EDP-978, a Potent KIT Inhibitor, Demonstrated Dose-Dependent Target-Engagement and a Favorable Pharmacokinetic Profile with Once-Daily Dosing Potential in Humans

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BACKGROUND

Mast cell activation in the skin and lungs plays a crucial role in chronic spontaneous urticaria (CSU) and asthma. The KIT receptor tyrosine kinase is a key regulator of mast cell function, making it an attractive therapeutic target. Inhibiting mast cell activity is a promising strategy for alleviating symptoms of allergic diseases. Here, we present EDP-978, a highly potent and selective small molecule inhibitor of the KIT receptor. EDP-978 displayed an excellent pharmacokinetic and pharmacodynamic profile in preclinical species, positioning it as a potential best-in-class oral therapeutic for CSU and asthma.

METHODS

Human oral absorption and metabolic stability of EDP-978 were assessed using Caco-2 cells and human hepatocytes, respectively. For *in vivo* evaluation, drug concentrations in plasma and tissues were quantified using LC/MS/MS. Mast cell depletion was quantified via Luna's toluidine blue staining in rat lungs. Plasma biomarker tryptase levels were measured using ELISA in rats and dogs.

RESULTS

EDP-978: Projected to Have Excellent Oral Absorption and High Stability in Humans

EDP-978 Displayed High Permeability in Human Caco-2 Cells

Compound	Papp (10^{-6} cm/s)		Efflux Ratio	Absorption Potential
	A-to-B	B-to-A		
EDP-978	24.9	14.9	0.6	High

P_{app} = permeability coefficient measured in human colon Caco-2 cells

EDP-978 Demonstrated High Metabolic Stability in Human Hepatocytes

Species	Sex	$t_{1/2}$ (min)
Human	Male	135.9
	Female	141.5

EDP-978 is projected to have a low human clearance of 0.05 L/h/kg.

RESULTS

EDP-978: Excellent Plasma Exposure and High Oral Bioavailability in Preclinical Species

Species	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg-h/mL)	F (%)
Mouse	9.4	34.7	42.6
Rat	7.0	57.0	48.0

Single oral dose = 25 mg/kg; formulation = 0.5% Methylcellulose (MC) in water; F(%) = oral bioavailability; AUC = area under the curve

EDP-978: Good Target Tissue Distribution for CSU and Asthma Without Brain Penetration in Mice

Compound	Tissue to Plasma Ratio		
	Skin	Lung	Brain
EDP-978	0.7	1.0	0.07*

*The brain to plasma ratio is <0.1, indicating no drug penetration into the brain.

EDP-978: No Reactive Metabolites Minimizing Liver Toxicity

Compound	Reactive Metabolites in Human Hepatocytes
EDP-978	No
THB001	Yes

Liver toxicity due to reactive metabolites of THB001 led to its discontinuation in clinical trial.

EDP-978: Low Drug-Drug Interaction Potential

Inhibition	CYP Inhibition IC_{50} (µM)						
	1A2	2B6	2C8	2C9	2C19	2D6	3A4/5
TDI	>10	>10	>10	>10	>10	>10	>10
DI	>10	>10	>10	>10	>10	>10	>10

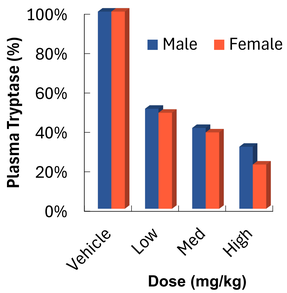
CYP= cytochrome P450 enzyme; DI = Direct Inhibition; TDI = Time-Dependent Inhibition

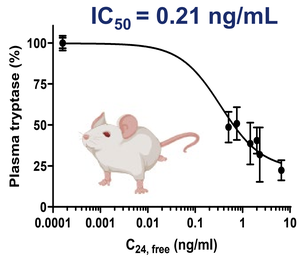
ACKNOWLEDGEMENTS

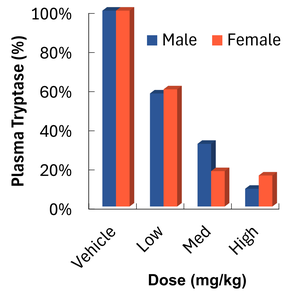
We would like to thank Drs. Jiajun Zhang and YukMing Siu at Enanta for their support.

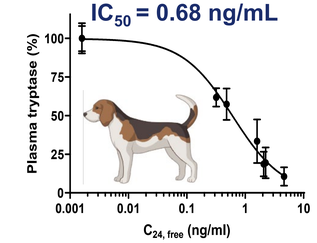
RESULTS

EDP-978: Dose-Dependent Reduction of Plasma Tryptase in Rats and Dogs



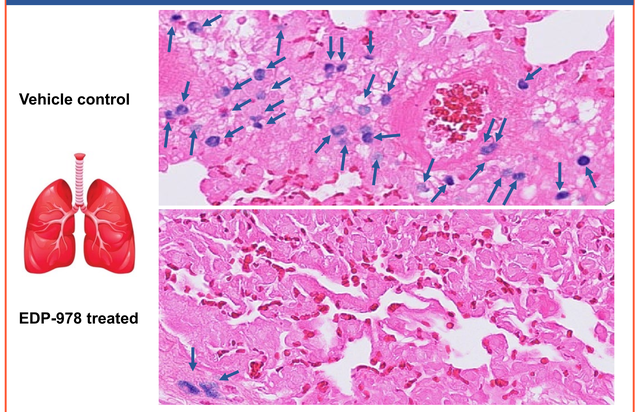






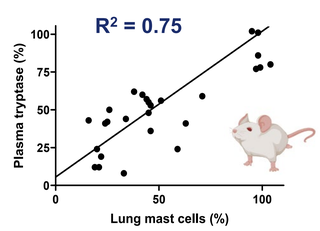
$C_{24,\ free}$: EDP-978 free plasma concentration at 24 hours post last dose

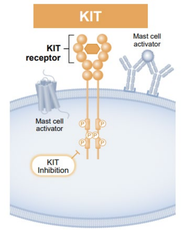
EDP-978: Significant Depletion of Mast Cells After 7 Days of Once Daily Oral Dosing in Rats



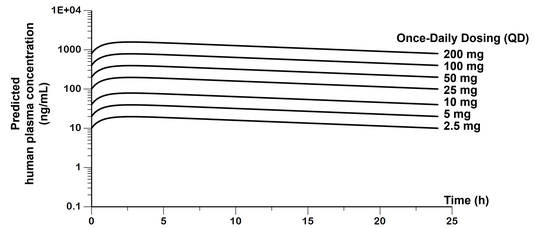
RESULTS

EDP-978: Good Correlation of Mast Cell Depletion with Plasma Tryptase Reduction in Rats





EDP-978: Projected Long Half-Life with Once Daily Oral Dosing in Humans



EDP-978 is projected to have a long half-life of >20 hours with oral QD dosing in humans.

CONCLUSIONS

- **EDP-978 is a potent KIT inhibitor with an *in vivo* IC_{50} in the picomolar range. It showed dose-dependent tryptase reduction and/or mast cell depletion in both rats and dogs.**
- **EDP-978 demonstrated excellent pharmacokinetics in preclinical species and is projected to have good oral bioavailability with a long half-life for QD dosing in humans.**
- **The highly favorable pharmacokinetic/pharmacodynamic profile of EDP-978 positions it as a best-in-class oral therapeutic for the treatment of mast cell-related diseases, including CSU and asthma.**

REFERENCES

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