Quantitative Systems Toxicology (QST) Modeling Using DILIsym Informed Safe Dose Selection of Emvododstat in Acute Myeloid Leukemia (AML) Patients

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BACKGROUND

Clinical investigation of emvododstat for the treatment of solid tumors was terminated after two patients who were heavily treated with other anticancer therapies experienced drug-induced liver failure. Subsequent investigations supported that emvododstat might be effective in treating AML at lower doses than administered in the solid tumor clinical trials. A QST model, DILIsym, was employed to predict liver safety of the proposed dosing of emvododstat in AML clinical trials.

METHODS

A PBPK model for emvododstat and its desmethyl metabolite was developed. In vitro assays were performed to assess effects of emvododstat and its desmethyl metabolite on bile acid transport, mitochondrial function, and oxidative stress (ROS). These data were integrated with in vivo exposure within DILIsym to predict hepatotoxicity responses in a simulated human population.

RESULTS

DILIsym simulations predicted the ALT elevations observed in prior emvododstat clinical trials for solid tumors, but ALT elevations were not predicted to occur with the emvododstat dosing proposed for the AML clinical trials. The modeling enabled regulatory approval to proceed with the AML clinical trial where significant liver safety concerns were not evident.

Protocol		Grade 1 (ALT 1-2.5X ULN*)		Grade 2 and above (ALT > 2.5X ULN)	
		Data	Sim	Data	Sim
Previous protocols	100mg BID 16 weeks	25% (13/52)	0.35% (1/285)	3.8% (2/52)	0.35% (1/285)
	160mg TID 16 weeks	14% (1/7)	8.4% (24/285)	0% (0/7)	22.5% (64/285)
	200mg TID 16 weeks	20% (1/5)	4.9% (14/285)	0% (0/5)	37.5% (107/285)
Prospective protocol (AML)	40mg (7)/20mg (21) QD 32 weeks†	3% 1/33	0% (0/285)	0% 0/33	0% (0/285)
	80mg (7)/40mg (21) QD 32 weeks†	3% 1/33	0% (0/285)	0% 0/33	0% (0/285)
	160mg (7)/80mg (21) QD 32 weeks†	3% (1/33)	N/A	0% (0/33)	N/A
	320mg (7)/160mg (21) QD 32 weeks†	3% (1/33)	N/A	0% (0/33)	N/A

*Upper limit of normal (ULN) in DILIsym is 40 U/L.
†Prospective clinical protocols. Tablet doses converted to capsule based on the relative bioavailability of 40%. Numbers in parenthesis represent the number of loading doses. *Clinical data were not available when simulations were performed.*

QST modeling using DILIsym *retrospectively* predicted the liver safety liabilities of emvododstat in the treatment of solid tumors and *prospectively* predicted the liver safety of reduced doses of emvododstat in a clinical trial of patients with AML.

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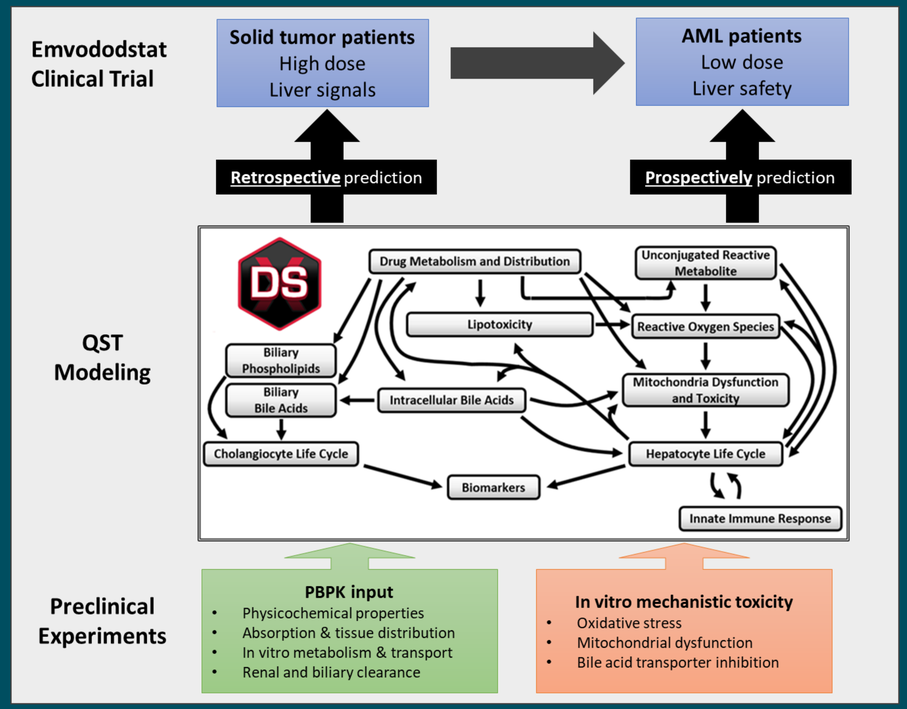
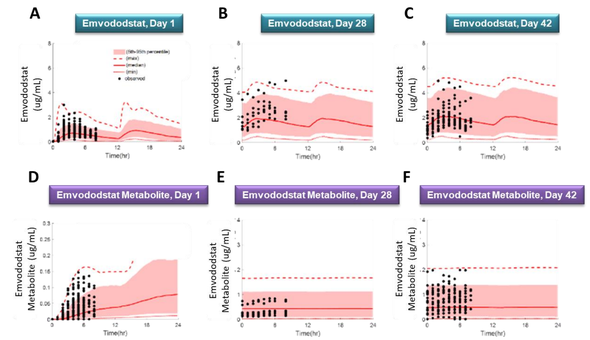
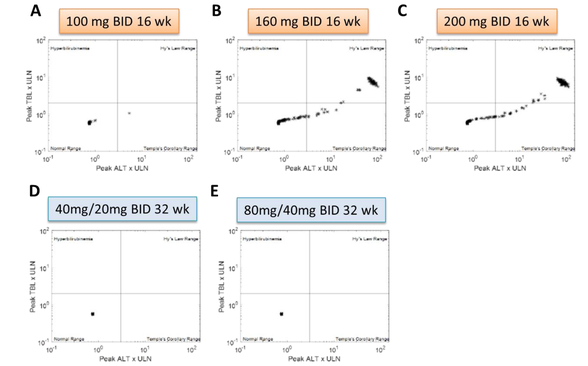


Simulated (lines and shades) and observed (symbols) plasma concentration-time profiles of Emvododstat (a-c) and its desmethyl metabolite (d-f) after administration of 100 mg emvododstat (capsule formulation) BID for 42 days.



Simulated eDISH plots for previous (a-c) and prospective (d, e) clinical protocols of emvododstat in the Human SimPops (n=285).



Emvododstat (EMV) metabolite-mediated mitochondrial dysfunction and ROS were presumed responsible for predicted ALT signals.

Case	DILI Mechanism			Simulated Grade 1 ALT and Above
	EMV ETCi	EMV Metabolite ETCi	EMV Metabolite ROS	
I	On	On	On	15/16
II	**Off**	On	On	15/16
III	On	**Off**	On	14/16
IV	On	On	**Off**	15/16
V	**Off**	**Off**	On	14/16
VI	On	**Off**	**Off**	0/16
VII	**Off**	On	**Off**	14/16

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