PBPK Modeling to Predict the Effect of Gastric pH on Bioequivalence of Palbociclib Tablets

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INTRODUCTION

- Palbociclib is a BCS Class II weak base drug substance that shows pH-dependent solubility and dissolution. Patients taking IBRANCE capsules (NDA 207103), are impacted by lower overall survival and progression-free survival when palbociclib capsules are taken with an acid-reducing agent (ARA).[1] The reduced efficacy of palbociclib capsules is implicated by a reduction in bioavailability due to reduced palbociclib solubility in the presence of ARAs.[1]
- IBRANCE tablets (NDA 212436), on the other hand, were formulated with a pH modifier to help minimize the pH-effect in the presence of ARAs. Different generic formulations of palbociclib immediate-release (IR) tablets, if not properly formulated with pH modifiers, can potentially have different dissolution behavior in the presence of an ARA. Therefore, the current FDA product-specific guidance (PSG) for palbociclib IR tablets recommends conducting an additional fasting BE study in the presence of an ARA.[2]
- This research aims to develop a PBPK model of palbociclib IR tablets to identify biopredictive dissolution and assess the impact of co-administration of ARAs on bioequivalence (BE) for palbociclib IR tablets. For this project, the reference listed drug (RLD) is NDA 212436.
- A secondary objective was to develop a fed PBPK model capable of predicting the observed positive food effect and impact on BE when palbociclib IR tablets are administered with a high fat meal.

METHOD

- GastroPlus® Version 9.9.0002 (Simulations Plus, Inc., Research Triangle Park, NC) was used to develop a PBPK model under fasting, fasting with ARA, and fed conditions. Intravenous PK data obtained from the literature were used to estimate disposition parameters. Two different approaches for incorporating dissolution data were considered: (1) fitting a Z-factor to dissolution data and (2) directly using tabulated dissolution data.
- Approach #2 in combination with the "Human – Dyn Vol 100% Mudie-fasted" physiology was chosen for its ability to predict virtual bioequivalence (VBE) under fasting and fasting with ARA conditions using dissolution data from pH 1.2 0.1N HCl and pH 4.5 phosphate buffer, respectively. The GastroPlus® human fed physiology was chosen to predict VBE under fed conditions using dissolution data from pH 4.5 phosphate buffer.
- The fasting PBPK model was validated using pH 1.2 dissolution data from two available in-house ANDA submissions (#1-2) and PK data from respective fasting BE studies. The fed PBPK model was validated using pH 4.5 dissolution data and fed BE criteria where available from fed BE studies.
- PBPK models were then used to predict PK and BE of generic palbociclib tablets in subjects administered with an ARA under the fasting condition.

Palbociclib PBPK modeling of fasting, fasting + ARA, and fed conditions

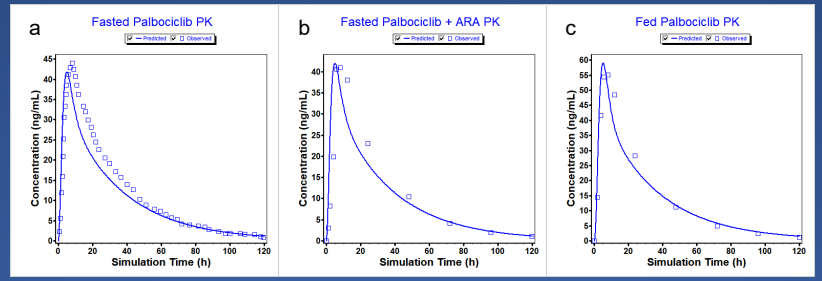

Fig 1. (a) Fasting, (b) fasting + ARA, and (c) Fed palbociclib predicted vs. observed (from NDA) PK.

	Fasted			Fasted + ARA			Fed		
	Obs	Pred	%PE	Obs	Pred	%PE	Obs	Pred	%PE
$AUC_{0\text{-}inf}$ (ng-h/mL)	1415.5	1256.5	-11.23	1422.8	1262.1	-11.29	1791.8	1671	-6.74
C_{max} (ng/mL)	43.96	41.79	-4.94	40.89	41.98	2.67	55.07	58.96	7.06

Table 1. Fasting, fasting + ARA, and fed palbociclib predicted vs. observed (from NDA) AUC and C_{max}.

ANDA #	1			2		
PK Parameter	Obs	Pred	%PE	Obs	Pred	%PE
Fasted						
C_{max} (ng/mL)	-	-	22.27	49.07	52.15	6.28
$AUC_{0\text{-}inf}$ (ng-h/mL)	-	-	0.5141	1572	1474	-6.23
Fed						
C_{max} (ng/mL)	-	-	-10.51	56.68	-	-
$AUC_{0\text{-}inf}$ (ng-h/mL)	-	-	-26.09	2043.8	-	-

Table 2. Validation of fasted and fed PBPK models using ANDAs #1 and 2 with %PE for C_{max} and $AUC_{0\text{-}inf}$. Note: C_{max} and $AUC_{0\text{-}inf}$ have been masked for ANDA #1 due to its tentatively approved status. Fed Cmax and $AUC_{0\text{-}inf}$ were not predicted for ANDA #2 because pH 4.5 dissolution data was not included in submission.

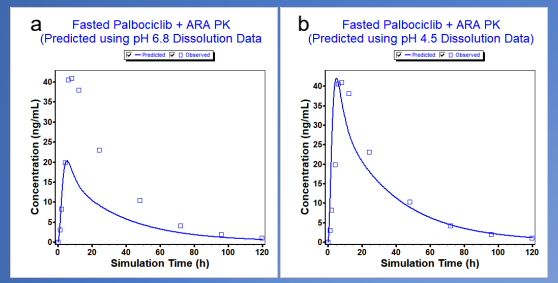

Fig 2. Fasting palbociclib + ARA PK prediction using (a) pH 6.8 dissolution data vs. (b) pH 4.5 dissolution data of RLD IR tablets

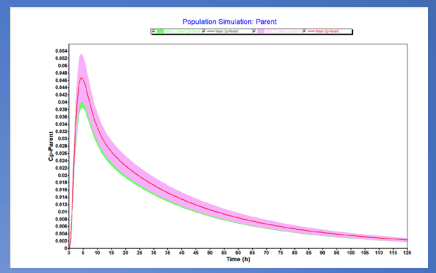

Fig 3. Representative VBE of fasting palbociclib + ARA using pH 4.5 dissolution data of Test and Reference IR tablets from ANDA #1

C_{max}	AUC	AUC_t
87.679→120.45	88.325→117.85	88.547→117.8

Table 3. Representative 90% Confidence Intervals of Geometric Mean of Test Palbociclib IR/Geometric Mean of Reference Palbociclib IR from ANDA #1

RESULTS

- PBPK models to predict palbociclib PK under fasting conditions were developed using NDA pH 1.2 dissolution data (Fig 1a.; Table 1). Models were validated using respective dissolution data from ANDA submissions. The PBPK model for the fasting condition generally predicted $AUC_{0\text{-}inf}$ and C_{max} well (%PE≤20) (Table 2) and predicted BE BE for all available ANDA submissions (data not shown).
- The PBPK model for the fasting with ARA condition predicted $AUC_{0\text{-}inf}$ and C_{max} of palbociclib RLD coadministered with raboprazole well (%PE≤20) using pH 4.5 dissolution data (Fig 1b.; Table 1). Results indicated that compared to pH 6.8 dissolution data, pH 4.5 dissolution data are more biopredictive for predicting PK under fasting conditions with the co-administration of ARAs (Fig. 2). BE was predicted under fasting conditions with the co-administration of ARAs for ANDA #1 (Fig 3, Table 3).
- The PBPK model for the fed condition predicted $AUC_{0\text{-}inf}$ and C_{max} of palbociclib RLD in the fed state (%PE≤20) using available pH 4.5 dissolution data from the NDA (Fig 1c.; Table 1). However, the model slightly underpredicted $AUC_{0\text{-}inf}$ of RLD tablets from ANDA# 1 (%PE was -26.09%). This may be due to dissolution being conducted in pH 4.5 aqueous buffer rather than biorelevant media such as Fed State Simulated Intestinal Fluid (FeSSIF) used in NDA application.

CONCLUSION

- A PBPK model with the direct dissolution incorporation method can be used to predict BE of generic palbociclib IR tablet products with and without the co-administration of ARAs under the fasting condition as well as to predict BE under the fed condition. On the other hand, fitting a Z-factor to dissolution data resulted in non-VBE if there was as much as a ~0.5-fold difference in Z-factor between test and reference dissolution curves.
- These validated PBPK models may be used to identify biopredictive dissolution and assess the impact of co-administration of ARAs on the BE of generic palbociclib IR tablets under the fasting condition.

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References:

1. Di Cosimo S, Pérez-García JM, Bellet M, Dalenc F, Gil Gil MJ, Ruiz-Borrego M, Gavilá J, Aguirre E, Schmid P, Marmé F, Gligorov J, Schneeweiss A, Albanell J, Zamora P, Wheatley D, Martínez de Dueñas E, Amillano K, Shimizu E, Sampayo-Cordero M, Cortés J, Llombart-Cussac A. Impact of coadministration of proton-pump inhibitors and palbociclib in hormone receptor-positive/HER2-negative advanced breast cancer. Breast. 2024 Aug;76:103761.
2. Draft Guidance on Palbociclib. May 2022. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_212436.pdf.