Physiologically-based pharmacokinetic modeling to support submission of brigimadlin (BI 907828) in dedifferentiated liposarcoma

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Objectives

The aims of this work were to inform brigimadlin's regulatory submission by:

1.) Developing a PBPK model using available preclinical and clinical data.

2.) Evaluating brigimadlin's PK and its potential DDIs as both a victim and perpetrator of OATP1B1, OATP1B3, and CYP3A4 interactions.

Introduction

- Brigimadlin is a highly potent, oral MDM2-p53 antagonist [1] for the treatment of cancer patients.
- After single dose administration, brigimadlin shows a long terminal half-life of ~40 h and high variability in time to maximum plasma concentration (tmax) median 4 h varying from 2-24h. In vitro studies indicate limited metabolism via CYP3A4 and UGT1A3, while rat studies suggest biliary excretion as a major clearance route.
- Brigimadlin is a substrate and inhibitor of OATP1B1/1B3 (IC_{50}: 0.70/0.66 µM) and potential inducer of CYP1A2/CYP3A4 (Figure 1). A drug–drug interaction (DDI) study using a single dose of rifampicin—an inhibitor and inducer of both CYP3A4 and OATP1B—was conducted to evaluate OATP1B-mediated effects. The single-dose approach aimed to minimize CYP3A4-related effects; however, concurrent induction and inhibition of CYP3A4 still complicated the interpretation of the results.
- A physiologically based pharmacokinetic model (PBPK) model for brigimadlin was developed to investigate the complex transport-enzyme interplay and support further DDI investigations in patients with advanced solid tumors receiving brigimadlin.
- A PBPK model for Brigimadlin was developed using the Open Systems Pharmacology Software Suite (PK-Sim® and MoBi®, v11.2). The modeling process followed a stepwise approach illustrated in Figure 2:

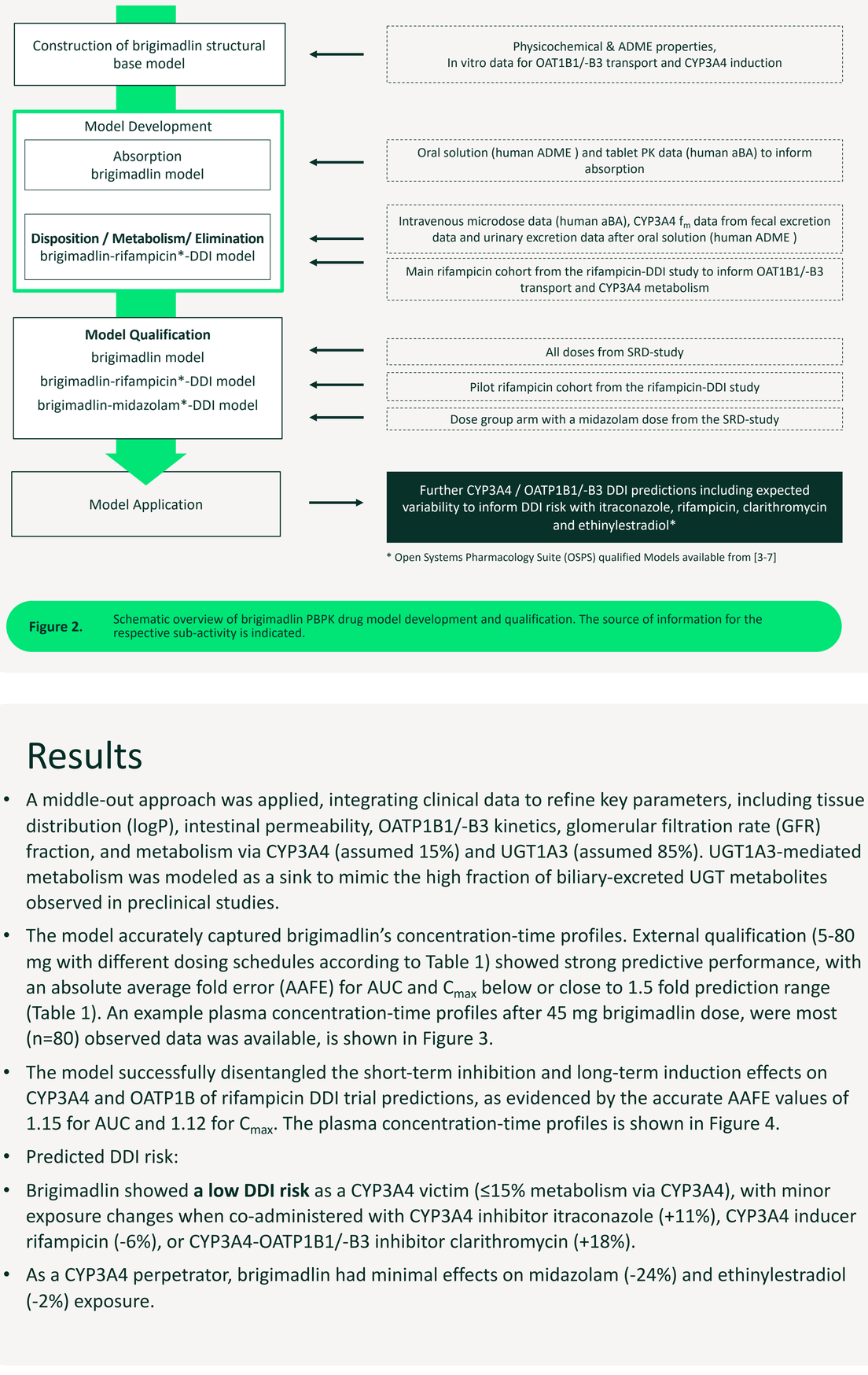

Figure 2. Schematic overview of brigimadlin PBPK drug model development and qualification. The source of information for the respective sub-activity is indicated.

Results

- A middle-out approach was applied, integrating clinical data to refine key parameters, including tissue distribution (logP), intestinal permeability, OATP1B1/-B3 kinetics, glomerular filtration rate (GFR) fraction, and metabolism via CYP3A4 (assumed 15%) and UGT1A3 (assumed 85%). UGT1A3-mediated metabolism was modeled as a sink to mimic the high fraction of biliary-excreted UGT metabolites observed in preclinical studies.
- The model accurately captured brigimadlin's concentration-time profiles. External qualification (5-80 mg with different dosing schedules according to Table 1) showed strong predictive performance, with an absolute average fold error (AAFE) for AUC and C_{max} below or close to 1.5 fold prediction range (Table 1). An example plasma concentration-time profiles after 45 mg brigimadlin dose, were most (n=80) observed data was available, is shown in Figure 3.
- The model successfully disentangled the short-term inhibition and long-term induction effects on CYP3A4 and OATP1B of rifampicin DDI trial predictions, as evidenced by the accurate AAFE values of 1.15 for AUC and 1.12 for C_{max}. The plasma concentration-time profiles is shown in Figure 4.
- Predicted DDI risk:
- Brigimadlin showed **a low DDI risk** as a CYP3A4 victim (≤15% metabolism via CYP3A4), with minor exposure changes when co-administered with CYP3A4 inhibitor itraconazole (+11%), CYP3A4 inducer rifampicin (-6%), or CYP3A4-OATP1B1/-B3 inhibitor clarithromycin (+18%).
- As a CYP3A4 perpetrator, brigimadlin had minimal effects on midazolam (-24%) and ethinylestradiol (-2%) exposure.

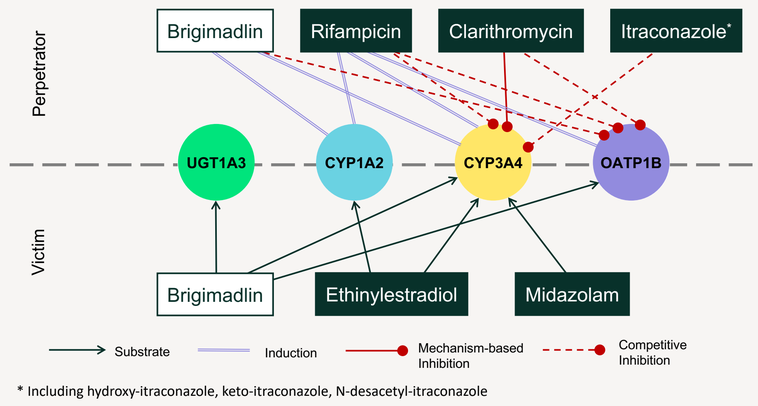

Figure 1. Overview of the implemented DDIs in the brigimadlin and the compounds used for development, qualification and application.

Administration scheme	AAFE AUC	AAFE C_{max}	Number of patients
every 3 weeks from 10 to 80 mg	**1.22**	**1.22**	29
at day 1 and 8 every 4 weeks from 5 to 60 mg	**1.61**	**1.28**	25
at day 1 and 3 every 4 weeks at 30 mg	**1.22**	**1.17**	2

Table 2. Overview of the average absolute fold error (AAFE) for the predicted pharmacokinetic parameters in the qualification datasets.

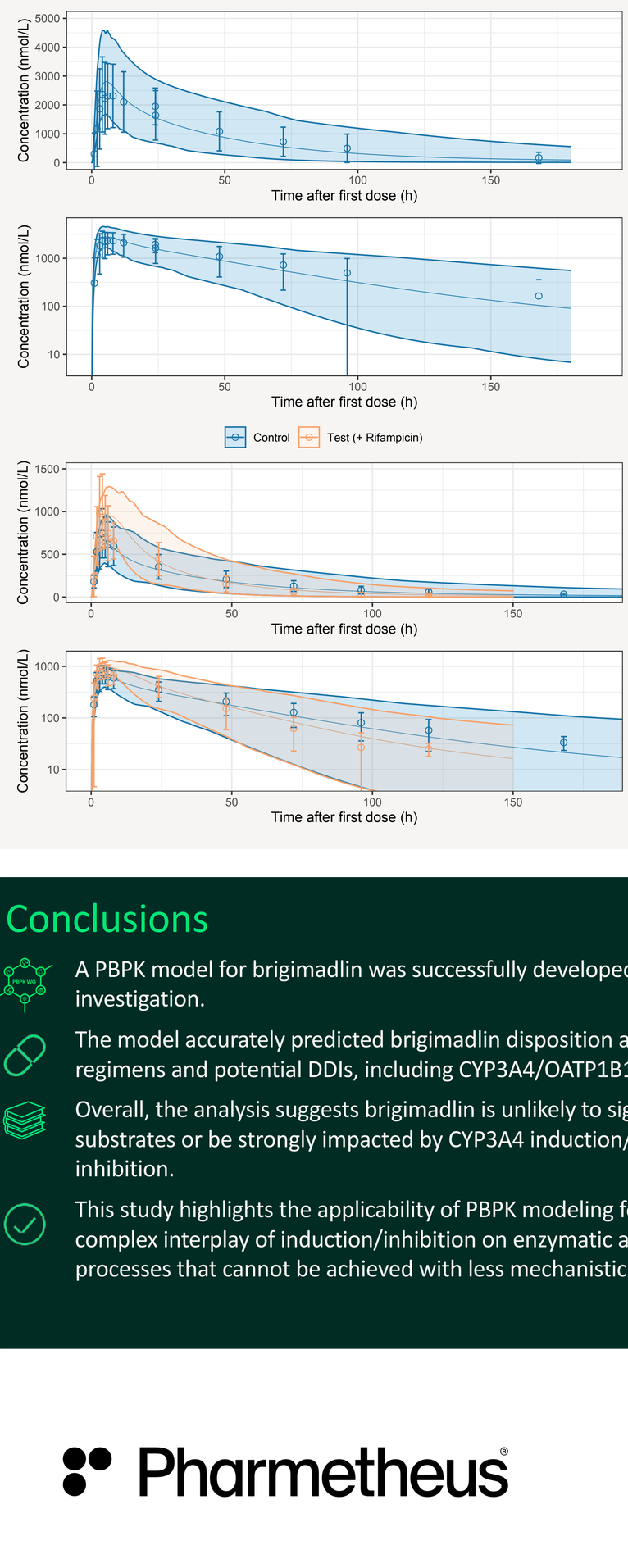

Figure 3. Brigimadlin plasma concentration-time profiles after 45 mg brigimadlin oral administration in fasted state as tablet on Day 1 q3w. Linear scale is shown at the top and log scale at the bottom.

Observations from the SRD-study are represented by open circles with error bars (geometric mean +/- standard deviation). Solid line and shaded area represent the simulated geometric mean and the 5-95% quantiles of the PBPK model for a virtual population (n=100).

Of note, in log scale the last error bar is missing as its value is below zero and the second to last error bar is cut of as its value is below 3 nM.

Figure 4. Brigimadlin plasma concentration-time profiles after 10 mg oral administered as tablet with (Test) and without (Control) rifampicin. Linear scale is shown at the top and log scale at the bottom. Observations until 180 hours post dose from the pilot cohort of the rifampicin-DDI study are represented by open circles with error bars (geometric mean +/- SD). Solid line and shaded area represent the simulated geometric mean and the 5-95% quantiles of the PBPK model for a virtual population (n=100). Of note, the second to last error bar for Test is cut of as its value is below 2 nM.

Conclusions

- A PBPK model for brigimadlin was successfully developed and applied for DDI investigation.
- The model accurately predicted brigimadlin disposition across various dosing regimens and potential DDIs, including CYP3A4/OATP1B1/-B3 interactions.
- Overall, the analysis suggests brigimadlin is unlikely to significantly affect CYP3A4 substrates or be strongly impacted by CYP3A4 induction/inhibition or OATP1B1/-B3 inhibition.
- This study highlights the applicability of PBPK modeling for analysis and predictions of complex interplay of induction/inhibition on enzymatic and transporter-mediated processes that cannot be achieved with less mechanistic modeling approaches.

Abbreviations

aBA, absolute Bioavailabilty; AUC_{last}, area under the plasma concentration–time curve from the first to the last time point of measurement; C_{max}, maximum plasma concentration; CYP, cytochrome P450; DDI, Drug–drug interaction; MDM2-p53, murine double minute 2 (MDM2)-tumor suppressor protein p53; OATP1, organic anion transporting polypeptide 1; PBPK, Physiologically based pharmacokinetic; SRD, single rising dose.

References

1. LoRusso P et al. Cancer Discov 2023 ; 13:1802–13.
2. Lippert J et al. CPT pharmacometrics Syst. Pharmacol. (2019) 8, 878–882.
3. https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/tree/master/Rifampicin
4. https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/tree/master/Midazolam
5. https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/tree/master/Itraconazole
6. https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/tree/master/Clarithromycin
7. https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/tree/master/Ethinylestradiol

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