Physiologically-based Pharmacokinetic (PBPK) Modeling of the Combination of Ivacaftor and Lefamulin in Cystic Fibrosis Patients

Nabriva Therapeutics
Dublin, Ireland
www.nabriva.com

Wolfgang. W. Wicha[1], Magali Amiel[2], Alice Ke[2], Jared L. Crandon[3], Hannah M. Jones[2], Steven P. Gelone[3]

[1]Nabriva Therapeutics GmbH, Vienna, Austria, [2]Certara UK Ltd, Simcyp Division - Sheffield (United Kingdom); [3]Nabriva Therapeutics US, Inc., Fort Washington, PA, USA

Scan this QR code to receive a PDF file of the poster or visit www.nabriva.com/news

INTRODUCTION

- Lefamulin is a first-in-class pleuromutilin antibiotic approved as both IV and oral formulations for the treatment of community-acquired bacterial pneumonia in adults.[1]
- The spectrum of activity for lefamulin includes activity against common causes of CABP, including: *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, and *Staphylococcus aureus* including both methicillin susceptible and methicillin resistant strains.[1]
- Given its potent activity against *S. aureus* and the propensity for patients with cystic fibrosis (CF) to be infected with this pathogen, lefamulin is currently being evaluated as a potential treatment for bacterial exacerbations in CF patients caused by *S. aureus*.[2]
- Lefamulin undergoes hepatic metabolism and is both a substrate and moderate inhibitor of CYP3A.[1]
- Ivacaftor is a CF transmembrane conductance regulator (CFTR) modulator that is a sensitive substrate of CYP3A.[3]
- Given that CFTR modulators, including ivacaftor, have become a foundational therapy for many patients with CF, it is important to evaluate the potential for drug-drug interactions between lefamulin and ivacaftor to support lefamulin's clinical development as a therapeutic for exacerbations in CF patients.
- Through use of PBPK modeling, we characterized the drug-drug interaction potential for lefamulin as compared with itraconazole, fluconazole, and ketoconazole.

METHODS

PBPK Model Development and Validation

- PBPK models were derived and simulated using Version 20 of the Simcyp ™ Simulator (www.simcyp.com) utilizing the minimal PBPK model with the non-physiological single adjustable compartment. Absorption was simulated using the Advanced Dissolution, Absorption, and Metabolism (ADAM) model. The chosen minimal PBPK model separates the liver and gastro-intestinal tract from the rest of the body to consider metabolism and inhibition/induction of the enzymes in these organs (**Figure 1**).
- **Lefamulin**: A PBPK model for lefamulin was previously developed from clinical and in vitro data and validated against observed single and multidose regimens (Data on File, Nabriva Therapeutics). Simulations for the final lefamulin PBPK model during validation experiments revealed mean AUC_{0-t} and C_{max} values within 1.07-fold that of observed values in healthy volunteers.
- **Ivacaftor**: A previously published PBPK model for ivacaftor[4] was used as a basis for development of a minimal PBPK model herein. Once the ivacaftor model was developed, it was validated by simulating concentration-time profiles for repeat oral doses (5 to 14 days) of 50 mg QD and 150 mg BID, comparing exposures with published observed data.[7,8,9]

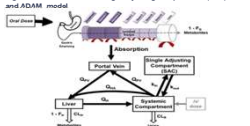
PBPK Model Verification For Drug-Drug Interaction Studies

- **Ivacaftor:** To characterize the contribution of CYP3A4 to the overall clearance for ivacaftor, simulations were run for combinations with itraconazole, fluconazole and ketoconazole (Simcyp Version 20 Standard Compound Library) and the ivacaftor exposures were compared with observed clinical data[7,8,9].
- **Lefamulin:** The previously developed PBPK model for lefamulin was similarly validated in its original development. Namely, simulations were made and compared with observed clinical drug-drug interaction studies with ketoconazole, rifampin, and midazolam. Of note, the final enzyme competitive inhibition constant (Ki) varied between IV and oral formulations of lefamulin. (Table 1, Data on File, Nabriva Therapeutics)

Evaluation of Lefamulin and Ivacaftor Drug-Drug Interaction Potential

- **Cystic Fibrosis Population**: For all drug-drug interaction simulations, patient demographic model inputs were derived from the literature and included a proportion of females (48.2%), average albumin concentration (41.9 g/L), a weighted distribution for age, and corrective coefficients for height and weight as a function of gender relative to the North European Caucasian population preidentified in Simcyp Simulator.[5,6]
- Given the availability of clinical pharmacokinetic data for ivacaftor as a single dose to cystic fibrosis patients, validations studies were conducted to evaluate predictability of the PBPK model in the cystic fibrosis population.[8]
- Simulations of 10 trials of 10 patients with CF (48.2% female) aged 18 to 35 years were generated with the following dosing regimens:

Figure 1. PBPK model with single adjusting compartment (SAC) and ADAM model



Experiment A: Simulation of a single Oral Ivacaftor Dose Administered within a Multi-dose Regimen of IV or Oral Lefamulin in Patients with CF		
	Ivacaftor (single dose)	Lefamulin (steady state)
Monotherapy	150 mg oral	---
Combination therapy	150 mg oral on Day 7	IV: 150 mg BID IV given as 1-hr infusion PO: 600 mg BID orally for 15 days in fed state
Experiment B: Simulation of Multiple Oral Doses of Ivacaftor Administered with a Single IV or PO Dose of Lefamulin in Patients with CF		
	Ivacaftor dose (steady state)	Lefamulin (single dose)
Monotherapy	150 mg BID x 8 days	---
Combination therapy	150 mg BID x 8 days	IV: 150 mg IV given as 1-hr infusion on day 7 PO: 600 mg BID orally in fed state on day 7
Experiment C: Simulation of Multiple Oral Doses of Ivacaftor BID Administered with Multiple IV or Oral Lefamulin Doses in Patients with CF		
	Ivacaftor dose (steady state)	Lefamulin (steady state)
Monotherapy	150 mg BID orally x 8 days	---
Combination therapy	150 mg BID orally x 8 days	IV: 150 mg IV given BID as 1-hr infusion PO: 600 mg BID orally in fed state x 8 days

Statistical Analysis

- Statistical comparisons were performed using least square geometric mean ratios (GMR) for ivacaftor pharmacokinetic profiles with and without lefamulin. Specific comparisons were evaluated for maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC). Classification of the strength of inhibition was as follows: changes in GMR by <1.25-fold was considered insignificant, 1.25-2.0-fold was considered weak inhibition, 2.0 – 5.0-fold was considered moderate inhibition, and >5.0-fold was considered strong inhibition.

RESULTS

Table 1. Input Parameters for ivacaftor and lefamulin PBPK Models

PARAMETER	Ivacaftor	Lefamulin
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	392.49	507.74
log P	5.68	2.8
Compound type	Diprotic acid	Monoprotic base
pKa	9.4, 11.6	9.41
B:P	0.55	0.71
fu	0.001	0.121
Main binding protein	Albumin	Albumin
Absorption model – ADAM model		
fu_{gut}	0.001	1
Caco-2 P_{app} ($x10^{-6}$ cm/s)	11.9	-
$P_{eff,man}$ (pred) ($x10^{-4}$ cm/s)	2.49	-
MechPeff model $P_{eff,man}$ ($x10^{-4}$ cm/s)		21400
Regional Permeability ($x10^{-4}$ cm/s)		
Duodenum	-	0.994
Jejunum I/II	-	4/1.45
Ileum I/II/III/IV	-	0.621/0.621/0.61/0.587
Colon	-	0.01
Formulation type	Immediate release	Immediate Release
Solubility (mg/mL)	0.003	500 (pH 7.4)
Distribution model – minimal PBPK model (lefamulin = full PBPK model)		
V_{ss} (L/kg)	1.74	1.79
SAC Q (L/h)	3.752	-
V_{sac} (L/kg)	0.67	-
K_p scalar	-	1
Elimination parameters – Enzyme kinetics		
fm_{CYP3A4}	97%	-
CYP3A4 K_m (uM)	4	-
CYP3A4 V_{max} (pmol/min/mg protein)	1519.2	-
Biliary CL_{int} (µL/min/10^6 cells)	30	-
CL_R (L/h)	-	1.6
CYP3A4 CL_{int} (µl/min/pmol)	-	0.153
Additional HLM CL_{int} (µL/min/mg)	-	39
fu_{inc}	0.105	1
Transport parameters		
P-gp J_{max} (pmol/min)	-	403.8
P-gp K_m (uM)	-	10
Interaction parameters		
CYP3A4 K_i (µM) (PO administration)	-	0.2
fu_{inc}	-	0.98
CYP3A4 K_i (µM) (IV administration)	-	0.86
fu_{inc}	-	0.98
CYP2C8 K_i (µM)	-	41
fu_{inc}	-	1

PBPK Model Development and Validation

- **Table 1** depicts the final input parameters for both ivacaftor and lefamulin in their respective PBPK models.
- In validation studies, simulations for the final ivacaftor PBPK model revealed mean $AUC_{0-\infty}$ and C_{max} values within 1.28-fold that of the observed values in healthy volunteers.
- Simulations of cystic fibrosis patients given single doses of ivacaftor resulted in $AUC_{0-\infty}$ and C_{max} values within 1.4-fold of the observed values, with simulated exposures being greater than observed.

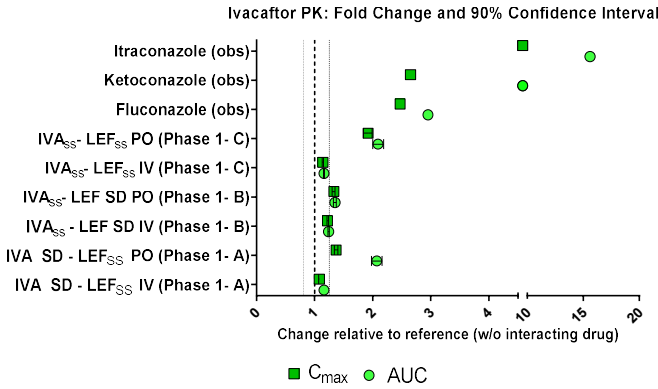
PBPK Model Verification For Drug-Drug Interaction Studies

- Simulated geometric mean rations for AUC and C_{max} were within 1.25, 1.25. and 1.5-fold of the observed values for itraconazole, fluconazole, and ketoconazole, respectively.

Evaluation of Lefamulin and Ivacaftor Drug-Drug Interaction Potential

- The results of the simulated drug-drug interaction between lefamulin and the sensitive CYP3A substrate, ivacaftor, are shown in **Figure 1** as compared with observed clinical data for the moderate and strong CYP3A inhibitors fluconazole, ketoconazole, and itraconazole.
- Simulations combining oral ivacaftor with IV lefamulin resulted in non-significant impacts on ivacaftor pharmacokinetics with GMRs for AUC of ≤1.24 and C_{max} of ≤1.22.
- Simulated effects of oral lefamulin on the pharmacokinetics of ivacaftor were classified as mild to moderate inhibition with GMRs of ≤2.09 for AUC and ≤1.92 for C_{max}, with greater inhibition observed when lefamulin was given as multiple doses (i.e. Experiment A and C) vs. as a single dose (Experiment B).

Figure 1: Impact of Lefamulin (LEF) and Comparators on the Pharmacokinetics (PK) of Ivacaftor (IVA)



PAGE meeting 2024, Roma, Italy, June 26-28, 2024

CONCLUSIONS

- **Simulations of PBPK models for lefamulin and ivacaftor were in reasonable agreement with observed clinical pharmacokinetic data with a ≤1.4-fold difference in AUC and Cmax values.**
- **For drug-drug interaction simulation studies of ivacaftor combined with IV lefamulin in cystic fibrosis patients, lefamulin's effects on ivacaftor were non-significant.**
- **Simulated changes in ivacaftor AUC when administer with oral lefamulin in cystic fibrosis patients was classified as weak to moderate.**
- **Lefamulin simulations resulted in a lesser impact on ivacaftor AUC as compared to combinations with fluconazole (a known moderate CYP3A inhibitor).**
- **Taken together, these results suggest a low liability for a CYP3A-mediated drug-drug interaction between lefamulin and ivacaftor in cystic fibrosis patients.**

REFERENCES

(1) XENLETA® (lefamulin) [package insert]. Fort Washington, PA: Nabriva Therapeutics; 2021.
(2) Study to Assess the Safety and PK of Oral and IV Xenleta in Adults With Cystic Fibrosis. https://clinicaltrials.gov/ct2/show/NCT05225805
(3) KALYDECO® (ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals; 2021.
(4) Tsai A, et. al. (2020). Physiologically based pharmacokinetic modeling of CTFR modulation in people with cystic fibrosis transitioning from mono or dual regimens to triple-combination Elexacaftor/Tezacaftor/Ivacaftor. *Pulm Ther* 6: 275-286.
(5) Keogh RH, et al. (2020). The changing demography of the Cystic Fibrosis population: forecasting future numbers of adults in the UK. *Sci Rep* 10:10660.
(6) Lai HC, et al. (1999). Comparison of growth status of patients with cystic fibrosis between the United States and Canada. Am J Clin Nutr 69: 531-8.
(7) Garg, et al (2019). Pharmacokinetic and Drug–Drug Interaction Profiles of the Combination of Tezacaftor/Ivacaftor. Clin Transl Sci 12: 267–275.
(8) FDA Center For Drug Evaluation and Research (2012). Ivacaftor Clinical Pharmacology and Biopharmaceutics Review(s). Application Number: 203188Orig1s000.
(9) FDA Center For Drug Evaluation and Research (2017). Tezacaftor/Ivacaftor Clinical Pharmacology and Biopharmaceutics Review(s). Application Number: 210491Orig1s000.

Acknowledgments and Disclosures

This work was supported by a grant from Nabriva Therapeutics US, Inc., Fort Washington, PA. M.A., A.K., and H.M.J. are employees of Certara, which was contracted by Nabriva Therapeutics to conduct the study. W. W., J. L. C., and S. P. G. are employees and stockholders of Nabriva Therapeutics plc.