

Potent STAT6 Inhibitor EPS-3903 Has Excellent Preclinical Pharmacokinetics Enabling Sustained STAT6 Inhibition with Once-Daily Oral Dosing in Humans

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BACKGROUND

STAT6 plays a pivotal role in driving type 2 inflammation. Here we present the preclinical pharmacokinetics of EPS-3903, a potent and selective STAT6 inhibitor with the potential for best-in-disease efficacy for the treatment of type 2 inflammatory diseases including asthma and atopic dermatitis.

METHODS

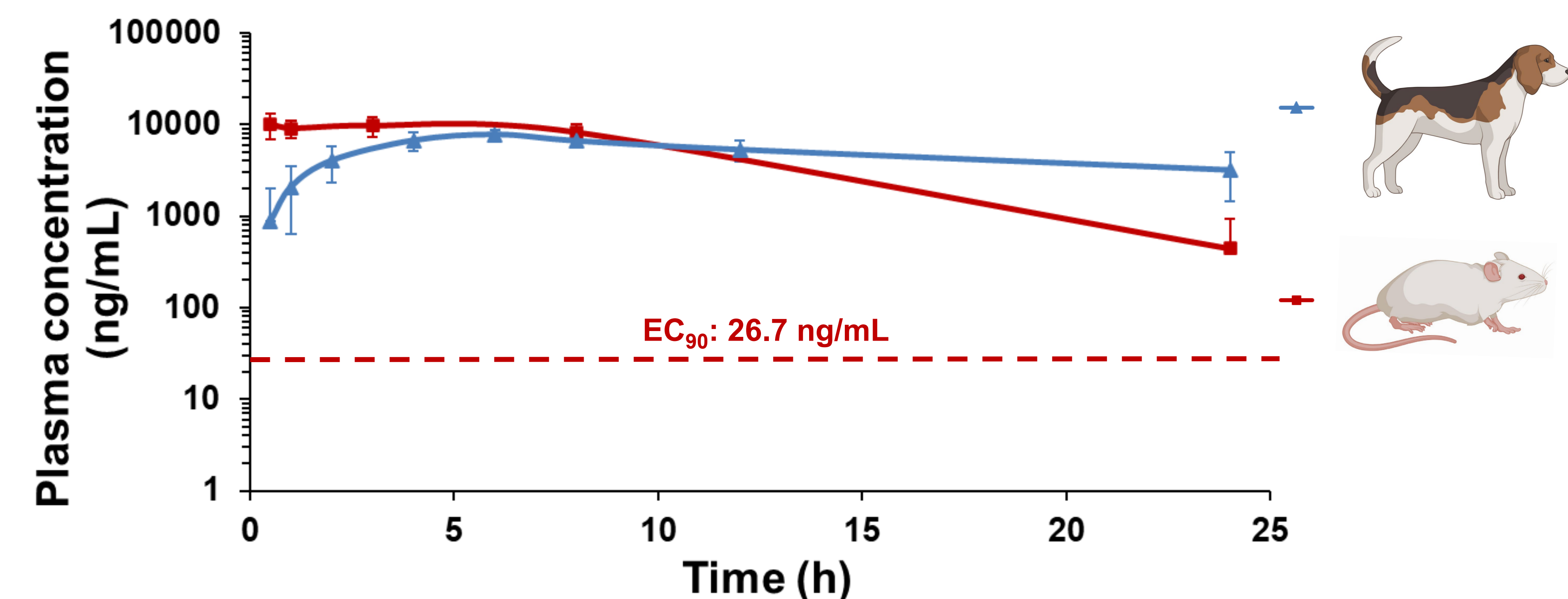
- Metabolic stability was evaluated in liver microsomes and hepatocytes across preclinical species and humans.
- The *in vivo* pharmacokinetic studies were conducted in mice, rats, and dogs following an intravenous administration of 2.5 (or 5) mg/kg or an oral dose (*p.o.*) of 25 mg/kg.
- Human PK was predicted based on allometric scaling and *in vitro/in vivo* DMPK data.

RESULTS

EPS-3903: Excellent Plasma Exposure and High Bioavailability After Single Oral Dose in Preclinical Species

Species	Gender	<i>p.o.</i> Dose (mg/kg)	C_{max} ($\mu\text{g/mL}$)	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$)	F%
Mouse	Male	25	10.0	141.7	100
	Female		12.7	170.0	100
Rat	Male		4.3	43.0	96
	Female		7.1	76.4	100
Dog	Male		7.8	174.0	100
	Female		9.2	166.3	100

Single Dose PK; *p.o.* Formulation: 0.5% methylcellulose (MC) in water; C_{max} = maximum concentration; AUC = area under the curve; F(%) = oral bioavailability.



EC_{90} value from inhibition of IL-4 induced STAT6 phosphorylation in human peripheral blood mononuclear cells (hPBMCs).

- The excellent exposure and long half-life observed in preclinical species supports continuous and sustained inhibition of STAT6 phosphorylation.

EPS-3903: Well-Tolerated with Dose-Dependent Plasma Exposure in Mice After Single Oral Ascending Dose

Species	Gender	<i>p.o.</i> Dose (mg/kg)	C_{max} ($\mu\text{g/mL}$)	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$)
Mouse	Male	50	20.3	192.0
		100	31.8	350.2
		200	36.5	472.2
	Female	50	17.8	208.5
		100	25.9	391.4
		200	35.3	479.7

Single Ascending Dose (SAD) PK; *p.o.* Formulation: 0.5% methylcellulose (MC) in water.

RESULTS (cont.)

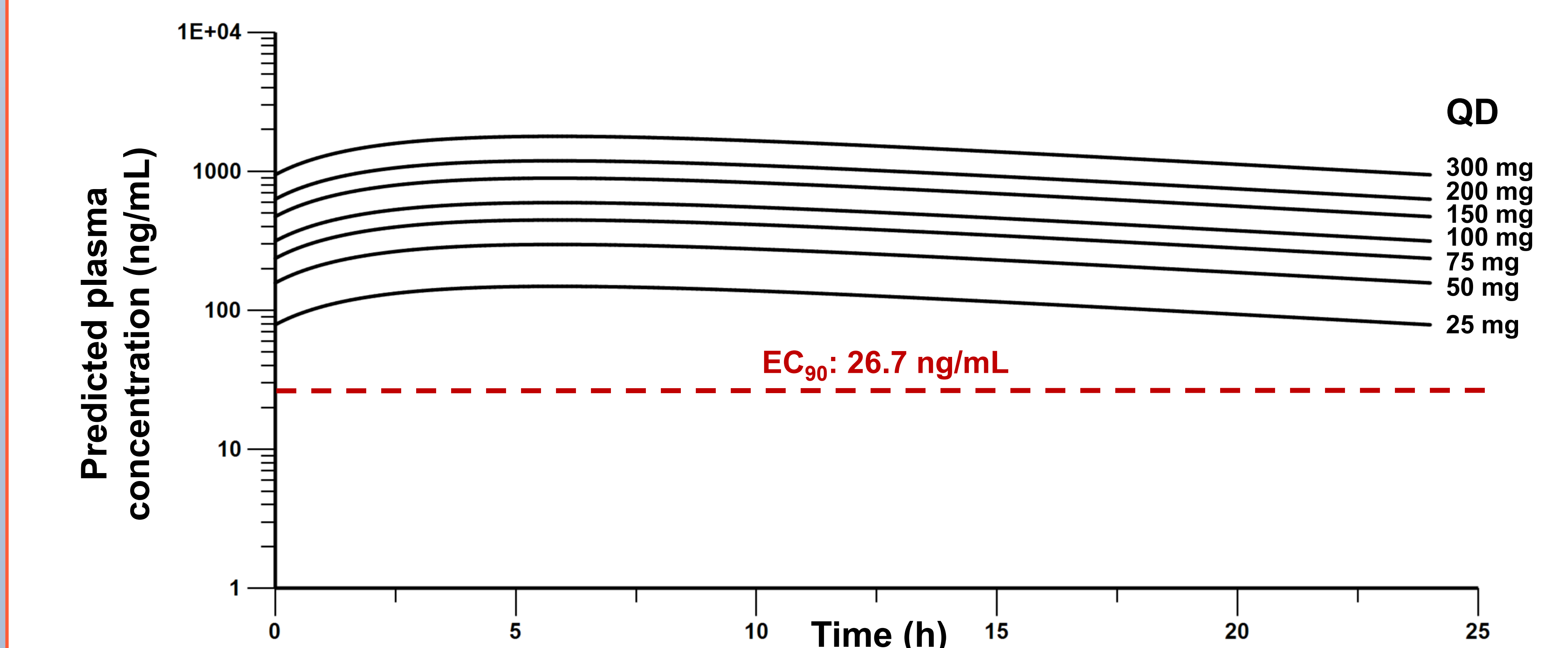
EPS-3903: Excellent Correlation of *In Vitro-In Vivo* Clearance in Preclinical Species

Species	Gender	Projected plasma clearance (L/h/kg)	<i>In vivo</i> plasma clearance (L/h/kg)
Mouse	Male	0.3	0.3
	Female	0.2	0.4
Rat	Male	0.3	0.6
	Female	0.3	0.5
Dog	Male	0.7	0.6
	Female	0.7	0.5

EPS-3903: Predicted Low Plasma Clearance in Humans

Species	Gender	$t_{1/2}$ (h)		Projected plasma clearance (L/h/kg)
		Hepatocytes	Liver Microsomes	
Human	Male	16.1	>2	0.1
	Female	19.9	>2	0.1

EPS-3903: Projected Once-Daily (QD) Oral Efficacious Dose in Humans



EC_{90} value from inhibition of IL-4 induced STAT6 phosphorylation in human peripheral blood mononuclear cells (hPBMCs).

- EPS-3903 is projected to have a long half-life of >16 hours.

CONCLUSION

- EPS-3903 displays favorable pharmacokinetics across preclinical species with high bioavailability and oral exposure.
- EPS-3903 exhibits drug-like characteristics with low clearance and excellent *in vitro-in vivo* correlation.
- With the possibility of once-daily oral dosing in humans, EPS-3903 has the potential for sustained STAT6 inhibition, highlighting its indication for treating type 2 inflammatory diseases.

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