Rodatristat is metabolically stable and has low potential for drug interactions with PAH medications

Low potential for metabolic drug-drug interactions (DDIs) between rodatristat ethyl and approved medications for pulmonary arterial hypertension (PAH)

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KEY FINDINGS

- **Rodatristat ethyl and rodatristat are low risk for being systemic inhibitors of CYPs**
- **Predicted unbound C_{max} for RE and R >100-fold lower than IC50 for most sensitive CYP isoform 2C8 (IC50 2.8 µM)**

BACKGROUND

- **Rodatristat ethyl** (**RE**) is in Phase 2 clinical development (**ELEVATE 1** Study) for pulmonary arterial hypertension **(PAH)**
- RE is an orally bioavailable pro-drug for the **tryptophan hydroxylase (TPH)** inhibitor, **rodatristat** (**R**)
- TPH1 is the rate-limiting enzyme for peripheral biosynthesis of serotonin (5-HT) and is up-regulated in PAH[1]
- Excess 5-HT has been implicated in the pathology of PAH[2]
- PAH treatment frequently employs combination therapy regimens and understanding DDI potential is important to best manage patient care

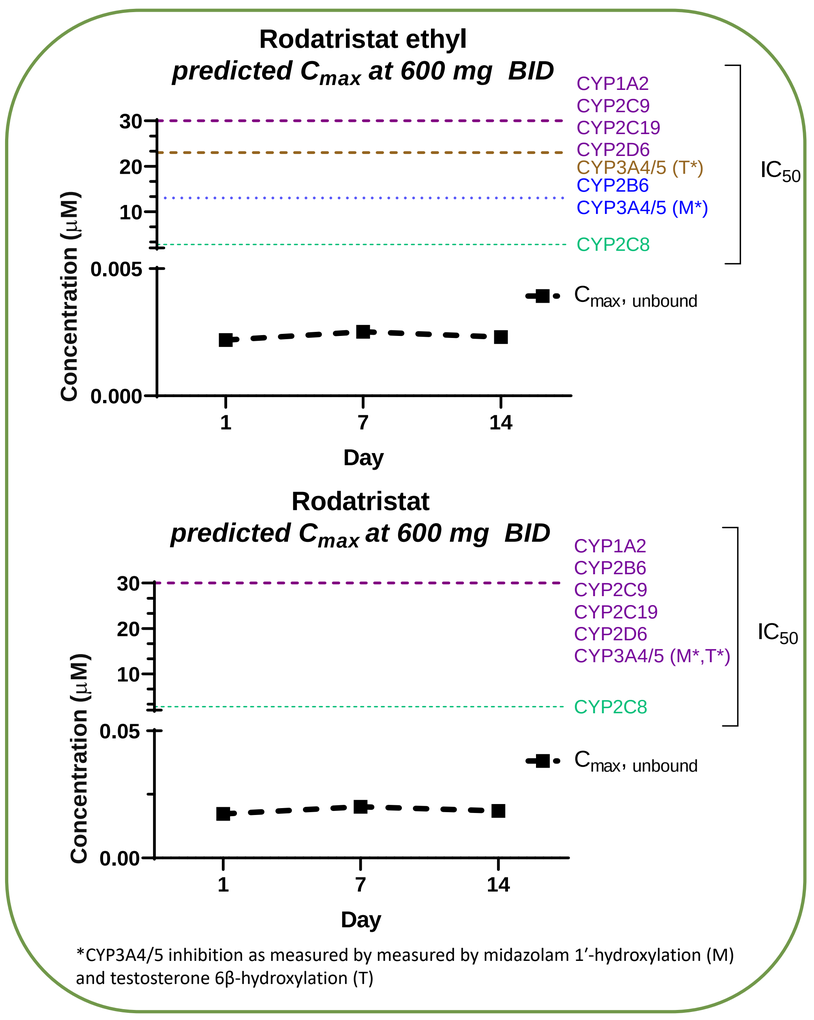
METHODS

- ***in vitro***
  - Cytochrome (CYP) inhibition was evaluated using a pool (n=200) of human liver microsomes incubated with RE or R concentrations of up to 30 µM (~120x RE C_{max} and ~15x R C_{max})
  - CYP induction was evaluated using cultured human hepatocytes (from 3 donors) treated once daily for 3 days with RE/R concentrations to 20 µM
- **FDA guidance risk assessment:**
  - Risk assessment was performed following the FDA guidance[3]. IC_{50} values were compared to the *predicted* maximum plasma concentrations (C_{max}) of RE (149 ng/mL, 0.252 µM) and R (1130 ng/mL, 2.01 µM) in plasma for **ELEVATE 1** patients receiving a 600mg RE twice-daily (BID) regimen
  - R1 and R3 values using free (non-protein bound) drug levels were calculated based on plasma protein binding (fraction bound, *fb*) of rodatristat ethyl (0.995) and rodatristat (0.991)
    - *Per FDA recommendation[3] when fb >0.99 a conservative 1% free fraction was used to calculate the* ***unbound C_{max} concentrations of 0.0025 µM and 0.0201 µM, for rodatristat ethyl and rodatristat****, respectively*

RESULTS

- Rodatristat, the active primary metabolite is produced by carboxylesterases and metabolically stable, supporting low risk for victim PK interactions
- RE and R are not time-dependent CYP inhibitors
- Overall, *in vitro* data indicate modest potential for perpetrator interactions by RE or R on CYP2B6 and CYP3A induction or inhibition of gut CYP3A – this will be evaluated by physiologically-based pharmacokinetic modeling

Predicted C_{max} for the ELEVATE 1 600 mg BID dose presents low risk for CYP inhibition



*CYP3A4/5 inhibition as measured by measured by midazolam 1′-hydroxylation (M) and testosterone 6β-hydroxylation (T)

FDA guidance[3]-based risk assessment for the 600 mg BID rodatristat ethyl dose

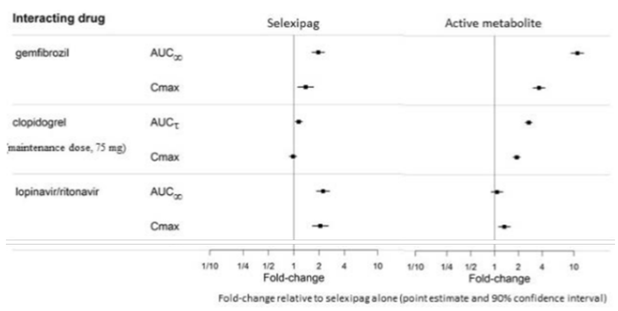
CYP Enzyme	Rodatristat ethyl: Perpetrator Potential							
	Direct Inhibition		Induction			Potential Clinical Interaction		
	In vitro IC_{50} (µM)	Calculated R1 Value*	In Vitro Induction parameters		Calculated R3 Value	Calculated AUCR*	Potential for interaction	Conduct clinical DDI stuy?
CYP1A2	0	NC	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP2B6	13	<1.02	EC_{50}	6.16	**0.960**	**0.511**	Yes	Should consider
			E_{max}	3.1				
CYP2C8	2.8	<1.02	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP2C9	0	NC	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP2C19	0	NC	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP2D6	0	NC	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP3A4 (M)	13	<1.02	EC_{50}	15.6	0.925	0.510	Yes	Should consider
		R1gut = 627	E_{max}	4.53				
CYP3A4 (T)	23	<1.02	EC_{50}	15.6	0.925	0.298		
		R1gut = 355	E_{max}	4.53				

CYP Enzyme	Rodatristat: Perpetrator Potential							
	Direct Inhibition		Induction			Potential Clinical Interaction		
	In vitro IC_{50} (µM)	Calculated R1 Value*	In Vitro Induction parameters		Calculated R3 Value	Calculated AUCR*	Potential for interaction	Conduct clinical DDI study?
CYP1A2	0	NC	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP2B6	0	NC	EC_{50}	5.8	0.766	0.464	**Yes**	**Should consider**
			E_{max}	2.95				
CYP2C8	2.8	<1.02	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP2C9	0	NC	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP2C19	0	NC	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP2D6	0	NC	EC_{50}	ND	NC	NC	No	No
			E_{max}	ND				
CYP3A4 (M)	0	NC	EC_{50}	26.7	0.476	0.015	Yes	Should consider
		R1gut = NC	E_{max}	4.5				
CYP3A4 (T)	0	NC	EC_{50}	26.7	0.476	0.184		
		R1gut = NC	E_{max}	4.5				

R1= $1+(I_{max,\ unbound}/K_i)$ **R3** = $1/[1+(d \times E_{max} \times 10 \times I_{max,u})/ (EC_{50} + (10 \times I_{max,u}))]$; where $I_{max,u}$ is the C_{max} of the unbound interacting drug; K_i is the unbound inhibition constant determined in vitro; E_{max} is maximum induction effect determined in vitro; EC_{50} is the concentration causing half-maximal effect determined in vitro[3]; see reference (3) for AUCR calculation
No time-dependent inhibition was observed for rodatristat ethyl or rodatristat.

SELECT APPROVED PAH MEDS + RODATRISTAT ETHYL: DDI RISK OVERVIEW

- **Treprostinil and Selexipag:**
  - sensitive CYP2C8 substrates
  Rodatristat inhibits CYP2C8 *in vitro* but presents low-risk for clinical interaction
    - Treprostinil: Coadministration with strong inhibitor gemfibrozil increased Cmax and AUC by ~2-fold (Orenitram® monograph[4]).
      - as a weaker inhibitor, it is unlikely that RE treatment would cause meaningful exposure changes
      - may be co-administered without dose adjustments but with appropriate clinical monitoring with a focus on changes in tolerability to treprostinil.
    - Selexipag: lowering of daily dose (to QD) is recommended with moderate inhibitors[6]. No dose adjustment is required with ritonavir (2C8 IC_{50}, 3.03µM[5]) suggesting low risk for clinically meaningful interaction for RE co-administration with selexipag.
      - Coadministration should be performed with appropriate clinical monitoring with a focus on changes in tolerability to selexipag.



**Figured modified from UPTRAVI® monograph[6] for fit*
***Glucuronide metabolite of Gemfibrozil and Clopidogrel are time-dependent 2C8 inhibitors*

- **Ambrisentan:** metabolized by CYPs 3A4, 2C19, UGTs 1A9S, 2B7S, 1A3S and is unlikely to require dose adjustment with RE[7]
- **Bosentan:** metabolized by CYPs 2C9 and 3A4 and is unlikely to require dose adjustment with RE[8]
- **Sildenafil:** metabolized by CYPs 3A (major route) and 2C9 (minor route) and is unlikely to require dose adjustment with RE[9]
- **Tadalafil:** metabolized primarily by CYP3A4 and is unlikely to require dose adjustment with RE[10]

The extent of these potential interactions will be evaluated by physiologically-based pharmacokinetic modeling and future clinical studies, if indicated.

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