

Efficacy of a Reversible Cathepsin B Inhibitor in a Rodent Model of Liver Fibrosis and Human Pharmacokinetic Profile



Poster #1696

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Abstract

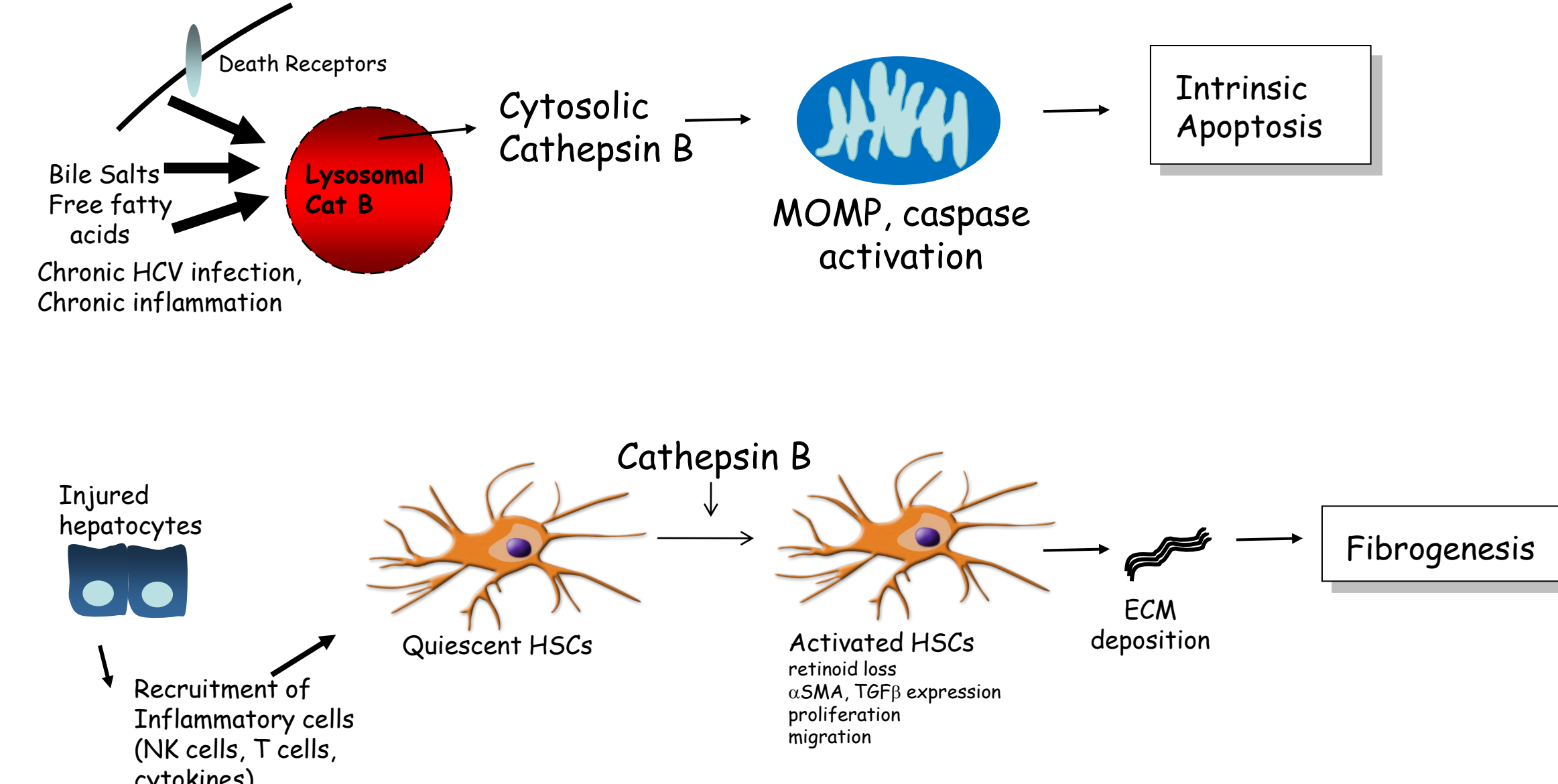
Introduction: Cathepsin B protease activity is a key mediator of hepatic apoptosis and hepatic stellate cell (HSC) activation during liver fibrosis. Genetic and pharmacologic inhibition of cathepsin B is efficacious in a number of rodent models of injury-induced liver disease and fibrogenesis. We report the preclinical characterization of a cathepsin B inhibitor VBY-376 and its efficacy in a rodent model of liver fibrosis. We also report the pharmacokinetic and safety profile of this inhibitor following oral dosing in humans in a Phase I study in healthy volunteers.

Results and Discussion: VBY-376 is a potent inhibitor of cathepsin B with a K_{iapp} value of 30nM for the isolated cathepsin B enzyme. A high degree of selectivity for the cathepsin B protease was demonstrated by screening against a panel of cellular proteases. VBY-376 was efficacious in a mouse model of fibrosis where liver damage was induced by repetitive administration of CCl₄. Therapeutic administration once daily for 4 weeks began following the confirmation of liver damage by administration of CCl₄. VBY-376 dose-dependently and significantly reduced liver damage (AST/ALT), liver hydroxyproline (a biomarker of fibrosis), and collagen deposition. When administered once daily for 4 weeks after fibrosis was fully established with 29 days of CCl₄ dosing, VBY-376 reversed established fibrosis. VBY-376 efficacy in reversing fibrosis is consistent with a block in the production of newly activated hepatic stellate cells, allowing subsequent collagen breakdown. A Phase I study was conducted to evaluate the safety and pharmacokinetics of VBY-376 in healthy human subjects after a single oral dose. The trial size was 48 subjects in six cohorts given 50-1200 mg or placebo. The human terminal half-life of VBY-376 is extended (11-15 hours) and importantly, plasma concentrations exceeded the exposure sufficient for cathepsin B inhibition and also achieved concentrations required for maximal efficacy in the rodent liver fibrosis model (125-655 ng/mL trough concentrations 24 hours after dosing). Adverse events were mild to moderate in nature, and no serious adverse events were observed at any dose level.

Introduction

Cathepsin B Biology

- Cathepsin B is a compelling new target in liver fibrosis
- Genetic or pharmacologic inhibition of cathepsin B results in efficacy in a wide range of animal models of liver injury-induced fibrosis
- Cathepsin B plays a role in two key pathways in fibrosis



Moles et al, 2009, Hepatology 49(4):1297-307; Feldstein et al, 2004, Hepatology 40:185-194; Guicciardi et al, 2001, Am J Path 159(6); Canbay et al, 2003, J. Clin. Invest. 112:152-9; Baskin-Bey et al, 2005, Am. J. Physiol. Gastrointest. Liver Physiol., 288, G396-402.

Results

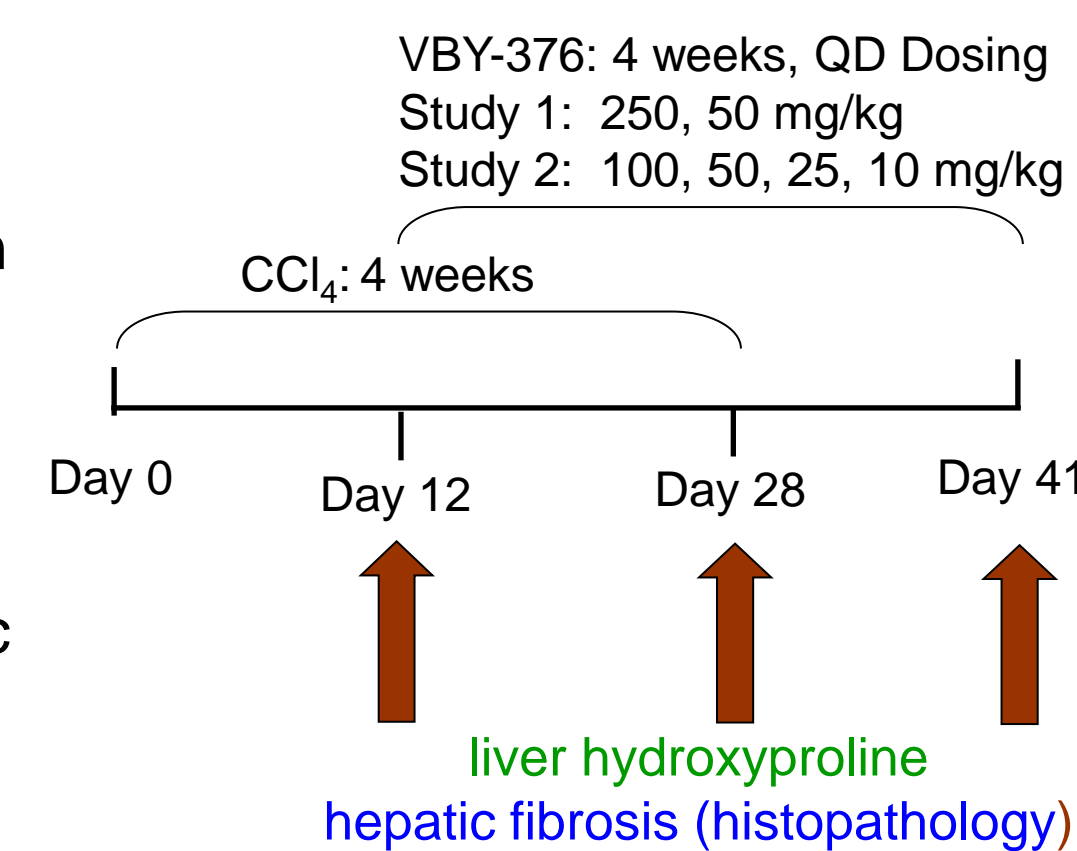
Table 1: VBY-376 is a potent, selective, and reversible inhibitor of cathepsin B with an inhibition constant (K_i) of 30nM.

Enzyme	K_i (app) (μM)	Fold Selectivity vs Cathepsin B
Cathepsin B	0.03	1
Cathepsin S	0.30	10
Cathepsin F	2.3	77
Cathepsin V	3.5	117
Cathepsin L	>10	>300
Neutrophil elastase	3.3	110
Thrombin, plasmin, trypsin, pepsin, FXa, pKallikrein	>50	>200,000

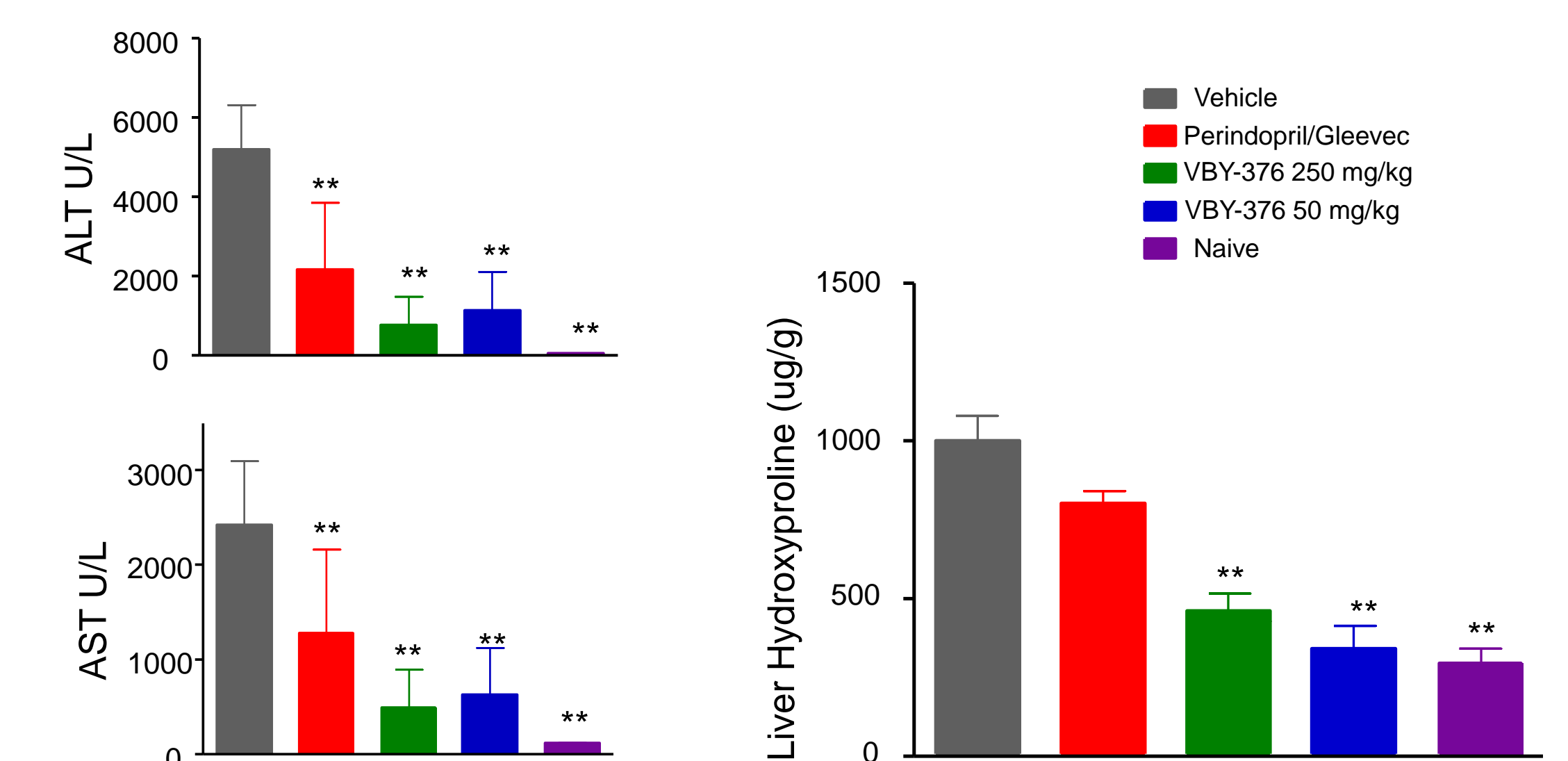
VBY-376 is a selective reversible bioavailable cathepsin B inhibitor in development for fibrosis

Figure 1: VBY-376 is efficacious in the CCl₄ Mouse Model of Liver Fibrosis

- VBY-376 assessed in a mouse model of liver fibrosis, with damage induced by repetitive administration of CCl₄
 - Model shows histological features in common with human fibrosis
 - Confirmed liver damage (ATL/AST) in satellite group of mice prior to dosing
 - Positive control: Perindopril/Gleevec



- Endpoints included
 - Liver damage (AST/ALT)
 - Fibrosis biomarker (hydroxyproline)
 - Histopathology (fibrosis/collagen deposition)



VBY-376 significantly reduced liver damage (ALT, AST) and reduced liver hydroxyproline, a fibrosis biomarker

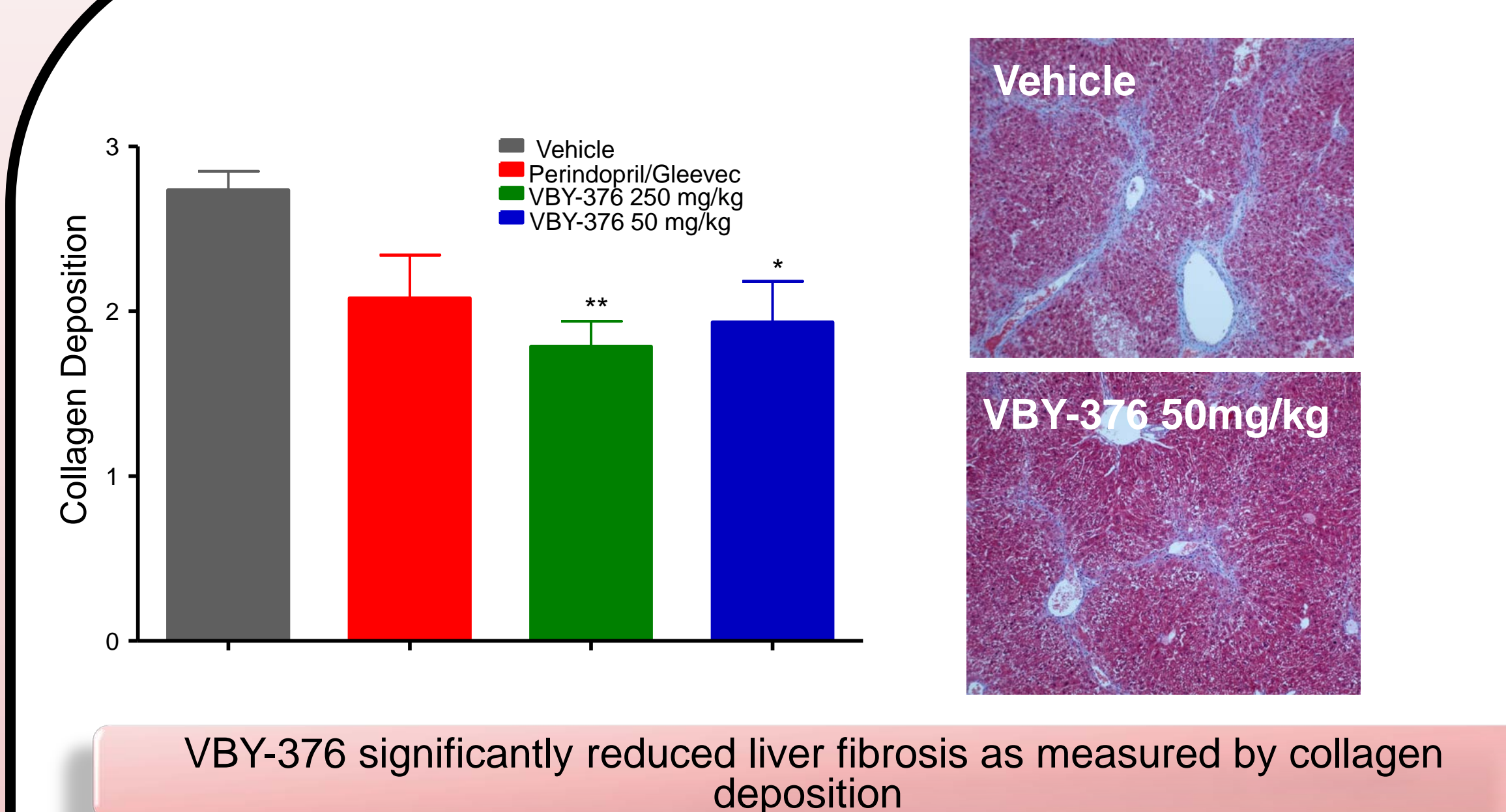


Figure 2: VBY-376 is efficacious in the CCl₄ mouse Model in a Dose-Dependent Manner

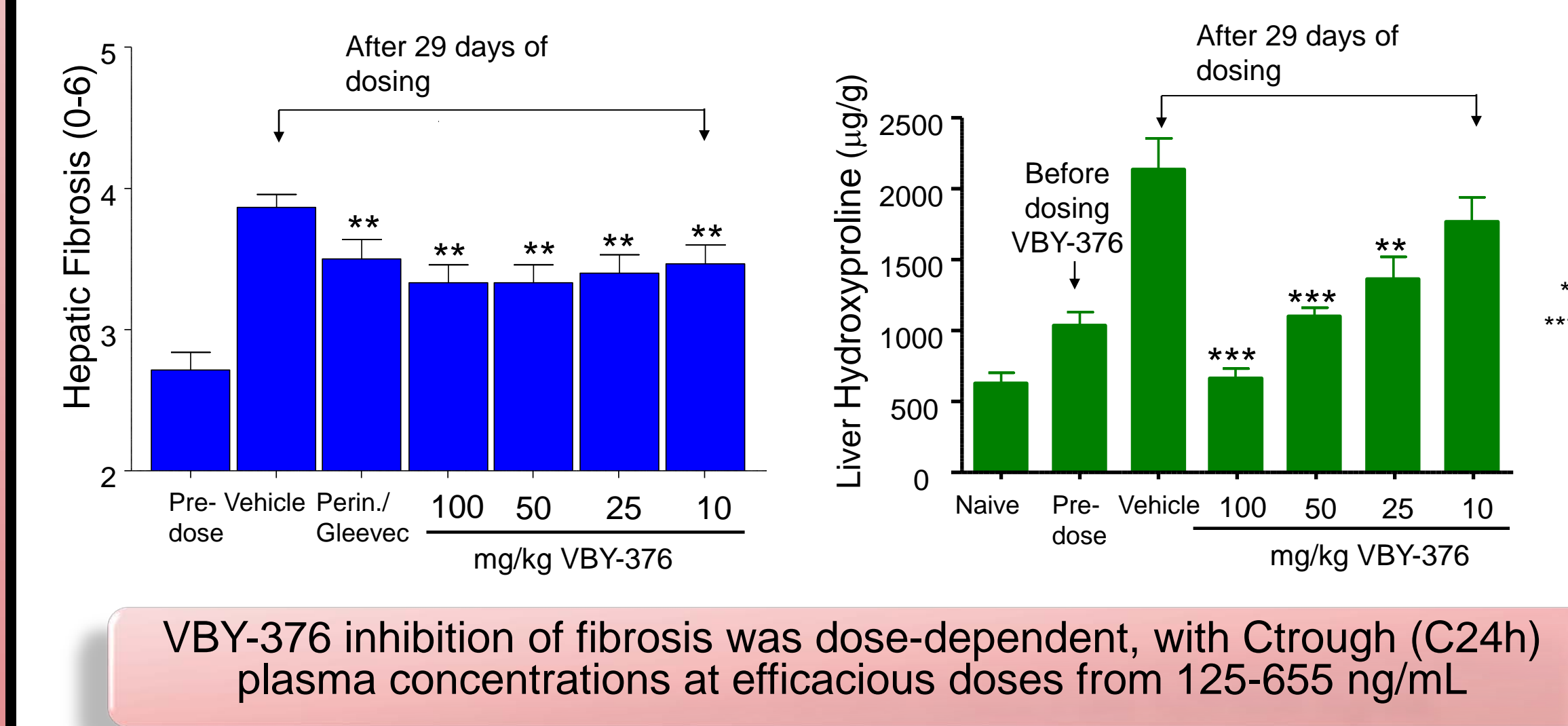
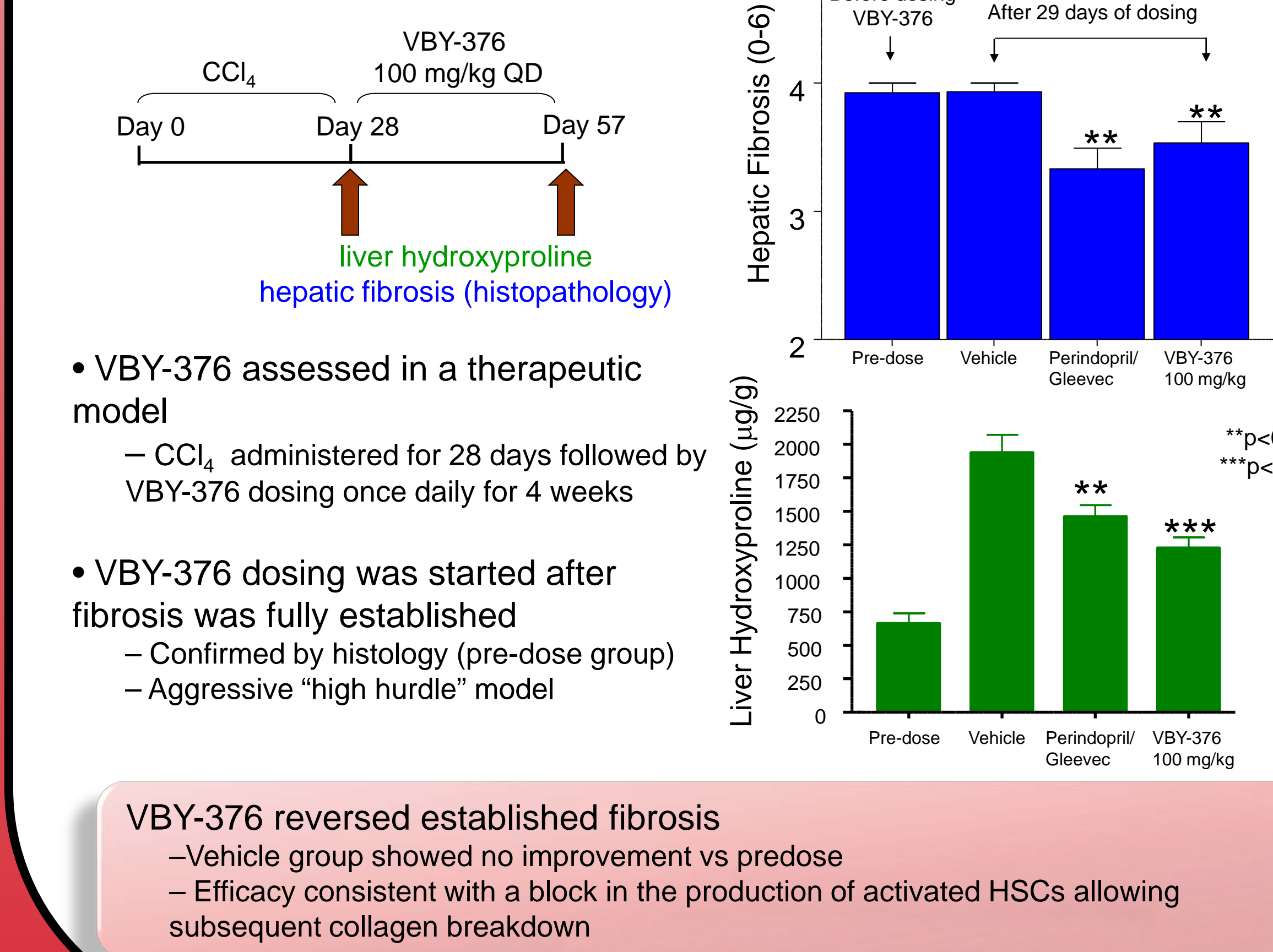


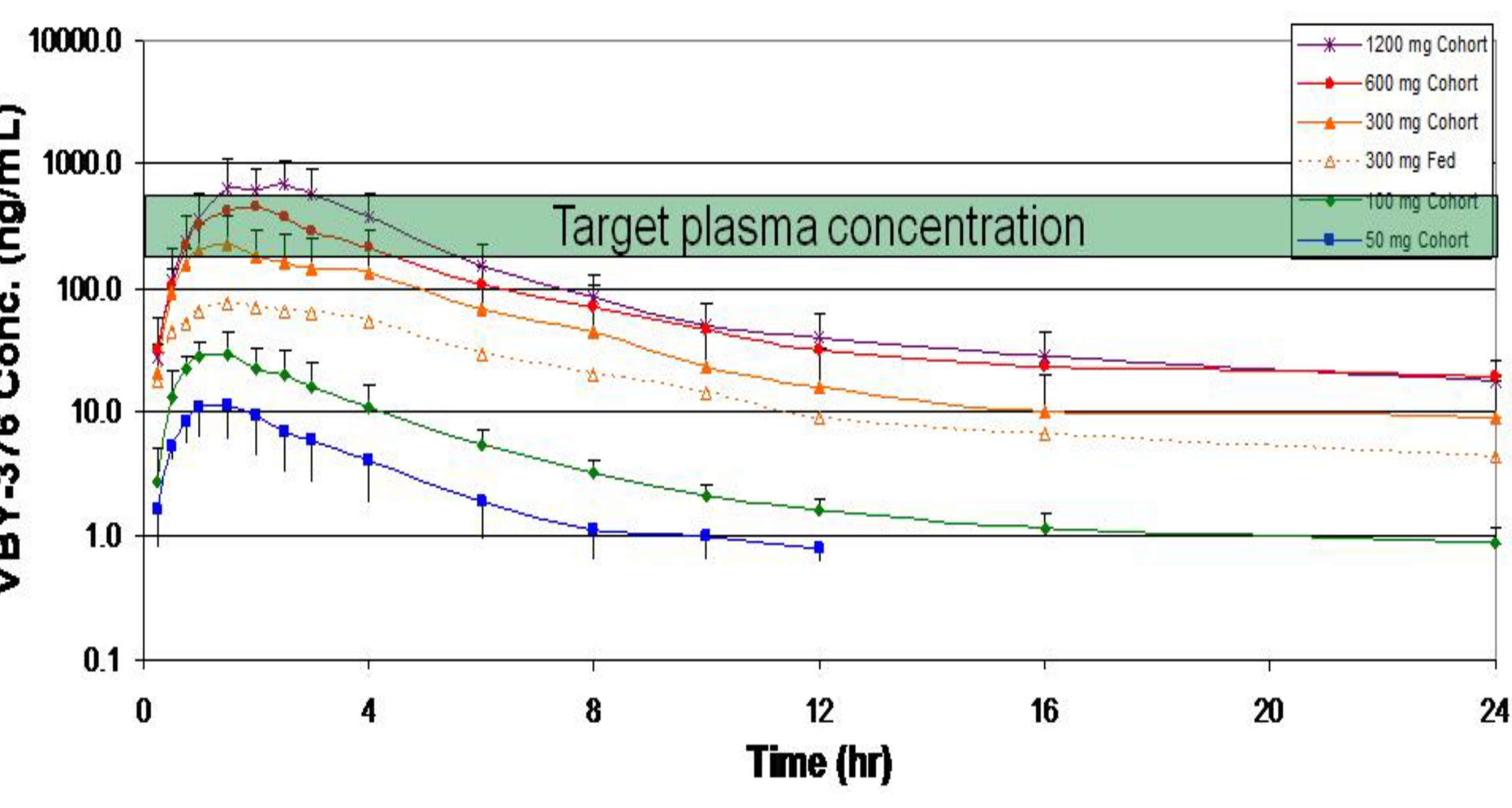
Figure 3: VBY-376 Reverses Established Liver Fibrosis in the CCl₄ mouse Model



VBY-376 reversed established fibrosis
 - Vehicle group showed no improvement vs predose
 - Efficacy consistent with a block in the production of activated HSCs allowing subsequent collagen breakdown

Figure 4: Safety and Pharmacokinetics of VBY-376 in a Phase I Trial in Healthy Volunteers

- Study Objective**
 - Safety of VBY-376 in single oral doses in healthy subjects
 - Plasma pharmacokinetics after single oral doses
 - 48 subjects in 6 cohorts (6 active, 2 placebo) given 50-1200 mg or placebo
- Pharmacokinetics**
 - VBY-376 has an extended terminal half-life (11-15 hrs)
 - Plasma concentrations obtained exceeded those required for inhibition of cathepsin B and C_{trough} levels of efficacious doses in the liver fibrosis model
- Safety**
 - All ECGs and vital signs within normal limits
 - No significant changes in laboratory values
 - Adverse events mild to moderate; no serious adverse events at any dose



Human exposure was safe and exceeded the concentration required for efficacy in the animal liver fibrosis model (125-655 ng/mL)

Conclusions

1. Cathepsin B inhibitor VBY-376 is efficacious in a mouse model of liver fibrosis
 - VBY-376 reduced liver damage
 - VBY-376 reduced liver fibrosis
 - VBY-376 rapidly reversed existing fibrosis
2. In a Phase I clinical trial, VBY-376 was safe and well tolerated and achieved plasma exposures that are highly efficacious in preventing and reversing fibrosis
 - The concentrations of VBY-376 in human plasma exceeded those demonstrated to inhibit cathepsin B in vivo
 - The terminal half-life of VBY-376 in humans is 11-15 hours
 - Adverse events were mild to moderate in nature and no serious adverse events were observed at any dose level
3. These studies support continued clinical development of VBY-376 in proof-of-concept Phase II studies in hepatic fibrosis