Poster #573

Oral STAT6 Inhibitor EPS-3903 Demonstrates Good Preclinical *In Vivo* Tolerability Without Reactive Metabolites or Metabolic/Safety Liability *In Vitro* or *In Vivo*

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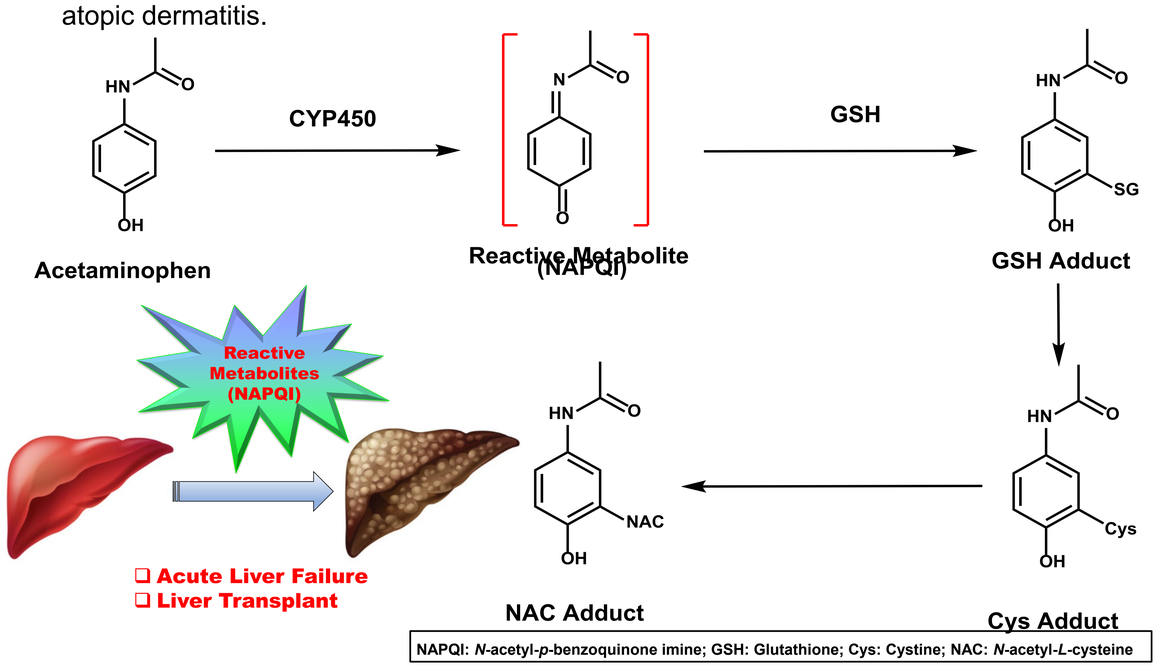
BACKGROUND

- Bioactivation or metabolic activation is a process in which drugs form reactive metabolites in the body and then covalently bind to macromolecules such as proteins, nucleic acids, and lipids.[1]
- These adducts lead to drug induced liver injuries, which have become the main cause of failure in clinical trials and often is the reason for additions of black box warnings to drugs.[2]
- Acetaminophen, an active ingredient in drugs such as Codeine, Percocet, and Vicodin, forms the reactive metabolite *N*-acetyl-*p*-benzoquinone imine in the liver. Accumulation of this reactive metabolite is the leading cause of acute liver failure in the US, accounting for 50% of all reported cases of liver failure and 20% of liver transplants.[3]
- Herein, we present the *in vitro* and *in vivo* reactive metabolite evaluations and *in vivo* tolerability in preclinical species of EPS-3903, a potent, selective, potentially best-in-class STAT6 inhibitor for the treatment of type 2 inflammatory diseases including asthma and atopic dermatitis.



NAPQI: *N*-acetyl-*p*-benzoquinone imine; GSH: Glutathione; Cys: Cystine; NAC: *N*-acetyl-*L*-cysteine

METHODS

- Reactive metabolite formation was assessed *in vitro* by cross-species hepatocytes, liver S9, and HepatoPac incubations, and *in vivo* across preclinical species plasma. GSH/thiol adducts were screened using high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS).
- Cross-species hepatocytes and animal plasma samples were compared to determine *in vitro-in vivo* correlation for reactive metabolite formation.
- To determine preclinical tolerability, mice were orally dosed with EPS-3903 up to 250 mg/kg for 8 days, and monkeys were orally dosed up to 150 mg/kg for 5 days. Plasma drug concentrations were analyzed using HPLC-MS/MS.

RESULTS

EPS-3903: No Reactive Metabolites Formed in Cross-Species Hepatocytes

Hepatocytes	Human	Mouse	Rat	Dog	Monkey
EPS-3903	No	No	No	No	No
Acetaminophen	Yes	--	--	--	--

- No GSH adducts nor any other thiol adducts were detected for EPS-3903 after incubation in cross species hepatocytes, liver S9 (data not shown), and HepatoPac (data not shown)

EPS-3903: No Reactive Metabolites Formed in Preclinical Species Plasma

Plasma	Human	Mouse	Rat	Dog	Monkey
EPS-3903	--	No	No	No	No

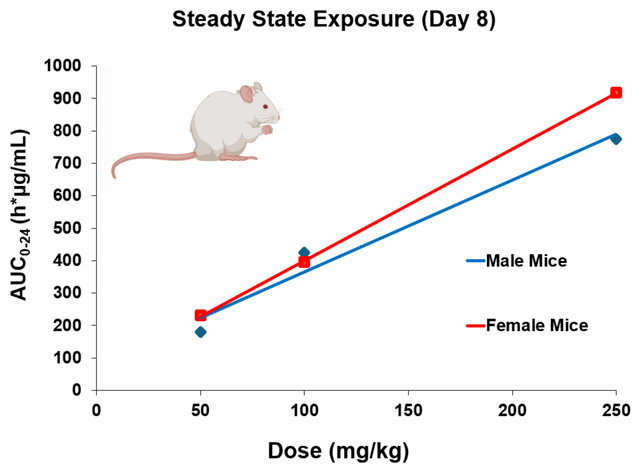
- No GSH adducts nor any other thiol adducts were detected for EPS-3903 in preclinical species plasma.

RESULTS (*Cont.*)

EPS-3903: Well-Tolerated with High Plasma Exposure in Mice

Species	*p.o.* Dose (mg/kg)	Plasma PK	
		C_{max} (µg/mL)	AUC_{0-24} (h*µg/mL)
Male Mouse	50	18.9	179.5
	100	37.4	424.7
	250	60.5	774.9
Female Mouse	50	19.4	232.0
	100	34.4	395.1
	250	58.6	918.4

p.o. Formulation: 0.5% methylcellulose (MC) in water;
C_{max} = maximum concentration; AUC = area under the curve.

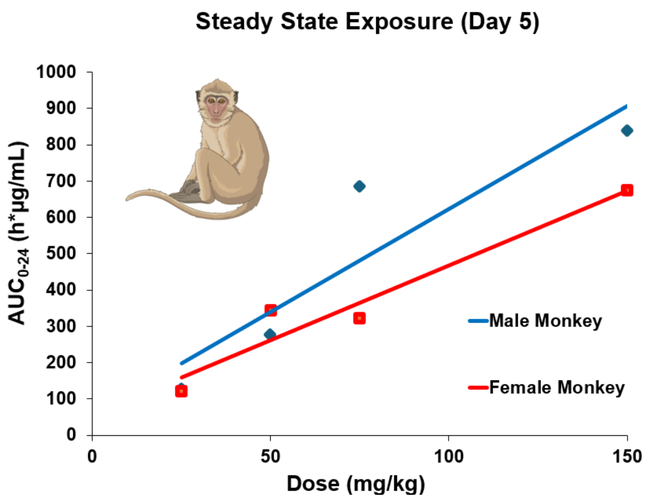


- EPS-3903 was well-tolerated in mice following 8 days of once-daily oral dosing with plasma exposure up to 918.4 h*µg/mL.
- Exposure increased in a linear, dose-dependent manner without CYP induction or gender differences.
- Body weight gain was consistent with historical data without macroscopic observations.

EPS-3903: Well-Tolerated with High Plasma Exposure in Monkeys

Species	*p.o.* Dose (mg/kg)	Plasma PK	
		C_{max} (µg/mL)	AUC_{0-24} (h*µg/mL)
Male Monkey	25	8.4	126.8
	50	15.5	274.9
	75	34.2	686.6
	150	40.7	838.3
Female Monkey	25	8.6	121.8
	50	17.4	343.5
	75	17.4	321.9
	150	35.1	675.8

p.o. Formulation: 0.5% methylcellulose (MC) in water;
C_{max} = maximum concentration; AUC = area under the curve.



- EPS-3903 was well-tolerated in monkeys following 5 days of once-daily oral dosing with plasma exposure up to 838.3 h*µg/mL.
- Exposure increased in a linear, dose-dependent manner without CYP induction or gender differences.

CONCLUSION

- EPS-3903 does not generate reactive metabolites *in vitro* or *in vivo,* minimizing metabolic/safety liabilities.
- Steady-state plasma exposure provides a safety margin up to 160 folds over anticipated exposure at human efficacious dose, based on human PK projection derived from preclinical data.[4]
- The highly favorable preclinical *in vivo* tolerability of EPS-3903 supports its development as an oral therapeutic for the treatment of allergic diseases including asthma and atopic dermatitis.

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