

Physiologically based pharmacokinetic modeling of elexacaftor - tezacaftor - ivacaftor during pregnancy with integrated ex vivo human placental transfer data to predict maternal and fetal exposure

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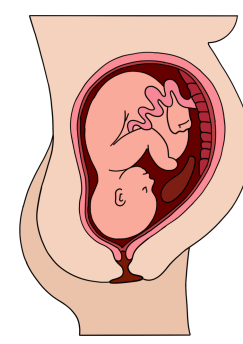
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Background

Elexacaftor-tezacaftor-ivacaftor (ETI).

- is a triple-combination of CFTR modulators
- administered orally to treat **cystic fibrosis (CF)** : **2 tabs qAM ETI 100/50/75 mg, 1tabqPM ivacaftor 150mg**
- and has become the standard of care for ~90% of CF patients¹



- Pregnancies** among women with CF (wwCF) **have increased** markedly over the last five years, with improved overall health status and life-expectancy²
- Pregnancy introduces **physiological and anatomical changes**, including modifications in hepatic enzyme activity, plasma volume, protein binding, and organ blood flow, **which can alter drug pharmacokinetics** (PK)³



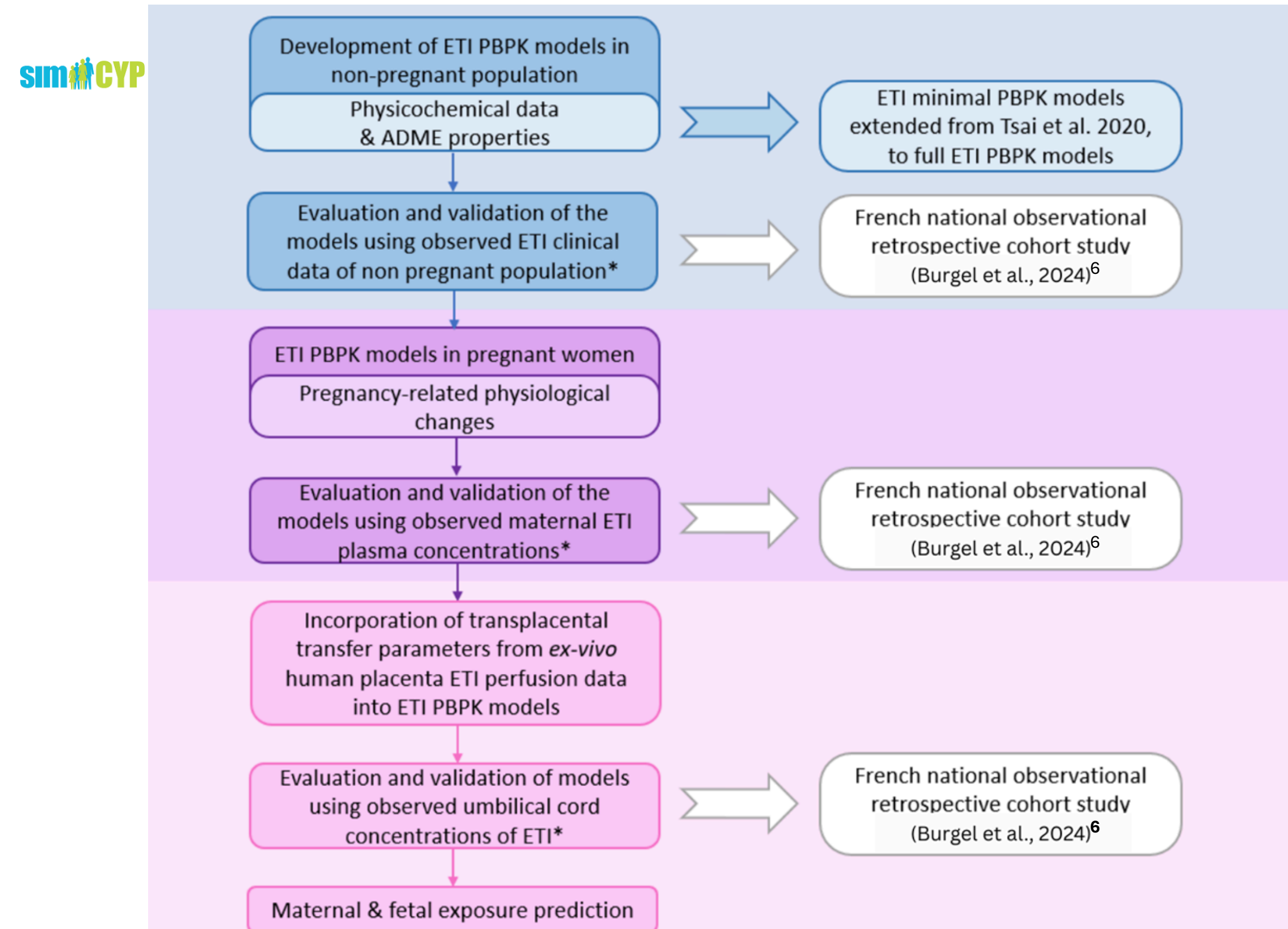
- There is **no evidence-based guidance for dose management** in the SmPC of ETI for pregnancy¹
- Optimal dosing strategies are further complicated by the need to balance maternal therapeutic goals with the potential pharmacological consequences of fetal drug exposure**
- Notably, **in utero treatment** is an emerging indication for the **management of meconium ileus in a fetus diagnosed with CF**⁴.

Objective

→ Develop and validate an **integrated maternal-fetal physiologically based pharmacokinetic (PBPK)** model for ETI during pregnancy, **incorporating ex vivo human placental transfer data** and real-world clinical PK, to predict maternal and fetal exposure to ETI.

Model development workflow

The PBPK models were developed using the **Simcyp™ PBPK Simulator version 22** (Certara, Sheffield, UK) and were developed based on the Tsai et al. framework⁵, and subsequently expanded to incorporate pregnancy-specific physiological adaptations and experimentally derived placental transfer parameters.



Datasets :

- Adult** plasma concentrations (**n = 552**)^{6,7}
- Maternal** plasma concentrations (**n=46**) collected across pregnancy at different gestational stages^{6,7}
- Umbilical cord vein** concentrations collected at delivery **from CF mothers (n = 8)**
- Umbilical cord vein** samples were collected **from healthy carrier mothers** receiving ETI for in utero therapy (**n=13**) as part of the MODUL-CF study.

Pregnancy PBPK model

- Ex vivo model** : A **five compartment physiologically based mechanistic placenta (PBMP)** model (Fig.1), adapted from Roelofsens et al., was used for modeling **maternal-fetal drug transfer across the placenta** to estimate placental transfer parameters based on ex vivo cotyledon perfusion data⁸

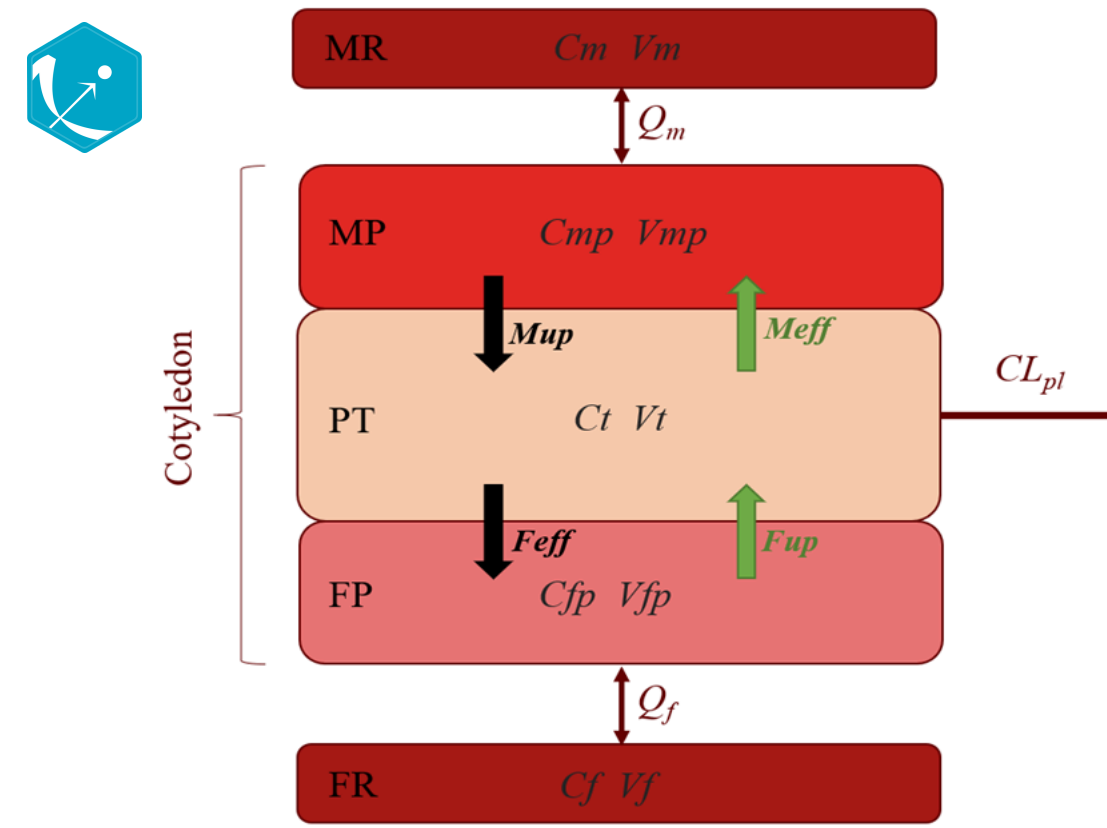


Figure 1. PBMP model adapted from Roelofsens et al. ⁸

- The **drug transfer parameters** were then integrated into the **ETI maternal-fetal PBPK model** (Fig.2)

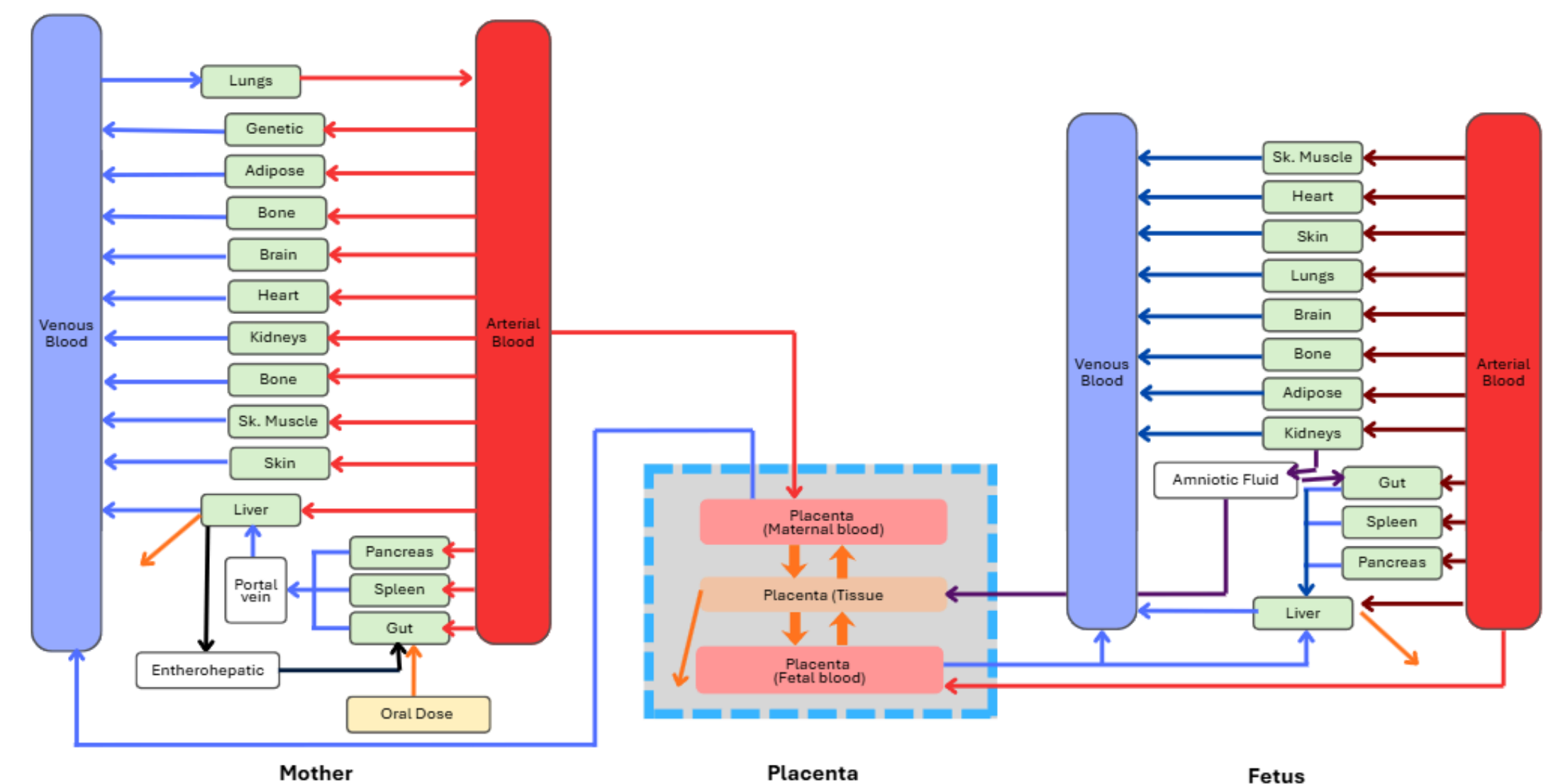


Figure 2. Structure of the maternal-fetal PBPK model adapted from Abduljalil et al. ⁹

Model evaluation

- Goodness-of-fits** : Predicted concentration-time profiles were **visually compared** with observed data at corresponding gestational ages : **observed concentrations fell within the 5th-95th percentile prediction intervals** of the simulated population distributions.
- Acceptable model performance** :
 - Geometric mean fold error (GMFE)**: $GMFE = 10^{\frac{1}{n} \sum_{i=1}^n \left| \log_{10} \left(\frac{Pred_i}{Obs_i} \right) \right|}$ → within a 0.5 and 2-fold error range
 - Average fold error (AFE)**: $AFE = 10^{\frac{1}{n} \sum_{i=1}^n \left(\frac{Pred_i}{Obs_i} \right)}$

Results

Ex vivo model :

- A total of 9 placentas (all perfused with ETI) were modeled using a population approach.
- The PBMP model satisfactorily described the ex vivo data.
- The maternal uptake/efflux (Mup, Meff) and fetal uptake/efflux (Fup, Feff) were estimated, with an additional placental clearance (CLpl) for all three compounds.

ETI PBPK model in pregnant women:

- The AFE and GMFE values were consistent with established criteria for **acceptable PBPK model performance**, across trimesters
- The ETI pregnant-specific PBPK models **accurately predicted maternal** (Table 1) **exposure across gestation**.
- The model predicted a **progressive, gestational age-dependent reduction in total maternal systemic exposure** for all three compounds (Table 1).
- The magnitude change in the corresponding pharmacologically active unbound ETI exposure was predicted to be milder than that predicted for total AUC_t for each compound.

Table 1. PBPK model – predicted mean percentage change in total elexacaftor, tezacaftor and ivacaftor maternal plasma (AUC, C_{max}, C_{res}) at steady state of standard dose, across gestational ages relative to non-pregnant metrics.

	GW (weeks)	AUC _{0-τ} (%)	C _{max} (%)	C _{res} (%)
Elexacaftor	5	-4.3	-3.6	-4.6
	10	-11.6	-10.3	-13.2
	15	-19.5	-18.1	-22.0
	20	-28.1	-26.0	-30.9
	25	-36.4	-33.9	-39.6
	30	-44.3	-41.3	-48.0
	35	-51.8	-48.2	-55.7
Tezacaftor	40	-58.3	-54.5	-63.0
	5	-4.3	-2.9	-6.3
	10	-12.3	-9.2	-17.2
	15	-21.0	-16.5	-28.1
	20	-29.7	-24.2	-38.0
	25	-38.3	-31.8	-47.5
	30	-46.3	-39.0	-56.6
Ivacaftor	35	-53.7	-45.5	-64.7
	40	-60.4	-51.2	-72.4
	5	-5.4	-4.2	-6.5
	10	-14.6	-11.9	-16.9
	15	-24.6	-20.2	-27.3
	20	-34.6	-28.6	-37.7
	25	-43.9	-36.9	-48.1
	30	-52.3	-44.1	-57.1
	35	-59.2	-51.1	-63.6
	40	-66.2	-57.1	-71.4

- Predicted umbilical cord vein concentration-time profiles** demonstrated **satisfactory predictive performance** for the fetal compartment: most observed ETI cord concentrations from either CF mothers or carrier healthy pregnant women fell within the predicted 5th–95th percentile interval
- Umbilical cord to maternal plasma AUC_{0-τ} ratio steadily increases with gestation** (Table2).

Table 2. Predicted fetal umbilical vein plasma-to-maternal plasma area under the curve ratios at steady state across gestational ages.

	GW (weeks)	Umbilical cord to maternal plasma AUC _{0-τ} ratio
Elexacaftor	15	0.20
	20	0.25
	25	0.37
	30	0.47
	35	0.56
	40	0.64
Tezacaftor	15	0.21
	20	0.26
	25	0.38
	30	0.48
	35	0.56
	40	0.65
Ivacaftor	15	0.14
	20	0.18
	25	0.27
	30	0.35
	35	0.42
	40	0.49

Conclusion

→ **The first ex vivo-informed maternal-fetal ETI PBPK model, evaluated at both the maternal and fetal level across two independent clinical populations.**

- Pregnancy is predicted to progressively reduce total maternal ETI exposure** (up to ~66% by T3), however observed and predicted maternal ETI concentrations remain above the reported ETI EC50 values⁵
- Predicted reductions in **unbound ETI exposure** are substantially more modest, urging caution against over-interpreting total concentration declines as clinically significant, and may support the hypothesis that **therapeutic efficacy is maintained** despite lower measured concentrations
- Model-predicted umbilical cord concentrations** were validated against observed measurements from both CF and healthy carrier mothers, the first such dual-population comparison reported, with **the large majority of observations falling within predicted intervals**
- These findings may provide a mechanistic rationale for therapeutic drug monitoring in pregnant wwCF and a quantitative framework for fetal risk contextualization

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