

CTX-343, a selective, potent, peripherally restricted LPA1 receptor (LPAR1) antagonist for IPF and other fibrosing lung diseases

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Background & Aims

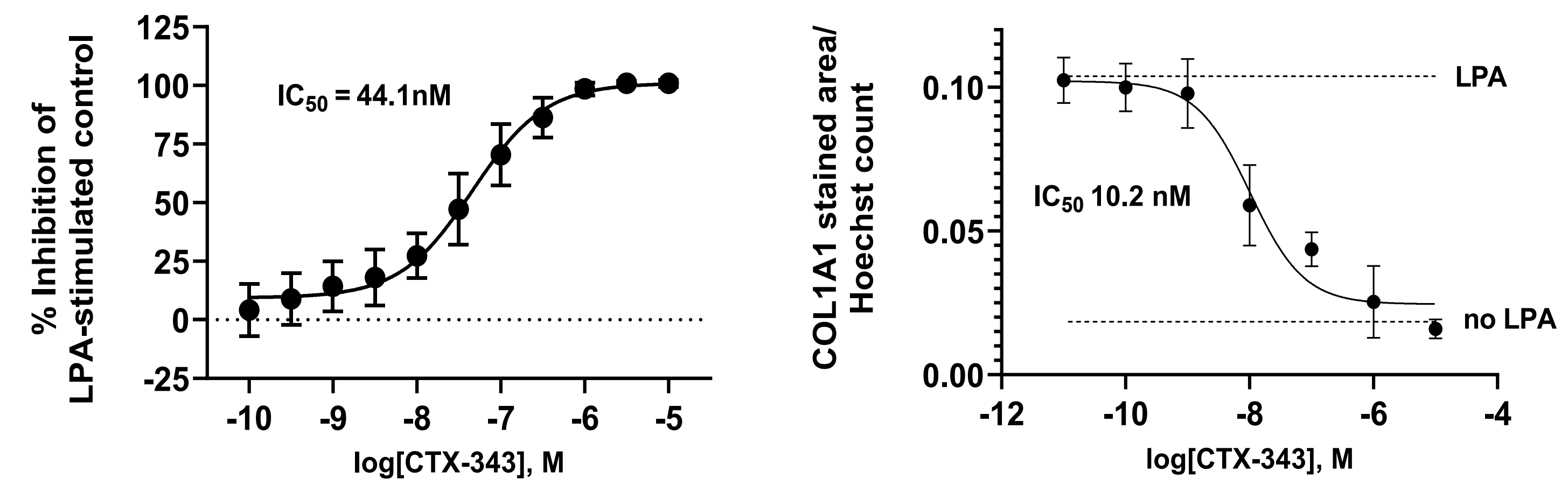
Lysophosphatidic acid (LPA) is a recognized mediator of wound healing, tissue fibrosis, and inflammation^{1,2,3}. Increased LPA1 receptor (LPAR1) expression and signaling are implicated in IPF and PPF. LPA1 antagonism with an oral, small molecule (BMS-986278; admilparant) improved IPF patient clinical outcomes^{4,5,6}. PIPE-791 has best-in-class potential, an improved potency and PK/PD profile versus BMS-986278 and is currently in a Phase 2 IPF trial. Here, we present *in vitro* and *in vivo* data for CTX-343, a second generation, peripherally restricted, structurally similar LPAR1 antagonist for treating fibrotic diseases of the lung and other organs.

Methods

- In vitro selectivity/potency:** Potency and selectivity were determined in cells transiently overexpressing human LPA1, 2, 3, 4, 5, or 6.
- In vitro binding:** The binding kinetics of CTX-343 were evaluated in membranes prepared from B103 cells stably overexpressing human lysophosphatidic acid receptor 1 (hLPA1) using radiolabeled CTX-343.
- Histamine release:** Histamine release into plasma was measured in CD-1 mice that received a single oral gavage administration of Vehicle (1%HPMC/0.1%TWEEN80) or CTX-343 (0.03, 0.3, or 3 mg/kg; n=6/group), followed by intravenous administration of LPA (300 µg), 3 or 24 hr later. Histamine concentration was analyzed by EIA (Oxford Biosciences).
- In vivo lung occupancy:** In vivo lung LPA1 occupancy was evaluated following orally dosed PIPE-791 or BMS-986278 using a filtration method of homogenized tissue after intravenous [3H]-PIPE-497, an LPA1-selective radioligand.
- Bleomycin model:** CTX-343 (0.03, 0.3, and 3 mg/kg; PO, QD) was evaluated in a 14-day mouse bleomycin-induced lung injury model to assess its ability to attenuate vascular leakage, inflammation, and fibrosis.

CTX-343 potency and selectivity for LPAR1

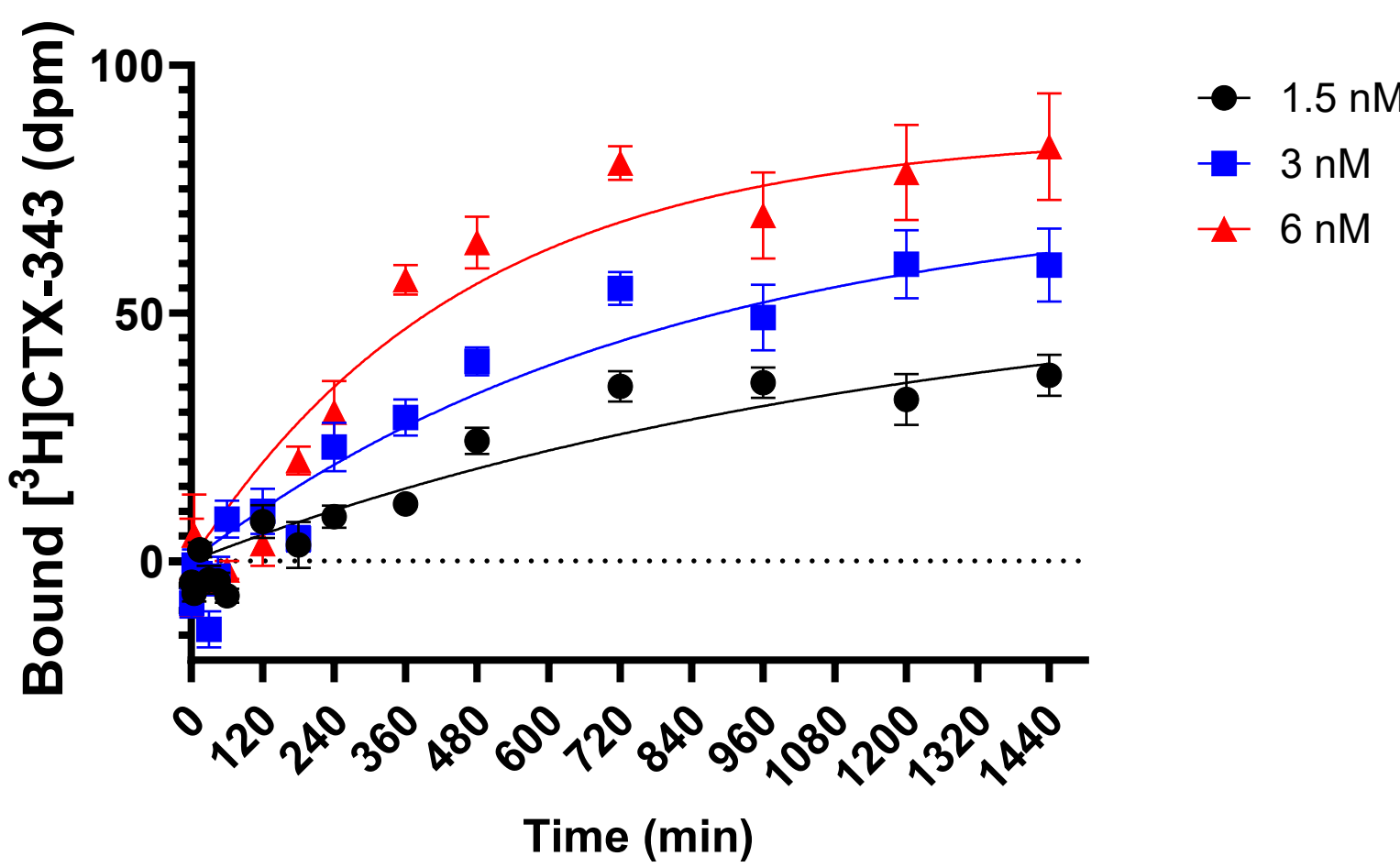
	LPA1	LPA2	LPA3	LPA4	LPA5	LPA6
LPA IC ₅₀ (µM)	0.122	2133	>10	>10	>10	>10
Fold Selectivity	--	17x	>82x	>82x	>82x	>82x



CTX-343 inhibits hLPA1 calcium flux B103 cells stably expressing hLPA1 and blocks LPA-induced COL1A1 production in primary human lung fibroblasts, with an average IC₅₀ of 44.1 nM and 10.2 nM, respectively.

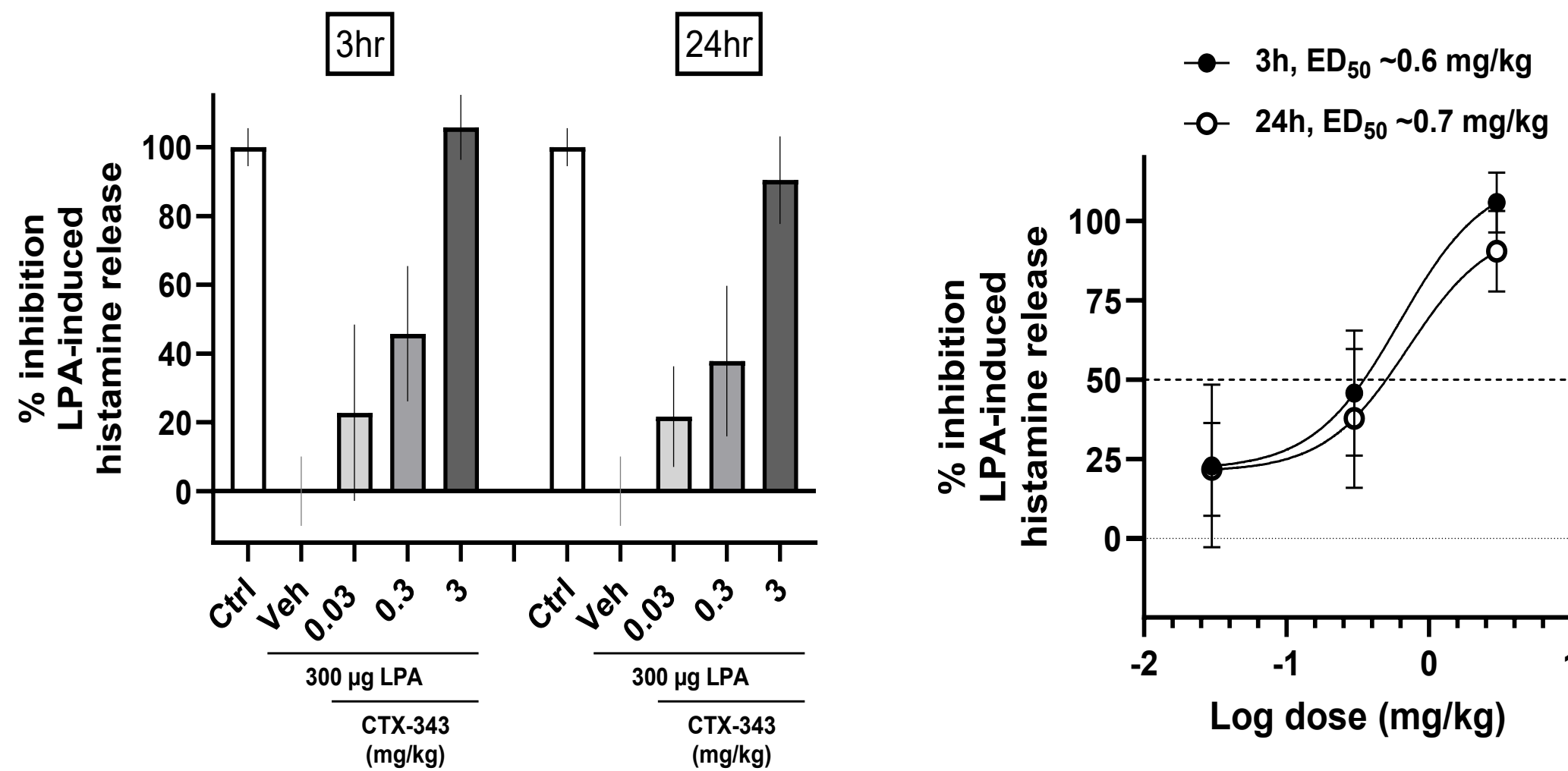
LPAR1 Binding kinetics

CTX-343 exhibited slow binding kinetics in a human LPAR1 membrane binding assay (3 h, K_i = 5.6 nM) with steady state reached at 12 h, a residence time (1/K_{off}) of 46 h, and a dissociation constant (K_d) of 1.2 nM. Data are n=4-8 replicates per time point.

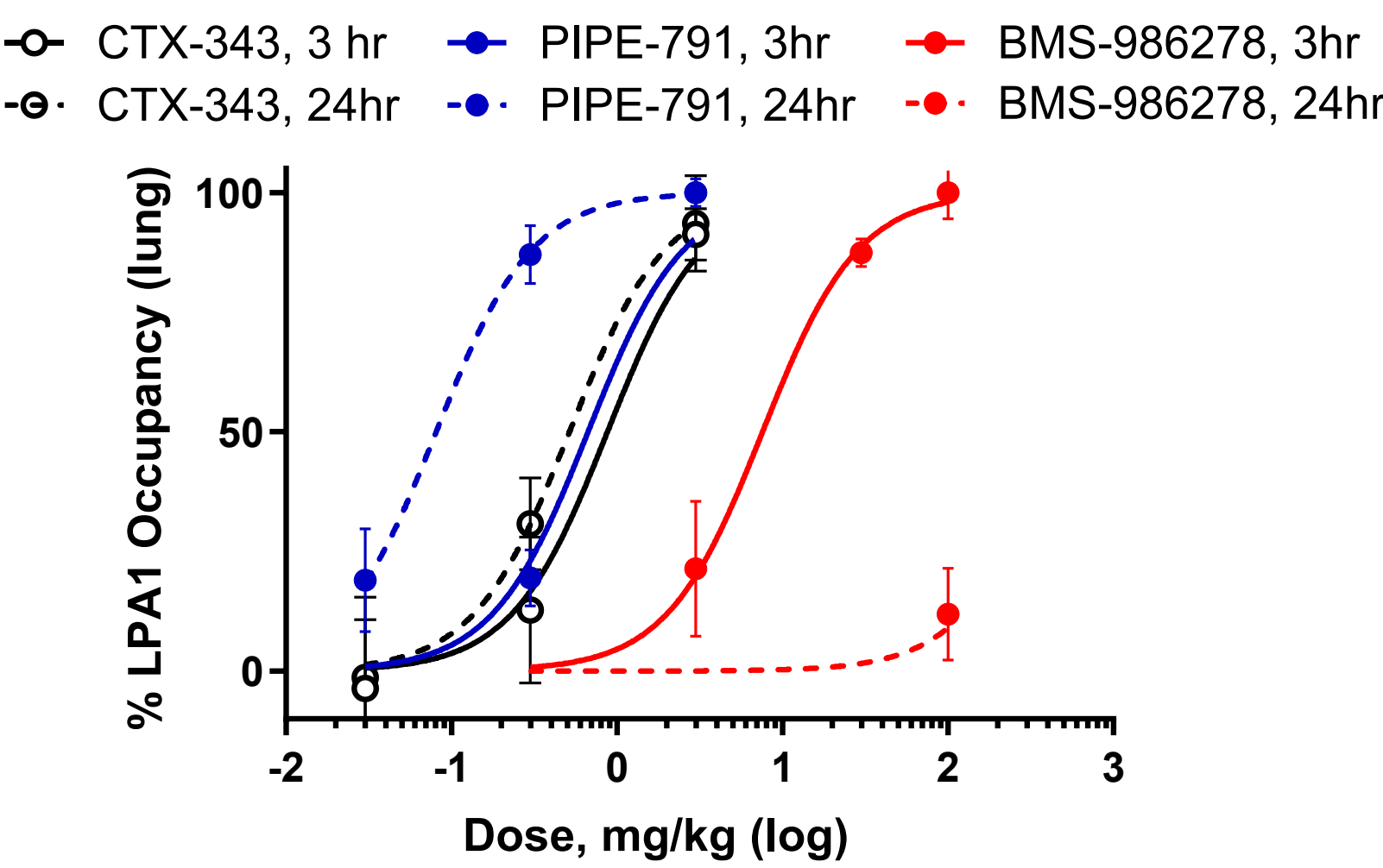


CTX-343 inhibits LPA-stimulated histamine in vivo

Intravenous LPA resulted in a rapid release of histamine into blood. When administered 3 hr or 24 hr prior to LPA delivery, CTX-343 dose-dependently inhibited histamine release with ED₅₀ values of approximately 0.6 mg/kg and 0.7 mg/kg, respectively. The corresponding EC₅₀ values were 110 and 4.6 nM, respectively.



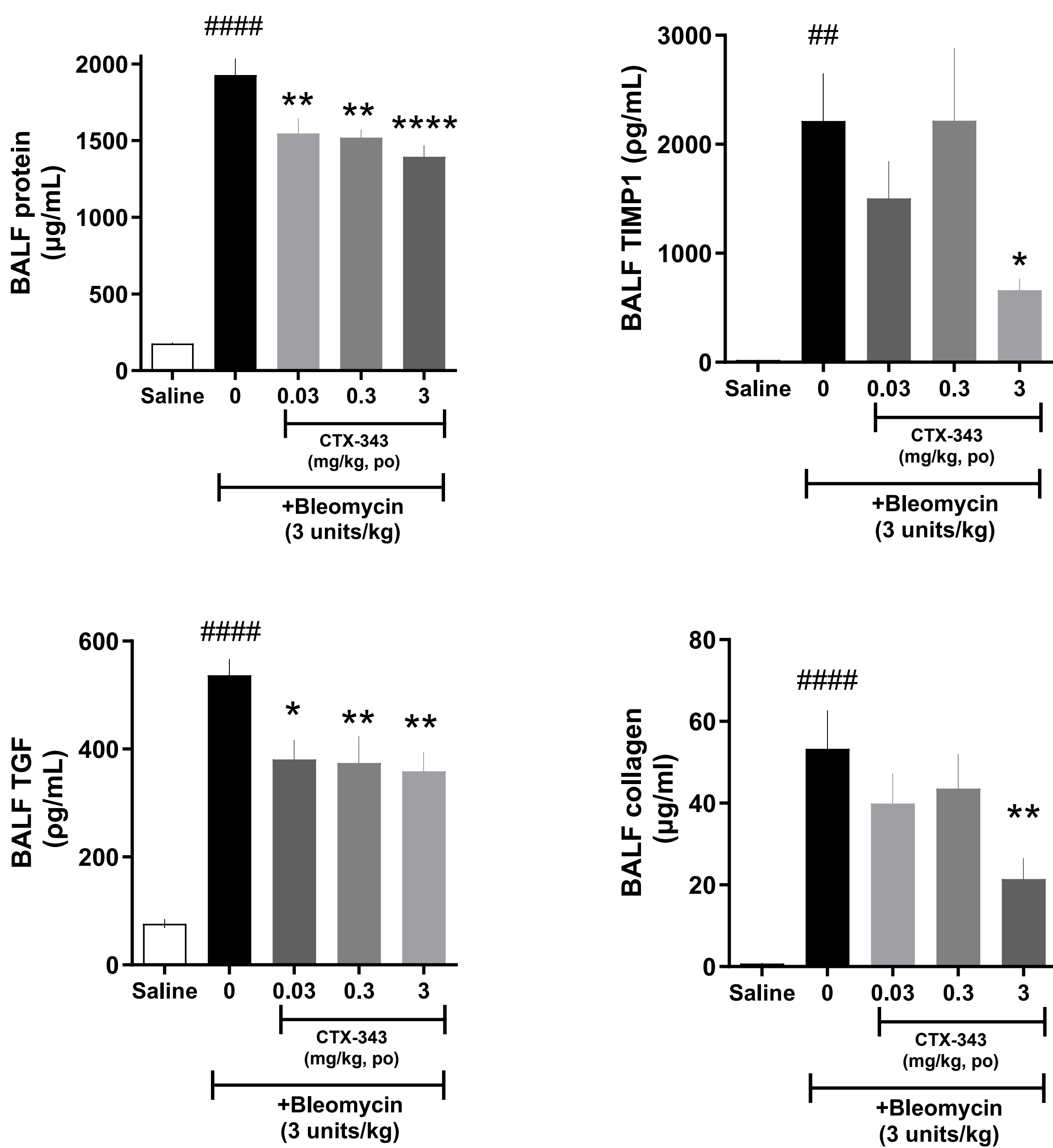
CTX-343 is a potent inhibitor of LPAR1



	3hr	24hr
CTX343 (ED ₅₀ , mg/kg)	0.9	0.5
PIPE-791 (ED ₅₀ , mg/kg)	0.4	0.1
BMS-986278 (ED ₅₀ , mg/kg)	7.5	>100

Similar to PIPE-791, CTX-343 shows sustained lung occupancy from 3 - 24-hours allowing once daily dosing, whereas BMS-986278 shows a large drop in occupancy over time suggesting the need for twice daily dosing. CTX-343 clinical efficacious dose prediction is <10 mg (QD) (versus BMS-986278, 60 - 120 mg (BID)).

CTX-343 inhibits lung injury and fibrosis in mice



In the 14-day study, CTX-343 significantly reduced vascular leakage (measured by total BALF protein), BALF TGF-β and TIMP-1 and total collagen, measured using tissue hydroxyproline analysis. Data represent the mean ± SEM of n= 8-12 mice/group. ##### p<0.0001 versus Saline; * p<0.05, ** p<0.01, **** p<0.0001 versus bleomycin only by One-way ANOVA with Dunnett's post-test.

Conclusions

Conclusions: CTX-343 is a potent, selective, peripherally-restricted LPAR1 antagonist with highly attractive PK/PD characteristics and in vivo efficacy, indicating that may a provide therapeutic benefit for IPF/PPF and other fibrotic diseases.

References

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