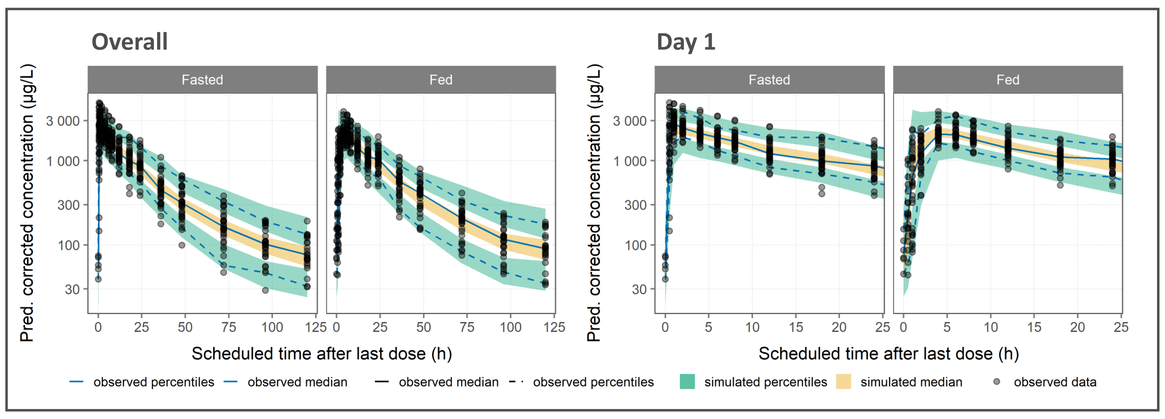

Fig. 3 Prediction corrected visual predictive check of the final PK model for roginolisib in **HV**

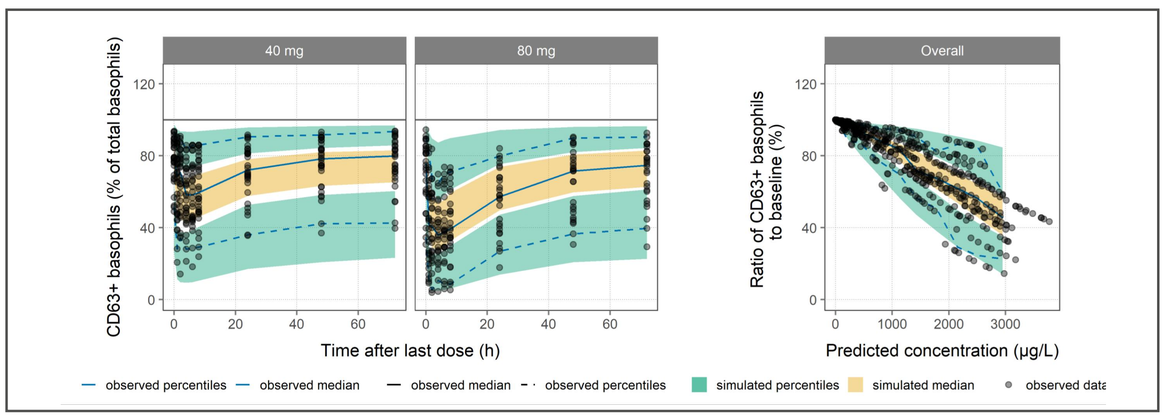

Fig. 4 Visual predictive checks of the final PK/PD model for roginolisib in **HV**

Impact of AAG in patient – Prediction of missing information

- Assuming relationship between CL/F, AAG and SEX are the same in patients and HV.
  - The model is capable of **predicting AAG** values that are **similar** to those reported in the **literature**.

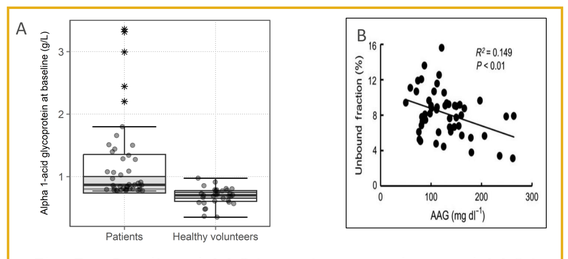

Fig. 5 Predicted AAG in patients *vs* observed AAG in HV (A), observed AAG in patients (B) [7].

Conclusion

- Two-compartment model incorporating time-varying AAG best describes roginolisib PK, highlighting drug binding to AAG as a key factor explaining inter-individual exposure variability.
- A direct-response model on the logit scale effectively describes roginolisib's inhibition of CD63 activation based on linear drug effect and good parameter precision.
- The developed PK/PD framework clarifies AAG-mediated protein binding effects on roginolisib exposure and supports using CD63⁺ basophil data as a surrogate marker for PI3Kδ target occupancy in early development.

[1] Johnson Z, et.al. Cancer Res Commun (2023) 3 576-591
[2] https://www.isrctn.com/ISRCTN11462643
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[7] Kenmotsu H, Br J Clin Pharmacol (2017) 83 2416–2425